Clive Rosendorff
Editor

Essential Cardiology

Principles and Practice

Third Edition

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ISBN 978-1-4614-6704-5 ISBN 978-1-4614-6705-2 (eBook)
DOI 10.1007/978-1-4614-6705-2
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2013941371

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Preface to the Third Edition

This third edition reflects the very rapid advances that have been made in our understanding and management of cardiovascular disease since the first (2001) and second (2005) editions. All of the chapters from the second edition have been extensively reviewed and rewritten. There are new chapters on Cardiovascular Disease in Women, Diabetes and the Cardiovascular System, and Cardiovascular Disease in Cancer Patients, reflecting an increasing awareness of the special features and needs of these populations. With the very rapid developments in the molecular and cell biology of cardiovascular disease, the previous chapter on Cardiovascular Gene and Cell Therapy has been split into separate chapters on Cardiovascular Gene Therapy and Cardiovascular Cell Therapy. Otherwise, the general format of the second edition has been retained, to include sections on epidemiology, cardiovascular function, examination and investigation of the patient, disorders of rhythm and conduction, heart failure, congenital heart disease, coronary artery disease, valvular heart disease, hypertension, other conditions affecting the heart (cardiomyopathies and myocarditis, pericardial disease, pulmonary vascular disease, diseases of the aorta), and special populations (women, pregnancy, elderly, renal disease, diabetes, cancer) and miscellaneous (preventive cardiology, peripheral vascular disease, preoperative assessment, gene therapy, cell therapy).

I am very happy to welcome Drs. Ralph B. D'Agostino, Rhian M. Touyz, Mark Crowther, Patrick T. O'Gara, Bruce B. Lerman, Francis E. Marchlinski, Martin R. Cowie, Michael A. Gatzoulis, John M. Canty, Jr., Arthur S. Leon, Ronald Victor, Bernhard Maisch, Nanette K. Wenger, Jolien W. Roos-Hesselink, Jorge Plutzky, Edward T. H. Yeh, and Piero Anversa as new senior authors. My thanks to all contributors for their part in producing an outstanding learning resource.

I also wish to acknowledge my assistant Indrawattie Naipal, the production editor Michael D. Sova, and the editorial, production, and composition departments of Springer, for their encouragement and hard work.

Preface to the First Edition

"A big book," said Callimachus, the Alexandrian poet, "is a big evil!" Not always. There are some excellent, very big encyclopedias of cardiology, wonderful as works of reference. There are also many small books of cardiology, "handbooks" or "manuals," which serve a different purpose, to summarize, list, or simplify. This book is designed to fill a large gap between these extremes, to provide a textbook that is both substantial and readable and compact and reasonably comprehensive, and to provide an intelligent blend of molecular, cellular, and physiologic concepts with current clinical practice.

A word about the title. "Essential" is used here not in the sense of indispensable or absolutely required in all circumstances, for there is much more here than the generalist needs in order to practice good medicine, especially if there is easy access to a cardiology consultant. Rather, the word as used here denotes the essence or distillation or fundamentals of the mechanisms and practice of cardiology. The *Principles and Practice* subtitle affirms the idea that theory without a practical context may be academically satisfying but lacks usefulness, and practice without theory is plumbing. Good doctors understand the basic science foundation of what they do with patients, and great doctors are those who, as researchers or as teachers, see new connections between the basic sciences and clinical medicine.

I have been very fortunate to be able to assemble a team of great doctors who are outstanding physicians and scientists, most of them internationally recognized for their leadership position in their areas of specialization. They represent a careful blend of brilliance and experience, and, most of all, they all write with the authority of undoubted experts in their fields. They have all been asked to write up-to-date reviews of their respective areas of expertise, at a level that will be intelligible to noncardiologists as well as cardiologists, medical students, internal medicine residents, general internists, and cardiology fellows. I believe that they have succeeded brilliantly, and I know that they are all very proud to have participated as authors in this project. I am deeply grateful to all of them for the care and enthusiasm with which they carried out this task.

The organization of the book reflects pretty much the key issues that concern cardiologists and other internists at present; I have no doubt that the field will develop and change in time so that many of the modes of diagnosis and therapy described here will become much more prominent (such as gene therapy), while others may diminish or even disappear. This is what later editions of textbooks are for.

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Multivariable Evaluation of Candidates for Cardiovascular Disease

1

Ralph B. D'Agostino Sr. and William B. Kannel†

Introduction

A preventive approach to the management of atherosclerotic cardiovascular disease (CVD) is needed. Once CVD becomes manifest, it is often immediately fatal. It is the leading cause of death in the USA and across most of the world [1, 2]. Further, those fortunate enough to survive can seldom be restored to full function. Extensive epidemiologic research and controlled randomized clinical trials have identified modifiable predisposing risk factors which, when corrected, can reduce the likelihood of the occurrence of CVD [3–5]. Further, because it is a multifactorial disease with the risk factors interacting multiplicatively over time to promote CVD [6–8], the risk factors need to be assessed jointly. To accomplish this, multivariate risk prediction functions (algorithms) which estimate the probability of cardiovascular events conditional on the burden of specified risk factors have been produced to facilitate evaluation of candidates for CVD in need of preventive management [9–16].

The risk-factor concept has become an integral feature of clinical assessment of candidates for initial or recurrent cardiovascular events. These risk factors represent associations that may or may not be causal. Most risk factors associated with an initial cardiovascular event are also predictive of recurrent episodes [17]. While the risk of a recurrent event is usually dominated by indicators of the severity of the first event, such as the number of arteries occluded or the amount of ventricular dysfunction, other predisposing risk factors continue to play an important role [18]. Risk factors enabling assessment of risk may be modifiable or non-modifiable. The presence of non-modifiable risk factors may assist in risk assessment and also may affect the degree of urgency for correction of modifiable risk factors (e.g., a strong family history of CVD).

Much of the information on CVD risk factors come from prospective observational studies such as the Framingham Heart Study. Absent evidence from clinical trials, observational studies can provide evidence supporting a causal link between risk factors and CVD. Strong associations are less likely to be due to confounding, and a causal relationship is more likely if exposure to the risk factor precedes the onset of the disease. Likewise, a causal relationship is likely if the association is dose dependent and consistently demonstrated under diverse circumstances. Finally, the causality is further supported if the association is also biologically plausible.

Risk of CVD events is usually reported as a relative risk or as an odds ratio. Risk can also be expressed as an attributable risk by subtracting the rate in those without the risk factor from the rate in those who have it. For CVD risk factors, the absolute attributable risk increases with age, whereas the relative risk tends to decrease. The population-attributable fraction takes into account the prevalence of the risk factor as well as the risk ratio, assessing the impact of the risk factor on the incidence of disease in the population and the benefit of removing it from the population. An unimpressive risk-factor risk ratio can have a major public health impact because of its high prevalence in the general population. Physicians and patients often have difficulty interpreting relative risks and the other measures listed above [19–22]. For example, a relative risk of 20 sounds high, but if the incidence rate in the referent group is close to zero, the incidence rate will also be close to zero in the group with relative risk of 20. In contrast to this, a relative risk of 1.2 may sound small but could be very important when the incidence rate in the referent group is high. Responding to this difficulty,

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_1, © Springer Science+Business Media New York 2013

researchers and policy makers have shifted to absolute risks, that is, the absolute probabilities of developing CVD within a given time interval, when using risk prediction functions. These are easier to interpret and can be used for recommendations for interventions when individuals exceed unacceptable risk thresholds [14, 19–22].

Over six decades of epidemiological research have identified a number of modifiable CVD risk factors that have a strong dose-dependent and independent relationship to the rate of development of atherosclerotic CVD [5, 9–17]. Importantly, these risk factors can be readily ascertained from ordinary office procedures. Framingham Study epidemiological research has documented classes of risk factors such as atherogenic personal traits, lifestyles that promote them, and innate susceptibility. Most of the relevant risk factors are easy to assess during an office visit and include systolic blood pressure, blood lipids (total and HDL cholesterol) diabetes status, and current smoking [5, 23]. These above listed risk factors in addition to age and sex are the standard CVD risk factors that are basic components in most risk prediction functions.

In the following, we summarize the data that established the standard risk factors. We then present the justification and need for multivariate evaluation and prediction functions along with some of its history. We illustrate them using examples of existing functions. Then we discuss the evaluation of the performance of the functions and the validity and transportability of existing functions. Then we end with the discussion of adding new variables (novel biomarkers) to risk prediction.

Establishing and Evaluating the Standard CVD Risk Factors

Disease-Specific Effects

CVD in this chapter is defined as coronary heart disease (CHD, consisting of myocardial infarction (MI), angina, coronary insufficiency, and angina), cerebrovascular disease (including stroke and transient ischemic attack (TIA)), peripheral artery disease (PAD), and congestive heart failure (CHF). Epidemiological cohort studies including the Framingham Study, which started in 1948, deliberately set out to identify the variables that relate to the development of CVD [6, 7]. The search was fruitful, and in 1961, William Kannel coined the term risk factors for what was identified [24]. These risk factors first were focused on CHD and then extended to the other components of CVD. Table 1.1 displays the event rates and age-adjusted relative risks of the dichotomized versions of the standard major risk factors (high cholesterol, hypertension, diabetes, and smoking) on various CVD events. Most relative risks are statistically significant. For CHD, all CVD risk factors contribute powerfully and independently to all its clinical manifestations. For atherothrombotic brain infarction (ABI), hypertension and diabetes predominate and lipids play a lesser role. For PAD, diabetes and cigarette smoking are paramount, with cholesterol being less important. For CHF, hypertension and diabetes are important, whereas total cholesterol appears to be unrelated. The standard risk factors also influence CVD rates with different strengths in men and women [4, 26, 27]. Some of the standard risk factors tend to have lower risk ratios in advanced age, but this reduced relative risk is offset by a high absolute incidence of disease in advanced age, making the standard risk factors highly relevant in the elderly. Data such as these provided convincing evidence of the importance of these risk factors.

Refinements in Standard Risk Factors

The atherogenic potential of serum total cholesterol was determined to be derived from its LDL cholesterol fraction, and its HDL component proved to be protective and inversely related to the development of coronary disease [28, 29]. The strength of the relation of total cholesterol to coronary disease declines after age 60 years in men, but the total/HDL cholesterol ratio continues to predict events reliably in the elderly of both sexes (Table 1.2). It also predicts equally well at total cholesterol values above and below 240 mg/dL. This ratio has been found to be one of the most efficient lipid profiles for predicting cardiovascular events [30, 31]. Comparing age-adjusted fifth to first quintile lipid CVD risk ratios for the individual lipids and their ratios, it is evident that the total/HDL and LDL/HDL cholesterol ratios are more powerful predictors of CHD than the individual lipids that comprise them (Table 1.3). However, knowledge of the individual (total and HDL-C) components is important, and in risk assessment and treatment recommendations, both are examined as two separate, but related, risk factors [14–16]. Also the joint consideration of HDL-C and non-HDL-C cholesterol is now common.

Evaluation of hypertension shifted from emphasis on diastolic blood pressure to the systolic blood pressure component and recognizes isolated systolic hypertension as a hazard for development of CVD. At all ages in either sex, for all the atherosclerotic CVD outcomes, systolic blood pressure has been shown to have a greater impact than the diastolic pressure (Table 1.4) [34]. Isolated systolic hypertension by definition denotes increased pulse pressure, and risk of CVD increases stepwise with the pulse pressure at all ages in each sex (Table 1.5). Framingham Study data suggest an important role of the pulse pressure at any level of systolic blood pressure [35]. Reliance on the diastolic blood pressure to evaluate the risk of CVD in the

Table 1.1 Risk of CVD events according to standard risk factors Framingham Study 36-year follow-up

	Age 35–64 year				Age 65–94 year			
	Rate/1,000		Rel. risk		Rate/1,000		Rel. risk	
CHD/risk factors	Men	Women	Men	Women	Men	Women	Men	Women
High cholesterol	34	15	1.9***	1.8**	59	39	1.2*	2.0***
Hypertension	45	21	2.0***	2.2***	73	44	1.6***	1.9***
Diabetes	39	42	1.5***	3.7***	79	62	1.6**	2.1***
Smoking	33	13	1.5**	1.1[a]	53	38	1.0[a]	1.2[a]
ABI								
High cholesterol	3	2	1.0[a]	1.1[a]	10	12	1.0[a]	1.0[a]
Hypertension	7	4	5.7***	4.0***	20	17	2.0***	2.6***
Diabetes	7	4	3.0***	2.4*	20	28	1.6[a]	2.9***
Smoking	4	1	2.5**	1.0[a]	17	20	1.4[a]	1.9***
PAD								
High chol.	8	4	2.0**	1.9[a]	18	8	1.4[a]	1.0[a]
Hypertension	10	7	2.0***	3.7***	17	10	1.6*	2.0**
Diabetes	18	18	3.4***	6.4***	21	16	9.7*	2.6**
Smoking	9	5	2.5***	2.0**	18	11	8.5**	1.8*
CHF								
High chol.	7	4	1.2[a]	1.1[a]	21	18	1.0[a]	1.0[a]
Hypertension	14	6	4.0***	3.0***	33	24	1.9***	1.9***
Diabetes	23	21	4.4***	8.0***	40	51	2.0***	3.6***
Smoking	7	3	1.5***	1.1[a]	23	22	1.0[a]	1.3*

Based on data from Kannel and Wilson [25]
Rates are biennial per 1,000 and age adjusted. Risk ratios are age adjusted
Risk ratio, relative risk for persons with a risk factor versus those without it. For cholesterol >240 compared to <200 mg/dL. Hypertension >140/90 mmHg
CHD coronary heart disease, *ABI* atherothrombotic brain infarction, *PAD* peripheral artery disease, *CHF* heart failure
*$p<0.05$
**$p<0.01$
***$p<0.001$
[a]NS

Table 1.2 Development of coronary heart disease by Total/HDL cholesterol ratio versus total cholesterol according to age:16-year follow-up Framingham Study

	Total/HDL-C ratio (quintile 5/quintile 1)			Total cholesterol (>240/<200 mg/dL)	
Age	49–59	60–69	70–81	35–64	65–94
Men	3.4*	2.9*	2.3*	1.9***	1.2[a]
Women	3.7*	6.7*	3.3*	1.8**	2.0***

Based on data from Kannel and Wilson [25]
Quintile 5/quintile 1: ratio fifth risk quintile to first for total/HDL-C
*$p<0.05$
**$p<0.01$
***$p<0.001$
[a]NS

Table 1.3 Efficiency of blood lipids and ratios in predicting coronary disease Framingham Study subjects ages 50–80 year

	Age-adjusted Q_5/Q_1 risk ratios	
	Men	Women
Total cholesterol	1.9	2.5
LDL cholesterol	1.9	2.5
HDL cholesterol	0.4	0.5
Total/HDL cholesterol	2.5	3.1
LDL/HDL cholesterol	2.5	2.8

Reprinted from Kannel and Wilson [32]. With permission from Elsevier
Q quintiles of blood lipid distribution

elderly with an elevated systolic blood pressure can be misleading because counter to expectations of those who do, risk *increases* the *lower* the accompanying diastolic pressure [35].

Diabetes and obesity are now conceptualized as components of an "insulin resistance or metabolic syndrome" consisting of abdominal obesity, elevated blood pressure, dyslipidemia, hyperinsulinemia, glucose intolerance, and

Table 1.4 Increment in risk of CVD events per standard deviation increase in blood pressure components Framingham Study 30-year follow-up

	Standardized increment in risk			
	Men		Women	
Pressure component	35–64 year	65–94 year	35–64 year	65–94 year
Systolic (%)	41*	51*	43*	23*
Diastolic (%)	35*	30*	33*	9[a]
Pulse pressure (%)	29*	42*	36*	22*
Mean arterial (%)	41*	44*	42*	18*

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*$p < 0.001$
[a]NS

Table 1.5 Risk of CVD events according to pulse pressure 30-yr follow-up Framingham Study age-adjusted rate per 1000

	Age 35–64		Age 65–94	
Pulse pressure (mmHg)	Men	Women	Men	Women
<40	9	4	2	17
40–49	13	6	16	19
50–59	16	7	32	22
60–69	22	10	39	25
>70	33	16	58	32
Increment per 10 mmHg (%)	19.7	20.9	23.4	10.5

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abnormal lipoprotein lipase levels [36]. The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) guidelines identified the metabolic syndrome as a target for therapy in the management of dyslipidemia [14]. The diagnosis of metabolic syndrome is designated when three or more of the following risk factors are present: waist circumference exceeding 88 cm in women or 102 cm in men, triglycerides of 150 mg/dL or greater, HDL-C under 40 mg/dL (men) or under 50 mg/dL (women), blood pressure of 130/85 mmHg or greater, and fasting plasma glucose of 110 mg/dL or greater. Using this definition of the metabolic syndrome, analysis of National Health and Nutrition Examination Survey (NHANES) II data suggests a 23.7 % age-adjusted prevalence of this syndrome in the USA [37].

Need for Multivariable Evaluation

As the above demonstrates the relations of the standard modifiable risk factors to CVD are striking and important. Also as the above shows the relations are not uniform across sexes and ages. A closer look at risk factors in the individual sexes and across ages demonstrates the need to consider the risk factors jointly. This is increased further in the presence of comorbidity (i.e., already having a CVD condition). Below we illustrate this by looking at risk factors in women, in the elderly, and in those with comorbid CVD events. These and the clustering of risk factors in individuals as is also presented below supply ample evidence of the need to consider the risk factors jointly. Along the way is also the indication that maybe more than the standard risk factors would be helpful in risk prediction.

Risk Factors in Women

CVD risk factors are highly prevalent in middle-aged and elderly women. Two thirds of such women have at least one major risk factor. The national burden of atherosclerotic CVD is projected to increase substantially as elderly women constitute a progressively greater proportion of the US population. Women and men share the same CVD risk factors, but some are more prevalent or exert a greater impact in women than in men. There are also some that are unique to women, such as early menopause and multiple pregnancies. With the exception of diabetes, the absolute risk for most risk factors is lower in women than men.

Because of the lower incidence of CVD in women than men, the most cost-effective preventive approach requires global risk assessment for targeting of high-risk women for preventive measures. Intensive risk-factor screening is particularly needed for elderly women, African American women, and those of lower socioeconomic status. High total/HDL cholesterol ratios and diabetes markedly reduce the female coronary disease advantage [27]. Diabetes is clearly a greater CVD hazard for women than men virtually eliminating their advantage over men for coronary disease, heart failure, and peripheral artery disease (Table 1.6). Women with diabetes require comprehensive screening to detect the usually accompanying elevated triglyceride, reduced HDL cholesterol, hypertension, and abdominal obesity. Minority

Table 1.6 Impact of diabetes on CVD events in men and women 36-year follow-up Framingham Study subjects ages 35–64 year

	Age-adjusted biennial rate per 1,000		Age-adjusted risk ratio		Excess risk per 1,000	
CVD events	Men	Women	Men	Women	Men	Women
CHD	39	21	1.5*	2.2**	12	12
PAD	18	18	3.4**	6.4**	13	15
CHF	23	21	4.4**	7.8**	18	18
Stroke	15	6	2.9**	2.6**	10	4
Total CVD	76	65	2.2**	3.7**	42	47

Based on data from Kannel and Wilson [25]
CHD coronary heart disease, *PAD* peripheral artery disease, *CHF* heart failure
*$p<0.01$
**$p<0.001$

women and those with gestational diabetes, who are prone to develop an adverse coronary risk profile, deserve particular attention.

Reduced HDL cholesterol predicts coronary disease even better in women than in men. Women on average have HDL cholesterol levels that are 10 mg/dL higher than those in men throughout life, and it is appropriate to characterize "low" HDL cholesterol as under 50 mg/dL. Despite controversy about hypertriglyceridemia as an independent risk factor, it is an important marker for increased vulnerability to CVD for women as well as for men, and the combination of low HDL and high triglyceride, reflecting insulin resistance and presence of small-dense LDL, imparts an increased CVD risk. The majority of elderly women have hypertension, and isolated systolic hypertension is more prevalent in elderly women than in men. Its concordance with risk-enhancing high pulse pressure, obesity, dyslipidemia, and insulin resistance should be noted.

Risk factors unique to women include early menopause and bilateral oophorectomy. Estrogen replacement therapy has failed to eliminate the more than twofold increase in risk of coronary disease in this subgroup of women. Women who undergo early menopause require close surveillance for development of an adverse cardiovascular risk profile.

Risk Factors in the Elderly

The major modifiable risk factors do remain relevant in the elderly. The strength of risk factors associated with CVD, however, diminishes with advancing age, but this lower risk ratio is offset by a higher absolute risk [14, 15]. This makes risk-factor control in the elderly at least as cost-effective as in the middle-aged. Epidemiologic research has quantified the impact of the standard CVD risk factors in the elderly well over 20 years ago [38]. Dyslipidemia, hypertension, glucose intolerance, and cigarette smoking all have smaller hazard ratios in advanced age, but this is offset by higher absolute and attributable risks. Diabetes operates more strongly in elderly women than men, further attenuating their waning advantage over men in advanced age (Table 1.1). Insulin resistance promoted by abdominal obesity in advanced age is an important feature of the CVD hazard of diabetes in the elderly. Hypertension, particularly the isolated systolic variety, is highly prevalent in the elderly and is a safely modifiable hazard. Dyslipidemia, particularly the total/HDL cholesterol ratio, remains a major risk factor in the elderly that, in contrast to the total cholesterol, continues to be highly predictive in advanced age (Table 1.2). As stated earlier, the joint evaluation of total cholesterol and HDL-C is important. Left ventricular hypertrophy is also an ominous harbinger of CVD in the elderly, indicating an urgent need for attention to its promoters including hypertension, diabetes, obesity, and myocardial ischemia or valve disease. High normal fibrinogen, C-reactive protein (CRP), and leukocyte counts in the elderly may indicate the presence of unstable atherosclerotic lesions. As in the middle-aged, all the major risk factors in the elderly tend to cluster so that the hazard of each one is powerfully influenced by the associated burden of the others. Multivariate risk assessment can quantify the joint effect of the burden of risk factors making it possible to more efficiently target elderly candidates for CVD for preventive measures [9–16].

Atherosclerotic Comorbidity

Atherosclerotic CVD is usually a diffuse process involving the heart, brain, and peripheral arteries. The presence of one clinical manifestation substantially increases the likelihood of having or developing others [39]. The major risk factors tend to affect all arterial territories and clinical atherosclerosis affecting the heart may also directly predispose to strokes and heart failure. Measures taken to prevent coronary disease should have an additional benefit in preventing atherosclerotic peripheral artery and stroke events as well as heart failure.

Coronary artery disease places a patient at considerable risk not only for a myocardial infarction, angina, sudden death, or heart failure but also for transient ischemic attacks, strokes, and intermittent claudication because of concomitant atherosclerotic disease in the other vascular territories [39]. The incidence of other cardiovascular disease accompanying coronary disease is substantial [40]. The Framingham Study found that in men and women, respectively, an initial myocardial infarction is accompanied by intermittent claudication 9 and 10 % of the time, by strokes or TIAs 5 and 8 % of the time, and by heart failure 3 and 10 % of the time [40]. Persons in the Framingham Study with intermittent claudication had a two- to threefold increased risk of developing coronary disease. Over 10 years, 45 % developed coronary heart disease. After an initial myocardial infarction, strokes and heart failure occurred at three to six times the rate of the general population. The 10-year probability of a stroke or TIA was 16 % in men and 24 % in women, a rate three to four times that of the general population. Heart failure occurred in about 30 % of patients who had experienced an MI, which represents a four- to sixfold increase in risk. After sustaining an atherothrombotic stroke, 25–45 % developed coronary disease, a twofold increase in risk.

After an MI, coexistence of intermittent claudication increased age-adjusted coronary mortality 1.7-fold in men and 1.5-fold in women and of recurrent MI increased twofold in men and 1.6-fold in women [40].

The Clustering of the Standard Risk Factors

While the first two sections above focused on woman and the elderly, the clustering of the standard risk factors is not limited to these. The standard risk factors tend to cluster together in men and women four to five times the rate expected by chance so that when one confronted with any risk factor, one is obliged to seek out the others. Isolated occurrence of the standard risk factor is uncommon ranging from 11 to 38 % (Table 1.7).

Multivariate Risk Stratification

Risk Scores/Risk Profiles

The standard CVD risk factors have strong relations to the development of CVD, they cluster together, and, while the effects vary, they are valid for both sexes and across age groups. The Framingham Heart Study recognized these facts and addressed the question of whether the individual risk factors could be combined into multivariate functions to give an assessment (i.e., the probability or risk) of developing CVD events over specific time periods (e.g., 10 years). In particular, attention was focused on the development of primary events (e.g., a first CVD event in a person who had no history of CVD at the time of evaluation). The study did produce these functions and continues to do [9–16, 42, 43]. These multivariable risk functions (also called Framingham risk functions, Framingham Risk Scores, or Framingham risk profiles) are for estimating the probability of a particular CVD event conditional on the burden of a number of specific risk factors and can be used for the evaluation of candidates for CVD in need of preventive management.

Major Framingham risk functions exist and have had widespread use for global CVD [16], CHD [9, 12], hard CHD events (MI and coronary deaths) [42], stroke [10, 43], CHF [13], and PAI [11]. The cholesterol treatment guideline for the Adult Treatment Panel III is based on a Framingham risk function for hard CHD events [14, 15, 44].

Table 1.7 Risk-factor clustering in the Framingham Study offspring cohort subjects ages 18–74 year

Index quintile variable (sex specific)	Percent with specified no. of additional risk factors		
	Sex	None (%)	Two or more (%)
High cholesterol	Men	29	43
	Women	26	57
Low HDL cholesterol	Men	27	45
	Women	38	36
High BMI	Men	23	48
	Women	15	54
High systolic BP	Men	25	46
	Women	19	53
High triglyceride	Men	11	61
	Women	20	50
High glucose	Men	23	45
	Women	29	44

Based on data from Kannel [41]
Risk factors: upper quintile of distribution of all variables except HDL-C (lowest quintile)

While Framingham risk functions have been used widely for clinical guidelines, it should be emphasized that other risk functions exist and have wide spread use. Some are the European Systematic Coronary Risk Evaluation (SCORE) function [45] and the Prospective Cardiovascular Munster (PROCAM) function [46].

Use in Treatment Guidelines

The Framingham and other risk functions estimate the absolute risk (probably) of developing a CVD within a fixed time period (such as 10 years). Some treatment guidelines take these absolute probability estimates in conjunction with the risk-factor burden and classify patients into risk categories. For example, the ATP III guidelines classify into high risk (CHD equivalent or two or more risk factors and 10-year risk of hard CHD greater than 20 %), moderately high risk (10-year risk between 10 and 20 % and more risk factors), moderate risk (10-year risk less than 10 % and two or more risk factors), and low risk (0 or 1 risk factors). Based on these risk categories, treatment recommendations are made [14].

It should be mentioned that other information such as triglycerides, weight, physical activity, and family history do enter into treatment implementation; however, they do add to risk estimation. For example, weight gain and abdominal obesity are particularly important because they are major determinants of risk-factor clustering by promoting insulin resistance. The average number of standard risk factors acquired increases with body mass index in both sexes (Table 1.8). In addition to medication to address the risk factors, lifestyle changes including exercise and diet are needed.

Specific Risk Functions

Coronary Risk Functions

Coronary heart disease (CHD) is the most common outcome of the standard risk factors, equaling in incidence all the other atherosclerotic CVD outcomes combined (Table 1.9). Further it is the most lethal of the atherosclerotic sequelae of the standard risk factors. Because of these, prevention of CHD deserves the highest priority. A number of early

Table 1.8 Risk-factor clustering according to body mass index in the Framingham Study offspring cohort with elevated blood pressure subjects ages 18–74 year

	Men		Women
BMI (kg/m^2)	Avg. no. risk factors	BMI (kg/m^2)	Avg. no. risk factors
<23.7	1.68	<20.8	1.80
23.7–25.5	1.85	20.8–22.3	2.00
25.6–27.2	2.06	22.4–23.9	2.22
27.3–29.5	2.28	24.0–26.8	2.20
>29.5	2.35	>26.8	2.66

Reprinted from Kannel [33]. With permission from Elsevier
Risk factors are top quintiles of systolic blood pressure, total cholesterol, triglycerides, and glucose and bottom quintile of HDL cholesterol

Table 1.9 Incidence of major cardiovascular events: Framingham Study, 44-year follow-up of cohort and 20-year follow-up of offspring cohort[a]

	Cardiovascular disease, (all types)		Coronary heart disease		Stroke and transient ischemic attack		Congestive heart failure	
Age (years)	Men	Women	Men	Women	Men	Women[a]	Men	Women
35–44	7	3	4	1	[b]	[b]	[b]	[b]
45–54	15	7	10	4	2	1	2	1
55–64	26	15	21	10	4	3	4	2
65–74	39	24	24	14	11	8	9	6
75–84	59	40	33	18	20	15	18	12
85–94	68	63	35	28	12	25	39	31
35–64[c]	17	9	12	5	2	2	2	1
65–94[c]	44	30	27	16	13	11	12	9

Based on data from The Framingham Study
[a]Average annual incidence per 100 persons free of specified disease
[b]Results are omitted when fewer than five individuals experience an event
[c]Age-adjusted rates

Framingham risks functions for CHD have been developed based on continuous variable relationships to coronary disease outcome [9]. In 1998, Framingham investigators [12] integrated categorical approaches that were part of the framework of blood pressure (JNC-VII) and cholesterol (NCEP) programs in the USA for a CHD risk function [12]. This was followed in 2001 by a hard CHD (MI and coronary deaths) function [42]. Finally the ATP III function was produced by the Framingham Study [14, 15]. These coronary heart disease functions enable physicians to pull together all the relevant risk-factor information into a composite estimate of the risk of having a coronary event. Further this risk can be compared to the risks of a person of the same age and sex with normal levels of risks factors and a person with optimal risk factors.

The ATP III function is used in national guidelines. Figure 1.1 contains a point chart (also called a score sheet) for the ATP III function [14, 15] that transforms, here for a male, the values of the risk factors to points and, which with step 7 of Fig. 1.1, takes the total number of points and transforms this to the 10-year risk of a hard CHD. As an example, consider a male age 54, with total cholesterol of 250, HDL-C of 39, treated systolic blood pressure of 146, and nonsmoking. The points are, respectively, 6, 4, 2, 2, and 0 for total of 14 points which corresponds to a 10-year hard CHD risk of 16 %. Figure 1.2 compares this man to the normal and optimal risk-factor profile for a person of the same age.

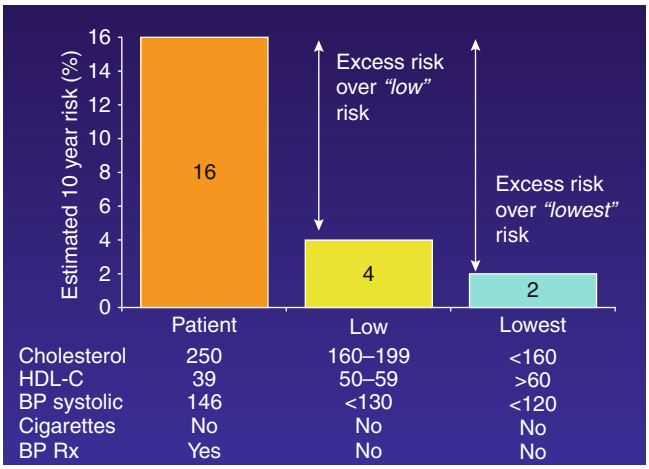

Fig. 1.2 Estimating 10-year hard CHD risk in 54-year-old man according to levels of various factors

Step 1: Age

Years	Points
20–34	–9
35–39	–4
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	11
70–74	12
75–79	13

Step 2: Total cholesterol

TC (mg/dL)	Points at age 20–39	Points at age 40–49	Points at age 50–59	Points at age 60–69	Points at age 70–79
<160	0	0	0	0	0
160–199	4	3	2	1	0
200–239	7	5	3	1	0
240–279	9	6	4	2	1
≥280	11	8	5	3	1

Step 3: HDL-cholesterol

HDL-C (mg/dL)	Points
≥60	–1
50–59	0
40–49	1
<40	2

Step 4: Systolic blood pressure

Systolic BP (mm Hg)	Points if untreated	Points if treated
<120	0	0
120–129	0	1
130–139	1	2
140–159	1	2
≥160	2	3

Step 5: Smoking status

	Points at age 20–39	Points at age 40–49	Points at age 50–59	Points at age 60–69	Points at age 70–79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

Step 6: Adding up the points

Age
Total cholesterol
HDL-cholesterol
Systolic blood pressure
Smoking status
Point total

Step 7: CHD risk

Point total	10-Year risk	Point total	10-Year risk
<0	<1 %	11	8 %
0	1 %	12	10 %
1	1 %	13	12 %
2	1 %	14	16 %
3	1 %	15	20 %
4	1 %	16	25 %
5	2 %	≥17	≥30 %
6	2 %		
7	3 %		
8	4 %		
9	5 %		
10	6 %		

Fig. 1.1 Assessing hard CHD risk in men (ATP III function score sheet) (Based on data from Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [14]

Table 1.10 CVD points for women

Points	Age	Hdl	Total cholesterol	SBP not treated	SBP treated	Smoker	Diabetic	
–3				<120				
–2		60+						
–1		50-59			<120			
0	30-34	45-49	<160	120-129		No	No	
1		35-44	160-199	130-139				
2	35-39	<35		140-149	120-129			
3			200-239		130-139	Yes		
4	40-44		240-279	150-159			Yes	
5	45-49		280+	160+	140-149			
6					150-159			
7	50-54				160+			
8	55-59							
9	60-64							
10	65-69							
11	70-74							
12	75+							Total Points
Points allotted								

Global CVD Risk Function

In 2008, Framingham investigators presented a global CVD risk function for estimating the risk of developing any CVD (i.e., CHD or cerebrovascular disease, PAD, or CHF) for a person free of CVD at the time of the risk assessment [16]. The motivation and objective behind the development of this function was to produce a simple mathematical model for global CVD which was valid for quantifying the global risk of CVD and, very importantly, with simple adjustments the risks for components of CVD. The exercise was successful. Tables 1.10, 1.11, 1.12 and 1.13 are the score sheets for women and men. For a given person, the score sheets can be used to estimate the risk of any CVD event over the next 10 years. From that, the estimated risks for the components of CVD can be found by multiplication of the global CVD risk by the calibration factors of Table 1.14. For example, for a female aged 52, with HDL-C of 46, total cholesterol of 245, treated systolic blood pressure of 145, a nonsmoker, and nondiabetic, the corresponding points are, respectively, 7, 0, 4, 5, 0, and 0 for a total point score of 16 which corresponds to a 10-year risk of CVD of 15.9 %. Using the calibration factors of Table 1.14, this yields 10-year risks of 9.7 % for CHD, 3.8 % for stroke (including TIA), 2.0 % for CHF, and 3.0 % for PAD.

The global CVD was not suggested as a replacement for the risks functions for individual CVD components but rather to bring a unity to the subject. First, explicit in it is that we are dealing with primary prevention. That is, the person whose risk is being evaluated is free of all manifestations of CVD. Second, given such a person, the standard CVD risk factors obtained routinely at an office visitor can be used to estimate the CVD risk and also to produce estimates of how this risk could be manifest across the components of CVD. There may be circumstances where direct estimation of specific components is desired. This is especially the case when the person already has a manifestation of CVD such as CHD and the interest is in quan-

Table 1.11 CVD risk for women

Points	Risk (%)	Points	Risk (%)	Points	Risk (%)
−2 or less	Below 1	6	3.3	14	11.7
−1	1.0	7	3.9	15	13.7
0	1.2	8	4.5	16	15.9
1	1.5	9	5.3	17	18.5
2	1.7	10	6.3	18	21.5
3	2.0	11	7.3	19	24.8
4	2.4	12	8.6	20	28.5
5	2.8	13	10.0	21+	Above 30

Table 1.12 CVD points for men

Points	Age	Hdl	Total cholesterol	SBP not treated	SBP treated	Smoker	Diabetic	
−2		60+		<120				
−1		50-59						
0	30-34	45-49	<160	120-129	<120	No	No	
1		35-44	160-199	130-139				
2	35-39	<35	200-239	140-159	120-129			
3			240-279	160+	130-139		Yes	
4			280+		140-159	Yes		
5	40-44				160+			
6	45-49							
7								
8	50-54							
9								
10	55-59							
11	60-64							
12	65-69							
13								
14	70-74							
15	75+							Total Points
Points alloted								

tifying the risk of another CVD type, such as stroke. We now address these.

Stroke Risk Function

A stroke is the most feared of the atherosclerotic diseases of the elderly. Risk stratification beyond what is obtained from the global CVD becomes important when a person has existing CVD events such as the presence of coronary disease, heart failure, or atrial fibrillation [10, 43]. The presences of atrial fibrillation can double the risk of a stroke. Using the functions in the above references, it is possible to estimate the joint effect of any combination of the major predisposing factors including these important manifestations.

Table 1.13 CVD risk for men

Points	Risk (%)	Points	Risk (%)	Points	Risk (%)
–3 or less	Below 1	5	3.9	13	15.6
–2	1.1	6	4.7	14	18.4
–1	1.4	7	5.6	15	21.6
0	1.6	8	6.7	16	25.3
1	1.9	9	7.9	17	29.4
2	2.3	10	9.4	18+	Above 30
3	2.8	11	11.2		
4	3.3	12	13.2		

Table 1.14 Calibration factors to convert global CVD risk to component risks

	Calibration factor	
Component	Women	Men
CHD	0.6086	0.7174
Stroke	0.2385	0.1590
CHF	0.1250	0.1148
PAD	0.1862	0.1804

Heart Failure Risk Function

Heart failure is a lethal terminal stage of cardiac disease, with a survival experience resembling that of cancer [47]. A substantial reduction in the incidence and mortality from heart failure can be achieved only by the early detection and treatment of persons prone to left ventricular dysfunction so that it can be corrected before overt failure ensues. High-risk candidates for heart failure must be cost-effectively targeted for echocardiographic evaluation to detect the presence of left ventricular dysfunction. The Framingham Study has identified and quantified major contributing risk factors for the development of heart failure [48]. Using these, multivariable risk profiles have been developed that efficiently predict failure, providing risk estimates in those with the major predisposing conditions such as hypertension, coronary disease, and valvular heart disease [13]. The ingredients of the profile consist of ECG-LVH, cardiomegaly on chest film, reduced vital capacity, heart rate, presence of heart murmurs, systolic blood pressure, and diabetes. Using this risk assessment, it is possible to identify high-risk candidates for heart failure who constitute good candidates for echocardiographic examination with a high likelihood of positive findings. Such persons stand to benefit from vigorous preventive measures such as therapy with angiotensin-converting enzyme (ACE) inhibitors, cardiac revascularization, or valve surgery.

Risk Stratification of Existing Coronary Disease

Based on Framingham Study data, risk formulations have also been developed for predicting another coronary event, a stroke, or a death from cerebrovascular disease in persons who have already sustained a coronary event [17, 18]. Risk of these adverse outcomes can be estimated from the joint effect of age, diabetic status, total and HDL cholesterol, and systolic blood pressure. The 2-year probability of these events conditional on the risk-factor burden in survivors of coronary events can be estimated over a wide range and compared to the average risk.

Score Sheets Versus Mathematical Model Estimated Risks

While Fig. 1.1 and Tables 1.10, 1.11, 1.12 and 1.13 give score sheets for estimating risks, the Framingham risk functions are based on mathematical functions for time to event analyses, usually Cox regressions [49]. The point system (the score sheet method) is only an approximation to the underlying mathematical function. Excel programs have been developed to produce the exact risks based on using the Cox regression model. The Excel program results for the various Framingham risk functions are available on the Framingham Web site [50]. Figure 1.3 contains the Excel sheet for the ATP III function. The score sheets were used in the above to illustrate the multivariate relations of the risk factors. For generating the risk estimates in practice, we strongly recommend the use of the Excel programs.

Evaluation of the Risk Function Performance

The above presentation is focused on the premise that because the individual standard risk factors relate individually and jointly to CVD, multivariable risk assessment should be made in assessing a person's CVD risk. Behind this are

From the framingham heart study	Enter values here		
CHD(MI and coronary death) risk prediction			*National Cholesterol Education Program Adult Treatment Panel III*
Risk factor	Units	(Type over place holder values in each cell)	Notes
Gender	Male (m) or Female (f)	M	
Age	Years	52	
Total cholesterol	mg/dl	220	
HDL	mg/dl	45	
Systolic blood pressure	mmHg	146	
Treatment for hypertension {Only if SBP ≥120}	Yes (y) or no (no)	N	
Current smoker	Yes (y) or no (no)	Y	
Time frame for risk estimate	10 years	10	
Your risk (The risk score shown is derived on the basis of an equation Other NCEP materials, such as ATP III print products, use a point-based system to calculate a risk score that approximates the equation-based one.		17 %	If value is <the minimum for the field, enter the minimum value. If value is >the minimum for the field, enter the maximum value.

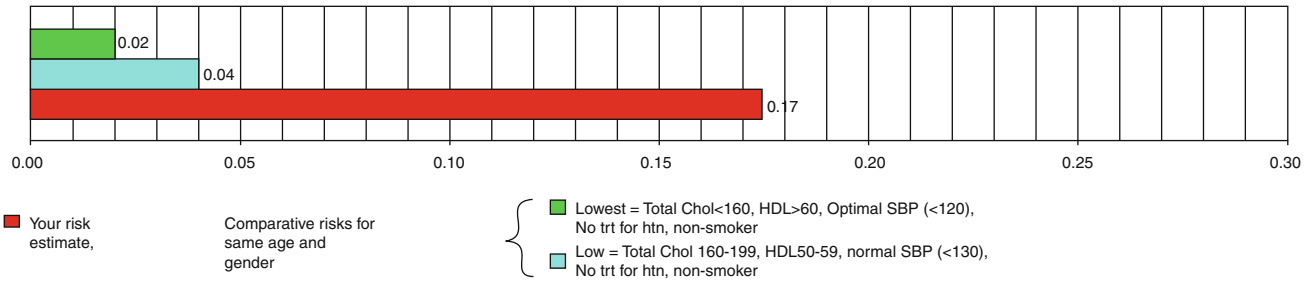

Fig. 1.3 Excel program for risk assessment (These functions and programs were prepared by Ralph B. D'Agostino, Sr., PhD. Lisa Sullivan, PhD, Boston University and the Framingham Heart Study. Daniel Levy, MD, Framingham Heart Study, National Heart, Lung and Blood Institute)

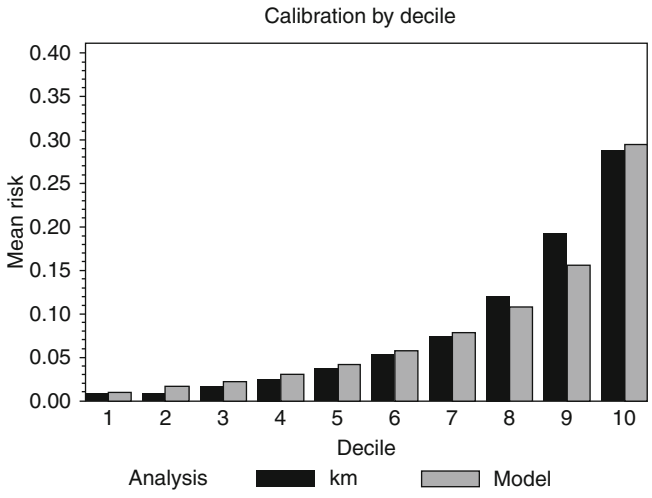

Fig 1.4 Calibration plot

serious and rigorous statistical analyses. In most of the development of the risk functions time to event analyses are performed employing methods such as the Cox regression [49, 51]. Basically the Cox regression model quantifies the relative risks (hazard ratio) of the risk factors and can also be used to compute the absolute risk (or probability) of an event occurring within a predetermined time period (often 10 years). The performance of the risk function is evaluated mainly by two measures: one for discrimination and the second for calibration.

Discrimination: The C Statistic

The most widely used measure of discrimination is the C statistic [42, 49, 51]. It relates to sensitivity, and specificity of the risk function is assessing CVD risk. Its most straightforward, and correct interpretation is that it is the probability that a randomly selected person who will develop the event (e.g., CVD) over the follow-up period will have a higher risk from the risk function than one who does not. The C statistic ranges from 0.5 to 1.0 where 0.5 is equivalent to guessing

and 1 is related to perfect prediction. Most of the Framingham risk functions have C statistics ranging from 0.75 to 0.85 which is in the acceptable to excellent range.

Calibration

Calibration relates to the ability of the function to produce the correct risk assessment or absolute probability [49]. For example, if we had a particular risk profile where over 10 years we see 12 % developing the outcome, we would want the risk function to assign a 12 % risk to individuals with this profile. Figure 1.4 shows a calibration plot where the estimated risk probabilities are divided into deciles and within each decile the observe incidence (the Kaplan Meier (km) values) is plotted against the model predictions which is the mean of the risk scores in the decile. A chi-square test has been developed by Byung-Ho Nam which extends the Hosmer-Lemeshow test to time to event analyses [49]. With this measure, it is desired to have a small chi-square value which indicates a good fit. A value of 20 or less has become a standard number for evaluation, but the formal statistical test is available.

Adding New Risk Factors to the Risk Function

An important activity is risk prediction is determining if a new variable (biomarker, risk factor, etc.) adds significantly to a risk function. A new variable must at a minimum achieve statistical significance in the risk model that contains the new variable and all the standard risk factors. However, the real issue under investigation is whether it will improve risk prediction (improve the C statistic and at least maintain good calibration). Framingham investigators have developed and refined measures that examine the reclassification of subjects in the presence of the new variable and examine if there is improvement in classification of both events (risk goes up in new function) and nonevents (risk goes down in new function) [52]. We will return to this topic below.

Validity and Transportability of Risk Functions

In the above, we have discussed a large number of Framingham risk functions [9–18, 42, 43]. All have been shown to have acceptable to excellent discrimination and good calibration when evaluated on the Framingham data. An important concern is will they perform well when transported to non-Framingham populations. Framingham participants are mainly white middle-class US citizens. The Framingham functions have shown to be transportable, sometimes needing a calibration adjustment when applied to populations with low CVD risk [42, 53–56]. In a NIH workshop, a Framingham hard CHD function [42] was applied to seven non-Framingham populations/studies in the USA. The C statistics using the Framingham function on the study data (white and nonwhite male and female populations) were basically as good as those from the best functions that could be generated directly by using the data from the studies. The Framingham function did overpredict on two of the studies (Japanese Americans and Hispanics), but with a calibration adjustment described in reference [42], the Framingham function performed very well. Figure 1.5a, b show, respectively, the overprediction (Fig. 1.5a) and the good fit after the calibration adjustment (Fig. 1.5b) on the Honolulu Heart Study data. The calibration adjustment involves adjusting for the average risk of the CVD event and means of the risk factors for the population under consideration. Similar calibration adjustments

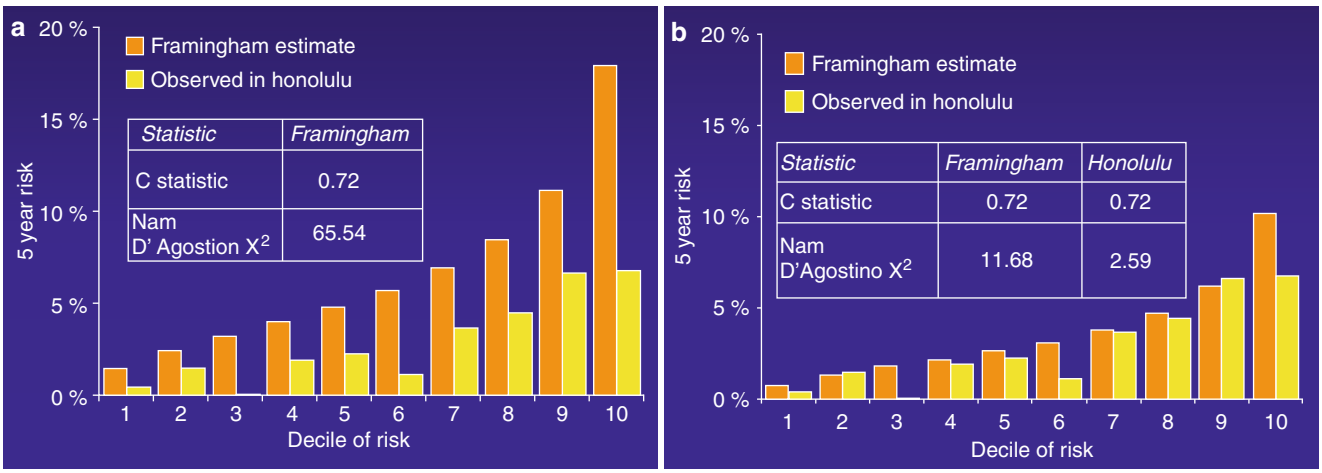

Fig. 1.5 Honolulu Heart Study hard CHD prediction with Framingham equations (**a**)no adjustment (**b**) adjustment for rates and risk-factor levels (Based on data from D'Agostino et al. [42])

were needed for individuals in Spain [53] and in China [54]. Recently the global CVD function has been shown to transport to the Tehran Study for males and females [55].

Novel Risk Factors

Because CVD often occurs in persons with what is considered acceptable or average standard risk-factor values, novel risk factors are being sought. The search extends back to the 1990s and continues today. Among these, novel risk factors are inflammatory parameters such as CRP, coronary artery calcium scores, lipoprotein (a) (Lp[a]), interleukin-6, fibrinogen, homocysteine, small-dense LDL, insulin resistance, metabolic syndrome, fibrinolytic function assessed by tPA and PAI-1 antigens, and platelet function [57–67]. To date there has been little success in identifying new risk factors that add significantly as judged by the addition to the C statistic or reclassification methods [52]. However, there have been positive results. Polak et al. [67] have shown that the carotid-wall intima-media thickness does add significantly to CVD prediction. Further, coronary artery calcium scores appear to add significantly [63]. Both of these variables are not routinely collected. It may be that their use will come in taking an individual with intermediate risk (e.g., 10–20 % with the ATP III model) and applying more procedures to add precision to the risk assessment.

Much more is needed both from epidemiologic studies and clinical trials to identify and evaluate the novel risk factors.

Preventive Implications of Existing Risk Functions

Comparison of the profiles for each of the various atherosclerotic CVD outcomes strongly suggests that correction of any particular set of risk factors imparts a bonus in reducing the risk of all outcomes. The global CVD function and its ability to estimate well the components of CVD further support this. Reliance on single-risk-factor detection and treatment may be justified on a population basis but is shortsighted on an individual basis. The goal in treating hypertension, diabetes, or dyslipidemia is not to simply correct these abnormalities but rather to prevent their CVD sequelae. They should be targeted for treatment from a multivariable risk profile, and the goal of treatment should be to improve the global risk. Because of the tendency of all the established risk factors to cluster, it is imperative that physicians, when confronted with any particular risk factor, seek out the others likely to be present and take these into account in evaluating the risk and formulating the treatment regimen required.

A substantial proportion of the elderly warrant preventive measures because they are free of overt disease and active in their retirement years. Also, because of the aging of the general population, it will be necessary to keep more of the elderly in the workforce, necessitating primary prevention of CVD. Because of the high average risk of CVD events in the elderly, there is actually a great potential benefit of preventive measures, but to avoid overtreatment, it is important to assess multivariable risk and to take into account general health status. There is little justification for pessimism about the efficacy of preventive measures in the elderly. The major risk factors can be safely modified without inducing intolerable side effects or adversely affecting the quality of the last years of life. The major risk factors remain highly relevant in the elderly not only for primary prevention but for secondary prevention as well.

Controlled trials have provided consistent evidence of the benefit of reducing elevated blood pressure and correcting dyslipidemia. Lowering LDL and raising HDL cholesterol have been shown to slow progression of atherosclerosis. Primary prevention trials have shown consistent benefit for coronary disease by reducing LDL and raising HDL cholesterol even in persons with only average lipid values.

Meta-analysis of hypertension trials indicates benefits of treatment of hypertension for overall vascular mortality, stroke morbidity and mortality, and fatal and nonfatal coronary events.

Clinical trials have also demonstrated the benefits of treating isolated systolic hypertension in the elderly for stroke, coronary disease, and heart failure. Antiatherogenic recommendations for diabetes now focus on correction of the metabolically linked dyslipidemia and hypertension that usually accompany it. Weight control appears to be an important preventive measure for avoiding atherosclerotic CVD (Table 1.8). Because of difficulty in achieving sustained weight reduction, there is as yet no direct evidence that weight reduction reduces the risk of clinical cardiovascular events despite convincing evidence that slimming improves the entire cardiovascular risk profile. Persons who maintain optimal weight have a 35–60 % lower risk of developing CVD than those who become obese.

Meta-analysis of the benefits of physical activity for coronary disease estimates a 50 % reduction in risk that is attributable to exercise. Even moderate exercise appears to improve both the predisposing risk factors and risk of developing coronary disease. Although controlled trial data are lacking, observational data indicate that after cessation of smoking, coronary disease risk declines to half that of those who continue to smoke. This benefit is observed in a matter of months without regard to the amount smoked or the duration of smoking. Quitting smoking deserves a high priority in prevention of CVD because it is ranked as a leading preventable cause of the disease.

Meta-analysis of randomized trials conducted in persons with clinical vascular disease has shown that low-dose aspirin can reduce the incidence of subsequent myocardial infarction, stroke, or cardiovascular mortality by about 25 %. In primary prevention trials, initial myocardial infarctions were reduced 33 %. As a result, aspirin has been recommended for primary prevention in men who are at high risk of coronary disease.

Coronary heart disease and stroke mortality has declined over the past several decades, but the incidence of new events has not, resulting in an increasing pool of persons with coronary disease, strokes, and heart failure. The specific challenges for the future are to implement comprehensive preventive programs using global risk stratification to target high-risk CVD candidates for preventive measures. The occurrence of an overt CVD event should come to be regarded as a medical failure rather than the first indication for treatment.

The Future of Multivariable Risk Prediction

We have attempted in the above to review the logic of risk prediction. The standard CVD risk factors have shown themselves to excellent as major variables in risk prediction functions. These variables are easily and routinely available. Risk functions for global CVD and the individual components with good performance features and their transportability across various populations have been established. The extension of these and development of new functions to further populations such as nonwhites and Latinos is needed. The identification of new novel biomarkers, including genetic markers, that add predictive ability should follow.

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Molecular and Cellular Basis of Myocardial Contractility

2

Arnold M. Katz

Introduction

The heart's pumping action is made possible by interactions between myosin, the major protein of the thick filaments, and actin which makes up the backbone of the thin filaments. These interactions are regulated by tropomyosin and troponins C, I, and T that are present along with actin in the thin filaments.

Contraction by working cardiac myocytes is initiated by a signaling process, called excitation-contraction coupling, that begins when an action potential opens L-type calcium channels in the plasma membrane. This allows a small amount of calcium to enter the cytosol from the extracellular fluid where it triggers the opening of calcium-release channels in the sarcoplasmic reticulum. The latter deliver a larger amount of activator calcium into the cytosol from intracellular stores. About a third of the calcium that binds to troponin C in the adult human heart enters the cytosol from the extracellular fluid through the L-type calcium channels (extracellular calcium cycle). The remainder is derived from the sarcoplasmic reticulum (intracellular calcium cycle).

Cardiac myocytes relax when calcium is transported out of the cytosol. Most of this activator is pumped back into the sarcoplasmic reticulum by an ATP-dependent calcium pump in this intracellular membrane system. The remainder is transported into the extracellular space by a sodium/calcium exchanger and a plasma membrane calcium pump.

Two mechanisms are usually viewed as regulating the heart's contractile performance. The first mechanism, length-dependent regulation (Starling' law of the heart) occurs when variations in end-diastolic volume modify cardiac myocyte length. Changes in myocardial contractility, the second mechanism, occur when interactions between the contractile proteins are modified by factors other than altered fiber length.

Rapidly occurring changes in myocardial contractility are brought about by variations in the amount of calcium delivered to the contractile proteins during excitation-contraction coupling; less important are posttranslational changes in the contractile proteins, ion channels, ion pumps, and other structures that participate in excitation-contraction coupling and relaxation. More slowly developing changes in contractility occur when isoform shifts and other changes in the myofibrillar proteins and membrane structures that participate in contraction, excitation-contraction coupling, and relaxation modify the interactions between the contractile proteins. These long-term changes in contractility are especially important in chronically overloaded and diseased hearts.

Myocyte Structure

The working cardiac myocytes of the atria and ventricles are filled with cross-striated myofibrils that contain the heart's contractile proteins (Fig. 2.1). The plasma membrane, which separates the cytosol from the extracellular space, and the intracellular membranes of the sarcoplasmic reticulum regulate excitation-contraction coupling and relaxation. Mitochondria, which generate most of the ATP that supplies the chemical energy for contraction and relaxation, do not play an important role in controlling cytosolic calcium in the normal heart.

Myofibrils

The contractile proteins of the heart are organized into thick and thin filaments that give rise to the characteristic cross striations in cardiac myocytes (Fig. 2.1). The morphological unit of striated muscle is the sarcomere, which lies between two Z-lines; each sarcomere therefore consists of a central A-band plus two adjacent half I-bands.

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_2,

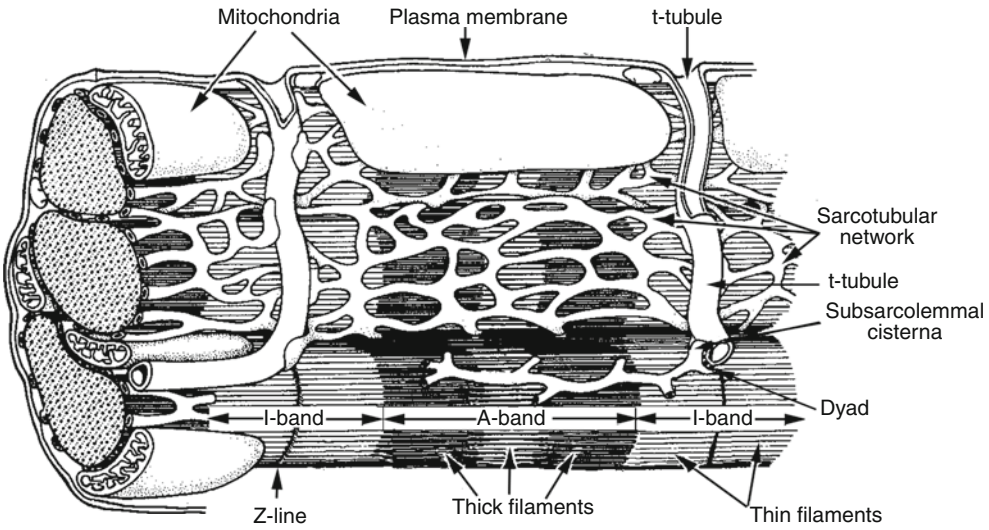


Fig. 2.1 Ultrastructure of a working cardiac myocyte. Contractile proteins are arranged in a regular array of thick and thin filaments (seen in cross section at the *left*). The A-band represents the region of the sarcomere occupied by the thick filaments into which thin filaments extend from either side. The I-band contains only thin filaments that extend toward the center of the sarcomere from Z-lines that bisect each I-band. The sarcomere, the functional unit of the contractile apparatus, lies between two Z-lines and contains one A-band and two half I-bands. The sarcoplasmic reticulum, an intracellular membrane system, consists of the sarcotubular network that surrounds the contractile proteins and the subsarcolemmal cisternae. The latter form specialized composite structures with the transverse tubular system (t-tubules) called dyads. The t-tubular membrane is continuous with the sarcolemma, so that the lumen of the t-tubules contains extracellular fluid. Mitochondria are shown in the central sarcomere and in cross section at the *left* (Reprinted from Katz [1], with permission from Lippincott Williams & Wilkins)

The darker A-bands contain thick filaments, while the more lightly staining I-bands are made up of thin filaments (see below). Each I-band is bisected by a narrow, darkly staining Z-line, and a broad M-band is seen at the center of the A-band. Both contain cytoskeletal proteins that serve both structural and signaling functions. Titin, a large cytoskeletal protein that contributes to myocardial stiffness, extends from the Z-line to the center of the A-band in the thick filament.

The thick filaments are composed largely of myosin, while two strands of polymerized actin make up the backbone of the thin filaments. At physiological sarcomere lengths, the thin filaments extend from the Z-lines almost to the center of the A-band. At short sarcomere lengths, the thin filaments from the two I-bands at either side of the A-band cross in the center of the sarcomere.

Cardiac myocytes shorten and develop tension when the thin filaments are pulled toward the center of the sarcomere by motion of crossbridges that project from the thick filaments. These crossbridges, which correspond to the heads of myosin molecules (see below), interact with actin using energy provided by ATP hydrolysis. Physiological control by calcium is mediated by the troponin complex and tropomyosin in the thin filaments.

Membranes

Two membrane systems regulate contraction and relaxation in the adult human heart: the plasma membrane and sarcoplasmic reticulum (Fig. 2.1). The plasma membrane (sarcolemma), which separates the cytosol from the extracellular space, penetrates the cell interior as a transverse tubular (t-tubular) system whose lumens open to the extracellular space and so contain extracellular fluid. Propagation of action potentials along the t-tubular membranes provides rapid transmission of electrical signals into the cell interior. Dyads, which are composite structures formed by the plasma membrane and sarcoplasmic reticulum (Fig. 2.2), mediate calcium release from intracellular stores during excitation-contraction coupling (see below).

The cardiac sarcoplasmic reticulum is made up of subsarcolemmal cisternae, which contain the calcium-release channels through which calcium enters the cytosol during excitation-contraction coupling, and a sarcotubular network that surrounds the contractile proteins. The membranes of the sarcotubular network contain a densely packed array of calcium pump ATPase proteins that relax the heart by transporting calcium out of the cytosol into the lumen of the sarcoplasmic reticulum.

Myocyte Function

The Contractile Proteins

Interactions between six proteins are responsible for contraction and relaxation in the heart (Table 2.1). These proteins, which use chemical energy released by hydrolysis of the terminal phosphate bond of ATP to initiate the physicochemical changes that cause tension development and

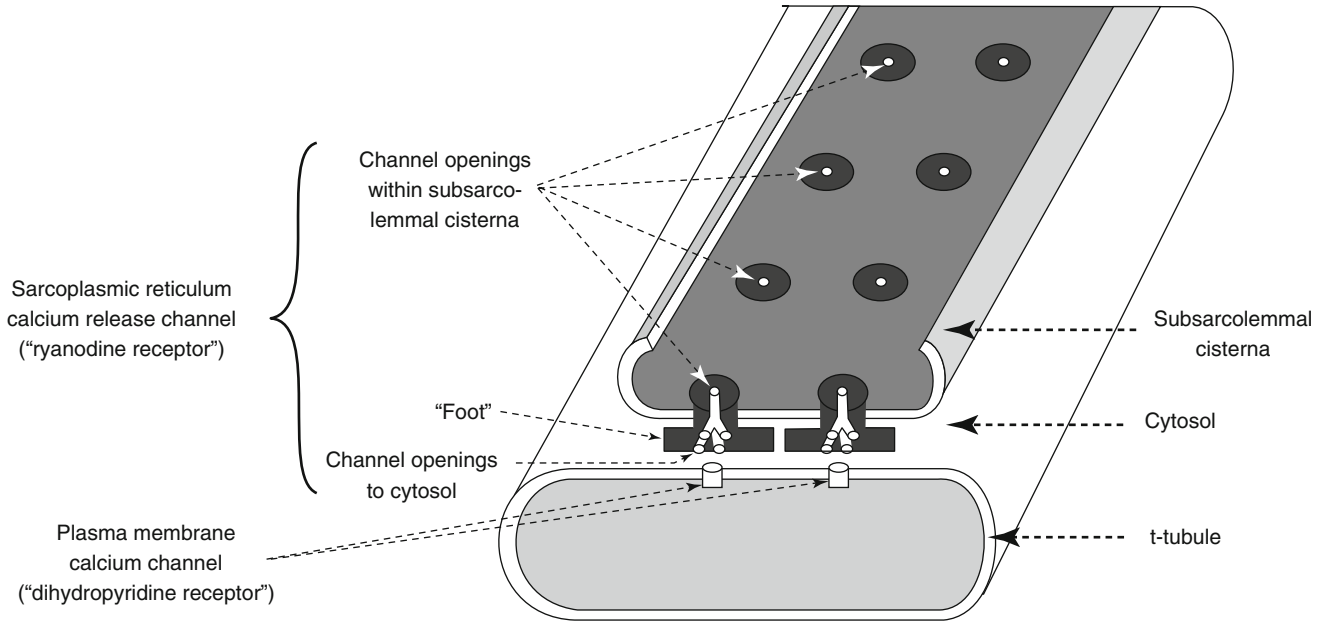


Fig. 2.2 Schematic diagram of a dyad showing sarcoplasmic reticulum calcium-release channels ("ryanodine receptors") adjacent to plasma membrane calcium channels ("dihydropyridine receptors") in the t-tubule. The former, which form "feet," have a single opening into the cytosol and four openings into the lumen of the subsarcolemmal cisterna (Reprinted from Katz [1], with permission from Lippincott Williams & Wilkins)

Table 2.1 Contractile proteins of the heart

Protein	Location	Salient properties
Myosin	Thick filament	Hydrolyzes ATP, interacts with actin
Actin	Thin filament	Activates myosin ATPase, interacts with myosin
Tropomyosin	Thin filament	Modulates actin-myosin interaction
Troponin C	Thin filament	Binds calcium
Troponin I	Thin filament	Inhibits actin-myosin interactions
Troponin T	Thin filament	Binds troponin complex to the thin filament

shortening, recognize a rise of calcium concentration in the cytosol as a signal to initiate contraction.

Myosin

Myosin, the major protein of the thick filament, is a large, elongated molecule with a filamentous "tail" and a paired globular "head" (Fig. 2.3). Myosin is an ATPase enzyme that hydrolyzes ATP in vitro; when the myosin heads interact with actin, they use chemical energy released by ATP hydrolysis to power contraction. Each myosin molecule contains two heavy chains and four light chains. The heavy chains extend the length of the molecule; in the head, they make up the crossbridges that project from the thick filament and interact with actin. The light chains are substrates for post-translational phosphorylations that regulate contractility. Several heavy and light chain isoforms are found in different regions of the heart and even in adjacent cells.

Myosin in the living heart is aggregated in the thick filaments where the tails are interwoven to form a rigid backbone and the heads project as crossbridges (Fig. 2.4). In the resting heart, the crossbridges are perpendicular to the long axis of the thick filament, whereas during systole, a shift in their orientation pulls the thin filaments toward the center of the sarcomere (Fig. 2.5).

The heavy chains are major determinants of myosin ATPase activity, muscle shortening velocity, and myocardial contractility. A high ATPase isoform, the α-myosin heavy chain, determines rapid shortening velocity, high contractility, and efficient contraction against light loads, whereas a lower ATPase myosin isoform, called β-heavy chain, is associated with lower shortening velocity, reduced contractility, and greater mechanical efficiency when wall stress is high. The myosin heavy chains in human atria are mostly a high ATPase isoform, whereas the human ventricle contains only a small amount of the fast α-myosin heavy chain. Isoform shifts involving these proteins occur in diseased hearts; in heart failure, for example, increased expression of the β-myosin heavy chain isoform decreases myosin ATPase activity in vitro and reduces contractility in the intact heart.

Actin

Actin, a globular protein, polymerizes to form a double-stranded macromolecular helix that serves as the backbone of the thin filament (Fig. 2.6). The adult human heart contains

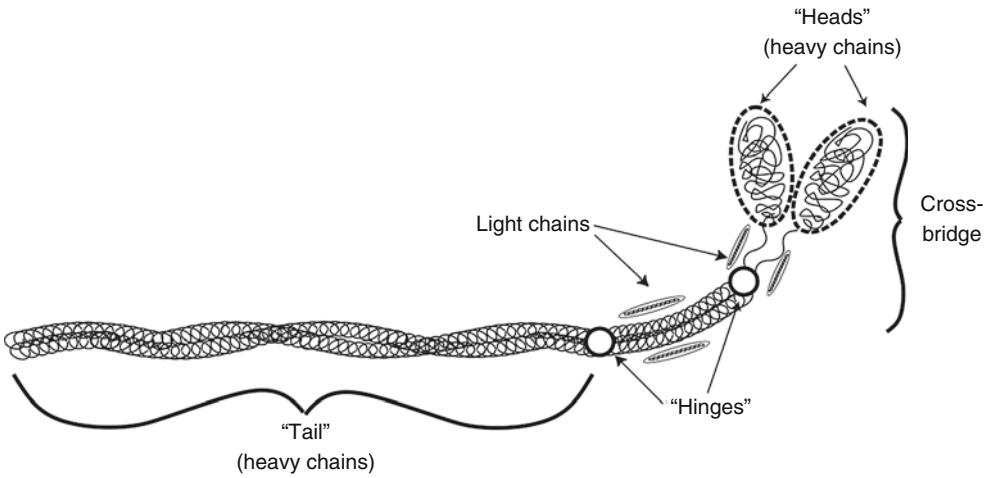


Fig. 2.3 Each myosin molecule contains two heavy chains and four light chains. The "tail" of the elongated molecule is made up of the two heavy chains; the latter continue into the paired "heads" that, along with the light chains, form the crossbridge. Myosin has two points of flexibility ("hinges"): one lies below the heads and the other divides the tail into two unequal lengths (Reprinted from Katz [1], with permission from Lippincott Williams & Wilkins)

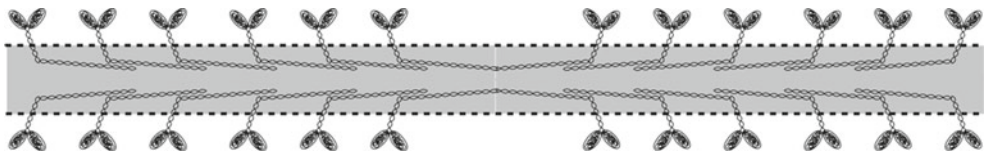
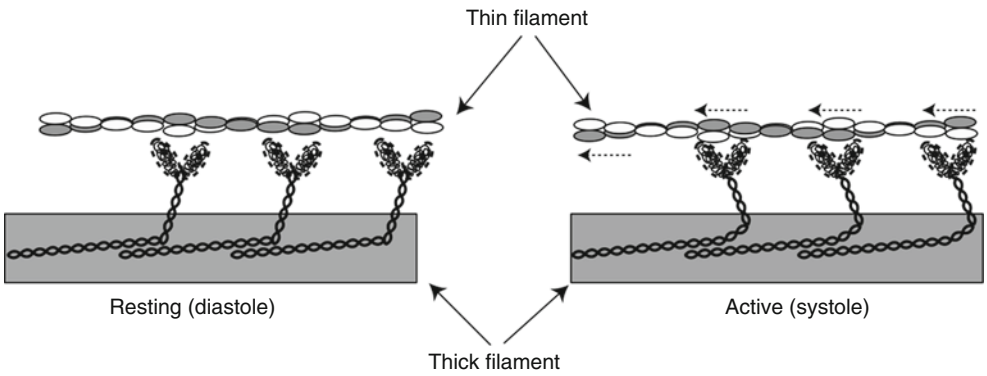


Fig. 2.4 Myosin aggregates make up the thick filament whose "backbone," delineated by *dashed lines*, contains the tails of the individual myosin molecules. The heads of individual myosin molecules, which project from the long axis of the thick filament, are the crossbridges whose polarities are opposite in the two halves of the filament (*left* and *right*) (Reprinted from Katz [1], with permission from Lippincott Williams & Wilkins)

Fig. 2.5 In the resting heart during diastole (*left*), the crossbridges project almost at right angles to the longitudinal axis of the thick filament. During systole (*right*), the crossbridges draw the thin filaments toward the center of the sarcomere (Reprinted from Katz [1], with permission from Lippincott Williams & Wilkins)



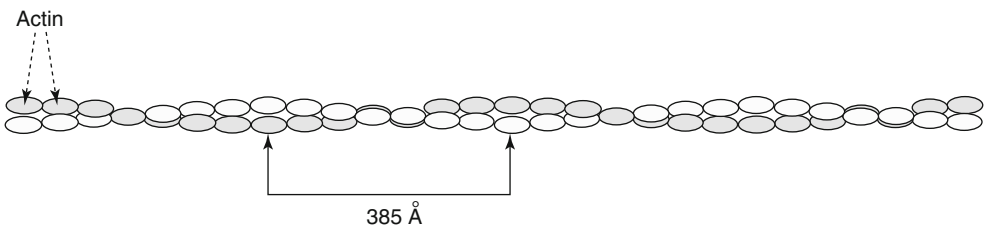


Fig. 2.6 The F-actin polymer, which forms the backbone of the thin filaments, is composed of two strands of G-actin monomers (*shaded* and *unshaded ovals*) wound around each other. The internodal distance is approximately 385 Å (Reprinted from Katz [1], with permission from Lippincott Williams & Wilkins)

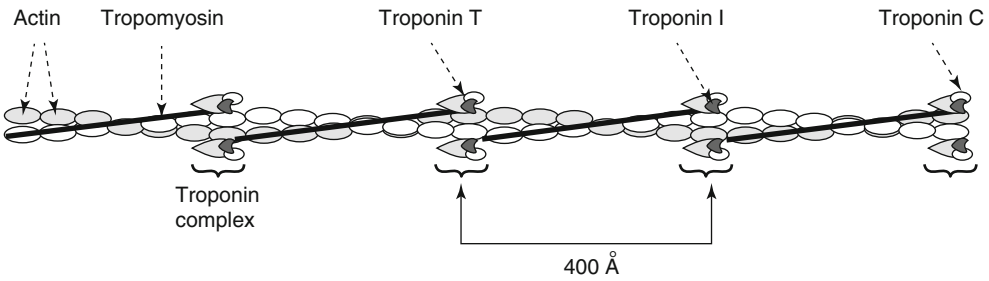


Fig. 2.7 Tropomyosin is located in the grooves between the two actin strands in the thin filament. Troponin complexes are distributed at ~400 Å intervals in the thin filament (Modified from Katz [1], with permission from Lippincott Williams & Wilkins)

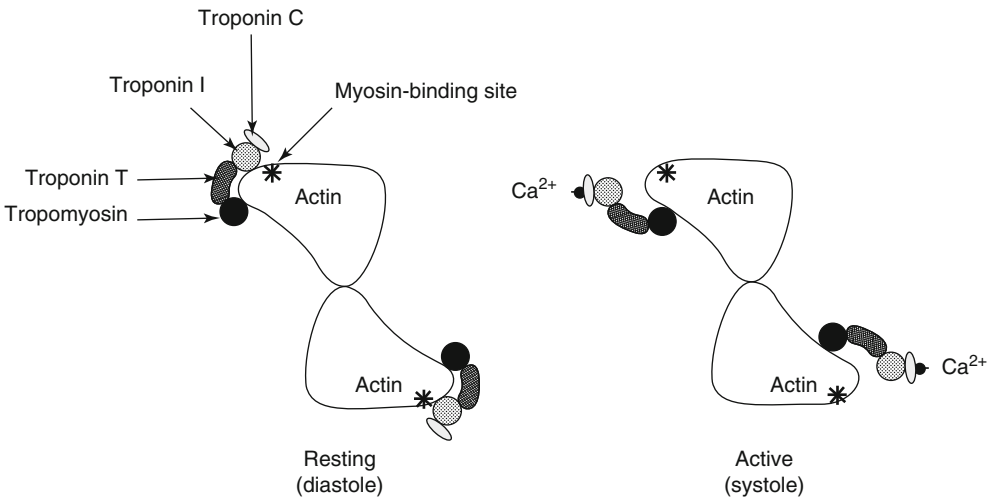


Fig. 2.8 Cross section of a thin filament at a region containing the troponin complex in resting (*left*) and active (*right*) muscle. At rest, the troponin complex holds the tropomyosin molecules toward the periphery of the groove between adjacent actin strands, which prevents myosin-binding sites on actin (*asterisks*) from interacting with the thick filaments. In active muscle, calcium binding to troponin C weakens the bond linking troponin I to actin. This rearranges the regulatory proteins so as to shift tropomyosin deeper into the groove between the strands of actin, thereby exposing active sites on actin for interaction with the myosin crossbridges (Modified from Katz [1], with permission from Lippincott Williams & Wilkins)

mainly α-cardiac actin, along with a smaller amount of α-skeletal actin.

Tropomyosin

Tropomyosin is an elongated molecule made up of two helical peptide chains. One tropomyosin molecule lies in each of the two grooves between the two strands of the thin filament (Figs. 2.7 and 2.8) where this protein regulates the interactions between the myosin crossbridges and actin. Cardiac myocytes can contain either or both of two tropomyosin isoforms, called α and β.

Troponin

The troponin complex includes three proteins (Figs. 2.7 and 2.8) that, along with tropomyosin, regulate the response to calcium. In resting muscle, troponin I, along with tropomyosin, inhibits the ability of the actin to interact with myosin; troponin T binds the troponin complex to tropomyosin; and troponin C contains the high-affinity binding sites that allow calcium to initiate contraction. Actin interacts with the myosin crossbridges when calcium binding to troponin C reverses the inhibitory effect of troponin I (see below). Troponin C is a member of a family of high-affinity calcium-binding proteins that includes the myosin light chains and calmodulin.

Posttranslational changes in the troponin complex regulate cardiac performance. These include phosphorylation of cardiac troponin I by cyclic AMP-dependent protein kinase (PK-A) which facilitates relaxation by reducing the calcium affinity of troponin C. This effect, along with phosphorylation of phospholamban in the sarcoplasmic reticulum by PK-A, contributes to both the inotropic and lusitropic effects of β-adrenergic stimulation (see below). Isoform switches involving these regulatory proteins

modify contractile performance in overloaded and diseased hearts.

Regulation of Contractile Protein Interactions

Cardiac performance is regulated on a beat-to-beat basis by changes in end-diastolic fiber length (Starling's law of the heart) and by variations in the amount of calcium that binds to troponin. More slowly evolving changes in performance are brought about by isoform shifts and other changes in myofibrillar proteins, changes in cellular composition and ultrastructure, and cardiac myocyte death.

Length-Dependent Changes: Starling's Law of the Heart

The first mechanism discovered to regulate cardiac performance, changing end-diastolic volume, depends largely on length-dependent modification of the calcium sensitivity of the contractile proteins brought about by changes in sarcomere length. Length-dependent variations in calcium release from the sarcoplasmic reticulum also play a minor role.

Calcium Binding to Troponin

At the low cytosolic calcium concentrations in resting muscle, where the high-affinity calcium-binding sites on troponin C are not occupied, interactions between actin and the myosin crossbridges are inhibited by tropomyosin and the troponin complex. This inhibitory effect is reversed when calcium binding to troponin C initiates cooperative interactions that shift the position of troponin I and tropomyosin in the thin filaments (Fig. 2.8). In resting muscle, tropomyosin blocks interactions between actin and myosin. Calcium binding to troponin C causes a shift in the position of tropomyosin that allows active sites on actin to interact with the myosin crossbridges. The heart relaxes when dissociation of calcium from troponin C returns tropomyosin to its inhibitory position.

The amount of calcium released into the cytosol during systole in adult human ventricles operating under basal conditions is sufficient to occupy fewer than half of the high-affinity calcium-binding sites on troponin C. Variations in the amount of calcium delivered to the cytosol by excitation-contraction coupling therefore represent a major determinant of myocardial contractility. The amount of calcium bound to troponin C can also be modified by changes in the calcium affinity of troponin C caused by isoform shifts and posttranslational changes in the troponin complex.

Excitation, Excitation-Contraction Coupling, and Relaxation

Excitation-contraction coupling is initiated when an action potential, an electrical signal transmitted along the plasma membrane (see below), delivers calcium to the cytosol. Unlike the smaller and more slowly contracting myocytes found in smooth muscle and the embryonic heart, which are activated when calcium enters the cytosol from the extracellular space, most activator calcium in the adult human heart is derived from intracellular stores within the sarcoplasmic reticulum.

The functional link between plasma membrane depolarization and calcium release from intracellular stores is provided by the dyads (Fig. 2.2). Activation begins when a small amount of calcium enters the cytosol through L-type plasma membrane calcium channels and opens sarcoplasmic reticulum calcium-release channels in adjacent subsarcolemmal cisternae. The latter then deliver a larger amount of calcium into the cytosol from stores within the sarcoplasmic reticulum. This process, often referred to as "calcium-induced calcium release," provides most of the calcium that activates contraction.

The heart relaxes when energy-dependent ion pumps and exchangers lower cytosolic calcium concentration, which causes calcium to dissociate from troponin C. Relaxation is therefore not simply the reversal of excitation-contraction coupling; instead, different structures use different mechanisms to deliver calcium to and remove calcium from the cytosol.

Energetics

Contraction and relaxation both require energy, but the energy is used by different structures and in different ways. During systole, energy is expended by the contractile proteins for tension development and shortening, whereas during diastole, ion pumps and exchangers use energy to transport calcium uphill out of the cytosol.

The calcium fluxes that activate contraction are passive (downhill) because the calcium concentration in the extracellular space and within the lumen of the sarcoplasmic reticulum is >1 mM, which is ~5,000 times higher than cytosolic calcium concentration in the resting heart (~0.2 μM) and ~100 times greater than the calcium concentration needed to saturate troponin C (~10 μM). In contrast, the calcium fluxes that relax the heart are active (uphill) and so require the expenditure of energy.

Calcium Cycles in Excitation-Contraction Coupling and Relaxation

The processes responsible for calcium entry and removal from the cytosol in the adult human heart can be viewed

in terms of two calcium cycles (Fig. 2.9). In the "extracellular calcium cycle," calcium enters and leaves the cytosol by crossing the plasma membrane from what is, in effect, an unlimited calcium store in the extracellular fluid. In the "intracellular calcium cycle" the activator enters and leaves the cytosol from a much more limited store within the sarcoplasmic reticulum.

Structures Involved in Excitation-Contraction Coupling and Relaxation

Plasma membrane depolarization opens L-type calcium channels that differ structurally from the calcium-release channels in the sarcoplasmic reticulum (Table 2.2). Both of these membranes also contain ATP-dependent calcium

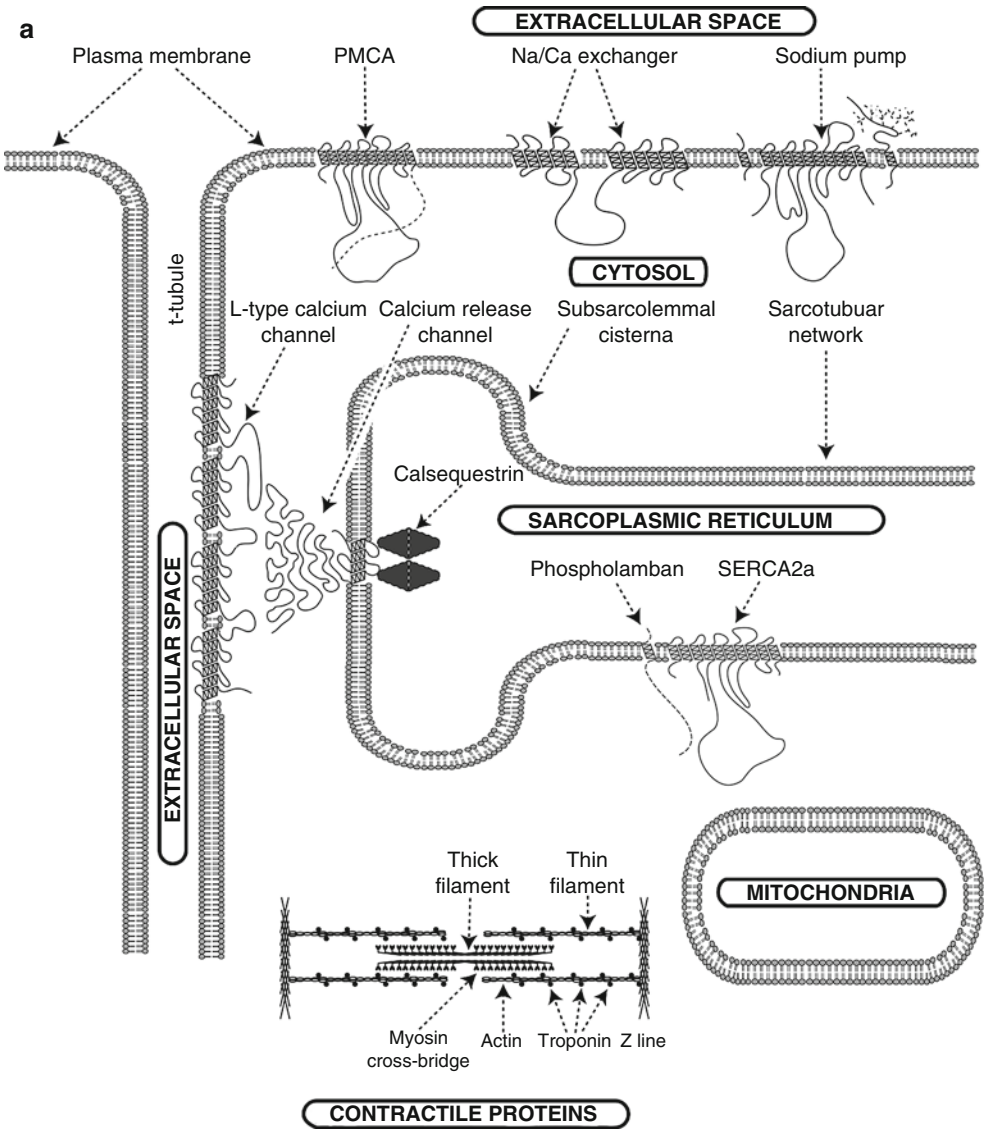


Fig. 2.9 Major structures (**a**) and calcium fluxes (**b**) that control cardiac excitation-contraction coupling and relaxation. In **a**, Calcium "pools" are labeled by *bold capital letters*. In **b**, the thickness of the *arrows* indicates the magnitude of the calcium fluxes, while their vertical orientations describe their "energetics": *downward arrows* represent passive calcium fluxes; *upward arrows* represent energy-dependent active calcium transport. The calcium that enters the cell from the extracellular fluid via L-type calcium channels (*arrow A*) directly activates the contractile proteins (*arrow A1*) and triggers calcium release from the sarcoplasmic reticulum (*arrow A2*). Calcium is actively transported out of the cytosol into the extracellular fluid by the plasma membrane calcium pump ATPase (PMCA; *arrow B1*) and the Na/Ca exchanger (NCX) (*arrow B2*). The sodium that enters the cell in exchange for calcium (*dashed line*) is pumped out of the cytosol by the sodium pump. Calcium fluxes mediated by the sarcoplasmic reticulum are calcium efflux from the subsarcolemmal cisternae via calcium-release channels (*arrow C*) and calcium uptake into the sarcotubular network by the calcium pump ATPase (*arrow D*). (*Arrow D1* identifies calcium that, after dissociating from troponin, is transported into the extracellular space by the PMCA and NCX.) Calcium diffuses within the sarcoplasmic reticulum from the sarcotubular network to the subsarcolemmal cisternae (*arrow G*), where it forms a complex with calsequestrin and other calcium-binding proteins. Calcium binding to (*arrow E*) and dissociation from (*arrow F*) high-affinity calcium-binding sites of troponin C activate and inhibit the interactions of the contractile proteins. Calcium movements into and out of mitochondria (*arrow H*) buffer cytosolic calcium concentration. The extracellular calcium cycle is shown by *arrows A*, *B1*, and *B2*, while the intracellular cycle involves *arrows C, D*, and *G* (Reprinted from Katz [1], with permission from Lippincott Williams & Wilkins)

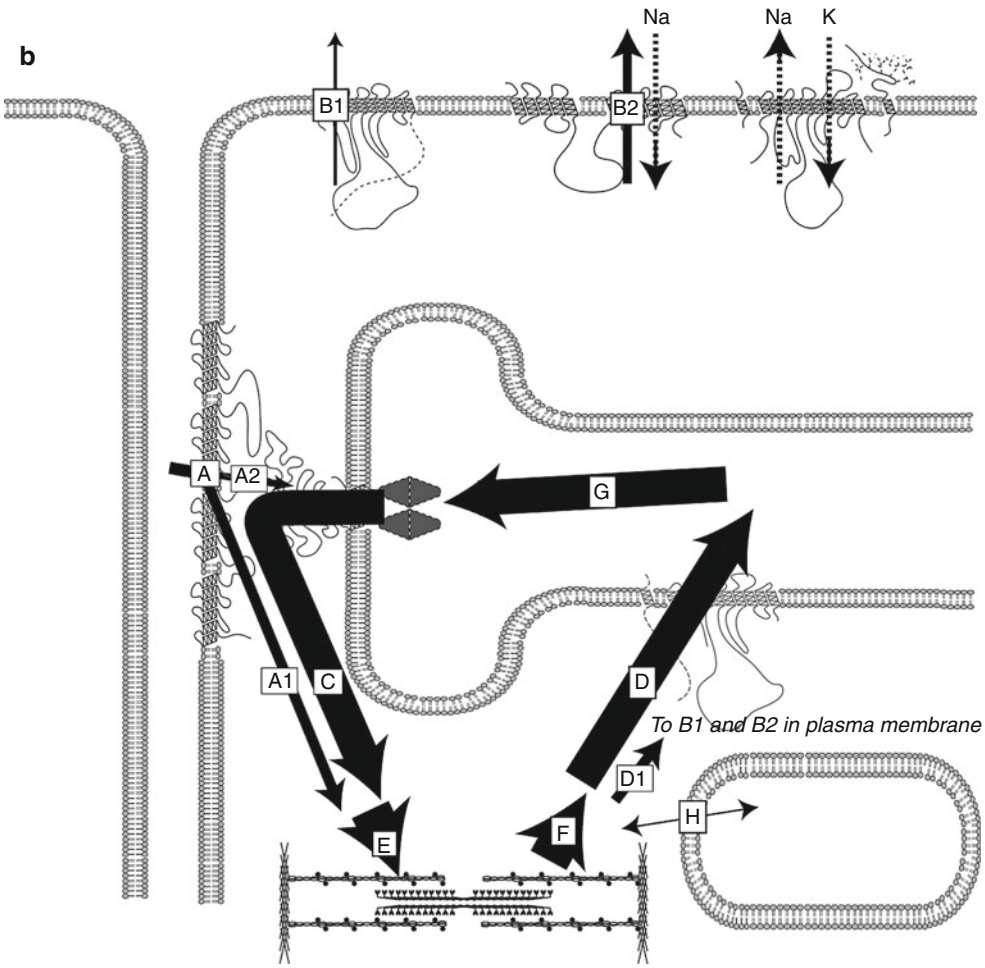


Fig. 2.9 (continued)

pumps that, along with the sodium pump (Na/K ATPase), are members of the P-type family of ion pump ATPases. The sodium/calcium exchanger, which plays a major role in transporting calcium out of the cytosol into the extracellular space, has no counterpart in the sarcoplasmic reticulum. Unlike the plasma membrane, where ion fluxes can generate electrical currents, there is no electrical potential across the sarcoplasmic reticulum membrane because the latter contains nonselective anion channels that neutralize any charge transfer associated with cation fluxes.

The Cardiac Action Potential and Plasma Membrane Ion Channels

Action potentials in the working cells of the adult myocardium begin with the opening of plasma membrane sodium channels (Fig. 2.10). The resulting entry of sodium cations into the cytosol generates a fast inward current that initiates a slow inward calcium current carried by L-type calcium channels. Cardiac myocytes are repolarized by a transient outward potassium current and delayed rectifier potassium channels that are opened by depolarization, after which opening of inward rectifier potassium channels maintains resting potential during diastole. The ion channels that carry all of these currents are "voltage gated," which means that ion fluxes are controlled by changes in membrane potential.

Cardiac ion channels, which are generally named for the ions that they carry (Table 2.2), are oligomers that can contain as many as five subunits, called α_1 or α_2, β, γ, and δ. Ions cross the hydrophobic core of the membrane bilayer through ion-selective pores contained within the large α-subunits. The α-subunits of sodium and calcium and both the transient inward and delayed rectifier potassium channels are made up of four domains (Fig. 2.11), each of which contains six α-helical transmembrane segments (Fig. 2.12). The four domains of the α-subunits of the sodium and calcium channels are linked covalently in a single large protein, whereas the four domains of these potassium channels, which also function as tetramers, are not covalently linked. The channel "pores" are made up of the S_5 and S_6 α-helices and the

Table 2.2 Structure-function relationships in excitation-contraction coupling of working cardiac myocytes

Structure	Role in systole	Role in diastole
Myofilaments		
Actin and myosin	Contraction	
Troponin C	Calcium receptor	
Other proteins	Regulation	
Plasma membrane		
Sarcolemma		
Sodium channels	Depolarization	
	Opens calcium channels	
Calcium channels	Action potential plateau	
	Calcium-triggered calcium release	
Calcium pump (PMCA)		Calcium removal
Sodium/calcium exchanger	Calcium entry	Calcium removal
Potassium channels	Repolarization	
Sodium pump		Sodium gradient for sodium/calcium exchange
Transverse tubule		
Sodium channels	Action potential propagation	
Calcium channels	Calcium-triggered calcium release	
Sarcoplasmic reticulum		
Subsarcolemmal cisternae		
Calcium-release channel	Calcium release	
Sarcotubular network		
Calcium pump (SERCA)		Calcium removal

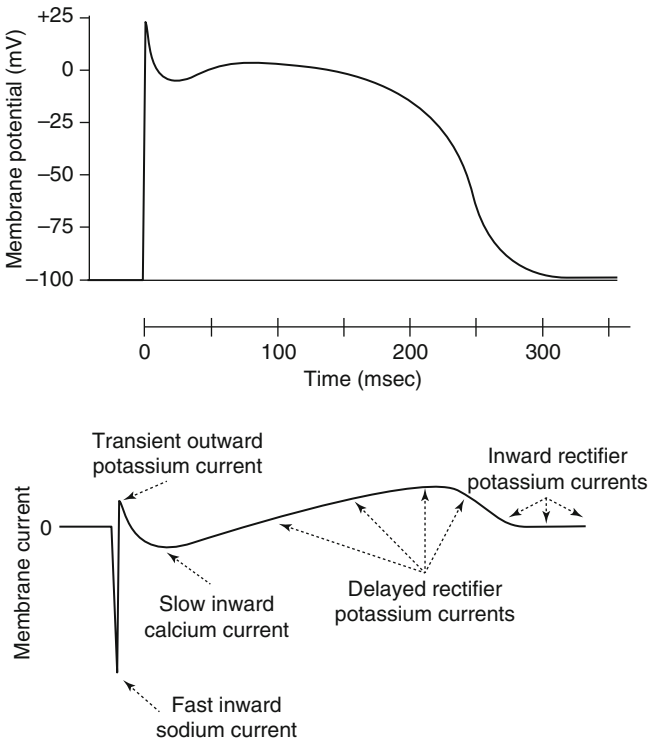


Fig. 2.10 Cardiac action potential (*upper tracing*) and approximate timing of five major membrane currents (*lower tracing*); inward currents are downward, and outward currents are upward (Modified from Katz [1], with permission from Lippincott Williams & Wilkins)

intervening amino acids. The "voltage sensors" that open (activate) sodium channels in response to membrane depolarization are the S_4 α-helices, which, because they are rich in positively charged amino acids, shift within the membrane in response to a change in membrane potential. Sodium channels are inactivated (closed) by the intracellular peptide chain that links domains III and IV, which forms an "inactivation particle" that blocks the inner mouth of the pore in depolarized cells. The α-subunits of inwardly rectifying potassium channels are smaller than those of the delayed rectifier potassium channels; they contain regions homologous to the S_5 and S_6 α-helical transmembrane segments and intervening amino acids sequence that make up the pore regions of the larger α-subunits (Fig. 2.11).

The upstroke of the cardiac action potential occurs when sodium channels in the resting plasma membrane are opened by an approaching action potential. The resulting depolarization activates L-type calcium channels, so named because of their relatively long-lasting openings, which are responsible for the long plateau of the cardiac action potential. These channels bind the familiar classes of calcium channel blockers (*dihydropyridines* such as nifedipine, *phenylalkylamines* such as verapamil, and *benzothiazepines* such as diltiazem); they are sometimes called *dihydropyridine receptors*. A second class of plasma membrane calcium channel, called T-type channels because

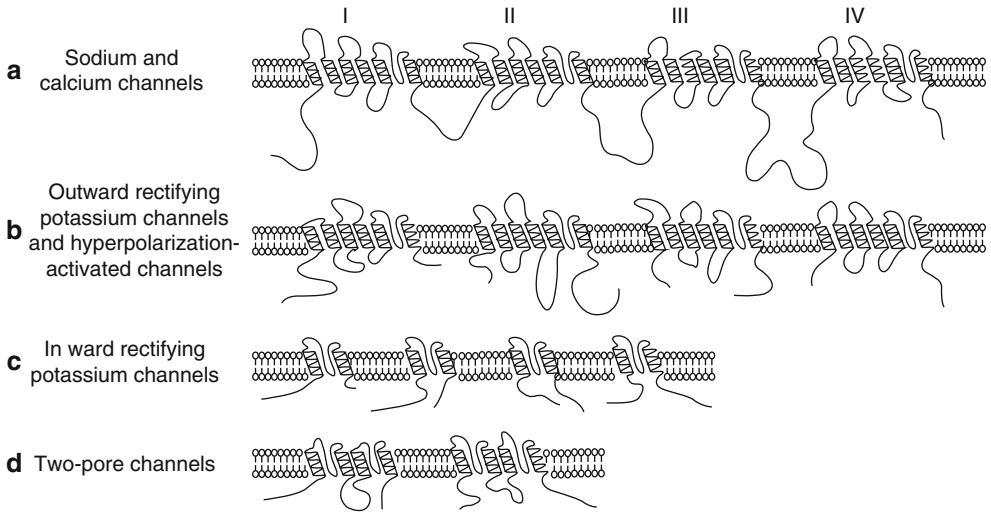


Fig. 2.11 Schematic representation of four types of voltage-gated ion channel. (**a**) Sodium and calcium channels are covalently linked tetramers made up of four α-subunits (numbered *I–IV*), each of which contains six α-helical transmembrane segments. (**b**) The channels that carry the transient outward potassium currents, outward rectifying potassium currents, and hyperpolarization-activated channels in pacemaker cells are also made up of four α-subunits that are not linked covalently. (**c**) Inward rectifier potassium channels are made up of four small α-subunits that contain pore-containing regions analogous to those of the α-subunits shown in **a** and **b**. (**d**) Two-pore channels are dimers of subunits each of which is made up of two pore-containing regions (Reprinted from Katz [1], with permission from Lippincott Williams & Wilkins)

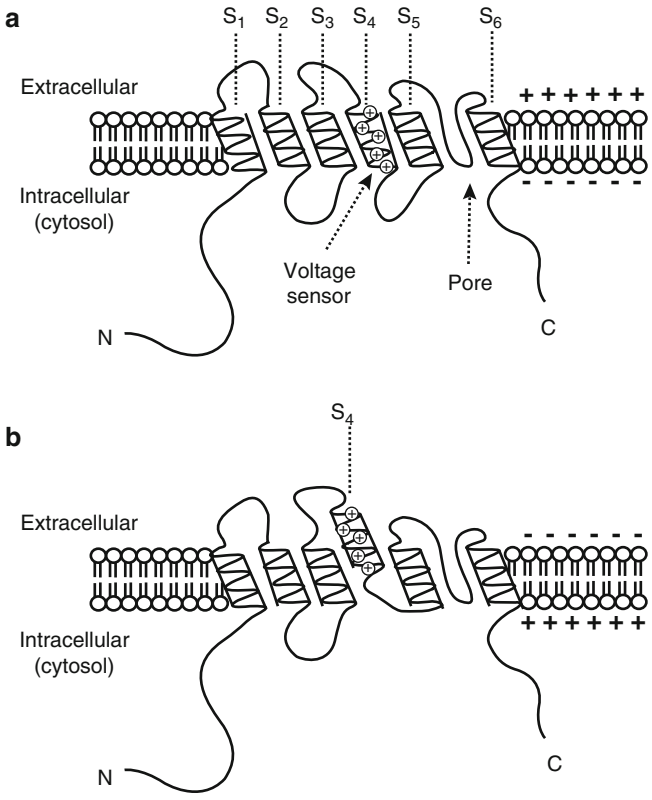


Fig. 2.12 Schematic diagram showing the m gate (voltage sensor) of a sodium channel. (**a**) In the closed (resting) state, where the extracellular surface of the membrane is positively charged and the interior is negatively charged, the S_4 transmembrane segment is in a conformation that closes the channel. (**b**) Depolarization of the plasma membrane opens the channel by shifting the position of the S_4 transmembrane segment away from the plane of the bilayer (Reprinted from Katz [1], with permission from Lippincott Williams & Wilkins)

they open only transiently, play a role in the SA node pacemaker but are virtually absent in working ventricular myocytes. The content of T-type channels increases in hypertrophied hearts where they appear to participate in proliferative signaling.

Repolarization of the heart is effected by several classes of voltage-gated potassium channels. The current carried by transient outward channels is responsible for early repolarization that plays an important role in determining the duration of the action potential plateau. Fast and slow delayed rectifier potassium channels open later during the plateau and generate outward currents that restore resting potential. The inwardly rectifying channels, which are open in resting cells and closed by depolarization, maintain resting potential and help prolong the action potential plateau.

Intracellular Calcium-Release Channels

The intracellular calcium channels that control calcium flux out of the sarcoplasmic reticulum, called calcium-release channels, differ from the calcium channels in the plasma membrane. There are two classes of calcium-release channels. Most important are the *ryanodine receptors*, whose name reflects their ability to bind to this alkaloid, that mediate excitation-contraction coupling by releasing calcium from the sarcoplasmic reticulum. A second class of intracellular calcium channels, called *$InsP_3$ receptors* because they are activated by inositol trisphosphate ($InsP_3$), regulate proliferative responses like cell

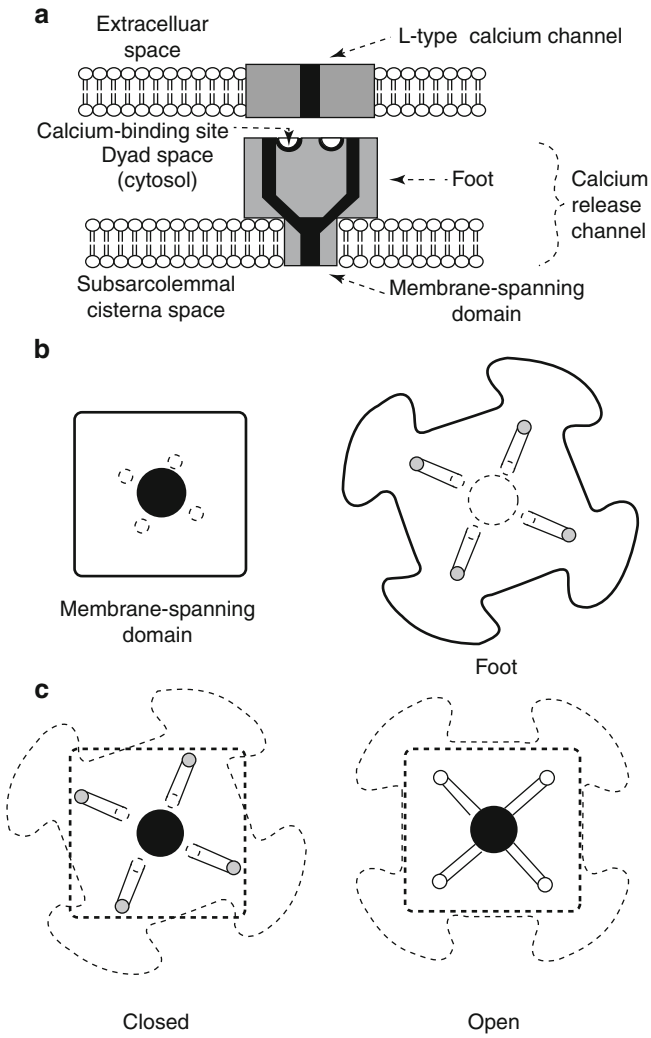


Fig. 2.13 Schematic representation of a dyad showing the relationship between an L-type calcium channel and a calcium-release channel. (**a**) View through the plane of the bilayer showing the plasma membrane (*above*) and subsarcolemmal cisternal membrane (*below*). The latter contains the sarcoplasmic reticulum calcium-release channel, which is made up of a membrane-spanning domain and a large "foot" that projects into the cytosolic space. *Dark areas* represent the pores through which calcium crosses the membrane when the channel is in the open state. (**b**) The membrane-spanning domain of the intracellular calcium-release channel as seen from subsarcolemmal cisternal space (*left*) and the foot as seen from the dyad space (*right*). The membrane-spanning domain contains a central pore, while each of the 4 ft subunits contains a radial pore. (**c**) Depiction of channel opening. In the closed state, the four radial pores do not connect with the central pore. Alignment of the central pore with the radial pores opens the channel and releases calcium from the sarcoplasmic reticulum (Reprinted from Katz [1], with permission from Lippincott Williams & Wilkins)

growth, differentiation, and programmed cell death (apoptosis). Both ryanodine receptors and $InsP_3$ receptors are tetrameric structures in which four subunits surround a central pore through which calcium moves when the channel is opened (Fig. 2.13).

Calcium Pump ATPases

The cardiac plasma membrane calcium pump, called PMCA, and the sarcoplasmic reticulum calcium pump, called SERCA [*s*arco(*e*ndo)plasmic *r*eticulum *c*alcium *A*TPase], are made up of ten membrane-spanning α-helices and a large peptide chain within the cytosol. The latter contains the ATPase site that provides chemical energy for active transport by coupling the hydrolysis of the high-energy phosphate bond of ATP to ion transport. The sarcoplasmic reticulum calcium pump is regulated by cyclic AMP-dependent proteins kinases (PK-A) that catalyze the phosphorylation of a small regulatory protein called phospholamban. Phosphorylation of phospholamban contributes to the lusitropic and inotropic effects of β-adrenergic stimulation by increasing the calcium sensitivity of the calcium pump. The resulting increased rate of calcium transport from the cytosol into the sarcoplasmic reticulum accelerates relaxation by favoring calcium dissociation from troponin C. Phospholamban phosphorylation also increases contractility because the more rapid uptake of calcium adds to the amount of this activator available for release from the sarcoplasmic reticulum.

The plasma membrane calcium pump is regulated by a site that, when bound to the calcium-calmodulin complex, stimulates calcium transport out of the cytosol. This response promotes the removal of calcium from the cytosol of calcium-overloaded cells.

The Sodium/Calcium Exchanger

The sodium/calcium exchanger is responsible for most of the calcium transport out the cytosol into the extracellular space. This exchanger, which utilizes osmotic energy provided by downhill sodium influx across the plasma membrane to provide energy for active calcium transport, generates a small ionic current because it transports three sodium ions in exchange for one calcium ion. The exchanger favors sodium efflux and calcium influx during systole, after the opening of sodium channels has increased cytosolic sodium and caused the cell interior to become positively charged. In contrast, the exchanger removes calcium from the cytosol at the end of systole, when cytosolic calcium is high and repolarization causes the cell interior to become negatively charged. The inward current generated when the exchanger exchanges cytosolic calcium for sodium in the extracellular fluid can initiate after depolarizations that, in calcium-overloaded hearts of patients with heart failure and ischemia, are an important cause of arrhythmias and sudden cardiac death. This arrhythmogenic mechanism is exacerbated by inotropic drugs, like β-adrenergic agonists and phosphodiesterase inhibitors, that increase calcium entry via L-type calcium channels

The Sodium Pump

The sodium pump, also called the sodium/potassium ATPase, is a P-type ion pump that exchanges the sodium that enters the cell during the action potential upstroke for the potassium needed to replace the potassium that leaves the cytosol during repolarization. The stoichiometry of the sodium pump is three sodium ions pumped out of the cell for two potassium ions brought into the cell, so that the sodium pump generates a small outward (repolarizing) current.

Calcium Storage Proteins Within the Sarcoplasmic Reticulum

Much of the calcium stored in the sarcoplasmic reticulum is associated with calcium-binding proteins that include calsequestrin, calreticulin, and a histidine-rich calcium-binding protein. These and other calcium-binding proteins are concentrated in the subsarcolemmal cisternae, where they provide a store of calcium that is available for release by calcium-release channels. Many of these proteins also serve regulatory functions.

Mitochondria

Mitochondria, whose function in the heart is primarily to regenerate ATP, can also take up calcium. However, the calcium affinity of mitochondrial calcium uptake is low, so that these energy-producing structures do not normally play a role in excitation-contraction coupling. Under conditions of calcium overload, however, the mitochondria protect the myocardium from the detrimental effects of excess calcium by taking up some of the excess cytosolic calcium.

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Ventricular Function

3

Lionel H. Opie

Introduction

Ventricular Contraction

The basic events of the cardiac cycle of Wiggers' cycle (Fig. 3.1) are (1) left ventricular (LV) contraction, (2) LV relaxation, and (3) LV filling. A natural starting point is with the arrival of calcium ions at the contractile protein that starts actin-myosin interaction and left ventricular contraction. During the initial phase of contraction, the LV pressure builds up until it exceeds that in the left atrium (normally 10–15 mmHg), whereupon the mitral valve closes. Now, with the aortic and mitral valves both shut, the LV volume cannot change and contraction must be *isovolumic* (iso = the same) until the aortic valve is forced open as the LV pressure exceeds that in the aorta. Once the aortic valve is open, blood is vigorously ejected from the LV into the aorta, which is the phase of *maximal or rapid ejection*. The speed of ejection of blood is determined both by the pressure gradient across the aortic valve and by the elastic properties of the aorta which undergoes systolic expansion.

Ventricular Relaxation

After the LV pressure rises to a peak, it then starts to fall. As the cytosolic calcium is taken up into the sarcoplasmic reticulum under the influence of active phospholamban, more and more myofibers enter the state of relaxation. As a result, the rate of ejection of blood from the aorta falls (*phase of reduced ejection*). Although the LV pressure is falling, blood flow is maintained by aortic recoil. Next, the aortic valve closes as the pressure in the aorta exceeds the falling pressure in the LV. Now the ventricular volume is sealed, because both aortic and mitral valves are closed. The left ventricle therefore relaxes without changing its volume (*isovolumic relaxation*). Next, the filling phase of the cardiac cycle restarts as the LV pressure falls to below that in the left atrium, which causes the mitral valve to open and the filling phase to start.

Ventricular Filling Phases

The *first phase of rapid or early filling* accounts for most of ventricular filling. It starts very soon after mitral valve opening, as the LV pressure drops below that in the left atrium. In addition, some evidence shows that there is also active diastolic relaxation of the ventricle (*ventricular suction*) that also contributes to early filling. In the next phase of *diastasis* (= separation), LV filling temporarily stops as pressures in the atrium and ventricle equalize. Thereafter atrial contraction (*atrial systole*), also called the *left atrial booster*, renews ventricular filling by increasing the pressure gradient across the open mitral valve.

Definitions of Systole and Diastole

In Greek, *systole* means contraction and *diastole* means to *send apart*. For the physiologist, systole starts at the beginning of isovolumic contraction when LV pressure exceeds the atrial pressure. The start of cardiological systole corresponds reasonably well with the start of physiological systole, because mitral valve closure (M_1) actually occurs only about 20 ms after the onset of physiological systole at the crossover point of pressures. Thus, in practice the term isovolumic contraction often also includes this brief period of early systolic contraction before the mitral valve shuts, when the heart volume does not change substantially.

Cardiological systole is demarcated by the interval between the first and second heart sounds (Fig. 3.1), lasting from the first heart sound (M_1) to (A_2), the point of closure of

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_3,

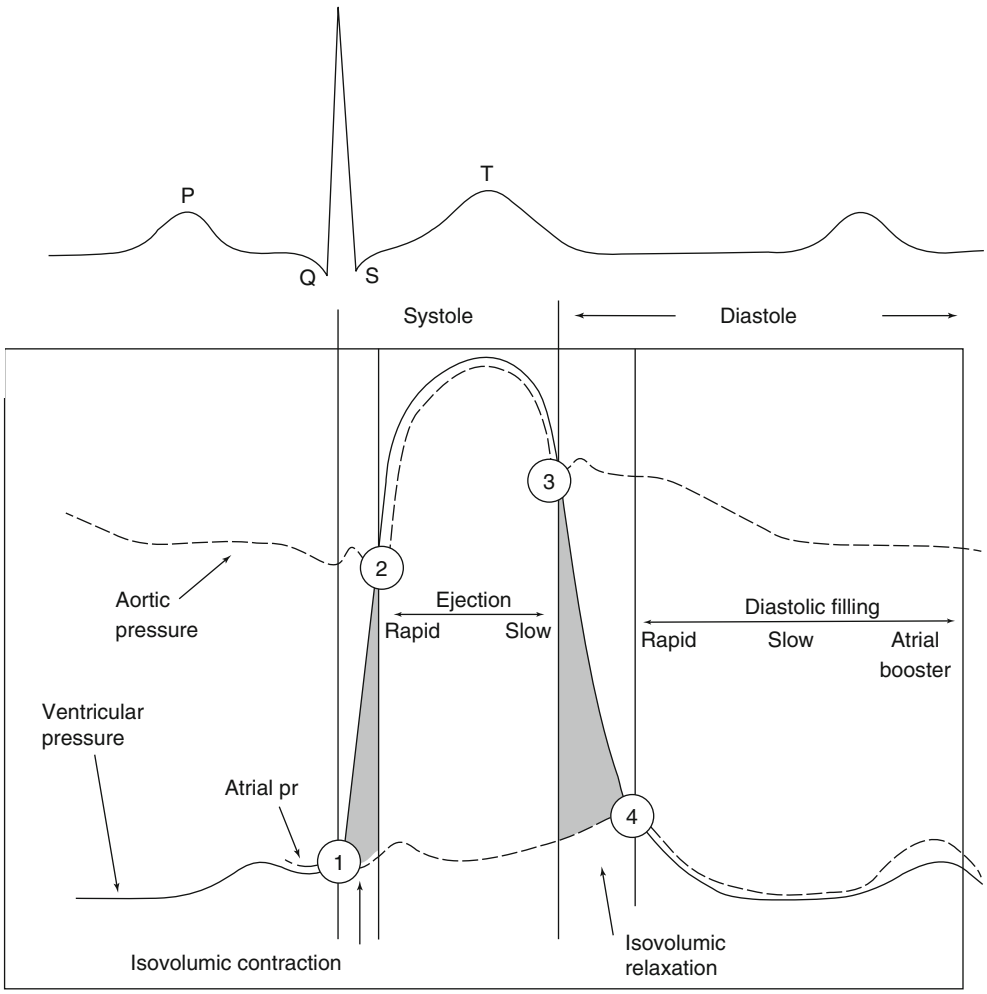

Fig. 3.1 The cardiac cycle, first assembled by Lewis in 1920 although conceived by Wiggers [1]. Systole and diastole relate to cardiological not physiological phases. *1* mitral valve closure that occurs shortly after the crossover point of atrial and ventricular pressures at the start of systole, *2* aortic valve opening, *3* aortic valve closure, and *4* mitral valve opening. Note the four phases of diastole: isovolumic relaxation, and three filling phases

the aortic valve [2]. The remainder of the cardiac cycle automatically becomes cardiological diastole. Thus, cardiological systole starts fractionally later than physiological systole but ends significantly later. By contrast, from the physiological point of view, end-systole is just before the ventricle starts to relax, a concept that fits well with the standard pressure-volume loop. Thus, diastole commences as calcium ions are taken up into the sarcoplasmic reticulum, so that myocyte relaxation dominates over contraction, and the LV pressure starts to fall as shown on the pressure-volume loop (Fig. 3.2).

In contrast stands another concept, argued by Brutsaert and colleagues [3], namely, that diastole starts much later than when relaxation starts or when the aortic valve closes and only when the whole of the contraction-relaxation cycle is over. According to this view, diastole would occupy only a small portion of the cardiac cycle (Fig. 3.1). This definition of diastole, although not often used in cardiological practice, does help to remind us that abnormalities of left ventricular contraction often underlie defective relaxation.

Contractility Versus Load

Contractility is the inherent capacity of the myocardium to contract independently of changes in the preload or afterload. Increased contractility means a greater rate of contraction, to reach a greater peak force. Often an increased contractility is associated with enhanced rates of relaxation, called the lusitropic effect. Alternate names for contractility are the *inotropic state* (*ino*, fiber; *tropos*, to move) or the contractile state. Contractility is an important regulator of the myocardial oxygen uptake. Factors that increase contractility include adrenergic stimulation, digitalis, and other inotropic agents. At a molecular level, an increased inotropic state is enhanced interaction between calcium ions and the contractile proteins. Such an interaction could result from either increased calcium transients or from sensitization of the contractile proteins to a given level of cytosolic calcium. Calcium-sensitizing drugs act by the latter mechanism, and conventional inotropes such as digitalis through an increase of internal calcium.

Preload and Afterload

Contractility is therefore a common part of the essential cardiological language. It is important to stress that any change in the contractile state must occur independently of the loading conditions. The two types of load are the preload and the afterload. The *preload* is the load present before contraction has started, at the end of diastole. The preload reflects the venous filling pressure which fills the atrium and hence the left ventricle during diastole. The *afterload* is the systolic load on the left ventricle after it has started to contract. When the preload increases, the left ventricle distends during diastole, and the stroke volume rises according to Starling's law (next section). The heart rate also increases by stimulation of the atrial mechanoreceptors that enhance the rate of discharge of the sinoatrial node. Thus, the cardiac output (stroke volume times heart rate) rises.

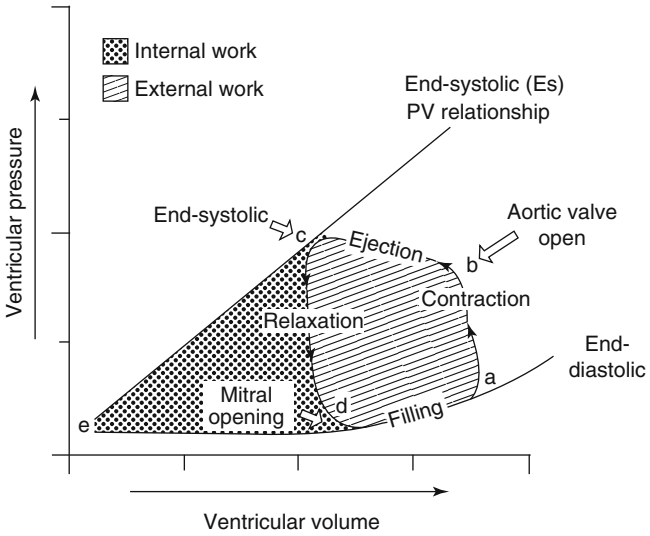

Fig. 3.2 Pressure-volume loop. Normal left ventricular pressure-volume relationship. The aortic valve opens at b and closes at *c*. The mitral valve opens at d and closes at a. External work is defined by *a–d*, while potential energy (less accurately called internal work) is given by the triangle *e*, *d*, *c*. The pressure-volume area is the sum of external work and potential energy

Venous Return and Heart Volume: Starling's Law of the Heart

Starling [4] related the venous pressure in the right atrium to the heart volume in the dog heart lung preparation (Fig. 3.3). He concluded that:

> Within physiological limits, the larger the volume of the heart, the greater the energy of its contraction and the amount of chemical change at each contraction

Thus, assuming that an increased diastolic heart volume means that the end-diastolic fiber length increases, Starling's law is often paraphrased to mean that (1) an increased right atrial venous filling pressure translates into an increased left ventricular end-diastolic fiber length, and (2) this increase in length increases the force of contraction and hence the stroke volume. Because the heart volume is difficult to determine even with modern echocardiographic techniques, the left ventricular diastolic *filling pressure* (the difference between the left atrial pressure and the left ventricular diastolic pressure) is often taken as a surrogate for heart volume. This is important because the venous filling pressure can be measured in humans albeit indirectly by the technique of Swan-Ganz catheterization (Fig. 3.4), as can the stroke volume. Nonetheless, there is a defect in this reasoning. The left ventricular pressure and volume are not

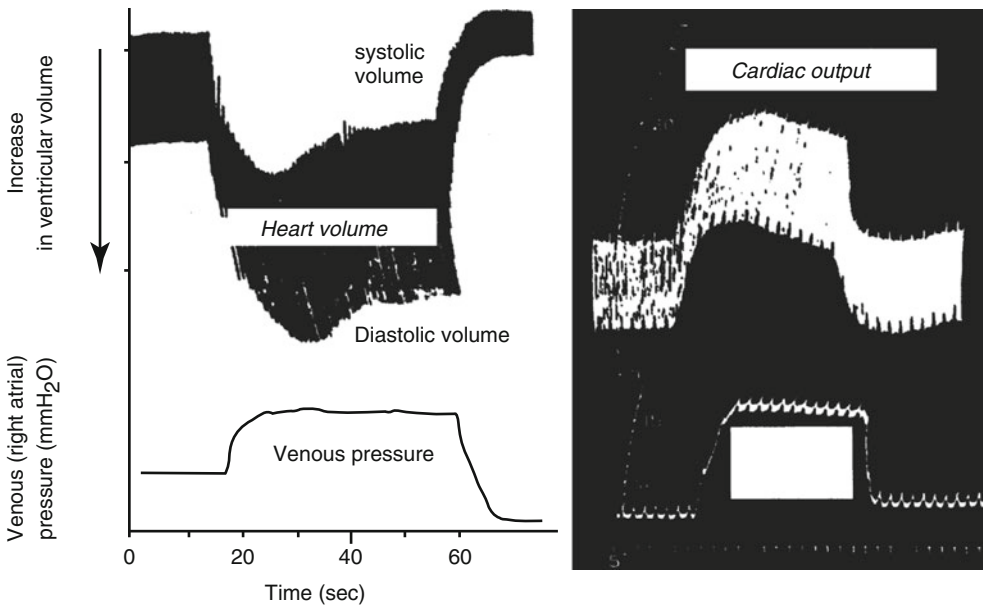

Fig. 3.3 Starling's law of the heart as applied to the preload (venous filling pressure). As the preload increases (*bottom* in both figures), the heart volume increases (*left top*), as does the cardiac output (*right top*). Starling's explanation was "The output of the heart is a function of its filling; the energy of contraction depends on the state of dilatation of the heart's cavities"

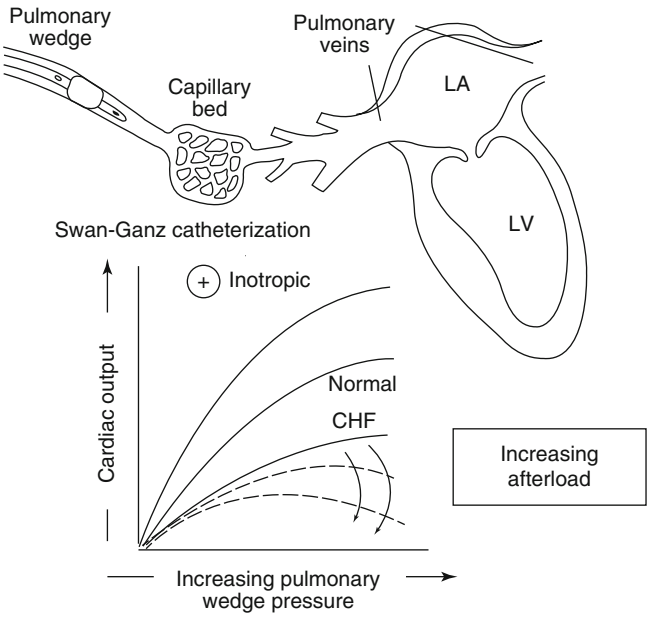

Fig. 3.4 A family of Starling curves with relevance to Swan-Ganz catheterization. Each curve relates the filling pressure (PCWP, pulmonary capillary wedge pressure) to the left ventricular (*LV*) stroke output and to the cardiac output. Note that the depressed inotropic state of the myocardium causes an abnormally low curve and that the downward limb can be related to an increased afterload. Clinically the measurements relating filling pressure to cardiac output are obtained by Swan-Ganz catheterization (a procedure presently undertaken less frequently than previously). Note the close association between LV diastolic dysfunction and pulmonary congestion. *LA* left atrium, *CHF* congestive cardiac failure (Courtesy of L.H. Opie © 2012)

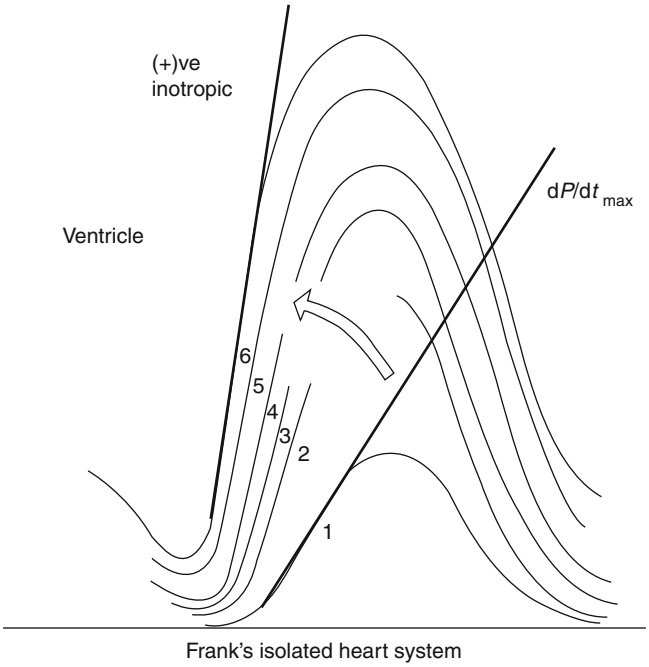

Fig. 3.5 Frank's family of isometric (isovolumic) curves. Frank related heart volume to what would now be recognized as an index of contractility, a term not know then, as can be seen if two tangential lines are added to the curves of the original figure. In modern terms, these lines give the maximal rate of change of the intraventricular pressure (d*P*/d*t* max). Each curve was obtained at a greater initial filling of the left ventricle by an increased left atrial filling pressure. Then valves were shut to produce isovolumic conditions. *Curve 6* has a greater velocity of shortening. Hence, the initial fiber length (volume of ventricle) can influence contractility. The line on *curve 6* has the much steeper slope and, therefore, indicates a greater rate of contraction or a greater, in contrast to the line drawn on *curve 1* which ascends more slowly and indicates a lower contractile state. The ascending *curves* (*2* to *5*) in between *curves 1* and *6* reflect increasing the patterns of contraction and relaxation found with increasing initial fiber lengths (Figure based on author's interpretation of [5])

linearly related because the myocardium cannot continue to stretch indefinitely. Rather, as the left ventricular end-diastolic pressure increases, so does the cardiac output reach a plateau. The LV volume can now be directly measured with two-dimensional echocardiography. Yet the value found depends on a number of simplifying assumptions such as a spherical LV shape and neglects the confounding influence of the complex anatomy of the left ventricle. In practice, the LV volume is not often measured. Although the Starling concept is valuable and may contribute to the hemodynamic management of those critically ill and receiving a Swan-Ganz catheter, several approximations are required to make these concepts clinically applicable.

Frank and Isovolumic Contraction

Starling emphasized that increasing the heart volume increased the initial length of the muscle fiber and thereby increased the stroke volume and cardiac output, which suggested but did not prove that diastolic stretch of the LV increased the force of contraction. In fact, his German predecessor, Frank, had already in 1895 [5] studied the relation between filling pressure and the force of contraction in an isolated heart (Fig. 3.5). He found that the greater the initial volume, the more rapid the rate of rise, the greater the peak pressure reached, the faster the rate of relaxation. Frank was, therefore, able to show that an increasing diastolic heart volume stimulated the ventricle to contract more rapidly and more forcefully, which is a positive *inotropic effect* (*ino*, fiber and *tropus*, move). Thus, the earlier observations of Frank could explain the contractile behavior of the heart during the operation of Starling's law. These findings of Frank and Starling are so complementary that they often referred to as the *Frank-Starling law*. The beauty of the dual name is that between them they described what accounts for the increased stroke volume of exercise, namely, both the increased inotropic state [5] and the increased diastolic filling [4].

Afterload

Starling and his colleagues gave a simple picture of the how an acute change in the afterload could influence an isolated muscle [4]:

> "The extent to which it will contract depends on..... the amount of the weight which it has to overcome" and "the tension aroused in it."

In clinical practice, the arterial blood pressure is one of three important measures of the afterload, the others being any aortic stenosis, and the *aortic compliance* – the extent to which the aorta can "yield" during systole. *Aortic impedance* is an index of the afterload and is the aortic pressure divided by the aortic flow of that instant, so that the afterload varies during each phase of the contraction cycle.

Preload and Afterload Are Interlinked

In practice, it is often difficult to separate preload from afterload. During the start of exercise, the venous return and the preload increases. When the left ventricle then starts to contract, the tension in the left ventricular wall will be higher because of greater distention of the left ventricle by the greater pressure. The load during systole also will rise, and the afterload will increase. Nonetheless, in general, the preload is related to the degree to which the myocardial fibers are stretched at the end of diastole, and the afterload is related to the wall stress generated by those fibers during systole.

Cellular Basis of Contractility and Starling's Law

Length-Dependent Activation

How could an increased end-diastolic muscle length increase the force and rate of muscular contraction? Previously this effect of increased muscle length was ascribed to a more "optimal" overlap between actin and myosin. Intuitively, however, if actin and myosin are stretched further apart, there would be less rather than more overlap. Another earlier proposal that troponin-C, one of the contractile proteins, is the length sensor and is currently less favored. A more current view is that there is a complex interplay between anatomic and regulatory factors [6], including the concept that an increased sarcomere length leads to greater sensitivity of the contractile apparatus to the prevailing cytosolic calcium. The major mechanism for this regulatory change, although not yet clarified, may reside in the interfilament spacing [7]. At short sarcomere lengths, as the lattice spacing increases, the number of strong cross bridges decreases [8]. Conversely, as the heart muscle is stretched, the interfilament distance decreases (Fig. 3.6), so that the Frank-Starling mechanism also affects cross-bridge cycling kinetics [8].

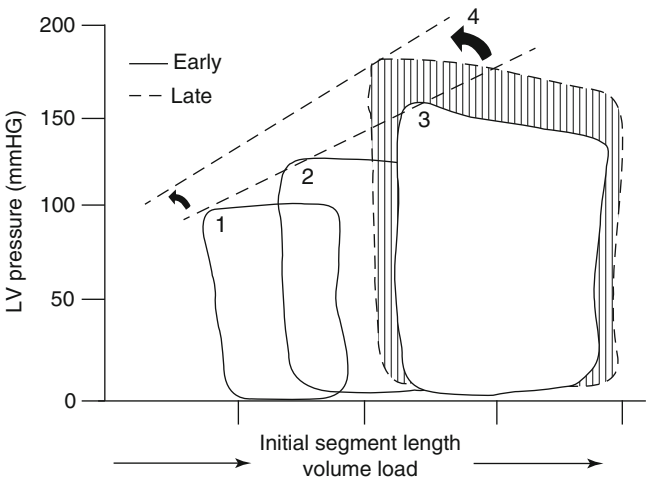

Fig. 3.6 Length-dependent activation. A volume load extends the initial segment length, which corresponds to the diastolic volume in Starling's observations. The result is that the resting PV loop (*loop 1*) increases in area and in peak left ventricular systolic pressure (see *loops 2* and *3*). This is the Starling effect (also see legend to Fig. 3.9). After a few minutes (*broken lines* and *shaded area*), contractility increases modestly, pushing the length-pressure slope upward and to the left [4], an example of length-dependent activation (Based on data from Lew [11])

β-Adrenergic Stimulation, Contractility, and Calcium

β-adrenergic stimulation mediates the major component of its inotropic effect through increasing the cytosolic calcium transient and the factors controlling it (Fig. 3.7). The following are all enhanced: the rate of entry of calcium ions through the sarcolemmal L-type channels, the rate of calcium uptake under the influence of phospholamban into the sarcoplasmic reticulum (SR), and the rate of calcium release from the ryanodine receptor on the SR in response to calcium entry, which in turn follows depolarization. Of all these factors, phosphorylation of phospholamban may be most important [12], acting on the calcium uptake pump of the SR to increase the rate of uptake of calcium during diastole. Thereby the SR is pre-loaded with increased Ca so that more can be liberated during ensuing depolarizations.

Conversely, contractility is decreased whenever calcium transients are depressed, as when β-adrenergic blockade decreases calcium entry through the L-type calcium channel. Alternatively, there may be faulty control of the uptake and release of calcium ions by the SR, as when the SR is damaged in congestive heart failure. Anoxia or ischemia depletes the calcium uptake pump of the SR of the ATP required for calcium uptake, so that the contraction-relaxation cycle is inhibited.

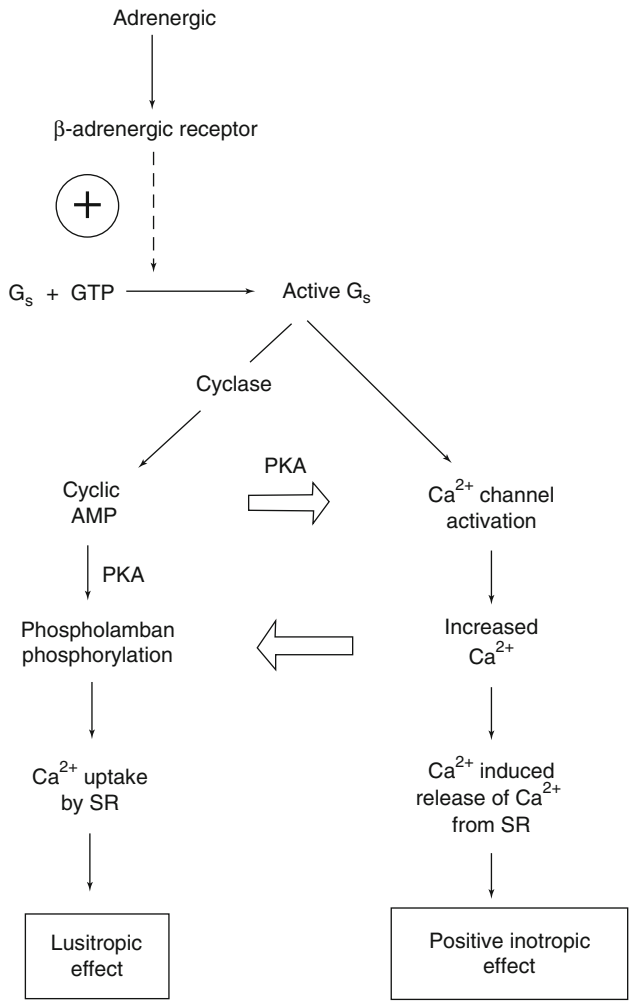

Fig. 3.7 β-Adrenergic signal systems when activated lead to changes in the cardiac calcium cycle that explain positive inotropic and lusitropic (enhanced relaxation) effects. When the β-adrenergic agonist interacts with the β-receptor, a series of G protein-mediated changes lead to activation of the stimulatory G protein, G_s, that interacts with GTP (guanosine triphosphate) that in turn activates adenylate cyclase (shown as cyclase) to form the adrenergic second messenger, cyclic adenosine monophosphate (*cyclic AMP*). The latter acts via protein kinase A (*PKA*) to phosphorylate phospholamban and to increase the activity of the calcium uptake pump on the sarcoplasmic reticulum (*SR*), hence decreasing cytosolic calcium and explaining the lusitropic (relaxant) effect of adrenergic stimulation. PKA also phosphorylates calcium channel protein. The result is an enhanced opening probability of the calcium channel, thereby increasing the inward movement of Ca^{2+} ions through the sarcolemma of the T tubule. Additionally, active Gs directly activates the calcium channel opening. More Ca^{2+} ions enter the cytosol, to release more calcium from the ryanodine release channel of the SR, rapidly to increase cytosolic calcium levels. The result is increased activation of troponin-C, explaining increased peak force development as result of adrenergic stimulation (positive inotropic effect) (Courtesy of L.H. Opie © 2012)

Problems with the Contractility Concept

The concept of contractility has at least two serious defects, including first the absence of any potential index that can be measured in situ and is free of significant criticism, especially the absence of any acceptable noninvasive index, and second the impossibility of separating the cellular mechanisms of contractility changes from those of load or heart rate. Thus, an increased heart rate acts by the sodium pump lag mechanism to give rise to an increased cytosolic calcium, giving the increased force of contraction of the Bowditch or treppe phenomenon. An increased preload involves increased fiber stretch, which in turn causes length activation, thought to be explicable in part by sensitization of the contractile proteins to the prevailing cytosolic calcium concentration. An increased afterload may indirectly, through stimulation of stretch-sensitive channels, increase cytosolic calcium. Thus, in relation to the underlying cellular mechanisms, there is a clear overlap between contractility (which should be independent of load or heart rate) and the effects of myocyte stretch and heart rate which have some effects that could be called an increased in contractility.

In clinical terms, it nonetheless remains important to separate the effects of a primary increase of load or heart rate on the one hand, from a primary increase in contractility on the other. This distinction is especially relevant in congestive heart failure, where a decreased contractility could indirectly or directly result in increased afterload, preload, and heart rate, all of which could then predispose to a further decrease in myocardial performance. Because muscle length can influence contractility, the traditional separation of length and inotropic state into two independent regulators of cardiac muscle performance is no longer valid if the end result is considered. However, it remains true that β-adrenergic stimulation has a calcium-dependent positive inotropic effect independent of loading conditions, which is therefore a true positive inotropic effect.

Cardiac Output

The *definition of the cardiac output* is the product of the stroke volume (SV) and the heart rate (HR):

$$\text{Cardiac output} = \text{SV} \times \text{HR} \left(\text{units} = \text{liters per minute}\right).$$

The normal value is about 6–8 L/min, doubling or sometimes even trebling during peak aerobic exercise. The stroke volume is determined by the preload, the afterload, and the contractile state. The heart rate is also one of the major determinants of the myocardial oxygen uptake. The heart rate responds to a large variety of stimuli, each of which thereby indirectly alters the myocardial oxygen uptake. The three physiological factors most consistently increasing heart rate are exercise, waking up in the morning, and emotional stress.

Heart Rate

Each cycle of contraction and relaxation performs a certain amount of work and takes up a certain amount of oxygen. The faster the heart rate, the higher the cardiac output and the higher the oxygen uptake. Exceptions are (1) when the heart rate is extremely fast, as may occur during a paroxysmal tachycardia, because an inadequate time for diastolic filling decreases the cardiac output and (2) in coronary artery disease when less degrees of tachycardia decrease the stroke volume because of ischemic failure of the left ventricle.

Force-frequency relation. An increased heart rate progressively increases the force of ventricular contraction even in an isolated papillary muscle preparation (*Bowditch staircase or treppe phenomenon*). In isolated human ventricular strips, increasing the stimulation rate from 60 to about 160 per min stimulates force development. In strips from failing hearts, there is no such increase [13]. In the human heart in situ, pacing rates of up to 150 per min can be tolerated, whereas higher rates cause AV block. Yet, during exercise, a maximal heart rate of 170 beats per min causes no block, presumably because of concurrent adrenergic stimulation of the AV node. Thus, an excessive heart rate decreases rather than increase cardiac contraction and cardiac output. *Tachycardia-induced cardiomyopathy* results from excessive prolonged tachycardia [14].

To explain the staircase during rapid stimulation, the proposal is that each wave of depolarization brings more sodium ions into the myocardial cells than can be ejected by the sodium pump. Sodium overload leads to an increase of cytosolic calcium by the sodium-calcium exchanger, with an increased force of contraction. Too rapid a rate of stimulation causes the force of contraction to decrease by limiting the duration of ventricular filling and probably by calcium overload.

Loading Conditions and Cardiac Output

In general, when the afterload decreases, the cardiac output increases. Physiological examples of this principle exist during peripheral vasodilation induced by a hot bath or sauna or by a meal. In these conditions, however, there is also an accompanying tachycardia, as during drug-induced vasodilation. Conversely, when the afterload increases, there is initially a compensatory mechanism, possibly acting by increased end-diastolic fiber stretch, to increase contractility (Fig. 3.5) and to maintain the stroke volume. If the afterload keeps rising, compensatory mechanisms cannot adapt, and eventually the stroke volume will fall. In exercise, although the peripheral vascular resistance decreases, systolic blood pressure rises, and the afterload increases. Thus, at really high rates of upright exercise, the stroke volume falls even though the cardiac output continues to rise, the latter as a result of heart rate increases [15]. In congestive heart failure with a failing left ventricle, the stage at which the stroke volume and hence the cardiac output starts to fall in response to the excess "compensatory" peripheral arteriolar constriction is much sooner than with the normal left ventricle.

Contractility and Cardiac Output

During β-adrenergic stimulation or exercise, the contractile state is enhanced to contribute to the increased cardiac output. Conversely, during congestive heart failure or therapy with β-adrenergic blockade, decreased contractility means a decreased stroke volume.

Effects of Exercise

During dynamic exercise the cardiac output can increase several fold (Fig. 3.8). There are three possible explanations: an increased heart rate, increased contractility, and an increased venous return. In humans, an increased heart rate provides most of the increased cardiac output, with the Starling mechanism and increased contractility playing lesser roles [15].

Tachycardia of Exercise

The mechanism of the increase in heart rate during exercise is a combination of withdrawal of inhibitory vagal tone and increased β-adrenergic stimulation. The signals for these changes come from the vasomotor center in the brainstem, which coordinates two types of input: one is from the cerebral cortex (e.g., the runner's "readiness to go" at the start of exercise), and the second is the Bainbridge reflex. The latter is stimulated by atrial distension, following the increased venous return during exercise. However, this is but a modest effect in humans. A tachycardia, from whatever cause, can further invoke a positive inotropic effect by the Bowditch (treppe) effect.

Venous Return During Exercise

Starling postulated (but did not measure) events at the start of exercise as follows: "If a man starts to run, his muscular movements pump more blood into the heart, so increasing the venous filling" [4]. Because the cardiac output must equal the venous return, the increase in cardiac output during exercise must reflect an equal increase in the venous return. This increase does not however necessarily prove the operation of the Starling mechanism, which requires an increased venous

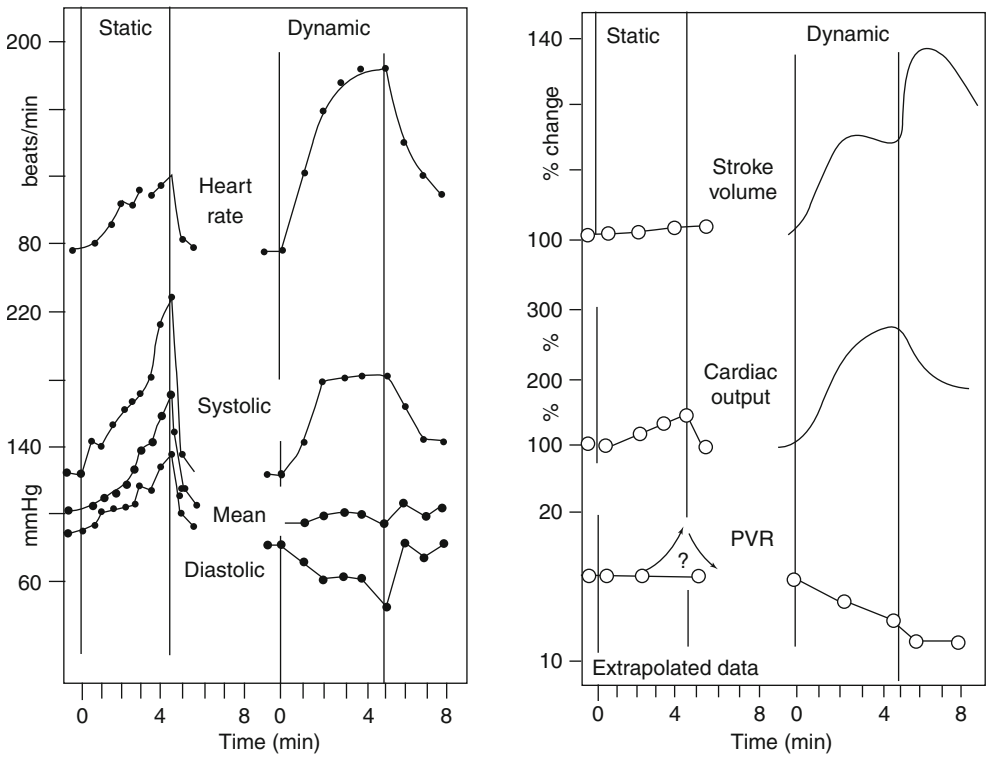

Fig. 3.8 Static versus dynamic exercise. Static exercise, at 30 % of maximum voluntary contraction (MCV), caused a much larger rise in mean blood pressure than did dynamic exercise, first at oxygen consumption values of 28.5 mL/kg/min and then at 43.8 mL/kg/min. Conversely, dynamic exercise increased heart rate much more (For original data, see Lind and McNicol [16]. Data on stroke volume are extrapolated from Flamm et al. [15]) Peripheral vascular resistance (*PVR*) for 0–2 min is based on [17] and for 2–4 min on [16], in which the blood pressure rises markedly at 2–4 min of static exercise even when the rise in heart rate has leveled off; therefore the PVR must have increased (Based on data from Lind and McNicol [16] and Waldrop et al. [17])

filling pressure. If there were an increased contractility from β-adrenergic stimulation during exercise, then the venous filling pressure could actually fall, despite the increase in the venous return. To be sure of the events at the start of exercise in humans would need simultaneous measurements of venous return, of the venous filling pressure, and of the heart volume. Such data are missing. Nonetheless, the combination of increased venous return and sympathetic stimulation can give extrapolated explanations.

An increased venous return and filling pressure could explain the increased diastolic heart volume during exercise, as found in radionuclide studies [18, 19]. Cardiac failure can be excluded, because the end-systolic volume decreases and the stroke volume increases. The Starling mechanism appears to operate in both supine and upright postures when low-level exercise is compared with rest [18]. This sequence is not inviolate and may be altered by posture [20], by exercise, training [21], and by increased contractility. Thus, the three major changes during exercise are, first, the increase in venous return which raises the venous filling pressure when comparing the initiation of exercise with rest; second, this increase usually but not invariably evokes a Starling response; and, third, sympathetic stimulation with an increased heart rate and contractility contributes variably but importantly. Once exercise has been initiated, the venous return must stay high and equal the cardiac output. The decrease in the systemic vascular resistance helps to keep the cardiac output and venous return high. The end result is that the increased venous return and increased cardiac output will have achieved a new and equally enhanced equilibrium.

Regarding static exercise, the major hemodynamic differences from dynamic exercise are (1) the lesser rise in heart rate, (2) the greater rise in blood pressure, and (3) the absence of increases in stroke volume and cardiac output (Fig. 3.8).

Wall Stress

Myocardial wall stress or *wall tension* increases when the myofilaments slide over each other during cardiac contraction as they are squeezing blood out of the ventricles into the circulation. An analogy is the human effort required to squeeze a ball in the palm of the hand. A small rubber ball can be compressed easily. A larger rubber ball (tennis ball in size) is compressed less readily, and two large rubber balls – or one really large ball – could be compressed only with the greatest difficulty. As the size of the object in the hand increases, so does the force required to compress it. Intuitively, the stress on the hand increases as the ball increases in diameter. However, what is wall stress?

At this point it is appropriate to deviate briefly into a description of force, tension, and wall stress. *Force* is a term frequently used in studies of muscle mechanics. Strictly,

$$\text{Force} = \text{mass} \times \text{acceleration}$$

Thus, when a load is suspended from one end of a muscle as the muscle contracts, it is exerting force against the mass of that load. In many cases, it is not possible to define force with such exactitude, but, in general, force has the following

properties. First, force is always applied by one object (such as muscle) on another object (such as a load). Second, force is characterized both by the direction in which it acts and its magnitude. Hence, it is a vector, and the effect of a combination of forces can be established by the principle of vectors. Third, each object exerts a force on the other, so that force and counterforce are equal and opposite (Newton's third law of motion).

Tension exists when the two forces are applied to an object so that the forces tend to pull the object apart. When a spring is pulled by a force, tension is exerted; when more force is applied, the spring stretches, and the tension increases.

Stress develops when tension is applied to a cross-sectional area, and the units are force per unit area. According to the *Laplace law*:

$$\text{Wall stress} = \frac{\text{pressure} \times \text{radius}}{2 \times \text{wall thickness}}$$

The increased wall thickness due to hypertrophy balances the increased pressure, and the wall stress remains unchanged during the phase of compensatory hypertrophy. In congestive heart failure, the heart dilates to increase the radius factor, thereby elevating wall stress. Furthermore, because ejection of blood is inadequate, the radius stays too large throughout the contractile cycle, and both end-diastolic and end-systolic tensions are higher.

Wall Stress and Myocardial Oxygen Demand

At a fixed heart rate, the myocardial wall stress is the major determinant of the myocardial oxygen uptake. Because myocardial oxygen uptake ultimately reflects the rate of mitochondrial metabolism and ATP production, any increase of ATP requirement will be reflected in an increased oxygen uptake. It is not only external work that determines the requirement for ATP. Rather, tension development (increased wall stress) is oxygen-requiring even without external work being done. The difference between external work and tension developed can be epitomized by the man standing and holding a heavy suitcase, doing no external work yet becoming very tired, compared with the man lifting a much lighter suitcase, doing external work yet not tired. The greater the left ventricular chamber size, the greater the radius, the greater the wall stress. Hence, ejection of the same stroke volume from a large left ventricle against the same blood pressure will produce as much external work as ejection of the same stroke volume by a normal size left ventricle, yet with a much greater wall stress in the case of the larger ventricle. Therefore, more oxygen will be required. In clinical terms, heart size is an important determinant of myocardial oxygen uptake, and in a patient with angina, a large left ventricle, the appropriate therapy to reduce left ventricular size will also reduce the myocardial oxygen demand.

The overall concept of wall stress includes afterload because an increased afterload generates an increased systolic wall stress. Wall stress also includes preload, which generates diastolic wall stress. Wall stress increases in proportion to the pressure generated and to the radius of the left ventricular cavity, factors that are responsive to increases in afterload and preload, respectively. Wall stress allows for energy required for generation of muscular contraction that does not result in external work. Furthermore, in states of enhanced contractility, wall stress is increased. Thus, thinking in terms of wall stress provides a comprehensive approach to the problem of myocardial oxygen uptake. Apart from a metabolic component usually small but which may be prominent in certain special circumstances, such as when circulating free fatty acids are abnormally high, changes in heart rate and wall stress account for most of the clinically relevant changes in myocardial oxygen uptake.

External Versus Internal Work and Oxygen Demand

Bearing in mind that the major factor in cardiac work is the product of pressure and volume, it follows that external work can be quantified by the integrated pressure-volume area that represents the product of the systolic pressure and the stroke volume. To relate work to the oxygen consumption, account must be taken of both the external work (a–d in Fig. 3.2) and *internal work*, which is the volume-pressure triangle joining the end-systolic volume-pressure point to the origin (c–d). The latter is more correctly called the *potential energy*, being the work generated in each contractile cycle that is into converted to external work.

Pressure Versus Volume Work and Oxygen Demand

In analyzing the difference between oxygen cost of pressure work and volume work, the established clinical observation is that the myocardium can tolerate a chronic volume load better than a pressure load. Thus, when cardiac work is chronically increased by augmenting the afterload, as during severe hypertension or narrowing of the aortic valve by aortic stenosis, the peak systolic pressure in the left ventricle must increase, and pressure power increases. However, because of the complex way in which the muscle fibers of the myocardium run, a greater proportion of the work is against the internal resistance. The result is that the efficiency falls. An extreme example of the loss of efficiency during pressure work would be if the aorta were completely occluded, so that none of the work would be external and all would be internal.

Internal work is done against the noncontractile elements of the myocardium and is not useful work in terms of calculating efficiency.

When the heart is subject to a chronic volume load as in mitral regurgitation, the increased work that the heart must perform is met by an increased end-diastolic volume. The myofibers stretch, and length-dependent activation occurs. The primary adaptation to increased heart volume is an increased fiber length and not increased pressure development, so that the amount of external work done is more, but that against the internal resistance is unchanged so that the efficiency of work rises. (The efficiency of work relates the amount of work performed to the myocardial oxygen uptake.)

Left Ventricular Function

Maximal Rate of Left Ventricular Pressure Generation

In relation to the cardiac contraction-relaxation cycle, it is easiest to consider left ventricular function during the early period of isovolumic contraction. During this period of isovolumic contraction, the preload and afterload are constant, and the maximal rate of pressure generation should be an index of the inotropic state:

$$\text{inotropic index} = dP / dt \max$$

where P is left ventricular pressure, t is time, and d indicates rate of change. Unfortunately, this index that has stood the test of years is not fully load independent – as Frank showed (Fig. 3.5), increasing the preload enhances the contractile state by length activation.

In humans, the measurements required for dP/dt can be obtained only by left ventricular catheterization, except in mitral regurgitation when Doppler echocardiography can measure changes in the LV-atrial pressure gradient. Bearing in mind that left ventricular pressure is changing during the period of isovolumic contraction, some workers prefer to make a correction for the change in pressure by dividing dP/dt by a fixed developed pressure, for example, $dP/dt(DP_{40})$ or by the pressure at the instant of the maximal rate of pressure development, $(dP/dt)/P$. Such corrections add little except complexity.

Ejection Phase Indices of Contractile State

During the ejection phase, the left ventricle contracts against the afterload. Hence, all indices of function in this period are afterload-dependent, a problem which is especially serious in the case of the failing myocardium which is adversely affected by afterload increases [22]. The initial fiber length helps to determine contractility which in turn influences the afterload, because a greater contractile state in the presence of a fixed peripheral (systemic) vascular resistance will increase the blood pressure and the afterload.

The *ejection fraction* of the left ventricle, measured by radionuclide or echocardiographic techniques, is one of the most frequently used indices and one of the least sensitive. The ejection fraction relates stroke volume to end-diastolic volume and is, therefore, an index of the extent of left ventricular fiber shortening. Nonetheless, this index is easy to obtain and particularly useful in evaluating the course of chronic heart disease. Because the ejection fraction measures the contractile behavior of the heart during systole, it is by definition afterload-sensitive. Another defect is that the ejection fraction relates the systolic emptying to the diastolic volume without measuring that volume, and the left ventricle could theoretically be markedly enlarged yet have reasonable systolic function by this measure. Thus, the correlation between the degree of clinical heart failure and the decrease in the ejection fraction is often only imperfect.

Echocardiographic Indices of Contractile State

The major advantage of echocardiographic indices is that the techniques are widely available and relatively rapid. The *fractional shortening* uses the percentage of change of the minor axis (defined in the next paragraph) of the left ventricular chamber during systole. An approximation often used by clinicians is to estimate the ejection fraction from *fractional shortening*. Despite obvious defects, this easily defined index is pragmatically useful in the management of heart failure. More accurately, ejection fraction can be determined from volume measurements.

The *end-systolic volume* reflects contractile state because the normal left ventricle ejects most of the blood present at the end of diastole (ejection fraction exceeds 50 %). Impaired contractility, shown by an abnormally increased end-systolic volume, is a powerful predictor of adverse prognosis after myocardial infarction [23]. The *end-diastolic volume* is a less powerful predictor but essential for the accurate measurement of the ejection fraction.

Increasingly sophisticated and noninvasive measurements of the pumping function of the heart can be obtained with echocardiographic techniques. The velocity at which the circumference of the heart in its minor axis (the distance from the left side of the septum to the posterior endocardial wall) changes during systole is one useful index of myocardial contractility. The mean *velocity of circumferential fiber shortening* (mean V_{cf}) can be determined from echocardiographic measurements of the end-diastolic and end-systolic sizes and the rate of change. The difference between the

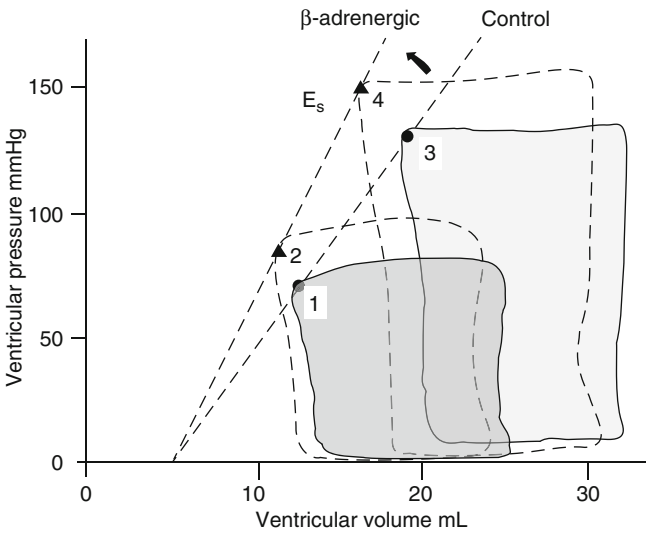

Fig. 3.9 β-adrenergic versus volume effects on pressure-volume (PV) loops. Contrasting effects of β-adrenergic stimulation and effects of volume loading on the slope E_s (end-systolic point), which is a good index of contractility. Upon β-adrenergic stimulation, the control loop with its end-systolic point number *1* becomes the loop with point number *2*. Likewise, the volume-loaded loop with point number *3* becomes the loop with point number *4* upon β-adrenergic stimulation. The mechanism of the volume response probably involves stretch of the molecular spring, titin [9]. Note that β-adrenergic stimulation induces a marked positive inotropic effect (increased contractility) as shown by the increased slope of the line E_s that joins the end-systolic points. By contrast, the effects of increased ventricular volume with increased PV loop area and increased external work occur with no early change in contractility as here, and with only a small delayed increase in contractility (Figs. 3.3, 3.4, 3.5, and 3.6) (Based on data from Suga et al. [10])

calculated circumferences is divided by the duration of shortening, which is the ejection time. Even more sophisticated are the data now being generated by *tissue Doppler imaging*. This technique records high-amplitude, low-frequency Doppler shifts, from which the endocardial velocity of systolic change can be calculated. This measure is currently one of the best indices of contractility of the human heart in situ.

Contractility Indices Based on Pressure-Volume Loops

There are two fundamental aspects of the Frank-Starling relationship that can be seen readily in a pressure-volume loop. First, as the preload increases, the volume increases. On the other hand, for any given preload (initial volume of contraction), a positive inotropic agent increases the amount of blood ejected, and for the same final end-systolic pressure, there is a smaller end-systolic volume. Thus, the slope of the end-systolic pressure-volume relationship is increased (Fig. 3.9). It follows that relating pressure to volume is one way of assessing both the Starling effect and the contractility of the left ventricle.

Accordingly, *measurements of pressure-volume loops remain among the best of the current approaches to the assessment of the contractile behavior of the intact heart*, and hence the key to one of the major determinants of the myocardial oxygen demand. The end-systolic pressure-volume relation can be estimated noninvasively from the arterial systolic pressure and the end-systolic echocardiographic dimension. Invasive measurements of the left ventricular pressure are required for the full loop, which is an indirect measure of the Starling relationship between the force (as measured by the pressure) and the muscle length (measured indirectly by the volume). It is proposed that conditions associated with a higher contractile activity (increased inotropic state) will have higher end-systolic pressures for a given end-systolic volume, will have a steeper slope E_s, and have correspondingly higher oxygen uptakes. Although useful, like all systolic phase indices, it is still not fully afterload independent.

Diastole and Diastolic Function

Among the many complex cellular factors influencing ventricular relaxation, four are of chief interest. First, the cytosolic calcium level must fall to cause the relaxation phase, a process requiring ATP and phosphorylation of phospholamban for uptake of calcium into the sarcoplasmic reticulum. Second, the inherent viscoelastic properties of the myocardium are of importance. In the hypertrophied heart, relaxation occurs more slowly. Third, increased phosphorylation of troponin-I enhances the rate of relaxation. Fourth, relaxation is influenced by the systolic load. The history of contraction affects crossbridge relaxation. Within limits, the greater the systolic load, the faster the rate of relaxation. This complex relationship has been explored in detail by Brutsaert [3] but could perhaps be simplified as follows. When the workload is high, peak cytosolic calcium is also thought to be high. This high end-systolic cytosolic calcium means that the rate of fall of calcium will also be greater, provided that the uptake mechanisms are functioning effectively. In this way a systolic pressure load and the rate of diastolic relaxation can be related. Furthermore, a greater muscle length (when the workload is high) at the end of systole should produce a more rapid rate of relaxation by the opposite of length-dependent sensitization, so that there is a more marked response to the rate of decline of calcium in early diastole. Yet, when the systolic load exceeds a certain limit, then the rate of relaxation is delayed, perhaps because of too great a mechanical stress on the individual crossbridges. Thus, in congestive heart failure caused by an excess systolic load, relaxation becomes increasingly afterload-dependent, so that therapeutic reduction of the systolic load should improve LV relaxation.

The *isovolumic relaxation* phase of the cardiac cycle is energy-dependent, requiring ATP for the uptake of calcium ions by the SR, which is an active, not a passive process. Impaired relaxation is an early event in angina pectoris. A proposed metabolic explanation is that there is impaired generation of energy, which diminishes the supply of ATP required for the early diastolic uptake of calcium by the sarcoplasmic reticulum. The result is that the cytosolic calcium level, at a peak in systole, delays its return to normal in the early diastolic period. In other conditions, too, there is a relationship between the rate of diastolic decay of the calcium transient and diastolic relaxation, with a relation to impaired function of the sarcoplasmic reticulum. When the rate of relaxation is prolonged by hypothyroidism, the rate of return of the systolic calcium elevation is likewise delayed, whereas opposite changes occur in hyperthyroidism. In congestive heart failure, diastolic relaxation also is delayed and irregular, as is the rate of decay of the cytosolic calcium elevation. Most patients with coronary artery disease have a variety of abnormalities of diastolic filling, probably related to those also found in angina pectoris. Theoretically, such abnormalities of relaxation are potentially reversible because they depend on changes in patterns of calcium ion movement.

Phases of Diastole

Hemodynamically, diastole can be divided into four phases, using the clinical definitions of diastole according to which diastole extends from aortic valve closure to the start of the first heart sound. The first phase of diastole (see preceding section) is the isovolumic phase, which, by definition, does not contribute to ventricular filling (Fig. 3.10). The second phase of early (rapid) filling provides most of ventricular filling. The third phase of slow filling or diastasis accounts for only 5 % of the total filling. The final atrial booster phase accounts for the remaining 15 %.

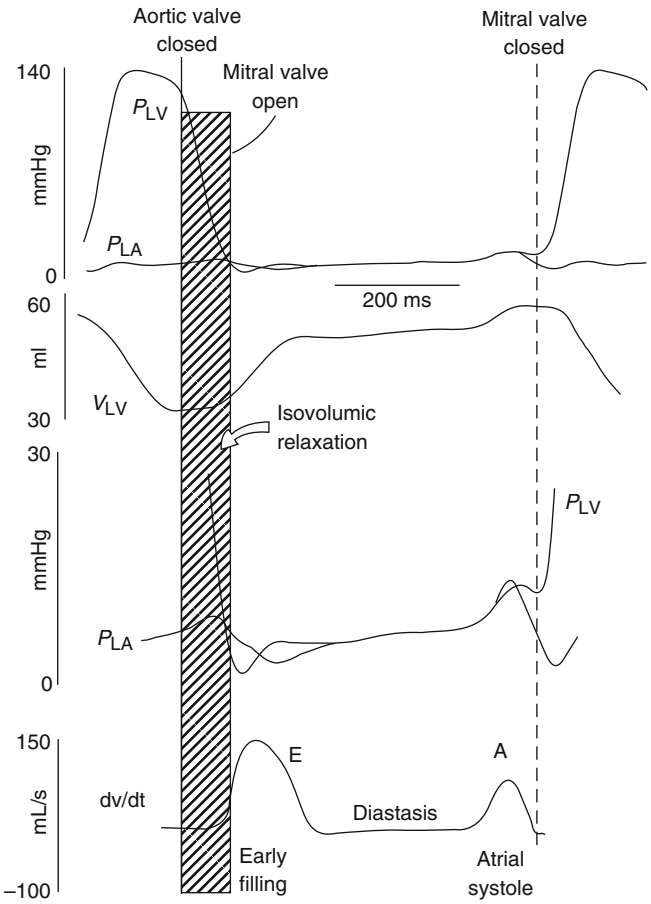

Fig. 3.10 Diastolic filling phases. *Top panel*, recording of left ventricular pressure (P_{LV}), left atrial pressure (P_{LA}), and left ventricular volume (V_{LV}). *Middle panel*, magnified scale of changes in P_{LV} and P_{LA}. *Lower panel*, rate of change of LV volume (d*V*/d*t*), an indication of the rate of left ventricular filling which occurs early in diastole and then again during atrial systole in response to pressure gradient from the left atrium to the left ventricle. In between is the phase of slow filling or diastasis. The early diastolic pressure gradient shown in the middle panel is generated as LV pressure falls below left atrial pressure and the late diastolic gradient is generated as atrial contraction increases left atrial pressure above LV pressure (Based on Cheng et al. [24])

Atrial Function

The left atrium, besides its well-known function as a blood-receiving chamber, also acts as follows. First, by presystolic contraction and its booster function, it helps to complete LV filling [25]. Second, it is the volume sensor of the heart, releasing atrial natriuretic peptide (ANP) in response to intermittent stretch. Third, the atrium contains receptors for the afferent arms of various reflexes including mechanoreceptors that increase sinus discharge rate, thereby making in humans only a small contribution to the tachycardia of exercise as the venous return increases (*Bainbridge reflex*).

The atria have a number of differences in structure and function from the ventricles, having smaller myocytes with a shorter action potential duration as well as a more fetal type of myosin (both in heavy and light chains). Furthermore, the atria are more reliant on the phosphatidylinositol signal transduction pathway, which may explain the relatively greater positive inotropic effect in the atria than in the ventricles in response to angiotensin-II. The more rapid atrial repolarization is thought to be due to increased outward potassium currents, such as I_{to} and I_{kACh}. In addition, some atrial cells have the capacity for spontaneous depolarization. In general, these histologic and physiologic changes can be related to the decreased need for the atria to generate high intra-chamber pressures, rather being sensitive to volume changes, while retaining enough contractile action to help with LV filling and to respond to inotropic stimuli. In *myocardial failure*, multiple abnormalities can be detected in the

transmitral flow pattern, including an early change in the E/A ratio. It must be stressed that the E/A ratio changes considerably as the LV failure progressively becomes more severe with late phase "pseudonormalization."

Compliance

The diastolic volume of the heart is influenced both by the loading conditions and by the elastic properties of the myocardium that confer on it the stiffness that develops in response to stretch. In clinical practice, *stiffness* is taken as the ratio of d*P*/d*V*, that is, the rate of pressure change divided by the rate of volume change. This relation is curvilinear, and the initial slope of the change is gentle. As the pressure increases, the volume increases less and less so that there is a considerable increase of pressure for only a small increase of volume. Resting *stiffness* may in part be attributed to the unique myocardial collagen network, thought to counter the high systolic pressure normally developed in the ventricles. Pathological loss of compliance is usually due to abnormalities of the myocardium. A true loss of muscular compliance occurs from a variety of causes – acute ischemia as in angina, fibrosis as after myocardial infarction, and infiltrations causing a restrictive cardiomyopathy. In angina, the increased temporary stiffness probably is caused by a combination of a rise of intracellular calcium and of altered myocardial properties. In myocardial infarction, the connective tissue undergoes changes after 40 min of occlusion. Eventually healing and fibrosis permanently increase stiffness. When muscle stiffness increases, so will *chamber stiffness* (the chamber referred to is the ventricle).

The opposite of stiffness is *compliance* (d*V*/d*P*) – as the heart stiffens, compliance falls. The term *diastolic distensibility* may be used in preference to compliance. Distensibility refers not to the slope of the pressure-volume relation but to the diastolic pressure required to fill the ventricle to the same volume. Thus, when stiffness increases and compliance falls, the distensibility is less, as in the failing human heart. The compliance of the heart influences the Starling curve in that a stiffer heart will be on a lower Starling curve. The pressure-volume loop and the early diastolic filling rate of the heart will also change, while the baseline of the pressure-volume loop will rise upward more steeply, so that a higher left atrial pressure will be required for early diastolic filling. For these reasons, stiffness and compliance are fundamental mechanical properties of the heart.

Contractile Properties in Human Heart Disease

The *failing human myocardium* has impaired contractile properties so that even when the venous filling pressure is adequate, the stroke volume is reduced when compared with normal, and the blood pressure tends to fall. An increased heart rate provides some compensation to help maintain the cardiac output and, thereby, the blood pressure. Nonetheless, the tachycardia fails to elicit the normal positive inotropic response (absence of treppe phenomenon). Furthermore internal work (potential energy component of the loop) is increased relative to external work so that there is decreased efficiency of work. It is controversial whether or not there is truly a defective Frank-Starling response or whether apparent defects can be explained by the decreased distensibility. Other defects include impaired generation of cyclic adenosine monophosphate (AMP) in response to β-adrenergic stimulation, and numerous defects of the patterns of handling of intracellular calcium. In response to an increased afterload, the intracellular calcium transients of cells from the severely failing human heart show a diminished systolic rise of calcium and delayed diastolic fall of calcium, which may help to explain defective contraction and relaxation patterns.

In aortic stenosis, kinetic work increases sharply as the cross-sectional area narrows, whereas pressure work increases as the gradient across the aortic valve rises. Both changes increase the myocardial oxygen demand even beyond the demands of the hypertrophied myocardium. In aortic regurgitation, heart work and oxygen demand is increased by the increased wall stress resulting from the greater ventricular volume (Chap. 16) and by an increased afterload resulting from the higher systolic pressure.

Diastolic Dysfunction and Heart Failure

In clinical terms, systolic heart failure is relatively well understood with clear concepts of therapy. Diastolic heart failure, although as frequent as systolic failure, remains poorly defined and without clear therapy. This is a syndrome with signs/symptoms of heart failure which in addition has echocardiographic evidence of LV diastolic dysfunction [25]. The clinical clue is heart failure accompanied by preserved rather than decreased ejection fraction (HF-Preserved EF, or HF-pEF), equal to or more than 50 %. There are no accepted mechanistic explanations. Those proposed include LV hypertrophy with increased muscle stiffness (as for example from fibrosis) with greater sensitivity to volume overload or LV remodeling and dilation with volume-dependent increased LV filling pressures [26]. In hypertension with HF-Preserved EF, as in the elderly, diastolic dysfunction and is one of the most common associated diseases. In elderly dogs with stiff LVs and poor diastolic filling on the basis of experimental hypertension, diastolic distensibility is improved by cyclic GMP enhancing treatment with sildenafil that acts at least in part by phosphorylating I-titin [27].

In *hypertrophic hearts without clinical HF*, as in chronic hypertension or severe aortic stenosis, abnormalities of

diastole are common. Conceptually, this situation may precede diastolic heart failure [25]. Experimentally, there are several defects including decreased rates of contraction and relaxation, and decreased peak force development. Loss of the load-sensitive component of relaxation may be due to impaired activity of the sarcoplasmic reticulum. Impaired relaxation is associated with an increase of the late (atrial) filling phase, so that E/A ratio on the mitral Doppler pattern declines. In time, with both increased hypertrophy and the development of fibrosis, LV chamber compliance decreases and the E wave again becomes more prominent. Thus, this becomes difficult to separate truly normal from *pseudonormal patterns of mitral inflow*.

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Vascular Function

4

Rhian M. Touyz, Augusto C. Montezano,
and Clive Rosendorff

Introduction

Vessels are composed of an outer adventitia consisting of fibroblasts, adipocytes and extracellular matrix, a medial layer of contractile smooth muscle cells, and an intima lined by endothelial cells. The vessel wall has traditionally been considered a relatively static structure that has as its main function contraction. However, the vasculature is a highly dynamic system that is continually adapting to local mechanical, hemodynamic, chemical, neurohumoral, and hormonal changes [1]. Fundamental to these changes are vascular smooth muscle cells, which have a significant degree of phenotypic variability [2]. Since the primary function of vascular smooth muscle cells is contraction, the "contractile phenotype" is defined as the differentiated phenotype. However, vascular smooth muscle cells also have many noncontractile functions. The "noncontractile" phenotypes include proliferative, migratory, synthetic, proinflammatory, and secretory.

In the aorta and large arteries, vascular smooth muscle contraction affects primarily compliance (the reciprocal of stiffness) of the vessel. Small arteries, with lumen diameter less than 300 μm, are responsible for the regional distribution of blood flow and blood pressure regulation, through effects on vascular resistance. The lumen diameter of resistance arteries is a function of vasomotor tone (contraction and relaxation) and structural characteristics of the vessel wall. Vasomotor regulation contributes to acute adaptation of vessel diameter, due to vasoconstriction, whereas structural modifications occur in response to chronic hemodynamic stimuli [3]. Initially, structural changes are adaptive but chronically may become maladaptive, resulting in changes in media thickness and lumen diameter, leading to vascular remodeling [4, 5]. Compliance of large vessels and resistance of small arteries contribute most of the impedance of the vascular circuit and therefore the afterload of the heart. The capacity of the circulation is determined by the degree of contraction of the veins ("capacitance vessels") especially in the splanchnic area; this will affect the venous filling pressure, or preload, of the heart.

Acute regulation of vascular diameter involves activation/deactivation of the contractile machinery, specifically actin–myosin interaction, in vascular smooth muscle cells [6]. Changes in membrane potential, transmembrane ion fluxes, and the intracellular calcium concentration influence calcium–calmodulin-mediated phosphorylation of the regulatory myosin light chains and actin–myosin cross-bridge cycling with consequent vascular smooth muscle cell contraction (Fig. 4.1) [6, 7]. Calcium-independent processes involving RhoA–Rho kinase also influence vasoconstriction. In addition to changes in vascular contractility, lumen diameter is influenced by structural characteristics of the vessel wall. Molecular and cellular processes impacting on vascular structure are cytoskeletal organization, cell-to-cell connections, microRNA, cell growth/apoptosis, fibrosis, inflammation, calcification, and extracellular matrix composition [8]. The present chapter focuses on mechanisms regulating vascular function (contraction/dilation) and discusses some processes contributing to vascular structural changes (remodeling) associated with vascular diseases.

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_4, © Springer Science+Business Media New York 2013

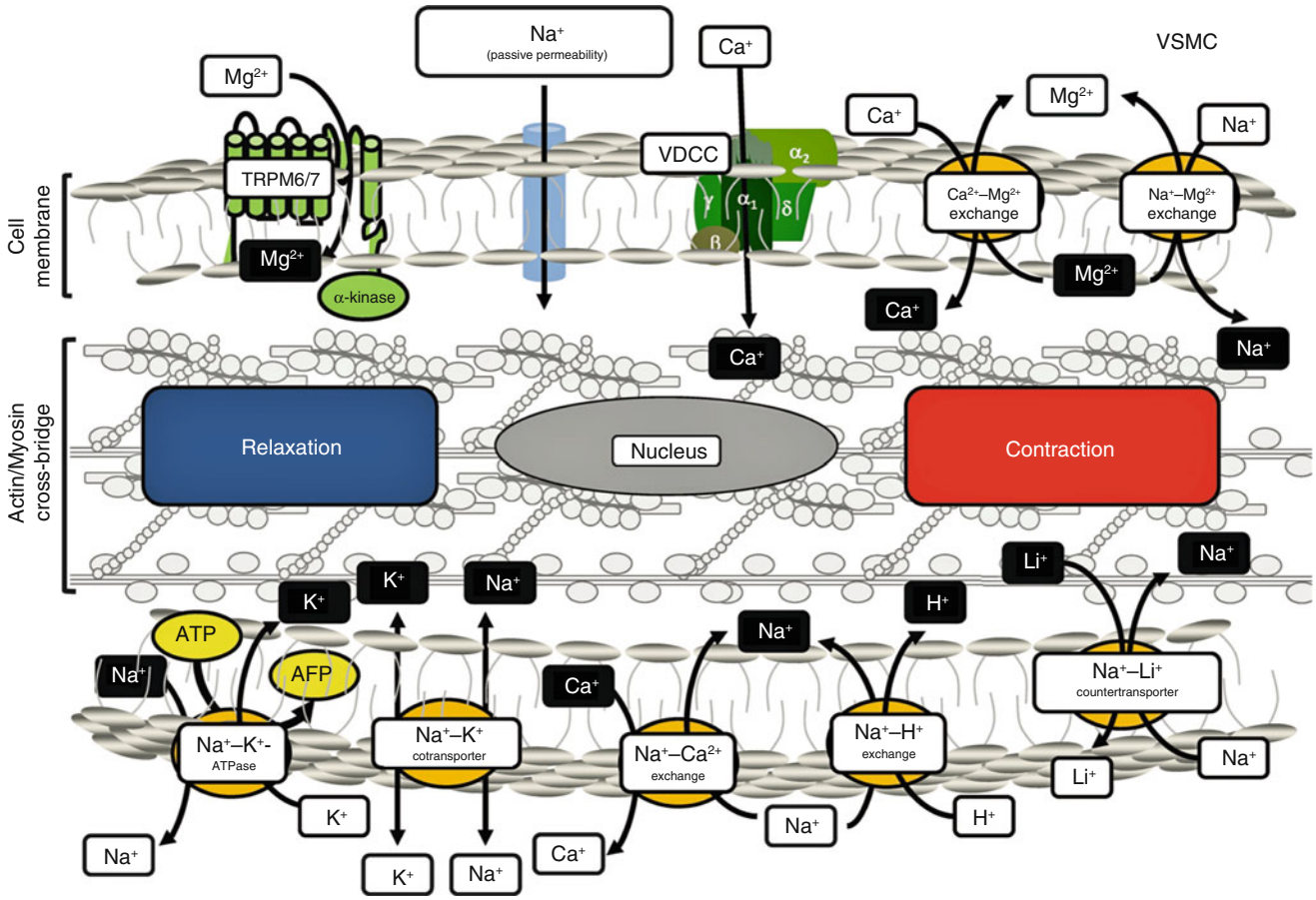

Fig. 4.1 Ion transport in the plasma membrane of VSMCs. Calcium, sodium, potassium, and magnesium intracellular levels are modulated by passive (cell membrane permeability) and active mechanisms, involving activation of channels, transporters, exchanges, and pumps. Differences in intracellular levels of these ions or stimulation by agonists regulate the activity of each process, leading to vascular responses such as vascular relaxation or contraction. Abbreviations: *Mg^{2+}* magnesium, *Ca^{2+}* calcium, *Na^{+}* sodium, *K^{+}* potassium, *Li^{+}* lithium, *TRPM6/7* transient receptor potential melastatin cation channel, subfamily M, member 6/7, *VDCC* voltage-dependent calcium channel, *ATP* adenosine triphosphate, *ADP* adenosine diphosphate

Vascular Contraction

Vascular Smooth Muscle Cells: Contractile Versus Noncontractile Phenotype

The major factor regulating vascular tone is vascular smooth muscle cell contraction, triggered by an increase in intracellular free calcium concentration ($[Ca^{2+}]_i$) in response to agonist or mechanical stimulation [6, 9] (Fig. 4.2). Normally, in adults, vascular smooth muscle cells maintain their contractile phenotype, although they have the potential to differentiate into a "noncontractile" form as an adaptive response to changes in the local environment or in response to injury, atherosclerosis, hypertension, aneurysms, diabetes, angiogenesis, and kidney disease. However, mechanisms underlying the shift from a contractile to a noncontractile phenotype still remain elusive.

Pathways regulating Ca^{2+} entry differ between contractile and noncontractile vascular smooth muscle cells. In contractile vascular smooth muscle cells, Ca^{2+} enters the cell mainly via voltage-gated L-type calcium channels (LTCC); Ca^{2+} entry in noncontractile vascular smooth muscle cells is through store-operated Ca^{2+} entry (SOCE) and receptor-operated Ca^{2+} entry (ROCE) pathways [9–11]. This shift from voltage-sensitive to voltage-insensitive Ca^{2+} entry influences the dynamics of intracellular Ca^{2+}. Typically, contractile cells are associated with transient increases in $[Ca^{2+}]_i$, whereas in noncontractile vascular smooth muscle cells, there is a sustained elevation of basal $[Ca^{2+}]_i$. As the contractile phenotype differentiates into a noncontractile form, expression of LTCCs and other Ca^{2+} regulators, such as sarco/endoplasmic reticulum Ca^{2+}ATPase (SERCA), ryanodine receptor type 2 (RYR2), plasma membrane Ca^{2+} pump 1 (PMCA1), and Na+/Ca^{2+} exchanger, is reduced [11, 12]. Downregulation of these proteins is accompanied by upregulation of other Ca^{2+} handling proteins, including SOCE, ROCE, stromal interaction molecule 1 (STIM1), sarcoplasmic reticulum

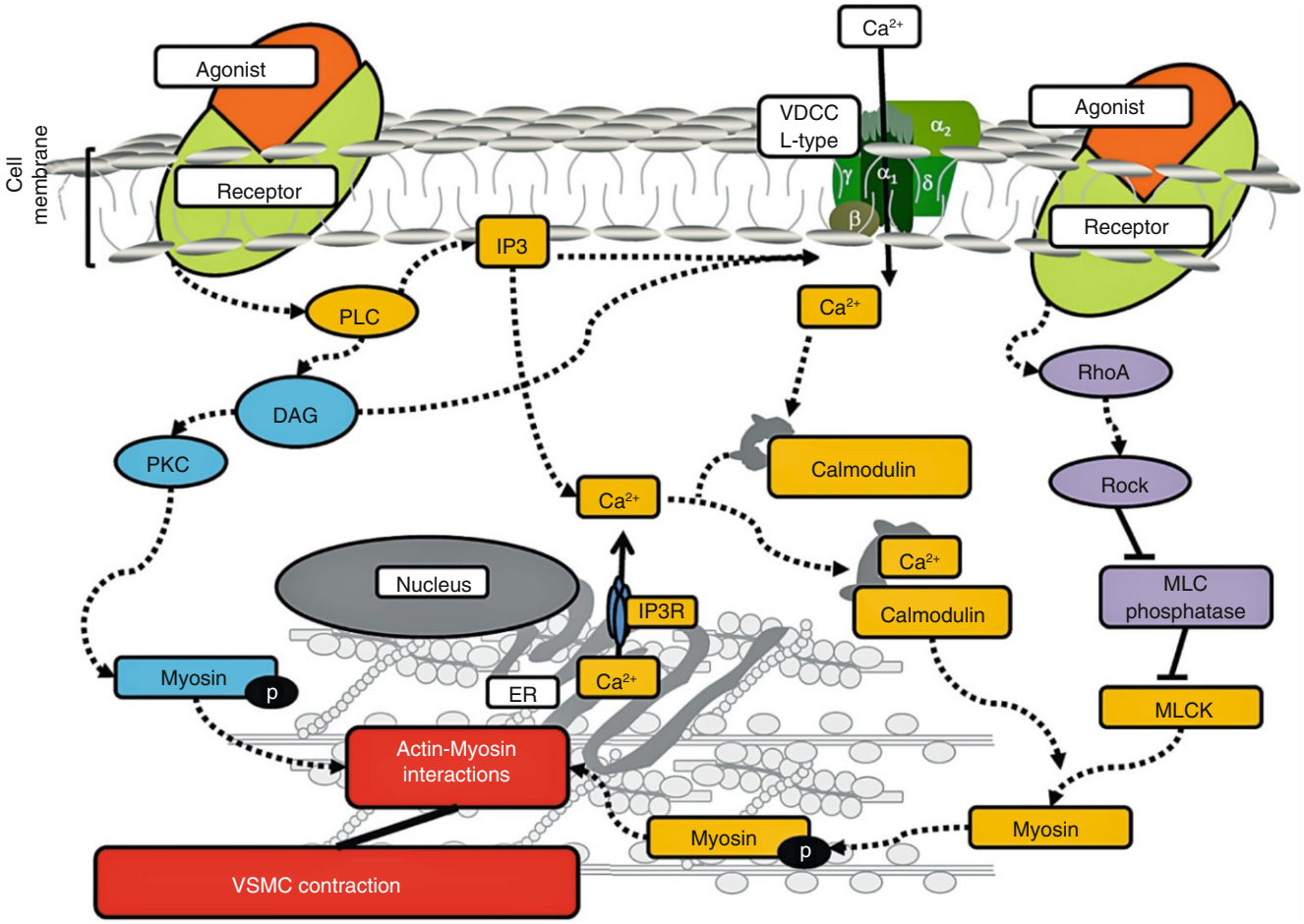

Fig. 4.2 VSMCs signaling and contraction. Vascular contraction is mediated by a series of different stimuli such as mechanical stretch and agonists. As depicted in the figure, an agonist can induce vascular contraction through activation of mechanisms that will increase intracellular calcium, leading to activation of calcium-dependent mechanisms that increase the interactions between actin and myosin filaments. Such mechanisms are the following: (1) activation of PLC and IP3, leading to release of calcium from intracellular storages (ER) and increased interaction of calcium and calmodulin, which in turn will increase phosphorylation of myosin light chain by MLC kinase, inducing VSMC contraction; (2) activation of DAG, which in addition to increase intracellular levels of calcium by activation of calcium channels, will activate PKC, leading to direct phosphorylation of myosin light chain; and finally (3) an agonist can induce activation of RhoA and its downstream signaling, RhoK, leading to inhibition of MLC phosphatase, a protein that dephosphorylates MLC. Abbreviations: *PLC* phospholipase C, *IP3* inositol-3-phosphate, *IP3R* inositol-3-phosphate receptor, *ER* endoplasmic reticulum, *DAG* diacylglycerol, *PKC* protein kinase C, *RhoA* Ras homolog gene family, member A, *Rock* Rho kinase, *MLC* myosin light chain, *MLCK* myosin light chain kinase

Ca^{2+} sensor and Ca^{2+} release-activated Ca^{2+} channel protein 1 (Orai1), inositol trisphosphate (IP_3) receptors, and C-type transient receptor potential channels [10].

Vascular Contraction: Molecular Mechanisms

The major events in vascular smooth muscle contraction [1–6, 13, 14] are shown in Figs. 4.2 and 4.3. The function of vascular smooth muscle cells is tightly regulated by the activity of neurotransmitters and hormones that mediate effects via guanine nucleotide-binding protein-coupled receptors (GPCR) [15]. G proteins function as ubiquitous signal transducers and regulators of intracellular signaling [16]. Increased GPCR activation is associated with hypertension and increased risk of cardiovascular disease and, accordingly, is an attractive target for therapy. In fact, most of the effective drugs used in cardiovascular medicine exert effects by blocking G-protein signaling.

G proteins transfer signals from membrane-bound GPCR to intracellular effectors, including adenyl cyclase, phospholipase C, ion channels, and NADPH oxidases. G proteins consist of three subunits: Gα, Gβ, and Gγ [16–18]. Under basal conditions, Gβ and Gγ subunits are tightly associated and form a Gβγ complex. Gα comprises a family of subunits, including $G_{q/11}$, G_s, $G_{i/0}$, and $G_{12/13}$. G proteins are activated when Gα subunits bind and hydrolyze GTP. Some of the most important GPCR vasoconstrictor pathways are

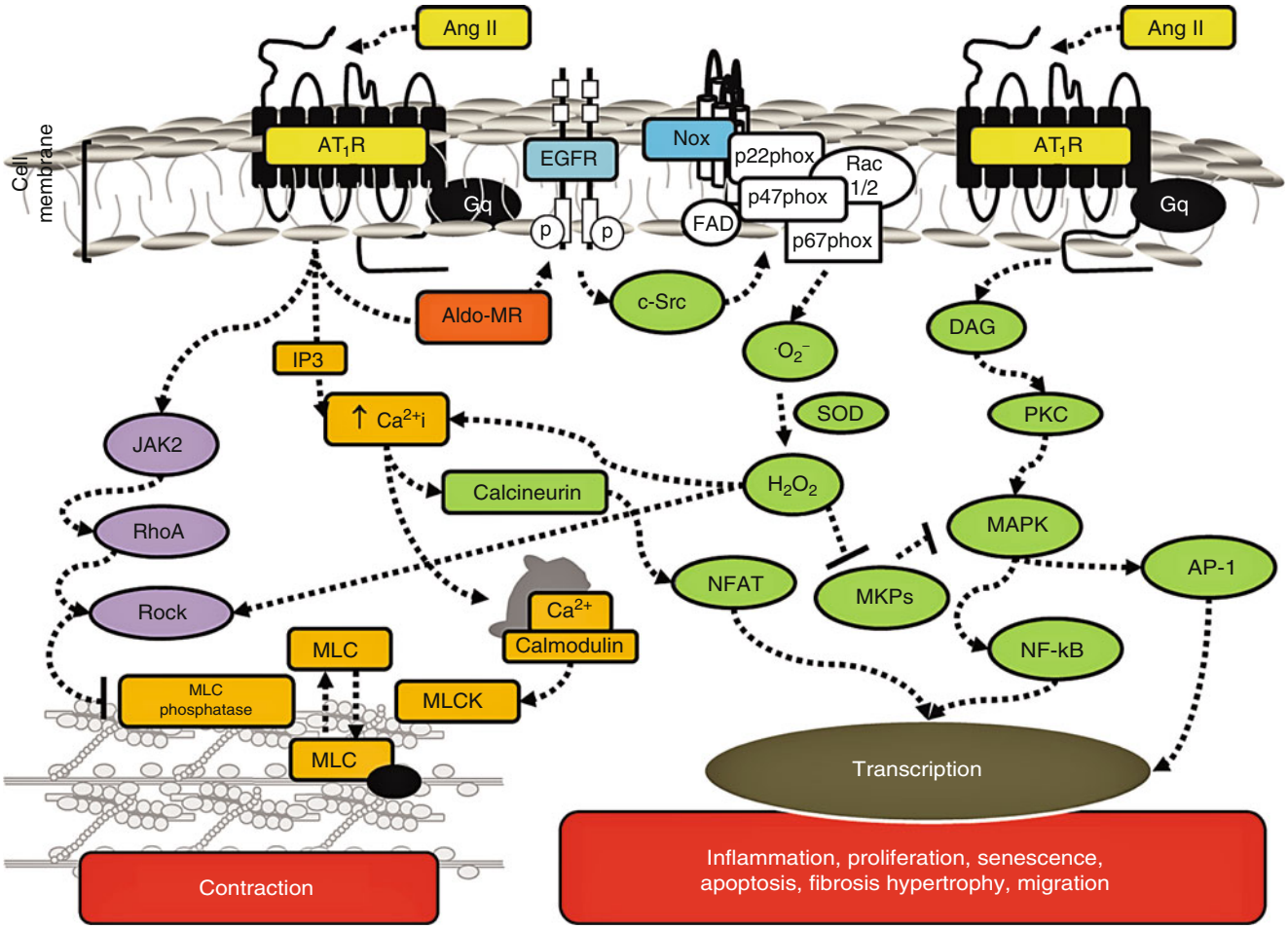

Fig. 4.3 Ang II-induced signaling in VSMCs. Ang II, through activation of AT1 receptors, induces contraction, inflammation, proliferation, senescence, apoptosis, fibrosis, hypertrophy, and increased VSMC migration. Ang II-induced contraction is mediated by activation of calcium-dependent signaling (described in Fig. 4.2) and Jak2–RhoA–Rock signaling. Other vascular actions of Ang II are mediated through activation of transcription factors and increased expression of proinflammatory transcription factors. There are many pathways involved in these actions, such as the following: (1) Ang II induces calcium-dependent activation of the calcineurin–NFAT pathway, leading to inflammation, growth, and hypertrophy; (2) Ang II, through transactivation of EGFR and phosphorylation of c-Src, induces Nox-derived ROS generation, which in turn will inactivate MKPs and increase phosphorylation of MAPKs and transcription factors such as NF-κB and AP-1; and (3) Ang II induces transcription by activation of DAG–PKC–MAPKs pathway. It is important to note that many of these processes, induced by Ang II, are also mediated by cross talk with aldosterone. Abbreviations: *AT1R* Ang II type I receptor, *JAK2* Janus kinase 2, *EGFR* epidermal growth factor receptor, *Nox* NADPH oxidase, *ROS* reactive oxygen species, *c-Src* protooncogenic tyrosine protein kinase Src, *NFAT* nuclear factor of activated T cells, *SOD* superoxide dismutase, *MKP* MAP kinase phosphatase, *MAPK* mitogen-activated protein kinase, *NF-κB* nuclear factor kappa B, *AP-1* activator protein-1

norepinephrine signaling via the α_1-adrenergic receptor, angiotensin II (Ang II) signaling via the AT_1 receptors, and endothelin-1 signaling via ET_A receptors [19–21]. Signaling through these receptors occurs primarily through $G_{q/11}$ and is important in the regulation of peripheral vascular tone and blood pressure. Ligand binding to GPCRs induces activation of PLCβ which converts the membrane lipid phosphatidylinositol 4,5-bisphosphate (PIP_2) into two important second messenger molecules inositol 1,4,5-trisphosphate (IP_3) and 1,2-diacylglycerol (DAG) [22]. The binding of IP_3 to its specific receptors (IP_3R) on the sarcoplasmic reticulum (SR) results in the release of Ca^{2+} from the SR, leading to increased $[Ca^{2+}]_i$ and formation of Ca^{2+}–calmodulin/MLCK-dependent activation of the contractile machinery. The second messenger, DAG, which is simultaneously released with IP_3 following ligand/GPCR-induced PLCβ activation is required for activation of protein kinase C (PKC), which phosphorylates many downstream proteins involved in contractile and noncontractile signaling in vascular smooth muscle cells [23].

Ca^{2+} influx channels, such as voltage-operated (VOC), receptor-operated (ROC), store-operated (SOC) Ca^{2+} channels, and Ca^{2+}-permeable nonselective cation channels (NSCC), are also involved in the elevation of $[Ca^{2+}]_i$. The primary target protein influenced by increased $[Ca^{2+}]_i$ is the calcium-binding protein calmodulin [24], which then activates myosin light chain kinase (MLCK). Activated MLCK

phosphorylates myosin (MLC), promoting cycling of myosin cross-bridges with actin and consequent contraction [25]. Vascular smooth muscle cell relaxation is induced by dephosphorylation of MLC by myosin light chain phosphatase (MLCP). Hence, the magnitude of MLC phosphorylation and vascular smooth muscle tone is determined by the relative activities of MLCK and MLCP [14, 24, 25].

Calcium Sensitization and Vascular RhoA–Rho Kinase

In addition to changes in $[Ca^{2+}]_i$, vascular smooth muscle is regulated in a Ca^{2+}-independent manner through a process of "calcium sensitization" and involves kinases such as Rho kinase, integrin-linked kinase (ILK), and zipper-interacting protein kinase (ZIPK) [26, 27] (Fig. 4.2). These Ca^{2+}-independent processes influence contraction by increasing Ca^{2+} sensitization and by actin filament remodeling. The Ca^{2+} sensitization mechanism maintains force generation by promoting MLC phosphorylation in an MLCK-independent manner and by reducing activity of MLCP activity through Rho kinase (ROCK) signaling [28]. The effect of RhoA–ROCK activity is enhancement of actomyosin interaction, prevention of actin depolymerization, and consequent contraction. ROCK not only modulates Ca^{2+} sensitivity but also the expression of smooth muscle cell differentiation genes, including α-actin, smooth muscle myosin heavy chain, and calponin. Hence, ROCK may be a key signaling pathway that modulates regulation of acute vasoconstriction simultaneously with chronic maintenance of the contractile phenotype. Vasoactive agonists that activate the ROCK pathway include endothelin-1 (ET-1), angiotensin II (Ang II), serotonin, dopamine, bradykinin, and adrenergic neurotransmitters [29–33]. In addition, aldosterone, through its mineralocorticoid receptor, can activate ROCK [34, 35].

Dysregulation of ROCK signaling has been demonstrated in many disorders, including hypertension, atherosclerosis, stroke, diabetes, erectile dysfunction, heart failure, and pulmonary hypertension [36]. The ROCK pathway may be an important therapeutic target in cardiovascular medicine. Clinically, the beneficial effects of fasudil, an inhibitor of ROCK, have been demonstrated for the treatment of several cardiovascular diseases in humans, particularly in cerebral vasospasm after subarachnoid hemorrhage [37–39].

Targets of Ca^{2+} Signaling

In addition to calmodulin, which regulates MLCK and consequent vascular contraction, $[Ca^{2+}]_i$ has many other downstream targets that influence vascular smooth muscle cell growth and migration. This occurs through activation of Ca^{2+}-sensitive transcription factors, such as serum response factor (SRF), cAMP response element-binding proteins (CREB), mitogen-activated protein (MAP) kinases, and nuclear factor of activated T lymphocytes (NFAT). This process, called excitation–transcription coupling, impacts on the phenotype of vascular smooth muscle cells [11, 40, 41].

Vasoactive Agents and Vascular Function

Regulation of vascular function and structure and maintenance of vascular integrity involve complex, interacting systems including physical factors (shear stretch, pressure, and flow), mechanical factors (elasticity, stiffness, and distensibility), and vasoactive agents (vasoconstrictors, vasodilators, and growth factors). Many of these factors are produced and secreted by endothelial cells (Table 4.1). Of the myriad vasoactive agents important in vascular (patho)biology, adrenergic neurotransmitters (epinephrine, norepinephrine, dopamine), angiotensin II (Ang II), endothelin (ET), serotonin, bradykinin, and natriuretic peptides appear to be

Table 4.1 Factors released by the endothelium

Vasodilators	Vasoconstrictors
Nitric oxide	Angiotensin II
Bradykinin	Endothelin
Prostacyclin	Thromboxane A_2, serotonin[a], arachidonic acid, prostaglandin H_2, thrombin
Endothelium-derived hyperpolarizing factor	
Serotonin[a], histamine, substance P	
C-type natriuretic peptide	
Inhibitors of smooth muscle cell growth	**Promoters of smooth muscle cell growth**
Nitric oxide, prostacyclin, bradykinin	Platelet-derived growth factor
Heparan sulfate	Basic fibroblast growth factor
Transforming growth factor-β	Insulin-like growth factor I
C-type natriuretic peptide	Endothelin, angiotensin II
Inhibitors of inflammation or adhesion	**Promoters of inflammation or adhesion**
Nitric oxide	Superoxide radicals
	Tumor necrosis factor-α
	Endothelial leukocyte adhesion molecule
	Intercellular adhesion molecule
	Vascular cell adhesion molecule
Thrombolytic factors	**Thrombotic factors**
Tissue-type plasminogen activator	Plasminogen activator inhibitor-1

[a]Serotonin functions mostly as a vasodilator in normal blood vessels, but it produces paradoxical vasoconstriction when the endothelium is impaired by hypertension, hypercholesterolemia, or other risk factors for cardiovascular disease

particularly significant because of their many pleiotropic actions and because they have been identified as potential therapeutic targets in cardiovascular disease. Endothelin, serotonin, and Ang II are critically involved in vasoconstriction, whereas natriuretic peptides play a role in regulating vasodilation. Many other agents, particularly adipocytokines, PPAR agonists, vasopressin, neuropeptide Y, and adenosine, have been implicated in the regulation of vascular function and will be briefly discussed.

Adrenergic Neurotransmitters, Adrenergic Receptors, and Vascular Function

The neurotransmitters including dopamine, norepinephrine (NE), and epinephrine (E) play important roles in cardiovascular functions. Biosynthesis of these agents occurs in adrenergic nerves (up to the NE stage) and in the adrenal medulla. Catecholamines are stored in adrenergic nerve terminals and in adrenal chromaffin cells in storage vesicles together with ATP and storage proteins called chromogranins. Catecholamine concentrations in vesicles are continually being replenished by de novo synthesis from precursors (dopamine β-hydroxylase is localized within the vesicle) and by neuronal reuptake of released NE. Of the three enzymes principally responsible for the metabolism of NE, two have inhibitors that are used clinically. Monoamine oxidase (MAO) inhibitors work to treat depression by blocking NE metabolism in the central nervous system, and the MAO inhibitor selegiline is used as an adjunct to L-dopa to treat Parkinson's disease [42]. Catechol-*O*-methyltransferase inhibitors are used with L-dopa for Parkinson's disease.

The main adrenergic receptors, α and β, comprise α_1, α_2, β_1, and β_2 with multiple subtypes, designated as $\alpha_{1A,B,C}$, $\alpha_{2A,B,C}$, and $\beta_{1,2,3}$ [43]. VSMC possess α_1-, α_2-, and β_2-receptors, which associate with G proteins. α_1-Adrenergic receptors are more sensitive to NE than E and induce vasoconstriction through G_{qa}-induced activation of PLC, Ca^{2+} channels, Na^+–H^+, and Na^+–Ca^{2+} exchange and via inhibition of K^+ channels. Vascular β-receptors, mainly β_2, are linked to a $G_{s\alpha}$ (stimulatory) protein; the $G_{s\alpha}$ protein activates adenylate cyclase, which converts ATP to cAMP. cAMP activates protein kinase A (PKA), which phosphorylates and inactivates MLCK, leading to vasodilation. β-Adrenergic-blocking drugs are therefore directly vasoconstrictor (and so are relatively contraindicated in patients with severe peripheral vascular disease); their antihypertensive action is due to their actions on the heart, to reduce cardiac output, and on the kidney, to block renin release.

α_2-Receptors have a potency order E>NE and, like α_1-receptors, are also vasoconstrictor, but via a different mechanism. α_2-Receptors couple with inhibitory G proteins ($G_{i\alpha}$) to inhibit membrane-related adenylate cyclase and therefore have inhibitory actions on the formation of cAMP, activated PKA, and phosphorylated MLCK, causing vasoconstriction. There are also α_2-ARs as autoreceptors on postganglionic sympathetic nerve terminals, which synthesize and release NE. These pre-junctional α_2-ARs respond to released (or circulating) catecholamines by inhibiting the further release of NE. Also, activation of brain α_2-ARs reduces sympathetic outflow, and stimulation of these receptors with clonidine and similar α_2-agonists lowers blood pressure.

Dopamine is not only a precursor of NE and E but also a neurotransmitter in its own right. Dopamine mediates effects via dopamine receptors, classified into D_1- and D_2-like receptor subtypes, based on their molecular and pharmacological characteristics [44]. D_1-like receptors, comprising D_1 and D_5 receptors, stimulate adenyl cyclase activity, whereas D_2-like receptors, comprising D_2, D_3, and D_4 receptors, inhibit adenyl cyclase activity and regulate activity of several ion channels. VSMC contain both D_1 and D_2 receptors. Stimulation of D_1 receptors causes vasodilation by increasing adenylase cyclase and cAMP-dependent PKA, resembling in this respect the β_2-receptor. It also causes natriuresis and diuresis by inhibiting Na^+–K^+ antiport activity in the renal tubular cells, to decrease Na^+ reabsorption. D_2 receptors are found in the endothelial and adventitial layers of blood vessels, where their function is unknown; on pituitary cells where they inhibit prolactin secretion and where bromocriptine, a D_2 receptor agonist, acts to reduce hyperprolactinemia; and in the zona glomerulosa of the adrenal gland, where they inhibit aldosterone secretion. There are also D_2 receptors on the sympathetic nerve terminal, where they inhibit NE release.

The normal circulating levels of dopamine are very low to stimulate vascular dopamine receptors, and vascular smooth muscle cells do not synthesize dopamine [44]. Hence, the physiological role of dopamine in the regulation of vascular function is probably not very important. However, it may be important in controlling natriuresis and diuresis and in pathological conditions, such as in hypertension.

Angiotensin II and Vascular Function

Ang II, produced systemically and locally within tissues, including the vascular wall, is a potent vasoactive peptide that also stimulates vascular smooth muscle cell growth, inflammation, and fibrosis through many signaling pathways [45–47]. Accordingly, Ang II plays an important physiological role in maintaining vascular tone by regulating immediate vasoconstriction and a pathophysiological role in cardiovascular diseases, such as hypertension, atherosclerosis, and heart failure, and conditions associated with endothelial dysfunction, vascular hyperactivity, and structural remodeling.

Ang II has a diverse array of vascular functions. Acute Ang II stimulation causes vasoconstriction and a rapid rise in blood pressure, while chronic Ang II stimulation leads to vascular smooth muscle cell proliferation, inflammation, and fibrosis, important in structural remodeling and sustained blood pressure elevation [48]. Ang II exerts its actions via two GPCR, Ang II type 1 (AT_1R) and type 2 (AT_2R) receptors [46, 47, 49, 50] (Fig. 4.3). The AT_1R mediates most of the actions of Ang II. The AT_2R is associated with antiproliferative, proapoptotic, and vasodilatory actions of Ang II and tends to counteract effects of the AT_1R.

Signaling pathways induced by Ang II/AT_1R involve interactions with several G proteins coupled to second messengers and cytosolic proteins, including PLC, phospholipase A2 (PLA2), and phospholipase D (PLD) [51]. PLC activation produces IP_3 and DAG. IP_3 in turn mediates SR release of Ca^{2+} to increase $[Ca^{2+}]_i$, the major trigger for contraction. Stimulation of Ca2+ influx through Ang II-activated Ca^{2+} channels also contributes to the pool of cytoplasmic Ca^{2+}. Increased Ang II-induced $[Ca^{2+}]_i$ promotes MLCK activation, interaction of myosin II with actin, enhanced cross-bridge cycling, and consequent contraction.

PLD activation by Ang II results in hydrolysis of phosphatidylcholine to choline and phosphatidic acid, which is rapidly converted to DAG, resulting in sustained PKC activation and associated sustained vasoconstriction [52]. In addition to the "classical" PLC- and PLD-dependent pathways, ERK1/2 and tyrosine kinases, typically involved in growth signaling, influence Ang II-stimulated vascular contraction, an effect mediated through changes in $[Ca^{2+}]_i$ and pH_i. A number of other signaling mechanisms have recently been identified to also play an important role in regulating vascular tone by Ang II, including the RhoA–Rho kinase pathway, TRP channels, ROS, and arachidonic acid metabolites (HETEs, ETEs) [53].

In addition, Ang II/AT_1R signals through activation of many receptor and non-receptor tyrosine kinases and serine–threonine kinases, important in cell growth and hypertrophy; activation of NADPH oxidase, which is a major source of vascular reactive oxygen species (ROS) involved in redox signaling; and activation of proinflammatory transcription factors [54, 55] and stimulation of small G proteins such as Ras, Rac, and RhoA [56]. Activation of RhoA and its downstream target ROCK is increasingly being recognized as an important mechanism of vasoconstriction by Ang II and accordingly has been implicated in the pathophysiology of hypertension [57]. Pharmacological inhibition of ROCK with fasudil or Y27632 suppresses acute pressor responses of Ang II, but does not reduce blood pressure chronically, further supporting the role of RhoA–Rho kinase in acute vasoconstriction, rather than in mechanisms associated with adaptive vascular remodeling that occur chronically with Ang II infusion.

Although the primary vascular cell target of Ang II is smooth muscle, it also influences the endothelium by modulating production of nitric oxide (NO) and ROS [58, 59] and by influencing the many ion channels expressed in endothelial and vascular smooth muscle cells.

Endothelin and Vascular Function

Endothelin Peptides

The endothelin (ET) family comprises four endogenous isoforms of 21-amino acid peptides: ET-1, ET-2, ET-3, and ET-4 [57, 60–62]. Endothelin-1 (ET-1), the predominant isoform of the ET peptide family, has potent vasoconstrictor, mitogenic, proinflammatory, and antinatriuretic properties, implicated in the pathophysiology of many cardiovascular diseases [57]. Urotensin-II (U-II), a peptide isolated from the urophysis of the teleost fish (and more recently from humans), has been called the "new endothelin" with initial studies showing that U-II contracts isolated monkey arteries more potently than ET-1. However, effects of U-II in vascular tissue from other mammalian species are variable.

ET-1 is continuously released from endothelial cells by a constitutive pathway, producing constriction of underlying smooth muscle and contributing to maintenance of endogenous vascular tone. ET-1 is also released from endothelial cell-specific storage granules (Weibel–Palade bodies) in response to physiological stimuli producing further vasoconstriction. In addition to endothelial cells, ET-1 is produced by vascular smooth muscle cells, cardiomyocytes, leukocytes, macrophages, and mesangial cells.

Bioactive endothelins are the product of posttranslational processing of the parent preproendothelin peptide. Transcription of the preproendothelin gene and translation of preproendothelin mRNA result in formation of the 203-amino acid peptide, which is later cleaved by a furin convertase to the 38-amino acid peptide big ET(1–38). Big ET is further processed into ET(1–21) by endothelin-converting enzymes (ECEs) and by carboxydipeptidases.

Endothelin Receptors and Signaling Pathways

Endothelins exert their effect by acting on two types of receptors, ET_A and ET_B, which are ubiquitously expressed [62]. Subtypes of ET_A are ET_{A1} and ET_{A2} receptors, whereas subtypes of ET_B are ET_{B1} and ET_{B2} receptors. ET_A and ET_{B2} receptors are involved in vasoconstriction, whereas transient vasodilation depends on the activation of ET_{B1} receptors. Based on the cellular localization within the vasculature, it was initially suggested that vascular smooth muscle cell ET_A receptors mediate vasoconstriction and endothelial ET_B receptors elicit

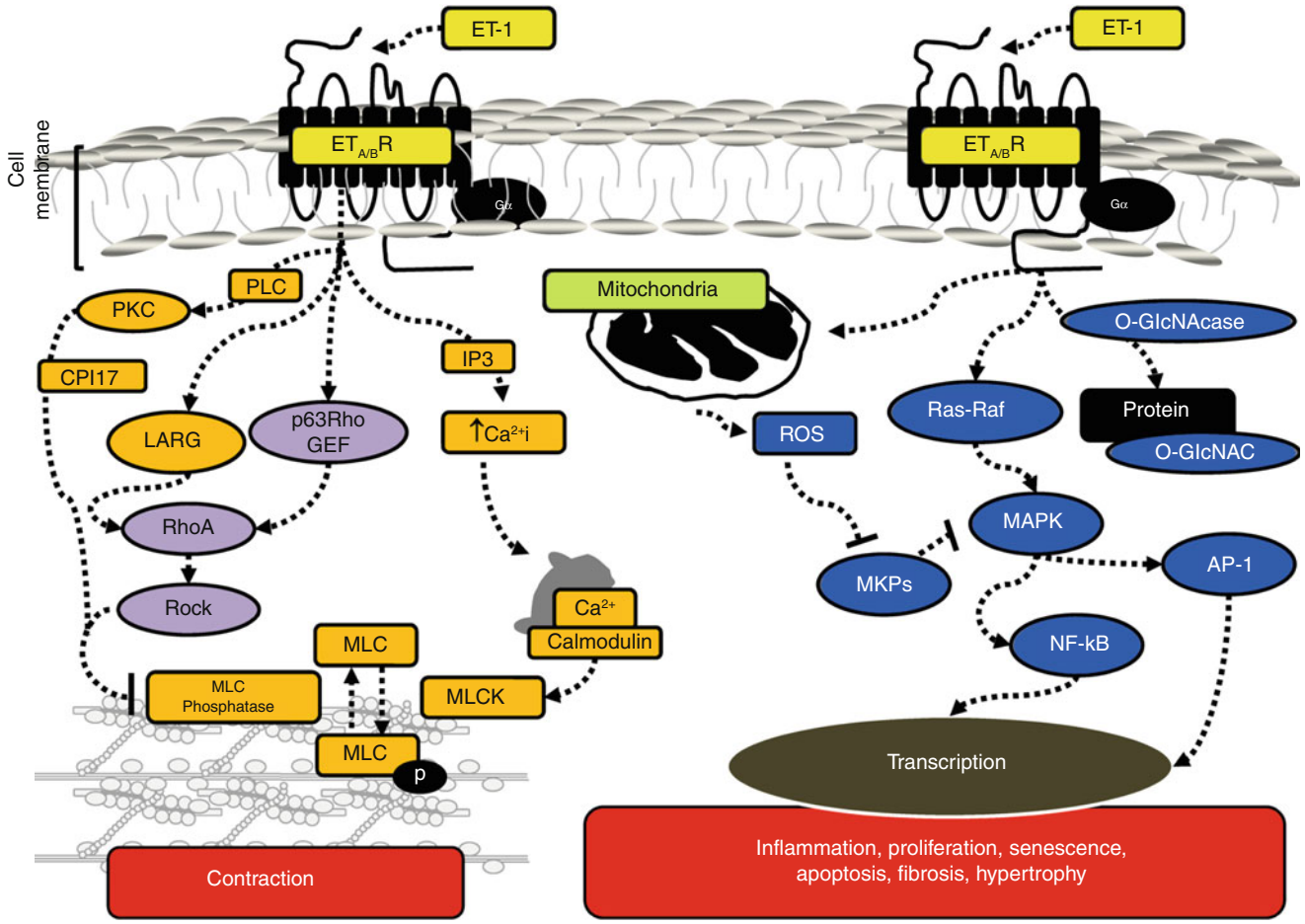

Fig. 4.4 ET-1-induced signaling in VSMCs. ET-1, through activation of ETA or ETB receptors, induces contraction, inflammation, proliferation, senescence, apoptosis, fibrosis, hypertrophy, and increased VSMC migration. ET-1-induced contraction is mediated by activation of calcium-dependent signaling (described in Fig. 4.2), phosphorylation of PLC–PKC–CPI17 pathways, leading to RhoA-independent inhibition of MLC phosphatase and LARG–p63RhoGEF–RhoA–Rock signaling. ET-1 is also a potent mediator of gene transcription and VSMC damage. Its damaging effects in the vasculature are mediated through activation of many pathways, such as (1) ROS generation by the mitochondria and (2) activation of Ras–Raf-dependent mechanisms and, as recently described, O-GlcNACation of proteins, which may increase or decrease protein function. Abbreviations: *ETA/B* ET-1 receptor subtype A or B, *CPI17* phosphoprotein inhibitor 17, *LARG* leukemia-associated Rho guanine nucleotide exchange factor, *p63RhoGEF* p63Rho guanine nucleotide exchange factor

vasodilation through the release of endothelium-derived relaxing factors. However, it was later shown that both ET_A and ET_B (ET_{B2}) receptors mediate constriction [63]. In humans, ET_A receptors predominate on vascular smooth muscle cells, with a low density of ET_B receptors (<15 %).

The overall ET-1 effect on vascular tone derives from the balance between the direct vasoconstrictor effect via ET_A and ET_B receptors on smooth muscle cells and nitric oxide (NO)- or prostacyclin-induced vasodilation mediated by endothelial ET_B receptors (Fig. 4.4) [64]. Therefore, although ET-1 is considered a potent vasoconstrictor, this activity can be indirectly attenuated by parallel vasodilation dependent on the expression of endothelial ET_B receptors and/or the integrity of ET_B-mediated activation of the NO pathway.

ET-1 activates transcriptional factors (such as NF-κB) responsible for increased expression of many cytokines (e.g., IL-6, MCP-1, IL-8) and enzymes (iNOS, COX-2) which in turn lead to production of inflammatory mediators. Depending on the cell type, NF-κB activation can be mediated by either ET_A or ET_B receptors.

ET_A and ET_B receptors belong to the seven-transmembrane domain of GPCRs. Binding of ETs to their receptors is "irreversible." The tight binding of ETs, especially ET-1 and ET-3, to their receptors may explain the long-lasting vasoconstrictor effects of these peptides [70]. Activation of ET receptors in vascular smooth muscle cells results in PLC activation, leading to generation of the second messengers IP_3 and DAG, which in turn stimulate intracellular Ca^{2+} release and PKC activation, respectively [65]. Calcium influx from the extracellular space is mediated by the activation of voltage-dependent Ca^{2+} channels and nonselective cation channel(s) and via store-operated Ca^{2+} channels. Other

signaling pathways are also activated and involve PLD, PLA_2, activation of the Na^+–H^+ exchanger, and activation of MAPKs. Additionally, ET-1 activates the RhoA–ROCK pathway ultimately promoting contraction via sensitization of the contractile smooth muscle apparatus. Many of these signaling events are mediated through NAD(P)H oxidase-derived reactive oxygen species (ROS). Activation of endothelial cell ET_B receptors stimulates release of NO and prostacyclin, negatively modulating the constrictor effects of ET-1 on smooth muscle cells [66].

Role of ET-1 in Cardiovascular Diseases

The endothelin system is involved in various cardiovascular diseases, including hypertension, pulmonary hypertension, atherosclerosis, heart failure, and coronary artery disease [67–69]. Extensive data support a role for ET-1 in salt-sensitive forms of experimental and human hypertension, with ET receptor blockers lowering blood pressure and protecting against target organ damage [70]. ET-1 also plays a role in cardiac remodeling and cardiovascular inflammation in salt-sensitive hypertension [71]. Increased cardiac metalloproteinase activity, NF-κB activation, x-inhibitor of apoptosis proteins (x-IAP) expression, and upregulation of VCAM-1 and platelet endothelial cell adhesion molecule (PECAM-1) expression occur in DOCA-salt rats. These markers were reduced with the ET_A receptor antagonist BMS182874.

In humans, local infusion of the selective ET_A receptor antagonist BQ-123 results in both vasodilation of the forearm vascular bed and antagonism of exogenous ET-1-mediated vasoconstriction, thus suggesting that endogenous ET-1 contributes to regulation of basal vascular tone in healthy humans [72]. Following local and systemic infusions of BQ-123, coronary vasodilation and reduced peripheral vascular resistance and mean arterial pressure have been reported. By contrast, systemic ET_B receptor blockade with BQ-788 increased peripheral vascular resistance in healthy humans

Endothelin-1 is also a potent venoconstrictor [73]. ET-1-mediated venoconstriction is significantly increased in hypertensive patients. The augmented responsiveness to ET-1 in capacitance vessels may be of clinical importance since a reduction in venous compliance may lead to increased cardiac preload.

Endothelin and Pulmonary Hypertension

The lungs represent a primary target for ET-1 effects and are a special site for ET-1 metabolic pathways [74]. Pulmonary vascular smooth muscle cells as well as endothelial cells synthesize and release ET-1, particularly when stimulated by cytokines. Both ET_A and ET_B receptors modulate ET-1 responses in small muscular pulmonary arteries of humans and are also found in bronchi and alveoli. Blockade of both receptor subtypes reduces ET-1-induced pulmonary vasoconstriction. Pulmonary ET-1 production is stimulated in response to increased pressure, and a significant correlation between serum levels of ET and pulmonary vascular resistance, right atrial pressure, and oxygen saturation in patients with pulmonary hypertension has been reported.

Endothelin in Congestive Heart Failure

The human heart, particularly the endocardium, contains all components of the ET system: ET-1 precursors, ECEs, ET-1, and its receptors ET_A and ET_B. Binding sites for both receptors are widely distributed throughout the heart. Circulating ET-1 levels correlate with the severity of hemodynamics and symptoms in patients with congestive heart failure [75]. In addition, tissue ET levels are increased in failing human heart, and big ET is an independent predictor of survival. ET-1 appears to exert differential effects on the normal and failing myocardium. Patients with reduced left ventricular function have increased contractility in response to ET_A receptor blockade, whereas patients with normal left ventricular function manifest reduced contractility. ET_A receptors are upregulated in heart failure, whereas ET_B receptors are downregulated.

Endothelin Antagonists

Available ET antagonists can selectively block either ET_A or ET_B receptors or both. ET_A selective or dual ET_A/ET_B receptor blockade in experimental hypertension results in regression of vascular damage and endothelial dysfunction, delayed progression of renal injury, cerebral edema reduction, cardiac hypertrophy regression, and improved survival [76]. Considering the opposing actions mediated by ET_A and ET_B receptors, differential effects are expected with selective blockers.

ET receptor antagonists have been studied in various pathological conditions, including cardiovascular, respiratory, neuroimmunological disease, and cancer. One of the earliest clinical studies showed that long-term administration of bosentan, a mixed ET_A/ET_B receptor antagonist, significantly lowered blood pressure in patients with essential hypertension [77]. Trials using darusentan, a selective ET_A receptor antagonist, showed promising results in the treatment of patients with resistant hypertension, and experimental evidence indicates that ET_A receptor blockade prevents progression of diabetic nephropathy and reduces renal injury in models of diabetes. Small clinical studies in

hypertensive patients have also been conducted with other ET blockers such as sitaxsentan (TBC-11251) and darusentan (LU-135152), but large clinical trials of ET receptor antagonists have not yet been undertaken for hypertension [78]. Hence, the therapeutic potential of these agents in the management of essential hypertension still awaits clarification.

The nonselective ET receptor antagonists bosentan and tezosentan and the selective ET_A receptor antagonist darusentan were studied in randomized clinical trials of chronic heart failure. These studies failed to demonstrate significant differences in clinical status between ET-1 antagonist and the placebo group. Also in the Endothelin A Receptor Antagonist Trial in Heart Failure (EARTH) trial in patients with chronic heart failure, darusentan did not significantly affect left ventricular remodeling, as assessed by cardiac magnetic resonance imaging [79]. Based on these findings, the use of ET receptor antagonists in the management of patients with cardiac failure still remains unclear.

On the other hand, ET receptor antagonists have an established place in the management of pulmonary arterial hypertension. Bosentan is approved for use in the USA and Europe for the treatment of pulmonary hypertension. More recently, selective ET_A receptor antagonists—ambrisentan, atrasentan, avosentan, clazosentan, darusentan, and sitaxsentan—have been studied in clinical trials, with promising results.

Acetylcholine

Acetylcholine (ACh) [80] is the neurotransmitter for postganglionic parasympathetic neurons (acting on muscarinic receptors), both sympathetic and parasympathetic preganglionic neurons (acting on nicotinic receptors), preganglionic autonomic neurons innervating the adrenal medulla, motor end plates in skeletal muscle, and some neurons in the central nervous system. ACh is synthesized by acetylation of choline, stored in vesicles, and then released from cholinergic nerves when these are depolarized. After acting on the ACh receptor, ACh is rapidly degraded by acetylcholinesterase.

Muscarinic Receptors

At least five subtypes of muscarinic receptors are known: M_1 to M_5. Although several vascular effects of ACh have been described—notably the release of nitric oxide from endothelial cells to produce vasodilation—the administration of atropine, a muscarinic antagonist, has no significant effect on vascular resistance. It is therefore unlikely that ACh has a major role in vascular homeostasis. However, the intense negative cardiac inotropic and chronotropic effects of parasympathetic (vagal) stimulation, opposed by atropine, are well known.

Nicotinic Receptors

All autonomic ganglionic neurotransmission is mediated by nicotinic cholinergic receptors. Ganglion-blocking drugs, such as trimethaphan and mecamylamine, were once among the few agents available for the treatment of hypertension. They caused blood pressure to fall, but what is effectively a blockade of the efferent pathway of the baroreceptor reflex frequently caused profound postural hypotension, dizziness, and syncope. These drugs are no longer used.

Serotonin

Serotonin, or 5-hydroxytryptamine (5-HT) [81], is found in the central and peripheral nervous system, in the enterochromaffin cells of the gastrointestinal tract, and in platelets. It is synthesized by the hydroxylation of tryptophan to 5-hydroxytryptophan, then by decarboxylation to 5-HT. The cardiovascular actions of 5-HT are complex. Serotonin mediates effects via seven major families of 5-HT receptors ($5\text{-}HT_1$–$5\text{-}HT_7$) and multiple subtypes. The $5\text{-}HT_{1A}$, $5\text{-}HT_{1B/1D}$, $5\text{-}HT_2$ receptor family ($5\text{-}HT_{2A}$ and $5\text{-}HT_{2B}$), $5\text{-}HT_3$, $5\text{-}HT_4$, and $5\text{-}HT_7$ receptors are found and are active in cardiovascular tissues; $5\text{-}HT_{1A}$ receptors mediate endothelium-dependent vasodilation, and $5\text{-}HT_{lB}$ receptors activate the phosphorylation of MAP kinase in aortic endothelial cell cultures. Receptors for $5\text{-}HT_2$ are involved with direct arterial and venous constriction, and $5\text{-}HT_3$ receptor activation causes bradycardia and hypotension. Intravenous serotonin causes a brief depressor phase mediated by $5\text{-}HT_3$ receptors, followed by a brief pressor effect due to $5\text{-}HT_2$ receptors in the renal, splanchnic, and cerebral circulation. This is followed by a more prolonged fall in blood pressure, due to vasodilation in skeletal muscle, probably mediated by $5\text{-}HT_{1A}$ receptors. Ketanserin is a $5\text{-}HT_2$ (and α_1-adrenergic) receptor antagonist, which has been used as an antihypertensive agent.

Adenosine

Adenosine [82], a purine nucleoside comprising a molecule of adenine attached to a D-ribose sugar, is distributed throughout all body tissues and, aside from its importance in AMP, ADP, and ATP, is a potent vasodilator with a short half-life of not more than 6 s. It also has negative inotropic and chronotropic effects on the heart and is used to treat supraventricular tachycardias. There are four adenosine receptors: A_1, A_{2a}, A_{2b}, and A_3. A_1 and A_3 receptors in the

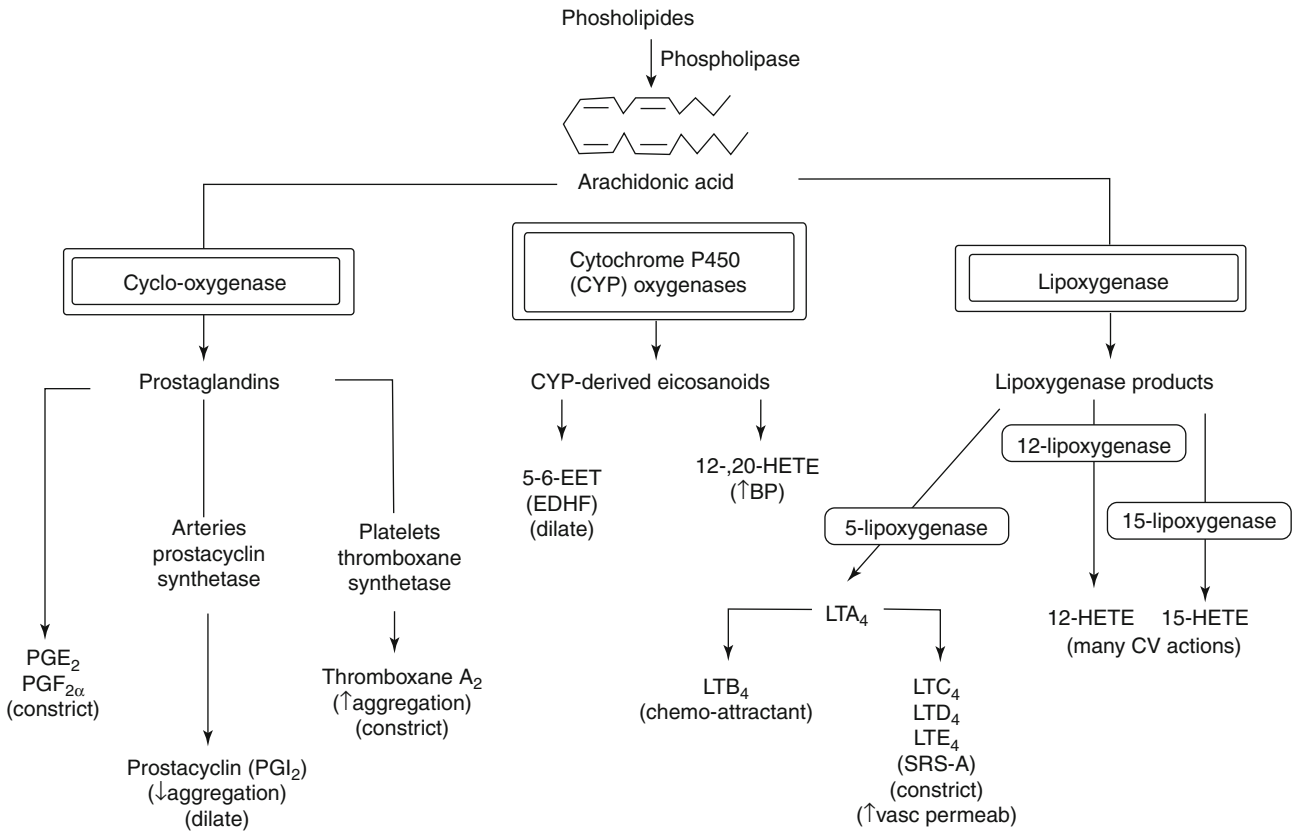

Fig. 4.5 The biosynthesis of prostaglandins, cytochrome P450-derived eicosanoids, and lipoxygenase products from arachidonic acid. *PG* prostaglandin. For other abbreviations, *see* text

heart inhibit adenylate cyclase and activate K^+ channels to decrease inotropy and to suppress sinus mode automaticity and atrioventricular nodal conduction. Vasodilation is mediated via A_{2a} and A_{2b} receptors, which activate adenylate cyclase via a Gs protein. Adenosine is also used as a test agent for imaging coronary artery disease; by causing vasodilation of normal coronary arteries, it produces a "steal" effect, revealing any area of myocardial ischemia.

Endogenous Ouabain

The plant glycoside ouabain has digitalis-like actions, particularly inotropic effects. The endogenous ouabain-like (EO) steroid hormone [83] has been shown to be a high-affinity, selective inhibitor of Na^+–K^+-ATPase, is positively inotropic, and is a vasopressor. All these actions would be expected to cause hypertension, and this has been shown with sustained infusions of EO in rats. Elevated EO levels have been described in humans with hypertension or heart failure. The primary site of EO production seems to be the adrenal zona glomerulosa, and EO release can be stimulated by adrenocorticotropin (ACTH) and by Ang II via AT2 receptors.

Eicosanoids

Eicosanoids are signaling molecules made by oxidation of twenty-carbon essential fatty acids (EFAs) [84]. They exert complex control over many systems, mainly in inflammation or immunity, as messengers in the central nervous system, and in the cardiovascular system. Eicosanoids derive from either omega-3 (ω-3) or omega-6 (ω-6) EFAs. The ω-6 eicosanoids are generally proinflammatory; ω-3 s are much less so. The amounts and balance of these EFAs in the diet will affect cardiovascular disease, triglycerides, blood pressure, and arthritis. Anti-inflammatory drugs such as aspirin and other NSAIDs act by downregulating eicosanoid synthesis.

There are four families of eicosanoids—the prostaglandins, the prostacyclins, the thromboxanes, and the leukotrienes. For each, there are two or three separate series, derived either from an ω-3 or ω-6 EFA. Prostacyclin (PGI_2) and PGE_2 are eicosanoid prostaglandins (Fig. 4.5) that are rapidly released from endothelial cells in response to a variety of humoral and mechanical stimuli. PGI_2 is the major product of arachidonic acid metabolism through the cyclooxygenase pathway in blood vessels. It is a vasodilator but also retards platelet aggregation and adhesion. This action is the opposite to that of the major metabolite of arachidonic acid

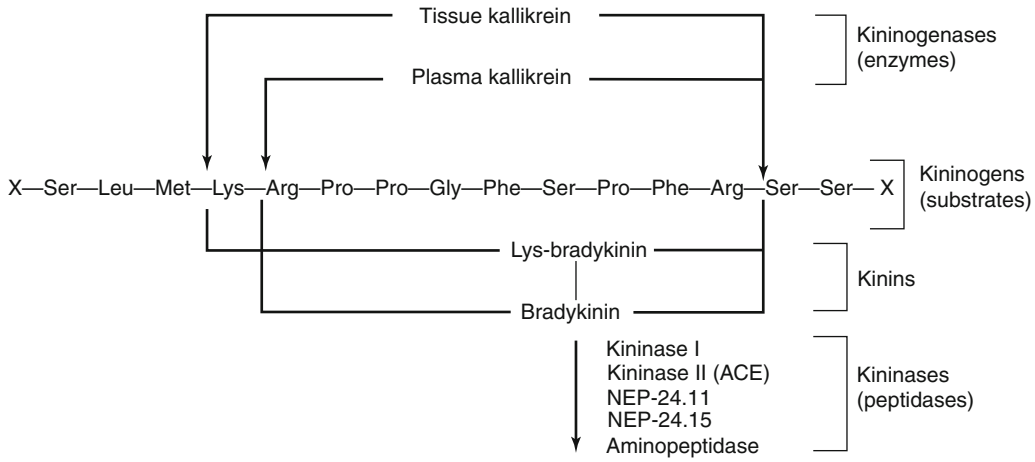

Fig. 4.6 Biosynthesis and metabolism of kinins. For description, *see* text

in platelets, thromboxane A_2, which is a vasoconstrictor and stimulates platelet aggregation. Recently, an enzyme, prostaglandin H synthase II (PHS-II), has been identified, which is an inducible form of a key enzyme in PGI_2 synthesis and which provides a mechanism for the sustained production of PGI_2 in chronic inflammation and vascular injury.

Other physiologically important eicosanoids are synthesized from arachidonic acid by cytochrome P450 oxygenases. These are (1) S,6-epoxy-eicosanienoic acid (S,6-EET), which is the endothelium-derived hyperpolarizing factor, which, like PGI_2 is a vasodilator; (2) 12(R)-hydroxyeicosatetraenoic acid (l2R-RETE) which inhibits Na^+–K^+-ATPase; and (3) 20-RETE, which elevates blood pressure via several different mechanisms, both directly and via the kidney.

The third enzyme pathway for the production of vasoactive arachidonic acid products is via lipoxygenases, of which there are three, designated 5-, 12-, and l5-lipoxygenase. The 5-lipoxygenase pathway produces leukotriene A4 (LTA_4), which is then converted to LTB_4, a potent chemoattractant substance that causes polymorphonuclear cells to bind to vessel walls, and may therefore be important in atherogenesis. LTA_4 can also be converted to LTC_4, LTD_4, or LTE_4, formerly collectively known as "slow-reacting substance of anaphylaxis" (SRS-A), made by mast cells, neutrophils, eosinophils, and macrophages, and which are potent vasoconstrictors and cause increased microvascular permeability. The 12- and 15-lipoxygenase pathways produce 12-HETE and 15HETE, respectively, in VSMC and endothelial cells. Also, platelets, adrenal glomerulosa cells, and renal mesangial and glomerular cells can make 12-HETE, and monocytes can make 15-HETE. These two lipoxygenase products have several potential roles in vascular disease. The eicosanoid 12-HETE may activate MAP kinase, suggesting a role in cell proliferation and atherogenesis. Both 12- and 15-HETE inhibit prostacyclin synthesis and vasoconstrict certain vascular beds. They are growth promoting on vascular smooth muscle cells, may increase monocyte adhesion to endothelial cells, and may be involved in the oxidation of LDL cholesterol. The recent development of inhibitors of sEH provides an emerging target for pharmacological manipulation of EETs.

Kinins

Kinins [85] are vasodilator peptides that are released from substrates known as kininogens by serine protease enzymes known as kininogenases. There are two main kininogenases, plasma and tissue kallikrein, and these produce bradykinin and lysyl-bradykinin from the high- or low-molecular-weight kininogens, made in the liver and circulating in the plasma (Fig. 4.6). Kinins are broken down by enzymes known as kininases, one of which is kininase II, also known as the angiotensin-converting enzyme (ACE). Others include neutral endopeptidases (NEP) 24.11 and 24.1S. Most kininases are found in the endothelial cells of capillaries.

Kinins activate B_1 and B_2 receptors. B_1 receptors are involved with inflammatory responses to bacterial endotoxins. B_2 receptors mediate vasodilator responses. In the kidney, kinins are vasodilator, natriuretic, and diuretic, actions that are possibly mediated by the kinin-induced release of PGE_2 and nitric oxide. In children, a low urinary kallikrein excretion is an important genetic marker for primary hypertension, so kinins may play some role in hypertension. At least some of the antihypertensive actions of both ACE inhibitors and NEP inhibitors may be due to potentiation of the effect of kinins.

Tissue kallikrein is present in heart, arteries, and veins. Kinin production is increased in myocardial ischemia, may be an important mediator of myocardial preconditioning (protection from damage during subsequent ischemic episodes), and may contribute to the beneficial effect of ACE inhibitors in reversing ventricular remodeling and in improving cardiac function. Kinins also have several important functions in hemostasis. Plasma kallikrein and high-molecular-weight kininogen are involved with the intrinsic pathway

of blood coagulation. Kinins also promote NO and prostacyclin (PGI_2) formation, both of which inhibit platelet aggregation and adhesion, and kinins stimulate the release of tissue plasminogen activator to promote fibrinolysis. All these effects are enhanced by inhibitors of kininases, such as ACE inhibitors and NEP inhibitors.

Endogenous Natriuretic Peptides

There are three structurally and functionally similar natriuretic peptides [86, 87]: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP), which all induce natriuresis and are vasodilators. ANP is released from atrial and ventricular myocytes in response to stretch (making the heart a true endocrine organ). The ANP prohormone contains 126 amino acids and is cleaved in cardiac myocytes to two fragments. The C-terminal 28-amino acid peptide is the active hormone. BNP, structurally similar to ANP, is synthesized and stored in the brain and in cardiac myocytes and is also released in response to atrial and ventricular stretch, although at lower concentrations than is ANP. The third member of the group, CNP, is made not in the heart but in the endothelium of blood vessels and probably acts not as a circulating hormone but in a paracrine manner, acting on adjacent VSMC as a vasodilator and antimitogenic agent.

ANP and BNP bind to the natriuretic peptide receptor-A (NPR-A), which is found on vascular endothelial cells and renal epithelial cells. CNP binds to the NPR-B receptor, on VSMC. NPR-A and NPR-B receptors activate guanylyl cyclase and cyclic GMP to cause natriuresis, diuresis, and vasodilation. They inhibit the renin–angiotensin system, endothelin, and sympathetic function and are antimitogenic in VSMC. Infusions of BNP (nesiritide) have been used, successfully, for the treatment of heart failure.

Vasopressin

Arginine vasopressin (AVP) [88], also known as the antidiuretic hormone (ADH), is released from the posterior pituitary in response to (1) increased plasma osmolality, via osmoreceptors in hypothalamus; (2) reduced blood volume, sensed by atrial stretch receptors; and (3) decreased blood pressure, via aortic and carotid baroreceptors. In addition to its action in promoting water reabsorption in renal collecting ducts (via V_2 receptors), AVP activates blood vessel V_{1a} receptors to cause vasoconstriction. The V_{1a} receptors are coupled to membrane G proteins, phosphatidylinositol phosphate (PIP), and phospholipase C (PLC), increasing free cytosolic Ca^{2+} released from the endoplasmic reticulum. The V_2 receptors, mediating water permeability of the collecting ducts and also vasodilation in skeletal muscle, are coupled to adenylate cyclase and cyclic AMP.

The normal concentration of AVP is 1–3 pg/mL (10–12 mol/L), and higher concentrations (10–20 pg/mL) can produce significant vasoconstriction in skin, splanchnic, renal, and coronary beds, and some V_2 receptors mediated skeletal muscle vasodilation, with variable effects on arterial blood pressure. AVP also enhances sympathoinhibitory responses to baroreceptor stimulation, so that quite high plasma AVP concentrations are not accompanied by hypertension, which allows the antidiuretic action of AVP to occur unopposed by any pressure-induced diuresis. The role of AVP in human hypertension is not clear. In a small percentage of patients with primary hypertension (30 % of males, 7 % of females), there is a significant elevation (5–20 pg/mL) of plasma AVP, but it is not known whether these changes in AVP concentrations are primary or secondary. These concentrations are lower than those required to increase blood pressure in normal humans but may contribute to the fluid retention and volume expansion seen in many hypertensive patients. There is, however, the phenomenon of "vasopressin escape"—the AVP-induced pressure diuresis overcomes the fluid-retaining effects of AVP, so that, after a few weeks, extracellular fluid volumes return to normal.

Neuropeptide Y

Neuropeptide Y (NPY) [89] is a 36-amino acid vasoconstrictor peptide, which is co-released with norepinephrine and ATP from sympathetic nerve terminals innervating small arteries, heart, and kidney. It is also abundant in the brain (hypothalamus, ventrolateral medulla, and locus coeruleus) and in sympathetic ganglia. Y_1 receptors in blood vessels inhibit adenylate cyclase and increase intracellular free Ca^{2+} to cause vasoconstriction. The Y_2 receptors are on the sympathetic nerve terminal and mediate feedback inhibition of neurotransmitter release.

In the central nervous system, NPY probably acts to lower blood pressure and heart rate. Unlike most other vasoconstrictor agents, NPY is diuretic and natriuretic. Plasma concentrations of NPY are elevated in some patients with hypertension, but the significance of this is unknown.

Adipokines

PVAT (perivascular adipose tissue) has recently been recognized as a novel system in vascular biology, with implications in the pathophysiology of cardiovascular disease. PVAT, composed mainly of adipocytes, releases various biologically active molecules that modulate vascular function (Table 4.2) [90, 91]. PVAT exerts an anti-contractile effect in

Table 4.2 Adipocyte-derived factors/hormones that modulate vascular function

Adipokines
Leptin
Adiponectin
Resistin
Visfatin
Adrenomedullin
Cytokines
IL-1
IL-6
IL-18
MCP-1
PAI-1
TNF-α
RANTES
Hormones
Ang II
Aldosterone
Reactive oxygen species
Superoxide
Nitric oxide
Hydrogen peroxide

various vascular beds which seems to be mediated by an as yet elusive PVRF [PVAT-derived relaxing factor(s)]. It also secretes factors that induce vasoconstriction, inflammation, and vascular growth. Moreover, increasing evidence indicates that adipocytes have an active renin–angiotensin system and that they are able to produce Ang II and aldosterone, which influence vascular function [92, 93].

Plasminogen Activator Inhibitor-l

Plasminogen activator inhibitor-l (PAI-1) [94] is found in the vascular endothelium, platelets, adipose tissue, and the liver. It binds to vitronectin in the extracellular matrix of blood vessels. PAI-l is an acute-phase reactant, induced by inflammatory cytokines such as interleukin-l (IL-I) and tumor necrosis factor-α (TNF-α), by growth factors such as transforming growth factor-β (TGF-β) and epidermal growth factor, and by hormones like Ang II and aldosterone. Plasma levels of PAI-1 are increased in hypertension, and PAI-l is present in atherosclerotic plaques, contributing to the development of atherosclerotic cardiovascular disease.

Peroxisome Proliferator-Activated Receptors

Peroxisomes are organelles that oxidize various molecules, including long-chain fatty acids [95].

Peroxisome proliferators (which activate peroxisome proliferator-activated receptors [PPAR]) are agents that increase the size and number of peroxisomes. There are three PPARs, named PPAR α, γ, and δ. PPAR-α, widely expressed, is activated by fibrates such as gemfibrozil and fenofibrate and regulates fatty acid and apolipoprotein A-I and lipoprotein lipase activation. PPAR-α also inhibits vascular inflammatory cytokines and tissue factor. PPAR-γ, expressed mainly in adipose tissue and the vasculature, is activated by the thiazolidinediones (pioglitazone and rosiglitazone) to increase insulin sensitivity, also to repress several stages in the atherosclerotic process, including cytokine-induced chemokines, monocyte cytokines, matrix metalloproteinases, and VSMC proliferation. The ubiquitous PPAR-ô is activated by fatty acids and prostacyclin and increases HDL cholesterol.

Vascular Relaxation: Role of Nitric Oxide and the Endothelium

Nitric oxide, a potent endothelium-derived relaxing factor, is synthesized from the oxidation of L-arginine by nitric oxide synthase (NOS) through the generation of *N*-hydroxyl L-arginine. Of the three characterized NOS isoforms—neuronal NOS (nNOS), inducible NOS (iNOS), and eNOS—it is the endothelial isoform that is localized mainly in endothelial cells, involved in endothelial-derived NO. Nitric oxide diffuses locally to the luminal surface of the endothelium and into the smooth muscle cells of the vascular wall, where it signals through many downstream pathways via guanylate cyclase to generate cGMP and by direct S-nitrosylation of cysteine residues in proteins, to activate signaling molecules such as transcription factors NF-κB and AP-1 and to inhibit Ca^{2+}-mediated vasoconstriction [6].

Multiple factors regulate eNOS activity, including calcium–calmodulin, depalmitoylation of eNOS, and caveolin-1. Changes in eNOS activity are mediated through Akt-dependent phosphorylation at Ser1177, which activates eNOS in response to stimuli, while phosphorylation at Thr459 decreases activation. Physiologically many stimuli promote eNOS expression to maintain NO production, whereas pathologically eNOS protein levels may be normal or even increased, despite endothelial dysfunction and reduced NO generation. These findings have led to the concept of "eNOS uncoupling," with a switch in the enzymatic activity of eNOS to generate superoxide ($^{\bullet}O_2^-$) rather than NO [96].

Physiologically NOS, in the presence of cofactors L-arginine and tetrahydrobiopterin (BH4), produces NO. BH4 is an essential cofactor for all 3 NOS isoforms, and all are capable of "uncoupling." Basal NOS activity correlates with the amount of BH4 bound to the enzyme. When BH4 levels are reduced, the oxidase domain of NOS yields molecular uncoupling and the catalytic activity becomes functionally "uncoupled." Enzymatic reduction of molecular oxygen by eNOS no longer couples to L-arginine, resulting in the

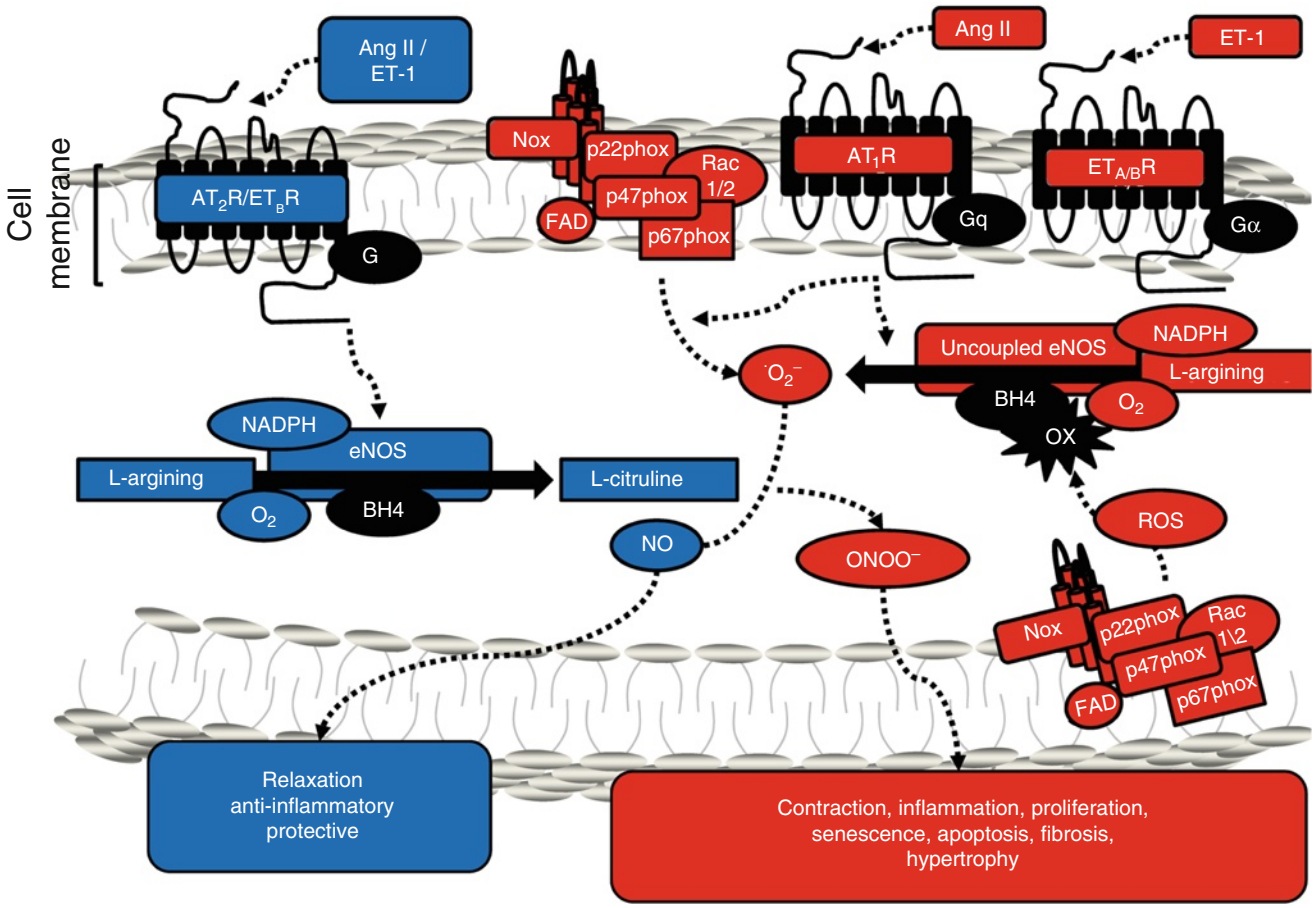

Fig. 4.7 NOS and ROS interactions in the vasculature. NO is produced by endothelial cells by the transformation of L-arginine and oxygen to L-citrulline and NO, by the enzyme eNOS. NO induces relaxation of VSMCs and is also a potent anti-inflammatory molecule. Ang II and ET-1, though AT2 and ETB receptors, induce NO formation. However, in vascular diseases, where endothelial dysfunction and damage to the vasculature is observed, eNOS becomes uncoupled, leading to production of superoxide, instead of NO. ROS induces eNOS uncoupling by oxidation of BH4 (cofactor for NO production induced by eNOS). High levels of superoxide can also react with NO and form $ONOO^-$, another ROS and potent proinflammatory and vasoconstrictor molecule. Abbreviations: *NO* nitric oxide, *eNOS* endothelial nitric oxide synthase, *BH4* tetrahydrobiopterin, *ONOO⁻* peroxynitrite

generation of injurious $^{\bullet}O_2^-$ rather than protective NO (Fig. 4.7) [96].

eNOS uncoupling, which shifts the nitroso–redox balance with adverse consequences, has been demonstrated in experimental hypertension and atherosclerosis. Uncoupled eNOS has also been demonstrated in essential hypertension, in patients with hypercholesterolemia and in chronic smokers. Reduced BH4 bioavailability and consequent NOS uncoupling and oxidative stress have been implicated in patients with diabetes, coronary artery disease, cardiac failure, and ischemia–reperfusion injury. In many of these conditions, exogenous BH4 has been shown to improve endothelial function and cardiovascular risk. Accordingly, there has been much interest in the potential use of BH4 in the treatment of hypertension and associated cardiovascular diseases. However, a recent clinical study failed to show beneficial effects of BH4 treatment in patients with coronary artery disease [97]. In addition to exogenous BH4 preventing uncoupling of NOS, some classical antihypertensive drugs, such as calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, and beta-blockers, may induce beneficial effects by preventing eNOS uncoupling.

Reactive Oxygen Species and Vascular Function

Reactive oxygen species (ROS) (Fig. 4.5) are generated by the reduction of oxygen and include unstable free radicals (species with an unpaired electron) such as the superoxide anion $^{\bullet}O_2^-$ and non-free radicals, such as hydrogen peroxide (H_2O_2) [98]. Reactive oxygen species, originally considered to induce damaging cellular effects, are now recognized to have important physiological actions such as the induction of host defense genes, activation of transcription factors, and stimulation of ion transport systems. In the vascular system,

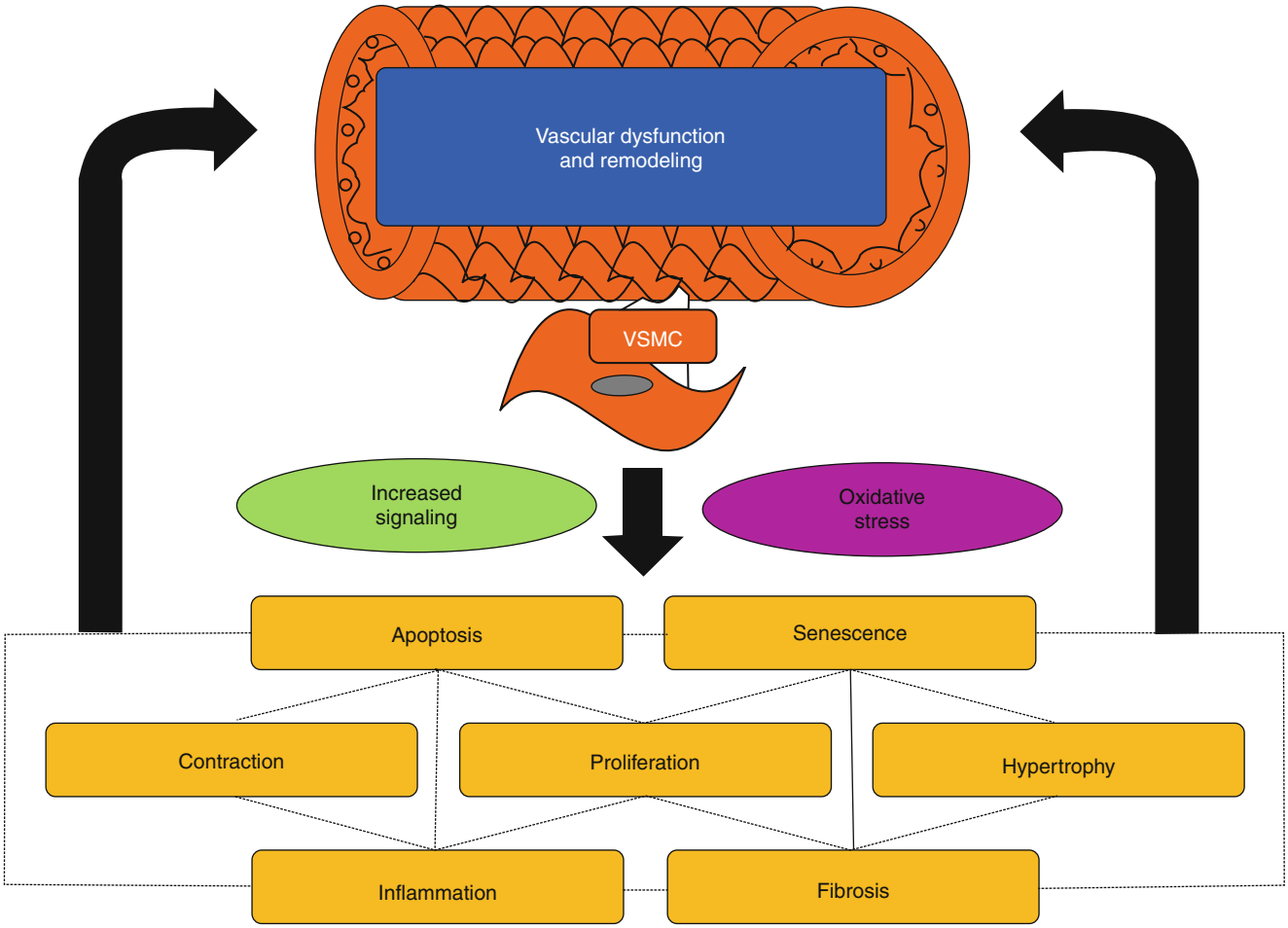

Fig. 4.8 Cellular responses associated with vascular damage. Increased signaling by vasoactive agents, peptides, or other molecules (ROS) leads to cellular responses such as apoptosis, senescence, increased contraction, growth, hypertrophy, inflammation, and fibrosis, which are all implicated (alone or in combination) with vascular dysfunction and remodeling. These deleterious responses play an important role on the development of many pathologies (hypertension, diabetes, atherosclerosis, chronic kidney disease, heart failure) where vascular disease is commonly observed

ROS play a physiological role in controlling endothelial function, vascular tone, and vascular integrity and a pathophysiological role in inflammation, hypertrophy, proliferation, apoptosis, constriction, migration, fibrosis, angiogenesis, and rarefaction, important factors contributing to endothelial dysfunction, vascular contraction, and arterial remodeling in cardiovascular diseases [99].

Molecular processes underlying ROS-induced cardiovascular injury involve activation of redox-sensitive signaling pathways. Superoxide anion and H_2O_2 stimulate MAP kinases, tyrosine kinases, Rho kinase, and transcription factors (NF-κB, AP-1, and HIF-1) and inactivate protein tyrosine phosphatases [100]. ROS also increase $[Ca^{2+}]_i$ and upregulate proto-oncogene and proinflammatory gene expression and activity. Oxidative stress was originally defined as molecular damage due to an imbalance between prooxidants and antioxidants. More recently, the definition has expanded to include the concept that molecular damage is due to impaired redox signaling and equilibrium.

A critical source of vascular ROS is a family of nonphagocytic NADPH oxidases (Noxs), including the prototypic Nox2-based NADPH oxidases, Nox1, Nox4, and Nox5 [101]. Other possible sources include mitochondrial electron transport enzymes, xanthine oxidase, cyclooxygenase, lipoxygenase, and uncoupled NOS [102]. Cross talk between ROS-generating enzymes, such as mitochondrial oxidases and Noxs, is increasingly implicated in cellular ROS production in the cardiovascular system. The role of ROS in the regulation of vascular function has been extensively reviewed [103].

Vascular Structural Changes in Cardiovascular Disease

In hypertension and other cardiovascular diseases, arteries undergo structural changes (remodeling) characterized by reduced vascular lumen with increased media thickness (Fig. 4.8) [104]. Myogenic tone, the intrinsic ability of

vessels to constrict in response to increased intraluminal pressure, contributes to structural alterations [105]. On the other hand, structural narrowing of the lumen may amplify vasoconstriction. Eutrophic vascular remodeling, characterized by reduced outer diameter and reduced lumen with no change in media mass and cross-sectional area, is observed in patients with mild–moderate hypertension. With chronic vasoconstriction and long-standing or severe hypertension, vessels become hypertrophic and fibrotic with increased extracellular matrix deposition. Other mechanisms that may participate in remodeling include inward growth encroaching on the lumen associated with apoptosis of cells in the periphery of the vessel wall. Vascular smooth muscle cell growth may predominate over apoptosis, and in this scenario, remodeling may be hypertrophic. This type of vascular remodeling is characterized by an increased media cross section and media to lumen ratio.

Molecular and Cellular Mechanisms of Vascular Remodeling

Molecular mechanisms underlying vascular remodeling are complex and multifactorial, but activation of the RAS, stimulation of growth signaling pathways, activation of tyrosine kinases, induction of proinflammatory responses, ROS, and modification of extracellular matrix components appear to be most important [105, 106]. Agonist-stimulated growth and profibrotic effects are modulated, in part, by endogenous production of mitogenic factors, such as TGF-β, PDGF, EGF, IGF-1, Ang II, and ET-1. Of these, TGF-β, a multifunctional cytokine, appears to be especially important. TGF-β increases extracellular matrix biosynthesis, downregulates matrix degradative enzymes, and influences integrin receptors, effects mediated, in part, by MAP kinases.

Arterial stiffness is associated with fibrosis, which involves accumulation of extracellular matrix proteins, such as collagen, elastin, fibrillin, fibronectin, and proteoglycans in the vascular wall [107]. Cell hypertrophy and proliferation and deposition of collagen and other components of the extracellular matrix contribute to media thickening in hypertrophic remodeling of resistance arteries. Cell growth and matrix deposition may result from blood pressure elevation or from growth-promoting factors including Ang II and ET-1 and from diminished activity of matrix metalloproteinases (MMPs), leading to accumulation of collagen type IV and V and fibronectin.

Apoptosis also contributes to structural remodeling [107]. Apoptosis influences fine-tuning of media growth and is increased in some vascular beds and decreased in others in hypertension. An imbalance between growth and apoptosis seems to be important.

Inflammation and Vascular Remodeling

Low-grade inflammation in the vascular wall is increasingly recognized as an important contributor to cardiovascular disease. Inflammation contributes to vascular remodeling, promoting growth and proliferation of VSMCs. Increased expression of adhesion molecules (VCAM-1, ICAM-1) on the endothelial cell membrane, accumulation of monocyte/macrophages, dendritic cells, natural killer (NK) cells, and B and T lymphocytes are some of the mechanisms that participate in the inflammatory response in the vascular wall [108]. Innate immunity has been implicated to contribute to the low-grade inflammatory response in hypertension where different subsets of T lymphocytes may be involved in processes leading to inflammation [109]. An imbalance seems to exist between the proinflammatory Th1, Th2, and Th17 and the anti-inflammatory T regulatory (Treg) subsets of T lymphocytes [110]. Mice deficient in T and B lymphocytes have a blunted hypertensive response to Ang II and DOCA salt and vascular remodeling in response to Ang II. Effector T cell but not B lymphocyte adoptive transfer corrected the lack of response to Ang II. The central and pressor effects of Ang II are also critical for T cell activation and development of vascular inflammation. One of the mechanisms whereby T lymphocytes participate in hypertension and peripheral inflammation is in response to increased oxidative stress.

Vascular Smooth Muscle, Endothelial Function, and Vascular Changes

Endothelial cells normally regulate vascular tone by releasing relaxing and constricting factors such as NO, arachidonic acid metabolites, ROS, and vasoactive agents. They also produce endothelial-derived hyperpolarizing factors (EDHF) that induce endothelium-dependent relaxation through hyperpolarization of underlying vascular smooth muscle cells independently of NO [111]. EDHF-mediated responses are important in hypertension, where they provide a vasorelaxation reserve for endothelial dysfunction due to decreased NO bioavailability. Endothelial dysfunction is a hallmark of hypertension and cardiovascular diseases and is characterized by impaired vasorelaxation, platelet activation, vascular permeability, and a proinflammatory and prothrombotic phenotype.

Of the many endogenous factors implicated to be important in the protection of the endothelium are endothelial progenitor cells (EPCs) [112]. EPCs are bone-marrow-derived cells capable of developing into mature endothelial cells. They contribute to vascular homeostasis through direct cell-to-cell contact and through autocrine and paracrine actions. EPCs mobilize out of the bone marrow in response to peripheral tissue hypoxia and injury and release EPC-activation factors, such as hypoxia-inducible factor-1 (HIF-1), VEGF,

erythropoietin, and NO, to facilitate endothelial healing, regeneration, and re-endothelialization after vascular damage. The number of circulating EPCs may reflect endothelial function since decreased numbers are associated with reduced arterial elasticity and decreased endothelial integrity. Circulating EPCs are reduced in hypertension.

Endothelial-derived microparticles are tiny fragments of cellular membranes that are generated from activated or apoptotic cells [113]. Microparticles circulate in healthy individuals, and their levels increase in cardiovascular and athero-thrombotic diseases. In vitro, endothelial microparticles are released in response to inflammatory stimuli such as TNF-α, thrombin, uremic toxins, ROS, and PAI-1. Although the precise mechanism leading to generation of microparticles is not fully understood, there is evidence that eNOS uncoupling, ROS, and low shear stress, features of endothelial dysfunction, enhance their production. The exact role of microparticles in vascular remodeling awaits clarification, but it is possible that they may be more than biomarkers, since microparticles themselves may influence endothelial function [114].

Conclusions

The vasculature is a highly dynamic system that is continually adapting to mechanical, hemodynamic, chemical, and neurohumoral stimuli. Of the many cell types that make up the vascular wall, vascular smooth muscle cells are particularly important since they have a high degree of phenotypic variability. The primary function of vascular smooth muscle cells is contraction, and accordingly, the "contractile phenotype" is considered as the differentiated phenotype. However, vascular smooth muscle cells also have many noncontractile functions, including migration, proliferation, inflammation, fibrosis, and secretion. Acute regulation of vascular diameter involves activation/deactivation of the contractile machinery, influenced by changes in transmembrane ion fluxes, intracellular calcium concentration, and membrane potential, regulated by mechanical, physical, and humoral factors. In addition to changes in vascular contractility, lumen diameter is influenced by structural characteristics of the vessel wall. Vasoactive agents, such as Ang II, ET-1, bradykinin, and neurotransmitters, regulate vascular function and structure and in pathological conditions contribute to vascular dysfunction and vascular remodeling. Signaling pathways implicated in these processes are complex, but changes in $[Ca^{2+}]_i$ play a pivotal role.

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Thrombosis

5

Farzana R. Bacchus and Mark Crowther

Introduction

Hemostasis is a preventative mechanism for blood loss after vessel injury, while thrombosis describes the pathogenic formation of thrombi. The precise balance of procoagulant and anticoagulant mechanisms keeps blood in a fluid state while circulating, yet can rapidly respond to vascular injury through clot formation. The initial formation of the platelet plug is classically termed "primary hemostasis," while propagation of the coagulation cascade is termed "secondary hemostasis."

Primary Hemostasis

Platelet Structure and Function

Platelets are central mediators in the hemostatic process. Platelets are small, anucleate fragments of megakaryocytes from the bone marrow. The platelet plasma membrane is a lipid bilayer which contains phospholipids with cholesterol, glycolipids, and glycoproteins embedded. Phospholipids are asymmetrically placed with negatively charged phospholipids predominantly on the inner layer; this becomes important in platelet activation and secondary hemostasis. Resting platelets retain a discoid shape, and with activation, there is remodeling of the cytoskeleton. This leads to formation of the open canalicular system with extensive pseudopodia, enhancing interaction with adjacent platelets. Platelets contain alpha and dense granules, the contents of which are released upon activation. Alpha granules contain a number of proteins including von Willebrand factor (vWF) which is a multimeric plasma protein, coagulation factors, beta-thromboglobulin, growth factors, and platelet factor 4. Dense granules contain calcium, adenosine diphosphate (ADP), adenosine triphosphate (ATP), and serotonin [1, 2].

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Platelet Adhesion

Injury to blood vessels allows exposure of the subendothelium. Platelets interact and adhere to exposed vWF through a glycoprotein (GP) complex on the platelet membrane, GPIb-V-IX (Fig. 5.1). This interaction is particularly important under conditions of high shear (such as small arteries, arterioles, and stenosed arteries) and is the initial step in platelet adhesion. Platelets may also adhere directly to collagen through GPVI and GPIa [3]. Platelets are able to roll, adhere, and spread along the extracellular matrix to form an activated platelet monolayer [4].

Platelet Activation, Recruitment, and Aggregation

Platelet activation is stimulated by platelet secretion products or by procoagulant activity via tissue factor (TF) and thrombin generation [5]. Multiple pathways lead to platelet activation by agonist stimulation including ADP, thromboxane A_2 (TXA_2), collagen, epinephrine, serotonin, and thrombin [6]. Many agonists exert their effect through G-protein-coupled receptors in the platelet membrane with intracellular cell signaling events. Together, these downstream events result in platelet shape change, platelet recruitment, expression of platelet procoagulant activity, and conversion of GPIIbIIIa into an active form. ADP and serotonin are secreted from dense granules and are thought to be the major agonists in initial platelet activation. ADP mediates platelet aggregation through the $P2Y_{12}$ and $P2Y_1$ receptors on the platelet surface [2].

C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_5, © Springer Science+Business Media New York 2013

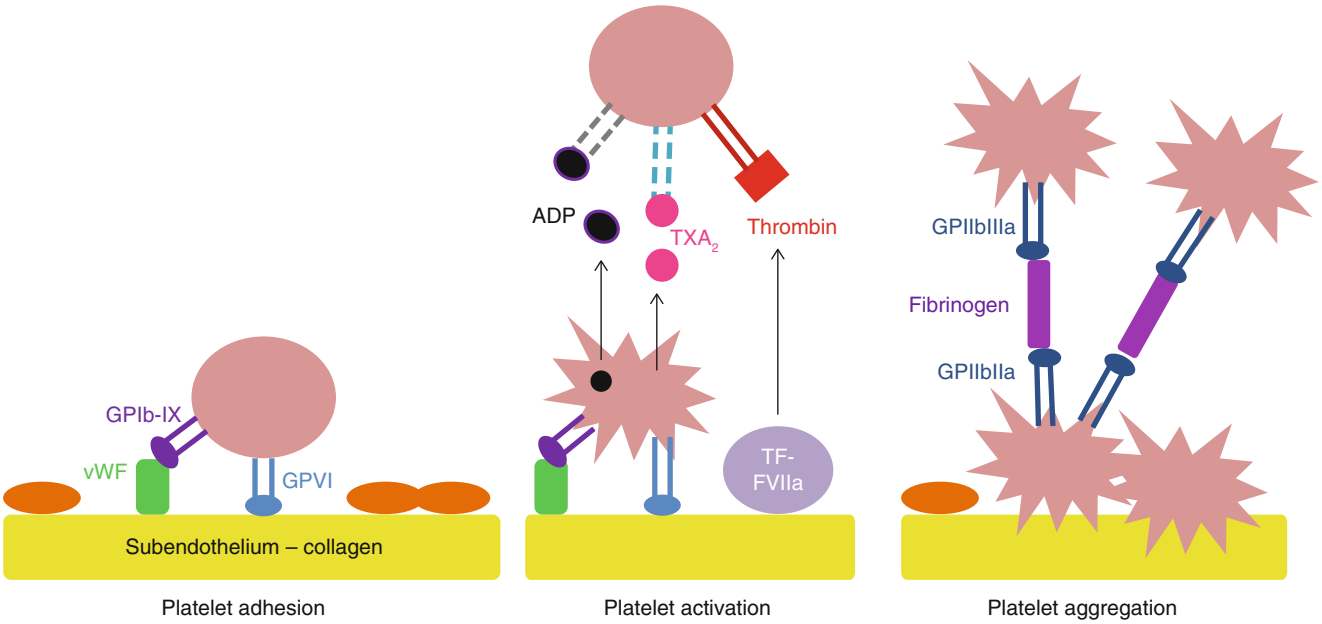

Fig. 5.1 Primary hemostasis: platelet adhesion, activation, and aggregation. Vessel injury exposes platelets to the subendothelium allowing platelet adhesion to von Willebrand factor (*vWF*) and collagen to the appropriate platelet receptors. Platelets become activated, releasing platelet agonists and further platelet activation and recruitment. Activated platelets express GPIIbIIIa on their surface allowing platelet aggregation via fibrinogen binding. *GP* glycoprotein, *TF* tissue factor, *ADP* adenosine phosphate, TXA_2 thromboxane A_2

Thromboxane production is induced through the arachidonic pathway during platelet activation, and its release potentiates platelet aggregation, while also exerting vasoconstrictive activity on blood vessels [2]. Thrombin is thought to be one of the most potent activators of platelets [7]. Thrombin binds to protease activator receptor (PAR)-1, cleaving the receptor and allowing the exposed ligand to bind and activate the receptor. Thrombin also binds to PAR-4, but activation is thought to require higher concentrations of thrombin [8].

The final pathways of platelet agonists is activation of platelet integrin GPIIbIIIa, resulting in an increased number of GPIIbIIIa integrins on the membrane surface with an increased affinity for its ligand, fibrinogen. This enables fibrinogen binding to the GPIIbIIIa platelet receptor. GPIIbIIIa activation and bridging of platelets by fibrinogen are the key players in platelet aggregation. vWF is also able to bind GPIIbIIIa and may play a role in platelet bridging and stabilization. During platelet activation, the phospholipid bilayer flips so that the platelet surface is negatively charged promoting procoagulant activity and facilitating secondary hemostasis [9].

Regulation of Platelet Activity

Under normal conditions, three pathways regulate platelet reactivity. Prostacyclin is produced by endothelial cells through the arachidonic acid pathway with the help of cyclooxygenase (COX)-1, COX-2, and prostacyclin synthase. Prostacyclin inhibits platelet function by altering cyclic adenosine monophosphate (cAMP) levels. Nitric oxide diffuses into platelets and stimulates intracellular cell signaling pathways resulting in decreased calcium flux. In turn, there is a reduction in GPIIbIIIA conformational change and, thus, decreased binding to fibrinogen. Ecto-ADPase, a component of the endothelial cell surface, limits the plasma level of ADP and ATP, limiting platelet reactivity [6].

Pharmacological Blockade of Primary Hemostasis

Given the thorough understanding of primary hemostasis, numerous inhibitors of platelet activation have been synthesized, and many are used in day-to-day clinical practice, while others are the subject of ongoing research. Pharmacological blockade of GPIIbIIIa, the ADP receptor, and the cyclooxygenase enzyme (and others) is widely employed in the prevention and treatment of cardiac disease, while other targets (such as the PAR receptors) are currently being investigated. The seminal importance of platelet-mediated primary hemostasis in cardiac disease is indicated by the frequency with which inhibitors of platelet function have been shown to improve outcomes in patients with or at risk of cardiovascular disease.

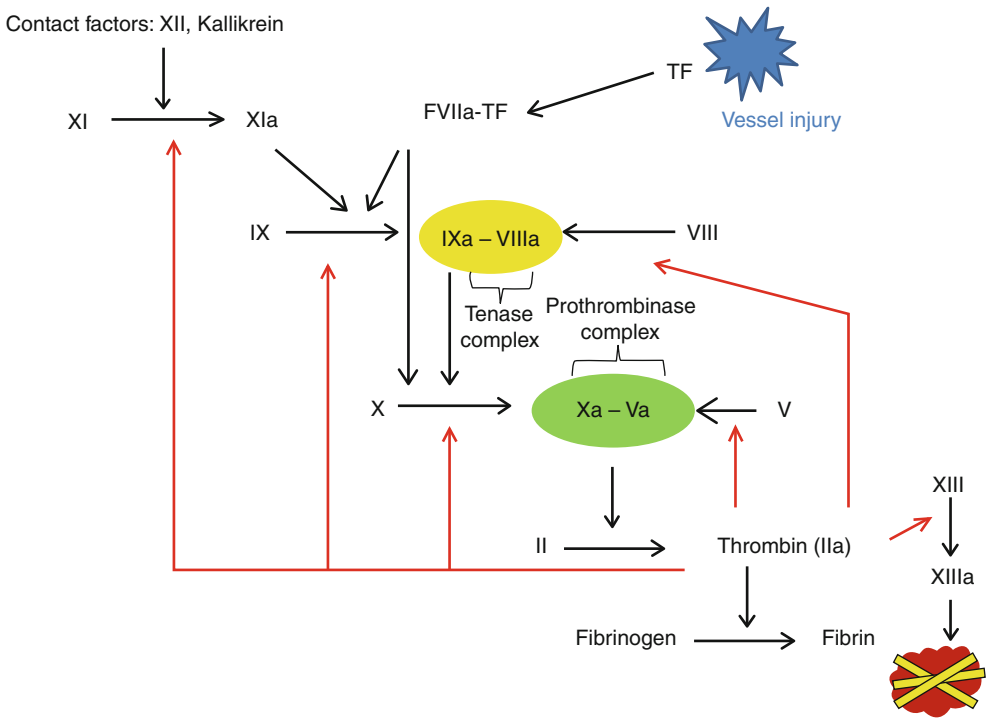

Fig. 5.2 The coagulation cascade. Vessel injury exposes tissue factor (*TF*) to FVIIa, which binds and activates FIX and FX. The first burst of thrombin is produced and feeds back to activate further coagulation factors (*red arrows*). In this way, thrombin generation occurs independently of TF-FVIIa complex

Secondary Hemostasis and the Coagulation Cascade

The classic approach to the coagulation cascade is the extrinsic pathway, initiated by tissue factor, and the intrinsic pathway, initiated by contact factors. Historically, coagulation factors were named in the order they were discovered rather than numerical order of event sequence. More recently, a cell-based model of coagulation has been proposed: initiation, amplification, and propagation [10].

Initiation

The coagulation cascade is initiated by tissue factor (TF), a membrane protein, when it comes in contact with factor VIIa (FVIIa). Circulating FVII exists predominantly in its zymogen, or inactive form, while small amounts exist in its active form, FVIIa. TF is exposed to flowing blood at the site of vessel injury and interacts with FVIIa, triggering initiation of the coagulation cascade. The TF-FVIIa complex converts FX and FIX to its active forms (FXa and FIXa). FIXa and FVIIIa form a complex on the negatively charged phospholipid platelet surface to form the "tenase complex" and activate FXa. FXa activates the coenzyme FV to FVa, and this complex of activated factors assembles on the negatively charged surface of the activated platelet to form the "prothrombinase complex." Prothrombin is converted to thrombin by the prothrombinase complex, in the presence of calcium and phosphatidylserine, a negatively charged phospholipid [11] (see Fig. 5.2).

Amplification and Propagation

The small amount of thrombin generated then feeds back and amplifies the system leading to a burst of thrombin. Thrombin activates platelets which lead to alpha-granule release of FV, which is also activated by thrombin. Thrombin cleaves FVIII from vWF, producing FVIIIa. FXI in the "intrinsic pathway" is converted to FXIa, which activates FIXa in the downstream cascade. FXI may be the initiator after TF-FVIIa is terminated [5]. The large thrombin burst results from the actions of the tenase and prothrombinase complexes. Finally, thrombin converts fibrinogen to fibrin monomers and activates FXIII. FXIIIa cross-links fibrin polymers to form the insoluble fibrin clot [11].

The intrinsic pathway involves plasma proteins that assemble when they come in contact with negatively charged surfaces. For this reason, FXII, kallikrein, and high molecular weight kininogen are also known as the plasma contact system. Once activated, FXIIa activates FXIa, which continues down the coagulation cascade with FIXa activation. While FXIIa activation is required for measurement of the activated partial thromboplastin time (aPTT), its role in initiating coagulation in vivo is less clear [12]. Patients who are severely deficient in factor XII will have very prolonged aPTTs without a bleeding disorder.

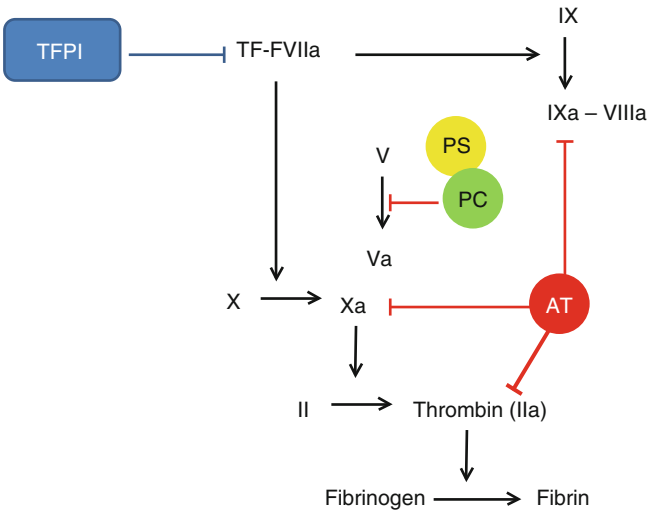

Fig. 5.3 Inhibitors of the coagulation cascade. Tissue factor pathway inhibitor (*TFPI*) inhibits TF-FVIIa complex. Antithrombin (*AT*) inhibits serine proteases especially thrombin and factor Xa. Protein C (*PC*) inhibits activation of factor Va, and protein S (*PS*) acts as a cofactor for PC

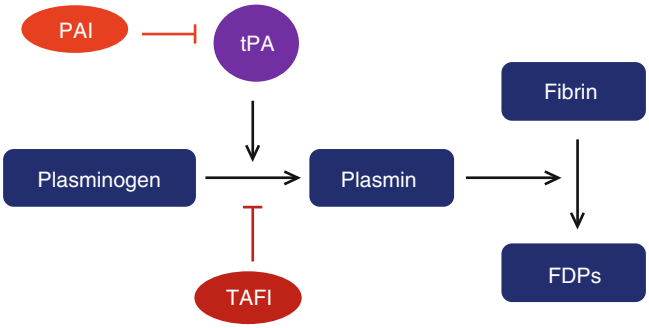

Fig. 5.4 The fibrinolytic process. Plasminogen is converted to plasmin by tissue-plasminogen activator (*tPA*). Plasmin then breaks down clot-bound fibrin to form fibrin degradation products (*FDPs*). Plasminogen activator inhibitor (*PAI*) inhibits tPA and thrombin-activatable fibrinolysis inhibitor (*TAFI*) inhibits the conversion of plasminogen to plasmin by tPA

Natural Anticoagulants

The principle inhibitor of the TF-FVIIa complex is tissue factor pathway inhibitor (TFPI). TFPI is produced by the endothelial cells and binds to the TF-FVIIa complex. TFPI ensures that small procoagulant stimuli in circulation do not lead to large thrombin bursts and pathologic thrombosis [13].

Antithrombin (AT) is a serine protease inhibitor and inactivates coagulation factors in their free unbound state, namely, thrombin, FVIIa, FXa, and FIXa. Protein C (PC), activated by thrombin after binding to thrombomodulin on healthy endothelial cells, cleaves and inactivates FVa and FVIIIa. Protein S (PS) acts as a cofactor to APC [13] (see Fig. 5.3). Congenital or acquired deficiencies of AT, PC, and PS are known to be associated with venous thrombosis; such deficiencies do not appear to be associated with arterial thrombosis.

Fibrinolysis

Fibrinolysis refers to the breakdown of the fibrin clot. Plasminogen, a serine protease zymogen, is converted to plasmin by tissue plasminogen activator (tPA). Plasmin causes breakdown of the fibrin protein to fibrin degradation products (FDP) [14]. Once fibrinolysis has been initiated, plasminogen and tPA are able to bind fibrin, accelerating the conversion of plasminogen to plasmin. Fibrinolysis provides a mechanism for homeostasis and prevention of thrombosis. Thrombin-activatable fibrinolysis inhibitor (TAFI) blocks the binding site of plasminogen and tPA, in this second stage of fibrinolysis, thereby decreasing the production of plasmin and inhibiting dissolution of the fibrin clot. Plasminogen activator inhibitor (PAI) inhibits the activity of tPA. Both TAFI and PAI are activated by thrombin [15] (see Fig. 5.4).

Atheromatous Thrombus Formation

Chronic atherosclerotic lesions are associated with plaque formation. Rupture of the fibrous cap of the plaque exposes blood to collagen and to TF in the macrophages of atheroma. There are distinct hemostatic factors in the platelet and coagulation systems that modulate atherosclerosis and have an effect on atherothrombosis. A systemic inflammatory environment leads to a proatherogenic endothelium, independent of vessel wall injury [16]. GPIb receptors are able to interact with vWF secreted by the endothelium. Once adherent, platelets secrete atherogenic mediators such as cytokines, chemokines, adhesion molecules, and coagulation factors. P-selectin is an adhesion ligand which becomes increased on platelets and further mediates platelet-endothelial interaction. Signaling by P-selectin stimulates monocytes and macrophages as well as engaging P-selectin glycoprotein ligand 1 on monocytes and neutrophils. This allows formation of platelet-monocyte aggregates and the growing platelet plug. In this way, leukocytes may be incorporated into thrombus formation and atheromatous thrombus. CD40 ligand and platelet factor 4 are released from activated platelets and also induce inflammatory responses [6].

TF is constitutively active on fibroblasts and smooth muscle cells of vessel walls. During inflammation, TF expression can be induced on monocytes and endothelial cells. Within the atherosclerotic lesion, TF is localized to macrophages and vascular smooth muscle cells. TF may also be expressed on circulating microparticles, small membrane-bound vesicles derived from various blood cells including platelets, leukocytes, and endothelial cells. TF is thought to exist in a latent or

"encrypted" (inactive) form – in this way, TF can exist in the circulation without causing thrombosis. The mechanism by which TF becomes activated is unknown, but may reside in molecular dimerization [5]. One theory is that the inflammatory environment may activate the encrypted form of circulating TF. TF activity is higher in patients with acute coronary syndromes rather than those with stable cardiovascular disease, suggesting a role for the "active" plaque in systemic activation of coagulation. The TF-FVIII complex may also be involved in cell signaling processes that are proatherogenic [16].

Other coagulation proteins, including FXa, thrombin, fibrinogen, and FXIII, are thought to contribute to the proinflammatory cytokines and increased expression of cell-adhesion molecules [16]. Although not considered to be essential for hemostasis in vivo, FXII may be involved in the pathogenesis of arterial thrombosis. The potential role of contact activation of thrombosis in coronary artery disease was highlighted by the observation that cardiac interventional procedures are associated with a higher failure rate in patients receiving fondaparinux (a highly specific inhibitor of factor Xa with no inhibitory activity against the contact pathway) than heparins (which, to a greater or lesser degree, are all able to inhibit contact activation of coagulation). FXII-deficient mice have been shown to be protected from arterial thrombosis and stroke, but further research is needed in this area [17].

Of the anticoagulant pathways, TFPI tends to be overexpressed in atherosclerotic lesions. TFPI deficiency has been associated with atherothrombosis [16].

Targeted Drug Therapy

Over the last 20 years, given the significant advances in our understanding of hemostasis and thrombosis, drug development is ongoing to target pathways involved in pathologic disease. Here we will review the mechanisms of action and characteristics of the currently available antiplatelet, anticoagulant, and antithrombolytic drugs. The safety and efficacy of each drug, along with their indications, are beyond the scope of this chapter. Readers are directed to the most recent 9th edition of the *American College of Chest Physicians Antiplatelet, Anticoagulant and Antithrombotic* chapters, which are referenced in the appropriate sections.

Antiplatelet Agents

Aspirin

Aspirin is the most studied antiplatelet drug. Normally, arachidonic acid is converted to prostaglandin (PGH_2) by COX-1 (also called prostaglandin synthase-1), and then

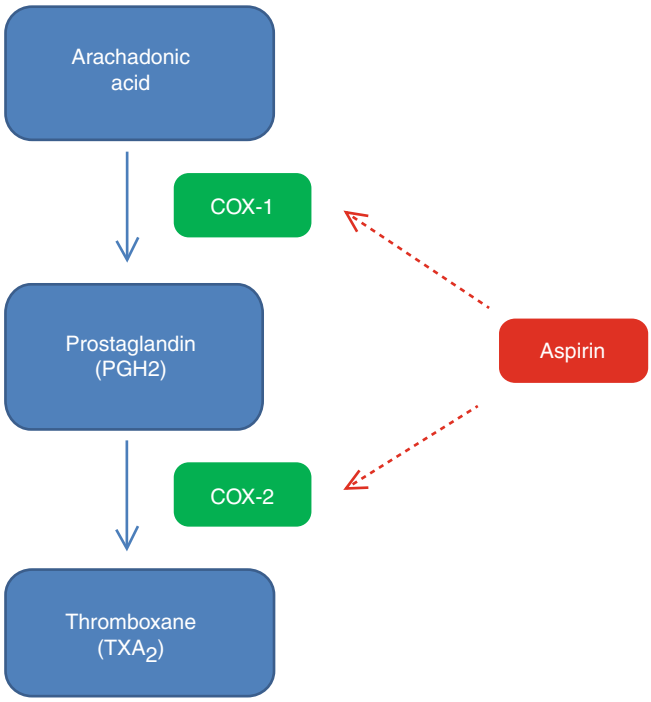

Fig. 5.5 Mechanism of action of aspirin in platelets. Aspirin inhibits cyclooxygenase (*COX*)-1 and COX-2 enzymes leading to decreased production of thromboxane A_2

PGH_2 is converted to its terminal product, thromboxane, by COX-2 (also called prostaglandin synthase-2) in platelets. COX-1 and COX-2 may be induced during platelet activation, while COX-2 alone may be induced by inflammatory mediators. Aspirin reduces thromboxane (TXA_2) production by acetylating a specific serine residue in COX-1 and COX-2, and thereby inhibiting these enzymes. This inhibition is irreversible. In this way, reduction of TXA_2 leads to decreased platelet activation and aggregation. Low-dose aspirin selectively inhibits COX-1, while higher doses of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are needed for COX-2 inhibition [18, 19] (see Fig. 5.5).

Aspirin has rapid absorption with serum peak level at 30–40 min (enteric-coated aspirin peaks at 3–4 h). Bioavailability is 40–50 % (lower with enteric-coated aspirin). Plasma half-life is 15–20 min, although the antiplatelet effect is irreversible for the life span of the platelet (7–10 days) [18].

Major complications are bleeding and gastrointestinal side effects, which appear to be dose dependent. Aspirin doses less than 100 mg/day are associated with less GI side effects than 300 mg/day. The incidence of other bleeding has not been shown to be different between the groups [18].

Aspirin has many indications in cardiovascular disease including coronary artery disease, acute coronary syndromes, transient ischemic attacks, ischemic stroke, and atrial fibrillation.

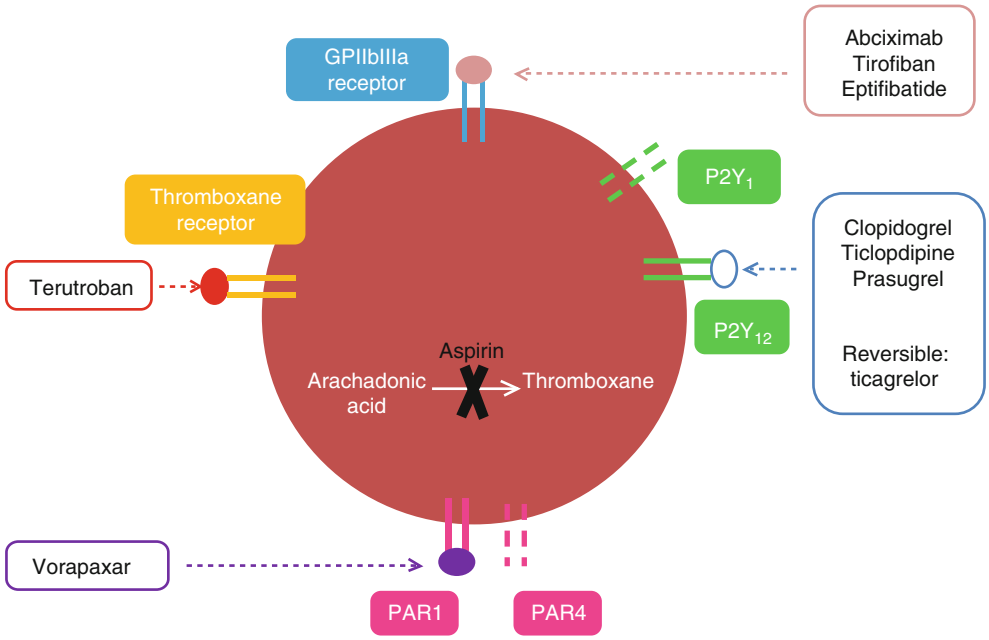

Fig. 5.6 Targets of antiplatelet drugs

Thienopyridines

Thienopyridines, including ticlopidine, clopidogrel, and prasugrel, are all oral prodrugs that must first be metabolized by the liver's CYP450 enzyme system. The active metabolites irreversibly inhibit the platelet $P2Y_{12}$ receptor, which is the site of action for ADP-associated platelet aggregation (Fig. 5.6). Cumulative dosing of these drugs alters their pharmacokinetics.

Ticlopidine

Ticlopidine is a first-generation thienopyridine with a significant toxicity profile. Bone marrow suppression and thrombotic thrombocytopenia purpura, with its high mortality rate, are reasons why ticlopidine has largely been replaced by clopidogrel in current therapeutics [18].

Clopidogrel

Clopidogrel undergoes two oxidization processes to produce the active metabolite. The CYP2C19 and CYP3A4 are the two major enzymes involved in clopidogrel bioactivation. CYP2C19 is involved in both of the two oxidative processes, while CYP3A4 is only involved in the second [18].

Clopidogrel is rapidly absorbed and metabolized. 15 % of the drug exists in the active form, while the rest is hydrolyzed to an inactive derivative. The half-life is 8 h and pharmacokinetics of the drug vary based on dosing. Loading doses of 300 mg achieve platelet inhibition more quickly than the 75 mg once-daily dosing, while the 600 mg loading dose may reach peak levels within 2–4 h [18].

"On-clopidogrel high platelet reactivity" describes the concept of clopidogrel resistance. Examples of drugs that may interfere with clopidogrel through modification of its hepatic activation include proton pump inhibitors like omeprazole and lipid-lowering agents like atorvastatin. Polymorphisms in the CYP2C19 gene have been identified with the most common loss of function mutation being "*2" [18]. Since CYP2C19 is involved in both steps of clopidogrel metabolism, these mutations may play an important role in clopidogrel "failure" as manifest by thrombosis in patients receiving "usual doses" of clopidogrel. However, there is currently no role to support platelet function or genetic testing – and, in fact, recent studies have failed to show reduced thrombosis in patients whose clopidogrel dosing has been guided by analysis of "on-drug" platelet activation.

There are numerous clinical trials of thienopyridines in acute coronary syndromes and percutaneous coronary intervention, some as single agents (e.g., CAPRIE) and as dual antiplatelet agents (e.g., CURE). These are discussed elsewhere in this text.

Prasugrel

Prasugrel is very rapidly absorbed with a peak serum level at 30 min. It is more potent and produces more consistent inhibition of platelet activation than clopidogrel. The faster onset of action may be due its single-step CYP450 hepatic metabolism compared to clopidogrel's two steps [19].

Clinical trials have shown its efficacy in ACS with higher bleeding risks.

GPIIbIIIa Inhibitors

GPIIbIIIa antagonists prevent binding of fibrinogen, the final stage of many platelet activation pathways. Thus, fibrinogen-dependent platelet bridging and aggregation is inhibited. In this way, GPIIbIIIa inhibitors are very potent antiplatelet agents.

Abciximab

Abciximab is a humanized chimeric Fab-fragment of the monoclonal mouse antibody, directed against GPIIbIIIa receptors on platelets. Abciximab is a noncompetitive inhibitor of the GPIIbIIIa receptor [19]. When available receptors are less than 50 % on the platelet surface, there is significant inhibition of platelet aggregation [18]. With its short half-life, it is given intravenously. Thrombocytopenia occurs in 1–2 % of patients receiving abciximab and is thought to be immune in nature. Platelets usually decrease within the first 24 h, but may fall as early as 2 h after the start of the infusion.

Tirofiban and eptifibatide are two small, competitive inhibitors of GPIIbIIIa receptors. Tirofiban is a non-peptide that selectively binds to GPIIbIIIa. Eptifibatide is a synthetic disulfide-linked cyclic heptapeptide, which has specificity for GPIIbIIIa. Both have been reported to cause immune thrombocytopenia.

Phosphodiesterase Inhibitors

Dipyridamole is a pyrimidopyrimidine derivative with vasodilator and antiplatelet properties. Its exact mechanism of action is unclear. Theories include enzyme inhibition resulting in higher intracellular concentrations of cAMP, an inhibitor of platelet aggregation, and direct stimulation of prostacyclin, involved in platelet activity regulation [18].

Other Antiplatelets

Reversible $P2Y_{12}$ inhibitors are associated with rapid onset and offset of platelet inhibition. An oral inhibitor, ticagrelor, is a noncompetitive antagonist of the $P2Y_{12}$ receptor and has been studied in a number of clinical trials [19].

Thrombin receptor agonists, such as vorapaxar, with PAR-1 selectively are currently under investigation [19].

Thromboxane receptor antagonists have been developed including terutroban. However, recent phase 2 and 3 studies have led to a halt in the development of this drug [19].

Anticoagulants

The last few years have seen an exciting time with the development of many new anticoagulants. This section will review the mechanism of action and drug characteristics of the heparin and heparinoid derivatives, vitamin K antagonists, and direct thrombin inhibitors (see Fig. 5.7). These anticoagulants have specific indications in a number of cardiac diseases including acute coronary syndromes, percutaneous coronary intervention, and atrial fibrillation. Readers are directed to the 9th edition ACCP guidelines and to current reviews in the literature for indications, safety, and efficacy data.

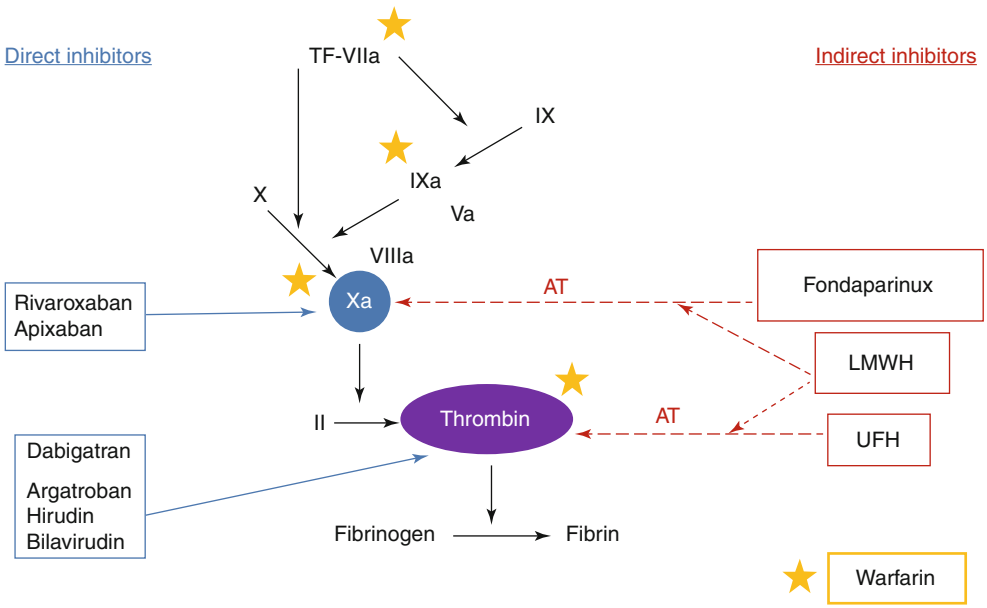

Fig. 5.7 Targets of anticoagulant drugs. *AT* antithrombin, *UFH* unfractionated heparin, *LMWH* low molecular weight heparin

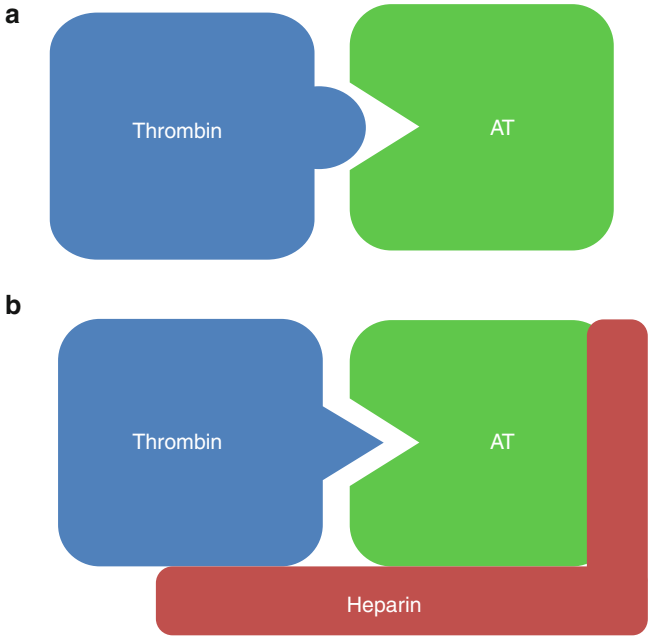

Fig. 5.8 Mechanism of action of heparin. (**a**) Slow inhibition of thrombin by antithrombin (*AT*). (**b**) Rapid inhibition of thrombin by antithrombin, in the presence of heparin

Heparin and Heparinoid Derivatives

Unfractionated Heparin

Unfractionated heparin (UFH) is an indirect inhibitor of thrombin and other serine protease coagulation factors, especially factors Xa and IXa. UFH is a sulfated polysaccharide molecule, with a unique pentasaccharide sequence, through which it binds antithrombin and exerts its effect. Only one third of heparin molecules bind to antithrombin, with the remainder having little anticoagulant effect [20]. In the absence of heparin, antithrombin binds to thrombin at a slow rate. In the presence of heparin, heparin binds to antithrombin causing a conformational change in antithrombin, allowing rapid binding to and inactivation of thrombin and other coagulation factors. Thereafter, heparin is able to dissociate and bind more antithrombin (see Fig. 5.8).

UFH is administered parenterally, either intravenously or subcutaneously, and is oftentimes initiated with an IV bolus. UFH is primarily cleared extrarenally and has an unpredictable dose-dependent anticoagulant response. Its initial half-life is 30 min and increases up to 90 min with an IV infusion. UFH may be monitored using the aPTT or by measuring heparin and anti-Xa levels. Heparin resistance may occur in the setting of antithrombin deficiency or rapid clearance of heparin [21]. Protamine sulfate may be used as a reversal agent.

Major side effects of heparin include bleeding, heparin-induced thrombocytopenia (HIT), and osteoporosis. Heparin may induce antibody binding to platelet factor 4, which causes platelet activation. This immune-mediated platelet activation may cause thrombosis and HIT. Heparin may also bind to osteoblasts which activated osteoclasts and cause osteoporosis [21].

Low Molecular Weight Heparin

Like UFH, low molecular weight heparin (LMWH) binds to antithrombin. However, LMWH is one third the mass of UFH and, due to a reduced chain length compared with UFH, has reduced inhibitory activity against thrombin relative to factor Xa. Compared to heparin, it has a more predictable dose-response relationship and longer half-life of 3–6 h [21]. It is administered by subcutaneous injection one to two times daily and is excreted renally. Monitoring is generally not required but is widely available should monitoring be required.

Major side effects of LMWH are similar to those of UFH. However, LMWH has reduced binding to platelets and osteoblasts and therefore reduced incidence of HIT and osteoporosis, respectively.

Fondaparinux

Fondaparinux is a synthetic analogue of the naturally occurring pentasaccharide found in UFH and LMWH that is required for UFH/LMWH to catalyze thrombin-mediated inactivation of coagulation factors. Fondaparinux inhibits only factor Xa and has a longer half-life (17 h) than LMWH. It is administered in a once-daily subcutaneous injection; the fixed dose for acute coronary syndromes is 2.5 mg. Monitoring is not required. It is almost completely renally cleared and should not be used in severe renal impairment [21].

The major side effect of fondaparinux is bleeding. Case reports and small case series suggest that fondaparinux can be safely used in patients with HIT (although use for this indication is “off label”). Safety data for use in pregnancy is lacking, and thus fondaparinux is not widely used in pregnancy.

Vitamin K Antagonist

Warfarin

Until recently, vitamin K antagonists were the only oral anticoagulant available. Warfarin (and related compounds, acenocoumarol and phenprocoumon) is a vitamin K antagonist, which inhibits the terminal modification of the vitamin K-dependent coagulation factors, II, VII, IX, X, and natural anticoagulants, proteins C and S. Vitamin K is

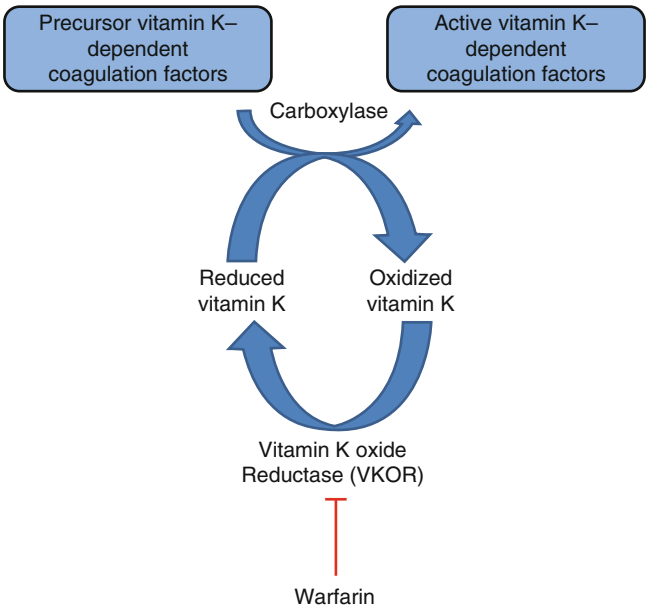

Fig. 5.9 Mechanism of action of warfarin

essential for conversion to the active forms of these coagulation proteins, which require carboxylation of the glutamate residues at the N-terminal region. Reduced vitamin K is a cofactor in the carboxylation process, which results in activated coagulation factors and vitamin K epoxide, the oxidized form of vitamin K. Vitamin K oxide reductase (VKOR) is the enzyme required for recycling and conversion back to reduced vitamin K. VKOR is the target of warfarin, which inhibits the enzyme and the production of the necessary cofactor, reduced vitamin K [22] (see Fig. 5.9).

Warfarin is a racemic mixture of two active isomers, R and S, with a half-life of 36–42 h, allowing for once-daily dosing. Warfarin is rapidly absorbed, but its full anticoagulant effect takes days to manifest, owing to the long half-life of coagulation factors already in circulation when warfarin is initiated. Warfarin is metabolized by the cytochrome P450 system of the liver: S-warfarin primarily by CYP2C9 and R-warfarin primarily by CYP3A4. As such, warfarin is subject to numerous drug interactions that inhibit or enhance the P450 system and may increase or decrease its anticoagulant effect [23]. Genetic mutations in CYP2C9 and the VKOR gene, as well as dietary vitamin K intake have all been identified as causes of variability in warfarin dosing and efficacy.

Monitoring is required with the international normalized ratio (INR) derived from the prothrombin time (PT). More frequent monitoring is necessary during initiation of warfarin or with introduction of new medications. For most indications the target INR is 2.0–3.0. Some patients with mechanical valves are treated with warfarin to achieve an INR of 2.5–3.5. A number of antidotes are available – choice of agent depends on the reason for reversal of anticoagulant effect and its urgency. Vitamin K allows reversal of warfarin inhibition, prothrombin complex concentrate (PCC) provides nonactivated vitamin K-dependent coagulation factors, and fresh frozen plasma (FFP) provides all coagulation factors. In general, for minor bleeding, simple warfarin dose reduction is sufficient, along with local measures. Major bleeding requires interruption of therapy, with consideration of reversal. Life-threatening bleeding requires interruption of therapy, administration of life-sustaining interventions, and rapid and complete reversal of the anticoagulant effect with parenteral vitamin K and, where available, a prothrombin complex concentrate.

The major adverse effect of the vitamin K antagonists is bleeding, the risk of which depends on individual patient risk and INR. Other non-hemorrhagic complications include skin necrosis, limb gangrene, and purple-toe syndrome, all of which are rare though significant if they do occur [22]. The most common use of warfarin in cardiovascular disease is in the setting of atrial fibrillation for stroke prevention.

Direct Thrombin Inhibitors

Direct thrombin inhibitors (DTI) are small polypeptides that bind directly to thrombin and do not require a cofactor like antithrombin to form a complex and exert their effects. DTIs can inhibit both soluble thrombin and clot-bound thrombin [24], unlike the heparins. There are three parenteral DTI agents available, all of which require intravenous administration and monitoring, making them unsuitable for long-term use. There are currently no antidotes for their reversal.

Hirudin was the first DTI in clinical use. It has a high affinity for thrombin and irreversibly binds, with reported higher rates of bleeding. It is renally cleared and is contraindicated in renal insufficiency. Its two derivatives are lepirudin and desirudin [21].

Bivalirudin is a synthetic analogue of hirudin. It reversibly binds to thrombin, giving it a more favorable side-effect profile. Only 20 % of the drug is cleared renally [21]. Bivalirudin is widely used in some cardiac centers and may be used for cardiopulmonary bypass in patients with heparin-induced thrombocytopenia.

Argatroban is a small molecule that competitively inhibits thrombin, reversibly. It is metabolized by the liver and so it is a good option in patients with HIT and renal insufficiency [21]. Argatroban is administered as a constant IV infusion, monitored by the aPTT. Its dose must be reduced in patients with hepatic impairment. Transitioning patients from argatroban to warfarin is problematic due to extreme INR prolongation in some patients receiving both drugs.

New Oral Anticoagulants

Many of the anticoagulants described above have potential advantages over heparin; however, they require parenteral administration. The only oral anticoagulant, warfarin, has

many disadvantages including the need for monitoring, narrow therapeutic index, and drug interactions. The new oral agents directly inhibit coagulation factors and have the advantages of their parenteral counterparts, with the added advantage of oral administration.

Dabigatran

Dabigatran binds to the active site of thrombin, thereby inhibiting its function. Dabigatran is a small synthetic molecule that is a reversible, highly selective, and competitive DTI. Dabigatran is not absorbed from the gut and so is administered as a prodrug, dabigatran etexilate. Peak plasma concentration is reached within 2 h, and once steady state is reached, the half-life is 12–17 h. After hepatic metabolism, dabigatran is predominantly cleared in the kidneys [25].

The major adverse effects include bleeding, especially GI bleeding, and dyspepsia. No routine monitoring is required. Routine coagulation testing does not correlate linearly with dabigatran dose; thrombin clotting time may be helpful. There is no antidote for reversal, but dialysis may be useful in removing drug in the setting of major bleeding [22]. Dabigatran is the first oral DTI approved for clinical use, in the setting of atrial fibrillation for stroke prophylaxis and venous thromboembolism (VTE).

Rivaroxaban

Rivaroxaban is a direct-acting, orally available inhibitor of factor Xa both within the prothrombinase complex and clot-bound FXa. Factor Xa inhibition blocks the positive feedback loop present in coagulation that allows one molecule of thrombin to produce more than 1,000 subsequent molecules of thrombin [26]. Rivaroxaban is a reversible, selective, and competitive inhibitor of factor Xa. Peak plasma concentration is reached in 3 h, and once at steady state, has a half-life of 4–9 h. Unlike dabigatran, there are few absorption issues and the oral bioavailability is 80 %. Sixty-six percent of rivaroxaban is excreted by the kidneys.

The major adverse effect is bleeding, although there is no antidote for reversal. Rivaroxaban is available for clinical use in some settings and has been studied in atrial fibrillation, acute coronary syndromes, and VTE.

Apixaban

Apixaban, similar to rivaroxaban, is also a small, reversible, and selective molecule that inhibits factor Xa in the prothrombinase complex and in formed clot. With greater than 50 % bioavailability, the peak plasma concentration is reached in 3–4 h and the half-life is 10–14 h. Apixaban is metabolized in part by the kidney and the liver, through CYP3A4-dependent and CYP3A4-independent mechanisms [27].

The major adverse effect is bleeding and there is no antidote for reversal. Apixaban has been studied in atrial fibrillation, acute coronary syndromes, and VTE.

Thrombolytic Agents

Thrombolytic (or fibrinolytic drugs) are intravenously infused plasminogen activators which activate the fibrinolytic system. There are four available thrombolytic drugs: streptokinase, alteplase (tPA), reteplase, and tenecteplase. Most are metabolized by the liver and have half-lives ranging from 15 to 23 h [28].

Streptokinase binds to plasminogen, cleaving peptide bonds and leading to plasmin activation. Unlike the other thrombolytics, streptokinase is not fibrin-specific, but instead acts as an activator complex. It has a long half-life of 18–23 h and is associated with significant rate of allergic reactions – additionally many patients have neutralizing antibodies. For these reasons, it is no longer commonly used as a thrombolytic agent in North America, but it is still widely used in many nations due to its low cost and relatively high efficacy.

Alteplase is recombinant tissue plasminogen activator (tPA), which is a naturally occurring enzyme. It is fibrin-specific, and when bound to fibrin, alteplase has an increased affinity for plasminogen. Non-fibrin-bound tPA in the systemic circulation does not extensively activate plasminogen. Alteplase has a short half-life of 3–8 h, giving it a more favorable side effect profile.

Reteplase is a recombinant plasminogen activator but is a nonglycosylated form. Reteplase is less fibrin-specific and has a half-life of 15–18 h. Unlike the other thrombolytics, reteplase is metabolized by the kidneys.

Tenecteplase is a genetically engineered mutant of tPA and is more fibrin-specific than alteplase. With its longer half-life of 18–20 h, it can be administered as a single IV bolus. It is as effective as alteplase, with a reduction in intracranial hemorrhages.

Summary

A profound understanding of the molecular basis of coagulation has led to the development of a broad range of specific inhibitors of primary and secondary hemostasis. Highly effective platelet inhibitors, oftentimes administered in combination, potently inhibit coagulation activation and are very widely used for the primary and secondary prevention of a variety of cardiovascular disorders. Innovation in this area

continues with the discovery and evaluation of both inhibitors of novel targets and more effective inhibitors of more traditional targets. Anticoagulants and thrombolytic agents have also been widely studied; most recently the introduction of two new classes of oral anticoagulants holds the promise of more effective, and easier to use, therapy than the oral vitamin K antagonists which have been the mainstay of oral anticoagulant therapy for more than 50 years.

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The History and Physical Examination of the Cardiovascular System

6

Rajat Gupta and Patrick O'Gara

Observe, record, tabulate, communicate. Use your five senses. Learn to see, learn to hear, learn to feel, learn to smell, and know that by practice alone you can become expert.

Sir William Osler

The art of medicine is built upon the patient-doctor interaction. Master clinicians establish an intimate connection with their patients that allows for the development of a differential diagnosis, all within the confines of time-limited interaction. In this chapter, we outline the general approach to the cardiovascular patient with specific emphasis on the history and physical examination.

The History

In a prior edition of this textbook, Dr. Jeremy Swan stated that the objective for the physician during the patient encounter is to initiate the process of interaction and confidence building. He wrote, "It is an exercise in unstructured probabilistics, and should be so regarded. In all this, the opportunity to establish a sense of trust and confidence between physician and patient is paramount. After all, it is the patient who 'hired' you, not the contrary." [1]

This second objective of establishing rapport is what forms the foundation of the patient-doctor relationship. Though the particulars cannot be taught in the pages of a textbook, respect for the process cannot be overemphasized. The great masters of the physical examination were giants in their time and studied the clinical approach of their contemporaries and predecessors. Sir William Osler was instrumental in bringing medical education to the patient's bedside. In doing so, he wrote to his students on the need to be "actuated by kindly feelings toward the patients." A more contemporary essay by James Li, entitled "Humility and the Practice of Medicine," advocates that competency, concern, compassion, and caring are the hallmark of best medical practice, but there is a place for the honest "I don't know," tactfully put [2].

Although time constraints challenge careful history taking [3], concerns regarding health care costs, driven in part by premature or inappropriate medical imaging, may reverse this trend. In detailing the nature of a patient's complaint, a diagnosis can often be made with little other than the patient's words in the appropriate clinical context. Cardiovascular symptoms can be further deconstructed to focus the subsequent evaluation and reduce both resource expenditure and time.

Chest Pain

Chest pain or angina pectoris must be distinguished from the pain associated with pulmonary embolism, pericarditis, aortic dissection, esophageal reflux, and costochondritis. Although a history of chest discomfort alone does not suffice to render a diagnosis of ACS, several aspects of the presenting symptom increase or decrease the likelihood of ACS. For example, pain that is sharp (likelihood ratio (LR) 0.3, 95 % CI 0.2–0.5), pleuritic (LR 0.2, 95 % CI 0.1–0.3), positional (LR 0.3, 95 % CI 0.2–0.5), or reproducible with palpation (0.3, 95 % CI 0.2–0.4) is usually noncardiac; whereas discomfort that radiates to both arms or shoulders (LR 4.1, 95 % CI 2.5–6.5) or is precipitated by exertion (LR 2.4, 95 % CI 1.5–3.8) increases the likelihood of ACS [4]. Less classic symptoms ("anginal equivalents") such as indigestion, belching, and dyspnea should also command the clinician's attention when other features of the presentation suggest ACS, even in the absence of chest discomfort. Less typical presentations are more common in women, the elderly, and patients with diabetes.

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_6, © Springer Science+Business Media New York 2013

Table 6.1 Symptom severity scores

Class	NYHA functional classification	CCS functional classification
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain	Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina occurs with strenuous or rapid or prolonged exertion at work or recreation
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina pain	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind, or when under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain	Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight in normal conditions
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased	Inability to carry on any physical activity without discomfort—anginal syndrome may be present at rest

Adapted from Braunwald and Bonow [7]. With permission from Elsevier

Dyspnea

Dyspnea may occur with exertion, recumbency (orthopnea), or even with standing (platypnea). Paroxysmal nocturnal dyspnea of cardiac origin usually occurs 2–4 h after onset of sleep, compels the patient to sit upright or stand, and subsides gradually over several minutes. The patient's partner should be questioned about any signs of sleep-disordered breathing, such as loud snoring and/or periods of apnea. Pulmonary embolism is often associated with dyspnea of sudden onset.

Palpitations

Patients may use a variety of terms to describe their awareness of the heartbeat (palpitations), such as "flutters," "skips," or "pounding." The likelihood of a cardiac arrhythmia is modestly increased with a known history of cardiac disease (LR 2.03; 95 % CI 1.33–3.11) and decreased when symptoms resolve within 5 min (LR 0.38, 95 % CI 0.22–0.63) or in the presence of panic disorder (LR 0.26, 95 % CI 0.07–1.01) [5]. A report of a regular, rapid-pounding sensation in the neck (LR 177, 95 % CI 25–1,251) or visible neck pulsations associated with palpitations (LR 2.68. 95 % CI 1.25–5.78) increases the likelihood that atrioventricular nodal reentrant tachycardia (AVNRT) is the responsible arrhythmia. The absence of a regular, rapid-pounding sensation in the neck makes detecting AVNRT much less likely (LR 0.07, 95 % CI 0.03–0.19) [5]. Prolonged electrocardiographic monitoring is required in most patients with recurrent palpitations when a significant arrhythmia is suspected.

Syncope

Syncope is defined broadly as the partial or complete loss of consciousness, and despite accounting for 1 in 30 visits to emergency rooms, there is no definitive diagnostic test. The elicitation of symptoms associated with a syncopal episode can provide the basis for further testing and diagnosis. The leading diagnoses associated with syncope are often benign conditions such as vasovagal syncope and postural hypotension [6]. However, the medical interview should address life-threatening etiologies such as tachyarrhythmias, bradyarrhythmias, seizure, and myocardial infarction. Cardiac syncope occurs suddenly and restoration of full consciousness occurs quickly. Patients with neurocardiogenic syncope may have an early warning (nausea, yawning), appear ashen and diaphoretic, and revive more slowly, albeit without signs of seizure or a prolonged postictal state.

Symptom Severity Scores

It is important to obtain a semiquantitative assessment of symptom severity and to document any change over time. The New York Heart Association (NYHA) and Canadian Cardiovascular Society (CCS) functional classification systems have served for decades and remain useful for both patient care and clinical research, despite their inherent limitations (Table 6.1). Assignment of symptom severity, as approximated by these classification systems, contributes importantly to risk assessment, clinical decision-making, and patient outcomes.

Family History

These heuristics for major cardiac conditions only touch on a few key elements. The complete history requires information pertaining to traditional cardiovascular risk factors, a general medical history, occupation, social habits, medications, drug allergies or intolerance, family history, and systems review. In the age of genomics, special mention should be made of the importance of a detailed family history. This information can target patients at high risk for developing cardiac conditions and guide the management of patients with known comorbidities. In a study of 122,155 Utah families, the 14 % with a strong family history of coronary heart disease accounted for 72 % of early manifestations (men before age 55 years, women before 65 years) and 48 % of coronary heart disease at all ages [8]. For diseases with Mendelian inheritance, the fruits of a good family history are even more dramatic. A patient with early-onset coronary artery disease should be screened for familial hypercholesterolemia, and use of drug-eluting stents in such a patient should be carefully considered if there is relative with Von Willebrand disease.

The barriers to obtaining a family history include the additional time required and the lack of understanding of its importance. The National Institutes of Health have launched a web-based tool that allows people to collect, organize, and maintain their family history securely on their own computers [9]. With further innovations, obtaining a complete family history will become easier and likely continue to gain importance as sequencing of the human genome becomes more affordable and its application more widespread [9].

Physical Examination

The history sets the stage for a focused physical examination in which the cardiovascular cause for a given symptom can be assessed. The systemic manifestations of cardiovascular disease, however, make the physical examination remarkably comprehensive. The following sections outline the important findings and their associations with specific cardiovascular diseases and related syndromes.

General Appearance

The examination begins with an appreciation of the general appearance of the patient, including his or her age, posture, demeanor, and general health status. Is the patient in pain, resting quietly, or visibly diaphoretic with a foreboding sense of doom? Does the patient choose to avoid certain positions to reduce or eliminate pain? The pain of acute pericarditis, for example, is often minimized by sitting up, leaning forward, and breathing shallowly. The respiratory pattern is also important. Pursing of the lips, a breathy quality to the voice, and an increased anteroposterior chest diameter would favor a pulmonary rather than cardiovascular cause of dyspnea. Pallor suggests that anemia may contribute to exercise intolerance or dyspnea, independent of cardiovascular disease. Cyanosis and jaundice can be readily appreciated. The chronically ill-appearing, emaciated patient suggests long-standing heart failure or another systemic disorder (malignancy, infection), with or without secondary cardiovascular involvement. The vital signs, including height, weight, temperature, pulse rate, blood pressure (both arms), respiratory rate, and peripheral oxygen saturation, dictate the pace and scope of the evaluation and provide initial clues as to the presence of a cardiovascular disorder. The height and weight are used to calculate body mass index (BMI) and body surface area (BSA). Mental status should be assessed continuously during the interview and examination. An impaired sensorium has multiple causes, of which reduced cerebral perfusion would be of concern in the appropriate context. The serendipitous observation of the respiratory pattern during sleep may reveal signs of disordered breathing (e.g., Cheyne Stokes, obstructive sleep apnea), a relatively common finding among patients with systolic heart failure, hypertension, obesity, and/or atrial fibrillation.

The Skin

The general assessment leads to inspection of the skin for evidence of systemic manifestations of cardiac disease. Central cyanosis is present with significant right-to-left shunting at the level of the heart or lungs, which allows deoxygenated blood to reach the systemic circulation. It is also a feature of hereditary methemoglobinemia. Though exclusively peripheral cyanosis (acrocyanosis) of the fingers, toes, nose, and ears can be a benign cosmetic condition, it is also characteristic of the reduced blood flow that accompanies small vessel constriction seen in severe heart failure, shock, or peripheral vascular disease. Differential cyanosis affecting the lower, but not the upper, extremities occurs with a patent ductus arteriosus and pulmonary artery hypertension with right-to-left shunting at the great vessel level. Hereditary telangiectases on the lips, tongue, and mucous membranes (Osler-Weber-Rendu syndrome) resemble spider nevi and, when present in the lungs, can be a source of right-to-left shunting and central cyanosis. Telangiectasias are also seen in patients with scleroderma with or without pulmonary hypertension. A tanned or bronze discoloration of the skin in unexposed areas can suggest iron overload and

hemochromatosis. Ecchymoses are often present with either antiplatelet or anticoagulant use, whereas petechiae are a feature of thrombocytopenia, and purpuric skin lesions can be seen with endocarditis and other causes of leukocytoclastic vasculitis. Various lipid disorders can manifest with xanthomas, subcutaneously, along tendon sheaths, or over the extensor surfaces of the extremities. Xanthoma within the palmar creases is specific for type III hyperlipoproteinemia (pre-beta, intermediate density). The leathery, cobblestone, "plucked chicken" appearance of the skin in the axilla and skinfolds of a young person is highly characteristic for pseudoxanthoma elasticum, a disease with multiple cardiovascular manifestations, including premature atherosclerosis [10].

Head and Neck

The state of the dentition should be assessed in all patients, both as a source of infection as well as an index of general health and hygiene. A high-arched palate is a feature of Marfan and other connective tissue disease syndromes. A large protruding tongue with parotid enlargement may suggest amyloid disease in the right setting. A bifid uvula has been described in patients with Loeys-Dietz syndrome. Orange tonsils are characteristic of Tangiers disease. Ptosis and ophthalmoplegia suggest muscular dystrophies, and congenital heart disease is often accompanied by hypertelorism, low-set ears, micrognathia, and a webbed neck, as with Noonan, Turner, and Down syndromes. Proptosis, lid lag, and stare denote Grave's hyperthyroidism. Similarly, the examiner should always palpate the thyroid gland and assess its size, symmetry, and consistency.

Blue sclerae, mitral or aortic regurgitation (AR), and a history of recurrent nontraumatic skeletal fractures are observed in patients with osteogenesis imperfecta. Premature arcus senilis and prominent earlobe creases may be associated with hyperlipidemia and coronary artery disease, respectively, although the correlations are weak. The funduscopic examination is an important and underutilized feature of the evaluation of patients with hypertension, atherosclerosis, diabetes, endocarditis, neurological symptoms, or known carotid or aortic arch disease. Lacrimal hyperplasia is sometimes a feature of sarcoidosis. The "mitral facies" of rheumatic mitral stenosis is characterized by pink, purplish patches with telangiectasias over the malar eminences and can also be seen with other disorders associated with pulmonary hypertension and reduced cardiac output.

Extremities

The temperature of the extremities, presence of clubbing, arachnodactyly, and nail findings can be quickly surmised, often while talking to the patient. Clubbing implies the presence of central shunting, although it has also been described with endocarditis. The appearance of clubbing can range from cyanosis and softening of the root of the nail bed to the classic loss of the normal angle between the base of the nail and skin ("drumsticking") (Fig. 6.1), to the skeletal and periosteal bony changes of hypertrophic osteoarthropathy. The striking appearance of the unapposable "fingerized" thumb is a classic finding in the autosomal dominant Holt-Oram syndrome in which secundum ASDs and conduction abnormalities are found. Arachnodactyly ("spider fingers," Marfan syndrome) can be assessed using the "wrist" (overlapping of the thumb and little finger around the wrist) or "thumb" signs (protrusion of the thumb beyond the ulnar aspect of the hand when the fingers are clenched over the thumb in a fist). Janeway lesions (nontender, slightly raised hemorrhages on the palms and soles), Osler's nodes (tender, raised nodules on the pads of the fingers or toes), and splinter hemorrhages (linear petechiae in the mid-nail bed) may be seen in some patients with endocarditis.

Lower extremity or presacral edema with elevated jugular venous pressure occurs in many volume-overloaded states, including heart failure. Chronic venous insufficiency can be diagnosed when jugular venous pressure is normal, and there are additional signs of venous disease, such as extensive varicosities, medial ulcers, or brownish pigmentation from hemosiderin deposition. Edema is also a common complication of dihydropyridine calcium channel blocker therapy. Anasarca is rare in heart failure unless long-standing, untreated, and accompanied by hypoalbuminemia. Asymmetrical swelling can reflect local or unilateral venous thrombosis, lymphatic obstruction, or the sequelae of previous vein graft harvesting. Homan's sign (calf pain upon forceful dorsiflexion of the foot), a classically described finding for deep venous thrombosis of the calf, is neither specific nor sensitive for this diagnosis. Muscular atrophy and the absence of hair in an extremity should suggest chronic arterial insufficiency or a neuromuscular disorder.

Chest and Abdomen

Cutaneous venous collaterals over the anterior chest may suggest obstruction of the superior vena cava or subclavian vein, especially in the presence of indwelling catheters or leads. Asymmetric breast enlargement unilateral to the device may also be present. Thoracic cage abnormalities, such as pectus carinatum (pigeon chest) or pectus excavatum (funnel chest), may be seen in connective tissue disorders; the barrel chest of emphysema or advanced kyphoscoliosis may be associated with cor pulmonale. The characteristically severe kyphosis and compensatory lumbar, hip, and knee flexion of ankylosing spondylitis ("bamboo spine disease")

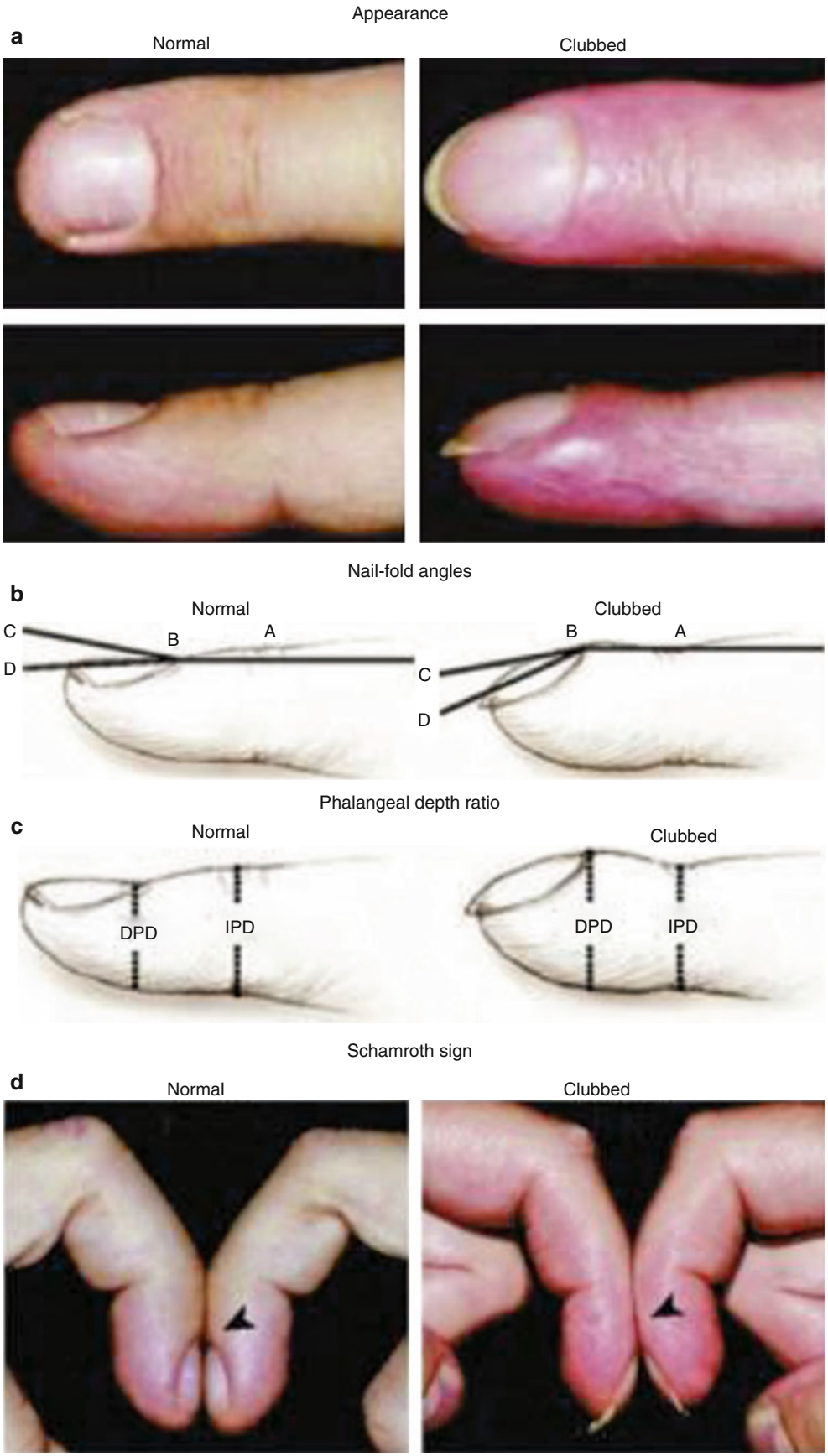

Fig. 6.1 (**a**) Normal finger viewed from above and in profile and the changes occurring in established clubbing, viewed from above and in profile. (**b**) The finger on the left demonstrates normal profile (*ABC*) and normal hyponychial (*ABD*) nail-fold angles of 169° and 183°, respectively. The clubbed finger on the *right* shows increased profile and hyponychial nail-fold angles of 191° and 203°, respectively. (**c**) Distal phalangeal finger depth (*DPD*)/ interphalangeal finger depth (*IPD*) represents the phalangeal depth ratio. In normal fingers, the *IPD* is greater than the *DPD*. In clubbing, this relationship is reversed. (**d**) Schamroth sign: in the absence of clubbing, opposition of the index fingers nail-to-nail creates a diamond-shaped window (*arrowhead*). In clubbed fingers, the loss of the profile angle due to the increase in tissue at the nail bed causes obliteration of this space (*arrowhead*) [11] (Adapted from Braunwald and Bonow [7]. With permission from Elsevier)

should prompt careful auscultation for aortic regurgitation (AR). The straight back syndrome (loss of normal kyphosis of the thoracic spine) can accompany mitral valve prolapse (MVP). Cyanotic congenital heart disease may result in asymmetry of the chest wall, with the left hemithorax displaced anteriorly. A thrill may be present over well-developed intercostal artery collaterals in patients with hypertension and severe aortic coarctation. The respiratory pattern should be noted during spontaneous breathing with attention to rate, depth, audible wheezing, and stridor. Palpation, percussion, and auscultation of the chest follow sequentially.

The cardiac impulse may be most readily felt in the epigastrium in patients with emphysema or substantial obesity. The liver is often enlarged and tender in heart failure; systolic hepatic pulsations signify severe tricuspid regurgitation (TR). Patients with infective endocarditis of long duration may have splenomegaly. Ascites is a nonspecific finding and is present with advanced and chronic right heart failure, constrictive pericarditis, hepatic cirrhosis, or intraperitoneal malignancy. This finding often leads to an erroneous pursuit of gastrointestinal pathology to explain abdominal pain, fullness, or nausea. The aorta may normally be palpated between the epigastrium and umbilicus in thin patients. Arterial bruits in the abdomen should be localized but are often diffuse and may be confused with murmurs radiating from the chest.

The Cardiovascular Examination

Jugular Venous Pressure and Waveform

The importance of estimating the jugular venous pressure in management and diagnosis of cardiovascular disease is unquestioned; yet it remains an inexact art. Understanding the physiology in addition to the nuances to the physical examination makes its estimation more accurate and useful to practitioners. The external (EJV) or internal (IJV) jugular vein may be used, although the IJV is preferred because the EJV is valved and not directly in line with the superior vena cava (SVC) and right atrium (RA). The EJV is easier to visualize when distended, and its appearance has been used to discriminate between a low and high central venous pressure (CVP) when tested among a group of attending physicians, residents, and medical students [12]. An elevated left EJV pressure may also signify a persistent left-sided SVC or compression of the innominate vein from an intrathoracic structure such as a tortuous or aneurysmal aorta. If an elevated venous pressure is suspected but venous pulsations cannot be appreciated, the patient should be asked to sit with the feet dangling over the side of the bed. The pooling of blood in the lower extremities with this maneuver may suffice to make the venous pulsations appear. Superior vena cava syndrome should be suspected if the venous pressure is elevated, pulsations are still not discernible, and the head and neck appear dusky or cyanotic. In the hypotensive patient in whom hypovolemia is suspected, the patient may need to be lowered to a supine position to appreciate the waveform in the right supraclavicular fossa.

The venous waveform can sometimes be difficult to distinguish from the carotid artery pulse. The venous waveform has several characteristic features such as a biphasic appearance and fall with inspiration that generally make it distinguishable. The estimated height of the venous pressure is a surrogate measure of the central venous, or RA, pressure. The venous pressure is measured as the vertical distance between the top of the venous pulsation and the sternal inflection point, where the manubrium meets the sternum (angle of Louis). A distance of >3 cm is considered abnormal. Many have challenged this approach because the anatomical distance between the angle of Louis and mid-RA varies considerably, especially in obese patients [13]. There is wide variability among observers in the estimation of the CVP. In many instances, however, knowledge that the pressure is elevated, and not its specific value, will suffice for diagnosis and management.

The venous waveforms are divided into several distinct peaks (*a*, *c*, and *v*; see Fig. 6.2). The *a* wave reflects RA presystolic contraction, occurs just after the electrocardiographic P wave, and precedes the first heart sound (S_1). A prominent *a* wave is seen in patients with reduced right ventricular (RV) compliance from any cause. A cannon *a* wave occurs with A-V dissociation and RA contraction against a closed tricuspid valve. Appreciation of cannon *a* waves in a patient with wide complex tachycardia identifies the rhythm as ventricular in origin. The *a* wave is absent with AF. The *x* descent defines the fall in RA pressure after the *a* wave peak. The *c* wave interrupts this descent as ventricular systole pushes the closed TV into the RA, elevating its pressure. In the neck, the underlying carotid pulse may also contribute to this wave. The *x′* descent follows and is the physiological consequence of atrial diastolic suction created by ventricular systole pulling the TV and floor of the RA downward. In normal individuals, the *x′* descent is the predominant waveform in the jugular venous pulse. The *v* wave represents atrial filling, occurs at the end of ventricular systole, and follows just after S_2. Its height is determined by RA compliance and by the volume of blood returning to the RA—either antegrade from the vena cavae and/or retrograde through an incompetent TV. The *v* wave is smaller than the *a* wave because of the normally compliant RA. In patients with ASD, the *a* and *v* waves may be of equal height; in tricuspid regurgitation (TR), the *v* wave is accentuated. With TR, the *v* wave will merge with the *c* wave because retrograde flow and antegrade right atrial filling will occur simultaneously. The *y* descent follows the *v* wave peak and reflects the fall in RA pressure after TV opening. If there is resistance to

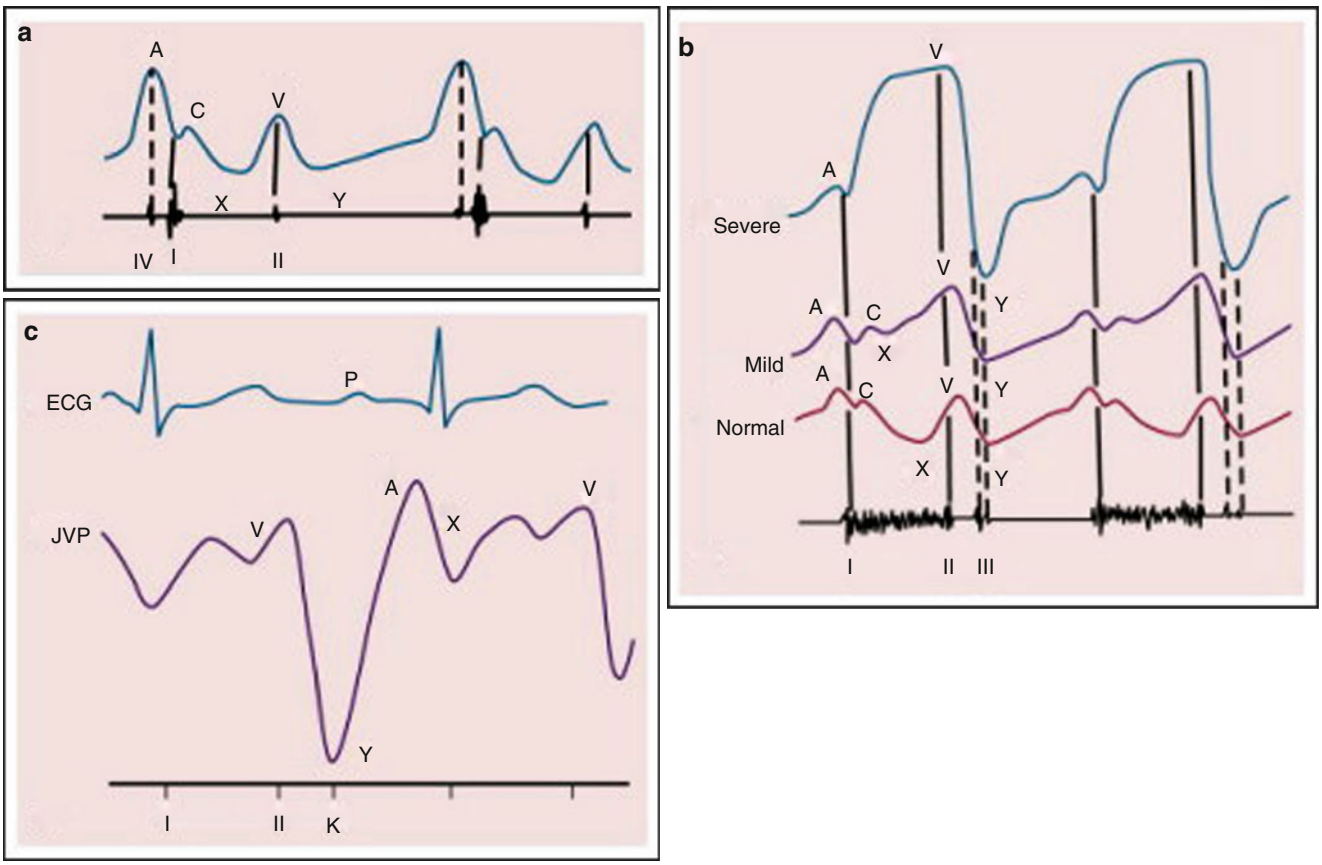

Fig. 6.2 Abnormal jugular venous waveforms. (**a**), Large *a* waves associated with reduced right ventricular (*RV*) compliance or elevated *RV* end-diastolic pressure. Phonocardiographic tracing (*below*) shows timing of the corresponding right-sided S4. (**b**) Normal jugular venous waveform (*bottom*), mild tricuspid regurgitation (*TR*) (*middle*), and severe TR (*top*), with corresponding phonocardiogram. With severe *TR*, there is "ventricularization" of the jugular venous waveform, with a prominent *V* wave and rapid *Y* descent. The *X* descent is absent. (**c**) Jugular venous waveform in constrictive pericarditis with a prominent *Y* descent. Note the timing of the pericardial knock (*K*) relative to S_2. The abrupt rise in pressure after the nadir of the *Y* descent is due to the rapid rise in venous pressure with ventricular filling. *ECG* electrocardiogram, *JVP* jugular venous pulse [14] (Adapted from Braunwald and Bonow [7]. With permission from Elsevier)

ventricular filling in early diastole, the *y* descent will be blunted, as is the case with pericardial tamponade or tricuspid stenosis (TS). The *y* descent will be steep when ventricular diastolic filling occurs early and rapidly, as with pericardial constriction or isolated, severe TR. The normal venous pressure should fall by at least 3 mmHg with inspiration. A rise in venous pressure (or its failure to decrease) with inspiration is known as the Kussmaul sign, and is classically associated with constrictive pericarditis, although it has been reported in restrictive cardiomyopathy, pulmonary embolism, RV infarction, and advanced systolic heart failure. A Kussmaul sign occurs with right-sided volume overload and reduced right ventricular compliance. Normally, the inspiratory increase in right-sided venous return is accommodated by increased right ventricular ejection, facilitated by an increase in the capacitance of the pulmonary vascular bed. In states of RV diastolic dysfunction and volume overload, the right ventricle cannot accommodate the enhanced volume and the pressure rises.

Venous hypertension can be elicited by the abdominojugular reflex or passive leg elevation. These signs indicate a volume-overloaded state and limited compliance of an overdistended or constricted venous system. The abdominojugular reflex is performed using firm and consistent pressure over the upper abdomen, preferably the right upper quadrant, for at least 10 s. A sustained rise of >3 cm in the venous pressure for at least 15 s after resumption of spontaneous respiration is a positive response. The patient should be coached to refrain from holding his or her breath or performing a Valsalva-like maneuver that can falsely elevate the venous pressure. The abdominojugular reflex is useful in predicting heart failure and a PA wedge pressure >15 mmHg [15].

Assessing the Pulses

The carotid artery pulse wave occurs within 40 ms of the ascending aortic pulse and reflects aortic valve and ascending

aortic function. The aortic pulse is best appreciated in the epigastrium (abdominal aorta). The peripheral arterial pulses that should be assessed include the subclavian, brachial, radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial. The temporal arteries can be easily palpated and should be examined in patients in whom the diagnosis of temporal arteritis or polymyalgia rheumatica has been raised. One of the two pedal pulses may not be palpable in a normal subject due to unusual anatomy (posterior tibial <5 %; dorsal pedis <10 %), but each pair should be symmetrical. True congenital absence of a pulse is rare (<2 %) and in most cases pulses can be obtained with a handheld Doppler device when not palpable [16]. The integrity of the arcuate system of the hand can be assessed using the Allen test. All pulses should be examined for symmetry, volume, timing, contour, size, and strength. Simultaneous auscultation of the heart sounds will help to discern delays in the arrival of the upstroke. Concomitant palpation of the brachial or radial pulse with the femoral pulse should routinely be performed; a femoral delay in a patient with hypertension may be a clue for aortic coarctation. The carotid pulses should not be examined simultaneously or before auscultation for a bruit; light pressure should be used to avoid precipitation of carotid hypersensitivity syndrome in a susceptible individual.

The character and contour of the pulses depend on the stroke volume, ejection velocity, vascular capacity/compliance, and systemic resistance. A bounding pulse indicates a large stroke volume with a rapid falloff and may occur in hyperkinetic states, such as fever, anemia, and thyrotoxicosis, or in pathological states such as severe bradycardia, AR, and arteriovenous fistula. A bifid pulse is created by two distinct pressure peaks. This phenomenon may occur with fever or after exercise in a normal individual and is consistent with increased vascular compliance. It is easily appreciated in patients on intra-aortic balloon counterpulsation (with augmentation of diastolic pressure). With chronic severe AR, a large stroke volume ejected rapidly into a noncompliant arterial tree (as with hypertension or aging) produces a reflected wave of sufficient amplitude to be palpated during systole. Hypertrophic obstructive cardiomyopathy (HOCM) can rarely produce a bifid systolic pulse with percussion and tidal (or reflected) waves (Fig. 6.3).

A >10 mmHg fall in systolic pressure with inspiration (*pulsus paradoxus*) is considered pathological and a sign of pericardial or pulmonary disease. It has also been described in obesity and pregnancy in the absence of clinical disease [19]. Pulsus paradoxus is measured by noting the difference between the systolic pressure at which the Korotkoff sounds are first heard (during expiration) and the systolic pressure at which the Korotkoff sounds are heard with each beat, independent of respiratory phase. Between these two pressures, the sounds are heard only intermittently (during expiration). The cuff pressure must be decreased slowly to appreciate the finding. Tachycardia, AF, and tachypnea make its assessment very difficult. Pulsus paradoxus may be palpable when the pressure difference exceeds 15–20 mmHg. The inspiratory fall in systolic pressure is an exaggerated consequence of interventricular dependence. This phenomenon becomes amplified when ventricular volumes are fixed by an external constraint, as in the case of pericardial tamponade [20]. There is also a contribution from the inspiratory increase in transmural aortic pressure, which increases aortic impedance and LV afterload. Pulsus paradoxus is not specific for pericardial tamponade and has been described with massive pulmonary embolus, hemorrhagic shock, severe obstructive lung disease, and tension pneumothorax.

Pulsus alternans is defined by the beat-to-beat variability of the pulse amplitude. Pulsus alternans is present when only every other phase one Korotkoff sound is audible as the cuff pressure is slowly lowered, in a patient with a regular heart rhythm, independent of the respiratory cycle. It should be distinguished from the expected beat-to-beat variability of the pulse in a patient with bigeminy. Pulsus alternans is generally seen in severe heart failure and is exaggerated in severe AR, hypertension, and hypovolemic states.

Severe aortic stenosis (AS) may be suggested by a weak and delayed pulse, *pulsus parvus et tardus*, and best appreciated by careful palpation of the carotid arteries. The delay is assessed during simultaneous auscultation of the heart sounds; the carotid upstroke should be coincident with S_1. This finding is less accurate in older, hypertensive patients with reduced vascular compliance and stiffer carotid arteries.

Inspection and Palpation of the Heart

The apical heartbeat may be visible in the mid-clavicular line at approximately the fifth intercostal space in thin-chested adults. Visible pulsations anywhere other than the normally located ventricular apex beat are abnormal. The left anterior chest wall may heave in patients with enlarged and hyperdynamic left ventricles. Right upper parasternal and sternoclavicular pulsations suggest ascending aortic aneurysm disease. A left parasternal lift indicates RV pressure or volume overload. A proximal PA pulsation in the 3rd intercostal space to the left of the sternum indicates PA hypertension. In very thin, tall patients, or in patients with emphysema and flattened diaphragms, the RV impulse may be visible in the epigastrium and should be distinguished from a pulsatile liver edge.

Palpation of the heart should begin with the patient in the supine position at 30°. If the heart is not palpable in this position, the patient should be examined either in the left lateral decubitus position with the left arm above the head or in the seated position, leaning forward. The point of maxi-

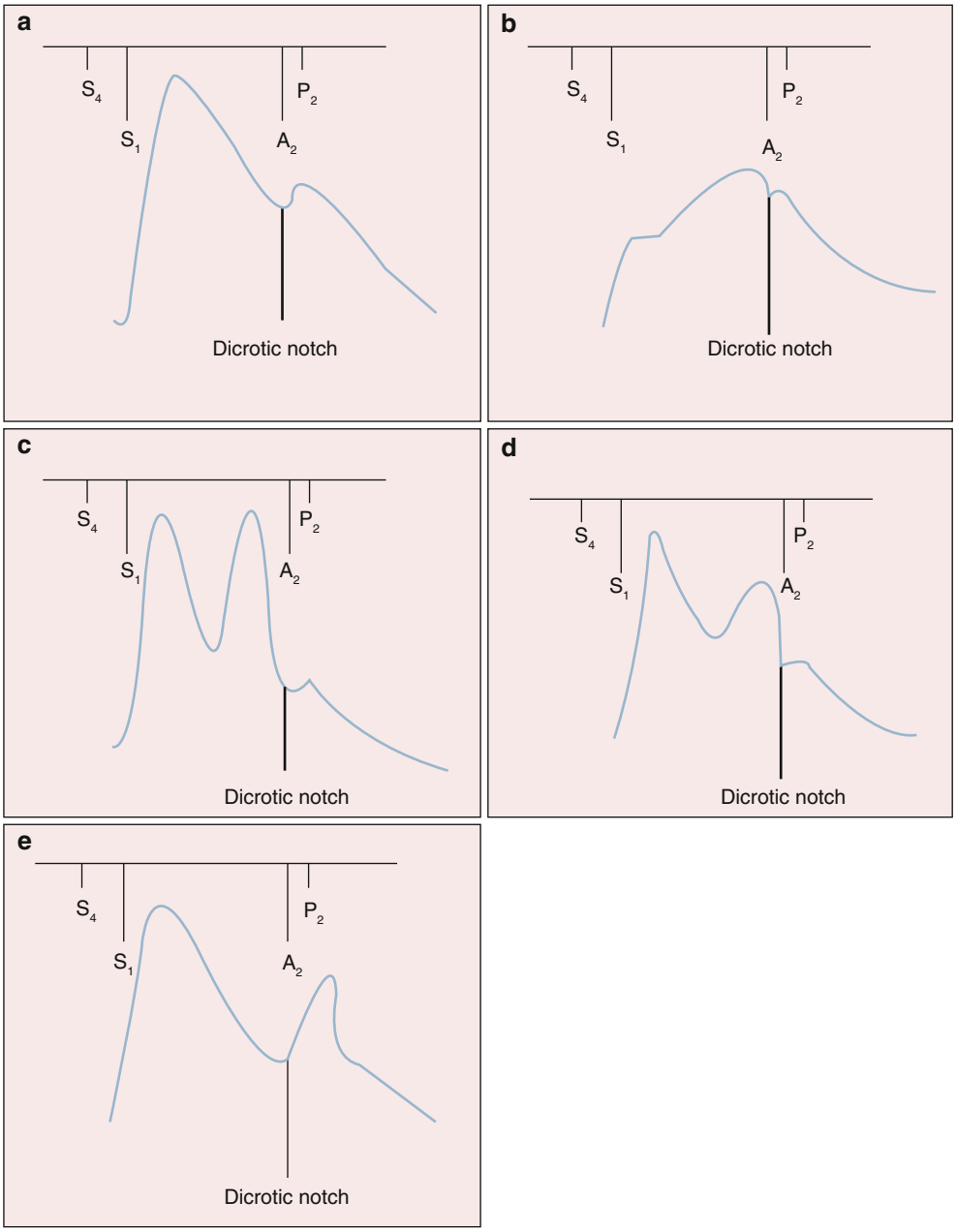

Fig. 6.3 Carotid pulse waveforms and heart sounds. (**a**) Normal. (**b**) Aortic stenosis. Anacrotic pulse with slow upstroke and peak near S_2. (**c**) Severe aortic regurgitation. Bifid pulse with two systolic peaks. (**d**) Hypertrophic obstructive cardiomyopathy (HOCM). Bifid pulse with two systolic peaks. The second peak (tidal or reflected wave) is of lower amplitude than the initial percussion wave. (**e**) Bifid pulse with systolic and diastolic peaks as may occur with sepsis or intra-aortic balloon counterpulsation. A_2 aortic component of S_2, *P2* pulmonic component of S_2, S_1 first heart sound, S_2 second heart sound, S_4 fourth heart sound [17, 18] (Adapted from Braunwald and Bonow [7]. With permission from Elsevier)

mal impulse is normally over the left ventricular apex beat and should be located in the mid-clavicular line at the fifth intercostal space. It is smaller than 2 cm in diameter and moves quickly away from the fingers. It is best appreciated at end expiration when the heart is closest to the chest wall. The apex beat is created by ventricular systole and counterclockwise rotation as the heart twists and shortens along its longitudinal axis. Rapid diastolic filling drops the apex beat away from the chest wall, producing a discrete, short, palpable impulse. The normal impulse may not be palpable in obese or muscular patients or in those with thoracic cage deformities. In such cases, the dominant pulse in the supine position may be in the epigastrium. The characteristics (size, amplitude, rate of development) of the left ventricular apex beat can be appreciated by placing the patient in the left lateral decubitus position.

Left ventricular (LV) cavity enlargement, the most common cause of cardiomegaly, is manifested by leftward and downward displacement of an enlarged apex beat. A sustained apex beat is a sign of LV pressure overload (AS, hypertension), but can be difficult to appreciate. In the presence of a large ventricular aneurysm, there may be a palpable and visible ectopic impulse, which is discrete from the apex beat. HOCM may rarely cause a triple cadence apex beat, with contributions from a palpable S_4 and the two components of the systolic pulse.

A parasternal lift occurs with RV pressure or volume overload. Signs of TR (jugular venous *cv* waves) and/or PA hypertension (loud, single, or palpable P_2) should be sought. An enlarged RV impulse can extend across the precordium and obscure left-sided findings. Rarely, patients with severe mitral regurgitation (MR) will have a prominent left parasternal impulse because of systolic expansion of the left atrium (LA) and forward displacement of the heart within the thorax. The parasternal movement of an enlarged LA will begin and end after the LV apex beat; RV and LV impulses, on the other hand, occur simultaneously. Lateral retraction of the chest wall may also be present with isolated RV enlargement and is due to posterior displacement of the systolic LV impulse. Systolic and diastolic thrills signify turbulent, high-velocity blood flow. Their locations help to identify the origins of heart murmurs.

Auscultation of the Heart

Heart Sounds

First Heart Sound (S_1)

Ventricular systole is defined by the interval between the first and second heart sounds. The normal first heart sound (S_1) comprises mitral (M_1) and tricuspid (T_1) valve closure. The two components are usually best heard at the lower left sternal border in younger subjects. Normal splitting of S_1 is accentuated with complete right bundle branch block. The intensity of S_1 varies predominantly as a function of both the distance over which the anterior leaflet of the mitral valve must travel to return to its annular plane after onset of systole as well as its mobility. Intensity is increased in the early stages of rheumatic mitral stenosis when the valve leaflets are still pliable, in hyperkinetic states, and with short PR intervals (<160 ms). S_1 becomes softer in the late stages of mitral stenosis, when the leaflets are rigid and calcified, with contractile dysfunction, beta-adrenergic receptor blockers, and long PR intervals (>200 ms). Other factors that can decrease the intensity of the heart sounds and murmurs include mechanical ventilation, obstructive lung disease, obesity, pendulous breasts, pneumothorax, and pericardial effusion.

Second Heart Sound (S_2)

The second heart sound (S_2) comprises aortic (A_2) and pulmonic (P_2) valve closure. With normal, or physiological, splitting, the A_2-P_2 interval increases during inspiration and narrows with expiration. The individual components are best heard at the second left interspace in the supine position. The A_2-P_2 interval widens with complete right bundle branch block because of delayed pulmonic valve closure and with severe MR because of premature aortic valve closure, although the normal directional variation with the respiratory cycle is maintained in both conditions. Unusually narrow but physiological splitting of S_2, with an increase in the intensity of P_2 relative to A_2, indicates pulmonary artery hypertension. With fixed splitting, the A_2-P_2 interval is wide and remains unchanged during the respiratory cycle. Fixed splitting of S_2 is a feature of ostium secundum ASD. Reversed, or paradoxical, splitting occurs as a consequence of a pathological delay in aortic valve closure, as may occur with complete left bundle branch block, RV apical pacing, severe AS, HOCM, and myocardial ischemia. A_2 is normally louder than P_2 and can be heard at most sites across the precordium.

Murmurs

The hallmark of a complete cardiovascular examination is identification of heart murmurs which result from audible vibrations caused by increased turbulence. Murmurs are defined by their timing within the cardiac cycle (systole or diastole), and their complete evaluation involves description of their duration, frequency, configuration, intensity, and response to provocative maneuvers.

Systolic Murmurs

Systolic murmurs are early, mid-, late, or holosystolic in timing.

Early Systolic Murmur: Acute Severe Mitral Regurgitation Acute severe MR results in a decrescendo, early systolic murmur, and is due to the progressive attenuation of the left ventricle—LA pressure gradient during systole because of the steep and rapid rise in pressure within the noncompliant LA. Severe MR associated with posterior mitral leaflet prolapse or flail radiates anteriorly and to the base; MR due to anterior leaflet involvement radiates posteriorly and to the axilla. With acute TR in patients with normal PA pressures, an early systolic murmur, which increases in intensity with inspiration, may be audible at the lower left sternal border, and regurgitant *cv* waves may be visible in the jugular venous pulse.

Mid-systolic Murmur: Aortic Stenosis, Benign Murmurs Aortic stenosis is the most common cause of a mid-systolic murmur in an adult. It is classically described as a crescendo-decrescendo murmur, as are most other mid-systolic murmurs heard in adults. A muffled S2, late-peaking sound, and radiation to the carotid arteries are hallmarks of more severe stenosis; pitch and intensity, however, do not correlate with severity. Accurate characterization of the severity of the valve lesion at the bedside depends on cardiac output, the stiffness of the carotid arteries, and associated

findings. There are several other causes of a mid-systolic heart murmur, including HOCM, pulmonic stenosis (PS), and increased pulmonary blood flow in patients with a large ASD and a left-to-right shunt. An isolated grade 1 or 2 mid-systolic murmur in the absence of symptoms or other signs of heart disease is a benign finding that does not warrant further evaluation, including echocardiography [21]. A grade 1 or 2 mid-systolic murmur can often be heard at the left sternal border with pregnancy, hyperthyroidism, or anemia—physiological states that are associated with accelerated blood flow across normal semilunar valves. A murmur of this type is also commonly heard in healthy children and adolescents.

Late Systolic Murmur: Mitral Valve Prolapse, Mitral Regurgitation, Tricuspid Regurgitation A mid-to-late, apical systolic murmur usually indicates MVP; one or more non-ejection clicks may be present. A similar murmur may be heard transiently during an episode of acute myocardial ischemia. Ischemic MR, however, refers more specifically to the MR that develops as a consequence of post-MI LV remodeling with apical tethering and mal-coaptation of the leaflets. The intensity of the MR murmur will vary with left ventricular afterload. MR is best heard over the cardiac apex, TR at the lower left sternal border, and a VSD murmur at the mid-left sternal border where a thrill is palpable in the majority of patients. With VSD, the murmur is also holosystolic in timing, as is the murmur of chronic MR. TR can be mistaken for MR when the RV is dilated and laterally displaced. For this reason, it is important to listen for changes in murmur with the respiratory cycle. Carvallo's sign is the increase in intensity of the TR murmur with inspiration. Although there are several causes of primary TR, it most commonly occurs secondary to PA hypertension, right ventricular enlargement, annular dilation, papillary muscle displacement, and failure of tricuspid leaflet coaptation.

Diastolic Murmurs

Diastolic murmurs invariably signify cardiac disease. Chronic AR causes a high-pitched decrescendo early to mid-diastolic murmur. With primary aortic valve disease, the murmur is best heard along the left sternal border; whereas with root enlargement and secondary AR, the murmur tends to radiate along the right sternal border. A mid-systolic murmur due to augmented and accelerated forward flow is also present with moderate to severe AR and need not signify valve or outflow tract obstruction. The diastolic murmur is both softer and of shorter duration in acute AR, due to the rapid rise in LV diastolic pressure and the diminution of the aortic-LV diastolic pressure gradient. Additional features of acute AR include tachycardia, a soft S_1, and the absence of peripheral findings of significant diastolic runoff. The murmur of pulmonic regurgitation (PR) is heard along the left sternal border and is most often due to annular enlargement from chronic PA hypertension (Graham Steell murmur). Signs of RV pressure overload are present. PR can also occur with a congenitally deformed valve and is invariably present after repair of tetralogy of Fallot. In these settings, the murmur is relatively softer and lower pitched. The severity of PR after surgical repair can be underappreciated. Mitral stenosis is the classic cause of a mid-to-late diastolic murmur. However, mitral stenosis may be "silent" and a murmur might be inaudible in patients with low cardiac output or large body habitus. The murmur is best heard over the apex in the left lateral decubitus position, is low-pitched (rumbling), and introduced by an OS in the early stages of the disease. Presystolic accentuation refers to an increase in the intensity of the murmur in late systole following atrial contraction in patients in sinus rhythm. Findings in patients with rheumatic tricuspid stenosis (TS) are usually obscured by left-sided events. Functional mitral stenosis or TS refers to mid-diastolic murmurs created by increased, accelerated transvalvular flow, without valvular obstruction, in the setting of severe MR, severe TR, or ASD with a large left-to-right shunt. The low-pitched mid-to-late apical diastolic murmur sometimes associated with AR (Austin Flint murmur) can be distinguished from mitral stenosis on the basis of its response to vasodilators and the presence of associated findings. Less common causes of a mid-diastolic murmur include atrial myxoma, complete heart block, and acute rheumatic mitral valvulitis (Carey Coombs murmur).

Continuous Murmurs

The presence of a continuous murmur implies a pressure gradient between two chambers or vessels during both systole and diastole. These murmurs begin in systole, peak near S_2, and then continue into diastole. They can be difficult to distinguish from systolic and diastolic murmurs in patients with mixed aortic or pulmonic valve disease. Examples include the murmurs associated with PDA, ruptured sinus of Valsalva aneurysm, and coronary, great vessel, or hemodialysis AV fistulas. The cervical venous hum and mammary souffle of pregnancy are two benign variants.

Third (S3) and Fourth (S4) Heart Sounds

The S3 and S4 gallops are low-frequency diastolic sounds that originate in the ventricles and best heard with the bell of the stethoscope. Effective atrial contraction and ventricular filling are both required for production of atrial gallop sounds. Thus, these sounds are usually absent in atrial fibrillation and in significant atrioventricular valve stenosis.

The S3 coincides with the y descent of the atrial waveform and occurs during passive filling of the ventricle. In children and young adults, a third heart sound may arise from rapid deceleration of the column of blood against the ventricular wall. In older patients, however, an S3 gallop can arise from volume overload of either the right or left ventricle. The third heart sound (S_3) predicts ejection fraction poorly because it reflects primarily diastolic rather than systolic performance. In patients with heart failure, an S_3 is equally prevalent in those with or without LV systolic dysfunction (EF cut point 0.50) [22].

An S4 is most frequently observed in patients with decreased left ventricular distensibility [23]. Thus, S4 is common in hypertensive heart disease, aortic stenosis, and hypertrophic cardiomyopathy. Left ventricular hypertrophy, which is present in all these conditions, contributes to decreased left ventricular distensibility. The S4 occurs after the P wave on the electrocardiogram and coincides with atrial systole. It can be heard in many healthy older adults without any other cardiac abnormality due to decreased ventricular compliance with age. It can also become audible in healthy patients with a prolonged PR due to the separation of S4 from S1. In young adults and children, however, the S4 is usually abnormal.

Other Cardiac Sounds

Many of the subtle findings heard with careful auscultation can reveal abnormal cardiac pathology. Though rarely appreciated, the specificity for valvular dysfunction and pericardial disease of these findings is quite high.

Opening Snap

This high-frequency, early diastolic sound is generally associated with mitral valve opening. While opening of the mitral valve is normally silent, it becomes audible in the presence of pathologic conditions such as rheumatic mitral stenosis. It is often absent when the mitral valve is heavily calcified and immobile, during the later stages of the rheumatic disease. However, the opening snap is heard in the vast majority of patients with earlier stage mitral stenosis, and along with an accentuated S1, frequently provides the first clue to the diagnosis.

Pericardial Knock

The pericardial knock is an early diastolic sound caused by loss of pericardial elasticity accompanying fibrosis that limits ventricular filling in states of constriction. It corresponds in timing to the trough of the rapid Y descent that is also characteristic of this disorder

Friction Rub

A pericardial rub is generated by the movement of two inflamed layers of the pericardium against each other during the cardiac cycle. The most vigorous movement of these layers occurs during atrial systole, ventricular systole, and the rapid-filling phase of the ventricle—creating the triphasic sound. The rub is a low-pitched, scratchy sound that should be differentiated by from the Means-Lerman scratch heard in thyrotoxicosis, acute postoperative mediastinal emphysema, or the tricuspid regurgitation of Ebstein's anomaly. The triphasic nature of the friction rub and the fact that it is best heard with held inspiration or with the patient leaning forward are its distinguishing features.

Dynamic Auscultation

Simple bedside maneuvers can help identify heart murmurs and characterize their significance. Right-sided events, save for the pulmonic ejection sound, increase with inspiration and decrease with expiration; left-sided events behave oppositely (100 % sensitivity, 88 % specificity) [24]. The intensity of the murmurs associated with MR, VSD, and AR will increase in response to maneuvers that increase LV afterload (handgrip, vasopressors) and decrease after exposure to vasodilating agents (amyl nitrite). Squatting is associated with an abrupt increase in ventricular preload and afterload; whereas rapid standing results in a sudden decrease in preload. In patients with MVP, the click and murmur will move away from S_1 with squatting, because of the delay in onset of leaflet prolapse at higher ventricular volumes. With rapid standing, the click and murmur move closer to S_1, as prolapse occurs earlier in systole at a smaller chamber dimension. The murmur of HOCM behaves in a directionally similar manner, becoming softer and shorter with squatting (95 % sensitivity, 85 % specificity) and longer and louder on rapid standing (95 % sensitivity, 84 % specificity) [24]. The intensity of the murmur of HOCM also increases with the Valsalva maneuver (65 % sensitivity, 95 % specificity) [24]. A change in the intensity of a systolic murmur in the first beat after a premature beat, or in the beat after a long cycle length in patients with AF, suggests AS rather than MR, particularly in an older patient in whom the murmur of AS is well transmitted to the apex (Gallavardin effect). Systolic murmurs due to LV outflow obstruction, including that due to AS, will increase in intensity in the beat following a premature beat because of the combined effects of enhanced LV filling and post-extrasystolic potentiation of contractile function. Forward flow accelerates, causing an increase in the gradient and a louder murmur. The intensity of the murmur of MR does not change in the post-premature beat, as there is relatively little further increase in mitral valve flow or change in the left ventricle-LA gradient.

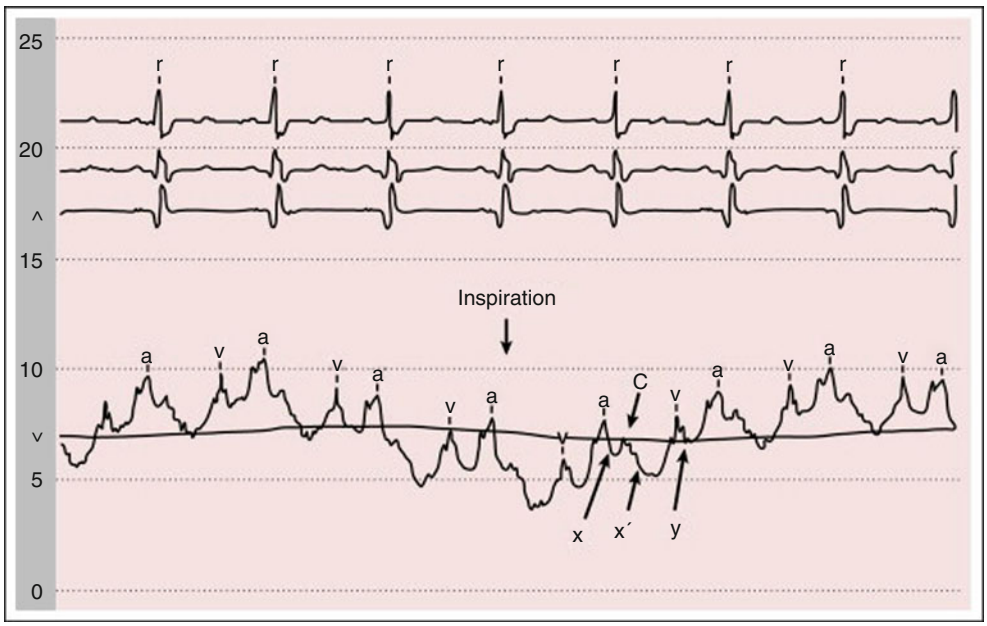

Fig. 6.4 The normal Valsalva response [26]. See text (Adapted from Nishimura and Tajik [26]. With permission from Elsevier)

The Valsalva Maneuver

Special mention should be made of the importance of the Valsalva maneuver in the cardiovascular physical examination. Though the Italian anatomist Antonio Maria Valsalva is eponymously credited with the first description of this physiologic phenomenon, his 1,704 writings were of the maneuver's use in expelling pus from the middle ear [25]. It was only in 1851, when Edward Weber associated the effects of forced expiration against the glottis ("all the sounds associated with the movement of the heart disappear"), that its role in the cardiovascular physical examination became known [25].

The Valsalva maneuver is composed of four phases, each with distinct effects on cardiac output and, by extension, blood pressure (Fig. 6.4).

Phase 1: Onset of Straining

The patient is instructed to tighten their abdominal muscles and "bear down" by forcing expiration against a closed epiglottis. These instructions are important, since the natural tendency is simply to hold one's breath. The sudden increase in intrathoracic pressure is associated with a short rise in arterial pressure.

Phase 2: Maintain Strain

The first hemodynamic effect is a sharp decrease in blood pressure as the Valsalva maneuver is maintained. This is due to the decreased venous return to the heart and is associated with increased peripheral vascular resistance and increased heart rate. Most cardiac murmurs decrease in length and intensity during phase two of the Valsalva maneuver, though the systolic murmurs of hypertrophic obstructive cardiomyopathy (HOCM) and mitral valve prolapse get louder.

Phase 3: Release Strain

With release there is normally a short decrease in arterial pressure due to sudden decrease in intrathoracic pressure.

Phase 4: Overshoot

With increased venous return after the drop in intrathoracic pressure blood pressure rises beyond baseline with a concomitant decrease in peripheral vascular resistance and reflex bradycardia.

In a normal response, Korotkoff sounds are audible only during phases 1 and 4, as the systolic pressure normally rises at the onset and release of the strain phase. There are two recognized abnormal responses to the Valsalva maneuver in heart failure: (1) absence of the phase 4 overshoot and (2) the square wave response (Fig. 6.5). The absent overshoot pattern indicates decreased systolic function; the square wave response indicates elevated filling pressures and appears to be independent of ejection fraction [28]. The responses can be quantified using the pulse amplitude ratio if the pulse pressure is measured during the maneuver. This ratio compares the minimum pulse pressure at the end of the strain phase to the maximum pulse pressure at the onset of the strain phase; a greater ratio is consistent with a square wave response.

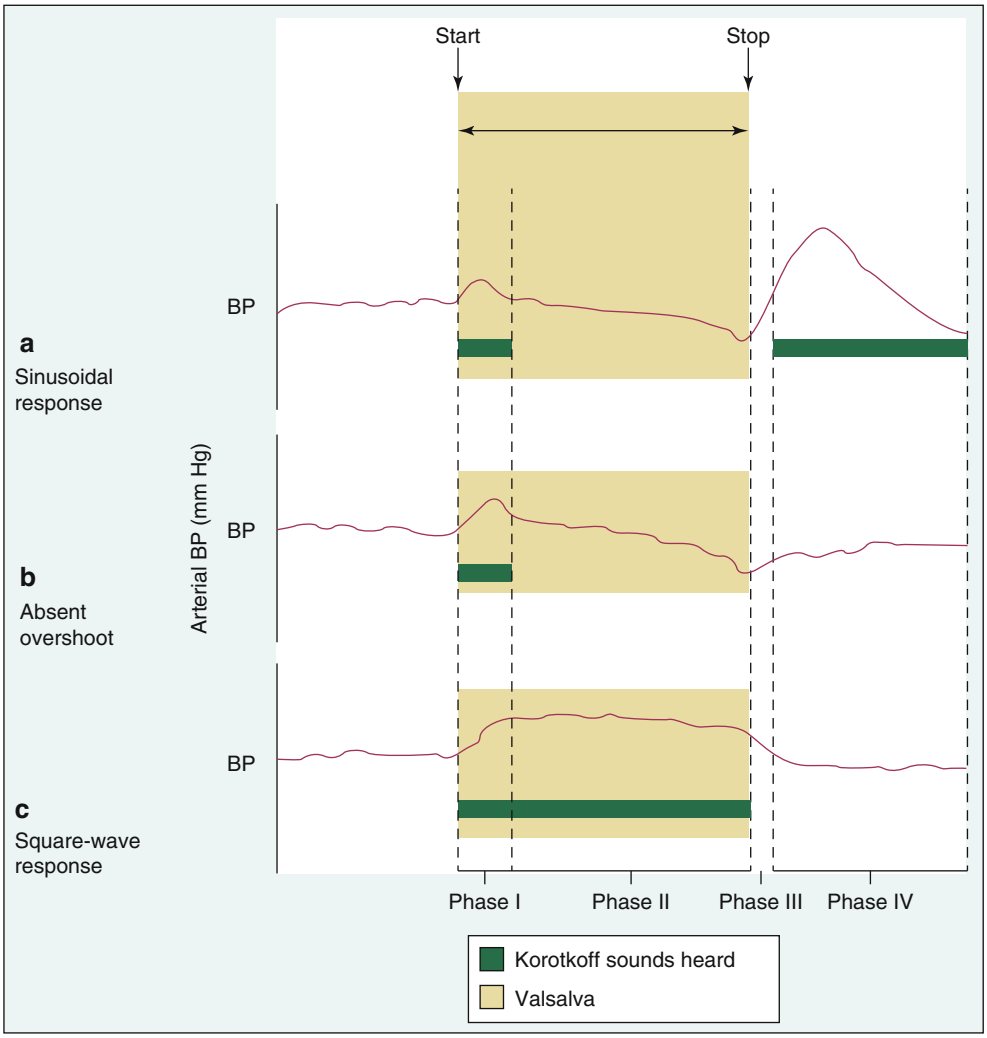

Fig. 6.5 Abnormal Valsalva responses assessed using the pattern of Korotkoff sounds. (**a**) Normal, sinusoidal response with sounds intermittent during strain and release. (**b**) Briefly audible sounds during initial strain phase suggests only impaired systolic function in absence of fluid overload. (**c**) Persistence of Korotkoff sounds throughout strain phase suggests elevated left ventricular filling pressures. *BP* blood pressure [27] (Adapted from Shamsham and Mitchell [27])

Conclusion

The history and physical examination constitute the oldest elements of the practice of medicine and remain the foundation of effective clinical care. Facilitating the patient narrative and searching at the bedside for visual, tactile, and auditory clues enable the clinician to identify the nature of the presenting illness in the vast majority of cases.

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Electrocardiography

7

Tara L. DiMino, Alexander Ivanov, James F. Burke, and Peter R. Kowey

Introduction

The electrocardiogram (ECG) records electric potential changes in the electrical field produced by the heart. Although it records only the *electrical* behavior of the heart, it can be used to identify numerous metabolic, hemodynamic, and anatomic anomalies. Electrocardiography is considered a gold standard for the diagnosis of arrhythmias (see Chap. 16). In this chapter, mostly nonarrhythmic ECG changes will be reviewed. Abbreviations and acronyms used in this chapter can be found in Table 7.1.

ECG Leads

The standard 12-lead ECG traditionally consists of tracings obtained from the bipolar limb leads (I, II, and III), unipolar limb leads (aVR, aVL, and aVF), and usually six unipolar chest or precordial leads (V_1 through V_6). The *bipolar limb leads* I, II, and III register the potential differences between the right arm and left arm, the right arm and left leg, and the left arm and left leg, respectively. The axis of a bipolar lead is an imaginary vector directed from the electrode assumed to be negative to the electrode assumed to be positive (Fig. 7.1). To record *unipolar limb leads*, the above three extremities are connected to a central terminal used as the indifferent electrode. The exploring electrode (called positive) can then be placed on one of the three extremities to register the potentials transmitted to that particular limb. The letter V denotes a unipolar lead. The letters *R*, *L*, and *F* identify the right arm, left arm, and left leg (foot), respectively. The letter "*a*" means that the potential difference is electrically augmented [1]. The axis of a unipolar lead is an imaginary vector directed from the indifferent electrode to the exploring (positive) electrode.

By combining the bipolar and unipolar limb leads, one may view the entire electrical picture of the heart in the frontal plane. With the heart at the center, this essentially creates a circle that is bisected by six imaginary vectors. These vectors, by the nature of their position, allow determination of the precise electrical axis of the heart. This information aids in the identification of conditions such as bundle branch block, improper lead placement, and axis shifts (Fig. 7.2).

Table 7.2 describes the placement of the precordial ECG leads, and Fig. 7.3 demonstrates their axes. When an exploring electrode is situated on the chest, it records potentials from that particular site on the chest wall. Typically, limb leads record electrical forces from the anatomic frontal plane, and precordial leads reflect potentials from the horizontal plane. Therefore, when approached as a whole, the ECG may provide an electrical map that corresponds to specific territories of the heart. For example, the inferior limb leads (II, III, and aVF) preferentially record the electrical activity from the inferior wall of the heart because of their proximity to that wall.

Generation of ECG Tracing

Before attempting to understand the electrical activity of the heart as an organ, one should appreciate its function on a cellular level (Fig. 7.4). A resting or polarized muscle strip is positively charged on the outside and negatively charged inside. Therefore, there is no potential difference along the uniformly charged surface of the resting muscle strip. Electrical activation at any given site of the strip produces

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DOI 10.1007/978-1-4614-6705-2_7,

Table 7.1 Abbreviations and acronyms

ARVD	Arrhythmogenic right ventricular dysplasia	LPFB	Left posterior fascicular block
		LV	Left ventricle
AV	Atrioventricular	LVH	Left ventricular hypertrophy
bpm	Beats per minute	MI	Myocardial infarction
CAD	Coronary artery disease	mm	Millimeter
cm	Centimeter	mV	Millivolt
CNS	Central nervous system	RAA	Right atrial abnormality
COPD	Chronic obstructive pulmonary disease	RBBB	Right bundle branch block
		RV	Right ventricle
ECG	Electrocardiogram	RVH	Right ventricular hypertrophy
ERP	Early repolarization pattern	QTc	QT interval corrected for heart rate
ICS	Intercostal space	SA	Sinoatrial
LAA	Left atrial abnormality	s	Second
LAD	Left axis deviation	VT	Ventricular tachycardia
LAFB	Left anterior fascicular block	WPW	Wolff-Parkinson-White syndrome
LBBB	Left bundle branch block		

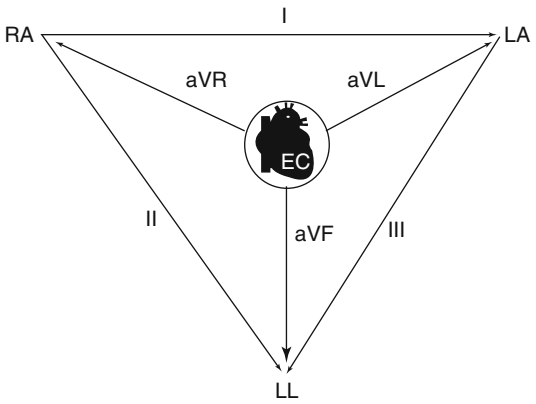

Fig. 7.1 Frontal lead axes. Leads I, II, and III are formed by connecting the right arm (*RA*) to the left arm (*LA*), the right arm to the left leg (*LL*), and LA to LL, respectively. *Arrows* indicate the axes of these leads in relation to the theoretical electrical center (*EC*) of the heart. The indifferent electrode of the unipolar system is obtained by connecting RA, LA, and LL into a central terminal

depolarization. Depolarization causes a charge shift that results in a negative charge outside the depolarized portion of the membrane. During spread of the depolarization wave, a potential difference develops between already depolarized (negative) and still polarized (positive or resting) portions of the membrane. An electric current flows from the negatively charged (depolarized) portions of the membrane to the positively charged ones. This current may be represented by a dipole or vector.

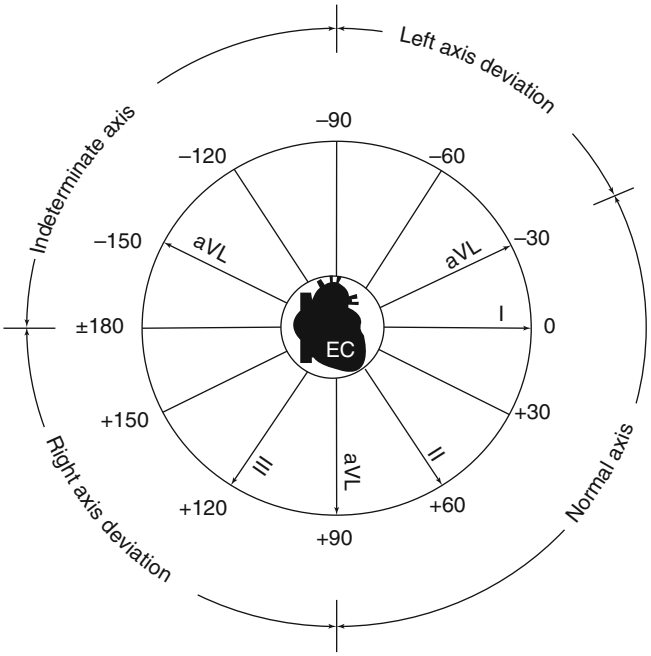

Fig. 7.2 The frontal plane hexaxial reference system. This represents the limb leads where axes are drawn with intersection at the electrical center (*EC*) of the heart (Modified from Fisch [1] and Wagner [2])

Table 7.2 Precordial lead placement

Name	Leads	Location
Septal	V_1–V_2	V_1 is in the fourth intercostal space (ICS) to the right of the sternum. V_2 is in the fourth ICS to the left of the sternum
Anterior (transitional or mid-precordial)	V_3–V_4	V_3 is midway between V_2 and V_4. V_4 is in the fifth ICS at the midclavicular line
Lateral	V_5–V_6	V_5 is at the anterior axillary line at the same horizontal level as V_4 (but not necessarily in the same ICS). V_6 is at the midaxillary line at the level of V_4
Right-sided	V_2, V_1, V_3R, V_4R,V_5R, V_6R	The same as standard precordial but on the right side of the chest

Depending on the anatomical position of the heart in the thorax, these leads may vary in which area they represent. For example, leads V_3 and V_4 may also represent potentials from the septum in a vertically oriented heart

A vector moves along the muscle strip from the point of excitation, and it reflects the constantly changing electrical activity of the strip [1]. Vector size is directly proportional to the number of depolarized muscle strips. The magnitude and direction of these changes can be recorded as positive or negative deflections from the baseline of an ECG tracing. By convention, a positive deflection is recorded if the vector that is directed from the negative to the positive portion of the muscle strip points in the *same* direction as the axis of the recording lead. A negative deflection is recorded if the

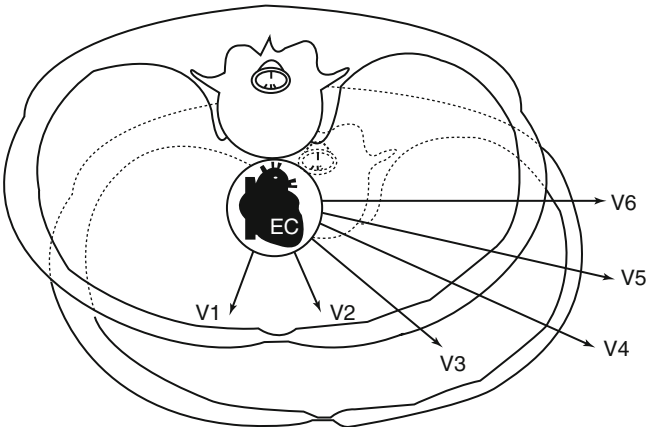

Fig. 7.3 Horizontal lead axes. *Arrows* indicate the axes of the unipolar leads. The indifferent electrode is obtained by connecting the precordial surface leads to a central terminal. Since the precordial electrodes are placed at different levels in relation to the electrical center (*EC*) of the heart, these leads also record some frontal vectors in addition to horizontal ones

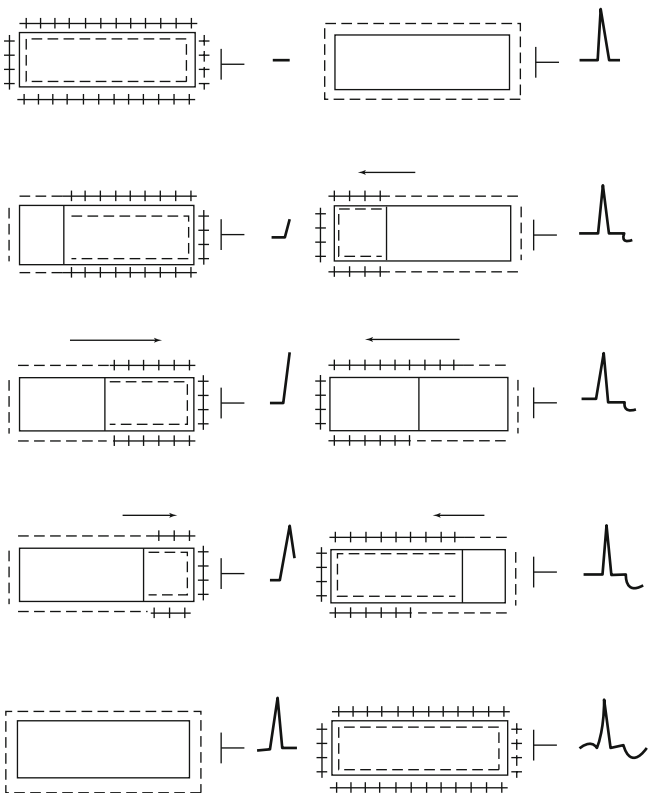

Fig. 7.4 Potential generated during depolarization (left vertical sequence) and repolarization (right vertical sequence) recorded with an exploring electrode located at one end of the muscle strip (Modified from Fisch [1]. With permission from Elsevier)

vector points in the direction *opposite* to the axis of the recording lead. No deflection is produced if the vector is perpendicular to the axis of the lead. At any given moment, the magnitude of the deflection depends on the strength of the electrical source, the distance from that source, and the cosine of the angle between the vector and the axis of the recording lead [1].

Repolarization restores muscle cells to their resting state: negative intracellularly and positive extracellularly. During this process, a wave of positivity proceeds in the same direction as the original wave of depolarization. However, it has the opposite potential vector in reference to the recording lead. This occurs because positive potentials produced outside the membrane during repolarization spread from the site of *initial* depolarization toward the still depolarized portion of the membrane (Fig. 7.4). Thus, the net area of the deflection caused by repolarization equals the area of depolarization [1].

In the intact ventricles, the subendocardial action potential normally lasts longer than the subepicardial. Therefore, repolarization proceeds from the subepicardium to the subendocardium in a direction approximately opposite to that of depolarization. In other words, since the subepicardium has a shorter action potential, it is ready to repolarize *before* the subendocardium. Consequently, the vector of repolarization has a direction more or less similar to that of the depolarization vector. The ECG deflections of depolarization and repolarization (represented by the QRS complex and T wave, respectively) therefore have the same polarity despite unequal shapes and areas under the curve. Furthermore, since the intact heart contains more than one muscle strip, the net ECG tracing reflects contributions of all such portions of the myocardium [1].

In the thin-walled atria, action potential duration of the subendocardium and subepicardium are equal. The ECG deflections of depolarization and repolarization therefore have opposite polarities. The deflection of atrial *de*polarization is called the P wave. The wave of atrial *re*polarization is usually hidden within the large QRS complex of ventricular depolarization.

Axis Determination

The amplitude of an ECG deflection, measured conventionally in millivolts, depends on the magnitude of the electrical source as well as the angle between the axis of the electrical vector and the axis of the recording lead. This means that the heart chamber with the most significant electrical contribution will produce the largest deflection, especially if the recording lead is very close to that chamber. A lead whose axis is most parallel to the electrical vector of the heart will record the largest ECG deflection. As illustrated in Fig. 7.2, the approximate spatial orientation of the lead axes is known. Therefore, by comparing the amplitude of deflections in different leads, one can infer the direction and amplitude of the electrical vector at any given moment.

Summation of *instantaneous* vectors of atrial or ventricular depolarization or repolarization over time is reflected by ECG deflections such as the P waves, QRS complexes, and T waves (see Sect. "Generation of ECG Tracing").

Table 7.3 Criteria for normal P wave, for RAA, and for LAA

	Normal	RAA	LAA
Duration (s)	0.08–0.11	0.08–0.11	≥0.12 in leads II, III, aVF (morphology is notched) Negative deflection V_1 >1 mm and ≥0.04 s
Axis (degree)	0–75°	>+75° (rightward axis)	–
Amplitude (mm)	–	>2.5 mm in leads II, III, aVF >1.5 mm of positive deflection on V_1 or V_2	Negative deflection in V_1 ≥1 mm and ≥0.04 s

The direction of the *mean* vector of these deflections is called the *axis* of that deflection. The axis of a wave is easy to calculate; it can therefore be used in everyday practice to assess relative electrical contribution of the atria or ventricles throughout depolarization or repolarization. Relative contribution of the chambers to electrical events in the heart commonly changes in the presence of abnormalities of those chambers or of the metabolic, anatomic, or hemodynamic milieu of the body.

By convention, the axes of the P, QRS, and T waves are calculated using the *hexaxial system* of the frontal plane leads (Fig. 7.2). The following two rules are frequently utilized to calculate an electrical axis. First, the axis of an ECG deflection is perpendicular to the axis of the lead with the algebraic sum of deflections equaling zero (*isoelectric* complexes). Second, the axis is parallel to and has the same direction as the axis of the lead with the largest positive deflection. Combining these rules improves the accuracy of axis determination.

For axis determination, the *area* of the deflection is more important than the *amplitude*. The normal QRS axis is the frontal plane is −30° to +90°. When the R wave equals the S wave in all three bipolar limb leads, the QRS axis is considered indeterminate. This relationship allows the ECG to provide useful information in many different clinical situations.

Standardization of ECG Recording

Most often, millimeters are used to describe the amplitude of ECG deflections. When potentials registered by the leads are recorded on paper, a 10-mm vertical deflection on the paper usually represents a 1-mV potential difference unless otherwise indicated.

Heart Rate Measurement

The heart rate can be easily determined by using several rules. The first assumes that the distance between two thick lines on ECG paper equals 0.5 cm, and the standard paper speed is 2.5 cm/s. If the distance between two consecutive R waves equals 0.5 cm (two thick lines), the heart rate is 300 bpm. If the distance is 1 cm, the heart rate is 150 bpm; 1.5 cm, 100 bpm; 2 cm, 75 bpm; 2.5 cm, 60 bpm; 3 cm, 50 bpm; 3.5 cm, 43 bpm; and 5 cm, 30 bpm.

The above method is not accurate when the heart rhythm is irregular. To estimate the heart rate when the rhythm is irregular, the number of QRS complexes between the 3-s marks (7.5 cm apart) on the paper can be measured and multiplied by 20. This method is not accurate for slow heart rates.

P Wave

Normal P Wave

Atrial depolarization begins within the SA node in the subendocardium and spreads through the right atrium, then to the interatrial septum, and then to the left atrium. Therefore, the mean vector of normal atrial depolarization is directed leftward and downward, producing a positive ECG deflection in the leads with the same axis (such as I and II). The vector of atrial repolarization, which is opposite to the vector of depolarization, produces an ECG deflection in the opposite direction (see Sect. "Generation of ECG Tracing"). This small wave may be seen occasionally after the P wave in a long PR interval when the QRS complex does not obscure it. Table 7.3 lists the criteria for the normal P wave.

Right Atrial Abnormality/Enlargement

Right atrial abnormality (RAA) implies RA hypertrophy, dilation, or primary intra-atrial conduction abnormality (Table 7.3). In this situation, electrical forces of the RA, which is located anteriorly, rightward, and inferiorly to the LA, dominate forces of the LA.

Left Atrial Abnormality/Enlargement

Left atrial abnormality (LAA) implies LA hypertrophy, dilation, or primary intra-atrial conduction abnormality (Table 7.3). In this situation, electrical forces of the LA, which is located posteriorly, leftward, and slightly superiorly, dominate forces of the RA. If evidence of LAA and RAA appears simultaneously, *biatrial* enlargement can be suspected.

Normal PR Interval

The normal PR interval represents the time from the beginning of atrial activation to the beginning of ventricular activation. During this time, the impulse travels from the

Table 7.4 Criteria for normal QRS complex

1. Duration 0.06–0.10 s
2. Axis −30° to approx +100°
3. Transitional zone between V_2 and V_4

Transitional zone is the precordial lead having equal positive and negative deflections

sinoatrial node through the atria, the atrioventricular (AV) node, and the His-Purkinje network toward the ventricular myocytes. Normal PR duration is 0.12–0.20 s. It increases with slower heart rates and advanced age. It shortens with preexcitation and certain disease states.

QRS Complex

Normal QRS

Ventricular excitation begins predominantly in the middle third of the left side of the interventricular septum. From there, the initial wave of depolarization spreads toward the right side of the septum. A small resultant vector that is rightward, anterior, and either superior or inferior produces the initial QRS deflection of the ECG. Next, the impulse spreads throughout the apex and free walls of both ventricles from the endocardium to the epicardium. Because of the larger mass of the left ventricle, the resultant mean vector is leftward and inferior. This vector produces the major deflection of the QRS complex. Finally, the wave of depolarization arrives at the posterobasal LV wall and the posterobasal septum. A small resultant vector is directed posteriorly and superiorly, producing the latest QRS deflection [3]. Criteria for a normal QRS complex may be found in Table 7.4.

Low Voltage

An amplitude of an entire QRS complex (R plus S) less than 5 mm in all limb leads and less than 10 mm in all precordial leads describes a low-voltage ECG. This abnormality is associated with chronic lung disease, pleural effusion, myocardial loss due to multiple myocardial infarctions, cardiomyopathy, pericardial effusion, myxedema, and obesity.

Axis Deviation

In patients with left axis deviation (LAD), the QRS axis is −30° to −90°. Common causes of LAD include left ventricular hypertrophy, left anterior fascicular block, and an inferior wall MI (when superior and leftward forces dominate). In patients with right axis deviation, the QRS axis is +90° to +180°. Common causes include right ventricular hypertrophy, a vertically oriented heart, COPD, and a lateral wall MI.

R Wave Progression

R wave progression and transition refers to the pattern of QRS complexes across the precordial leads (V_1–V_6). With properly placed leads, the R waves *in a normal heart* should become progressively larger in amplitude as the S waves become smaller when looking from V_1 to V_6. The transition zone, defined as the lead where the positive R wave deflection equals that of the negative S wave, should usually be between V_2 and V_4.

In *early R wave progression*, there is a shift of the transitional zone to the right of V_2 (counterclockwise rotation of the heart when looking up from the apex). R is bigger than S in V_2 and possibly in V_1. The differential diagnosis of early R wave progression includes lead malposition, normal variant, right ventricular hypertrophy (RVH), and posterior wall MI. Some congenital malformations and deformations such as dextrocardia may also exhibit this. In *late* or *poor R wave progression*, the transitional zone shifts to the left of V_4 (clockwise rotation). Here, the differential includes lead malposition, mild RVH (as in COPD), left bundle branch block (LBBB), left anterior fascicular block (LAFB), left ventricular hypertrophy (LVH), and anteroseptal MI.

Left Ventricular Hypertrophy

Leftward and posterior electrical forces increase when LV mass increases. Delay in completion of subendocardial-to-subepicardial *de*polarization may result in *re*polarization that begins in the subendocardium instead of the subepicardium. Reversal of repolarization forces ensues; this causes inversion of the T waves and sometimes of the QRS complexes (see Table 7.5a–d for common LVH criteria) [4, 5].

In subjects younger than 30 years or when LVH is accompanied by LBBB or right bundle branch block (RBBB), the usual voltage criteria for LVH no longer apply. However, research into these and other special circumstances has yielded some acceptable criteria for accurate diagnosis. For example, the sum of an S in V_2 plus an R in V_6 greater than 45 mm has been shown to have 86 % sensitivity and 100 % specificity for LVH in LBBB [4].

In Table 7.5d, ranges of sensitivity are listed for four separate LVH criteria. These data were collected from patients with LVH who had either coronary artery disease (CAD), hypertension, cardiomyopathy, or valvular disease. Overall, the criteria seemed to be more sensitive in each case for those patients with hypertension or valvular disease [7].

Right Ventricular Hypertrophy

In RVH, anterior and rightward forces increase when RV mass increases. Usually, these forces are masked by LV forces unless RVH is significant. Occasionally, posterior and

Table 7.5a Romhilt-Estes scoring system for LVH

1. R or S in any limb lead ≥2 mV (20 mm) or S in lead V_1 or V_2 or R in lead V_5 or V_6 ≥3 mV (30 mm)	3 points[a]
2. Left ventricular strain	
ST segment and T wave in opposite direction to QRS complex	
Without digitalis	3 points
With digitalis	1 point
3. Left atrial enlargement	
Terminal negativity of the P wave in lead V_1 is ≥1 mm in depth and ≥0.04 s in duration	3 points
4. Left axis deviation of ≥−30	2 points
5. QRS duration ≥0.09 s	1 point
6. Intrinsicoid deflection in lead V_5 or V_6 ≥0.05 s	1 point
Total	13 points

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[a]LVH, 5 points; probable LVH, 4 points

Table 7.5b Sokolow-Lyon criteria for LVH

S wave in lead V_1 + R wave in lead V_5 or V_6 >35 mm
Or
R wave in lead V_5 or V_6 >26 mm

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Table 7.5c Cornell voltage criteria for LVH

Females	R wave in lead aVL + S wave in lead V_3 >20 mm
Males	R wave in lead aVL + S wave in lead V_3 >28 mm

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Table 7.5d Other criteria for left ventricular hypertrophy

1. Amplitude of R wave in lead aVL >11 mm
2. Amplitude of R wave in lead I >13 mm (0–25 % sensitivity)
3. Amplitude of Q or QS wave in lead aVR >14 mm
4. Amplitude of R wave in lead aVF >20 mm
5. Sum of R wave in lead I and the S wave in lead III >25 mm
6. Sum of R wave in V_5 or V_6 and S wave in V_1 >35 mm (6–67 % sensitivity)
7. Amplitude of R wave in V_5 or V_6 >26 mm (2–44 % sensitivity)
8. Sum of maximum R wave and deepest S wave in the precordial leads >40 mm (14–78 % sensitivity)

Modified from Murphy et al. [6]. With permission from Elsevier

rightward forces also increase secondary to a posterior tilt of the cardiac apex. Delay in completion of subendocardial-to-subepicardial depolarization may cause repolarization to begin in the subendocardium instead of the subepicardium. Consequently, the ECG manifests this delay of depolarization and reversal of repolarization as QRS complexes and T waves opposite their normative vectors.

Table 7.6 Criteria for right ventricular hypertrophy

1. RAD ≥+110°
2. R > S in V_1
3. R < S in V_6
4. QR in V_1 without prior anteroseptal myocardial infarction
5. Right atrial abnormality
6. Secondary ST–T changes, namely, downsloping ST depression with upward convexity and asymmetric T wave inversion in the right precordial and inferior leads
7. S_I, S_{II}, S_{III} pattern (R/S ≥ 1 in I, II, and III)

The diagnosis of RVH requires two or more criteria to be present [4], and the sensitivity and specificity of these criteria span a wide range. Most likely, this is secondary to the population observed in the study. See Table 7.6 for RVH criteria.

Biventricular Hypertrophy

In a patient with combined RVH and LVH, LV and RV forces may cancel each other. Because of its relatively larger size, LV forces usually predominate. EKG criteria for biventricular hypertrophy, however, are only 24.6 % sensitive and 86.4 % specific [7]. Criteria for biventricular hypertrophy usually require criteria for both left and right VH or criteria for LVH associated with a right axis.

Right Bundle Branch Block

The right bundle branch does not contribute significantly to septal activation. Therefore, the *early* part of the QRS complex is unchanged in RBBB. LV activation proceeds normally. The RV, which is located anteriorly and to the right of the LV, is activated late and from left to right. Therefore, terminal forces are directed anteriorly and rightward. In addition, this late (terminal) depolarization of the RV propagates by slow, cell-to-cell conduction without using the right-sided His-Purkinje system. This phenomenon gives wide and slurred terminal deflections of the QRS. Repolarization proceeds from the subendocardium to the subepicardium secondary to alteration of the recovery process (see Sect. "Generation of ECG Tracing" for comparison to normal repolarization). Thus, the ST and T vectors are opposite to the terminal part of the QRS. Table 7.7 lists the RBBB criteria. The diagnosis requires all the criteria to be present (see Fig. 7.5 for example) [4, 5].

Any discussion of RBBB would be incomplete without mention of two entities that most likely represent a continuum of disease: the Brugada syndrome and arrhythmogenic RV dysplasia (ARVD). The Brugada syndrome describes a persistent combination of ST-T elevation in the precordial

leads, RBBB, and sudden cardiac death. Occasionally, ST-T segment elevation is not apparent at baseline; it may require provocation with procainamide in the electrophysiology laboratory. This syndrome has been described predominantly in young men. Families of probands should be evaluated.

Arrhythmogenic RV dysplasia, a rare cardiomyopathy caused by progressive fibro-fatty infiltration of the RV, may also present with RBBB and/or T wave inversion in leads V_1 through V_3. This disease also seems to afflict young men most commonly, and it is associated with sudden cardiac death as well. Once again, family members of the proband should be evaluated.

RSR′ Pattern in V_1

RSR′ pattern in V_1 is a common ECG pattern. It may be seen as a normal variant, or it may be present in association with abnormalities of the RV or the posterior wall of the LV.

Left Anterior Fascicular Block

The left anterior fascicle travels toward the anterolateral papillary muscle (i.e., superiorly, anteriorly, and leftward). Thus, in LAFB, the *initial* depolarization is directed inferiorly, posteriorly, and rightward through the posterior fascicle. *Delayed* depolarization of both anterior and lateral walls is directed leftward and superiorly. Therefore, leftward and superior terminal forces of the LV free wall are unopposed and prominent. The LAFB criteria may be found in Table 7.8 [4, 5].

Table 7.7 Criteria for right bundle branch block

1. Prolonged QRS (≥0.12 s)
2. R′ (secondary R wave) taller than the initial R wave in the right precordial leads
3. Wide S wave in I, V_5, V_6
4. Axis of initial 0.06–0.08 s of QRS should be normal
5. Secondary ST–T changes (downsloping ST depression with upward convexity and asymmetric T inversion) in inferior and posterior leads

In incomplete RBBB, QRS complex has typical RBBB morphology but QRS duration is only 0.09–0.11 s

Left Posterior Fascicular Block

True left posterior fascicular block is rare. Differential diagnosis includes asthenia, COPD, RVH, and extensive lateral wall MI. The transitional zone is often displaced leftward which may cause the Q waves in the left precordial leads to disappear. This happens because the mean QRS vector is directed posteriorly in the horizontal plane (see Fig. 7.3). Table 7.9 lists the LPFB criteria [5].

Left Bundle Branch Block

Normally, the left bundle *does* contribute to septal activation. Thus, in LBBB, septal activation develops late. Therefore, early forces manifested on ECG originate from the RV apex, which is located to the left, in front of, and below the electrical center of the heart. Depolarization spreads from the subendocardium of the RV apex to the subepicardium. Consequently, the resultant vector is directed leftward, forward, and down. Leftward orientation of the forces remains as depolarization progresses. Terminal depolarization proceeds by slow, cell-to-cell conduction. This causes slurring and widening of the terminal deflection. *Repolarization* proceeds from the subendocardium to the subepicardium secondary to changes in the course of the recovery process (see Sect. "Generation of ECG Tracing"). Thus, the ST and T vectors are opposite to the terminal part of the QRS (Fig. 7.6). Table 7.10 lists LBBB criteria. All criteria should be present to diagnose LBBB [4, 5].

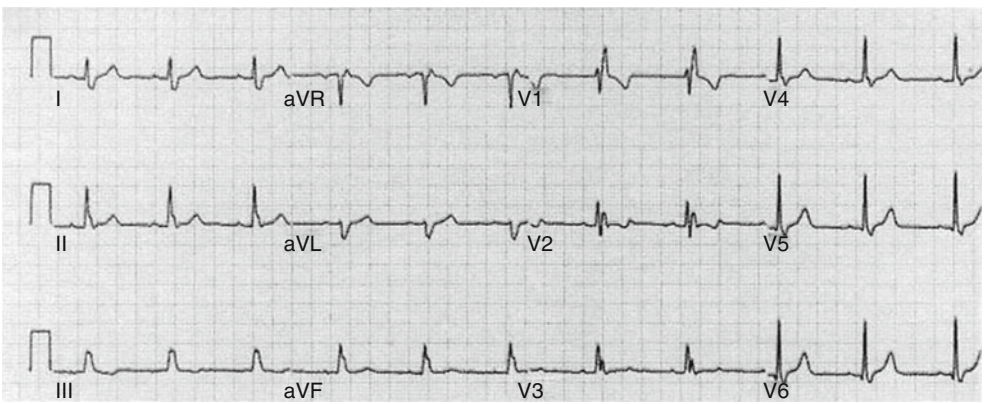

Fig. 7.5 ECG demonstrating typical complete right bundle branch block

Other Types of Block

Nonspecific intraventricular conduction disturbance is characterized by QRS duration greater than 0.11 s when the QRS morphology does not satisfy all criteria for either LBBB or RBBB. Common causes of other various blocks below the AV node include coronary artery disease, hypertensive heart disease, aortic valve disease, cardiomyopathy, sclerosis of the conduction tissue or cardiac skeleton (usually seen in elderly people), and surgical trauma [4]. Heart rate-related RBBB (and less commonly LBBB) or other conduction abnormalities are not rare in clinical practice.

Abnormal/Pathological Q Wave

Electrically inert myocardium, like that affected by previous MI, fails to contribute to normal electrical forces. Thus, the vector of the opposite wall takes over. The Q wave is larger, and the R wave may become smaller. Larger S waves are often obscured by ST changes. Table 7.11 lists the criteria for abnormal Q waves.

In a normally positioned heart, the right-sided precordial leads V_3R and V_4R are located over the mid-RV. The usual lead V_1 is located over the high RV or septum and opposite to the posterior LV wall. V_2 is placed over the septum and opposite to the posterior LV wall. Leads V_3 and V_4 cover the middle anterior LV. V_5 and V_6 are situated over the low lateral LV, and I and aVL are across the high lateral LV. Leads II, III, and aVF are closest to the inferior LV. Therefore, the location of an infarction may be deduced from the location of abnormal Q waves (Table 7.12).

In a posterior MI, reciprocal changes of the ST segment (i.e., depression in the anteroseptal leads) are often seen in acute ischemia/injury. When diagnosing posterior MI, one should rule out juvenile ECG changes, early R wave progression, and RVH. RV infarction is characterized by ST elevation more than 10 mm in the right precordial lead(s). V_4R is considered more sensitive and specific than V_1 for this diagnosis.

Table 7.8 Criteria for left anterior fascicular block

1. Mean QRS axis of −45° to −90° (S_{II} amplitude is less than S_{III} amplitude)
2. QR complex (or a pure R wave) in I and aVL; RS complex in leads II, III, and aVF
3. Normal to slightly prolonged QRS duration (0.08–0.12 s)
4. Deep S waves may be seen in the left precordial leads secondary to occasional extreme superior deviation of the mean QRS vector in the frontal plane

Table 7.9 Criteria for left posterior fascicular block

1. Frontal plane QRS axis of +100° to +180°
2. S_I Q_{III} pattern (as opposed to left anterior fascicular block)
3. Normal or slightly prolonged QRS duration (0.08–0.12 s)

ST Segment/T Wave Changes

The normal ST segment reflects steady membrane polarization from the end of depolarization to the beginning of repolarization. Its vertical baseline is that of the T-to-Q interval. Usually,

Table 7.10 Criteria for left bundle branch block

1. Prolonged QRS duration (≥0.12 s)
2. Broad, monophasic R in leads I, V_5, or V_6 that is usually notched or slurred
3. Absence of any Q waves in I and V_5–V_6
4. Direction of the ST segment shift and the T wave is opposite to that of the QRS complex. T waves in "lateral" leads (i.e., I, aVL, V_4–V_6) may become tall (Fig. 7.7e)

See Fig. 7.6

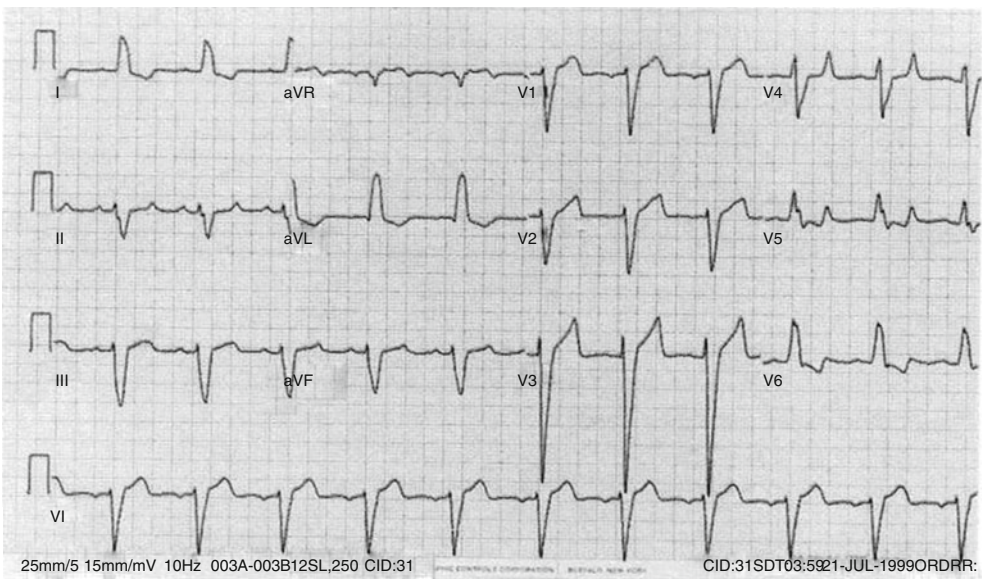

Fig. 7.6 ECG demonstrating typical complete left bundle branch block

the ST segment is almost absent because the ascending limb of the T wave begins right at the J point (the junction of the end of the QRS complex and the beginning of the ST segment).

Normal T waves represent ventricular repolarization. As previously described, longer action potential duration in the ventricular subendocardium as compared to the subepicardium causes repolarization to proceed in the direction opposite that of depolarization; it begins in the subepicardium and spreads toward the subendocardium; see Sect. "Generation of ECG Tracing." Therefore, the vector of repolarization (T wave) has the same direction as the vector of depolarization (QRS). Usually, the T wave is asymmetric: the ascending limb is longer than the descending one. It is at least 5 mm tall in I, II, and the left precordial leads [4], but it may be slightly inverted or biphasic in other leads.

Juvenile T waves are a normal variant characterized by persistence of negative T waves in V_1–V_3 after approximately 20 years of age. They are usually neither symmetric nor deep. The degree of T wave inversion decreases progressively from V_1 to V_4. In normal tracings from subjects with this ECG pattern, however, the T waves are always upright in I, II, and the left precordial leads.

Peaked T waves may also be seen as a normal variant. In this case, the T wave is more than 6 mm high in the limb leads or more than 10 mm in the precordial leads (Fig. 7.7a) [1]. Early repolarization is due to a dominant parasympathetic effect on the heart [8]. This normal variant (Fig. 7.7a) is characterized by (1) an elevated J point and ST segment, (2) a distinct notch or slur on the downstroke of the R wave, and (3) upward *concavity* of the ST segment. There are no reciprocal changes of the ST segment in the leads with opposite axes. *Increased vagal tone* is accompanied by tall, peaked T waves. It is usually associated with a characteristic ST elevation; this is called early repolarization.

Nonspecific ST segment and/or T wave abnormalities may show either (1) slight ST depression or elevation (less than 1 mm) or (2) flattening, decreased amplitude, or slight inversion of the T wave. On a normal ECG, the T wave should be at least 5 mm tall in I, II, and the left precordial leads. These ST-T changes may be local or diffuse. Numerous physiologic and pathologic conditions can cause this.

As illustrated in the preceding paragraphs, variations in the normative ST segment and T wave patterns may provide invaluable information to the clinician. Two such variations include those of myocardial ischemia and injury as well as J-point elevation or the early repolarization pattern.

Table 7.11 Criteria for Q wave abnormality

1. Duration of the Q wave ≥0.04 s
2. Amplitude of the Q wave in the limb leads ≥4 mm or ≥25 % of the R wave in that lead (even deeper required for leads III, aVF and aVL)
3. Normally, QRS in V_2–V_4 begins with the R wave. Thus, even small Q waves are abnormal if seen in V_2–V_4 (unless the transitional zone is markedly shifted secondary to another cause)

Note that a new myocardial infarction may mask ECG changes from a previous one

Table 7.12 Electrocardiographic localization of Q wave myocardial infarction

Site of infarct	Signs of electrically inert myocardium
Anteroseptal	Pathological Q or QS in V_1–V_3 and sometimes V_4
Anterior	Absence of Q in V_1; QS or QR in V_2–V_4; and late R progression or reversal of R progression in precordial leads may also be present
Anterolateral	Abnormal Q in V_4–V_6
Lateral	Abnormal Q in V_5–V_6
Extensive anterior	Abnormal Q in V_1–V_6
High lateral	Abnormal Q in I and aVL
Inferior	Pathological Q in II, III, aVF (Q in III and aVF >25 % of the amplitude of the R wave)
Inferolateral	Abnormal Q in II, III, aVF, V_5–V_6
Posterior	Initial R wave in V_1 and V_2 longer than 0.04 s with R larger than S

This is based on a normal anatomic position of the heart

ST Segment and T Wave Changes in Ischemia/Injury

Any ischemic area exhibits prolonged repolarization which causes a difference of potentials between ischemic and nonischemic areas during phase III of action potential repolarization. This results in QT prolongation and T wave changes [6]. Consequently, a difference in potential between injured and uninjured areas is formed which produces a diastolic or resting current of injury. The ECG machine automatically adjusts for this baseline shift by shifting the tracing in the opposite direction. Therefore, the whole QRS-T complex is shifted to keep the baseline (TQ segment) at the same level. This causes the ST segment to look elevated or depressed depending on what layer of the myocardial wall it involves.

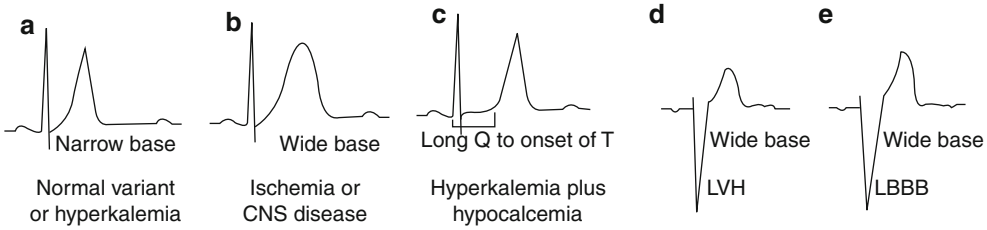

Fig. 7.7 (**a**–**e**) Some examples of tall T waves

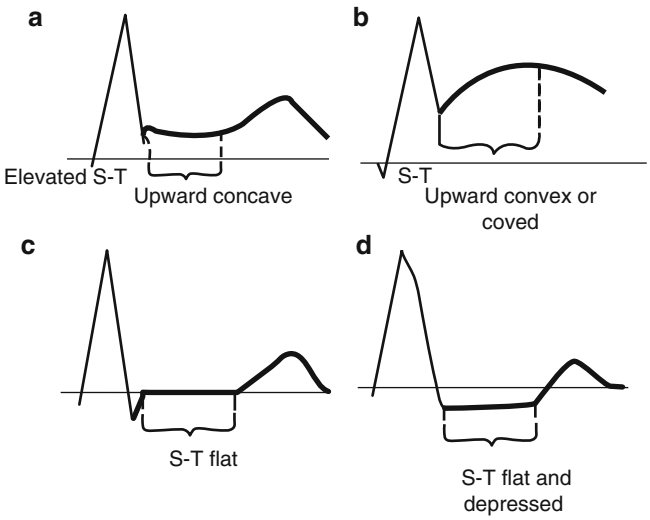

Fig. 7.8 (**a–d**) Early repolarization and the ST segment changes in injury/ischemia (Modified from Constant [9]. With permission from Parthenon Publishing Group)

Secondly, the injured area shows early completion of repolarization or diminished depolarization. Thus, phase II, the plateau phase of the action potential, is shortened. Systolic difference in potentials between the injured and uninjured area ensues. The second mechanism, systolic current of injury, plays a lesser role [1].

T wave abnormalities suggesting *myocardial ischemia* may include (1) abnormally tall, upright T waves (see Fig. 7.7 for common types of tall T waves); (2) symmetrically and/or deeply inverted T waves; (3) "pseudonormalization" of inverted T waves (when previously inverted T waves become positive secondary to ischemia-induced changes in repolarization); and (4) nonspecific T wave abnormalities. Hyperacute T waves may be seen occasionally in the earliest stage of coronary occlusion. They are tall, symmetric or asymmetric, and peaked or blunted [1, 4]. More often, however, T waves on the initial ECG are isoelectric, biphasic, or inverted. The T wave changes of angina may be transitory or persistent.

ST segment abnormalities suggesting *myocardial injury* may be pronounced or subtle. These abnormalities include acute ST segment elevation with upward convexity in the leads facing the area of transmural or subepicardial injury (Fig. 7.8b). There may be reciprocal ST depression. Posterior wall transmural or subepicardial injury may cause ST segment depression in V_1–V_3. In clinical as opposed to experimental coronary occlusion, any ST or T changes may reflect CAD. The ECG may also be completely normal. Subendocardial injury, ischemia, and necrosis commonly cause horizontal or downsloping ST segment depression and/or flattening with or without the T wave changes described above (see Fig. 7.8b–d for some examples). Usually, the depressed ST segment is flat or sagging in contrast to the upward convexity of the "strain pattern." To diagnose CAD, ECG changes should be present in at least two contiguous leads.

J-Point Elevation or the Early Repolarization Pattern

J-point elevation or the early repolarization pattern (ERP) has been defined as QRS-ST junction elevation ≥0.1 mV from the baseline with a discrete notch or terminal slurring of the QRS complex into the ST segment that is found in two or more inferior (II, III, aVF) or lateral (I, aVL, V4–V6) leads [10]. This pattern, found in approximately 5–13 % of the general population [11, 12], was long thought to be a "normal variant" [13]. However, Antzelevitch and Yan have proposed that the ERP may exist on a continuous spectrum of disease [14]. At one end of the spectrum is the early repolarization *pattern*, frequently observed in young, athletic, healthy males; at the other is the early repolarization *syndrome*, which may present with sudden cardiac death, often in the context of a structurally normal heart [15, 16]. Nunn et al. [17] lend further support to this theory by demonstrating that J-point elevation is more prevalent in the first-degree relatives of sudden arrhythmic death syndrome probands than in controls. In addition, Derval et al. [18] characterized two types of ERP in the Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER). Figure 7.9 illustrates type I ERP [18] and Fig. 7.10 type II ERP [18] in two different idiopathic ventricular fibrillation patients. That variations within the ERP itself have been described in some populations illustrates the complexity of its significance in clinical medicine and demonstrates the need for further research.

QT Interval

The QT interval represents the duration of electrical systole. The normal QT corrected for the heart rate is less than 0.44 s. It is usually less than half of the preceding RR interval.

Many formulas for correction of the QT interval exist. Two of the most commonly applied are Fridericia's (the measured QT interval divided by the cube root of the preceding RR interval) and Bazett's (the measured QT interval divided by the square root of the preceding RR interval). In choosing a formula, consideration should be given to the stability of the heart rate (i.e., the beat-to-beat variation) and the rhythm. A certain formula may be more suitable to one condition over another. This becomes particularly important in situations such as drug development.

Prolonged QT Interval

A prolonged QT interval may be caused by dyssynchrony or prolongation of ventricular repolarization. The prolonged corrected QT interval is associated with numerous pathological conditions. These include ischemia and infarction, the

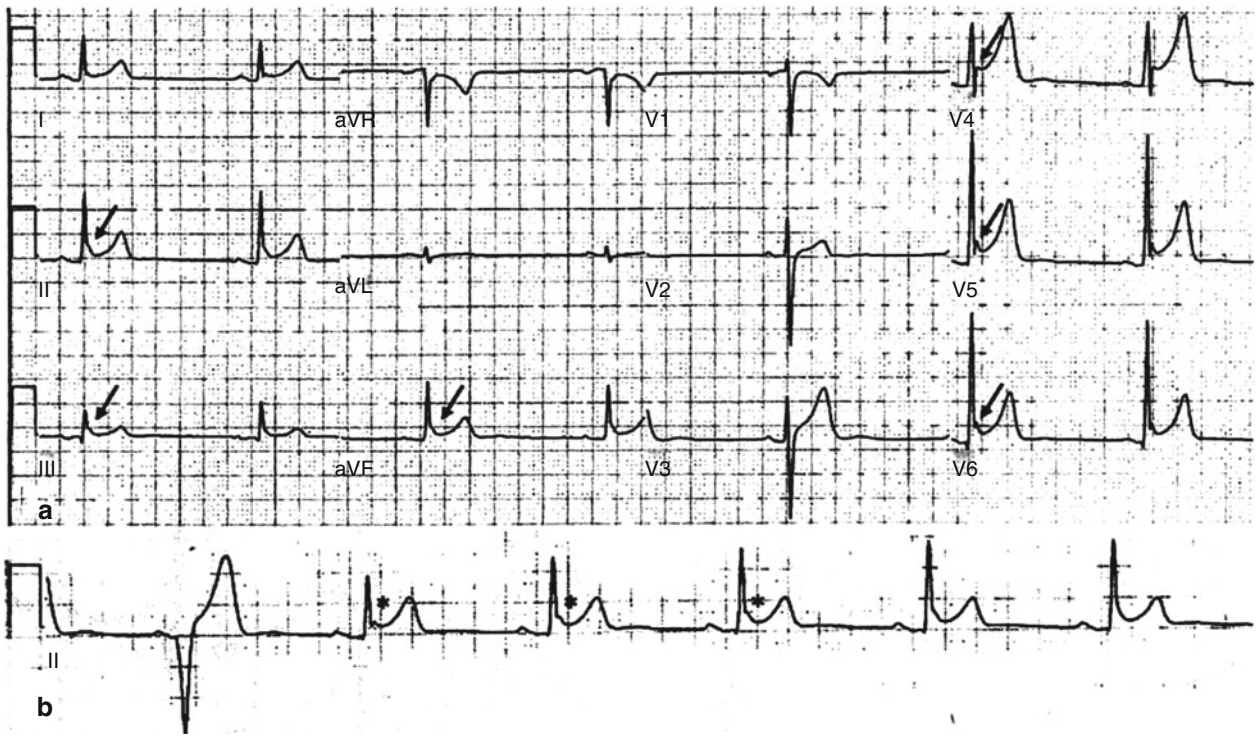

Fig. 7.9 Type I early repolarization pattern in an IVF patient. (**a**) A 12-lead electrocardiogram (ECG) type 1 inferolateral early repolarization pattern (ERP) (*arrows* indicate J-wave elevation). (**b**) Rhythm strip with beat-to-beat fluctuation of the J-wave. Note the post-extrasystolic pause increase of the J-wave (*). *IVF* idiopathic ventricular fibrillation (Reproduced from Derval et al. [18]. With permission from Elsevier)

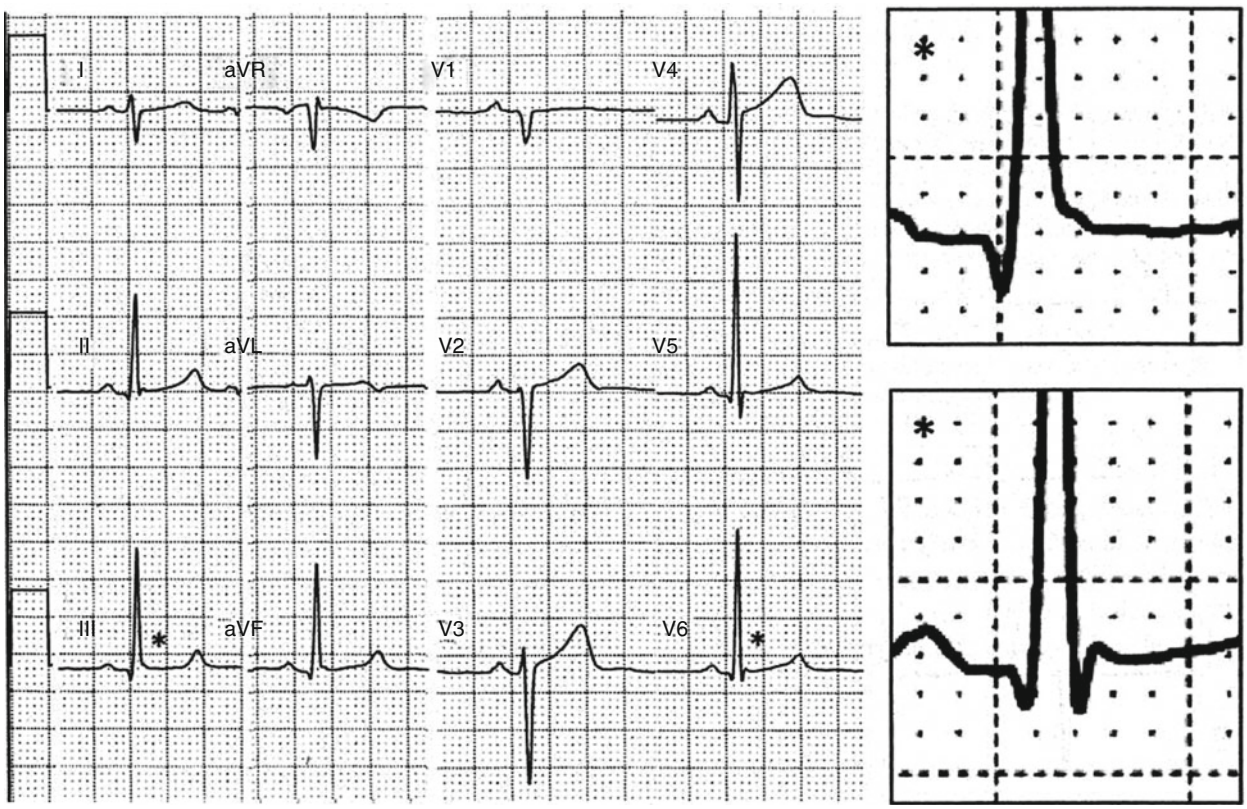

Fig. 7.10 Type II early repolarization pattern in an IVF patient. A 12-lead ECG of a patient with type II ERP in the inferolateral leads. (*Right*) Discrete J-wave elevation in leads III and V_6 (*). Abbreviations as in Fig. 7.9 (Reproduced from Derval et al. [18]. With permission from Elsevier)

most common causes, and central nervous system (CNS) disorders. In hypokalemia, prominent U waves merge with T waves and result in *pseudo*-QT prolongation. In this case, "bifid T waves" may be present.

Drugs can cause QT prolongation. This has become a major regulatory consideration in the development of new pharmaceutical entities throughout the world. When measuring the QT interval, a clinician must remember to review the medication list of a patient to rule medications out as a cause of prolongation. Previously recorded ECGs should also be evaluated for comparison.

Congenital QT prolongation comes in many forms. Some types result from discrete genetic variants and present with specific patterns associated with T wave changes on ECG. Other genetic variations may not be so obvious, that is, they may require a stressor such as a drug or exercise to induce prolongation. Since its first recognition, many different genetic lesions have been described, and new ones continue to be discovered. A complete discussion of the congenital prolonged QT syndrome is beyond the scope of this chapter.

It is well-known that a prolonged QT interval confers a risk of torsade de pointes, a form of polymorphic ventricular tachycardia that may be fatal upon its first presentation. This is why meticulous measurement of the QT interval on every ECG tracing is imperative.

Shortened QT Interval

A shortened QT interval is most often caused by digitalis or hypercalcemia. However, in 2003, Giustetto and Schimpf et al. [19] recognized the short QT syndrome (SQTS) as a new clinical entity related to familial sudden death with an autosomal dominant inheritance [20]. According to population studies, QTc of 360 ms or less or QT of 88 % or less of the predicted QT have been proposed as the lower limit of the normal QTc and QT because these correspond to the mean values minus 2 standard deviations in the general population [21, 22]. Treatment includes an implantable cardioverter-defibrillator or hydroquinidine [19].

U Wave

The normal U wave represents afterpotentials of the ventricular myocardium or delayed repolarization of the Purkinje fibers. Normally, it should be upright in all leads except aVR. Prominent, clinically significant U waves often have an amplitude larger than 25 % of the T wave in the same lead, or they are larger than 1.5 mm. Common causes include bradycardia, hypokalemia, and LVH. *U wave inversion* is highly specific for organic heart disease.

Normal ECG

Normal variants of the ECG include early repolarization (refer to discussion in the Sect. "ST Segment/T Wave Changes" above), juvenile T waves, occasionally the S_I S_{II} S_{III} pattern, rSR' in V_1, Parkinson's tremor, and the "athlete's heart." The mechanism of ECG changes in the "athlete's heart" reflects increased vagal tone, RVH or LVH, and asymmetry of ventricular repolarization. In this condition, one may see sinus bradycardia with a junctional escape rhythm, first-degree or second-degree type I AV block, and increased P wave and QRS amplitude. Early repolarization is also more common in athletes. T waves in the precordial leads may be tall, inverted, or biphasic. Parkinson's tremor can simulate atrial flutter or ventricular tachycardia with a rate of 330 bpm.

Incorrect electrode placement in a normal healthy person may produce characteristic ECG changes. The most common error is reversal of the right and left arm leads, which causes P, QRS, and T inversion in leads I and aVL.

Myocardial Infarction

Distinction between *Q wave* and *non-Q wave* MI may be less relevant clinically than once thought. Subendocardial or nontransmural MI often shows abnormal Q waves whereas transmural MI may not.

The typical evolution of the ECG in acute Q wave MI includes these stages:

1. *Tall T waves* (Fig. 7.7b) may appear within the first minutes or hours, but more often isoelectric, negative, or biphasic T waves are seen on presentation.
2. *ST segment elevation* (Fig. 7.8b) appears within hours after coronary occlusion and may last approximately 2 weeks. If it lasts longer than 2 weeks, ventricular aneurysm, pericarditis, or concomitant early repolarization should be considered.
3. *Abnormal Q waves* appear within hours or days after MI and persist indefinitely.
4. *Decline in ST elevation* occurs simultaneously with or after the onset of the T wave inversion. In acute pericarditis, in contrast, the ST segment becomes isoelectric before the T wave becomes inverted.
5. *Isoelectric ST segment with symmetric T wave inversion* may last months to years or persist indefinitely.

The ECG interpretation of myocardial infarction may be complicated by the fact that the QRS wave, ST segment, and T wave may normalize transiently in the course of its evolution. If the ST segment is elevated, the infarction is probably recent or acute (within approximately 2 weeks) (Fig. 7.11). If there is no ST segment elevation, the infarction is probably old or of indeterminate age. Traditional teaching also holds that T wave changes reflect ischemia, ST segment changes

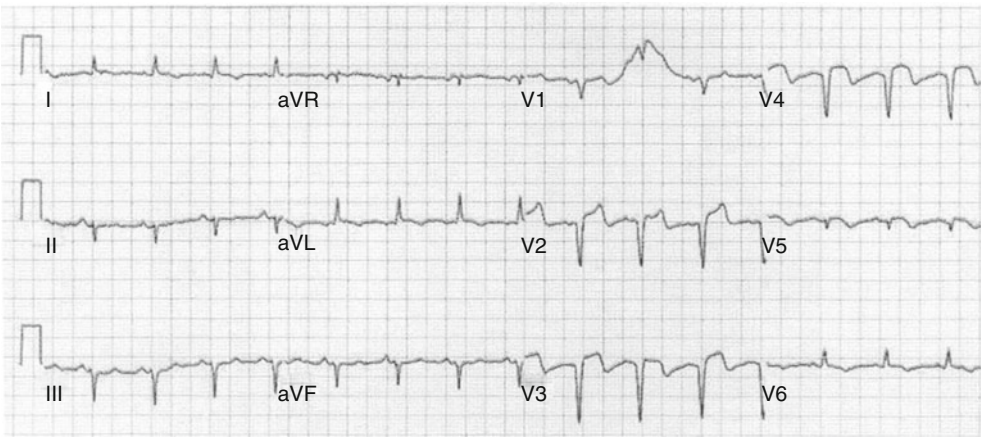

Fig. 7.11 Acute extensive anterior MI. Note upward convexity of the ST segment elevation in leads V4 and V5, which is typical for myocardial injury. Also note that upward convexity is obscured by acute T waves in lead V2. Motion artifact is apparent in lead V1

Table 7.13 Results of the univariate analysis of electrocardiographic criteria in LBBB

Criterion	Sensitivity (95 % CI)	Specificity (95 % CI)
ST segment elevation ≥1 mm and concordant with QRS complex	73 (64–80)	92 (86–96)
ST segment depression ≥1 mm in lead V_1, V_2, or V_3	25 (18–34)	96 (91–99)
ST segment elevation ≥5 mm and discordant with QRS complex	31 (23–39)	92 (85–96)
Positive T wave in lead V_5 or V_6	26 (19–34)	92 (86–96)

Modified from Sgarbossa et al. [24]. With permission from Massachusetts Medical Society

reflect injury, and abnormal Q waves reflect necrosis. This is an overly simplistic and artificial approach. Both T wave and ST segment changes may be due to ischemia, injury, or necrosis. The Q wave may reflect temporary electrical silence and not necessarily necrosis.

The presence of LBBB on the baseline ECG has presented a challenge in the face of an acute MI. This was recognized more than 50 years ago when Cabrera studied the tracings of such patients in 1953 [23]. Other investigators followed suit, but none of their proposed signs have gained widespread acceptance [24].

In order to aid in this diagnosis, criteria have been proposed based on a review of ECGs from patients enrolled in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial (see Table 7.13). This provides some guidelines, but continued research is needed in this area.

Recent publications suggest predictive and prognostic value in ST segment elevation in lead aVR during a first acute, non-ST segment elevation MI. One study published in 2003 suggests that ≥1-mm ST segment elevation in lead aVR correlates positively with adverse events, including death (Fig. 7.12). Another significantly smaller study stated that acute left main coronary artery obstruction may be predicted using a similar criterion [26]. Based on these new findings, lead aVR should be carefully scrutinized on any ECG suspicious for infarction.

Prompt identification of the culprit artery during a myocardial infarction can help the clinician to choose the appropriate acute therapies for patients. Historically, the electrocardiogram has played a major role in locating the vessel. Variations in coronary artery anatomy, both subtle and obvious, can occasionally make this diagnosis quite difficult. For example, the His bundle may receive dual blood supply from septal perforators from the LAD as well as the AV nodal artery from the posterior descending artery. An inferior MI could therefore cause a LAFB pattern on the ECG [7]. Figure 7.13 is an algorithm for ECG identification of the infarct-related artery in inferior MI.

Differential Diagnosis of Myocardial Infarction

A QS pattern in the right precordial leads or late R wave progression may indicate *LVH*. In LVH, however, this pseudoinfarction pattern is not present in the chest leads if they are recorded one intercostal space lower than usual. The "strain" pattern of LVH may also mimic or mask ischemia or injury. Ischemia or subendocardial injury is favored over hypertrophy with the strain pattern when (1) the ST segment changes are disproportional to the R wave amplitude in the same lead, (2) ST segment depression is present without T wave inversion, and (3) T wave inversion is symmetric.

In *RVH*, T wave inversion in the inferior or right precordial leads may imitate CAD. However, other ECG changes often suggest this diagnosis. In patients with *pulmonary disease*, late R wave progression in the precordial leads may be mistaken for an anterior MI. However, in COPD and cor pulmonale, this "abnormality" disappears when the leads are placed one intercostal space lower than usual. With pulmonary diseases, there may also be other signs of RV involvement. Sometimes patients with diseases exhibit abnormal Q waves in the inferior leads that may mimic inferior infarction. Abnormal Q waves are rarely seen in lead II, but they

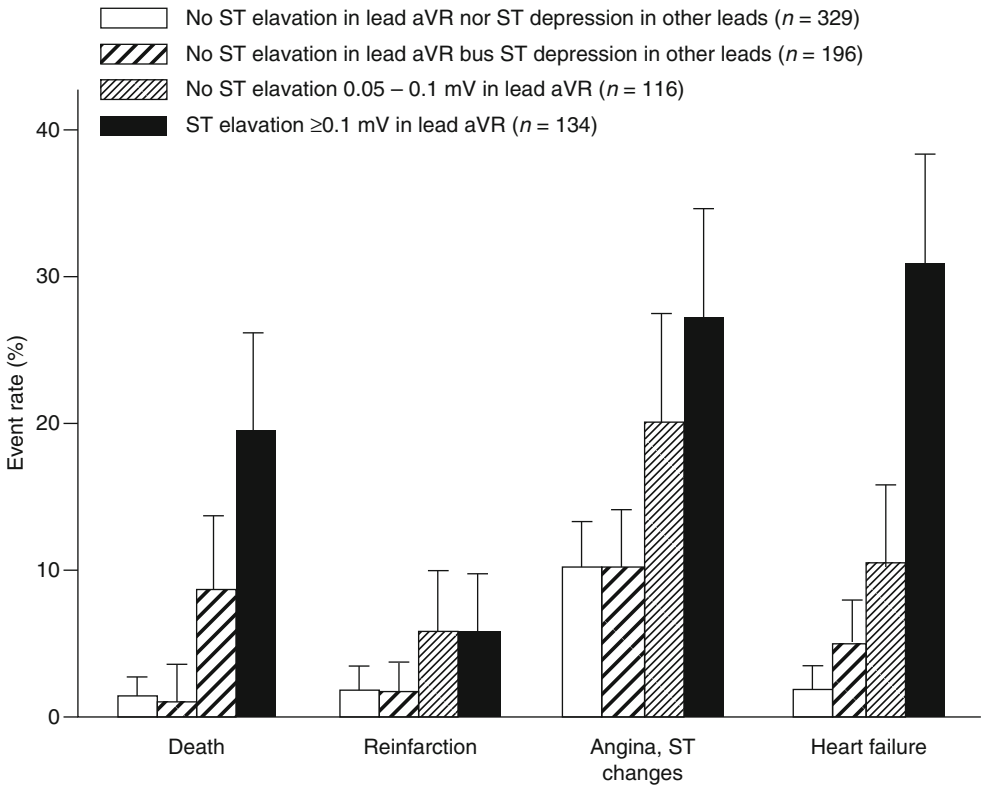

Fig. 7.12 Rates of major in-hospital adverse events in patients with and without ST segment depression ≥0.1 mV on admission after stratifying for ST segment elevation in lead aVR. This latter variable identified a high-risk subgroup, whereas the remaining patients had low complication rates irrespective of ST segment depression in other leads. Error bars represent the upper limits of the 95 % CIs (Reprinted from Barrabes et al. [25]. With permission from Lippincott Williams & Wilkins)

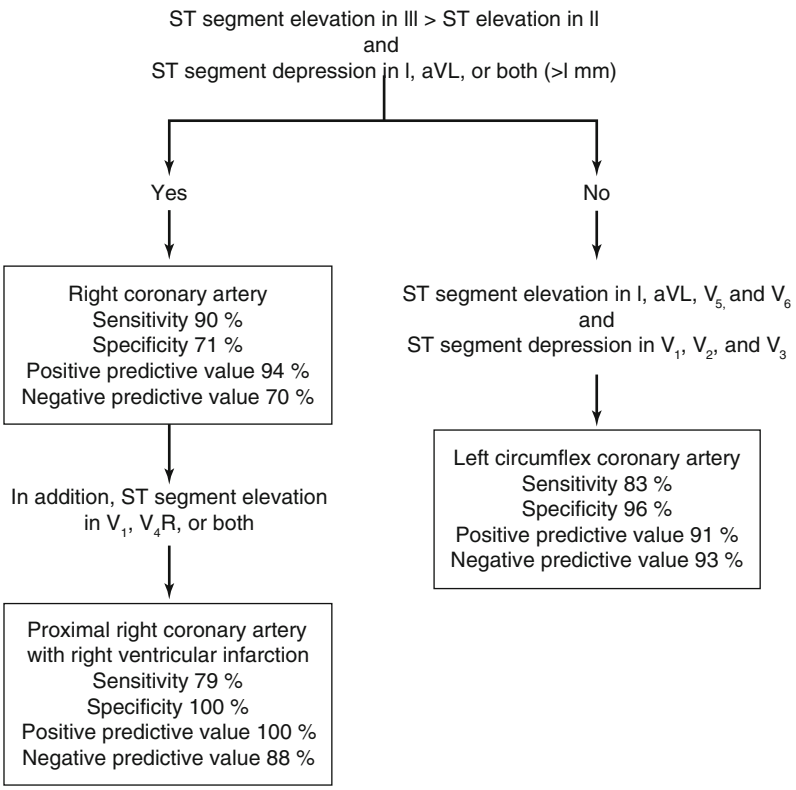

Fig. 7.13 Algorithm for electrocardiographic identification of the infarct-related artery in inferior myocardial infarction (Reproduced Zimetbaum and Josephson [27]. With permission from Massachusetts Medical Society)

may appear along with ST segment and T wave changes in myocardial diseases secondary to localized fibrosis and in repolarization abnormalities.

In *Wolff-Parkinson-White* (*WPW*) *syndrome*, preexcitation of a ventricle significantly changes the initial QRS forces. The resultant *delta wave* can mimic an abnormal Q

wave if it is negative. An upward or positive delta wave may mask abnormal Q waves. The degree of preexcitation and ST/T change may vary in any given person, a finding that mimics evolutionary changes of an acute ischemic event. In WPW syndrome, however, the PR interval is usually short, and the QRS complex is wide with initial slurring. Marked ST segment elevation in the leads with an upright QRS complex or ST depression in the leads with a downward QRS complex is also very unlikely in WPW syndrome.

Among *CNS disorders*, ECG changes are most often present in subarachnoid or intracranial hemorrhage. One can observe ST elevation or depression; large, wide, inverted, or upright T waves; a long QT segment; and occasionally, abnormal Q waves. Often, only the clinical picture helps to make a definitive diagnosis.

In *hyperkalemia*, the T wave is tall, and the ST segment may be elevated or depressed. In contrast to ischemia, the QT is normal or shortened (only if there is no QRS complex prolongation or other reasons for QT lengthening). In addition, the T wave is narrow-based (Fig. 7.7a). ST segment depression slopes upward, not horizontal or downward, as it does in ischemia. Presence of a U wave tends to rule out hyperkalemia.

Patients with *acute pericarditis* very often have ST segment elevation that mimics acute injury. In pericarditis, however, ST segment elevation is usually present in almost all leads on the ECG (except aVR and V_1), and there is no reciprocal ST segment depression. In contrast to MI, the ST segment elevation in pericarditis has an upward concavity, and it is rarely greater than 5 mm from the baseline [7]. T wave inversion tends to be less pronounced but more diffuse in pericarditis than in ischemia.

Digitalis effect or *toxicity* may cause horizontal or downsloping ST segment depression that looks similar to MI. Digitalis-induced ST depression often has a sagging, upwardly concave shape. In addition, the QT interval is often shortened.

In *RBBB*, the initial forces of depolarization are not altered. In MI, they are abnormal. Therefore, RBBB usually does not interfere with signs of MI. In *LAFB* and *LPFB*, the initial forces may occasionally be altered. Thus, both LAFB and LPFB can imitate or mask MI. Abnormal Q waves may also be prominent if the precordial leads are recorded one intercostal space higher than usual.

Both *LBBB* and *pacing* cause significant alteration of initial and late QRS forces. Therefore, both LBBB and pacing may imitate or mask MI. In the presence of these conditions, correct diagnosis of MI from the ECG alone may be impossible. Occasionally, MI can be diagnosed in the presence of LBBB or pacing by the presence of (1) pathologic Q waves, (2) ST-T deflections that have the same direction as the QRS complex, (3) ST segment elevation disproportionate to the amplitude of the QRS complex (greater elevation is required for leads V_1–V_2), or (4) notched upstroke of the S wave in two precordial leads.

Drug Effects: Digitalis

Many classes of drugs have the potential to affect the appearance of the ECG. Antiarrhythmics directly interfere with molecular myocardial conduction channels; diuretics may alter serum electrolyte concentrations. These changes may cause subtle variations in myocardial depolarization and repolarization, and the resultant ECG will reflect these variations. The altered ECG may mimic certain disease states, and recognition is therefore essential. Because of its well-described findings, only digitalis will be discussed here.

Digitalis increases vagal tone as well as the amount of calcium in myocytes. The drug may also improve bypass tract conduction should one exist. The *digitalis effect* may be accompanied by QT interval shortening, PR interval lengthening, and increased U wave amplitude. Another characteristic finding is a sagging ST segment depression with upward concavity. This may also be seen in CAD.

In *digitalis toxicity*, there is increased automaticity of the myocytes and/or impaired conduction in the His-Purkinje system. Ventricular premature depolarizations are common. Tachyarrhythmias with different degrees of AV block are considered diagnostic.

Metabolic Abnormalities

In *hyperkalemia*, the main electrophysiological abnormality is shortening of phase III of the action potential. This phase generates the T wave on the ECG. Therefore, the earliest and most prominent ECG findings involve the T waves. In *hypokalemia*, phase III of the action potential is prolonged. Therefore, many of the ECG changes are opposite to those of hyperkalemia. Prominent U waves with decreased T wave amplitude are typical.

In *hypercalcemia*, the main electrophysiologic finding is shortening of phase II of the action potential. This "plateau" phase is not usually accompanied by significant deflections on the ECG tracing. The ST segment is shortened or nearly absent, and the entire QT interval consequently shortens. There is usually little effect on the QRS complex or the P or T waves. *Hypocalcemia* is usually accompanied by the opposite ECG changes, a prolonged QT interval due to a long ST segment. The combination of hyperkalemia and hypercalcemia (often seen in renal disease) causes QT prolongation combined with peaked T waves, which may occasionally be exceptionally tall.

Table 7.14 Criteria for chronic obstructive pulmonary disease

1. The P wave axis is >+75°
2. Any of the right ventricular hypertrophy criteria (increased R/S ratio in V_1 is the least common right ventricular pattern in COPD)
3. Late R wave progression in precordial leads
4. Low voltage
5. Abnormal Q waves in the inferior or anterior leads
6. Supraventricular arrhythmias, especially atrial tachycardia, multifocal atrial tachycardia, and atrial fibrillation

Table 7.15 Criteria for acute cor pulmonale

1. Sinus tachycardia (most common ECG sign)
2. Transient right bundle branch block (incomplete or complete)
3. Inverted T waves in V_1–V_3
4. $S_I\ Q_{III}$ or $S_I\ Q_{III}\ T_{III}$ pattern with pseudoinfarction in the inferior leads
5. Right axis deviation
6. Right atrial abnormality with various supraventricular tachyarrhythmias

Pulmonary Diseases

Chronic Lung Disease

In patients with lung disease, ECG changes may possibly be caused by a vertical heart position (due to hyperinflation of the lungs), RVH, or RAA. The ECG criteria for pulmonary disease are listed in Table 7.14.

Acute Cor Pulmonale Including Pulmonary Embolism

One mechanism of ECG change in acute cor pulmonale involves sudden RV dilatation. Dilatation causes RV myocardial conduction abnormalities. On ECG, this may manifest as a vertically positioned heart with counterclockwise rotation in the precordial leads. ECG abnormalities in these patients are frequently transitory. See Table 7.15 for the diagnostic criteria [5].

Acute Pericarditis

ECG changes in pericarditis reflect subepicardial myocarditis with subepicardial injury.

Typically, the ECG in acute pericarditis has the following evolution:

Stage 1: The ST segment elevates (upward concave) in almost all leads except aVR and V_1. Reciprocal changes are absent.

Stage 2: The ST segment returns to the baseline, and the T wave amplitude begins to decrease. At this point, the ECG may look completely normal.

Stage 3: The T wave inverts.

Stage 4: Electrocardiographic resolution may occur.

Other clues may also help in diagnosis. In the early stages, PR segment depression reflects atrial injury (as ST elevation reflects ventricular injury). Low-voltage QRS complexes and electrical alternans of ECG waves may occur in the presence of a pericardial effusion, which may or may not be associated with pericarditis. Sinus tachycardia and atrial arrhythmias are very common [5].

The differential diagnosis of acute pericarditis should include early repolarization. Absence of serial ST/T changes, the presence of tall T waves, and a characteristic notching of the terminal QRS favor early repolarization. PR segment depression in *both* limb and precordial leads (as opposed to *either* limb or precordial leads) favor pericarditis. In addition, ST segment depression in lead V_1, occasionally present in pericarditis, is not present in early repolarization.

Pericardial Effusion

As mentioned above, *pericardial effusion* may cause electrical alternans on ECG. It may also cause low-voltage QRS complexes that are defined as complexes less than 5 mm in amplitude in all limb leads and less than 10 mm in all precordial leads.

Central Nervous System Disorders

The most common CNS disorders associated with ECG abnormalities are subarachnoid and intracranial hemorrhage. The mechanism of ECG changes in these patients includes altered autonomic tone with resultant changes in repolarization. The most common ECG findings are deeply inverted T waves and a markedly prolonged QT_C interval. Occasionally, the T waves may be upright and tall.

Preexcitation (Wolff-Parkinson-White) Syndrome

In WPW syndrome, one or more accessory AV pathways allow the atrial impulse to bypass the AV node and activate the ventricles prematurely. AV delay is shortened. Ventricular activation may follow the usual course through the normal conduction system, or it may begin from the site of attachment of the bypass tract within one of the ventricles. Commonly, both pathways contribute to the QRS complex. Refer to Table 7.16 for WPW criteria.

Table 7.16 Criteria for Wolff-Parkinson-White syndrome

1. Normal P wave with a PR interval generally <0.12 s
2. Initial slurring of the QRS (delta wave)
3. Wide QRS interval >0.10 s (except with septal insertion of a bypass tract)
4. Secondary ST/T changes (similar to the "strain pattern")
5. Atrioventricular reentrant tachycardias (most common arrhythmias)
6. Atrial fibrillation or flutter with a wide QRS complex and a rate >200 bpm is suggestive

Congenital and Acquired Heart Disease

Although beyond the scope of this chapter, no reference in electrocardiography could be completed without at least a brief word on congenital and acquired heart disease. Many defects and malformations have very specific findings on ECG: incomplete RBBB, a rightward axis, and precordial changes of a secundum atrial septal defect; the reversal of normal septal activation in L-transposition of the great vessels; and the possible RVH with persistent truncus arteriosus. Similarly, acquired disease, including valvular disease such as mitral stenosis, has specific characteristics. Recognition of these abnormalities will undoubtedly aid in following the clinical course.

Summary

Electrocardiography offers a glimpse into many aspects of cardiac function. When combined with a clinical scenario, physical examination, and other methods of diagnosis, it permits a fuller understanding of both acute and chronic disease states in the heart. Its use has proven invaluable in the practice of modern medicine.

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Echocardiography

8

Daniel G. Blanchard and Anthony N. DeMaria

Introduction

Echocardiography is the evaluation of cardiac structures and function utilizing images produced by ultrasound (US) energy. Echocardiography started as a crude one-dimensional technique but has evolved into one that images in two and three dimensions (2-D, 3-D) and that can be performed from the chest wall, from the esophagus, and from within vascular structures [1, 2]. Clinically useful M-mode recordings became available in the late 1960s and early 1970s. In the mid-1970s, linear-array scanners that could produce 2-D images of the beating heart were developed. Eventually, these evolved into the phased-array instruments currently in use. In addition to 2-D imaging, the Doppler examination has become an essential component of the complete echocardiographic evaluation. Doppler US technology blossomed in the early 1980s with the development of pulsed-wave (PW), continuous-wave (CW), and 2-D color-flow imaging. The field of cardiac US continues to grow rapidly: recent clinical additions include tissue Doppler imaging, "speckle" tracking and myocardial strain imaging, and real-time 3-D echocardiography [3].

Physics and Principles

US is sonic energy with a frequency higher than the audible range (greater than 20,000 Hz). US is created by a transducer that consists of electrodes and a piezoelectric crystal that deforms when exposed to an electric current. This crystal creates US energy and then generates an electrical signal when struck by reflected US waves. US is useful for diagnostic imaging because, like light, it can be focused into a beam that obeys the laws of reflection and refraction. An US beam travels in a straight line through a medium of homogeneous density, but if the beam meets an interface of different acoustic impedance, part of the energy is reflected. This reflected energy can then be evaluated and used to construct an image of the heart [1].

Because the velocity of sound in soft tissue is relatively constant (approx 1,540 m/s), the distance from the transducer to an object that reflects US can be calculated using the time a sound wave takes to make the round trip from the transducer to the reflector and back again. Sophisticated computers can examine reflections from multiple structures simultaneously and display them on a screen as 1-D images. If the US beam is then electronically swept very rapidly across a sector, a 2-D image can be generated.

Several characteristics of US are important in obtaining high-quality images. High-frequency US energy yields excellent resolution, and such beams tend to diverge less over distance than low-frequency signals. High-frequency beams, however, tend to reflect and scatter more as they pass through tissue and are thus subject to greater attenuation than low-frequency signals. Therefore, echocardiographic examinations should utilize the highest frequency that is capable of obtaining signals from the targets in the US field of interest [1].

Two-Dimensional Echocardiography: Standard Examination

A US beam can image the heart from multiple areas on the chest wall. Several years ago, M-mode imaging (which detects motion along a single beam of US) was the primary tool of clinical echocardiography. M-mode has been largely supplanted by 2-D imaging. To help standardize the 2-D examination, the American Society of Echocardiography recognizes three orthogonal imaging planes: the long axis,

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_8,

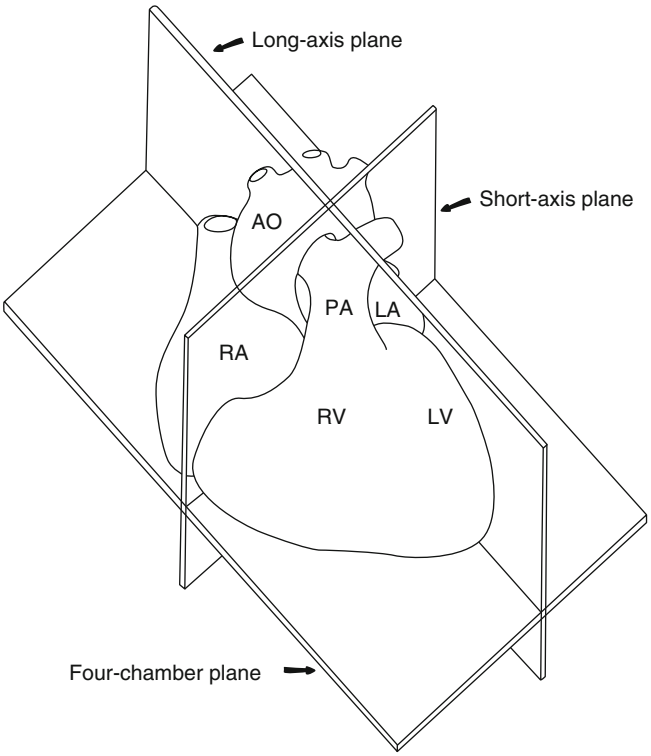


Fig. 8.1 The three basic tomographic imaging planes used in echocardiography: long axis, short axis, and four chamber. *LV* left ventricle, *LA* left atrium, *RV* right ventricle, *RA* right atrium, *PA* pulmonary artery, *AO* aorta (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

the short axis, and the four-chamber planes (Fig. 8.1) [2]. *It is important to remember that the long and short axes are those of the heart, not of the entire body*. These three planes can be imaged in four basic transducer positions: parasternal, apical, subcostal, and suprasternal (Fig. 8.2). From these parasternal positions, the transducer angle can be modified to obtain views of the mitral valve, the base of the heart, the tricuspid valve, and the right ventricular outflow tract (Fig. 8.3a, b). From the apical and subcostal transducer positions, both ventricles and all cardiac valves can be examined (Fig. 8.3c–e). The transducer can also be placed in the suprasternal position to image the thoracic aorta and great vessels.

A complete examination utilizing these imaging planes and transducer positions visualizes the cardiac valves, chamber sizes, and ventricular function in the great majority of cases. Echocardiography is an accepted method for evaluating cardiac systolic function, and assessments of ejection fraction and regional ventricular dysfunction correlate well with those made with angiographic and radionuclide methods. In occasional patients, however, examination is limited owing to US artifacts, marked obesity, severe lung disease (with lung tissue interposed between chest wall and heart), or chest wall deformities.

Doppler Echocardiography

Two-dimensional imaging provides abundant information about cardiac structure but no direct data on blood flow. This important area of cardiac imaging is addressed by Doppler echocardiography. When a sound signal strikes a moving object, the frequency of the reflected signal is altered in a way that is proportional to the velocity at which the object is moving and to its direction. The velocity of the moving object can be calculated by the Doppler equation:

$$v = f_d \, c / 2 f_0 (\cos\theta),$$

where v is the velocity of red blood cells under examination, f_d is the Doppler frequency shift recorded, f_0 the transmitted frequency, and c the velocity of sound [4]. The angle θ is the angle between the US beam and the direction of red blood cell flow (i.e., if the US beam is directed parallel to blood flow, the angle is 0°). The importance of this angle cannot be overstated, as echocardiography computer systems assume it to be 0°. If the angle θ is greater than 20°, significant errors in velocity calculation occur [5].

Thus, the echocardiography system evaluates the change in frequency (the Doppler shift) of US reflected by red blood cells and translates this into velocity of blood flow. By convention, spectral Doppler tracings (1) plot velocity with respect to time and (2) display blood flow toward the transducer above an arbitrary "zero" line and flow away from the transducer below this line. As an example, Fig. 8.4a shows a normal Doppler tracing of blood flow through the mitral valve and the typical early filling (E) and late filling from atrial contraction (A). In this example, the transducer is in the apical position.

There are three main forms of Doppler flow imaging: PW, CW, and color-flow Doppler. Through a technique called *range gating*, PW Doppler can examine flow in discrete, specific areas in the heart and vasculature. This capability is extremely useful in assessing local flow disturbances, but because of the phenomenon of "aliasing," high velocities cannot be accurately recorded (for a more complete discussion of this phenomenon, the reader is referred to refs. [5, 6]). The normal velocity of flow through the tricuspid valve is 0.3–0.7 m/s and through the pulmonary artery 0.6–0.9 m/s. Normal flow velocity through the mitral valve is 0.6–1.3 m/s and 1.0–1.7 m/s through the LV outflow tract.

Unlike PW Doppler, CW Doppler records all blood flow velocities encountered along the Doppler US beam. Therefore, there is ambiguity of flow location, but CW Doppler can successfully record very high flow velocities. Color-flow imaging, a major advance in echocardiography, is an extension of PW Doppler. This technique assesses the velocity of flow in multiple sample volumes along multiple beam paths and then assigns a color to each velocity. This

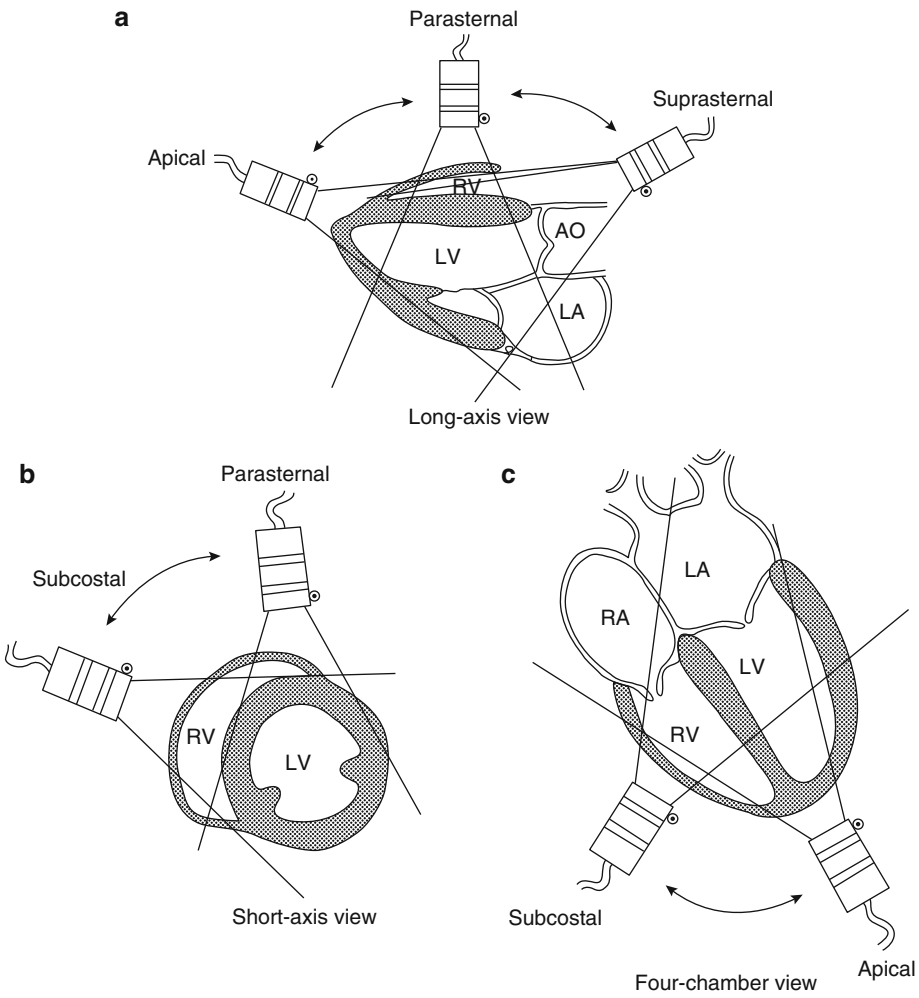


Fig. 8.2 Visualization of the heart's basic tomographic imaging planes by various transducer positions. The long-axis plane (**a**) can be imaged in the parasternal, suprasternal, and apical positions; the short-axis plane (**b**) in the parasternal and subcostal positions; and the four-chamber plane (**c**) in the apical and subcostal positions

color "map" is then superimposed on the 2-D image to obtain a real-time, moving description of blood flow. By convention, flow moving toward the transducer is color coded in shades of red, flow moving away from the transducer in blue (Fig. 8.5). Very high-velocity flow is assigned a speckled or green color. Color-flow Doppler is an essential part of the complete echocardiographic examination and is an excellent tool for both screening and semiquantitation of valvular regurgitation and stenosis.

There has been considerable interest in using mitral inflow velocity patterns to evaluate left ventricular (LV) diastolic function [7]. Normally, the E wave is larger than the A wave (see Fig. 8.4a). In cases of LV relaxation impairment, the early diastolic transmitral pressure gradient is blunted, causing a decrease in the peak E wave velocity and the rate of flow deceleration. Accompanying this, the peak A wave velocity increases (Fig. 8.6a). In patients with advanced diastolic dysfunction and markedly increased left atrial pressure and LV stiffness, the E/A ratio becomes abnormally high, and the E wave develops a very rapid deceleration of flow velocity (i.e., a short deceleration time). This is the so-called "restrictive" filling pattern (Fig. 8.6b). In general, the former "relaxation" abnormality (small E, large A) shown in Fig. 8.6a represents mild diastolic dysfunction, whereas the "restrictive" pattern shown in Fig. 8.6b indicates severe diastolic dysfunction and significantly elevated left atrial pressure. This restrictive pattern can occur in restrictive cardiomyopathy, advanced LV systolic dysfunction, pericardial disease, and severe valvular disease (e.g., severe mitral or aortic regurgitation). The restrictive pattern also has been associated with increased risk of death in patients with advanced heart failure.

Despite the utility of transmitral flow patterns in assessing diastolic properties, these should not be interpreted as pathognomonic findings of diastolic dysfunction but rather as a component of a complete clinical and echocardiographic evaluation. In this regard, pulmonary vein flow patterns and tissue Doppler imaging of the mitral annulus (Fig. 8.4b) are also quite useful and may help detect elevated left atrial pressure when mitral inflow patterns are equivocal or (falsely) appear normal (Fig. 8.6c) [7]. The reader is referred to ref. [7] for a complete discussion of the use of US in diastolic function.

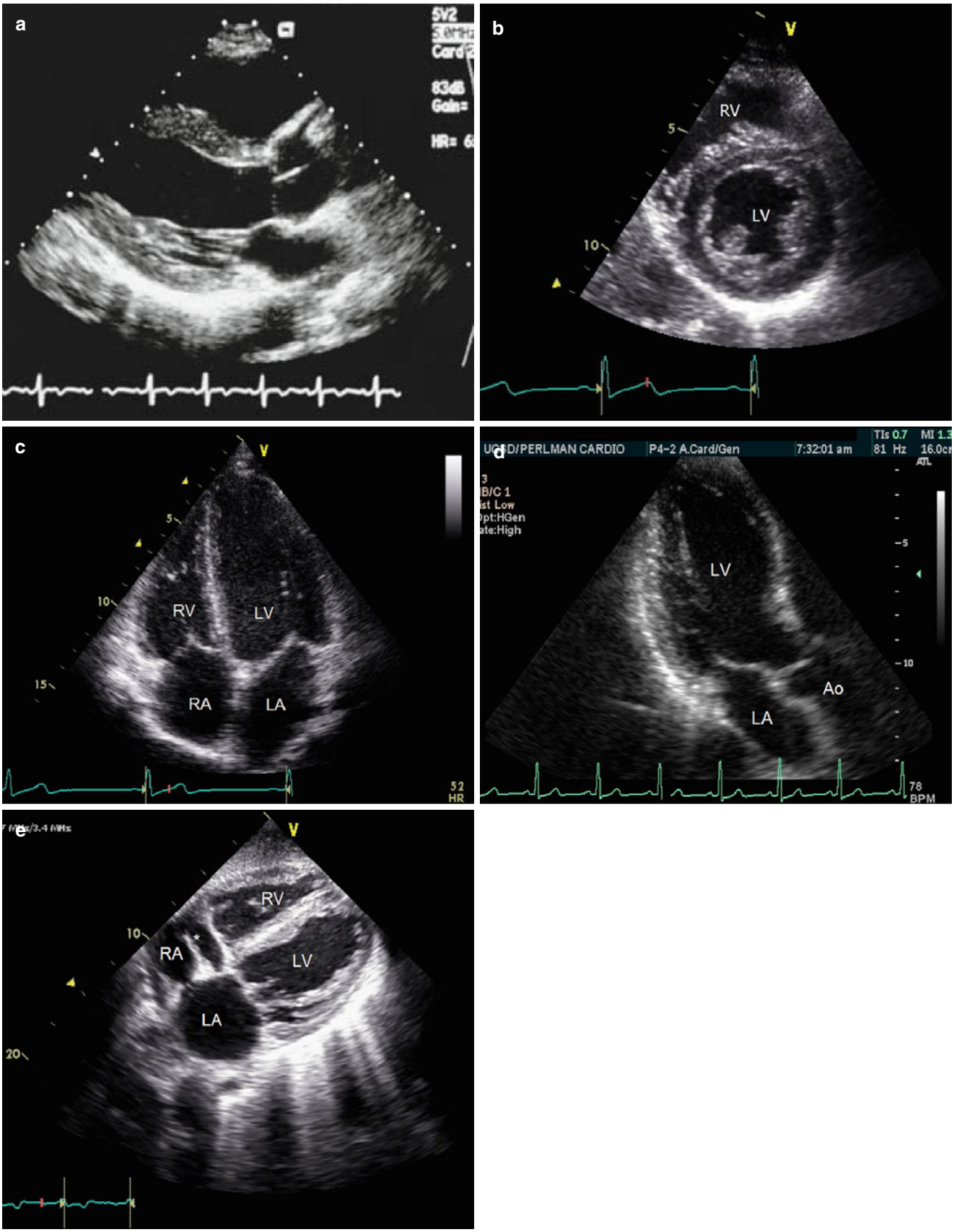


Fig. 8.3 (**a**) Two-dimensional image of the heart in the parasternal long-axis view. The cardiac chambers correlate with the diagram in Fig. 8.2a. (**b**) Short-axis plane through the heart at the level of the papillary muscle. (**c**) Two-dimensional image of the apical four-chamber plane. (**d**) Two-dimensional image of the apical three-chamber plane. (**e**) Two-dimensional image of the subcostal four-chamber plane. *RA* right atrium, *RV* right ventricle, *LV* left ventricle, *LA* left atrium (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

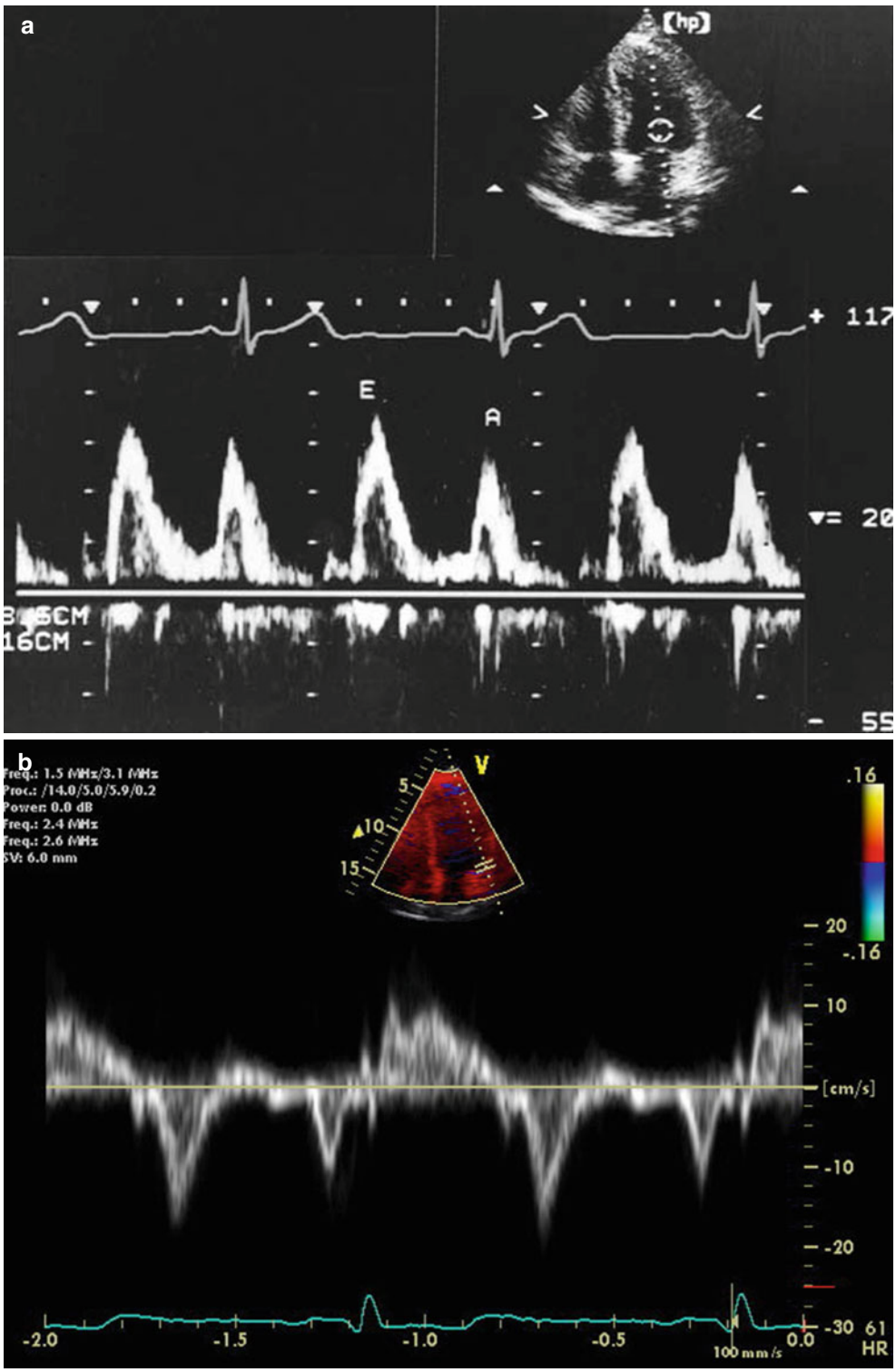


Fig. 8.4 (**a**) Normal pulsed-wave Doppler tracing from the left ventricular inflow tract displays the early rapid filling (*E*) and atrial contraction (*A*) phases of diastolic flow. The transducer is in the apical position, and the sample volume is at the mitral leaflet tips. (**b**) Normal tissue Doppler tracing from the lateral portion of the mitral valve annulus (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

Bernoulli and Continuity Equations

The *modified Bernoulli equation* states that the gradient across a discrete stenosis in the heart or vasculature can be estimated; thus,

If the blood velocity proximal to the stenosis is less than 1.5 m/s, this proximal velocity term can be ignored. The resulting equation states that the pressure gradient across a discrete stenosis is four times the square of the peak velocity through the orifice. This equation can be used to calculate

$$\text{Pressure gradient} = 4\,([\text{Stenotic orifice velocity}]^2 - [\text{Proximal velocity}]^2).$$

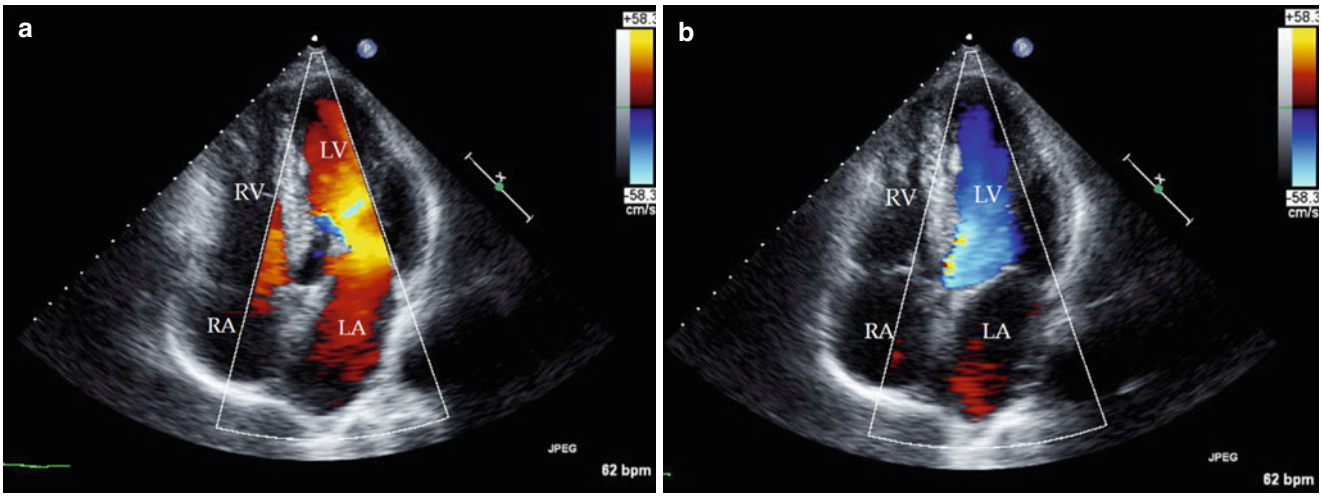


Fig. 8.5 Apical four-chamber images with color-flow Doppler during diastole (**a**) and systole (**b**). *Red flow* indicates movement toward the transducer (diastolic filling); *blue flow* indicates movement away from the transducer (systolic ejection). *RA* right atrium, *RV* right ventricle, *LV* left ventricle, *LA* left atrium (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

pressure gradients across any flow-limiting orifice [8]. In addition, if valvular regurgitation is present, the Bernoulli equation can be used to calculate pressure gradients across the tricuspid and mitral valves. This is quite helpful in measuring pulmonary artery pressure, as the peak right ventricular (RV) and therefore the peak pulmonary artery pressure equals 4 (peak TR velocity)^2 plus the right atrial pressure (which can be estimated on physical examination of the jugular venous pressure).

The *continuity equation* states that the product of cross-sectional area (A) and velocity (V) is constant in a closed system of flow:

$$A_1V_1 = A_1V_2.$$

The most common use of the continuity equation is calculating aortic valve area, where the product of the cross-sectional area and flow velocity of the LV outflow tract (LVOT) equals the product of the cross-sectional area and velocity of the aortic valve orifice [9]. LVOT area is defined as $\pi(d/2)^2$. This area is multiplied by the LVOT peak systolic velocity (measured by PW Doppler) and then divided by the peak velocity through the stenotic orifice (measured by CW Doppler) to obtain the aortic valve (AV) area. Thus,

$$\mathrm{A_{LVOT}V_{LVOT}} = \mathrm{A_{AV}V_{AV}}.$$

$$\text{Since } \mathrm{A_{LVOT}} = \pi(d/2)^2, \text{ then } \mathrm{A_{AV}} = (\pi[d/2]^2 \cdot \mathrm{V_{LVOT}})/\mathrm{V_{AV}}.$$

Transesophageal Echocardiography

Occasionally, transthoracic echocardiography (TTE) does not provide adequately detailed information regarding cardiac anatomy. This is most often true in the evaluation of posterior cardiac structures (e.g., the left atrium and mitral valve), prosthetic cardiac valves, small vegetations or thrombi, and the thoracic aorta. Transesophageal echocardiography (TEE) is well-suited for these situations, as the esophagus is, for much of its course, immediately adjacent to the left atrium and the thoracic aorta [10].

TEE images can be recorded from a variety of positions, but most authorities recommend three basic positions: (1) posterior to the base of the heart, (2) posterior to the left atrium, and (3) inferior to the heart (Fig. 8.7a, b). There are several specific instances in which TEE is recommended. These include assessment and evaluation of (1) cardiac anatomy when TTE is inadequate; (2) valvular vegetations and infective intracardiac abscesses (Fig. 8.8a); (3) prosthetic valve function; (4) cardiac embolic sources, including atrial appendage thrombi (Fig. 8.8b), patent foramen ovale, and interatrial septal aneurysm; and (5) aortic dissection and atherosclerosis [12].

Handheld Echocardiography

Recent technologic advances have led to production of small, lightweight echocardiographic units that fit in the pocket of a white coat. These handheld devices are very portable and facilitate point-of-care echo evaluation by the physician. The

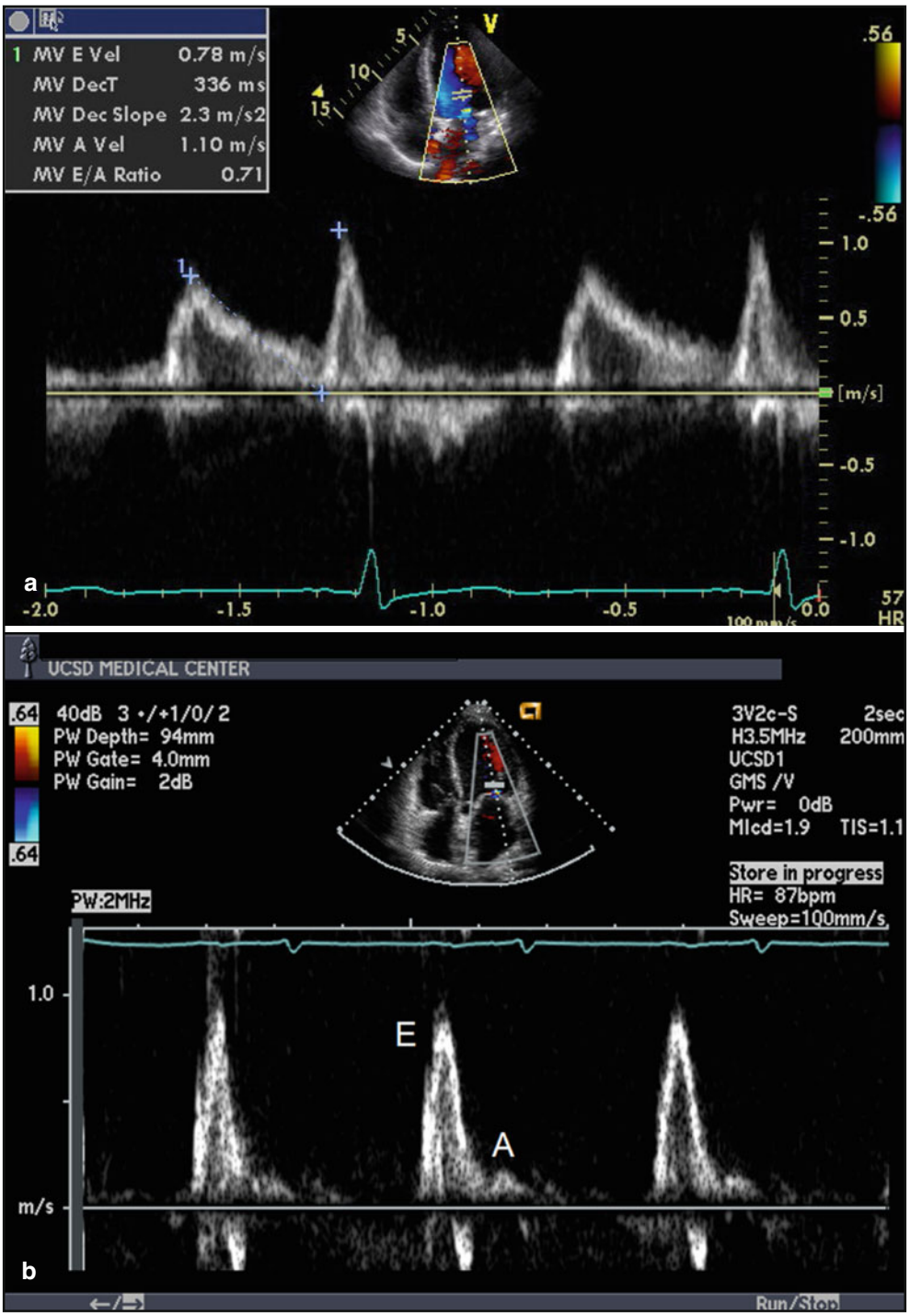
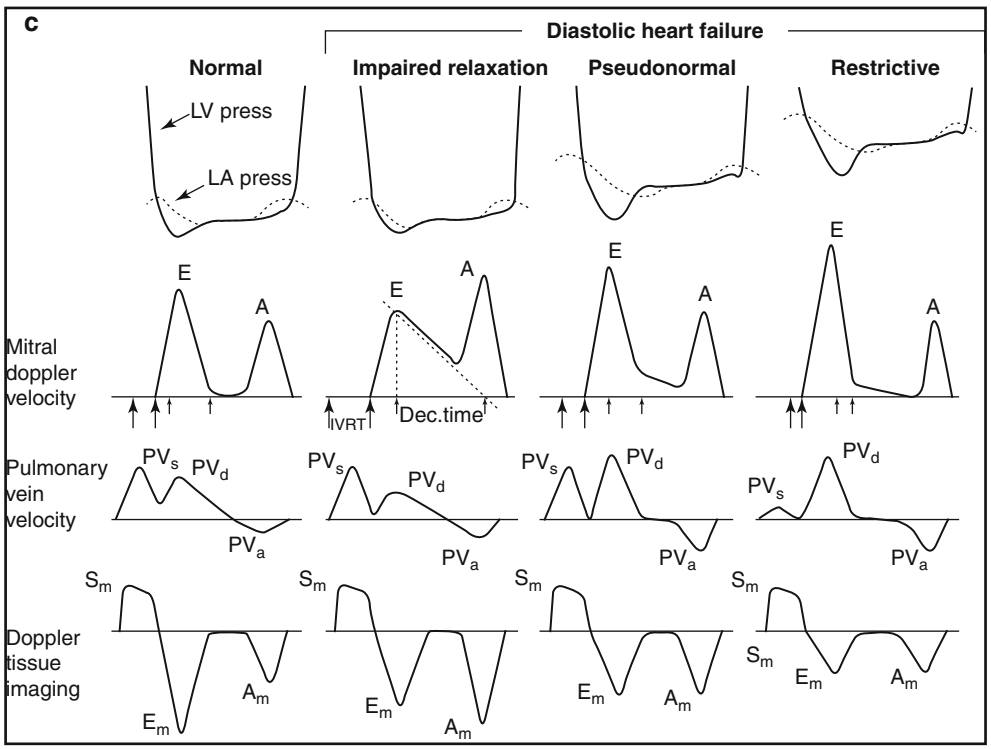


Fig. 8.6 (**a**) Pulsed-wave Doppler tracing of diastolic relaxation abnormality. The transducer is in the apical position with the sample volume at the mitral leaflet tips. (**b**) Pulsed-wave Doppler tracing of diastolic restrictive abnormality (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill). (**c**) Doppler assessment of progressive diastolic dysfunction utilizing transmitral pulsed-wave Doppler, pulmonary venous Doppler, and mitral annular tissue Doppler imaging. *IVRT* isovolumic relaxation time, *Dec. Time* E wave deceleration time, *E* early LV filling velocity, *A* atrial component of LV filling, PV_s systolic pulmonary vein velocity, PV_d diastolic pulmonary vein velocity, Pv_a, pulmonary vein velocity resulting from atrial contraction, S_m systolic myocardial velocity, E_m early diastolic myocardial velocity, A_m myocardial velocity during LV filling produced by atrial contraction (Reprinted from Zile and Brutsaert [7]. With permission from Wolter Kluwers Health)

Fig. 8.6 (continued)



quality of images from these scanners has improved in recent years. The appropriate use of these scanners is somewhat controversial, and recommendations will evolve over time. Several studies have shown benefits from handheld scanning in detection of cardiac and aortic pathology.

This area is definitely in flux, but at this time, it may be best to view handheld and limited echo examinations as extensions of the stethoscope. Performed by a competent individual, the diagnostic capability of handheld scanning is at least the equal of auscultation and probably significantly superior [13].

Contrast Echocardiography

Contrast echocardiography has grown explosively in the last few years. For many years, the main agent used for echocardiographic "contrast" injection was agitated saline, which contains numerous air microbubbles that are strong reflectors of US energy. When injected intravenously, agitated saline produces dense opacification of the right heart structures and is an excellent method for detecting intracardiac shunts. As the air microbubbles dissolve rapidly into the bloodstream, they do not pass through the pulmonary circulation. Therefore, any air microbubbles entering the left side of the heart must arrive there through a shunt (Fig. 8.9).

Direct injection of agitated saline into the aorta or left ventricle produces US opacification of the myocardium and LV cavity, respectively [14]. Extensive research in the past few years has resulted in the creation of several echocardiographic contrast agents that survive transit through the pulmonary circulation and reach the left side of the heart after intravenous injection. The current generation of these agents has microbubbles filled with various perfluorocarbon gases instead of air. Because these gases are dense and much less soluble than air in blood, they can persist in the circulation, producing consistent and dense opacification of the LV cavity. These microbubbles also flow along with blood through the coronary vessels and new technology now permits quantitation of myocardial blood flow by measuring contrast transit characteristics through the myocardium. In addition, harmonic imaging enhances the US backscatter from contrast microbubbles (which resonate in an US field) while it decreases the signal returning from the myocardium (which does not resonate) [15]. Echocontrast agents are especially useful in stress echocardiography, as the enhanced LV endocardial border definition improves detection of regional dysfunction.

Valvular Heart Disease

Aortic Valve

Aortic Stenosis

The thin leaflets of the aortic valve are usually well visualized by echocardiography. Aortic valve disease is often best imaged from the parasternal views. In cases of acquired

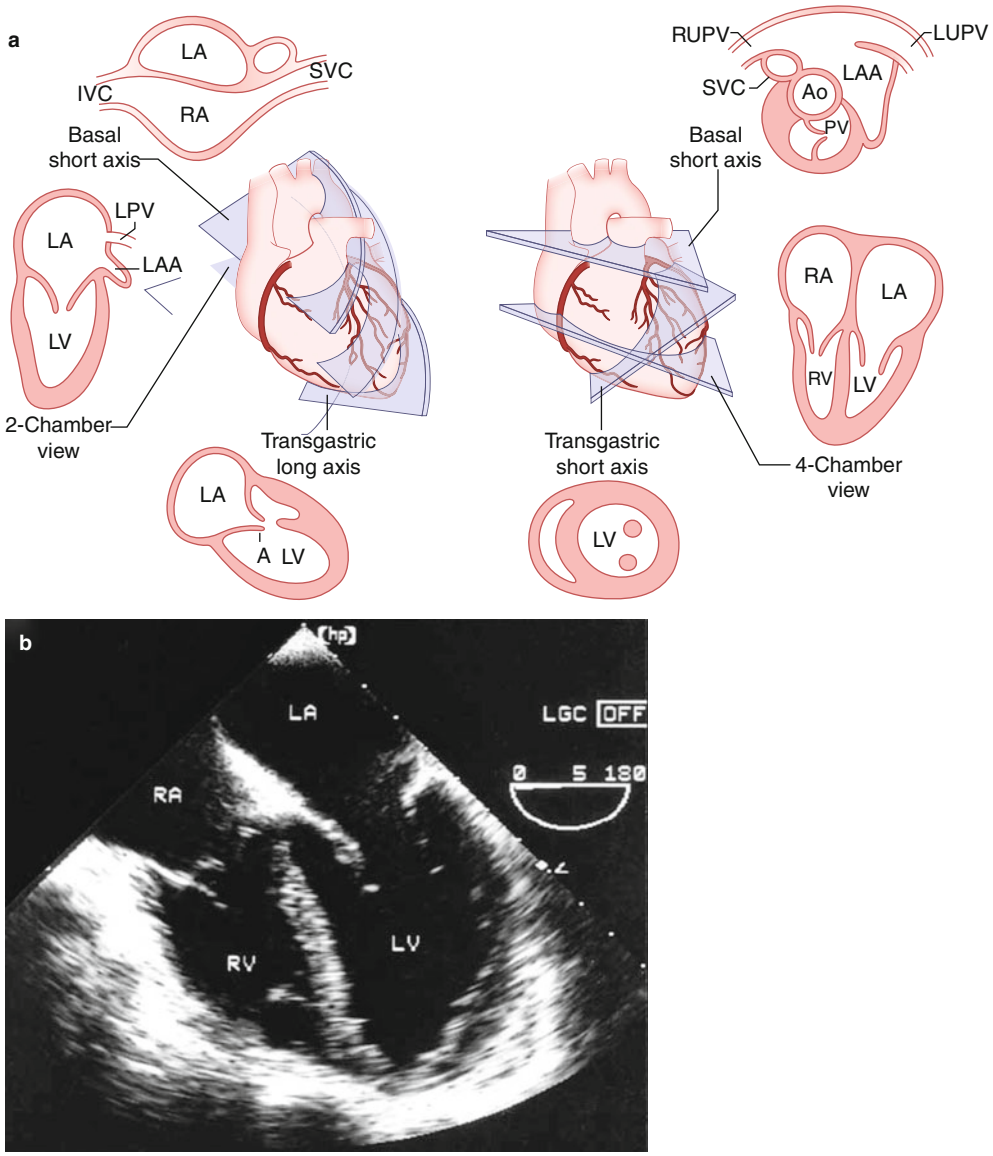


Fig. 8.7 (**a**) Standard TEE imaging planes in transverse and longitudinal axes (Adapted from Fisher et al. [11] with permission from Elsevier) (**b**) Transverse four-chamber TEE plane; *SVC*, *IVC* superior and inferior vena cava, *LAA* left atrial appendage, *RUPV*, *LUPV* right and left upper pulmonary vein, *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

(calcific) aortic stenosis (AS), the valve leaflets are markedly thickened and calcified, and their motion severely restricted (Fig. 8.10). In congenital AS, systolic "doming" of the leaflets is seen, often along with congenital anomalies of the valve leaflets (e.g., bicuspid, unicuspid). Attempts at valve area planimetry by transthoracic echocardiography have generally been unsuccessful, although planimetry with TEE has yielded better results. Thus, standard 2-D imaging accurately detects AS, but not its severity.

The cornerstone of quantification is the Doppler examination. CW Doppler can record the peak velocity of blood flow through the aortic valve, which then can be used to calculate the peak instantaneous systolic gradient with the modified Bernoulli equation. As mentioned above, the aortic valve orifice area is then calculated via the continuity equation described above. These calculations correlate quite well with catheterization-derived values and are valid as long as the LVOT flow velocity is less than 1.5 m/s [8, 9].

Aortic Insufficiency

Two-dimensional imaging may show a normal aortic valve in cases of aortic insufficiency (AI), but it can also demonstrate leaflet abnormalities, aortic root enlargement, LV dilation, and diastolic "flutter" of the anterior mitral valve leaflet. In acute severe AI, M-mode imaging can reveal early diastolic closure of the mitral valve (an uncommon but extremely important finding). Although 2-D imaging provides clues to the presence of AI, the Doppler examination is much more useful and easily detects the abnormal flow. Indeed, color-flow Doppler is a very rapid screening tool that detects AI with nearly 100 % sensitivity. Quantitation of AI, however, is considerably more difficult.

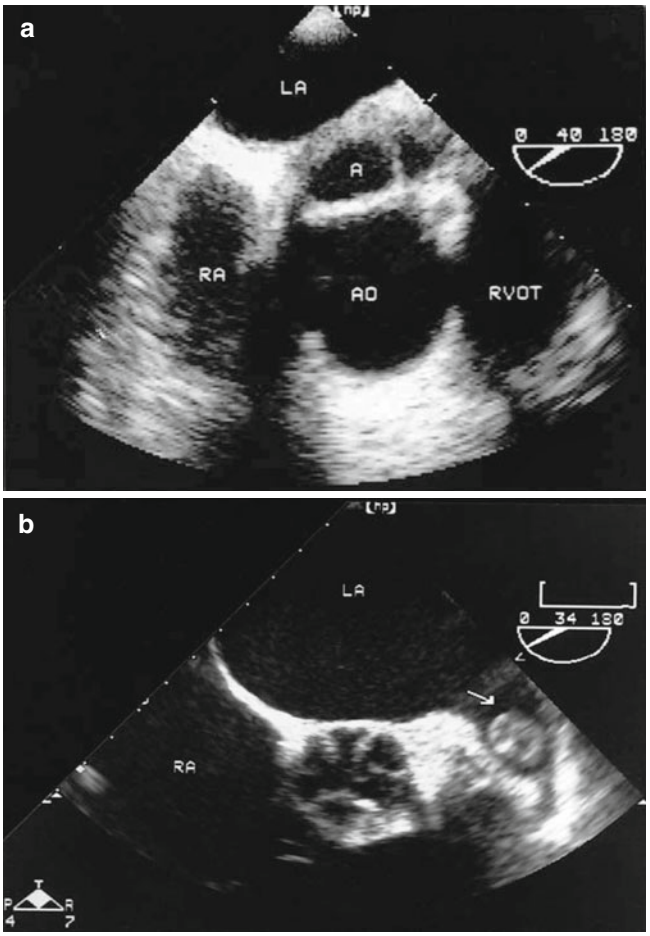


Fig. 8.8 (**a**) Short-axis TEE image through the cardiac base. A large septated abscess cavity (*A*) is present between the aortic root (*AO*) and the left atrium (*LA*). (**b**) TEE image of a thrombus in the left atrial appendage (*arrow*). *RVOT* right ventricular outflow tract (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

There are several approaches for semiquantitation of AI by echocardiography. The first utilizes color-flow imaging. In the parasternal views, severity can be estimated by the diameter (or cross-sectional area) of the color jet in the LVOT. Mild AI generally has a jet diameter smaller than 25 % of the outflow tract diameter, whereas a severe AI color jet often occupies more than 75 % of the outflow tract during diastole (Fig. 8.11a). Findings with moderate AI fall between these.

A second method uses CW Doppler to calculate the AI "pressure half-time" (see section "Mitral Stenosis"). This parameter is a function of the gradient between the aorta and left ventricle during diastole. In severe AI, this gradient decreases very quickly (producing a short pressure half-time), but with mild AI, it decreases much more slowly (producing a long pressure half-time).

In the third method, PW Doppler is utilized to detect diastolic reversal of flow in the descending aorta. Holodiastolic flow reversal suggests severe AI (Fig. 8.11b). Several other techniques for evaluating severity of AI (e.g., calculation of regurgitant flow volume and orifice area using flow convergence measurements) are beyond the scope of this chapter [1].

Although echocardiographic assessment of aortic stenosis is quantitative and generally accurate, assessment of AI is semiquantitative at best. Therefore, clinical examination and correlation are essential. Despite this, echocardiography is quite useful with aortic valve disease and can help to determine proper timing of valve surgery.

Mitral Valve

Mitral Stenosis

Detection of mitral stenosis (MS) was one of the earliest clinical applications of cardiac US. Rheumatic MS is characterized by tethering and fibrosis of the mitral leaflets, principally at the distal tips. The leaflets are sometimes calcified and usually are thickened and display characteristic "doming" during diastole (Fig. 8.12a, b). The posterior leaflet of the valve may be pulled anteriorly during diastole secondary to commissural fusion with the longer anterior leaflet. The left atrium is almost always enlarged. In the parasternal short-axis view, the commissural fusion is apparent and produces a "fishmouth" appearance of the orifice [16]. Doppler examination reveals abnormally high diastolic flow velocity through the mitral valve and often detects coexistent mitral regurgitation.

Echocardiographic quantitation of MS severity is done in two ways. First, the mitral orifice area can be measured directly via planimetry in the parasternal short-axis view. Gain artifacts must be avoided, and care must be taken to find the smallest orifice area at the distal end of the leaflets. Properly done, this technique is accurate and correlates well with catheterization data. The second commonly used technique is the "pressure half-time" method [17]. The pressure half-time is the interval required for transmitral flow velocity to decrease from its maximum to the velocity that represents half of the pressure equivalent. As the severity of MS increases, the rate of flow deceleration decreases (i.e., the pressure gradient between left atrium and LV remains high during diastole), prolonging the pressure half-time. The pressure half-time method also correlates well with planimetry measurements but is not accurate immediately after mitral valvuloplasty.

In addition to valve area quantitation, echocardiography is useful in predicting success of percutaneous mitral valvuloplasty. A score based on four variables (mitral valvular thickening, calcification, mobility, and subvalvular involvement) has been devised and tested. Each variable is rated on a scale of 1–4 (where 4 is most severe) and the individual

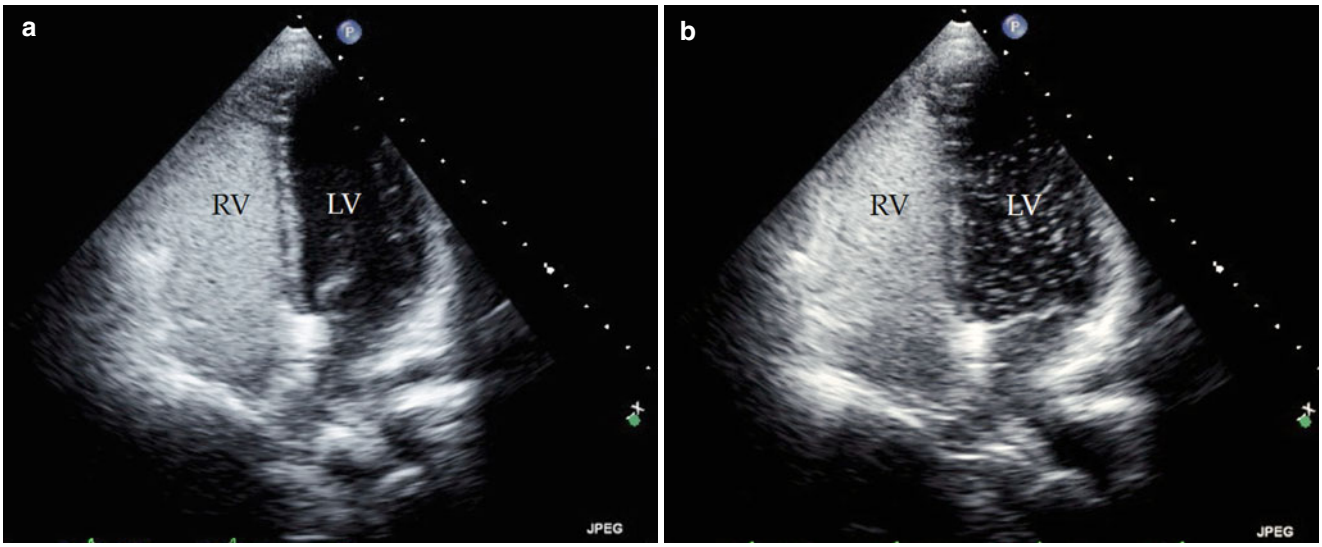


Fig. 8.9 (**a**) Microbubble injection with contrast filling right ventricle. (**b**) Microbubbles in the left ventricle 2 heartbeats later, demonstrating the presence of an interatrial shunt. *RV* right ventricle, *LV* left ventricle (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

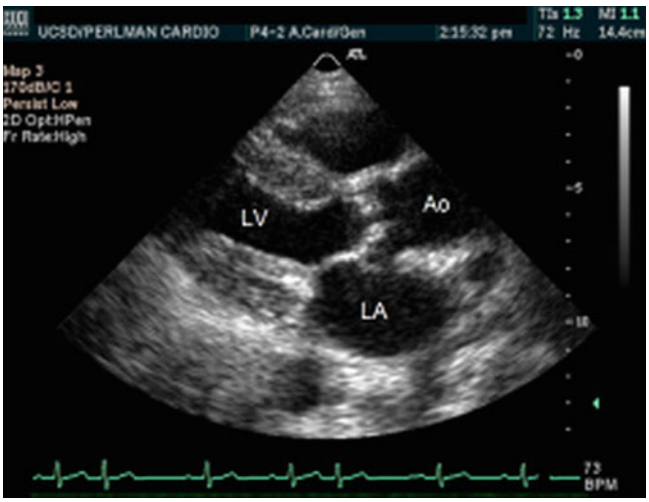


Fig. 8.10 Parasternal long-axis view demonstrates a thickened, stenotic aortic valve. *Ao* aorta, *LV* left ventricle, *LA* left atrium (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

components are summed. A score of 8–12 or greater predicts a poor response to valvuloplasty and an increased risk of complications.

Mitral Regurgitation

As it is for AI, echocardiography is extremely accurate for detecting mitral regurgitation (MR), but quantitation is more difficult. Two-dimensional imaging in MR may reveal thickened, abnormal mitral valve leaflets (e.g., in cases of rheumatic disease, myxomatous degeneration, mitral valve prolapse, or ruptured mitral chordae tendineae). With severe MR, the left atrium and ventricle are often enlarged. Doppler echocardiography is the primary method of semiquantitation of MR. Color-flow imaging shows a jet of aliased flow in the left atrium during systole, and the size of this color jet correlates roughly with angiographic MR severity [18]. Eccentrically directed MR, however, may produce a color jet of misleadingly small cross-sectional area on US imaging (Fig. 8.13), even when left ventriculography demonstrates severe MR.

Volumetric analysis with PW Doppler can be used to calculate regurgitant volumes and effective regurgitant orifice area, but its accuracy is limited. PW Doppler interrogation of the pulmonary veins (by TTE or TEE) is helpful in quantifying MR, as systolic flow reversal within the vein is quite specific for severe regurgitation. Recent work has shown that flow convergence is a useful marker in cases of valvular regurgitation [19]. With significant MR, there is often a large zone of high-velocity (aliased) color flow proximal to the mitral valve leaflets. This finding (even with a relatively small color jet in the left atrium) often indicates MR of at least moderate severity.

Mitral Valve Prolapse

Echocardiography is the diagnostic procedure of choice for mitral valve prolapse. This condition is defined by the bulging back of the mitral valve leaflets into the left atrium, with a portion of the leaflets passing the level of the mitral valve annulus on the parasternal long-axis view (Fig. 8.14).

Rupture of a chordae tendineae is well visualized by US. Imaging usually reveals the involved chord and leaflet as well as the severity of MR. TEE is especially beneficial for assessing the feasibility of mitral valve repair.

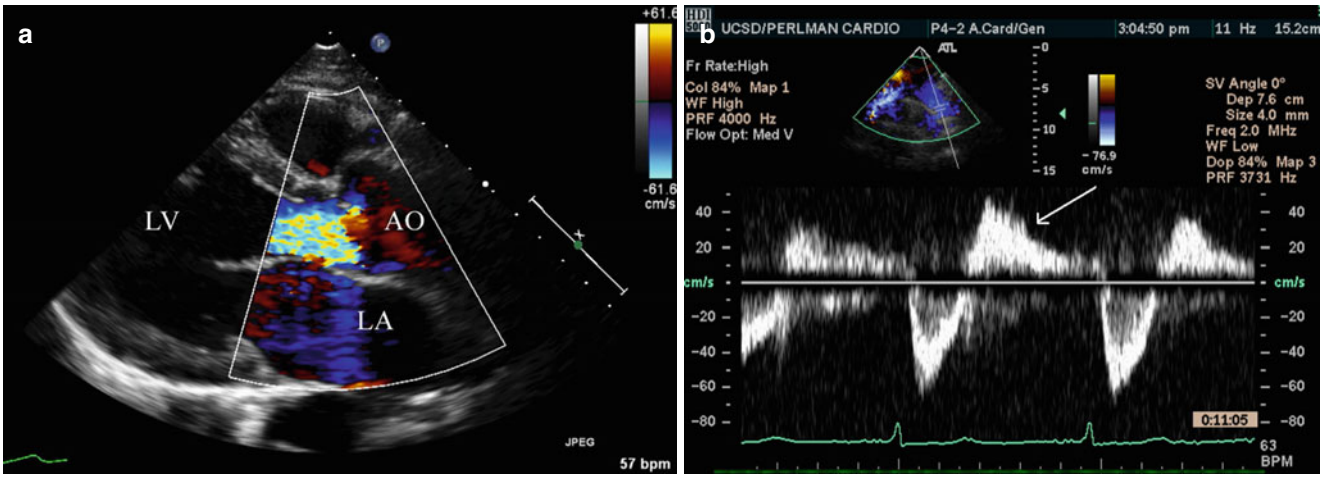


Fig. 8.11 (**a**) Parasternal long-axis image showing a multicolored jet (indicating turbulent flow) of aortic regurgitation in the left ventricular outflow tract. The jet fills the width of the outflow tract, suggesting severe regurgitation. (**b**) Pulsed-wave Doppler tracing (from the suprasternal transducer position) in a case of severe aortic regurgitation. The transducer beam is directed down the descending thoracic aorta, and holodiastolic flow reversal (*arrow*) is present. *AO* aorta, *LA* left atrium, *LV* left ventricle (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

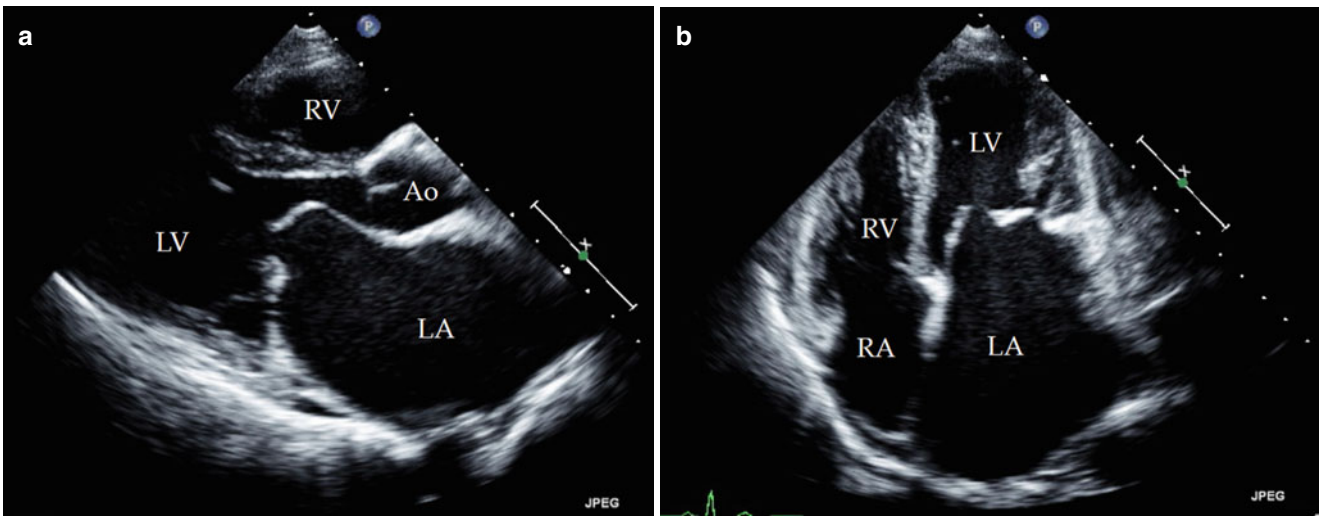


Fig. 8.12 (**a**) Parasternal long-axis view of mitral stenosis. The left atrium (*LA*) is enlarged, mitral opening is limited, and "doming" of the anterior mitral leaflet is present. (**b**) Apical four-chamber plane in mitral stenosis. *RA* right atrium, *RV* right ventricle, *LA* left atrium, *LV* left ventricle, *Ao* aorta (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

Prosthetic Cardiac Valves

Echocardiography can assess the anatomy and function of bioprosthetic and mechanical heart valves. In general, however, evaluation is considerably more limited than that of native valves. Because of acoustic shadowing, the areas distal to prosthetic (especially mechanical) valves are obscured, limiting detection of valvular regurgitation, thrombi, and vegetations. Because of this, TEE has become indispensable in the evaluation of prosthetic valve dysfunction and associated abnormalities.

Right-Sided Valvular Disease and Pulmonary Hypertension

Two-dimensional echocardiography can detect rheumatic involvement of the tricuspid and pulmonic valves and congenital pulmonic stenosis. Color-flow imaging detects and helps to semiquantify tricuspid and pulmonic regurgitation, similar to insufficiency of the mitral and aortic valves. Measurement of the peak tricuspid regurgitation velocity by CW Doppler is helpful for estimating peak systolic pulmonary artery and right ventricular pressures (via the modified Bernoulli equation) [5].

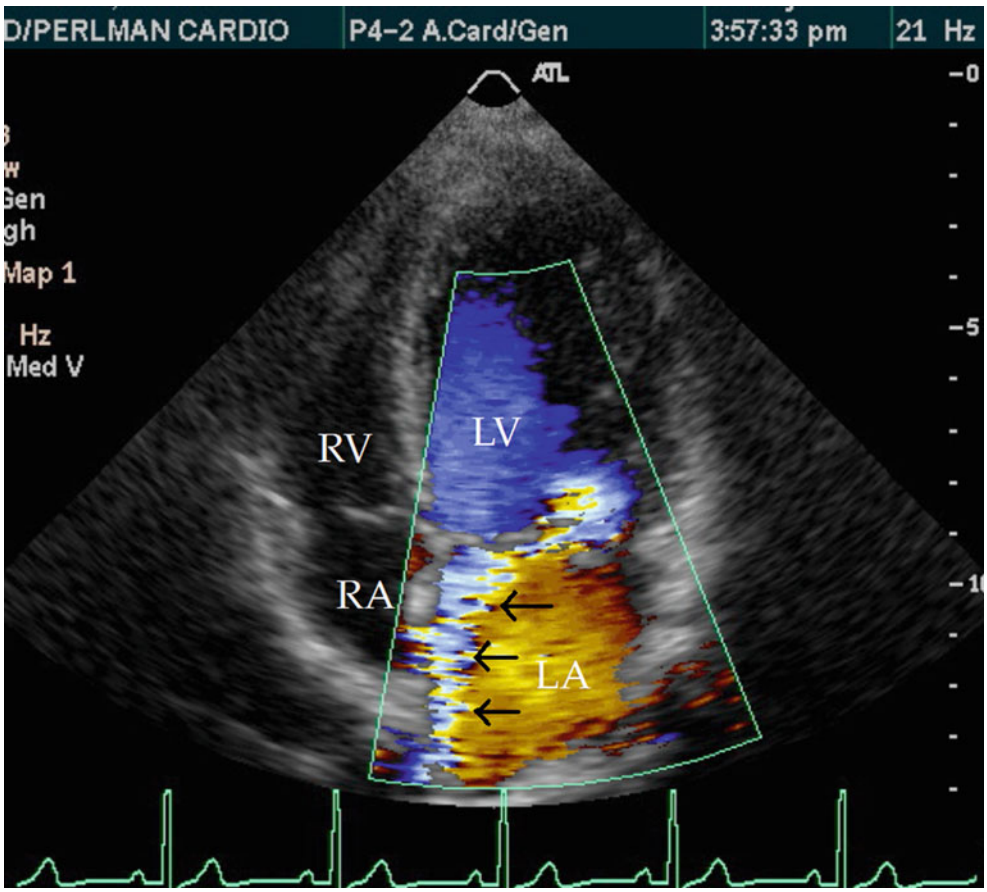


Fig. 8.13 Apical four-chamber view in a case of severe mitral regurgitation. The color Doppler jet is directed medially and is eccentric (*arrows*). The jet "hugs" the wall of the left atrium (*LA*). *LV* left ventricle, *RA* right atrium, *RV* right ventricle (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

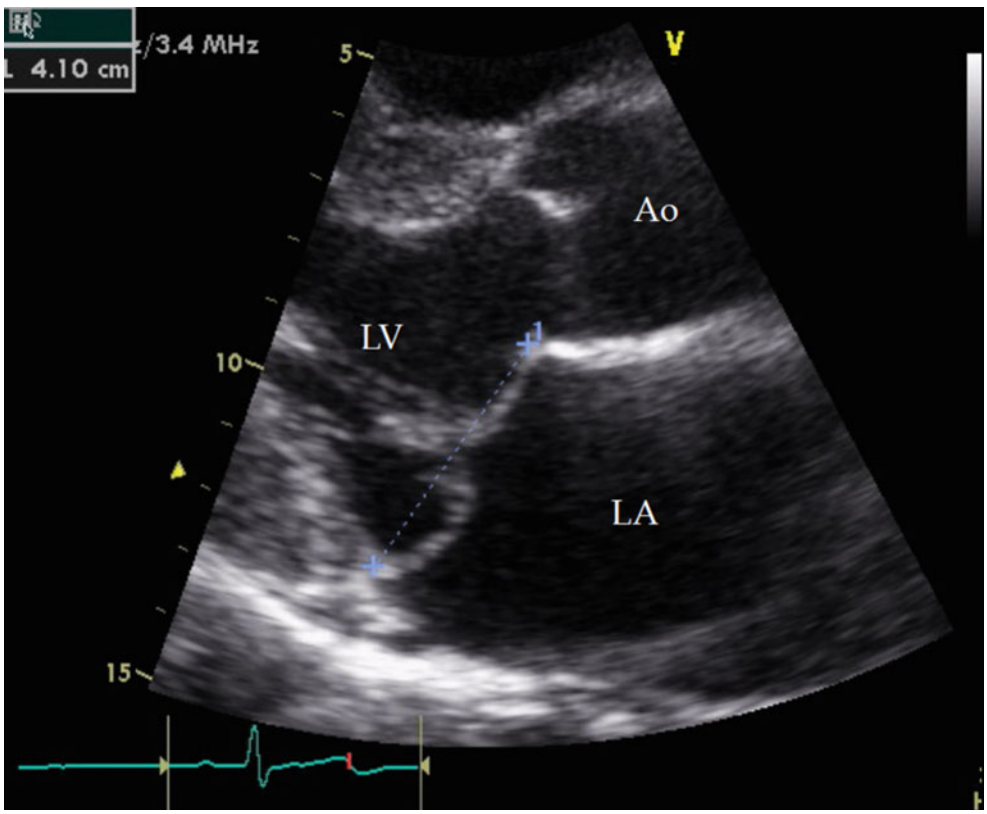


Fig. 8.14 Parasternal long-axis image through the mitral valve in late systole. The plane of the annulus (*A*) is drawn in a dotted line. The mitral leaflets prolapse past the level of the annulus. *LA* left atrium, *Ao* aorta, *LV* left ventricle (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

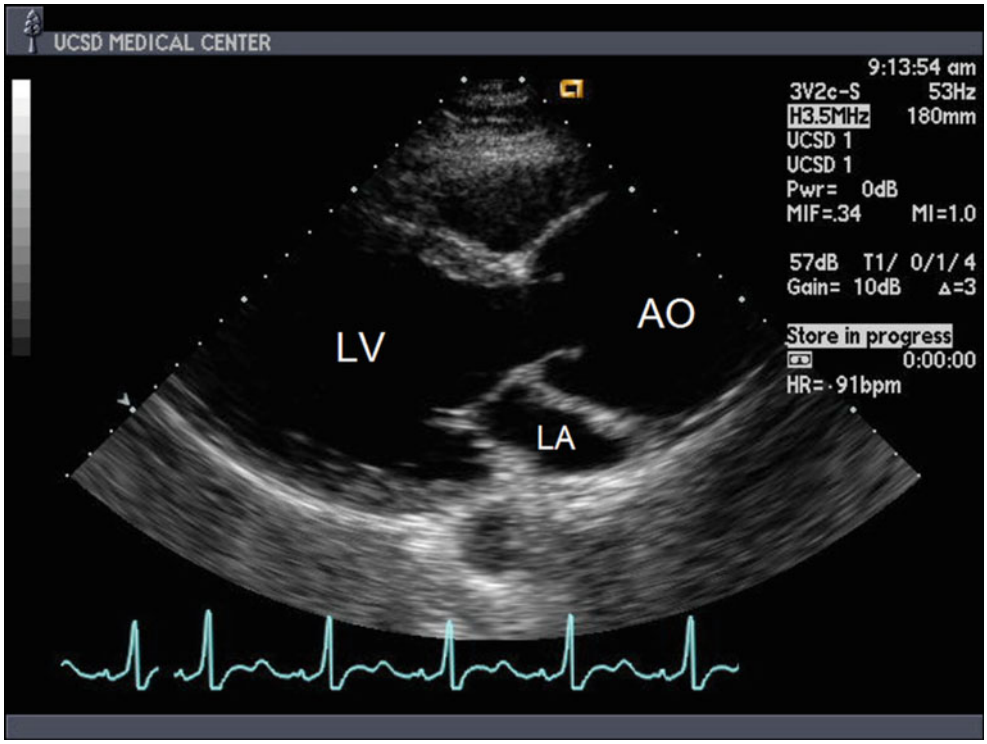


Fig. 8.15 Parasternal long-axis image demonstrates severe aortic root (*AO*) enlargement. *LA* left atrium, *LV* left ventricle (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

The 2-D findings associated with right ventricular overload and pulmonary hypertension include enlargement of the right ventricle and right atrium, dilation of the pulmonary artery and inferior vena cava, flattening of the interventricular septum (with loss of the normal curvature toward the right), and hypertrophy of the right ventricular free wall. Doppler examination often shows moderate to severe tricuspid regurgitation in these cases.

Diseases of the Aorta

Aortic Dissection

Echocardiography has fundamentally changed the diagnostic approach to suspected aortic dissection. TTE is a reasonably accurate screening tool for ascending aortic dissection (type A) but is not sensitive for detecting descending aortic dissection (type B) (see Chap. 36). Diagnostic findings include a dilated aorta with a thin, linear mobile signal in the lumen representing the dissected intimal flap. Color Doppler imaging may reveal normal or high-velocity flow in the true lumen and slow (stagnant) flow in the false channel. Occasionally, the entrance into the false channel is defined. Although TTE is sometimes helpful, TEE has become a diagnostic procedure of choice for aortic dissection [13]. Its sensitivity and specificity rival those of computed tomography, and TEE has the advantage of being portable and rapid. In addition, LV and valvular function can be defined during the examination. TEE can also help detect thrombosis of the false lumen, traumatic transection of the aorta, and intramural aortic hematoma (an increasingly recognized disorder with a prognosis similar to that of dissection) [20].

Aortic Aneurysm and Atherosclerosis

Aneurysms of the aorta may appear saccular or fusiform and, on echocardiography, are seen as focal or diffuse areas of aortic enlargement. TTE is useful for detecting ascending aortic dilation and can sometimes visualize descending thoracic and abdominal aortic aneurysms (Fig. 8.15). Sinus of Valsalva aneurysms (asymmetric dilations of the aortic root) are also well visualized, and the aortic insufficiency or shunts often associated with these aneurysms are well defined. Echocardiography has been used extensively to aid decision making on the timing of aortic valve and root replacement in patients with Marfan's syndrome [13].

TEE has played a major role in the detection of aortic atherosclerosis. This disease has been underappreciated in the past but appears to be a powerful risk factor for stroke and peripheral emboli. TEE is currently the procedure of choice for detecting aortic atheromas, which characteristically appear as asymmetric, calcified plaques that protrude into the aortic lumen [13].

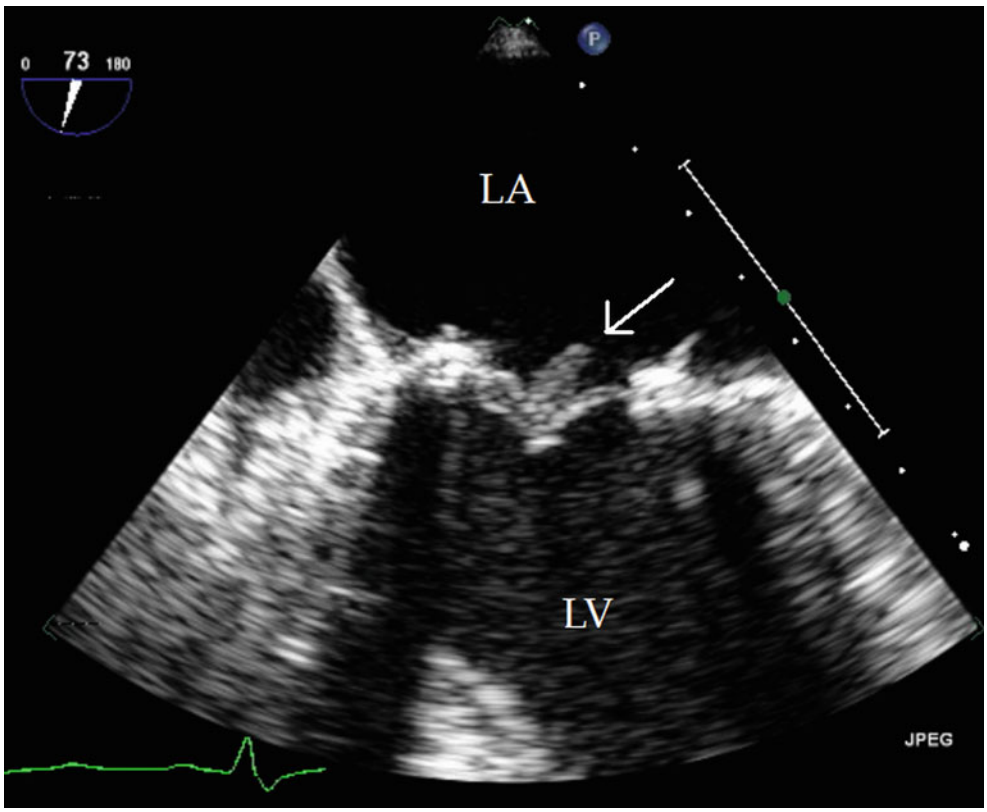


Fig. 8.16 Transesophageal echo image demonstrating a vegetation (*arrow*) on a mitral valve replacement. *LV* left ventricle, *LA* left atrium (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

Infective Endocarditis

Echocardiography is an integral part of the diagnosis and management of infective endocarditis. Clearly, the diagnosis remains a clinical one, but echocardiographic detection of vegetations is now included in most modern diagnostic algorithms and strategies. The hallmark of endocarditis is an infective valvular vegetation (Fig. 8.16), and TTE detects these with reasonable sensitivity (although as many as 20 % of patients with proven native valve endocarditis may have unremarkable TTE findings).

TEE is considerably more accurate than TTE for visualizing vegetations and is significantly better in detecting valvular abscesses (see Fig. 8.8a) and prosthetic valve endocarditis [21]. Echocardiography also helps visualize associated abnormalities such as valvular regurgitation, purulent pericarditis, and intracardiac fistulae. Accurate visualization of these abnormalities helps guide management and is useful in assessing the need for cardiac surgery. A common clinical dilemma concerns the appropriate use of TEE in persons with endocarditis. It seems reasonable to use TTE as the first screening test for most patients with suspected endocarditis. If the study is technically limited or findings are equivocal or diagnostic of vegetations in patients at high risk for perivalvular complications, TEE should be performed. If TTE findings are unremarkable or vegetations are detected in patients at low risk for complications, TEE is probably unnecessary. Patients at high risk (e.g., those with prosthetic cardiac valves, congenital heart disease, or infection with virulent organisms) should undergo TEE if endocarditis is strongly suspected, even if TTE results are unremarkable [21].

Despite all technologic advances, infective endocarditis remains a clinical diagnosis, and the utility of echocardiography should not be overestimated. Myxomatous valvular degeneration can masquerade as vegetations, and an old, healed vegetation can be mistaken for an active lesion. Therefore, echocardiographic results should be integrated with all available clinical data.

Ischemic Heart Disease

Echocardiography is an important technique for detecting and analyzing myocardial ischemia and infarction (MI). LV ischemia quickly produces dysfunction and hypokinesis of the involved ventricular segment. If coronary flow is not restored, permanent damage occurs with resulting akinesis and thinning of the affected myocardial segment. If the region of dysfunctional myocardium is identified, the infarct-related coronary artery often can be inferred [22]. Echocardiography detects these abnormalities, along with the LV dilation and depression of ejection fraction that accompany severe ischemic heart disease. The LV myocardium can be divided into 16 wall segments according to a

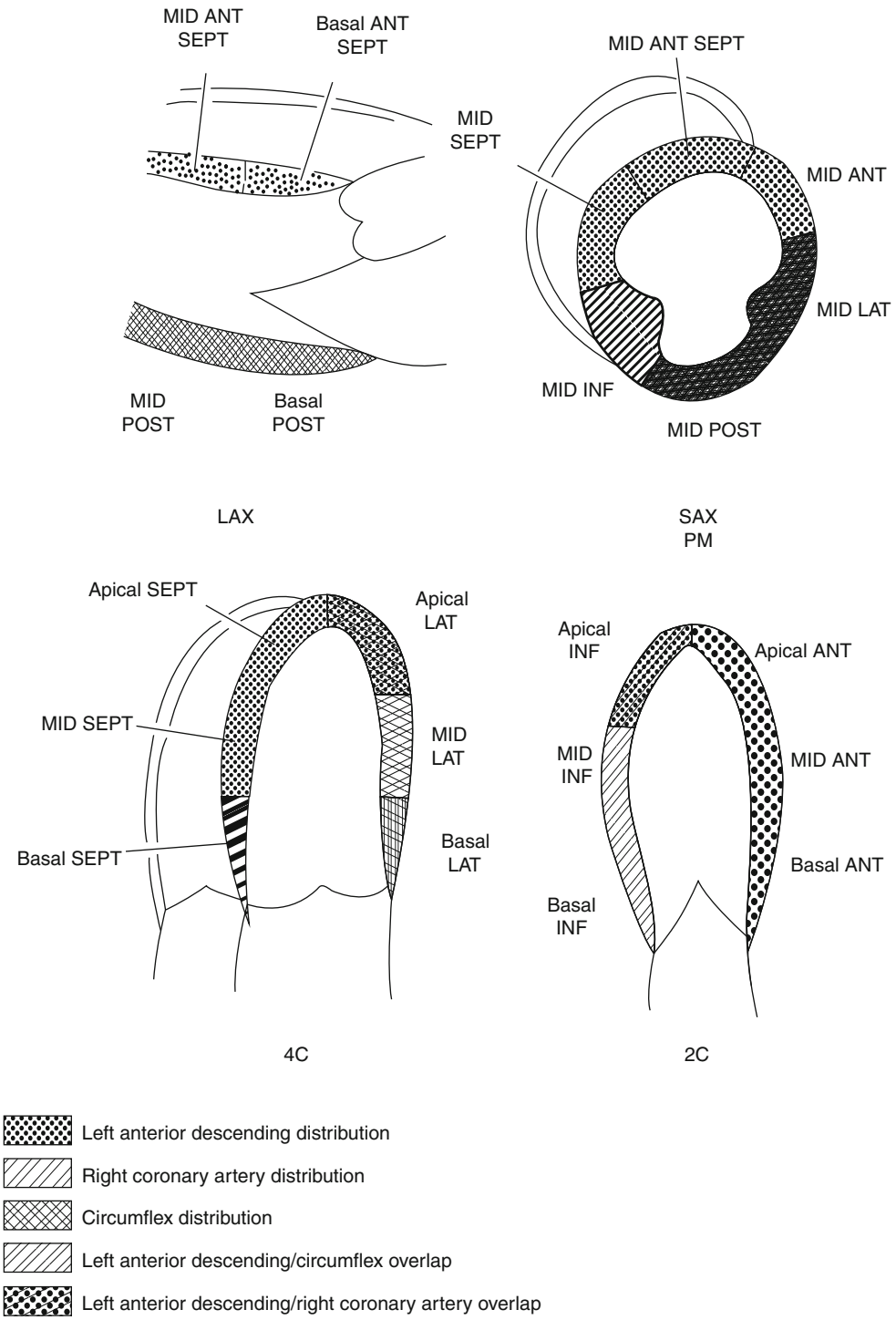


Fig. 8.17 Sixteen-segment format for identification of left ventricular wall segments. Coronary arterial territories are also included. *LAX* parasternal long axis, *SAX PM* short axis at papillary muscle level, *4C* apical four chamber, *2C* apical two chamber, *ANT* anterior, *SEPT* septal, *POST* posterior, *LAT* lateral, *INF* inferior (Reprinted from Segar et al. [22]. With permission from Elsevier)

format adopted by the American Society of Echocardiography (Fig. 8.17) [22]. By grading the contraction of each of these segments, a semiquantitative wall motion score can be calculated. This parameter has been used to assess prognosis for both acute MI and chronic ischemic heart disease.

Although echocardiography can help estimate the extent of damage in acute MI (Fig. 8.18), the technique is also valuable for detecting post-MI complications. Easily visualized findings include pericardial effusion (from pericarditis or LV free wall rupture), ventricular septal rupture, mitral regurgitation (from LV enlargement or papillary ischemia), LV pseudoaneurysm, and RV dysfunction associated with inferior wall MI. Long-term LV remodeling and aneurysm formation can also be assessed [23].

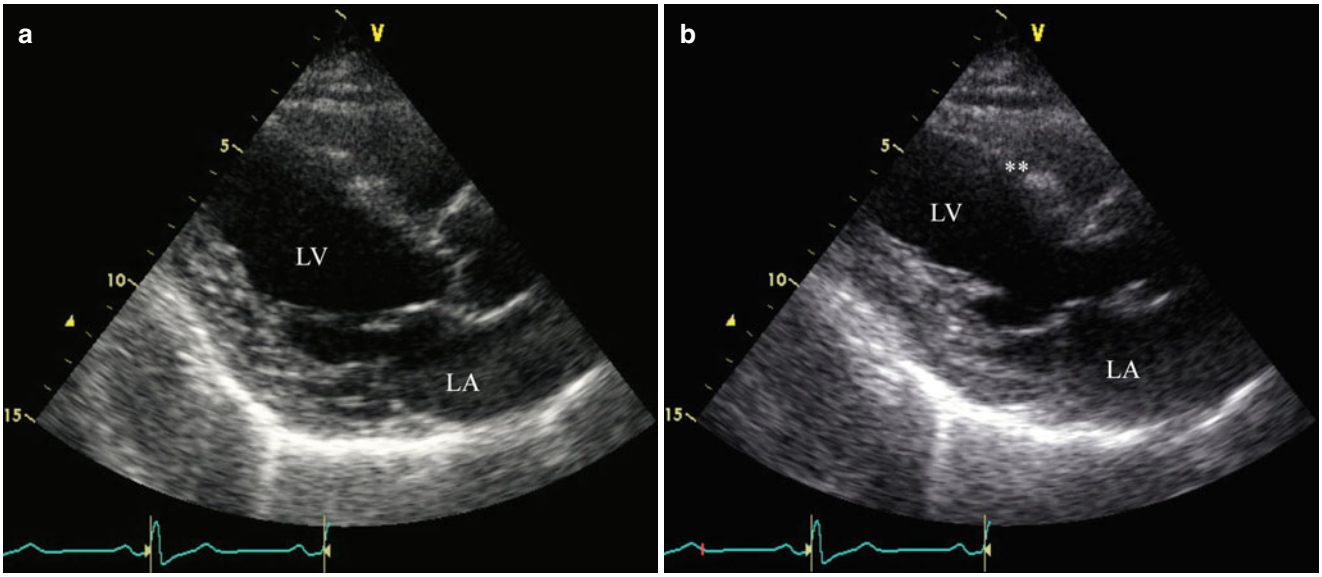


Fig. 8.18 (**a**) Parasternal long-axis view in a case of anteroapical myocardial infarction during diastole. (**b**) During systole, the anteroseptal wall (*asterisks*) of the left ventricle (*LV*) is dyskinetic and bulges outward instead of contracting. *LA* left atrium

Stress Echocardiography

Echocardiography can be combined with stress testing to increase the accuracy of ischemia detection [24]. In this technique, side-by-side cine loops of 2-D images made before and after (or during) stress are displayed on a computer monitor. Normally, the LV myocardium becomes hypercontractile with exercise, and end-diastolic LV cavity size decreases. Stress-induced segmental hypokinesis is abnormal, and the affected coronary artery can be predicted from which particular area(s) exhibit inducible ventricular dysfunction. Multiple wall segment abnormalities and LV dilation with stress are ominous findings that suggest severe stenoses in multiple coronary arteries and widespread ischemia [24].

Stress echocardiography can be performed with either exercise or a graded infusion of dobutamine. In general, both types of stress are safe and are tolerated well, and accuracy rates are comparable with those of nuclear stress imaging. Stress echocardiography tends to be slightly less sensitive than nuclear stress imaging but slightly more specific. Dobutamine echocardiography has assumed an important role in the detection of myocardial viability and the phenomenon of "hibernation" [25]. Technical innovations such as 3-D imaging and contrast echocardiography have increased the accuracy and applicability of stress echocardiography.

Cardiomyopathies

Cardiomyopathies are generally separated into three categories: dilated (DCM), hypertrophic (HCM), and restrictive (RCM). Echocardiography plays an important role in the clinical evaluation, providing information on cavity size, ventricular wall thickness, valvular lesions, and systolic function. In cases of classic HCM, echocardiography alone may be diagnostic. In cases of dilated, restrictive, and nonclassic HCM, however, additional clinical information may be needed to arrive at a firm diagnosis. These diseases are discussed in further detail in Chap. 33. In this section, we focus primarily on their US features.

Hypertrophic Cardiomyopathy

HCM is a primary abnormality of the myocardium that exhibits unprovoked hypertrophy and often affects the septum disproportionately. The first and fundamental echocardiographic abnormality is LV hypertrophy, which is often severe. Classically, the septum is involved more extensively than other areas (Fig. 8.19a), but the hypertrophy may also be concentric or apical. Asymmetric septal hypertrophy leads to the second classic US feature of HCM: dynamic LVOT obstruction. This is associated with systolic anterior motion (SAM) of the mitral valve (see arrow, Fig. 8.19a). Systolic encroachment of the abnormally thickened septum into the LVOT creates a pressure drop via the Venturi effect, which then draws the mitral leaflets toward the septum, causing dynamic obstruction. Like severe LVH, SAM is not pathognomonic for HCM and can occur in other conditions such as hypovolemia and hyperdynamic states [1].

The third manifestation of classic HCM is mid-systolic partial closure of the aortic valve. This occurs only in obstructive HCM cases and is probably a manifestation of the sudden late systole pressure drop caused by SAM. Therefore,

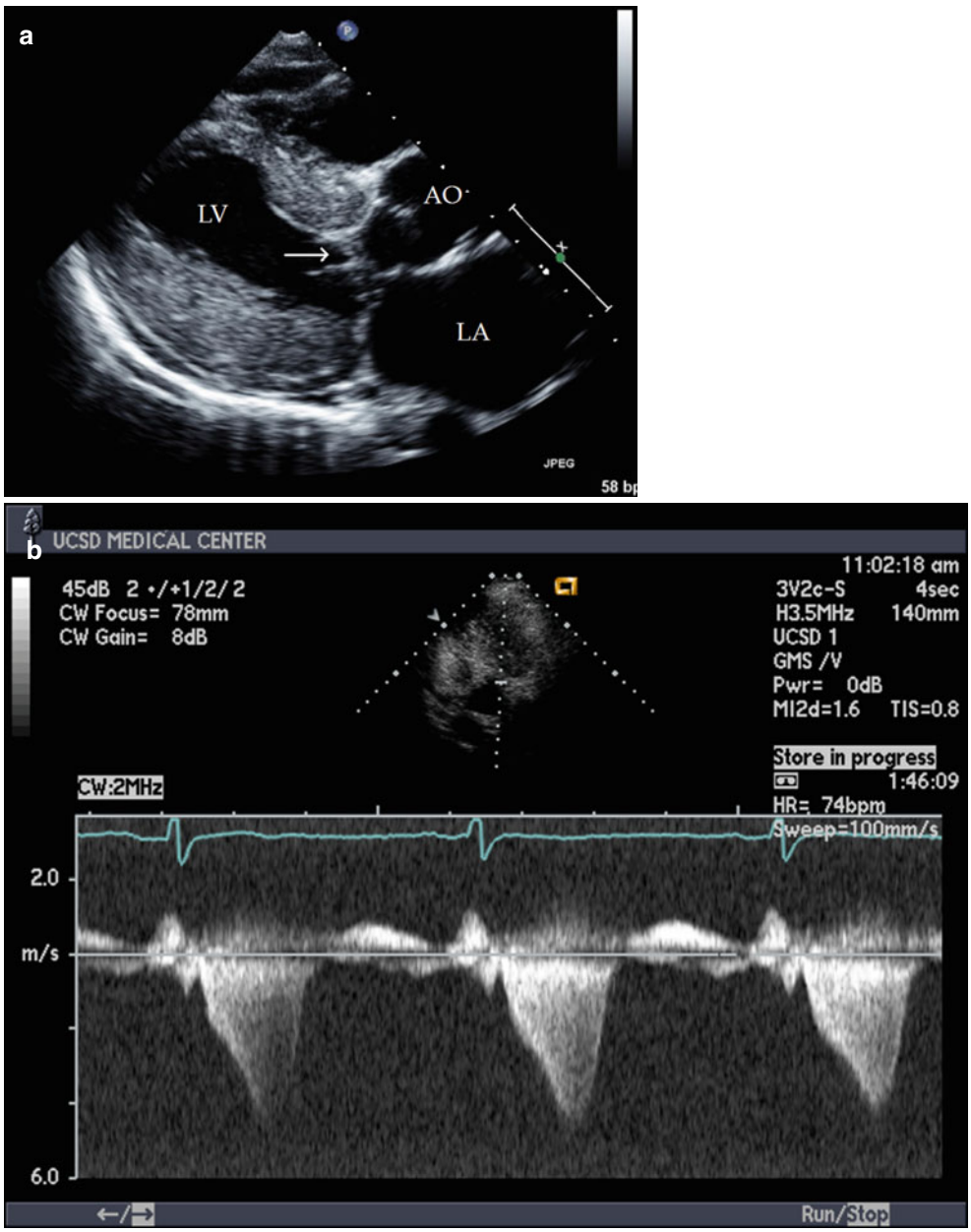


Fig. 8.19 (**a**) Parasternal long-axis view (during systole) of hypertrophic cardiomyopathy (HCM). Asymmetric septal hypertrophy is present, as well as systolic anterior motion of the anterior mitral leaflet (*arrow*). (**b**) Continuous-wave Doppler tracing through the left ventricular outflow tract (from the apical transducer position) in hypertrophic obstructive cardiomyopathy. In comparison to valvular aortic stenosis, the rise in systolic flow velocity is delayed (reflecting dynamic rather than fixed outflow obstruction). *LV* left ventricle, *LA* left atrium, *Ao* aorta (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

when this sign is present, significant LVOT obstruction is likely [26]. The fourth sign of HCM is seen on CW Doppler imaging through the LVOT. Normally, flow velocity in this area peaks early during systole and has a maximum of 1.7 m/s. In HCM with outflow tract obstruction, the peak systolic flow velocity is abnormally high. As opposed to valvular aortic stenosis, however, the CW spectral tracing of obstructive HCM peaks late in systole, creating a characteristic "sabertooth" or "dagger" pattern (Fig. 8.19b). Catheterization data would predict this type of tracing, as the outflow tract gradient is not severely elevated in early systole but rises in mid- and late systole because of dynamic obstruction. The peak CW velocity can be used to calculate the systolic gradient via the modified Bernoulli equation, although recent studies have suggested that this calculation may not be consistently accurate in HCM.

Dilated Cardiomyopathy

Echocardiographic findings in DCM include four-chamber cardiac dilation and marked LV enlargement. Systolic function is depressed, often severely. In addition, the LV walls are often thin, with concomitant left atrial enlargement, limited mitral and aortic valve opening (due to low stroke volume), and mitral annular dilation (with secondary mitral

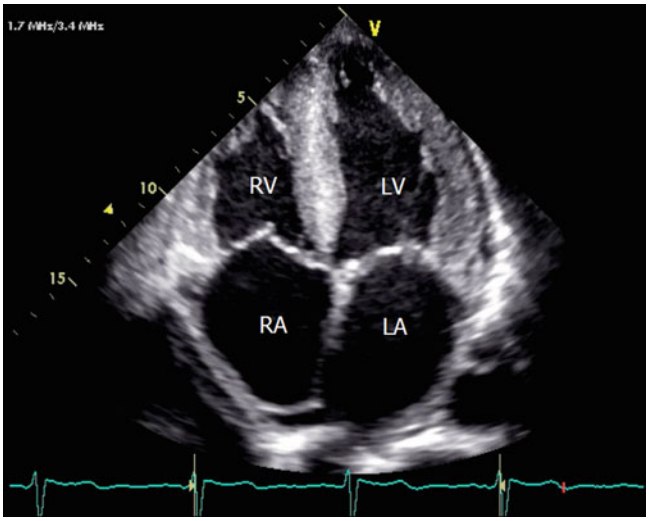


Fig. 8.20 Apical four-chamber view of cardiac amyloid. *RV* right ventricle, *RA* right atrium, *LA* left atrium, *LV* left ventricle (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

regurgitation) [27]. Unfortunately, these findings are not specific for DCM and can be caused by severe ischemic heart disease, viral myocarditis, cardiac toxins, and nutritional deficiencies. Ischemic heart disease can often be predicted by the presence of regional LV dysfunction, but, again, this finding is not always reliable. Diastolic dysfunction is common in DCM, and Doppler interrogation of mitral inflow may show an abnormal relaxation, restrictive, or "pseudonormal" pattern, depending on left atrial pressure and loading conditions. A restrictive pattern of inflow is associated with poor prognosis for DCM.

A separate form of cardiomyopathy with depressed LV systolic function has been described recently. This disorder, "tako-tsubo" cardiomyopathy, mimics the findings of a large myocardial infarction, but the coronary arteries are essentially normal. This sudden cause of LV dysfunction often comes on after a stressful event and is more common in women. LV systolic function generally normalizes within a few weeks.

Restrictive Cardiomyopathy

RCM is a fairly rare condition that is characterized on US by (1) a diffuse increase in LV wall thickness in the absence of severe cavity dilation and (2) marked biatrial enlargement [28]. Systolic function may be normal or modestly decreased. Doppler examination may show a mitral inflow relaxation abnormality early in the course of RCM, but this tends to evolve into a restrictive pattern as the disease progresses. RCM may be idiopathic or secondary to infiltrative diseases such as hemochromatosis and hypereosinophilic endocardial disease. The most common cause of RCM, however, is amyloidosis, which causes biventricular hypertrophy and diffuse thickening of the interatrial septum and cardiac valves (Fig. 8.20). A "ground glass" or speckled appearance of the myocardium has been described with amyloid, but this sign has minimal clinical usefulness. As with the other cardiomyopathies, the echocardiographic findings in RCM are often helpful but ultimately nonspecific.

Cardiac Masses

Echocardiography has become the procedure of choice for the detection of intracardiac thrombi, vegetations, and tumors. It also visualizes a number of "pseudo-masses" or benign anatomic variants (e.g., prominent eustachian valve, Chiari network, prominent right ventricular moderator band, and LV false chordae tendineae). US can also detect intracardiac foreign bodies, including pacemaker leads, intracardiac catheters, and endomyocardial bioptomes.

Intracardiac Thrombi

Thrombi can develop in any chamber of the heart and may cause embolic events [29]. The major predisposing factors for intracardiac thrombus formation include low cardiac output, localized stasis of flow, and myocardial injury. The echocardiographic appearance of thrombi is quite variable: thrombi can be freely mobile or attached to the endocardium, and they may be laminar and homogeneous in density or heterogeneous with areas of central liquefaction or calcification. Thrombi typically have identifiable borders on US and should be visible in multiple imaging planes [29].

Thrombi within the right heart are often laminar but can be quite mobile (especially venous thromboemboli that have migrated to the right side of the heart), and they increase the risk of pulmonary embolism. Left atrial thrombi occur most often in the setting of LV systolic dysfunction, mitral stenosis, atrial fibrillation, and severe left atrial enlargement. TEE is clearly superior to TTE for detecting these thrombi, especially those within the left atrial appendage (see Fig. 8.8b). Because approximately 75 % of left atrial thrombi are limited to the appendage, TEE is the procedure of choice for detecting them. Left atrial thrombi are often accompanied by spontaneous US contrast (or "smoke") in the left atrium, which indicates stagnant flow and increased likelihood of embolic events.

LV thrombi usually occur in settings of systolic dysfunction [29], including DCM, acute MI, and chronic LV aneurysm. Most LV thrombi are located in the apex and thus are best visualized in the apical views (Fig. 8.21a).

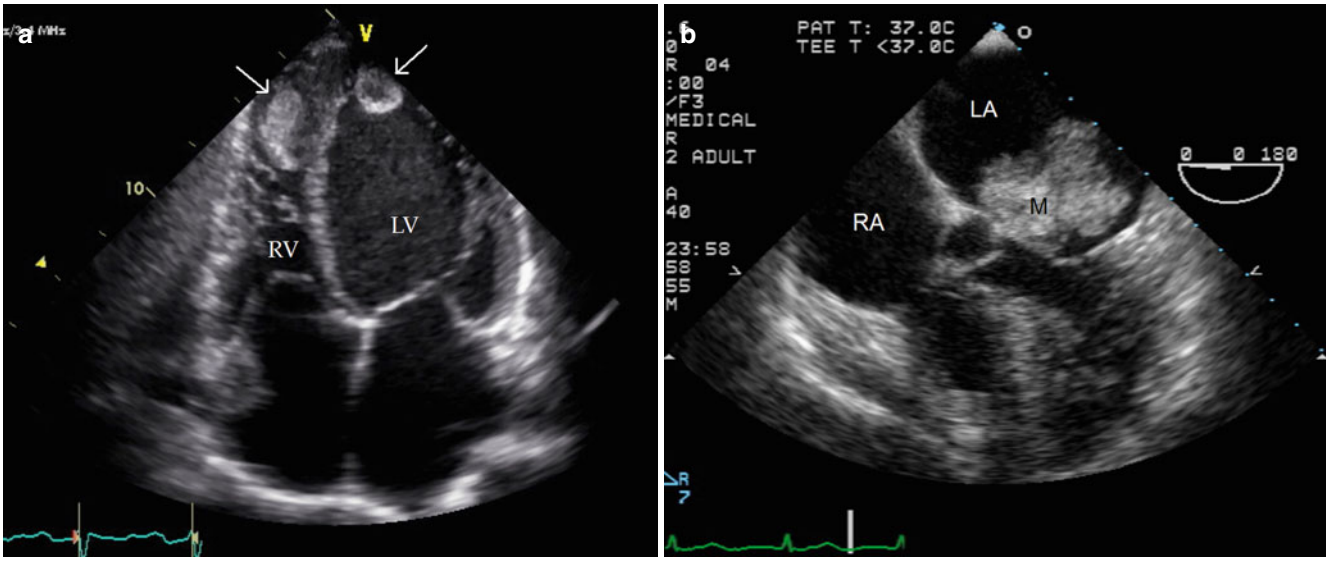


Fig. 8.21 (**a**) Apical four-chamber view demonstrating thrombi (*arrows*) in the apexes of the right ventricle (*RV*) and left ventricle (*LV*). (**b**) Transesophageal echo image of a large left atrial myxoma (*M*). *RA* right atrium, *LA* left atrium (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

LV thrombi may be laminar and fixed, protruding or mobile, and homogeneous or heterogeneous in US density. Artifacts can sometime mimic apical thrombi. A true LV thrombus has a density that is distinct from that of the myocardium, moves concordantly with the underlying tissue, and is visible in multiple imaging planes. Finally, an LV thrombus rarely occurs in areas of normally functioning myocardium.

Cardiac Tumors

Cardiac tumors can be benign or malignant; malignancies may be primary, metastatic, or the result of direct extension from adjacent tumors. Although primary cardiac malignancies are exceedingly rare, metastatic spread to the heart from lung cancer, breast cancer, lymphoma, or melanoma is fairly common, especially in the later stages of disease. Such tumors may be seen within the cardiac chambers, but pericardial or epicardial involvement is more common.

Myxomas are by far the most common primary cardiac tumors, and about 75 % are found in the left atrium [30]. On 2-D imaging, these tumors generally appear gelatinous, speckled, and sometimes globular (Fig. 8.21b). Tissue heterogeneity is frequently seen, but calcifications are rare. Although they can originate from any portion of the atrial wall, myxomas are usually attached by a pedicle to the interatrial septum. Large myxomas are almost always mobile and may move back and forth into the mitral annulus. Doppler examination may demonstrate valvular regurgitation, obstruction, or both. TTE accurately detects most large myxomas, but TEE is superior for delineating small tumors [30]. Less common benign primary cardiac tumors include rhabdomyomas (associated with tuberous sclerosis), fibromas (which tend to grow within the LV myocardial wall), and papillary fibroelastomas (which grow on valves and tend to embolize systemically).

Congenital Heart Disease

In this section, we focus primarily on the echocardiographic recognition of the more common congenital lesions seen in adults.

Atrial Septal Defect

Most ostium secundum and ostium primum atrial septal defects (ASD) are easily seen with TTE [31]. Sinus venosus defects, however, can be difficult to detect without TEE. As the normal interatrial septum is thin and parallel to the US beam from the apical position, artifactual "dropout" in the area of the fossa ovalis can be mistaken for ASD. Therefore, subcostal imaging is usually superior. Ostium secundum defects (the most common form of ASD) are distinguished by localized absence of tissue in the middle portion of the interatrial septum (Fig. 8.22a). The absence of any septal tissue interposed between the

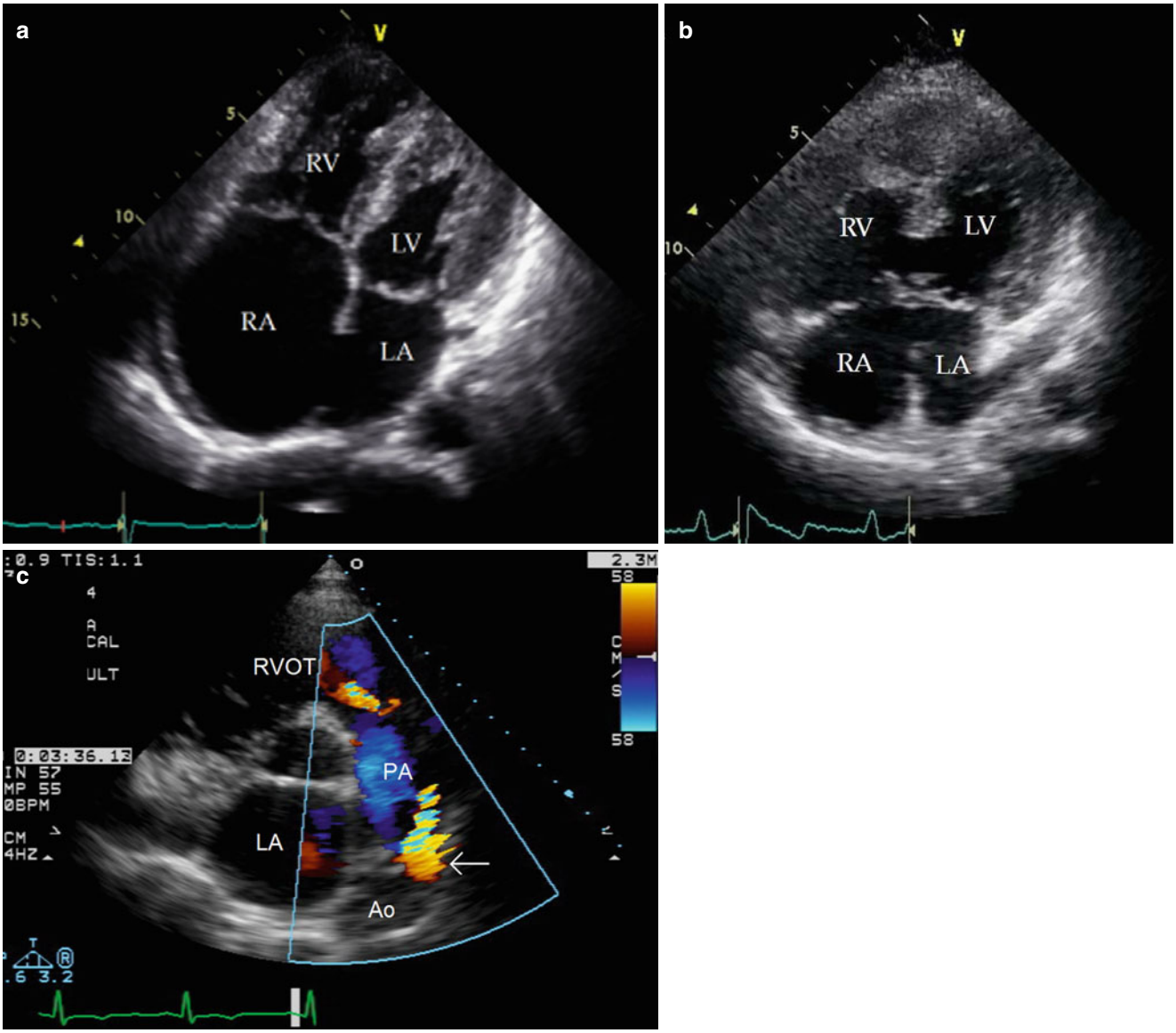


Fig. 8.22 (**a**) Apical four-chamber view of an ostium secundum atrial septal defect. The right heart is larger than the left, suggesting a significant shunt volume. *RA* right atrium, *RV* right ventricle, *LA* left atrium, *LV* left ventricle. (**b**) Apical four-chamber image of a complete atrioventricular canal defect. Both an inlet ventricular septal defect and an ostium primum atrial septal defect are present. *RV* right ventricle, *RA* right atrium, *LA* left atrium, *LV* left ventricle. (**c**) Parasternal short-axis view of a patent ductus arteriosus (*arrow*). *RVOT* right ventricular outflow tract, *Ao* descending aorta, *PA* pulmonary artery, *LA* left atrium (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

defect and the base of the interventricular septum together with the loss of normal apical displacement of the tricuspid annulus suggests an ostium primum defect. Cleft anterior mitral valve leaflet, mitral regurgitation, and inlet ventricular septal defect often occur with ostium primum ASDs. Sinus venosus ASDs are seen in the superior and posterior portions of the interatrial septum and are usually associated with anomalous drainage of one or more pulmonary veins into the right atrium [1].

Additional 2-D findings seen in ASD include right atrial and RV enlargement, flattening of the interventricular septum, and paradoxical septal motion. Doppler interrogation often demonstrates blood flow though the defect, but atrial inflow from the vena cava and pulmonary veins sometimes mimics ASD. To prevent misdiagnosis of ASD, intravenous injection of agitated saline is recommended (see section "Contrast Echocardiography"). Finally, Doppler and 2-D imaging can be used to estimate roughly the

pulmonary-to-systemic blood flow ratio in patients with ASD or other intracardiac shunts.

Ventricular Septal Defect

The majority of VSDs in adults are perimembranous. Inlet (AV canal), trabecular, and outlet (supracristal) defects are much rarer. Although large VSDs are often visible on 2-D imaging alone (Fig. 8.22b), color-flow imaging is essential for detection of small defects [32]. CW Doppler measurement of peak systolic flow velocity through a VSD can be used to estimate the pressure gradient between the two ventricles via the modified Bernoulli equation (the estimated RV systolic pressure is the systolic arterial pressure minus the calculated Bernoulli gradient) [5]. Associated 2-D and Doppler findings include cardiac enlargement (possibly with RV pressure overload), mitral and tricuspid valvular abnormalities and regurgitation, coexistent ASD (most often with inlet VSD), ventricular septal aneurysms, and aortic insufficiency (especially with supracristal VSD). During intravenous injection of agitated saline, "negative" contrast jets are sometimes seen at the right ventricular aspect of the VSD.

Patent Ductus Arteriosus

Patent ductus arteriosus (PDA) is a connection between the distal portion of the aortic arch and the pulmonary artery (usually just to the left of its bifurcation). Two-dimensional imaging occasionally detects a PDA, but color Doppler interrogation is considerably more likely to demonstrate the characteristic high-velocity diastolic flow in the proximal pulmonary artery (Fig. 8.22c) [33]. Additional 2-D findings include LV enlargement and volume overload. If Eisenmenger physiology supervenes, the right side of the heart enlarges and LV dilation may reverse to some degree. Therefore, absence of LV or RV enlargement suggests a small shunt.

Conotruncal and Aortic Abnormalities

The most common congenital cardiac anomaly in adults is a bicuspid aortic valve (prevalence of 1–2 % in men and somewhat less in women). This anomaly is often associated with aortic insufficiency or stenosis, as well as coarctation of the aorta. Tetralogy of Fallot is one of the more frequent conotruncal abnormalities. The classic echo features include a large perimembranous VSD, pulmonic stenosis, RV enlargement and hypertrophy, and anterior displacement of the aortic valve. Coarctation of the aorta, which is often associated with a bicuspid aortic valve, is best visualized from the supersternal position. Two-dimensional imaging sometimes detects the coarctation, but acoustic shadowing and dropout may limit evaluation of the descending aorta. Doppler examination is more reliable and shows abnormally high flow velocity in the descending aorta. A classic finding in coarctation is holodiastolic antegrade flow in the descending aorta, indicating a pressure gradient throughout diastole and, therefore, severe coarctation. Another congenital abnormality seen occasionally in adult patients is Ebstein's anomaly. Two-dimensional imaging in classic cases reveals a deformed tricuspid valve, including an elongated anterior leaflet and an apically displaced septal leaflet. Associated findings include enlargement of the right side of the heart and tricuspid regurgitation. ASDs are present in a significant minority of cases.

Pericardial Disease

Echocardiography is an accurate, reliable tool for the detection of pericardial effusion, intrapericardial masses, and cardiac tamponade. Pericardial fluid is identified as a "dark" or echo-free space immediately adjacent to the epicardium (Fig. 8.23a). Pericardial effusions may be concentric or loculated and may vary in size. Large, nonloculated effusions generally contain at least 400 mL of fluid and often allow free motion of the heart within the pericardial space. Multiple fibrinous strands in the pericardial effusion raise the possibility of infection, hemorrhage, or malignancy.

There are several echocardiographic clues to the presence of tamponade. Collapse of the right atrial wall (especially with associated tachycardia) is a sensitive, although not specific, sign of increased pericardial pressure. A more specific sign of tamponade is RV free wall diastolic collapse or compression, which indicates marked elevation of intrapericardial pressure. Finally, PW Doppler interrogation of mitral inflow in cardiac tamponade demonstrates an abnormal respiratory variation of peak velocity [34]. A respiratory variation in peak E velocity greater than 25 % suggests cardiac tamponade when an effusion is present (and pericardial constriction when an effusion is absent or minimal) (Fig. 8.23b). This Doppler finding is useful for differentiating constrictive pericarditis from restrictive cardiomyopathy, as exaggerated respiratory variation of mitral inflow velocity is not seen in the latter [35].

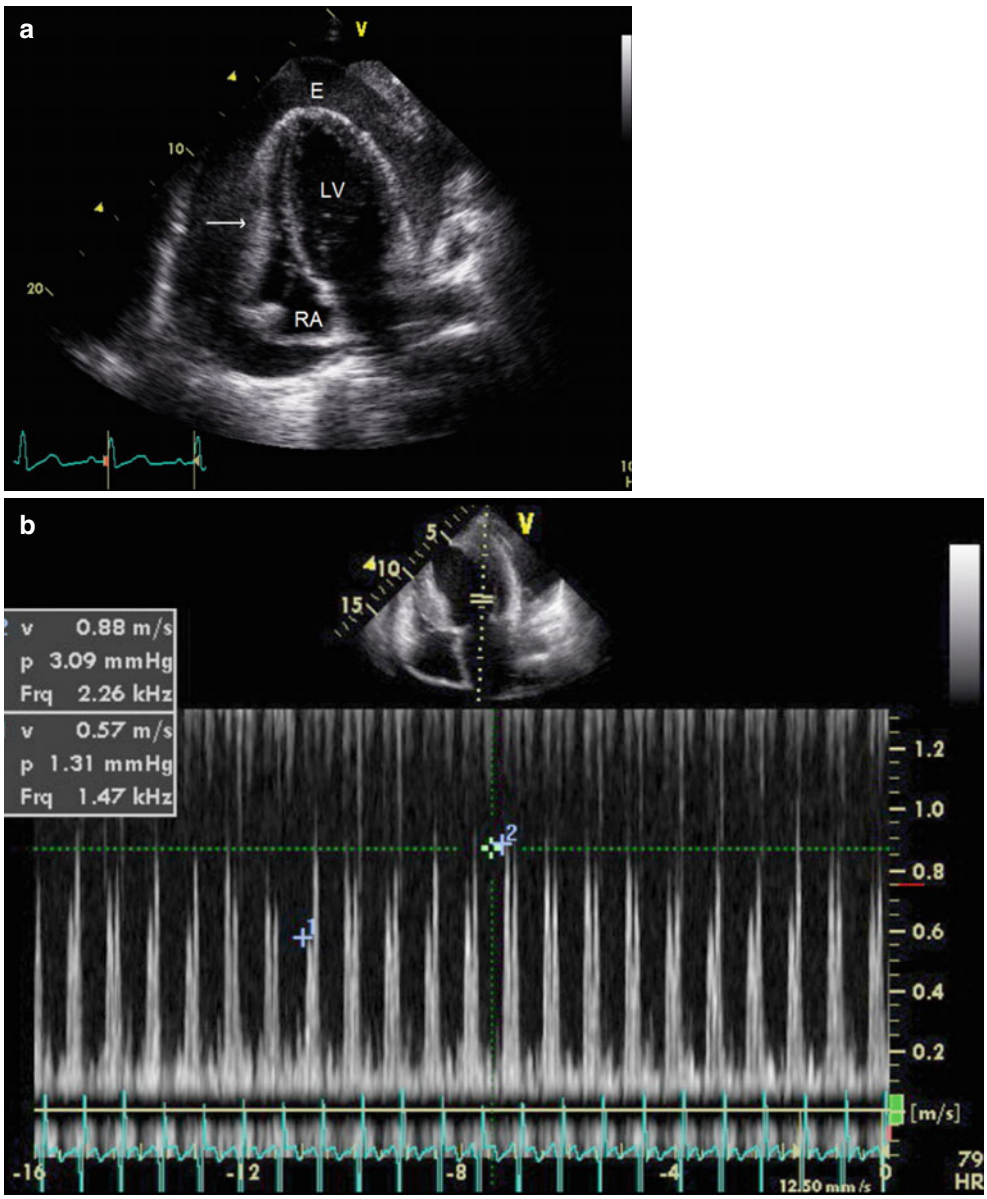


Fig. 8.23 (**a**) Apical four-chamber image of a large pericardial effusion (*E*). The right ventricle is compressed (*arrow*). *LV* left ventricle, *RA* right atrium. (**b**) Pulsed-wave Doppler tracing from the apical position demonstrating abnormal respiration variation of mitral inflow velocity, consistent with cardiac tamponade (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

Evolving Areas of Echocardiography

Three-dimensional (3-D) echocardiography has been available for over a decade, but imaging resolution has significantly improved in the last few years. 3-D imaging may improve assessment of global LV systolic function and can shorten scanning time in stress echocardiography. Currently, its main use is in transesophageal echocardiography, where 3-D imaging significantly enhances visualization of cardiac valves and prosthetic devices (Fig. 8.24) [36]. Strain and strain rate imaging (particularly with "speckle-tracking" software) is a relatively new technology that may improve assessment of regional myocardial performance and may also be useful in predicting response to biventricular pacing [37].

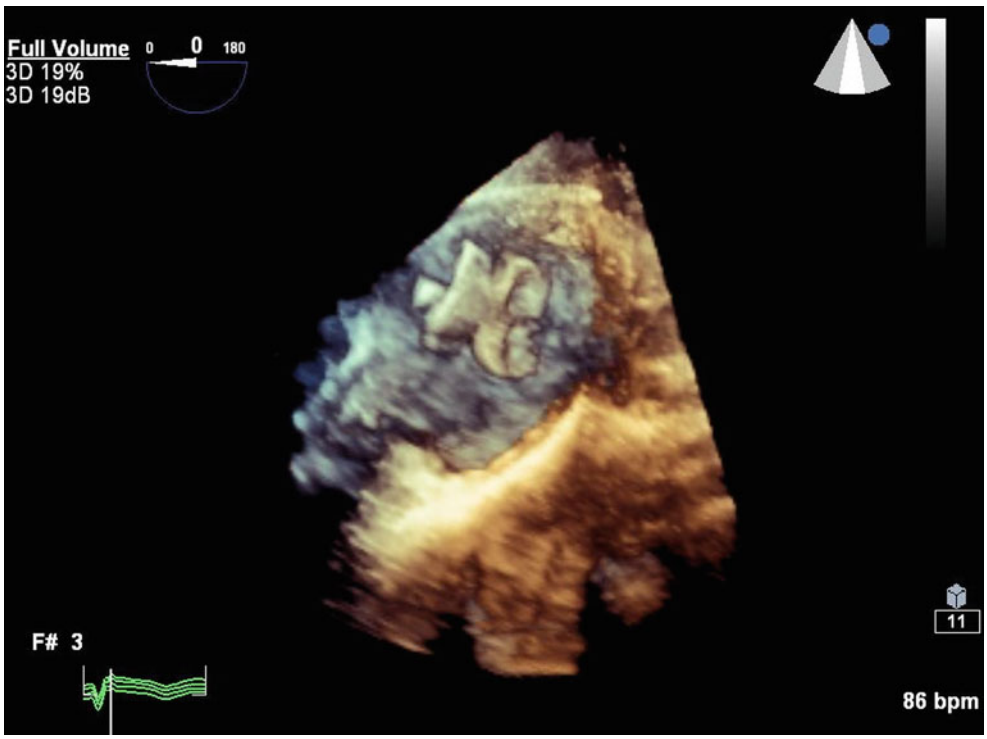


Fig. 8.24 3-D transesophageal image of a PFO occluder in the interatrial septum (Reprinted from DeMaria and Blanchard [1]. With permission from McGraw-Hill)

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Exercise Testing

9

Abhimanyu (Manu) Uberoi, Shirin Zarafshar, and Victor Froelicher

Introduction

Exercise can be considered the true test of the heart because it is the most common everyday stress that humans undertake. Therefore, some consider the exercise test the most practical and useful procedure in the clinical evaluation of cardiovascular status.

Despite the many recent advances in technology related to the diagnosis and treatment of cardiovascular disease, the exercise test remains an important test modality. Its many applications, widespread availability, and high yield of clinically useful information continue to make it an important gatekeeper for more expensive and invasive procedures. Previously, the numerous approaches to the exercise test may have been a drawback to its proper application; however, with the development of excellent guidelines based on a multitude of research studies over the last 20 years, there is greater uniformity in methods and consensus for the efficacy of this examination.

Indications

The common clinical applications of exercise testing to be discussed in this chapter are diagnosis and prognosis. The other applications listed in Table 9.1 are discussed below [1]. The ACC/AHA guidelines will be followed in regard to diagnosis and prognosis [2].

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Advantages and Disadvantages of Exercise Testing

Surprisingly, the standard exercise test has characteristics similar to newer, more expensive tests. Table 9.2 lists its advantages and disadvantages.

Methods

Safety Precautions and Risks

The safety precautions outlined by the AHA are very explicit in regard to the requirements for exercise testing. All items required for cardiopulmonary resuscitation must be available

Table 9.1 Further applications of the exercise test

Determination of exercise capacity after an MI
Preoperative evaluation
Screening for CAD risk
Cardiac rehabilitation
Exercise prescription
Arrhythmia evaluation
Treatment evaluation
Intermittent claudication evaluation

Table 9.2 Advantages and disadvantages of the standard exercise test

Advantages	Disadvantages
Low cost	Limited sensitivity and specificity
Convenient and highly available	Cannot localize ischemia or coronary lesions
Exercise capacity determined	Cannot estimate LV systolic function
Short duration of test (<1 h)	Not suitable for certain patient groups
Patient willingness to participate due to noninvasiveness	Requires patient cooperation, may be effort dependent
Ready availability of trained personnel	Requires strenuous effort by the patient

C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_9,

Table 9.3 Absolute and relative contraindications to exercise testing

Absolute	Relative[a]
Untreated unstable angina	Left main stenosis (or equivalent disease)
Symptomatic or uncontrolled arrhythmia	Hypertrophic cardiomyopathy (or other outflow obstruction)
Recent MI (within 48 h)	High degree AV block
Symptomatic heart failure	Moderate stenotic valvular disease
Symptomatic aortic stenosis	Severe arterial hypertension
Acute myocarditis or pericarditis	Tachy- or brady-arrhythmias
Acute pulmonary embolus or infarction	Impairment preventing adequate exercise

[a]Relative contraindications can be discarded if benefits outweigh risks of exercise

in the performing facility, and regular drills must be performed to ensure that both personnel and equipment are prepared and satisfactory for a cardiac emergency. The classic survey of clinical exercise facilities by Rochmis and Blackburn [3] showed exercise testing to be a safe procedure, with approximately one death and five nonfatal complications per 10,000 tests. Gibbons et al [4]. reviewed 71,914 tests conducted over 16 years and reported a complication rate of only 0.8 per 10,000 tests. Despite this excellent safety record, however, there is still a real risk in exercise testing in patients with coronary artery disease than cannot be disregarded. Cobb and Weaver [5], for example, estimated that the risk of arrhythmic events may be up to 100 times higher in the recovery period.

Most adverse events can be prevented by having an experienced physician, nurse, or exercise physiologist in close proximity to the patient, measuring blood pressure and assessing patient appearance during the test. If the patient's appearance is worrisome, systolic blood pressure drops or plateaus, there are alarming electrocardiographic abnormalities, chest pain occurs and becomes worse than the patient's baseline pain, or the patient wants to stop the test for any reason, the test should be stopped, regardless of the level of exercise achieved. In most instances, a symptom-limited maximal test is preferred, but it is usually advisable to stop if 2 mm of additional ST segment elevation occurs or if 2 mm of flat or down-sloping ST depression develops.

Exercise testing should be considered an extension of the history and physical examination. Prior to onset of exercise test, a physical examination should always be performed to rule out significant obstructive aortic valvular disease. The patient's activity history should help determine appropriate work rates for testing. A physician's reaction to signs or symptoms should be taken in context with the information a patient provides regarding his or her usual physical activity. That way, if abnormal findings occur at levels of exercise that the patient usually performs, it may not be necessary to stop the test for them.

Contraindications

Table 9.3 lists the absolute and relative contraindications to performing and exercise test. First and foremost, good clinical judgment should be exercised in determining indications and contraindications for exercise stress testing. In selected cases even when a patient has relative contraindications, testing can provide valuable information, even if only performed sub-maximally.

Patient Preparation

Preparations for exercise testing include the following:

1. Determine the indication for the test. If the reason for the test is not apparent, contact the referring physician.
2. Instruct a patient come dressed for exercise and to not eat or smoke at least 2–3 h prior to the test.
3. A history and physical examination should be conducted to rule out any contraindications to testing, particularly evaluating for systolic murmurs.
4. Specific questioning should ascertain which drugs are being taken or if potential electrolyte abnormalities should be considered.
5. The examiner should carefully explain why the test is being performed and the details of what to expect during testing, including how the test is performed and risks or possible complications. The patient should be informed that initially he or she may hold on to the rails, but later these should only be used if needed for balance.
6. A 12-lead electrocardiogram should be obtained in both supine and standing positions. A baseline abnormality may prohibit testing.

Beta-Blockers

For routine exercise testing, there is no need to discontinue or hold beta-blockade. In consecutive groups of males being evaluated for coronary artery disease, no differences in exercise scores or test performance were found when comparing those taking beta-blockers with those who were not [6]. Of note, in this population, when only ST segment depression criteria is being used, then 0.5 mm is needed to maintain sensitivity. Furthermore, the risk of cessation of beta-blockade for an exercise test should not be overlooked. Due to the life-threatening rebound phenomena associated with discontinuation of beta-blockers, if they are going to be stopped, it should be done gradually with careful supervision of the tapering process by a physician or nurse.

Table 9.4 Pretest probability of coronary disease by symptoms, gender, and age[a]

Age	Gender	Typical (definite) angina	Atypical (probable) angina	Nonanginal chest pain	Asymptomatic
30–39	Male	Intermediate	Intermediate	Low	Very low
	Female	Intermediate	Very low	Very low	Very low
40–49	Male	High	Intermediate	Intermediate	Low
	Female	Intermediate	Low	Very low	Very low
50–59	Male	High	Intermediate	Intermediate	Low
	Female	Intermediate	Intermediate	Low	Very low
60–69	Male	High	Intermediate	Intermediate	Low
	Female	High	Intermediate	Intermediate	Low

There are no data for patients <30 years old or >69 years old. It can be assumed that coronary artery disease prevalence increases with age
[a]High= >90 %; Intermediate = 10–90 %; Low = <10 %; Very low = <5 %

Protocols

As there are multiple exercise protocols, there may be some confusion regarding how physicians compare tests between one patient and another or in serial tests of the same patient. The most common protocols, their stages, and the predictive oxygen cost of each stage are illustrated in Fig. 9.1.

When treadmill and cycle ergometer testing were first introduced into clinical practice, practitioners adopted protocols used by major researchers (i.e., Balke [7], Astrand [8], Bruce [9], and Ellestad [10]) and their coworkers. In 1980, Stuart and Ellestad surveyed 1,375 exercise laboratories in North America and reported that of those performing treadmill testing, over half used the Bruce protocol for routine clinical testing [11] and it continues to predominate. This protocol uses relatively large and unequal 2–3 metabolic equivalent (MET) increments in work every 3 min. Unfortunately, these large and uneven work increments have been shown to result in a tendency to overestimate exercise capacity [12]. Accordingly, investigators have since recommended protocols with smaller and more equal increments [13, 14].

Ramp Testing

An approach to exercise testing that has subsequently gained interest is the ramp protocol, in which work increases constantly and continuously (Fig. 9.2).

The ramp approach facilitated the success in "optimization" of exercise testing, as the work increments are small and allow for increases in work to be individualized. Furthermore, a given test duration can be targeted for each patient. In 1991, Myers et al. [15]. compared the ramp treadmill and bicycle tests to more commonly utilized clinical protocols. In this study, ten patients with chronic heart failure, ten with coronary artery disease who were limited by angina during exercise, ten with coronary artery disease who were asymptomatic during exercise, and ten age-matched normal subjects performed three bicycle tests (25W/2 min stage, 50W/2 min stage, and ramp protocol) and three treadmill tests (Bruce, Balke, and ramp protocols) in randomized order on different days. For the ramp tests on a bicycle and treadmill, ramp rates were individualized to yield test duration of approximately 10 min for each subject. Maximal oxygen uptake was significantly higher on the treadmill protocols versus the bicycle protocols collectively, confirming previous observations. Only minor differences in maximal oxygen uptake, however, were observed within the treadmill protocols themselves or between the cycle ergometer protocols themselves.

As this approach appears to offer several advantages, convention supports the use of ramp protocol in most clinical and research testing. Subsequently, various equipment manufacturers have developed treadmills that can easily facilitate ramp exercise protocols, though simple individual manual stepping up of the grade and speed is possible.

Recovery Heat Rate

Heart rate usually falls rapidly at the end of a bout of progressive exercise. The rate of the drop in heart rate is related to fitness, but has been shown to be inversely related to survival [16] as well. In general, there is an increased risk of death associated with a decline in heart rate of less than 20 beats per minute by the first or second minute of recovery [17]. However, there does not appear to be a correlation between low rate of heart recovery and coronary artery disease.

Diagnostic Use of the Exercise Test

The ACC/AHA Guidelines

In 1986 a task force was established to develop guidelines for the use of exercise testing, and these guidelines were later updated/revised in 1997, then again in 2002 [2]. Over the years some dramatic changes were instituted, including the

Functional class	Clinical status	O_2 cost mL/kg/min	METS	Bicycle ergometer	Treadmill protocols					METS
					Bruce	Balke-Ware	Ellestad	McHenry	Naughton	
				1 Watt-6-kpds	3 min stages	% GR at 3.3 mph 1-min stages	3/2/3 min stages		2-min stages 3.0 mph % GR	
				For 70 kg body weight, kpds	mph % GR		mph % GR			
Normal and I	Healthy, dependent on age, activity	56.0	16		5.5 5.5	26				
		52.5	15		5.0 18	25	6 15		32.5	16
		49.0	14	1,500		24			30.0	15
		45.5	13		4.2 16	23	5 15	mph % GR	27.5	14
		42.0	12	1,350		22		3.3 3.3	25.0	13
		38.5	11	1,200		21		3.3 18	22.5	12
		35.0	10			20	5 10		20.0	11
		31.5	9	1,050	3.4 14	19		3.3 15	17.5	10
		28.0	8	900		18			15.0	9
	Sedentary healthy	24.5	7	750		17	4 10		12.5	8
		21.0	6	600	2.5 12	16		3.3 12	10.0	7
II	Limited	17.5	5	450		15	3 10		7.5	6
		14.0	4			14		3.3 9	5.0	5
III	Symptomatic	10.5	3	300	1.7 10	13			2.5	4
		7.0	2	150		12	1.7 10	3.3 6	0.0	3
IV		3.5	1		1.7 5	11				2
						10		2.0 3		1
					1.7 0	9				
						8				
						7				
						6				
						5				
						4				
						3				
						2				
						1				

Fig. 9.1 The most common protocols, their stages, and the predicted oxygen cost of each stage are illustrated

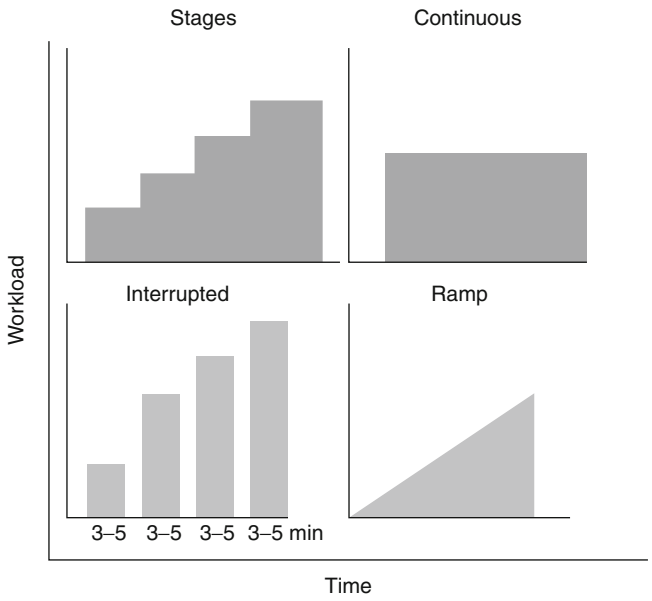

Fig. 9.2 Comparison of different exercise protocols

recommendation to make the standard exercise test the first diagnostic procedure in women and most other patients with resting ECG abnormalities, rather than performing imaging studies. The following is a brief synopsis of the recommendations from the evidence-based guidelines for the use of exercise testing to diagnose obstructive coronary artery disease:

Class I. Conditions for which there is evidence and/or general agreement that the standard exercise test is useful and effective.

- Adult male or female patients (including those with complete right bundle branch block or with less than 1 mm of resting ST depression) with intermediate pretest probability[1] of coronary artery disease (specific exceptions are discussed in Class II and III sections)

Class II. Conditions for which there is conflicting evidence and/or a divergence of opinion that the standard exercise test is useful and efficacious. Usefulness/efficacy is less well established by evidence/opinion.

- Patients with a high pretest probability of coronary artery disease[1]
- Patients with a low pretest probability of coronary artery disease[1]

[1]Pretest probability was determined from the Diamond-Forrester estimates by age, symptoms, and gender (see Table 9.4).

- Patients taking digoxin with less than 1 mm of baseline ST depression
- Patients with ECG criteria for left ventricular hypertrophy with less than 1 mm of baseline ST depression[1]

Class III. Conditions for which there is evidence and/or general agreement that the standard exercise test is not useful or efficacious and in some cases may be harmful.

- Patients who demonstrate the following baseline ECG abnormalities
  - Preexcitation (Wolff-Parkinson-White) syndrome (though testing may help demonstrate risk of the ancillary pathway)
  - Electronically paced ventricular rhythm
  - More than 1 mm of ST depression (lowered specificity for CAD but still prognostic)
  - Complete left bundle branch block
- Patients with a well-documented myocardial infarction or significant disease demonstrated on coronary angiography

Standards for Studies of Diagnostic Test Performance

Reid, Lachs, and colleagues updated the "methodological standards" for diagnostic tests in 1995 [18]. The purpose of refining these standards was to improve patient care, reduce health-care costs, improve the quality of diagnostic test information, and eliminate useless tests or testing methodologies. Some of the logical and easily appreciated ways to conform to diagnostic test standards in evaluating exercise testing are by blinding to test interpretation, exclusion of patients with prior MIs, and classifying chest pain. The two subtle standards that are the least understood but affect test performance most drastically, and are most commonly not fulfilled, are *limited challenge* and *workup bias*. Limited challenge could be justified as the first step of looking at a new measurement or test. This is because an investigator may choose a healthy and sick person, test them using a new measurement, and assess whether they are different. If no differences are noted between them, then no further investigations are indicated. This approach favors the measurement; however, a better evaluation would be performed by testing consecutive patients presenting for evaluation. Workup biases occur because the decision whether to treat or not (i.e., catheterization) is made by the physician ordering the test, his/her interpretation of the test results, and his/her clinical acumen. Therefore, the patients in the study are different from patients presenting for evaluation before applying the test. Populations chosen for test evaluation that fail to avoid limited challenge will result in overestimated predictive accuracy and receiver operating characteristic (ROC) curves greater than those truly associated with the test measurement. Workup bias can affect the calibration of the measurement cut-points. In other words, a score or ST measurement can have a different sensitivity and specificity for a particular cut-point when workup bias is present. The two studies that have removed workup bias by protocol have considerably different test results [19].

Test Performance Definitions

Sensitivity and specificity are the terms used to define how reliable a test distinguishes diseased from non-diseased individuals. They are parameters of the accuracy of a diagnostic test. Sensitivity is the percentage of times that a test gives an abnormal ("positive") result when those with the disease are tested. Specificity is the percentage of times that test gives a normal ("negative") result when those without the disease are tested. This is quite different from the colloquial use of the word "specific." Table 9.5 shows how to calculate sensitivity, specificity, and other test characteristics. Table 9.6 presents an example in which test performance characteristics are calculated and the effects of differences in the prevalence of disease are demonstrated. Table 9.7 demonstrates the importance of prevalence on positive predictive value of a test.

Hemodynamic Responses

Age-predicted maximal heart rate targets are relatively useless for clinical purposes. There is a relatively poor relationship between maximal heart rate to age. Correlation coefficients of −0.4 are usually found with a standard error of the estimate of 10–25 beats/min. Since prediction of maximal heart rate is inaccurate, exercise should be symptom-limited and not targeted on achieving a certain heart rate.

Exceptional hypotension, best defined as a drop in systolic blood pressure below resting blood pressure or a drop of 20 mmHg after a rise, is very predictive of severe angiographic coronary artery disease and of poor prognosis. We strongly recommend that blood pressure be taken manually with a cuff and stethoscope.

Exercise Capacity

The MET is a unit of basal oxygen consumption equal to approximately 3.5 mL of O2 per kilogram of body weight per minute and is the approximate amount of oxygen required to sustain life in the resting state. An individual's maximal oxygen uptake is normally estimated from the workload reached using a formula based on speed and grade. Maximal oxygen uptake is most precisely determined by direct measurement using ventilatory gas-exchange techniques. In certain circumstances where precision is important, such as in athletes, research studies, and patients considered for cardiac transplantation, a direct measurement is essential.

Table 9.5 Definitions and calculation of the terms used to quantify diagnostic accuracy

True positive (TP) = number of patients with the disease and a positive test result
False-negative (FN) = number of patients with the disease but a negative test result
True negative (TN) = number of patients without the disease and a negative test result
False-positive (FP) = number of patients without the disease but a positive test result
Total population = $TP + TN + FP + FN$
Sensitivity = percentage of those with the disease who test positive $= TP / (TP + FN) \times 100$
Specificity = percentage of those without the disease who test negative $= TP / (TP + FN) \times 100$
Positive predictive value $(PV+)$ = percentage of those with a positive test result who have the disease $= TP / (TP + FN) \times 100$
Negative predictive value $(PV-)$ = percentage of those with a negative test result who do not have the disease $= TP / (TP + FN) \times 100$
Predictive accuracy (PA) = percentage of correct classifications, both positive and negative $= (TP + TN) / (\text{total population}) \times 100$
Receiver operating characteristic (ROC) curve = plot of sensitivity vs specificity
Risk ratio (RR) = ratio of disease rate in those with a positive result vs those with a negative result $= (TP / (TP + FP)) / (FN / FN + TN)$ $= (PV+) / (FN / (FN + TN))$

Table 9.6 Example of calculating test performance to predict CAD with a test that has 50 % sensitivity and 90 % specificity in a population of 10,000 individuals

CAD prevalence (%)	Subjects	Positive (abnormal) test	Negative (normal) test	Predictive value of positive test result
5	500 with CAD	250	250	250/(250 + 950) = 21 %
	9,500 without CAD	950	8,550	
50	5,000 with CAD	2,500	2,500	2,500/(2,500 + 500) = 83 %
	500 without CAD	500	4,500	

Table 9.7 Illustration of the importance of prevalence on positive predictive value of a test

CAD prevalence (%)	Sensitivity (%)/specificity (%)	Predictive value of positive test result (%)	Risk ratio
5	70/90	27	27×
	90/70	14	14×
	90/90	32	64×
	66/84	18	9×
50	70/90	88	3×
	90/70	75	5×
	90/90	90	9×
	66/84	80	3×

Exercise capacity should always be reported in METs and not in minutes of exercise. In this way, the results from different protocols and exercise modalities can be compared directly. Achieved workload in METs has been shown to be a major prognostic variable.

ST Analysis

ST segment depression is a representation of global subendocardial ischemia, with a direction determined largely by the orientation of the heart in the chest. Importantly, ST depression does not localize coronary artery lesions. V5 is

the lead that most frequently demonstrates clinically significant ST depression. ST depression in the inferior leads (II, AVF) is most often due to the atrial repolarization wave that begins in the PR segment and can extend to the beginning of the ST segment. When ST depression is isolated to these leads and there are no diagnostic Q waves, it is usually a false-positive. ST segment depression limited to the recovery period should not be considered a "false-positive" response. Inclusion of analysis during this time period increases the diagnostic yield of the exercise test and greatly increases the specificity.

When the resting ECG shows Q waves of an old myocardial infarction, ST elevation can be due to wall motion abnormalities, whereas accompanying ST depression can be due to a second area of ischemia or reciprocal changes. When the resting ECG is normal, ST elevation is due to severe ischemia (spasm or a critical lesion). Such ST elevation is uncommon and very arrhythmogenic. Exercise-induced ST elevation (not over diagnostic Q waves) and ST depression both represent ischemia, but they are quite distinctive: *elevation* is due to transmural ischemia, is arrhythmogenic, has 0.1 % prevalence, and localizes the artery where there is spasm or a tight lesion, while *depression* is due to subendocardial ischemia, is not arrhythmogenic, has a 5–50 % prevalence, is rarely due to spasm, and does not localize. Figure 9.3 illustrates the various patterns. The standard criterion for abnormality is 1 mm of horizontal or down-sloping ST depression below the PR isoelectric line or 1 mm further depression if there is a baseline depression.

The most important times to look for ST depression are during maximal exercise in lead V5 and 3 min into recovery [20]. Patients should be placed supine as soon as possible after exercise, avoiding a cool-down walk, to maximize sensitivity for the ST abnormalities. ECG recordings should continue for 5 min in recovery or until any new changes from baseline normalize.

Non-sustained ventricular tachycardias are uncommon during routine clinical treadmill testing (prevalence less than 2 %) and are well tolerated, and its prognosis is determined by any accompanying ischemia or LV damage [21].

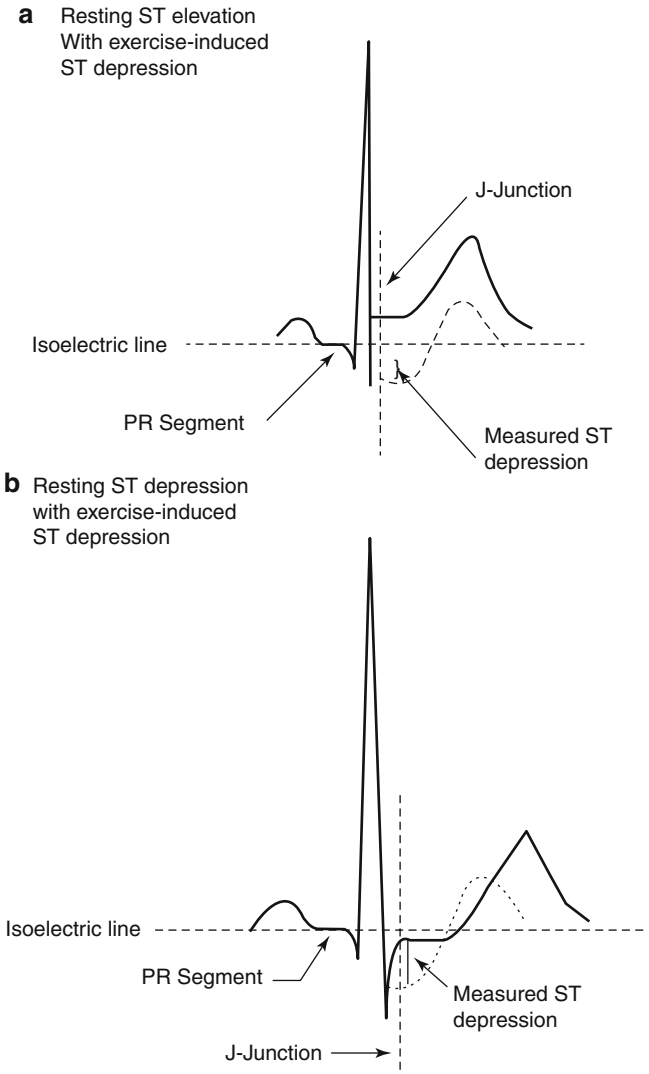

Fig. 9.3 (**a**) The various patterns of exercise ST shifts possible with ischemia are shown below. (**b**) ST amplitude measurement depends on the ST level at baseline

Effects of Digoxin, LVH, and Resting ST Depression

Digoxin, LVH, and resting ST depression were evaluated in the meta-analysis done as part of the guidelines [2]. Only the studies that provided sensitivity, specificity, and total patients' numbers (with at least 100 patients) were considered. The conclusion from this analysis was that only digoxin had a major effect on test performance.

Gender

There has been controversy regarding the use of the standard exercise ECG test in women. In fact, experts previously recommended that only imaging techniques be used for testing women because of the impression that the standard exercise ECG did not perform as well as it did in men. The recent ACC/AHA guidelines, however, reviewed this subject in detail and came to another conclusion. The new position was based on evidence from meta-analysis and 15 other studies that considered *only* women. Exercise testing for the diagnosis of significant obstructive coronary disease in adult patients

a

Variable	Circle response	SUM	
Maximal heart rate	Less than 100 bpm = 30		Men
	100 –129 bpm = 24		
	130 –159 bpm = 18		
	160 –189 bpm = 12		
	190 – 220 bpm = 6		
Exercise ST depression	1– 2 mm = 15		<40 = Low probability
	> 2 mm = 25		
Age	> 55 year = 20		
	40 – 55 year = 12		
Angina history	Definite/typical = 5		40 – 60 = Intermediate probability
	Probable/atypical = 3		
	Non-cardiac pain = 1		
Hypercholesterolemia?	yes = 5		
Diabetes?	yes = 5		>60 = High probability
Exercise test induced angina?	Occurred = 3		
	Reason for stopping = 5		
	Total score:		

b

Variable	Circle response	SUM	
Maximal heart rate	Less than 100 bpm = 20		Women
	100 – 129 bpm = 16		
	130 – 159 bpm = 12		
	160 – 189 bpm = 8		
	190 – 220 bpm = 4		
Exercise ST depression	1–2 mm = 6		<37 = Low Probability
	> 2 mm = 10		
Age	> 55 year = 25		
	40 – 55year = 15		
Angina History	Definite/Typical = 10		37–57 = Intermediate Probability
	Probable/atypical = 6		
	Non-cardiac pain = 2		
Hypercholesterolemia?	yes = 10		
Diabetes?	yes = 10		>57 = High Probability
Exercise Test Induced Angina?	Occurred = 9		
	Reason for stopping = 15		
Estrogen status	Positive = 5 Negative = 5		
	Total Score:		

Fig. 9.4 Calculation of the simple exercise test score for (**a**) men and (**b**) women

including women, with symptoms, or other clinical findings suggestive of intermediate probability of coronary artery disease is a Class I indication (i.e., definitely indicated). Women with intermediate pretest probability are those age 30–59 with typical or definite angina pectoris, 50–69 with atypical or probable pectoris, and 60–69 with nonanginal chest pain (*see* Fig. 9.4).

Prognostic Use of Exercise Test

ACC/AHA Guidelines

Indications for exercise testing to assess risk and prognosis in patients with symptoms or a prior history of coronary artery disease:

Class I. Conditions for which there is evidence and/or general agreement that the standard exercise test is useful and effective.

- Patients undergoing initial evaluation with suspected or known CAD. Exceptions are noted below in Class IIb
- Patients with suspected or CAD previously evaluated with significant change in clinical status
- Low-risk unstable angina patients 8–12 h after presentation who have been free of active ischemic or heart failure symptoms
- Intermediate-risk unstable angina patients 2–3 days after presentation who have been free of active ischemic or heart failure symptoms

Class IIa. Conditions for which there is conflicting evidence and/or a divergence of opinion that the standard exercise test is useful and efficacious. Weight of evidence/opinion is in favor of usefulness/efficacy.

- Intermediate-risk unstable angina patients who have initial and 6–12 cardiac markers that are normal, a repeat ECG without significant change, and no other evidence of ischemia

Class IIb. Conditions for which there is conflicting evidence and/or a divergence of opinion that the standard exercise test is useful and efficacious. Usefulness/efficacy is less well established by evidence opinion.

- Patients who demonstrate the following baseline ECG abnormalities
  - Preexcitation (Wolff-Parkinson-White) syndrome
  - Electronically paced ventricular rhythm
  - More than 1 mm of resting ST depression
  - QRS duration greater than 120 ms
- Periodic monitoring to guide management of patients with a stable clinical course

Class III. Conditions for which there is evidence and/or a divergence of opinion that the standard exercise test is not useful and efficacious and in some cases may be harmful.

- Patients with severe comorbidity likely to limit life expectancy and/or candidacy for revascularization
- High-risk unstable angina patients

Exercise Test Scores

Improved exercise test characteristics can be obtained by considering additional information in addition to the ST response. Studies have confirmed that this approach is effective [22]. The Duke score, originally developed for prognostic use, has been extended to diagnosis [23]. Simplified scores derived from multivariable equations have been developed to determine the probability of disease and prognosis. All variables are coded with the same number of intervals so that coefficients are proportional. For instance, if five is the chosen interval, dichotomous variables are 0 if not present and 5 if present. Continuous variables, such as age and maximal heart rate, are coded into groups associated with increasing prevalence of disease. Therefore, the relative importance of the selected variables becomes obvious, and the healthcare provider merely compiles the variables in the score, multiplies by the appropriate number, and then adds up the products. Calculation of the "simple" exercise test score can be done using Fig. 9.4 [24, 25] for men and women.

Prognostic Scores

The Duke and VA predictive equations represent the "state of the art" in prognostication [26, 27]. There is an abundance of data supporting the use of exercise testing as the first noninvasive step after the history, physical examination, and resting ECG in the prognostic evaluation of CAD patients. Exercise testing serves two purposes: (1) prognostication—providing information regarding the patient's status—and (2) facilitates clinical decision making, elucidating optimal management strategies. This assessment should always include calculation of a properly designed score such as the Duke treadmill score or the VA treadmill score.

Duke Treadmill Score and Nomogram

Mark et al. studied 2,842 consecutive patients who underwent exercise testing and cardiac catheterization and subsequently had their data entered into the Duke computerized medical information system [28]. The median follow-up for the study population was 5 years and 98 % complete. All patients underwent a Bruce protocol exercise test and had standard ECGs recorded. A treadmill angina index was assigned a value of 0 points if angina was absent, 1 point if typical angina occurred during exercise, or 2 points if angina was the reason the patient stopped exercising. This nomogram is shown in Fig. 9.5.

VA Predictive Equation

The VA predictive rules demonstrate that simple noninvasive clinical indicators can stratify patients with stable coronary

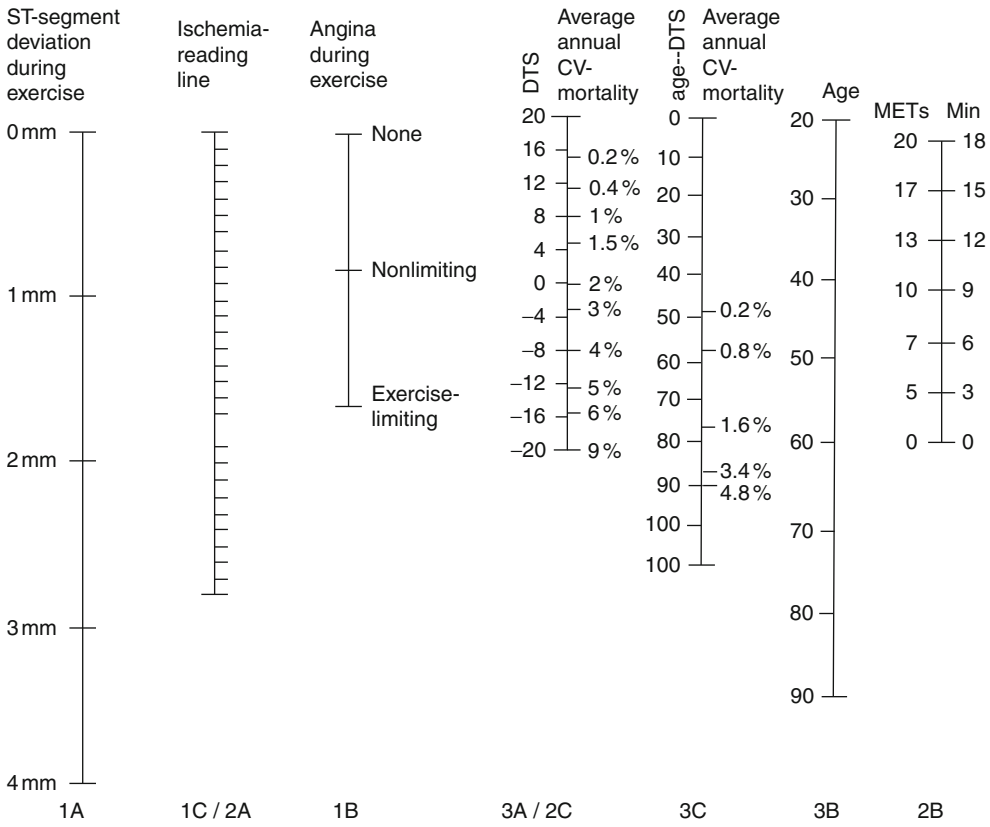

Fig. 9.5 The Duke treadmill prognostic nomogram with age added to determine the average annual cardiovascular mortality adjusted for age: draw a line between the observed amount of ST segment deviation at maximal exercise (*1A*) and degree of angina (*1B*). Note where this line intersects the ischemia-reading line (*1C*). Then draw a line between the ischemia-reading line value (*1C*) and exercise duration of equivalent METs (*2B*). The point where this line intersects the DTS (Duke treadmill score) line indicates the DTS score (*3A*) and the average annual cardiovascular mortality (*2C*). Finally, draw a line between the DTS line (*3A*) and the patient's age (*3B*). The point where this line intersects age-DTS (*3C*) indicates the average annual cardiovascular mortality adjusted for age

artery disease into high- or low-risk groups. In our VA population, a simple score based on one item of clinical information (history of congestive heart failure or digoxin use) and three exercise test responses (ST depression, exercise capacity, and change in systolic blood pressure) can identify a group of patients at high risk for cardiovascular death [29]. Table 9.8. Clinical judgment must be applied to decide whether intervention is likely to improved survival in our high-risk patients.

Comparison with Other Diagnostic Tests

Meta-analysis of Exercise Testing Studies

Gianrossi et al. investigated the variability of the reported diagnostic accuracy of the exercise electrocardiogram by performing a meta-analysis [30]. One hundred forty-seven consecutively published reports were summarized, involving 24,074 patients who underwent both coronary and angiography and exercise testing. Details regarding population characteristics and methods were evaluated including number of ECG leads, exercise protocol, pre-exercise hyperventilation, definition of an abnormal ST response, exclusion of certain subgroups, and blinding of test interpretation. Wide variability in sensitivity and specificity was found (mean sensitivity was 68 % with a range of 23–100 % and a standard deviation of 16 %; mean specificity was 77 % with a range of 17–100 % and a standard deviation of 17 %). The median predictive accuracy (percentage of total true calls) was approximately 73 %.

To more accurately portray the performance of the exercise test, only the results in 41 studies out of the original 147 were considered [31]. These 41 studies removed patients with a prior MI from this meta-analysis, fulfilling one of the criteria for evaluating a diagnostic test, and provided all the numbers for calculating test performance. These 41 studies, including nearly 10,000 patients, demonstrated a lower mean sensitivity of 68 % and a lower mean specificity of 74 %; this means that there is also a lower predictive accuracy of 71 %. In several studies in which workup bias has been lessened, fulfilling another major criterion, the sensitivity is approximately 50 % and the specificity 90 %; the predictive accuracy is 70 % [32]. *This demonstrates that the key feature of the standard exercise test is high specificity and that low sensitivity is a problem.*

Nuclear Perfusion and Echocardiography

The performances of exercise echocardiography and exercise nuclear perfusion scanning in the diagnosis of coronary artery

disease were compared in a meta-analysis of 44 studies published between 1990 and 1997 [33]. Articles were included if they discussed exercise echocardiography and/or exercise nuclear imaging with thallium or sestamibi for detection and/or evaluation of coronary artery disease, if data on coronary angiography were presented as the reference test, or if the absolute numbers of true-positive, false-negative, true-negative, and false-positive observations were available or derivable from the data presented. Studies performed exclusively in patients after myocardial infarction, after percutaneous transluminal coronary angioplasty, after coronary artery bypass grafting, or with recent unstable coronary syndromes were excluded. When the discriminatory abilities of exercise echo and exercise nuclear were compared to exercise testing without imaging, both echo and nuclear performed significantly better than the exercise ECG.

Table 9.8 Prognostic scores: the Duke treadmill score and the VA treadmill score

Duke score	VA score
= METs	= 5 × (CHF or dig)
− 5 × (mmE-I ST depression)	+ mm E-I ST depression
− 4 × (TMAP index)	+ change in SBP score
	− METs
MET = metabolic equivalent	CHF = congestive heart failure
E-I = exercise-induced	Dig = digoxin
TMAP = treadmill angina pectoris	SBP = systolic blood pressure
TMAP score:	SBP score:
0 = no angina	0 = increase > 40 mmHg in standing systolic BP
1 = angina during test	1 = increase 31 – 40 mmHg
2 = angina was the reason for stopping the test	2 = increase 21 – 31 mmHg
	3 = increase 11 – 21 mmHg
	4 = increase 0 – 11 mmHg
	5 = reduction below standing pre-exercise systolic BP
	CHF/digoxin score:
	0 = no
	1 = yes
Duke scores:	VA scores:
≥ +5: low risk	<−2: low risk
−10 to +4: moderate risk	−2 to 2: intermediate risk
≤ 11: high risk	≥2: high risk

Predictive Accuracy

Some test results are dichotomous (normal vs abnormal, positive vs negative) rather than graded or continuous, like a score. Predictive accuracy (true positive plus true negatives divided by the total population studied) can be used to compare dichotomous test results. On the other hand, any score can also be dealt with as a dichotomous variable by choosing a cut-point. An advantage of predictive accuracy is that it provides an estimate of the number of patients correctly classified by the test out of 100 tested. However, when predictive accuracy is used to compare tests, populations with roughly the same prevalence of disease should be considered. Table 9.9, based on published meta-analyses, summarizes the sensitivity, specificity, and predictive accuracy of the major diagnostic tests for coronary artery disease that are currently available [34]. While the non-exercise stress tests are very useful, the results shown are probably better than their actual performance because of patient selection. For studies of diagnostic characteristics, patients with a prior MI should be excluded, as diagnosis of coronary disease is not an issue in them.

Table 9.9 Comparison of exercise testing subgroups and different test modalities

Grouping	Studies	Patients (*n*)	Sensitivity (%)	Specificity (%)	Predictive accuracy (%)
Meta-analysis of standard ETT	147	24,047	68	77	73
Meta-analysis without MI	58	11,691	67	72	69
Meta-analysis of treadmill scores	24	11,788	85		80
Consensus treadmill score	1	2,000	85	92	88
Electron beam computed tomography	4	1,631	90	45	68
Thallium scintigraphy	59	6,038	85	85	85
SPECT without MI	27	2,136	86	62	74
Persantine thallium	11		85	91	87
Exercise echo	58	5,000	84	75	80
Exercise echo without MI	24	2,109	87	84	85
Dobutamine echo	5		88	84	86

Summary

The exercise test is relatively inexpensive, noninvasive, and readily available. It can be performed in the doctor's office and does not require injections or exposure to radiation. It provides both diagnostic and prognostic information and can also help determine functional capacity and degree of disability. Many physicians' experiences have taught them that the exercise test uniquely complements the medical history and the physical exam, so it remains the second most commonly performed cardiology procedure next to the routine ECG. Furthermore, convincing evidence that treadmill scores enhance the diagnostic and prognostic power of the exercise test will add to this movement.

The ACC/AHA guidelines for exercise testing clearly indicate the correct uses of exercise testing. Since the preceding guidelines, exercise testing has been extended as the first diagnostic test in women, in individuals with a right bundle branch block, and in those with resting ST segment depressions. When diagnostic scores and prognostic scores were used with exercise testing, test characteristics approach that of the nuclear and echocardiographic add-ons to the exercise test.

The following rules are important to follow for getting the most information from the standard exercise test:

- The exercise protocol should be progressive, with even increments in speed and grade whenever possible; consider using a manual or automated ramp protocol.
- The treadmill protocol should be adjusted to the patient; one protocol for all is not appropriate.
- Report exercise capacity in METs, not minutes of exercise.
- ST segment measurements should be made at ST_0 (J-junction) and ST segment depression should be considered abnormal only if horizontal or down-sloping.
- Raw ECG waveforms should be considered first then supplemented by the computer-enhanced (filtered and averaged) waveforms when the raw data are acceptable.
- The recovery period is critical to include in the analysis of the ST segment response.
- Patients should be placed supine as soon as possible after exercise.
- Measurement of systolic blood pressure during exercise is extremely important and exertional hypotension is ominous; manual blood pressure measurement techniques are preferred.
- Age-predicted heart rate targets are largely useless because of the wide scatter for age, and therefore, exercise tests should be symptom-limited.
- A treadmill score should be calculated for every patient; use of multiple scores or a computerized consensus score should be considered as a part of the treadmill report.

To ensure the safety of exercise testing, the following list of the most dangerous circumstances in the exercise testing lab should be considered:

- Testing patients with aortic valvular disease should be done with great care because these patients are at risk for cardiovascular collapse.
- ST segment elevation without diagnostic Q waves is due to transmural ischemia and can be associated with dangerous arrhythmias and infarction.
- Exertional hypotension accompanied by ischemia (angina or ST depression) can be an ominous sign.
- A cool-down walk is advisable in any high-risk patient where ST segment changes are not critical to diagnosis or the evaluation purpose.

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Radiology of the Heart

10

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Introduction

Diagnostic imaging plays a critical role in the diagnosis of heart disease. In the past 30–35 years, advanced imaging modalities such as digital angiography, echocardiography, magnetic resonance imaging (MRI), computed tomography (CT), and nuclear cardiology have become increasingly valuable for the evaluation of the heart. However, the chest radiograph remains the most appropriate initial test performed in patients presenting with chest pain or dyspnea. This chapter will discuss the role of the chest radiograph in the diagnosis of cardiac disease in adults, with an emphasis on both normal cardiovascular anatomy and pathology in a variety of diseases. Correlation will be made with cross-sectional imaging in order to illustrate important anatomic points.

Normal Anatomy

The standard radiographic examination of the chest consists of upright [posteroanterior (PA)] and lateral projections (see Fig. 10.1). If a patient is acutely ill or is unable to stand upright, an anteroposterior (AP) frontal radiograph may be obtained with the patient in the supine position, and the lateral radiograph is usually omitted. It is important to ensure that the patient is properly positioned in both the frontal and lateral views so that cardiac structures can be accurately evaluated.

In the normal chest radiograph, there is excellent inherent contrast between the air-filled lungs, pulmonary vessels, and mediastinum. Therefore, the chest film is the primary imaging study for evaluation of the lung parenchyma and vessels. However, the components of the mediastinum, including the heart, the blood, and the fat, have similar radiographic densities and cannot be easily distinguished. Nevertheless, the margins of the heart and mediastinal vessels are clearly demarcated, and variation from the normal appearance suggests the presence of disease.

Left Subclavian Artery

On the frontal radiograph, the left subclavian artery forms the superior portion of the left mediastinal border above the aortic arch (see Fig. 10.1a). This artery usually forms a concave border with the lung. A convex border may be seen if there is increased blood flow, such as in coarctation of the aorta, or if the vessel is tortuous because of atherosclerosis or hypertension. A persistent left superior vena cava is suggested by a straight or convex left supra-aortic border or by a venous catheter extending down the left side of the mediastinum (see Fig. 10.2).

Aorta

On the frontal view, the ascending aorta forms a convex margin above the right heart border (see Fig. 10.1a). When the ascending aorta enlarges, it projects farther to the right. On the lateral view, the anterior margin of the ascending aorta lies above the right ventricle but is not seen in the normal individual due to an abundance of mediastinal fat.

The distal aortic arch or "aortic knob" forms a convex border just below the left subclavian artery on the frontal radiograph (see Fig. 10.1a). The aortic arch displaces the

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_10,

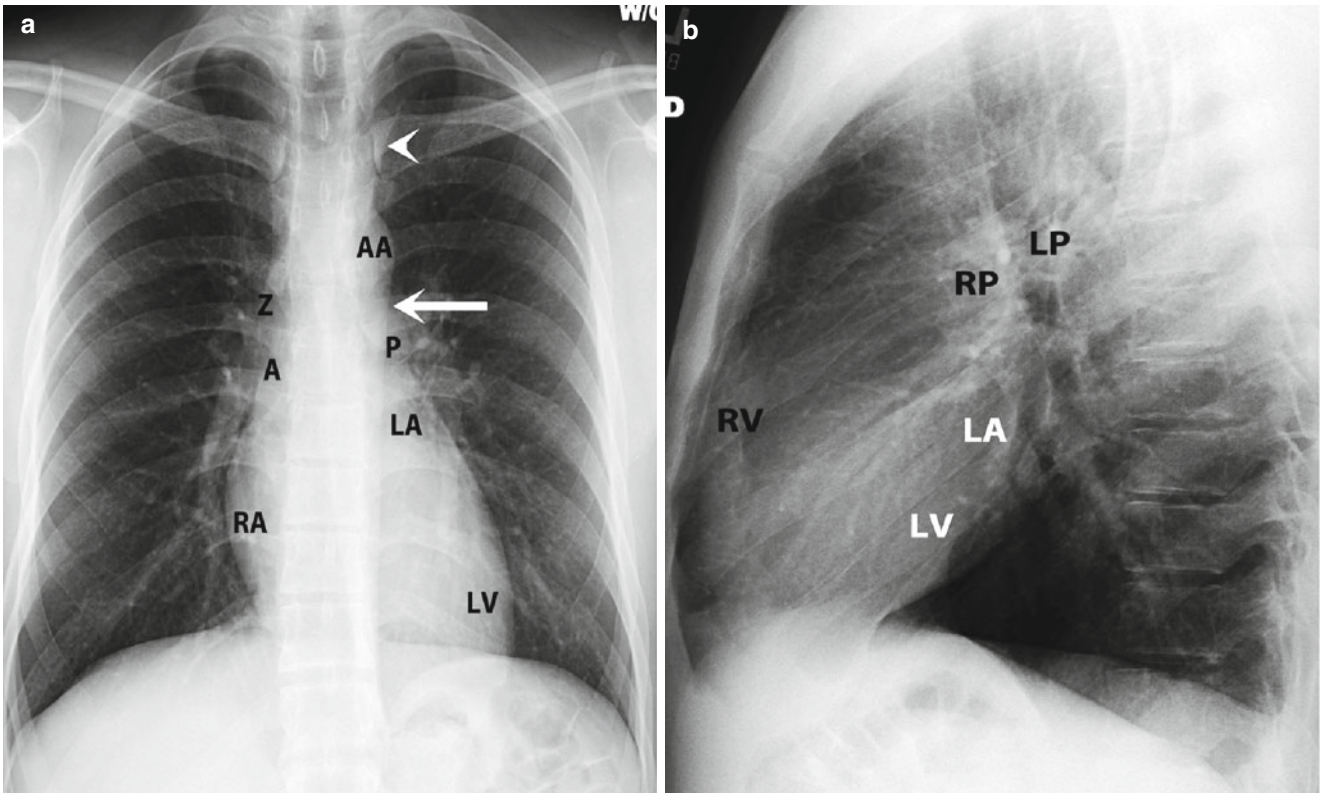

Fig. 10.1 Normal chest radiograph in a 32-year-old man. (**a**) PA frontal projection. (**b**) Lateral projection. *A* ascending aorta, *AA* aortic arch, *LA* left atrium, *LP* left pulmonary artery, *LV* left ventricle, *P* main pulmonary artery, *RA* right atrium, *RP* right pulmonary artery, *RV* right ventricle, *Z* azygos vein. *Arrowhead* left subclavian artery, *straight arrow* aorticopulmonary window

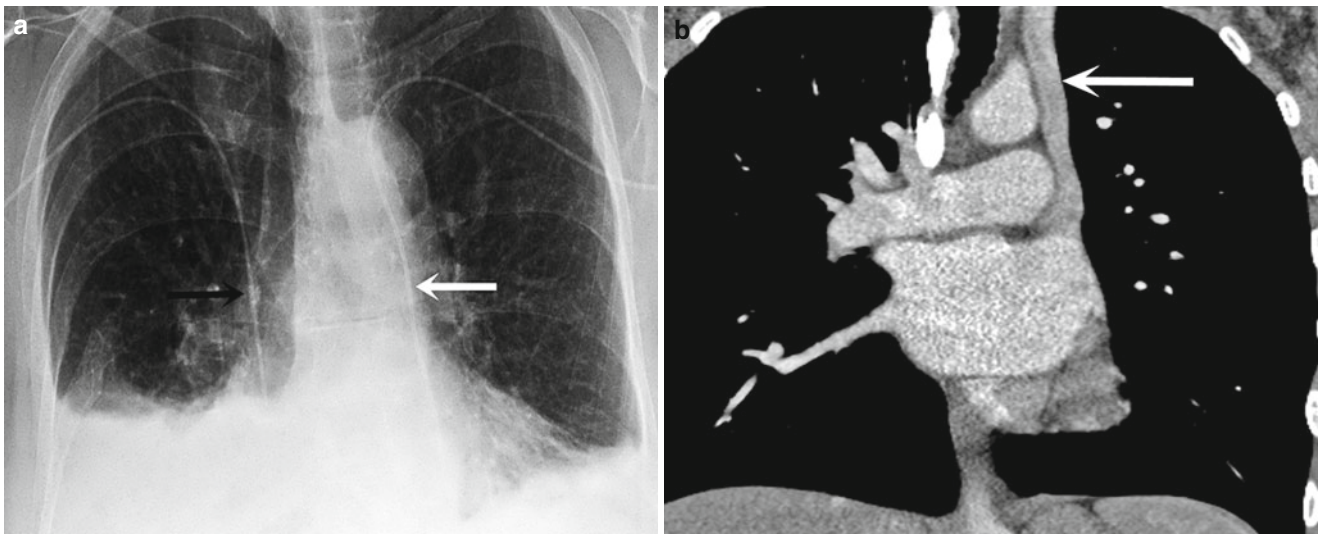

Fig. 10.2 Duplicated superior vena cava. (**a**) AP chest radiograph shows two peripherally inserted central catheters (PICCs), one in the left superior vena cava (*white arrow*) and the other in the right superior vena cava (*black arrow*). (**b**) Coronal CT in another patient shows a left superior vena cava (*arrow*). Note dense contrast filling the right superior vena cava

trachea slightly to the right. In a patient with a right aortic arch, the trachea is deviated slightly to the left [1]. The arch is usually small in the young, healthy individual. An enlarged aortic arch is higher and wider than the normal aorta.

The ascending aorta or arch may be enlarged on the frontal view in individuals with aortic aneurysm, aortic regurgitation, systemic hypertension, or atherosclerosis (see Fig. 10.3). Unfortunately, accurate measurement of the

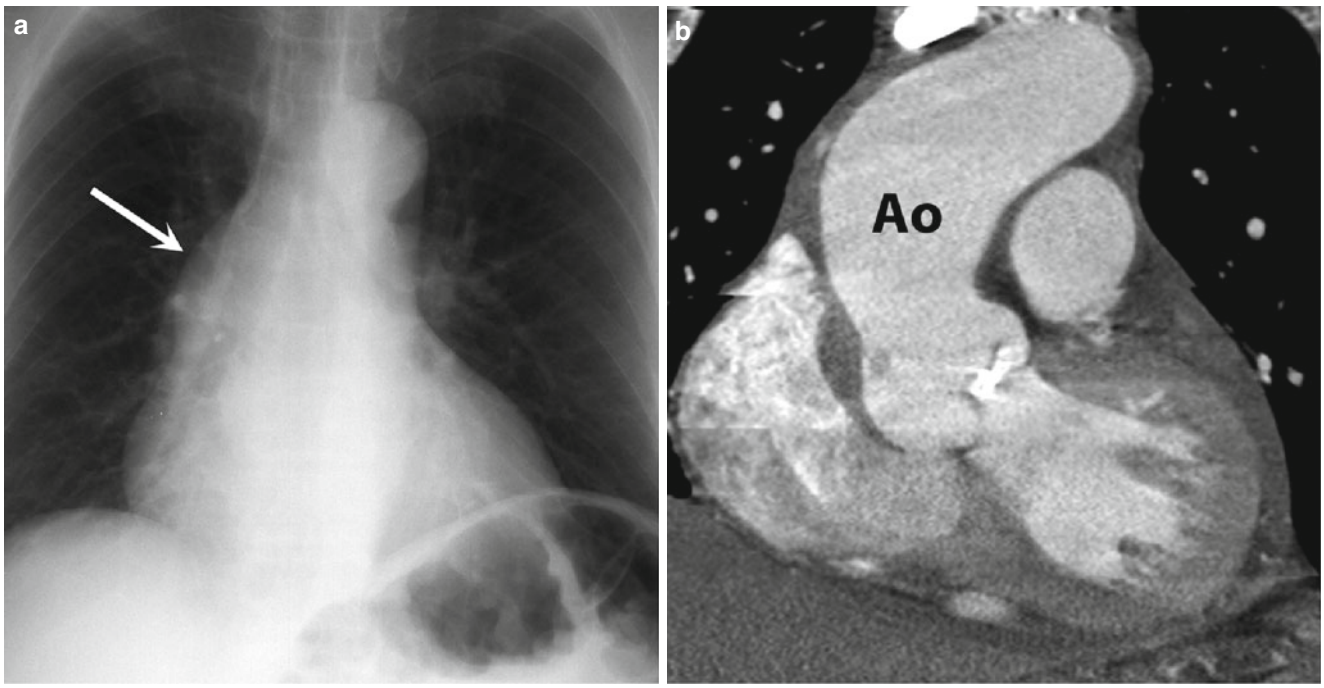

Fig. 10.3 Aortic stenosis. (**a**) PA radiograph shows ascending aortic enlargement (*arrow*). (**b**) Coronal CT confirms aortic enlargement (*Ao*). Note aortic valvular calcification. This patient had severe aortic stenosis documented by echocardiography

diameter of the aorta in order to determine if an aneurysm is present is unreliable on the chest radiograph and requires confirmation with cross-sectional imaging.

Immediately below the aortic arch along the left mediastinal border is a concave indentation known as the aorticopulmonary window, bordered by the lower margin of the aortic arch and the superior margin of the left pulmonary artery (see Fig. 10.1a). Convex bulging of the aorticopulmonary window may reflect lymphadenopathy, a ductus diverticulum, or other mass [2].

Pulmonary Vasculature

The main pulmonary artery forms a slightly convex border along the left side of the mediastinum between the aortic arch and the left atrial appendage (see Fig. 10.1a). A prominent convex bulge in this location indicates enlargement of the main pulmonary artery which may be related to pulmonary arterial hypertension; increased blood flow, as in anemia or a left-to-right shunt; or turbulent flow, as in patients with pulmonic valvular stenosis. On the other hand, the main pulmonary artery border may be flat or concave in patients with transposition of the great vessels, truncus arteriosus, tetralogy of Fallot, or pulmonary atresia. On the lateral projection the anterior border of the main pulmonary artery, located above the right ventricle, is not clearly seen due to the presence of mediastinal fat.

The left pulmonary artery is visualized as a smooth arc just inferior to the aorticopulmonary window. The left pulmonary artery arches over the left mainstem bronchus, as seen on the lateral projection (see Fig. 10.1b). On the other hand, the right pulmonary artery is a round or oval opacity anterior to the right mainstem bronchus on the lateral view (Fig. 10.1b).

The intrapulmonary branch arteries parallel the airways and gradually decrease in size toward the lung periphery. The arteries and bronchi are of approximately the same size at any given level; comparison of arterial and bronchial diameters is therefore useful when assessing increase or redistribution of blood flow. When a patient is upright, lower lobe vessels are larger than upper lobe vessels due to differences in blood flow, partly due to the effects of gravity [3].

Heart

On the well-positioned PA frontal radiograph, the normal heart occupies no more than 50 % of the transverse diameter of the thorax [4]. The respective widths of the heart and chest can be measured to determine the "cardiothoracic ratio," calculated as the maximum transverse diameter of the heart divided by the maximum width of the thorax [4]. In practice, the size of the heart is usually assessed subjectively. Low lung volumes, lordotic projection of the radiograph, or pectus excavatum deformity can cause the heart to appear larger

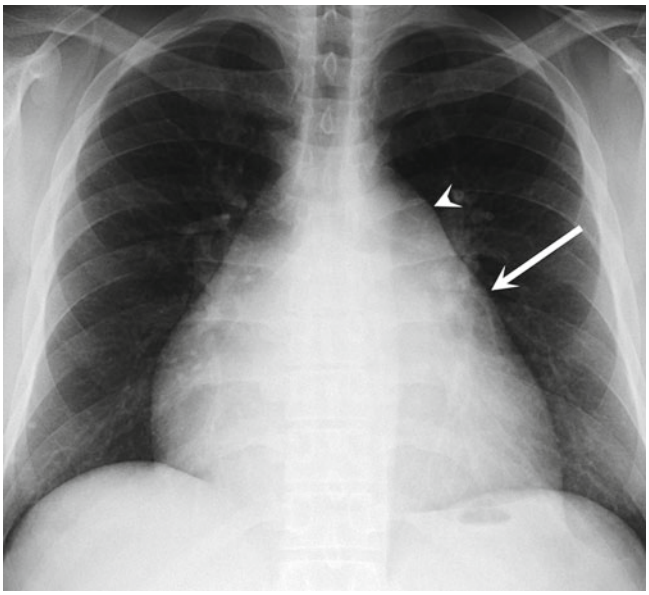

Fig. 10.4 Rheumatic mitral stenosis. PA chest radiograph shows left atrial appendage enlargement (*arrow*) in keeping with rheumatic mitral stenosis. Main pulmonary artery enlargement (*arrowhead*) suggests pulmonary hypertension

than it really is. The heart can be enlarged in the setting of a well-conditioned athlete due to normal physiologic dilatation. A large heart may appear to be of normal size if the lungs are hyperinflated as in patients with emphysema or if the cardiac apex is displaced inferiorly. When evaluating the size of the heart, it should be kept in mind that AP frontal projections result in magnification of the cardiac silhouette by 10–13 % [5].

Left Atrium

The left atrial appendage is identified as a smooth, slightly concave segment of the left heart border immediately inferior to the left mainstem bronchus in the frontal view (see Fig. 10.1a). When the left atrial border is straightened or convex, atrial enlargement is suggested (see Fig. 10.4). It is important to recognize that noncardiac pathology, such as a pericardial cyst, a mediastinal tumor, or lymphadenopathy, may mimic enlargement of the left atrial appendage on the frontal radiograph. The right side margin of the normal left atrium is visualized deep to the right atrial border as a convex "double" density. If the left atrium is severely dilated, the left atrial border may project lateral to the margin of the right atrium [6]. Elevation of the left mainstem bronchus is another sign of left atrial enlargement [7]. On the lateral projection, the normal left atrium forms a slight bulge at the upper posterior cardiac border (see Fig. 10.1b). Enlargement of the left atrium results in posterior displacement of the esophagus, most easily seen when the esophagus is filled with contrast medium.

Left Ventricle

The borders of the left ventricle blend with the left atrial margins on both the frontal and lateral radiographs (see Fig. 10.1). On both projections, the slightly convex left ventricular border extends to the diaphragm. The cardiac apex can be displaced inferiorly and laterally when the left ventricle is dilated due to aortic or mitral regurgitation. When the ventricle is hypertrophied because of aortic stenosis or hypertrophic cardiomyopathy, it may be rounded and the apex may be elevated.

Right Atrium

The right atrium forms a gentle convex border with the right middle lobe (see Fig. 10.1a). The margins of the right atrium blend with the inferior and superior vena cavae. The border of the inferior vena cava below the right atrium is usually straight [8]. On the lateral view, the right atrium is not seen directly because this chamber does not form a cardiac border.

Right Ventricle

The right ventricle cannot be visualized directly on the frontal projection because it is not border-forming. A large right ventricle can displace the left ventricle posteriorly and to the left, causing cardiac enlargement on the frontal view. On the lateral view, the right ventricle comprises the anterior margin of the heart in the subxiphoid area, occupying the inferior one-third of the thorax (see Fig. 10.1b). A dilated right ventricle extends superiorly into the retrosternal space [9].

Azygos Vein

The azygos vein is an oval structure seen on the frontal radiograph at the right tracheobronchial angle (see Fig. 10.1a). The size of the azygos vein is a good marker of cardiovascular dynamics. It enlarges in left and right heart failure, obstruction of the superior vena cava, and absence of the intrahepatic segment of the inferior vena cava (see Fig. 10.5) [10]. A change in size of the azygos vein will parallel changes in pulmonary venous pressure, making it a useful radiographic indicator of congestive heart failure.

Specific Abnormalities

Abnormal Pulmonary Blood Flow and Pulmonary Edema

Pulmonary blood flow reflects the hemodynamics of the heart itself. Increased, decreased, or asymmetrical pulmonary blood flow can be recognized on chest radiographs and correlated with other signs of disease.

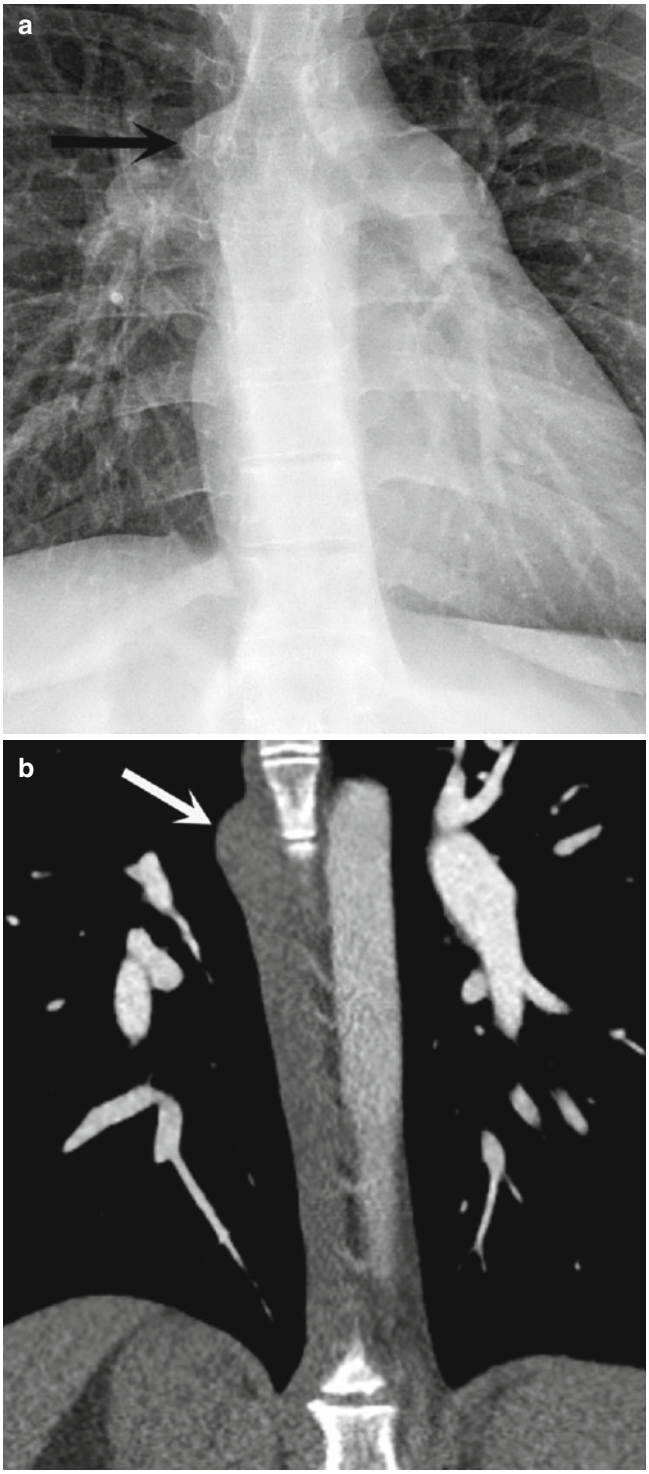

Fig. 10.5 Azygos enlargement in interrupted inferior vena cava. (**a**) There is a prominent bulge (*arrow*) adjacent to the right tracheobronchial angle. (**b**) CT confirms a dilated azygos vein in the setting of an interrupted inferior vena cava

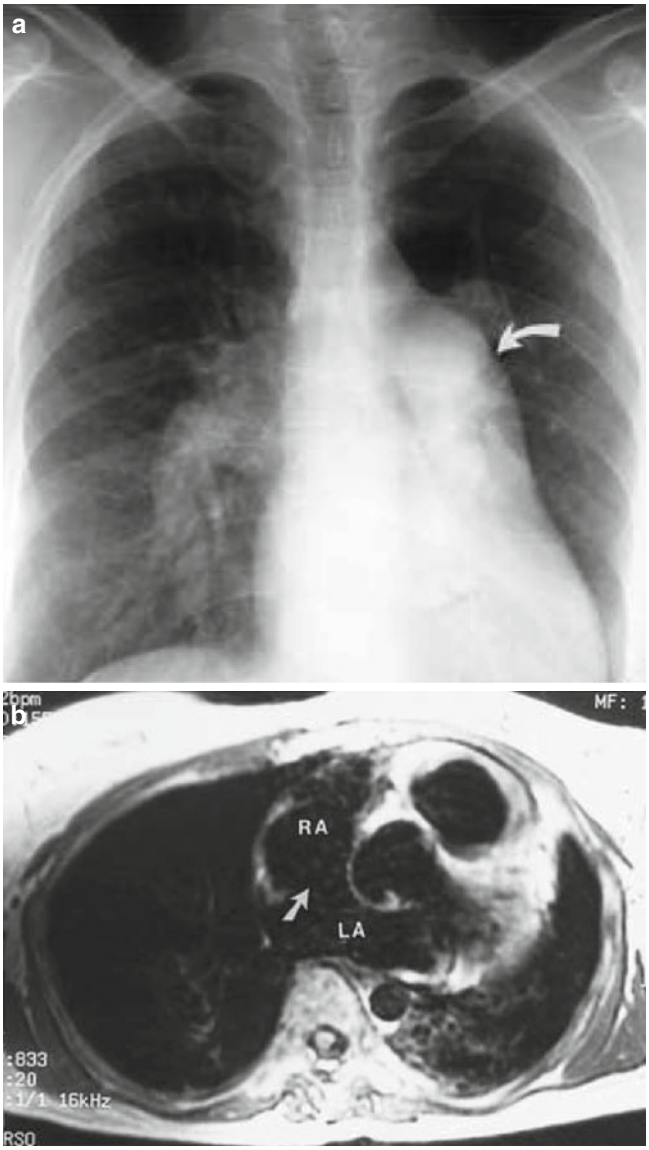

Fig. 10.6 Pulmonary arterial hypertension secondary to Eisenmenger syndrome in a 32-year-old woman with atrial septal defect. (**a**) Frontal chest radiograph. The main (*arrow*), left, and right pulmonary arteries are enlarged. (**b**) Transverse electrocardiographically gated spin echo MRI image shows a large defect (*arrow*) of the atrial septum. *LA* left atrium, *RA* right atrium

The size of the pulmonary arteries is related either to blood flow and blood pressure or to pressure alone [4]. Enlarged pulmonary arteries are present in a variety of conditions including left-to-right shunt, increased cardiac output due to chronic anemia or pregnancy, and pulmonary hypertension, which may be primary or may be secondary to conditions such as chronic interstitial lung disease, emphysema, Eisenmenger syndrome, or chronic thromboembolism (see Fig. 10.6). A left-to-right shunt can often be distinguished from pulmonary arterial hypertension by noting the size of vessels in the periphery of the lung. In the setting of a left-to-right shunt, the pulmonary arteries are typically enlarged out to the periphery due to increased blood flow, whereas in pulmonary arterial hypertension, the pulmonary arteries are enlarged centrally and smaller in the lung

periphery due to vessel constriction. Central pulmonary artery calcification indicates chronic, severe pulmonary arterial hypertension [11]. A prominent convex main pulmonary artery may also be seen in normal individuals, particularly teenage girls, marathon runners, and during the third trimester of pregnancy.

Elevation of pulmonary venous pressure can be due to left ventricular failure, mitral stenosis, and other causes of vascular obstruction distal to the pulmonary arterial bed. As pulmonary venous pressure increases, pulmonary interstitial edema and pleural effusions occur. Radiographically, thin horizontal septal lines, also called "Kerley B lines," are visible at the lung bases (see Fig. 10.7a,b), and subpleural thickening is seen along fissures [12, 13]. Further increases in pulmonary venous pressures cause alveolar edema. In the setting of alveolar edema, chest radiographs demonstrate opacities that may involve the central portions of the lungs, producing a "batwing" appearance (see Fig. 10.7c). If the pulmonary edema is related to heart failure, the cardiac silhouette is often enlarged. Acute pulmonary edema is rarely associated with dilated vessels and redistribution of blood flow to the apices (cephalization) as the vessels are not compliant. Cephalization is usually only seen in long-standing pulmonary venous hypertension such as in patients with mitral stenosis or prolonged left heart failure [13]. An important point is the radiographic findings of pulmonary edema may lag the resolution of symptoms by hours to days.

Valvular Heart Disease

Isolated aortic valve stenosis is frequently related to a congenital bicuspid valve in younger individuals (see Fig. 10.8). As a patient ages, a tricuspid aortic valve can also undergo degeneration leading to aortic stenosis. Mild to moderate aortic stenosis causes left ventricular hypertrophy. Radiographically, the right side of the ascending aorta enlarges due to post-stenotic dilatation (see Fig. 10.3). If valve calcification is seen on a chest radiograph, this typically indicates severe aortic stenosis (see Fig. 10.9). The left ventricular border may be rounded, or the cardiac apex may be elevated due to concentric hypertrophy of the left ventricle [14]. More severe narrowing of the valve can lead to enlargement of the left ventricle and atrium [15], in proportion to the degree of stenosis and the severity of associated mitral regurgitation. Pulmonary venous hypertension and pulmonary edema also can develop in patients with severe aortic stenosis.

Aortic regurgitation can develop in a stenotic valve, or it can be due to rheumatic valvulitis, infective endocarditis, aortic dissection, or annular dilatation resulting from enlargement of the ascending aorta in conditions such as annuloaortic ectasia. With mild aortic regurgitation, the heart size usually remains normal, and the ascending aorta is normal or mildly dilated. Enlargement of the left atrium suggests coexisting mitral regurgitation. In patients with moderate or severe aortic regurgitation, the left ventricle and the aorta are enlarged. In contrast to aortic stenosis, diffuse dilatation of the aorta can occur in patients with aortic regurgitation. When aortic regurgitation is secondary to annuloaortic ectasia, the aortic root is disproportionately enlarged. Valve calcification often occurs in patients with aortic insufficiency due to a congenital bicuspid valve or rheumatic valve disease but is often not visualized on the chest radiograph. In chronic aortic regurgitation, the left ventricle is enlarged, but the lungs appear essentially normal [16]. When aortic regurgitation is acute, such as in trauma or dissection, there is often pulmonary edema without left ventricular enlargement.

Mitral stenosis is most commonly secondary to rheumatic heart disease with mild enlargement of the left atrium as the initial radiographic manifestation. When the stenosis is more severe, the left atrium dilates further, and the left atrial appendage can enlarge disproportionately [17]. Pulmonary venous hypertension and cephalization develops later in the course of the disease, and the central pulmonary arteries enlarge (see Fig. 10.4). The mitral valve is frequently calcified. The left ventricle is normal in most patients with mitral stenosis unless there is concomitant aortic stenosis or mitral regurgitation.

Chronic mitral regurgitation is due to a variety of causes, including myxomatous valve prolapse, ischemic cardiomyopathy, rheumatic heart disease, and calcification of the mitral annulus. Chest radiographs show enlargement of the left atrium and left ventricle (see Fig. 10.10). Because of volume overload and elevated pressure, chamber enlargement is often severe. Acute mitral regurgitation can be caused by rupture of the chordae tendineae or papillary muscles, ischemic dysfunction, and bacterial endocarditis. Although the heart size may be normal, these patients have left heart failure, which causes severe pulmonary alveolar edema. Occasionally asymmetric pulmonary edema, more severe in the right upper lobe, can result from selective retrograde flow from the mitral valve into the right upper lobe pulmonary veins [18]. The valve can be evaluated and the regurgitant flow can be quantified with either echocardiography or MRI.

Tricuspid valve regurgitation (see Fig. 10.10) can be due to ischemic cardiomyopathy, rheumatic heart disease, Ebstein anomaly, and other causes. Typically the right-sided chambers enlarge, and the right atrium can be disproportionately dilated [19]. Patients with tricuspid regurgitation can have massive cardiac enlargement, known as a "wall-to-wall heart."

Ischemic Heart Disease

Several imaging techniques can be used for evaluation of ischemic heart disease, including coronary angiography,

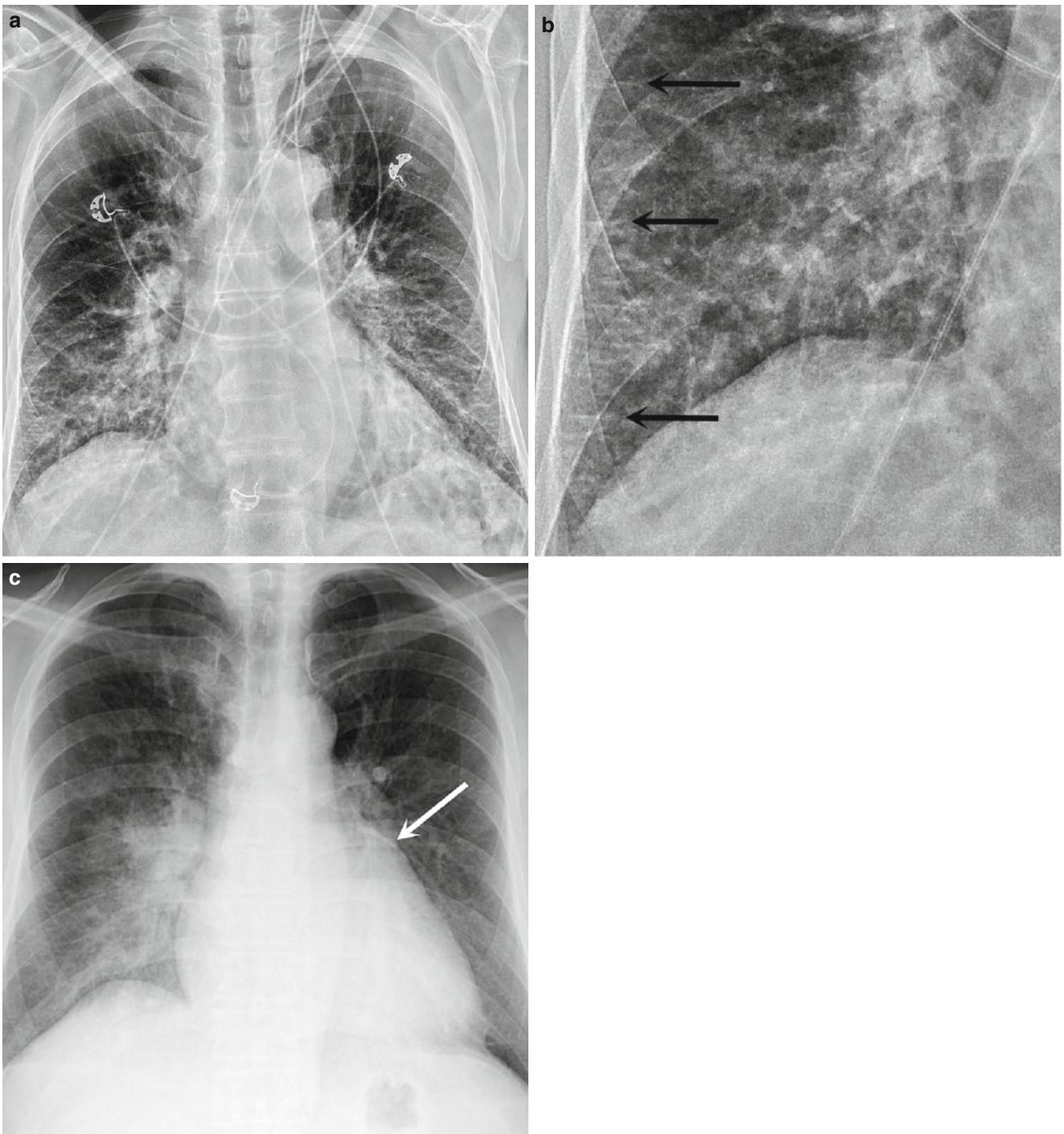

Fig. 10.7 Congestive heart failure. (**a**) Radiograph performed when the patient was in acute cardiac decompensation. The cardiac silhouette is enlarged, and there is cephalization of the pulmonary vasculature. (**b**) Kerley B lines are identified in the right lower lobe, indicating pulmonary interstitial edema. (**c**) Radiograph in a different patient shows pulmonary edema with alveolar opacities. Convexity of the left heart border (*arrow*) indicates left atrial appendage enlargement and coexisting rheumatic mitral stenosis

radionuclide scintigraphy, echocardiography, cardiac CT, and MRI. In patients with ischemic cardiomyopathy, the chest radiograph can be completely normal, even in patients who have severe disease. However, many of these patients have cardiomegaly, especially left ventricular enlargement. These patients may also have a left ventricular aneurysm related to an old myocardial infarction. Pulmonary edema may be present, especially in patients who are acutely short of breath.

Dressler syndrome, or post-myocardial infarction syndrome, may present with enlargement of the cardiac

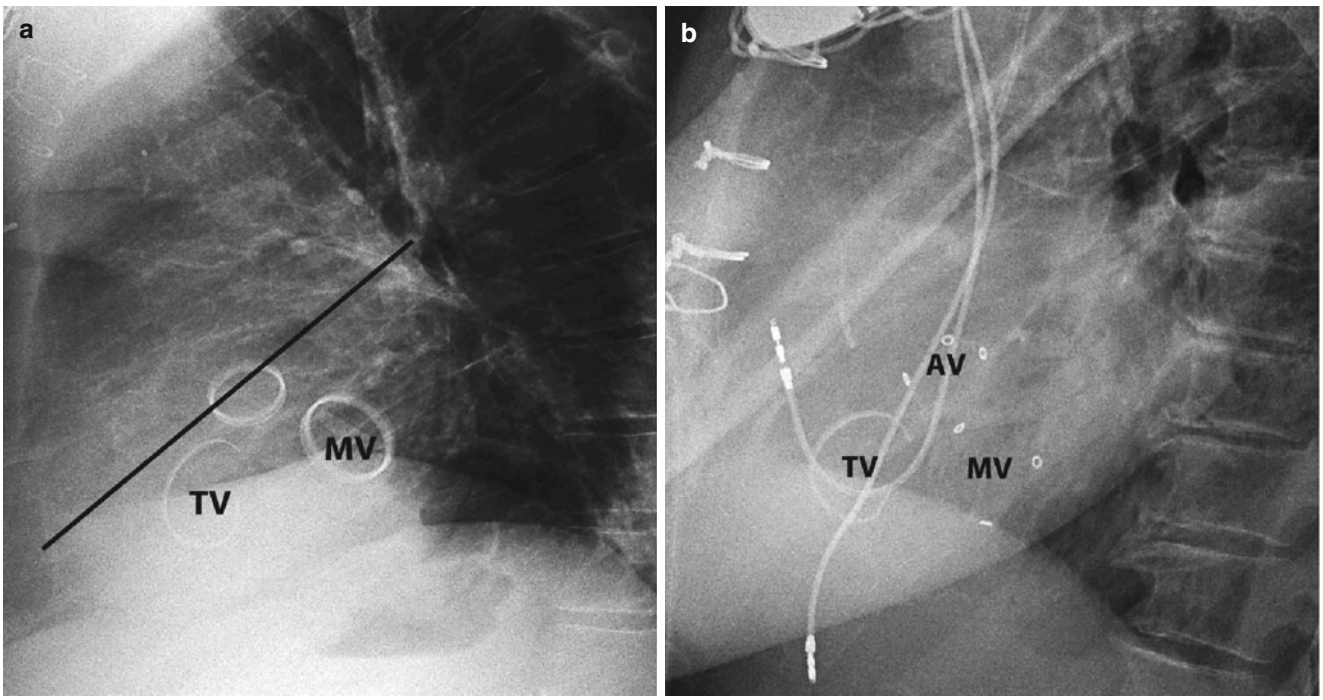

Fig. 10.8 (**a**) Lateral radiograph shows method of defining the cardiac valves. A *line* drawn from the carina to the point of the sternal contact with the diaphragm will pass through the aortic valve. The mitral valve (*MV*) is located inferiorly and posteriorly to the aortic valve. The tricuspid valve (*TV*) is immediately inferior to the line. (**b**) Lateral radiograph in this second example demonstrates different configuration of the aortic valve, mitral valve, and tricuspid valve

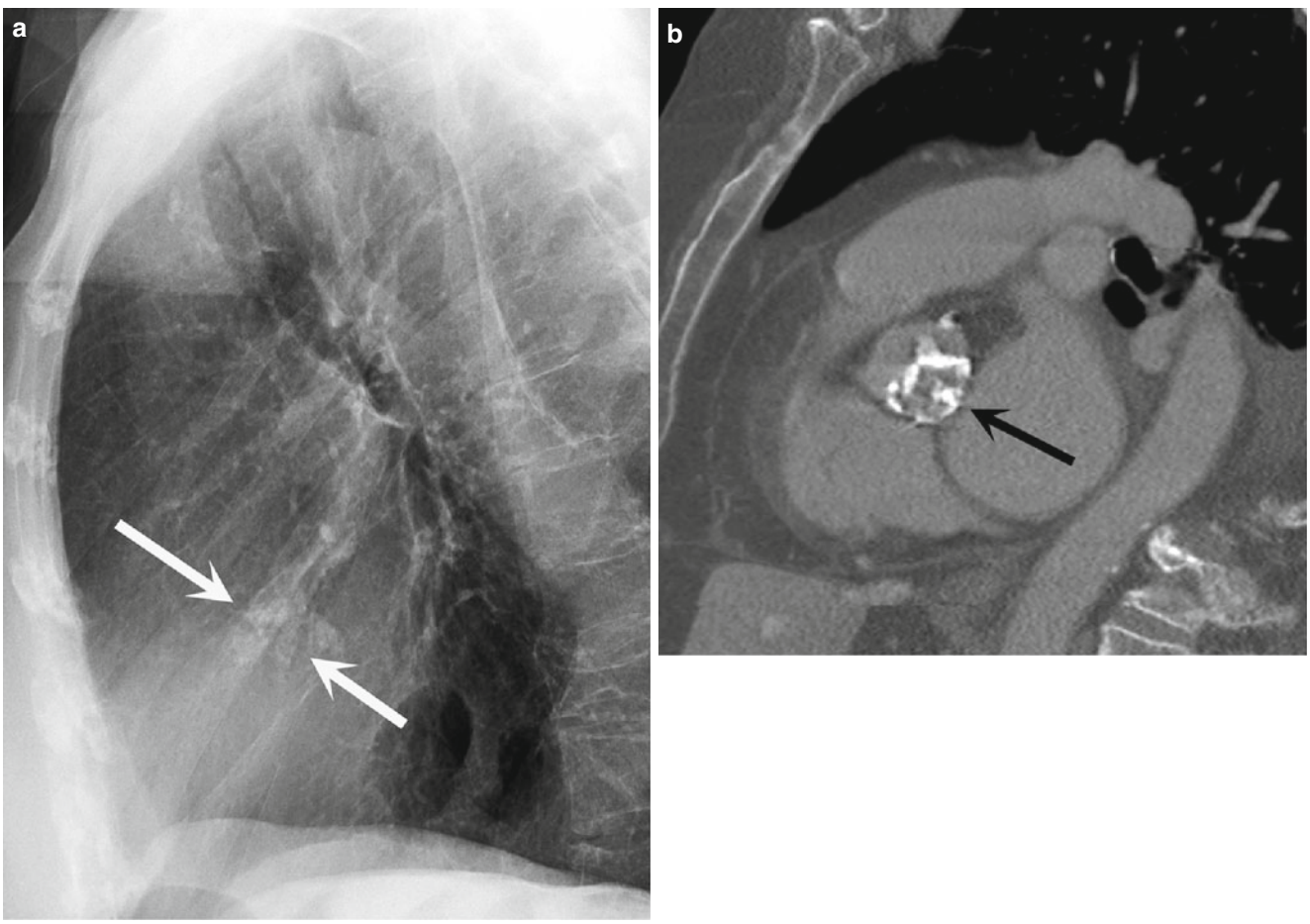

Fig. 10.9 Lateral radiograph (**a**) and sagittal CT (**b**) show extensive aortic valvular calcification (*arrows*) in this patient with severe aortic stenosis

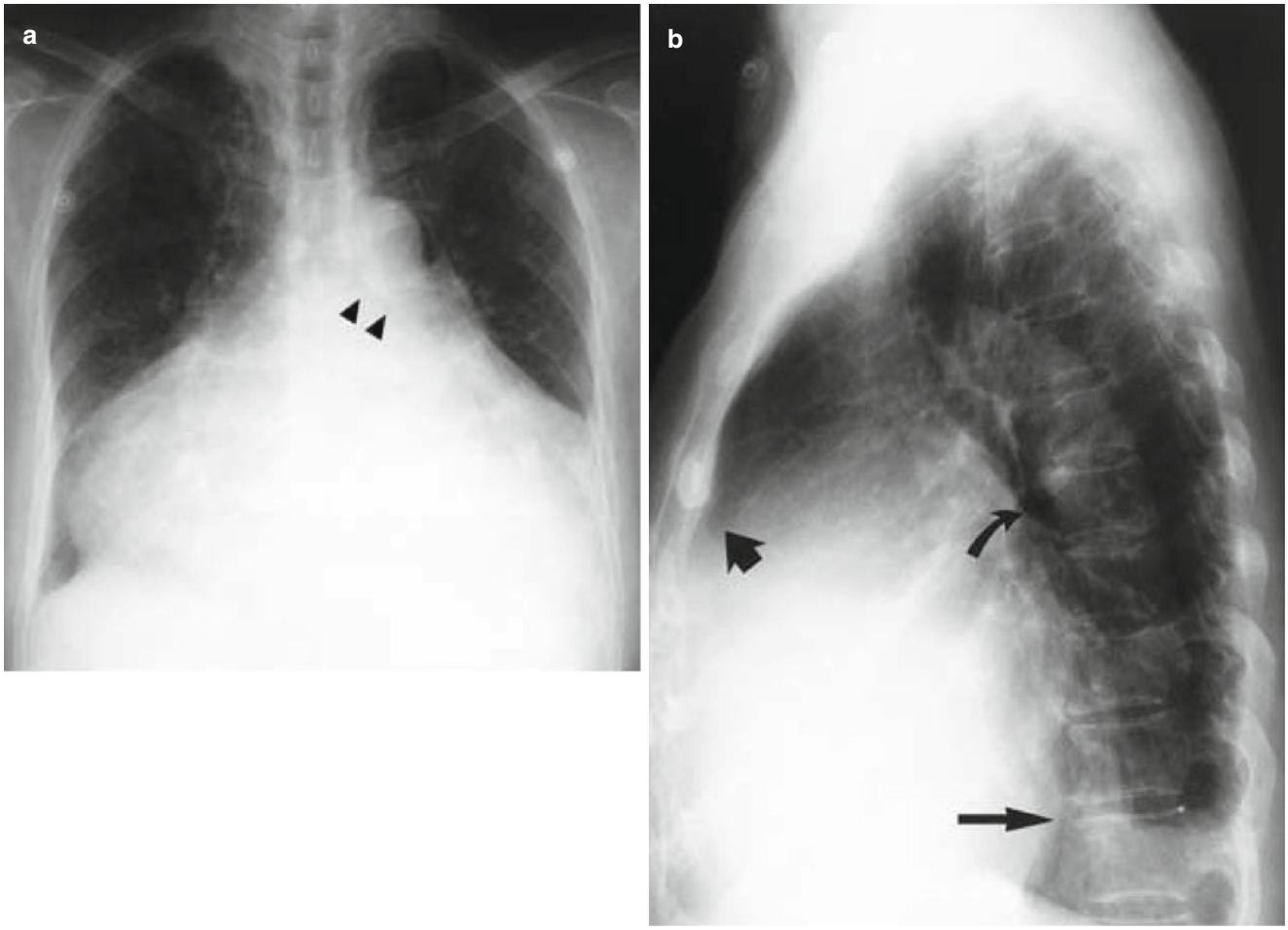

Fig. 10.10 Severe tricuspid and mitral regurgitation. (**a**) Frontal projection reveals a markedly enlarged cardiac silhouette with global cardiomegaly. The prominent right heart border indicates severe right atrial dilatation. The elevation of the left mainstem bronchus (*arrowheads*) suggests left atrial enlargement. (**b**) Lateral view demonstrates enlargement of the right ventricle (*short*, *wide arrow*), left ventricle (*long*, *straight arrow*), and left atrium (*curved arrow*)

silhouette due to pericardial effusion. Pleural effusion (usually unilateral on the left side) is common, and pulmonary consolidation is present in a minority of patients [20].

Occasionally a left ventricular aneurysm may develop after myocardial infarction. A true aneurysm is most frequently located at the cardiac apex or on the anterior ventricular wall. On chest radiographs, the aneurysm appears as a focal bulge along the left heart border [21]. A thin rim of calcification is sometimes seen within the wall of the aneurysm. A false aneurysm can arise after left ventricular rupture secondary to acute transmural infarction [22]. Although most patients with cardiac rupture die immediately, in a small percentage the rupture is contained by the surrounding soft tissues, resulting in a false aneurysm. Chest films can be normal or will demonstrate a contour abnormality, most commonly along the posterior or diaphragmatic aspect of the heart [22]. Definitive diagnosis of a false aneurysm is established by MRI, CT, or echocardiography. Cross-sectional imaging can differentiate a false aneurysm, with its narrow neck, from a true aneurysm, which has a wide neck communicating with the ventricular chamber. Distinction is important as false aneurysms are treated surgically because they are contained only by a single layer of adventitia and are thus more prone to rupture.

Papillary muscle rupture, an unusual complication of myocardial infarction, demonstrates a wide spectrum of findings, from no abnormality to marked cardiomegaly and pulmonary edema. Echocardiography or MRI can be performed to diagnose the abnormal mitral valve leaflets and to quantify the severity of mitral regurgitation [23].

In patients with dilated cardiomyopathy and ischemic cardiomyopathy, the left ventricular ejection fraction is decreased. Left ventricular and later biventricular failures develop in most patients. Radiographic presentation can vary from a normal heart to diffuse globular enlargement, which may simulate a large pericardial effusion.

Coronary artery calcification is an indicator of atherosclerosis, and the quantity of calcification correlates significantly

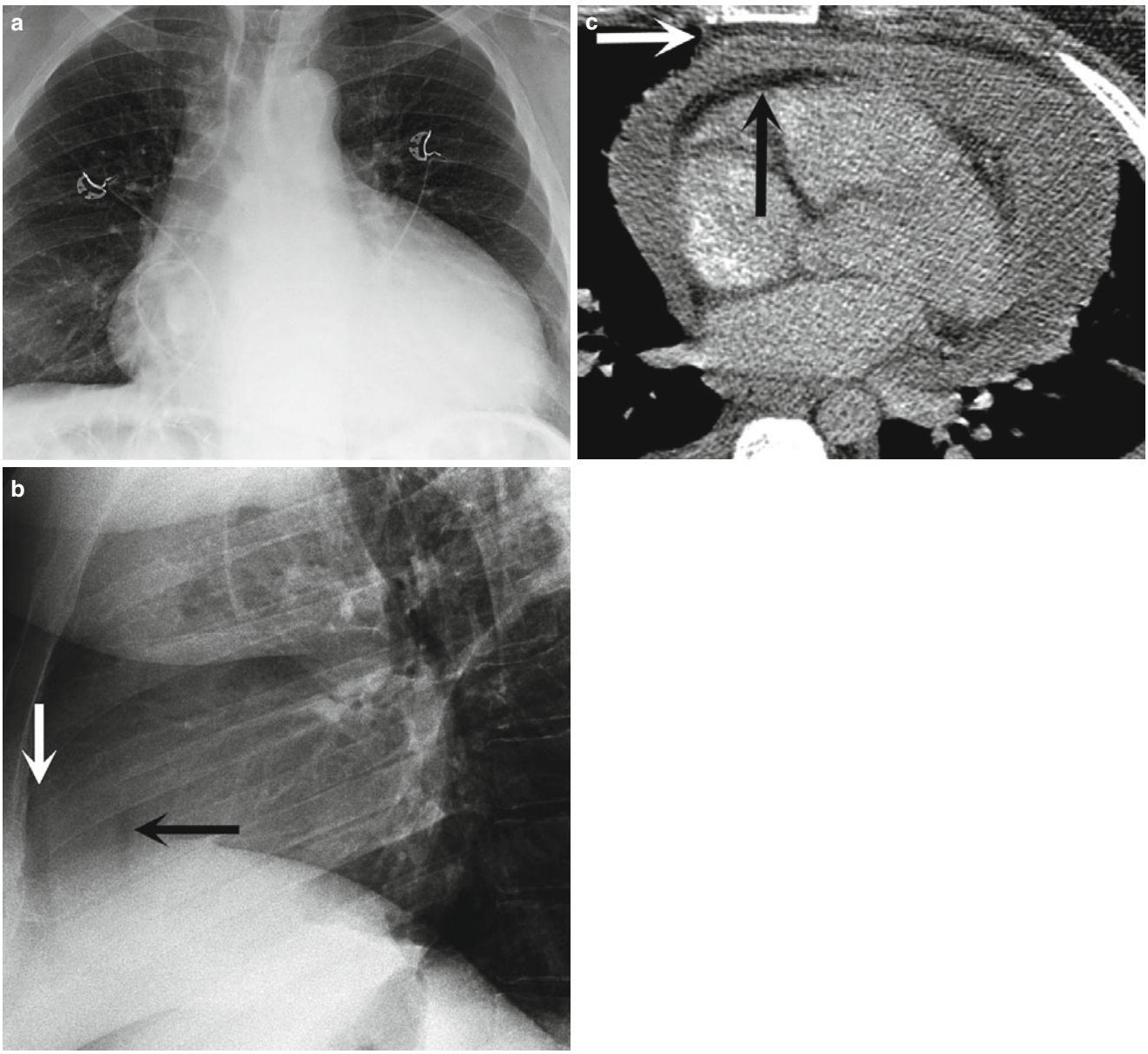

Fig. 10.11 Pericardial effusion in a man with invasive thymic carcinoma. (**a**) PA radiograph shows global cardiomegaly with obscuration of the hilar structures. (**b**) The lateral view shows the "fat pad or Oreo cookie sign." There is a dense layer of fluid (*arrows*) between the lucent epicardial and pericardial layers of fat (*arrows*). (**c**) Contrast-enhanced CT scan demonstrates a large pericardial effusion (*arrows*)

with the total atherosclerotic burden [24]. Coronary artery calcification may be identified by both radiography and CT although CT has the highest diagnostic accuracy for detection of coronary artery calcification [24].

Pericardial Disease

On the lateral chest radiograph, the normal pericardium is identified in some patients as a curvilinear soft tissue opacity between the pericardial and subpericardial fat. Because of their excellent contrast resolution, CT and MRI depict the pericardium more readily than chest radiographs [25, 26].

A small pericardial effusion is usually not seen on the chest radiograph. As the quantity of pericardial fluid increases, the cardiac silhouette may acquire a "water bottle" or globular configuration (see Fig. 10.11a). The normal bulges and indentations of the cardiac borders may become obscured, and the contours of the heart may become smooth and featureless. Because a pericardial effusion can cause enlargement of the cardiac silhouette [26], it may be difficult to distinguish pericardial effusion from

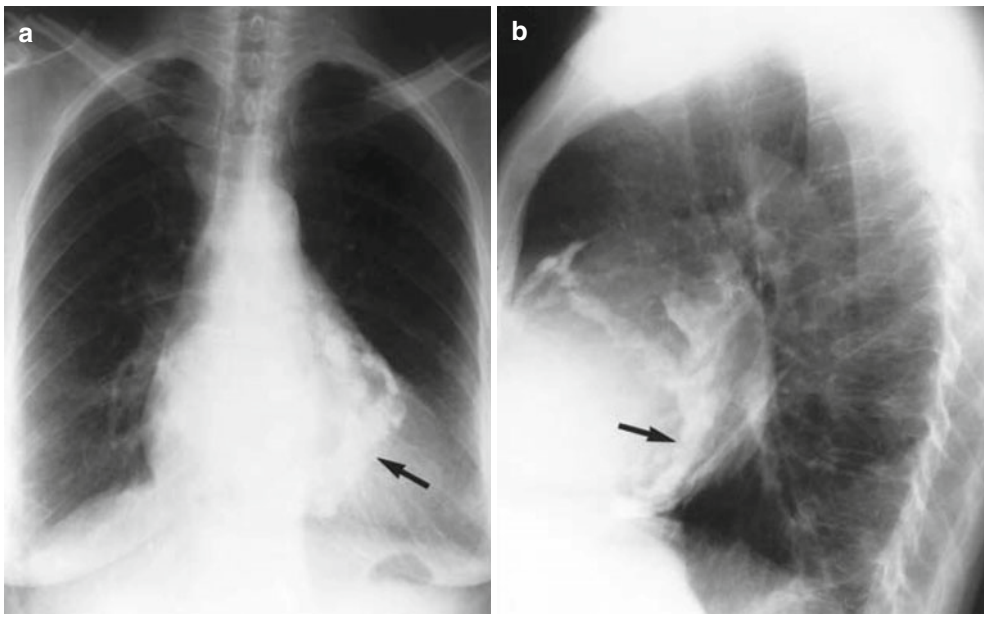

Fig. 10.12 Calcific pericarditis in a patient with a history of tuberculosis. (**a**) Frontal and (**b**) lateral radiographs demonstrate dense calcium (*arrows*) in the interventricular groove

cardiomegaly. Since the pericardium extends to the main pulmonary artery, a large pericardial effusion can obscure the hilar vessels, which should not occur with cardiomegaly alone. Occasionally, pericardial effusion may be seen on a lateral chest radiograph as an opaque band between the pericardial fat and the subpericardial fat, known as the "fat pad sign" or "Oreo cookie sign" (see Fig. 10.11b). Although this sign is specific for a pericardial effusion, its sensitivity is limited.

Echocardiography is more sensitive than plain radiographs for the diagnosis of pericardial effusion [27]. When a pericardial effusion is suggested by clinical or radiographic findings, echocardiography can be used for more definitive evaluation. CT and MRI also can identify pericardial effusion and are specifically useful for the identification of a hemorrhagic or loculated effusion (see Fig. 10.11c) [28].

Constrictive pericarditis may occur as a result of open heart surgery, radiation therapy, viral or tuberculous infection, uremia, or hemopericardium [29]. The cardiac silhouette usually is normal or small, and the right heart border may be flattened [30]. A pericardial effusion is present in the majority of these patients, and enlargement of the left atrium and azygos vein is seen in a minority. In a small proportion of patients with pericardial constriction, calcification of the pericardium may be seen. Pericardial calcification is most often due to tuberculous or viral pericarditis and is seen most readily along the anterior and inferior borders of the heart and in the atrioventricular and interventricular grooves (see Figs. 10.12 and 10.13).

Because constrictive pericarditis and restrictive cardiomyopathy may have overlapping clinical presentations and findings, MRI and CT can play an important role in distinguishing the two diagnoses. Pericardial thickening of ≥4 mm is highly sensitive and specific for constrictive pericarditis [28]. Ancillary supportive findings include abnormal diastolic septal motion ("septal bounce"), enlargement of the right atrium, inferior vena cava, and hepatic veins, in addition to a narrowed, "tubular" configuration of the right ventricle. Although pericardial calcification and thickening indicate chronic pericardial inflammation and can be used to support the diagnosis of pericardial constriction, the diagnosis must be based on clinical criteria in addition to imaging findings.

When a mediastinal mass is identified on chest radiography, CT or MRI may be performed for more precise evaluation (see Fig. 10.14). A pericardial cyst appears as a smooth, well-marginated fluid-filled paracardiac structure. Because they are benign and generally asymptomatic, these cysts may be clinically important only because cross-sectional imaging must be performed to differentiate a cyst from a solid mass. Echocardiography also can be used to establish the diagnosis of a pericardial cyst.

Congenital Heart Disease in the Adult

There are three groups of adults with congenital heart disease: those who were treated surgically in childhood, those who were diagnosed as children but did not receive surgical intervention, and those whose disorder was not recognized until adulthood.

Coarctation of the Aorta

In adults, a focal juxtaductal stenosis is most common. Chest radiographs may demonstrate a characteristic abnormal

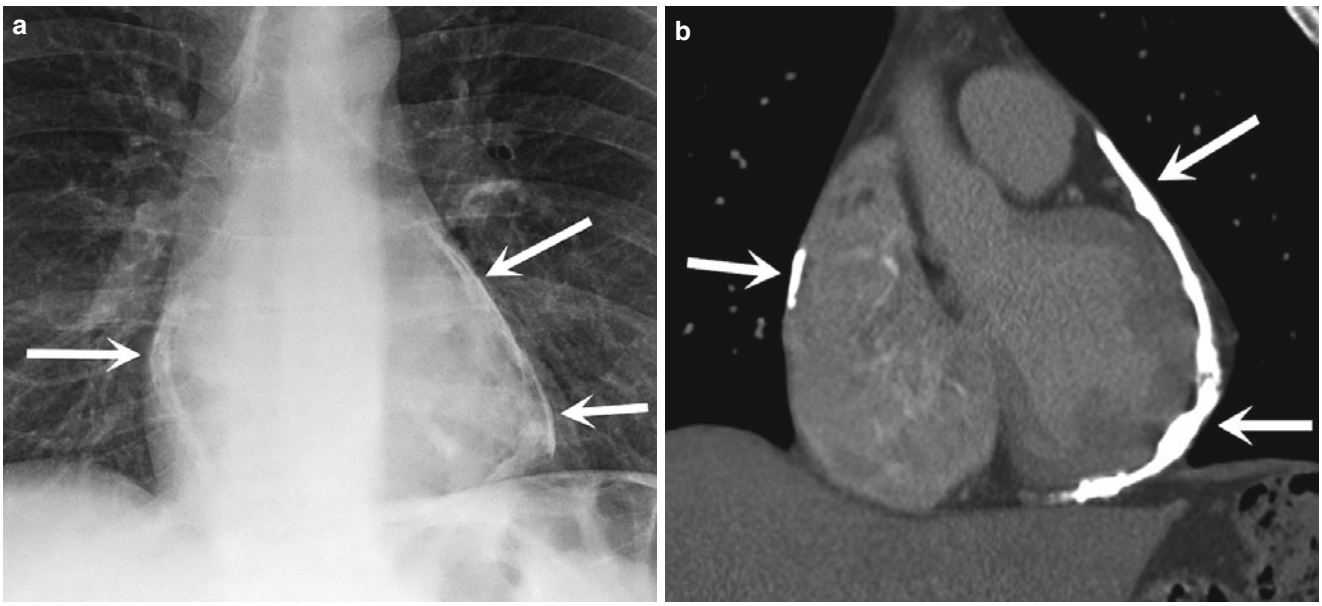

Fig. 10.13 Frontal (**a**) radiograph and coronal CT (**b**) in a patient with constrictive pericarditis shows pencil-thin calcification (*arrows*) surrounding much of the pericardium

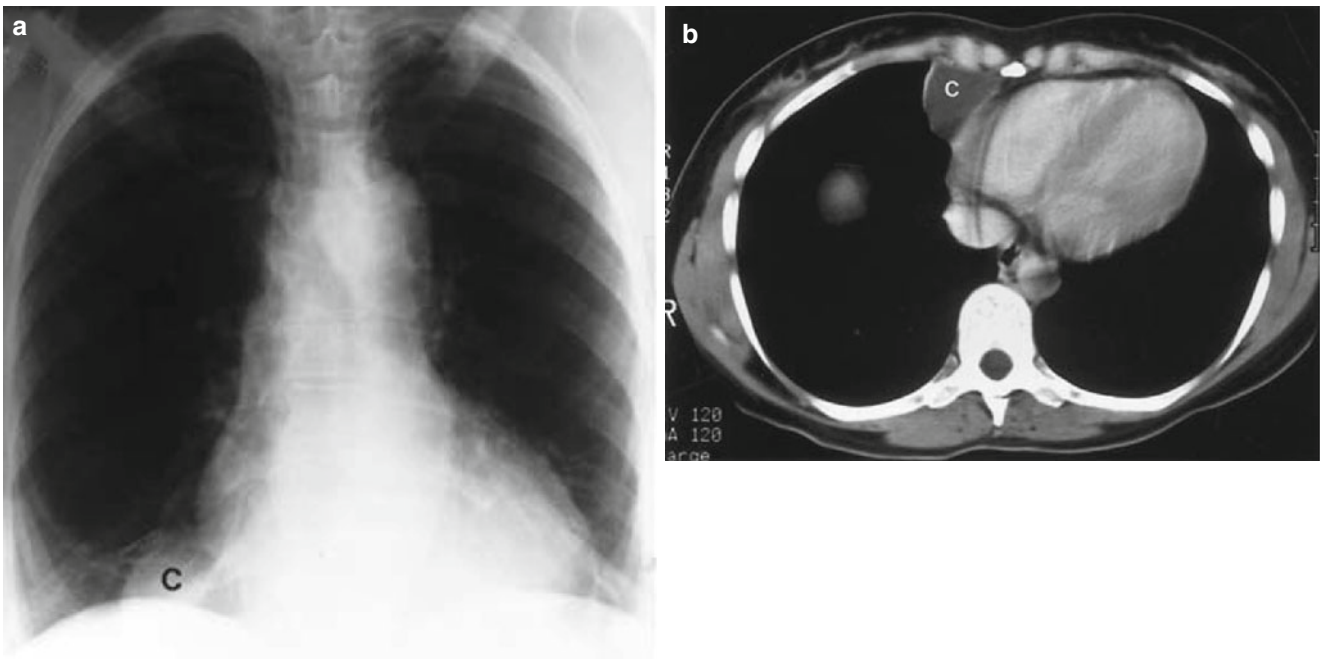

Fig. 10.14 Pericardial cyst. (**a**) Frontal chest film reveals a smoothly marginated round mass in the right cardiophrenic angle. Main differential considerations for this mass on the chest radiograph include a prominent pericardial fat pad, pericardial cyst, and enlarged lymph nodes related to lymphoma or metastatic disease. (**b**) Contrast-enhanced CT demonstrates a well-circumscribed, thin-walled mass of fluid density, consistent with a pericardial cyst

contour of the aortic arch, known as the "figure 3" sign, which is a double bulge immediately above and below the region of the aortic knob (see Fig. 10.15a) [31]. Bilateral symmetrical rib notching in an older child or adult is diagnostic of coarctation. MRI or CT can be used in place of diagnostic angiography for the evaluation of coarctation of the aorta both before and after surgical repair (see Fig. 10.15b) [32]. Advantages of MRI over CT include the absence of ionizing radiation and the capability of obtaining quantitative functional information such as pressure gradients and volume of collateral flow.

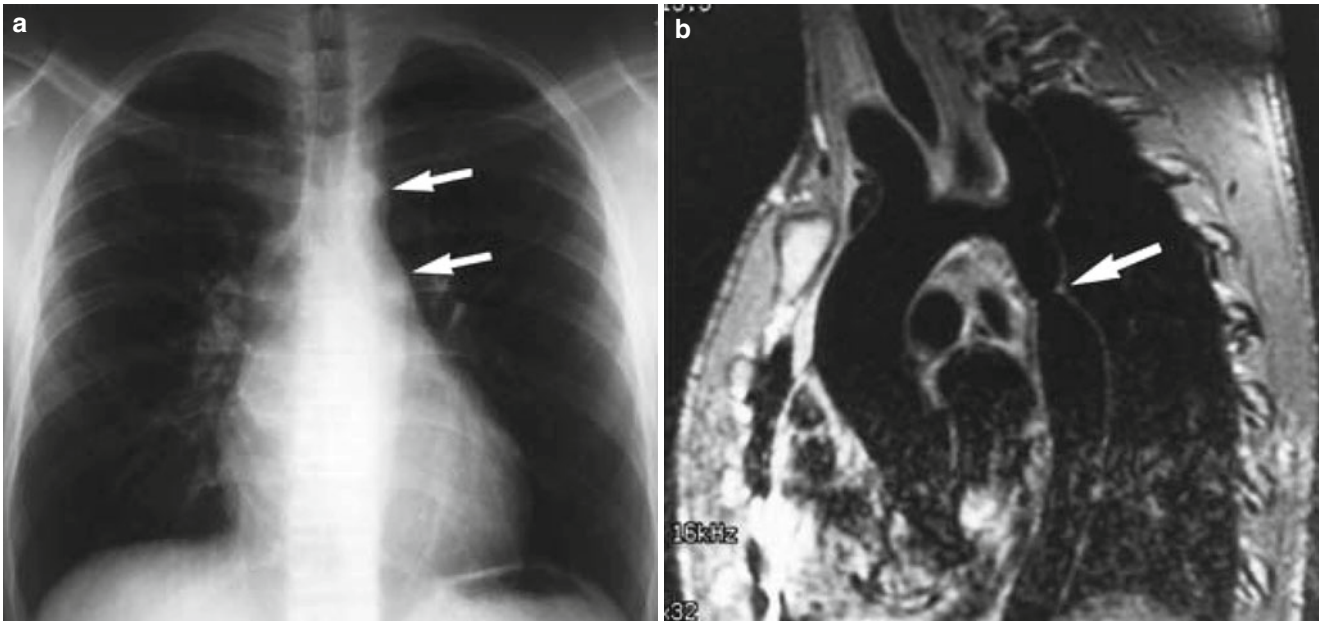

Fig. 10.15 Young man with hypertension. (**a**) Frontal chest radiograph shows a "figure 3" sign (*arrows*), consistent with coarctation of the aorta. Rib notching is not seen on this film. (**b**) Oblique sagittal electrocardiographically gated spin echo MRI image demonstrates a severe discrete postductal narrowing of the aorta

Left-to-Right Shunts

Ostium secundum atrial septal defect (ASD) is the most common left-to-right shunt diagnosed in adult life, accounting for over 40 % of adult congenital heart defects [33]. Although the chest radiograph may be normal in a patient with a small shunt, typically the main pulmonary artery, the peripheral pulmonary branches, the right atrium, and the right ventricular borders are enlarged (see Fig. 10.6a). Echocardiography can delineate the size and location of the ASD as well as associated abnormalities such as mitral valve prolapse. MRI can be performed if echocardiography does not reveal the ASD (see Fig. 10.6b).

If a ventricular septal defect (VSD) is small, the chest film is normal. However, the pulmonary arteries, both ventricles and the left atrium, are enlarged if the left-to-right shunt is large or if there is secondary pulmonary hypertension. Echocardiography usually will demonstrate the site of the defect. MRI is performed in certain cases to evaluate associated abnormalities or to define certain lesions such as a supracristal VSD, which may be difficult to image by echocardiography [34].

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Cardiac Catheterization

11

Nirat Beohar, Mark J. Ricciardi, and Charles J. Davidson

Indications for Diagnostic Cardiac Catheterization

While the most common indication for cardiac catheterization in an adult population is the identification of the extent and severity of coronary artery disease, diagnostic cardiac catheterization is recommended whenever it is clinically important to define the presence or severity of a suspected cardiac lesion that cannot be evaluated adequately by noninvasive techniques. The recommendation for cardiac catheterization should always be based on an appropriate assessment of risk-benefit ratio. Cardiac catheterization should be used in combination with complementary noninvasive tests such as echocardiography, cardiac magnetic resonance (CMR), or computerized tomography (CT). This allows for catheterization to be directed and simplified without obtaining redundant information.

The specific indications for cardiac catheterization have been elucidated in the AHA/ACC/SCAI guidelines on diagnostic coronary angiography [1], percutaneous coronary interventions [2], ST-elevation myocardial infarction (MI) [3], unstable angina/non-ST-elevation MI [4], coronary artery bypass surgery [5], valvular heart disease [6], chronic heart failure [7], and congenital heart disease [8]. Additional guidance is provided by the so-called appropriateness criteria [9]. The optimal timing for catheterization and revascularization has also been described in these guidelines. As an example see Table 11.1.

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There is no true absolute contraindication to cardiac catheterization other than refusal of the competent patient. The relative contradictions of cardiac catheterization are summarized in Table 11.2.

Technical Aspects of Cardiac Catheterization

Catheterization Laboratory Facilities

Cardiac catheterization is performed in traditional hospital-based laboratories with in-house cardiothoracic surgical programs, hospital-based laboratories without on-site surgical programs, freestanding laboratories, and mobile laboratories. At present about 75 % of cardiac catheterization laboratories have on-site surgical backup. High-risk diagnostic studies and all elective percutaneous interventions should be performed in laboratories with on-site surgical facilities [2].

Laboratory Caseload

In order to maintain proficiency, laboratories for adult studies should perform a minimum of 300 procedures per year. The minimum caseload for established physicians in practice has not been established [10]. According to ACGME guidelines for diagnostic catheterization, physicians in training must spend a total of 8 months and perform >300 cases including >200 as a primary operator in order to be credentialed for level II diagnostic cardiac catheterization procedures in practice [11].

Radiographic Equipment

The basic principle of radiographic coronary imaging is that radiation produced by the x-ray tube is attenuated as it passes through the body and is detected by the image intensifier or a flat panel detector. Iodinated contrast medium injected into the coronary arteries enhances the absorption of x-rays and produces a sharp contrast with the surrounding cardiac tissues. The x-ray shadow is then converted into a visible light image by an image intensifier, displayed on fluoroscopic

C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_11, © Springer Science+Business Media New York 2013

Table 11.1 Indications for coronary arteriography

Class I	Class IIA	Class IIB	Class III
Asymptomatic or stable angina			
CCS class III and IV on medical therapy	CCS class III or IV that improves to class I or II with medical therapy	CCS class I or II angina with demonstrable ischemia but no high-risk criteria on noninvasive testing	Angina in patients who prefer to avoid revascularization
High-risk criteria on noninvasive testing irrespective of angina	Worsening abnormalities on noninvasive testing	Asymptomatic men or postmenopausal women with ≥2 major clinical risks with low-risk criteria on noninvasive testing and no prior CAD	Angina in patients who are not candidates for revascularization or in whom it will not improve QOL
	Patients with angina and severe illness that precludes risk stratification	Asymptomatic patients with prior MI, normal LV function, and no high-risk criteria on noninvasive testing	As a screening test for CAD
	CCS class I or II angina with intolerance to medical therapy		After CABG when there is no evidence of ischemia on noninvasive testing
	Individuals whose occupation affects the safety of others		Coronary calcification on fluoroscopy or EBCT
Unstable angina			
High or intermediate risk for adverse outcome in patients refractory to medical therapy	None	Low short-term risk unstable angina without high-risk criteria on noninvasive testing	Recurrent chest discomfort suggestive of unstable angina but without objective signs of ischemia and with a normal coronary angiogram within the past 5 years
High or intermediate risk that stabilizes after initial treatment			Unstable angina in patients who are not candidates for revascularization
Initially low short-term risk that is high risk on noninvasive testing			
Suspected prinzmetal variant angina			
Postrevascularization ischemia			
Suspected abrupt closure or subacute stent thrombosis after PCI	Recurrent symptomatic ischemia within 12 months of CABG	Asymptomatic post-PCI patient suspected of having restenosis within the first months after PCI because of an abnormal but not high-risk noninvasive test	Symptoms in a post-CABG patient who is not a candidate for revascularization
Recurrent angina and high-risk criteria on noninvasive evaluation within 9 months of PCI	Noninvasive evidence of high-risk criteria occurring anytime after CABG	Recurrent angina without high-risk criteria on noninvasive testing occurring 1 year postoperatively	Routine angiography after PCI or CABG unless part of an approved research protocol
	Recurrent angina inadequately controlled by medications	Asymptomatic post-CABG patient in whom a deteriorating noninvasive test is found	
After STEMI or Non-STEMI			
Spontaneous myocardial ischemia or ischemia provoked with minimal exertion	Suspected MI due to coronary embolism, arteritis, trauma, certain metabolic diseases, or coronary spasm	For a suspected persistent occlusion of the IRA to perform delayed PCI	Patients who are not candidates for or refuse revascularization
Before surgical therapy for acute MR, VSD, true aneurysm or pseudoaneurysm	Survivors of acute MI with LVEF <0.40, CHF, prior PCI or CABG, or malignant ventricular arrhythmias	Coronary arteriography performed without risk stratification to identify the presence of left main or three-vessel CAD	
Persistent hemodynamic instability		All patients after NQWMI	
		Recurrent ventricular tachycardia despite antiarrhythmic therapy without ongoing ischemia	

Table 11.1 (continued)

Nonspecific chest pain			
High-risk features on noninvasive testing	None	Patients with recurrent hospitalizations for chest pain who have abnormal or equivocal findings on noninvasive testing	All other patients with nonspecific chest pain

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Class I: conditions for which there is agreement that the procedure is useful and effective
Class IIa: weight of the evidence is in favor of usefulness and efficacy
Class IIb: weight of the evidence is less well established by evidence and opinion.
Class III: conditions for which there is general agreement that the procedure is not useful and effective and in some cases may be harmful
CABG coronary artery bypass graft surgery, *CAD* coronary artery disease, *CCS* Canadian Cardiovascular Society, *CHF* congestive heart failure, *EBCT* electron beam computed tomography, *IRA* infarct-related artery, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *MR* mitral regurgitation, *NQWMI* non1/NQ = wave MI, *PCI* percutaneous coronary intervention, *QOL* quality of life, *STEMI* ST-elevation MI, *VSD* ventricular septal defect, *VT* ventricular tachycardia

Table 11.2 Relative contraindications to coronary angiography

Acute renal failure
Chronic renal failure secondary to diabetes
Active gastrointestinal bleeding
Unexplained fever, which may be due to infection
Untreated active infection
Acute stroke
Severe anemia
Severe uncontrolled hypertension
Severe symptomatic electrolyte imbalance
Severe lack of cooperation by patient due to psychological or severe systemic illness
Severe concomitant illness that drastically shortens life expectancy or increases risk of therapeutic interventions
Refusal of patient to consider definitive therapy such as PTCA, CABG, or valve replacement
Digitalis intoxication
Documented anaphylactoid reaction to angiographic contrast media
Severe peripheral vascular disease limiting vascular access
Decompensated heart failure or acute pulmonary edema
Severe coagulopathy
Aortic valve endocarditis
Acute renal failure

Reprinted from Scanlon et al. [1]. With permission from Elsevier
PTCA percutaneous transluminal coronary angioplasty, *CABG* coronary artery bypass grafting

monitors, and stored on 35-mm cinefilm or a digital storage system. High-resolution x-ray imaging is required for optimal performance of catheterization procedures. While a detailed description is beyond the scope of this chapter, Fig. 11.1 shows the necessary angiographic equipment [12]. Flat panel detectors rather than an image intensifier are commonly used and therefore do not use video cameras. The flat panel detector produces a direct digital video signal from the original visible light fluorescence without the intermediate visible light stage. The development of Digital Imaging and Communication (DICOM) standards for cardiac angiography has allowed compatibility among different vendor systems.

Radiation Safety

Radiation effects can be classified as either deterministic effects or stochastic effects. Both have a delay between radiation and effect. Deterministic effects are dose related in that below a certain dose, there is no effect. However, when exceeding a threshold, the severity increases with dose. Examples of deterministic effects include skin erythema, desquamation, cataracts, hair loss, and skin necrosis. Skin injury is the most common deterministic effect from radiation. Early transient erythema can develop within hours, but most skin injuries do not appear for 2–3 weeks following exposure.

Stochastic effects are related to probability and not proportional to dose, although the likelihood of an effect is related to dose. Examples of this effect include neoplasms and genetic defects. The estimated dose range for cardiac catheterization is 1–10 millisievert (mSv), which is the equivalent of 2–3 years of natural background radiation. The typical dose is 3–5 mSv [12].

The main guiding principle of x-ray exposure is ALARA (as low as reasonably achievable). This implies that no level of radiation is completely safe to patients or providers. The dose-area product (DAP) is the absorbed dose to air (air kerma) multiplied by the x-ray beam cross-sectional area at the point of measurement. It is an approximation of the total x-ray energy delivered to the patients and is a measure of the patient's risk of stochastic effect [12]. Another measure of skin dose is the interventional reference point (IRP). This is located 15 cm from the isocenter of the x-ray tube and is an estimation of the skin entrance point of the beam.

The basic principles of minimizing radiation exposure include minimizing fluoroscopic beam on time for fluoroscopy, using beam collimation, positioning the x-ray source and image reception optimally, using the least magnification as possible, changing radiographic projection in long procedures to minimize entrance port skin exposure, recording the estimated patient dose, and selecting equipment with dose-reduction features including low fluoroscopy mode.

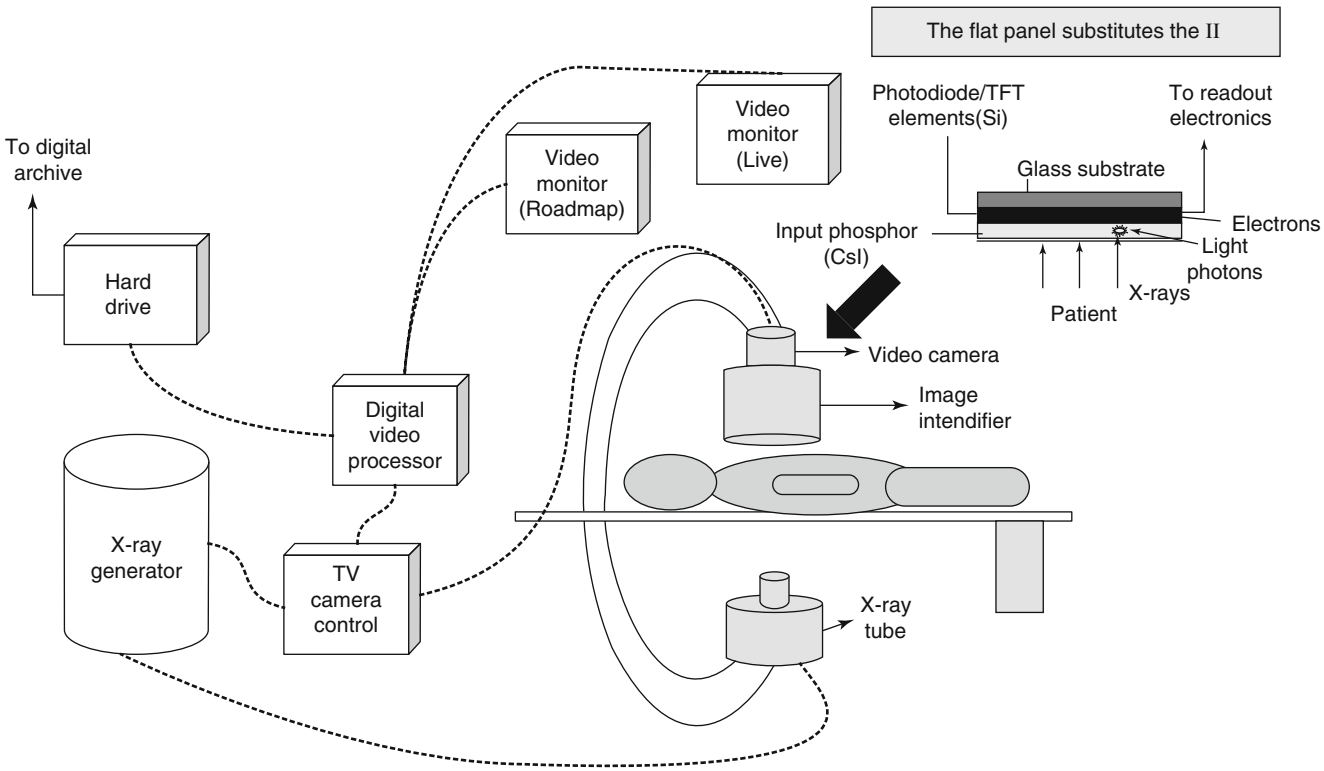

Fig. 11.1 Cineangiographic equipment. The major components include a generator, x-ray tube, image intensifier attached to a positioner such as a C-arm, optical system, video camera, videocassette recorder (*VCR*), analog to digital converter (*ADC*), and television monitors. The x-ray tube is the source of the x-ray beam, which passes superiorly through the patient

For laboratory personnel, the most important factors are maximizing distance from the source of x-rays and using appropriate shielding including lead aprons, thyroid collars, lead eyeglasses, and movable leaded barriers. Severely angulated views, particularly the left anterior oblique view, substantially increase the radiation exposure of the operators.

A method for measuring radiation exposure for personnel is required. It is recommended that two film badges are worn, one on the outside of the apron at the neck and another under the apron at the waist. The latter monitors the effectiveness of the lead apron. The maximum allowable whole body radiation dose per year for those working with radiation is 5 roentgen equivalents man (rem = 50 mSv) or a maximum of 50 rems in a lifetime [12].

Catheterization Laboratory Protocol

Preparation of the Patient for Cardiac Catheterization

Before arrival in the catheterization laboratory, the cardiologist responsible for the procedure should explain the procedure fully, including the risk and benefits, and answer questions from the patient and/or family. Precatheterization evaluation includes obtaining the patient's history, physical examination, and ECG. Routine laboratory studies include complete blood count with platelets, serum electrolytes with creatinine and glucose, prothrombin time with international normalized ratio (INR), and partial thromboplastin time (in patients receiving heparin). Important components of the history that need to be addressed include diabetes mellitus (insulin or non-insulin requiring), kidney disease, anticoagulation status, and peripheral arterial disease, as well as previous contrast media or latex allergy. Full knowledge of any prior procedures, including cardiac catheterizations, PCIs, peripheral arterial interventions or surgery, and cardiac surgery, is necessary.

Patients should be fasting at least 6 h, and an intravenous line should be established. Oral or intravenous sedation is usually administered (e.g., benzodiazepine). Pulse oximetry should be used to monitor respiratory status. Oral anticoagulants should be discontinued and the INR should be less than 1.8 to avoid increased risk of bleeding. Aspirin or other oral antiplatelet agents are continued prior to the procedure. Patients with diabetes mellitus receiving metformin should have the medication discontinued the morning of the procedure and not restarted until renal function is stable at least 48 h after the procedure [13].

Prevention of Contrast-Induced Nephropathy (CIN)

The most important risk factors for CIN are advanced age, chronic kidney disease, congestive heart failure, diabetes mellitus, and the volume of contrast administered [2]. A risk

scoring system is available to predict the risk of CIN using these risk factors and additional variables [14]. The only strategies clearly shown to reduce the risk of CIN are hydration and minimizing the volume of contrast medium. Other than saline hydration, measures that were believed to reduce the risk of CIN (e.g., sodium bicarbonate or N-acetylcysteine administration) have been found to be neutral, to have deleterious effects, or have conflicting data.

Isotonic saline is preferable to half isotonic saline, intravenous hydration is preferable to oral hydration, and hydration for hours before and after the procedure is preferable to bolus of saline immediately before or after contrast administration. A reasonable hydration regimen would be 0.95 saline (1–1.5 ml/kg/h) for 3–12 h before the procedure and continuing for 6–24 h after the procedure. The amount of hydration is dependent on the ventricular function and baseline fluid status.

Prior studies of N-acetyl-L-cysteine and sodium bicarbonate have produced conflicting results. Some, often small, earlier studies suggested benefit, but many other more contemporary studies and meta-analyses found no clear evidence of benefit, and there are potential issues of publication bias and poor methodology issues in several analyses. The recently completed largest randomized study on N-acetyl-L-cysteine and contrast nephropathy in patients undergoing angiographic procedures, ACT (Acetylcysteine for Contrast-Induced Nephropathy Trial), demonstrated no benefit in primary or secondary endpoints. Taken as a whole, there is sufficient data to conclude that N-acetyl-L-cysteine does not prevent contrast-induced AKI in patients undergoing angiographic procedures, and the current PCI guidelines give it a class III indication in prevention of CIN [2].

The correlation between the volume of contrast media and the risk of contrast-induced AKI has been well documented. Thus, minimization of contrast media volume is important to prevent contrast-induced AKI in patients undergoing angiography.

Comparative studies of different contrast media (e.g., low osmolar vs. iso-osmolar, one agent vs. another agent) have produced variable and sometimes contradictory results. Thus, current data are insufficient to justify specific recommendations about low- and iso-osmolar contrast media. This issue is discussed in detail in the 2011 UA/NSTEMI focused update [15]. For guidance on the prevention of CIN in high-risk populations, readers are referred to additional literature on this subject [16].

Contrast Agent-Related Anaphylactoid Reactions

Those with a prior history of contrast medium allergy need prophylaxis before the procedure [17]. The incidence of anaphylactoid reactions to contrast media is ≤1 %, and the incidence of severe reactions may be as low as 0.04 % [18]. In patients with a history of prior anaphylactoid reaction, the recurrence rate without prophylaxis is in the range of 16–44 %. Adequate pretreatment of patients with prior anaphylactoid reactions reduces the recurrence rate to close to zero. A regimen of 50 mg of prednisone administered 13, 7, and 1 h before the procedure (as well as 50 mg of diphenhydramine 1 h before the procedure) has been shown to reduce the risk of recurrent anaphylactoid reaction. In practice, a regimen of 60 mg of prednisone the night before and morning of the procedure (as well as 50 mg of diphenhydramine 1 h before the procedure) is often used. There are minimal data on the "pretreatment" of patients undergoing emergency angiography and PCI. One group has suggested IV steroids (e.g., 80–125 mg of methylprednisolone, 100 mg of hydrocortisone sodium succinate), as well as oral or IV diphenhydramine and possible IV cimetidine [17, 18].

There are no data to suggest that those patients with seafood or shellfish allergies are at risk for an anaphylactoid reaction from exposure to contrast media. Iodine does not mediate seafood, or shellfish, reactions. The iodine in shellfish is not the allergen. Rather, tropomyosin appears to be the allergen. Pretreatment of patients with steroids based only on a history of seafood or shellfish allergy has a small risk of adverse effect (e.g., hyperglycemia in a patient with diabetes) without any demonstrated benefit. The current PCI guidelines do not recommend pretreatment for shellfish or seafood allergy [2].

Catheterization Protocol

The particular technical approach and necessary procedures should be established individually for each patient so that the specific clinical questions can be addressed. In general, hemodynamic measurements and cardiac output determination should be made before angiography to reflect basal conditions most accurately and to guide angiography. However, in a high-risk case, the approach is to gather the most important diagnostic information first due to the possibility of an adverse event.

Right-heart catheterization is indicated when a patient has LV dysfunction, congestive heart failure, complicated acute myocardial infarction, valvular heart disease, suspected pulmonary hypertension, congenital disease, intracardiac shunts, or pericardial disease.

Catheters and Associated Equipment

Catheters used for cardiac catheterization are available in various lengths, sizes, and configurations. Typical catheter lengths vary between 50 and 125 cm, with 100 cm being the most commonly used length for adult left-heart catheterization via the femoral approach (Fig. 11.2). The outer diameter of the catheter is specified using French units, where one French unit (F) = 0.33 mm. The inner diameter of the catheter is smaller than the outside diameter owing to the thickness of

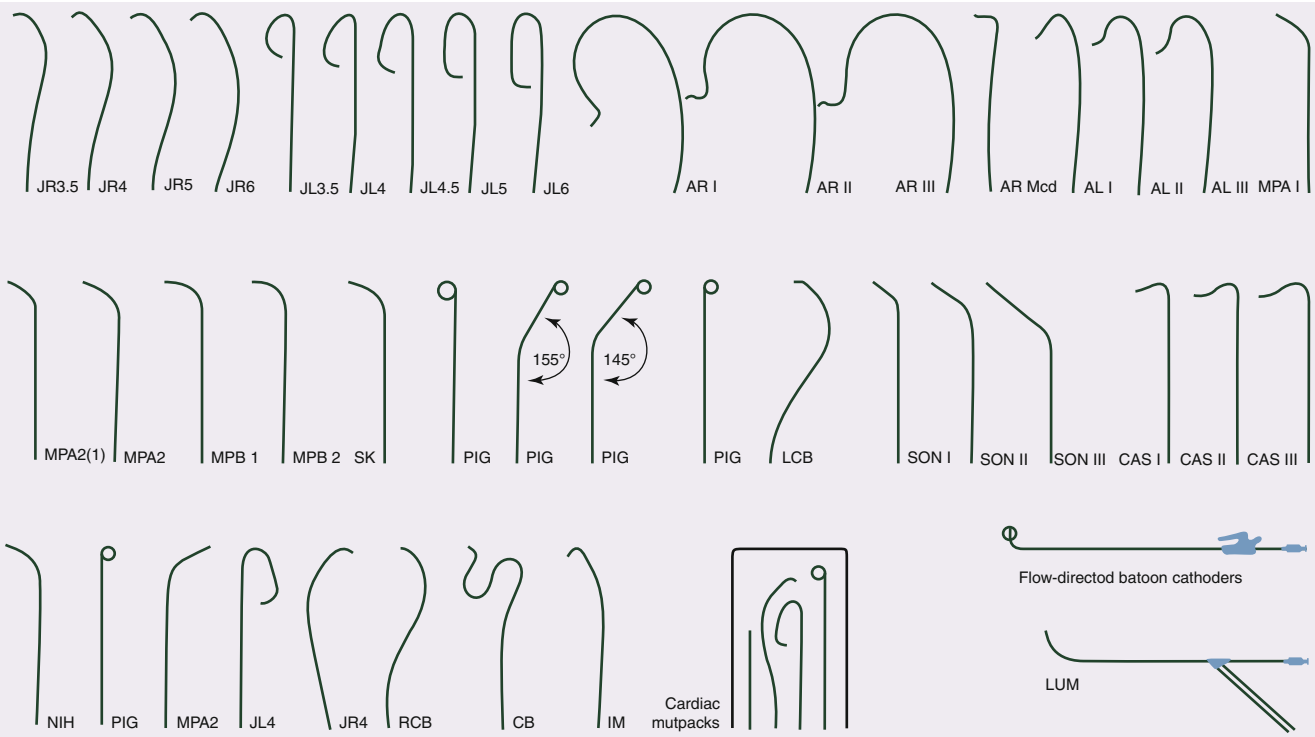

Fig. 11.2 Tip configurations for several catheters useful in coronary arteriography. *AL* amplatz left, *AR* amplatz right, *CAS* castillo, *CB* coronary bypass catheter, *IM* internal mammary, *JL* Judkins left, *JR* Judkins right, *LCB* left coronary bypass graft, *LUM* lumen, *Mod* modified, *MP* multipurpose, *NIH* National Institutes of Health, *PIG* pigtail, *RCB* right coronary bypass graft, and *SON* Sones

the catheter material. Guidewires are described by their length in centimeters, diameter in inches, and tip conformation. A commonly used wire is a 150-cm, 0.035-inch J-tipped wire. The French number of the largest catheter that passes freely through the inner diameter of the sheath, rather than its outer diameter, specifies the introducer sheaths. Therefore, a 6F introducer sheath accepts a 6F catheter (6F = 1.98 mm) but has an outer diameter of more than 1.98 mm.

The choice of the size of the catheters to be used is made by balancing the needs to opacify the coronary arteries and cardiac chambers adequately, to have adequate catheter manipulation, to limit vascular complications, and to permit early ambulation. The relationship between sheath size and vascular complications is not clear. Rather, the arterial puncture technique, anticoagulation status including use of thienopyridines, glycoprotein IIb/IIIa receptor inhibitors, and coagulopathies are more important factors related to vascular complications [19].

Techniques

Right-Heart Catheterization

Right-heart catheterization allows measurement and analysis of right atrial, right ventricular, pulmonary artery, and pulmonary capillary wedge pressures; determination of cardiac output; and screening for intracardiac shunts. Screening blood samples for oximetry should be obtained from the superior vena cava (SVC) and pulmonary artery in all patients. Right-heart catheterization is performed antegrade through either the inferior vena cava (IVC) or SVC. Percutaneous entry is achieved through the femoral, internal, jugular, subclavian, or antecubital vein. The Swan–Ganz catheter, which allows estimation of cardiac output with thermodilution and assessment of pressures in cardiac chambers, is typically used for right-heart catheterization.

The femoral vein is used most often for access to the right heart. However, when the right-heart catheter is left indwelling following the procedure, the internal jugular approach is preferable. This approach allows the patient to sit up in bed. The internal jugular approach is preferred to the subclavian to lessen the risk of pneumothorax. The use of a micropuncture kit utilizing a 21-gauge needle and introducer can minimize potential trauma due to inadvertent puncture of the carotid artery. Also, the adjunctive use of portable vascular ultrasound probes can help to locate and establish the patency of the jugular vein particularly in patients with short, thick necks or following multiple previous catheterizations.

Balloon Flotation Catheters

Balloon flotation catheters are the simplest and most widely used right-heart catheters. If thermodilution cardiac outputs must be determined, catheters that contain thermistors, such

as Swan–Ganz catheters, are used. Intracardiac right-heart pressures and oxygen saturation to evaluate intracardiac shunts can also be obtained. They are both flexible and flow directed, but when the femoral approach is used, fluoroscopic guidance is almost always necessary to cannulate the pulmonary artery and to obtain pulmonary capillary wedge position. Right-heart catheters have either a J-shaped or S-shaped curvature distally to facilitate passage from the SVC to the pulmonary artery or an S-shaped distal end for femoral insertion, respectively. Other right-heart balloon flotation end-hole catheters are more rigid and torquable and allow passage of conventional 0.035- or 0.038-in. guidewires. Although these lack the ability to obtain thermodilution cardiac outputs, they yield better pressure fidelity due to less catheter whip artifact and a larger end hole.

Left-Heart Catheterization and Coronary Arteriography

The Judkins Technique

Because of its relative ease, speed, reliability, and low complication rate [1], the Judkins technique has become the most widely used method of left-heart catheterization and coronary arteriography. After local anesthesia with 1 % lidocaine (Xylocaine), percutaneous entry of the femoral artery is achieved by puncturing the vessel 1–3 cm (or one to two fingerbreadths) below the inguinal ligament (Fig. 11.3). The ligament can be palpated as it courses from the anterior superior iliac spine to the superior pubic ramus. This ligament, not the inguinal crease, should be used as the landmark. The inguinal crease can be misleading, particularly in the obese patient. A hemostatic clamp can be used under fluoroscopy to verify that the nick is made over the inferior edge of the femoral head. A transverse skin incision is made over the femoral artery with a scalpel. Using a modified Seldinger technique, an 18-gauge thin-walled needle is inserted at a 30–45° angle into the femoral artery, and a 0.035- or 0.038-in. J-tip polytetrafluoroethylene (Teflon)-coated guidewire is advanced through the needle into the artery. The wire should pass freely up the aorta without tactile resistance and feel like a hot knife passing through butter.

After arterial access is obtained, a sheath is usually inserted into the femoral artery. The routine use of heparin for diagnostic cardiac catheterization has not been established. However, in prolonged procedures, such as patients with bypass grafts or stenotic valve disease, it may be administered at 2,000–3,000 units IV push. The routine administrator of protamine following the procedure to reverse heparin is not recommended. Although rare, hypotensive reactions to protamine can be severe and are more common in patients with diabetes mellitus using NPH insulin. In patients receiving heparin prior to arrival in the laboratory, an activated clotting time should be obtained following access. Sheath removal is usually not recommended until the activated clotting time is less than 170 s unless a vascular closure device is being utilized.

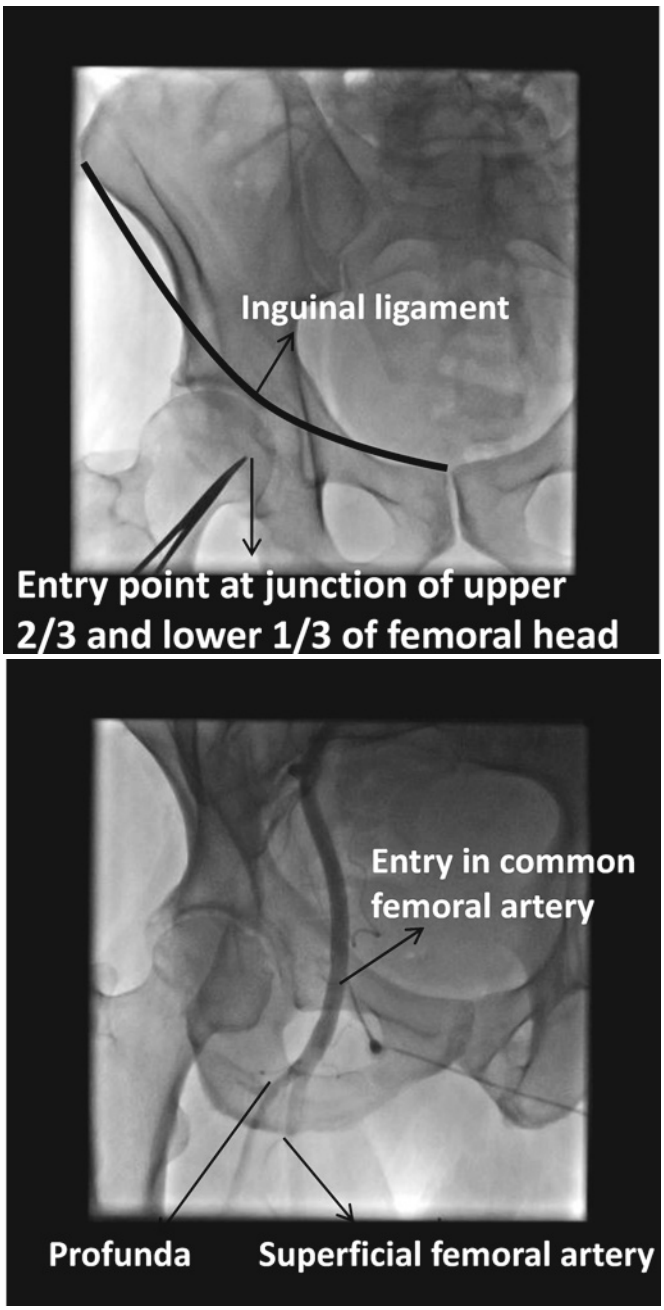

Fig. 11.3 Regional anatomy relevant to percutaneous femoral arterial catheterization. Fluoroscopic localization of entry point into the common femoral artery (marked by clamp tip) at the junction of the upper 2/3 and lower 1/3 of the femoral head. Catheter inserted through this skin nick has entered the common femoral artery, above its bifurcation into the superficial femoral artery and profunda branches

LV systolic and end-diastolic pressures can be obtained by advancing a pigtail catheter into the left ventricle. In assessing valvular aortic stenosis, LV and aortic or femoral artery pressures should be recorded simultaneously with two

transducers. The aortic catheter should be placed at least into the ascending or abdominal aorta rather than the femoral artery. The attenuation of pressure can be severe in the elderly with peripheral arterial disease, and the estimation of aortic pressure from the femoral artery pressure will be inaccurate for determination of valvular severity. Alternatively, pigtail catheters with both a distal and proximal lumen can be used. These specially designed catheters measure supravalvular aortic and LV pressure simultaneously when two transducers are used. In suspected mitral stenosis, LV and wedge or left atrial pressures should be obtained simultaneously with two transducers.

Left ventriculography is performed in the 30° right anterior oblique and 45–50° left anterior oblique views. A pigtail catheter is most commonly used for this purpose. Power injection of 30–40 ml at 12–15 cc/s of contrast medium into the ventricle is used to assess LV function and the severity of mitral regurgitation. After ventriculography, LV systolic and end-diastolic pressure measurements may be repeated and the systolic pressure recorded as the catheter is withdrawn from the left ventricle into the aorta. If an aortic transvalvular gradient is present, obtaining both of these pressures can detect it. For measurement of suspected intraventricular gradients, a multipurpose catheter with an end hole is desirable to localize the gradient in the left ventricle. Pigtail catheters contain side holes, which obscure the capacity to define whether the gradient is intraventricular, subvalvular, or transvalvular.

Post-procedure Care

After coronary arteriography and left-heart catheterization have been completed, the catheters are removed and firm pressure is applied to the femoral area for 10 min, by hand. The patient should be instructed to lie in bed for several hours, with the leg remaining straight to prevent hematoma formation. With 4–6F catheters, 2 h of bed rest is usually sufficient, whereas use of >6F catheters usually involves at least 3–4 h.

Alternatively, vascular closure devices may be used. Four types are currently commercially available: collagen plugs, suture closure, metallic clips, and hemostatic patches. Each allows early ambulation of the patients, within 1–2 h after the procedure and a shorter time to hemostasis than manual compression. They also permit early sheath removal in patients receiving anticoagulation. Although one meta-analysis raised concern regarding the increased risk of pseudoaneurysm and hematoma with arterial puncture closure devices [20], another study demonstrated reduced vascular complications compared to manual compression [21]. The ultimate success of any means of achieving hemostasis often relies on a single front-wall puncture of the common femoral artery.

The main advantage of the Judkins technique is speed and ease of selective catheterization. These attributes do not, however, minimize the importance of extensive operator experience to ensure quality studies with acceptable safety. The main disadvantage of this technique is its use in patients with severe iliofemoral atherosclerotic disease, in whom retrograde passage of catheters through areas of extreme narrowing or tortuosity may be difficult or impossible. However, with careful technique, fluoroscopic guidance and torquable floppy-tipped wires (e.g., Wholey wires) passage through synthetic aortofemoral grafts can be achieved with low complication rates.

Brachial Artery Technique: Sones Technique

Sones and colleagues introduced the first technique for coronary artery catheterization by means of a brachial artery cutdown. The technically demanding Sones technique is still used in some centers, but a detailed description is beyond the scope of this chapter.

Percutaneous Brachial Artery Technique

A modification of the Sones technique is the percutaneous brachial artery technique using preformed Judkins catheters. This technique uses the modified Seldinger method of percutaneous brachial artery entry. A 4–6F sheath is placed into the brachial artery, and 3,000–5,000 U of heparin is infused into the side port. A guidewire is then advanced to the ascending aorta under fluoroscopic control. Judkins left, right, and pigtail catheters are passed over the guidewire for routine arteriography and ventriculography. The guidewire may occasionally be necessary to direct the left coronary catheter into the left sinus of Valsalva and the ostium of the left main coronary artery. Alternatively, an Amplatz left or multipurpose catheter is used to intubate the coronary ostium. Following removal of the sheath, the arm should be maintained straight with an arm board for 4–6 h with observation of radial and brachial pulses.

The main advantage of the percutaneous brachial technique is that it avoids a brachial artery cutdown and repair. The main disadvantage is that manipulation of catheters can be difficult. Compared with the femoral technique, patients' comfort, hemostasis time, and time to ambulation favor the brachial technique, whereas procedural efficiency, time of radiation exposure, and diagnostic of image quality are favorable with the femoral approach. The complication rates appear similar.

Percutaneous Radial Artery Technique

Left-heart catheterization by the radial artery approach was developed as an alternative to the percutaneous trans-brachial approach in an attempt to limit vascular complications. The inherent advantages of the transradial approach are that the hand has a dual arterial supply connected through the palmar arches and that there are no nerves or veins at the site of puncture. In addition, bed rest is unnecessary after the procedure, allowing more efficient outpatient angiography.

The procedure requires a normal Allen test result. The Allen test consists of manual compression of both the radial and ulnar arteries during fist clenching until the hand is blanched. Normal color returns to the opened hand within 10 s after releasing pressure over the ulnar artery, and significant reactive hyperemia is absent on releasing pressure over the radial artery. Alternatively, the pulse-oximetry method can be used to determine the adequacy of the palmar arch. The traditional modified Allen test was compared to pulse oximetry and plethysmography in a consecutive series of 1,010 patients referred for diagnostic cardiac catheterization [22]. The modified Allen test was considered abnormal if palmar blanching persisted for ≥10 s after release of ulnar compression. Plethysmography was observed for 2 min during radial artery compression. Plethysmography was characterized as follows:

- A—no change in the amplitude of the pulse tracing during compression
- B—reduction in amplitude with compression
- C—loss of pulse tracing with initial compression, but recovery of flow during 2 min of compression (signifying development of collateral flow)
- D—loss of pulse tracing with no recovery

Patients in categories A, B, and C were considered to have a patent ulnopalmar arch and therefore eligible for radial catheterization [22].

One approach to the radial technique is detailed here although others are also in vogue. In this radial technique, the arm is abducted and the wrist hyperextended over a gauze roll. Routine skin anesthesia is used. A micropuncture needle or a 20-gauge angiocath is introduced at a 30–45° angle into the radial artery 2–3 cm proximal to the flexor crease of the wrist. A 7–16 cm-long 5F sheath is then introduced over a short 0.025-in. wire. Next, about 10 cc of blood is drawn into a syringe containing heparin (2000 IU) and vasodilators (e.g., 2.5 mg of verapamil plus 200 mcg of nitroglycerin) to prevent radial artery spasm. The cocktail is buffered with blood to minimize the burning sensation and is then injected into the sidearm of the sheath. Coronary catheters are then advanced over a standard 0.035-in. J-tipped exchange wire into the ascending aorta. The left and right coronary arteries are intubated in a manner similar to the brachial approach. Typically JL 3.5 and JR 4.0 catheters are used although dedicated radial catheters are also available. Hemostasis is obtained at the end of the procedure after sheath removal using direct pressure or an inflatable balloon cuff. It is recommended that the arterial puncture site be allowed to bleed for several beats before maintaining direct pressure. The radial pulse should be monitored regularly for several hours after the procedure.

The transradial approach for left-heart catheterization has gained in popularity [23–26]. Radial access decreases the rate of access-related bleeding and complications compared to femoral access [24–27]. The potential limitations of this procedure include loss of the radial pulse in ≤5 % of radial procedures [28]. Infrequent complications include compartment syndrome, pseudoaneurysm (<0.01 %), and sterile abscess (occurring with previous-generation hydrophilic sheaths) [29]. Radial artery spasm may occur and treatment at times may be challenging. Local hematomas may occur from small-branch vessel hydrophilic wire perforation or inexperience with wristband use. If intervention is contemplated, device selection may be limited by guide catheter size.

Transseptal Catheterization

The details of performing a transseptal left-heart catheterization are beyond the scope of this book chapter. This technique has increased in popularity due to percutaneous balloon mitral commissurotomy as a preferential option to surgical commissurotomy, electrophysiological procedures requiring access to pulmonary veins and use of percutaneous mitral valve repair [30].

In cases in which transseptal puncture is technically difficult because of a large right atrium, postsurgical condition, or anatomical variant, intracardiac echocardiography can be useful to localize the fossa ovalis and interatrial septum [31].

The major risk of transseptal catheterization lies in inadvertent puncture of atrial structures, such as the atrial free wall, left atrial appendage, or coronary sinus, or entry into the aortic root or pulmonary artery. Transseptal heart catheterization can be performed with a complication rate of less than 1 % in experienced centers.

Direct Transthoracic Ventricular Puncture

The sole diagnostic indication for direct LV puncture is to measure LV pressure and to perform ventriculography in patients with mechanical prosthetic valves in both the mitral and aortic positions, preventing retrograde arterial and transseptal catheterization. Crossing tilting-disc valves with catheters should be avoided because it may result in catheter entrapment, occlusion of the valve, or possible dislodgment of the disc with embolization. The risks of this procedure include cardiac tamponade, hemothorax, pneumothorax, laceration of the left anterior descending coronary artery, embolism of LV thrombus, vagal reactions, and ventricular arrhythmias. The risk of pericardial tamponade, however, is limited in patients who have undergone prior cardiac surgery because mediastinal fibrosis is present. With current noninvasive imaging techniques including transesophageal echocardiography, this procedure is rarely indicated. The advent of transapical aortic valve implantation utilizes this technique when femoral access is limited due to vessel size. Direct visualization of the LV apex is accomplished through intercostal incision followed by apical puncture using the Seldinger technique.

Details of the technique of direct ventricular puncture are beyond the scope of this chapter but the interested reader is provided suitable references [32].

Endomyocardial Biopsy

Procedural details are beyond the scope of this chapter. There are two class I indications for endomyocardial biopsy for clinical scenarios. The first is new onset heart failure of <2 weeks duration associated with either normal or enlarged LV size or hemodynamic compromise. The second is new onset heart failure up to 3 months duration complicated by LV dilation, new ventricular arrhythmias, advanced heart block, or failure to respond to usual care within 2 weeks. The use of biopsy for suspected anthracycline toxicity or restrictive disease is considered a IIa indication. Cardiac transplant monitoring for rejection is the most common indication for biopsy [33, 34].

Complications of endomyocardial biopsy include cardiac perforation with cardiac tamponade, emboli (air, tissue, or thromboembolus), arrhythmias, electrical conduction disturbances, injury to the tricuspid valve, vasovagal reactions, and pneumothorax. The overall complication rate is between 1 and 3 %, with the risk of cardiac perforation with tamponade generally reported as less than 0.05 % [33]. Endomyocardial biopsy is the most common cause of severe tricuspid regurgitation after cardiac transplantation [35].

Percutaneous Intra-aortic Balloon Pump Insertion

Intra-aortic balloon counterpulsation devices are positioned in the descending thoracic aorta. They have a balloon volume of 30–50 ml, use helium as the inflation gas, and are timed to inflate during diastole and deflate during systole. Balloon size is based on the patient's height. The device is inserted through the femoral artery using the standard modified Seldinger technique, so that the tip is 2–3 cm below the level of the left subclavian artery. 7F–8F systems are utilized. Optimal positioning requires fluoroscopic guidance. Timing of the balloon is adjusted during (e.g., 1:2 one inflation for each two beats) pumping so that inflation of the balloon occurs at the aortic dicrotic notch and deflation occurs immediately before systole. This timing ensures maximal augmentation of diastolic flow and maximal systolic unloading [36]. Favorable hemodynamic effects include reduction in LV afterload and improvement in myocardial oxygenation [37]. IABP insertion is indicated for patients with angina refractory to medical therapy, cardiogenic shock, or mechanical complications of myocardial infarction (including severe mitral regurgitation, ventricular septal defect) or for those who have severe left main coronary artery stenosis. IABP may also be valuable in patients undergoing high-risk PCI or after primary angioplasty in the setting of acute myocardial infarction [38]. IABP insertion is contraindicated in patients with moderate or severe aortic regurgitation, aortic dissection, aortic aneurysm, patent ductus arteriosus, severe peripheral vascular disease, bleeding disorders, or sepsis.

Complications of IABP insertion include limb ischemia requiring early balloon removal or vascular surgery, balloon rupture, balloon entrapment, hematomas, and sepsis. The incidence of vascular complications ranges from 12 to greater than 40 %. Most patients in whom limb ischemia develops after insertion of a balloon pump device have resolution of the ischemia on balloon removal and do not require surgical intervention (thrombectomy, vascular repair, fasciotomy, or amputation). The risk of limb ischemia is heightened in patients with diabetes or peripheral arterial disease, women, and in patients with a postinsertion ankle-brachial index of less than 0.8. However, with the use of smaller catheters (7F), vascular complications are reduced.

Coronary Angiography

Arterial Nomenclature and Extent of Disease

The coronary artery surgery study (CASS) investigators established the nomenclature most commonly used to describe the coronary anatomy, defining 27 segments in three major coronary arteries. The bypass angioplasty revascularization investigators (BARI) modified these criteria by addition of two segments for the ramus intermedius and the third diagonal branch. In this system, the three major coronary arteries include the left anterior descending (LAD) artery, left circumflex (LCx) artery, and RCA with a right-dominant, balanced, or left-dominant circulation (the vessel that supplies the posterior descending coronary artery). The RCA is dominant in 85 % of patients, supplying the PDA and at least one posterolateral branch). CAD is defined as a more than 50 % diameter stenosis in one or more of these vessels, although it is clear that stenoses of less than 50 % have major prognostic implications because these lesions most commonly lead to plaque rupture and acute myocardial infarction. Subcritical stenoses of less than 50 % are best characterized as nonobstructive CAD; obstructive CAD is classified as one-, two-, or three-vessel disease.

Standardized Projection Acquisition

Although general recommendations can be made for sequences of angiographic image acquisition that are applicable to most patients, tailored views may be needed to accommodate individual variations in anatomy. As a general rule, each coronary artery should be visualized with a number of different projections that minimize vessel foreshortening and overlap. Since

coronary artery stenoses are often eccentric, each vascular segment of the coronary artery must be recorded in two orthogonal or nearly orthogonal views to avoid missing important diagnostic information about eccentric stenoses (Fig. 11.4).

Angiographic Projections

The major coronary arteries traverse the interventricular and atrioventricular grooves, aligned with the long and short axes of the heart, respectively. Because the heart is oriented obliquely in the thoracic cavity, the coronary circulation is generally visualized in the right anterior oblique (RAO) and left anterior oblique (LAO) projections to furnish true posteroanterior and lateral views of the heart, but these views are limited by vessel foreshortening and superimposition of branches. Simultaneous rotation of the x-ray beam in the sagittal plane provides a better view of the major coronary arteries and their branches. A simple nomenclature has evolved for the description of these sagittal views that characterizes the relationship between the image intensifier and the patient. Assuming that the x-ray tube is under the patient's table and the image intensifier is over the patient's table, the projection is referred to as the cranial view if the image intensifier is tilted toward the head of the patient (Figs. 11.5 and 11.6). The projection is referred to as the caudal view if the image intensifier is tilted down toward the feet of the patient.

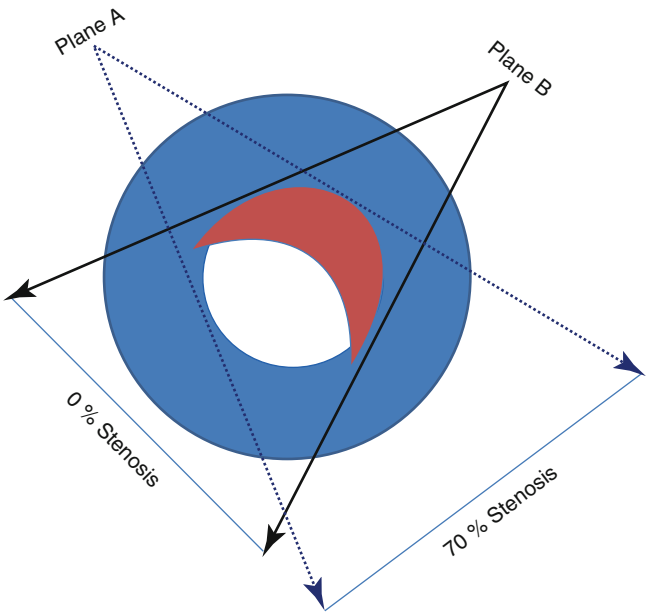

Fig. 11.4 Importance of orthogonal projections. Each vascular segment of the coronary artery must be recorded in two orthogonal or nearly orthogonal views to avoid missing important diagnostic information about eccentric stenoses. In *plane A*, the image is associated with 70 % stenosis, but in *plane B*, the image results in 0 % stenosis

Hemodynamic Data

The hemodynamic component of the cardiac catheterization procedure focuses on the pressure measurements, the measurement of flow (e.g., cardiac output, shunt flows, flow across a stenotic orifice, regurgitant flows, and coronary blood flow), and the determination of vascular resistances. Simply stated, flow through a blood vessel is determined by the pressure difference within the vessel and the vascular resistance as described by Ohm's law: $Q = \Delta P/R$ (Q = Flow, P = Pressure, R = Resistance).

Pressure Measurements

Accurate recording of pressure waveforms and correct interpretation of physiological data derived from these waveforms are major goals of cardiac catheterization. A pressure wave is the cyclical force generated by cardiac muscle contraction, and its amplitude and duration are influenced by various mechanical and physiological parameters. The force of the contracting chamber and its surrounding structures, including the contiguous chambers of the heart, the pericardium, lungs, and vasculature, influences the pressure waveform from a particular cardiac chamber. Physiological variables of heart rate and the respiratory cycle also influence the pressure waveform. An understanding of the components of the cardiac cycle is essential to the correct interpretation of hemodynamic data obtained in the catheterization laboratory.

Pressure Measurement Systems

Details of measurement of intravascular pressures using fluid-filled systems and other details such as artifacts in pressure measurement and the use of micromanometers are beyond the scope of the present chapter but are well described.

Normal Pressure Waveforms

An understanding of the normal pressure waveform morphologies is necessary for comprehending the abnormalities that characterize certain pathological conditions. Normal pressures in the cardiac chambers and great vessels are listed in Table 11.3.

Atrial Pressure

The right atrial pressure waveform has three positive deflections, the a, c, and v waves. The a wave is due to atrial systole and follows the P wave of the ECG. The height of the a wave depends on atrial contractility and the resistance to right ventricular filling. The x descent follows the a wave and represents relaxation of the atrium and downward pulling of

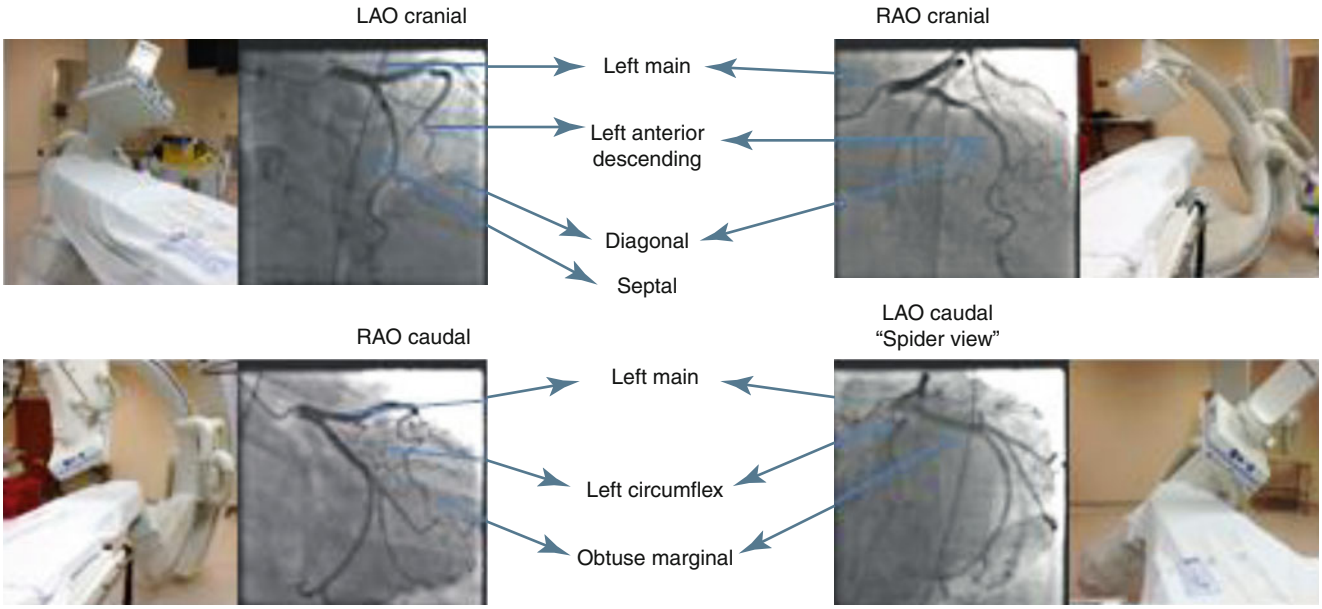

Fig.11.5 Angiographic views of the left coronary artery. The approximate positions of the x-ray tube and image intensifier are shown for each of the commonly used angiographic views

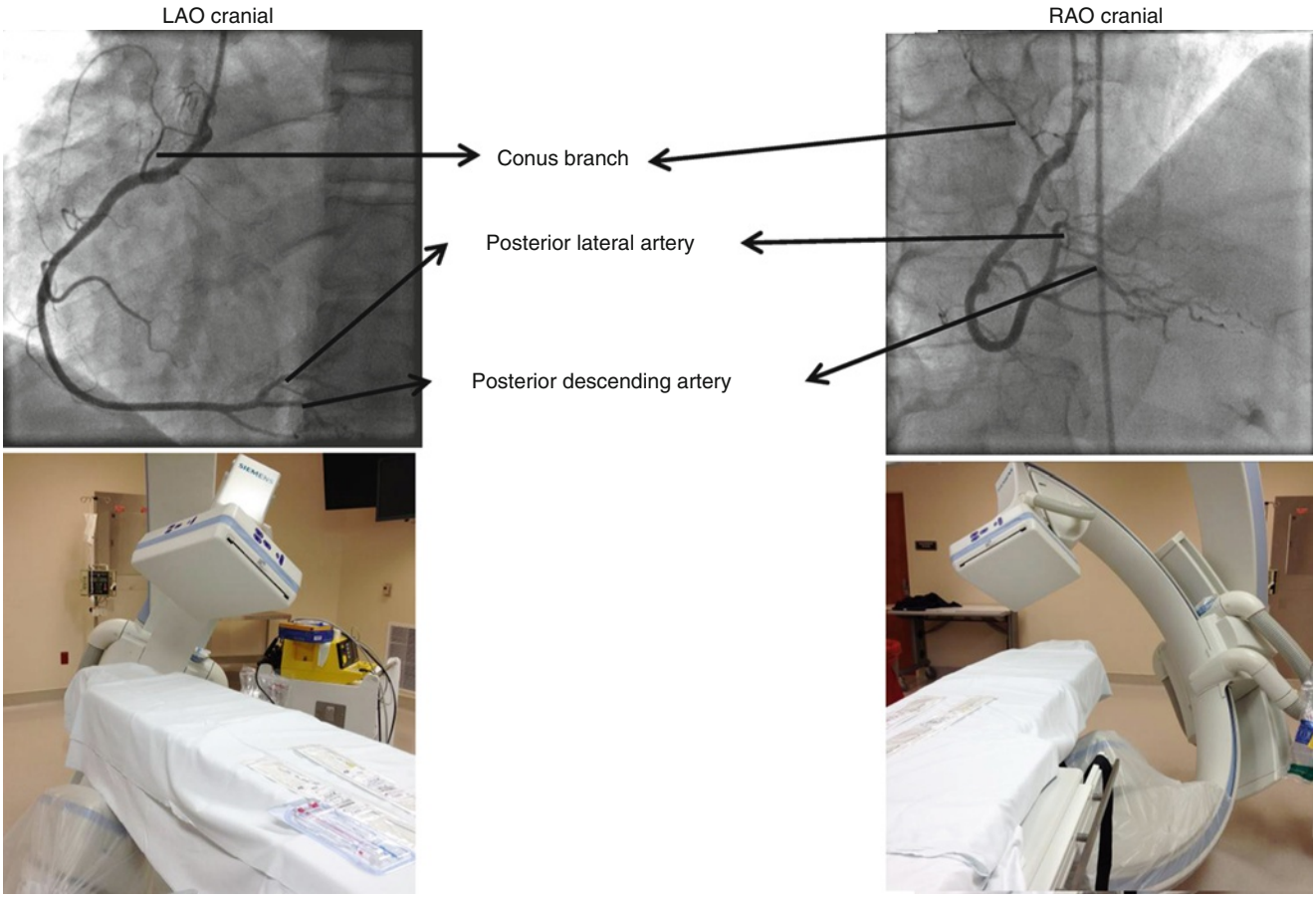

Fig. 11.6 Angiographic views of the right coronary artery (*RCA*). The approximate positions of the x-ray tube and image intensifier are shown for each of the commonly used angiographic views

Table 11.3 Normal pressures and vascular resistances

Pressures (location)	Average (mmHg)	Range (mmHg)
Right atrium		
a wave	6	2–7
v wave	5	2–7
Mean	3	1–5
Right ventricle		
Peak systolic	25	15–30
End diastolic	4	1–7
Pulmonary artery		
Peak systolic	25	15–30
Diastolic	9	
Mean	15	9–19
Pulmonary capillary		
Mean wedge	9	4–12
Left atrium		
a wave	10	4–16
v wave	12	6–21
Mean	8	2–12
Left ventricle		
Peak systolic	130	90–140
End-diastolic	8	5–12
Central aortic		
Peak systolic	130	90–140
End-diastolic	70	60–90
Mean	85	70–105
Vascular resistance		
	Mean (dyne-sec cm-5)	Range (dyne-sec cm-5)
Systemic vascular resistance	1,100	700–1,600
Total pulmonary resistance	200	100–300
Pulmonary vascular resistance	70	20–130

the tricuspid annulus by right ventricular contraction. The x descent is interrupted by the c wave, which is a small positive deflection caused by protrusion of the closed tricuspid valve into the right atrium. Pressure in the atrium rises after the x descent owing to passive atrial filling. The atrial pressure then peaks as the v wave, which represents right ventricular systole. The height of the v wave is related to atrial compliance and the amount of blood returning to the atrium from the periphery. The right atrial v wave is generally smaller than the a wave. The y descent occurs after the v wave and reflects tricuspid valve opening and right atrial emptying into the right ventricle. During spontaneous respiration, right atrial pressure declines during inhalation as intrathoracic pressure falls. Right atrial pressure rises during exhalation as intrathoracic pressures increase. The opposite effect is seen when patients are mechanically ventilated.

The left atrial pressure waveform is similar to that of the right atrium, although normal left atrial pressure is higher, reflecting the high-pressure system of the left side of the heart. In the left atrium, as opposed to the right atrium, the v wave is generally higher than the a wave. This difference occurs because the left atrium is constrained posteriorly by the pulmonary veins, whereas the right atrium can easily decompress throughout the IVC and SVC. The height of the left atrial v wave most accurately reflects left atrial compliance.

Pulmonary Capillary Wedge Pressure

The pulmonary capillary wedge pressure waveform is similar to the left atrial pressure waveform but is slightly damped and delayed as a result of transmission through the lungs. The a and v waves with both x and y descents are visible, but c waves may not be seen. In the normal state, the pulmonary artery diastolic pressure is similar to the mean pulmonary capillary wedge pressure because the pulmonary circulation has low resistance. In certain disease states that are associated with elevated pulmonary vascular resistance (hypoxemia, pulmonary embolism, and chronic pulmonary hypertension), and occasionally after mitral valve surgery, the pulmonary capillary wedge pressure may overestimate true left atrial pressure. In this circumstance, accurate measurement of the mitral valve gradient may require obtaining direct left atrial pressure [39].

Ventricular Pressure

Right ventricular and LV waveforms are similar in morphology. They differ mainly with respect to their magnitudes. The durations of systole and isovolumic contraction and relaxation are longer and the ejection period shorter in the left than in the right ventricle. There may be a small (5 mmHg) systolic gradient between the right ventricle and the pulmonary artery. Ventricular diastolic pressure is characterized by an early rapid filling wave during which most of the ventricle fills, a slow filling phase, and the a wave denoting atrial systolic activity. End-diastolic pressure is generally measured at the C-point, which is the rise in ventricular pressure at the onset of isovolumic contraction. When the C-point is not well seen, a line is drawn from the R wave on the simultaneous ECG to the ventricular pressure waveform, and this is used as the end-diastolic pressure.

Great Vessel Pressures

The contour of the central aortic pressure and the pulmonary artery pressure tracing consists of a systolic wave, the incisura (indicating closure of the semilunar valves), and a gradual decline in pressure until the following systole. The pulse pressure reflects the stroke volume and compliance of the arterial system. The mean aortic pressure more accurately

reflects peripheral resistance. As the systemic pressure wave is transmitted through the length of the aorta, the systolic wave increases in amplitude and becomes more triangular, and the diastolic wave decreases until it reaches the mid-thoracic aorta and then increases. The mean aortic pressures, however, are usually similar, with the mean peripheral arterial pressure typically equal to or less than 5 mmHg lower than the mean central aortic pressure.

The difference in systolic pressures between the central aorta and the periphery (femoral, brachial, or radial arteries) is greatest in younger patients owing to their increased vascular compliance. These potential differences between proximal aorta and peripheral artery must be considered in order to measure and interpret the peak systolic pressure gradient between the left ventricle and systemic arterial system in patients with suspected aortic stenosis. When a transvalvular gradient is present, the most accurate measure of the aortic pressure is obtained at the level of the coronary arteries. This measurement avoids the effect of pressure recovery, which is defined as the variable increase in lateral pressure downstream from a stenotic orifice. This approach can become clinically important in cases of mild to moderate aortic stenosis, particularly when the aorta is small [40]. There will be an underestimation of the transvalve gradient and overestimation of aortic valve area due to higher pressure in the femoral artery in younger patients when supraventricular pressure is not obtained. This can be avoided with a dual-lumen pigtail catheter, which measures pressure in the left ventricle and ascending aorta simultaneously.

Abnormal Pressure Characteristics

Abnormal pressure waveforms may be diagnostic of specific pathological conditions. Table 11.4 summarizes the more commonly encountered waveforms.

Cardiac Output Measurements

There is no completely accurate method of measuring cardiac output in all patients, but it can be estimated on the basis of various assumptions. The two most commonly used methods are the Fick method and thermodilution method. For comparison among patients, cardiac output is often corrected for the patient's size on the basis of the body surface area and expressed as cardiac index.

Thermodilution Techniques

The thermodilution procedure requires injection of a bolus of liquid (usually normal saline) into the proximal port of the catheter. The resultant change in temperature in the liquid is measured by a thermistor mounted in the distal end of the catheter. The change in temperature versus time is estimated. The cardiac output is then calculated using an equation that considers the temperature and specific gravity of the injectate and the temperature and specific gravity of the blood along with the injectate volume. A calibration factor is also used. The cardiac output is inversely related to the area under a thermodilution curve, shown as a function of temperature versus time, with a smaller area under the curve indicative of a higher cardiac output. Temperature fluctuation in the circuit can affect accuracy [41], however, and the use of two thermistors can significantly improve the accuracy of this technique [42].

The thermodilution method has several advantages. It obviates the need for withdrawal of blood from an arterial site and is less affected by recirculation. Perhaps its greatest advantage is the rapid display of results using computerized methods. However, a significant error occurs in patients with severe tricuspid regurgitation. Also, in patients with low outputs (especially <2.5 l/min), thermodilution tends to overestimate the cardiac output.

Fick Method

The Fick principle assumes that the rate at which oxygen is consumed is a function of the rate of blood flow times the rate of oxygen pickup by the red blood cells. The basic assumption is that the flow of blood in a given period of time is equal to the amount of substance entering the stream of flow in the same period of time divided by the difference between the concentrations of the substance in the blood upstream and downstream from its point of entry into the circulation.

The same number of red blood cells that enter the lung must leave the lung if no intracardiac shunt is present. Thus, if certain parameters were known (the number of oxygen molecules that were attached to the red blood cells entering the lung, the number of oxygen molecules that were attached to the red blood cells leaving the lung, and the number of oxygen molecules consumed during travel through the lung), the rate of flow of these red blood cells as they pass through the lung could be determined. This can be expressed in the following terms:

$$\text{Fick Cardiac Output}\left(\text{l/min}\right)=\frac{\text{Oxygen consumption}\left(\text{ml/min}\right)}{\text{A-VO}_2\times 1.36\text{Hgb}\times 10}$$

where A-VO_2 is the arterial-venous oxygen saturation difference, Hgb is the hemoglobin concentration (mg/dl), and the constant 1.36 is the oxygen-carrying capacity of hemoglobin (expressed in ml O_2/g Hgb).

Measurements must be made in the steady state. Automated methods can accurately determine the oxygen content within the blood samples. Thus, the greatest source of measurement variability is the oxygen consumption. In the original Fick determinations, expiratory gas samples were collected in a large bag over a specified period. By

Table 11.4 Selected commonly encountered abnormal wave forms

Selected abnormal right atrial waveforms				
Elevated a wave	1. Tricuspid stenosis	2. Decreased ventricular compliance: ventricular failure, pulmonic stenosis, pulmonary hypertension		
Cannon a wave	A-V asynchrony, e.g., (1) complete heart block, (2) premature ventricular contraction, (3) ventricular tachycardia, (4) ventricular pacemaker			
Absent a wave	1. Atrial fibrillation	2. Atrial flutter		
Elevated v wave	1. Tricuspid regurgitation	2. Right ventricular failure	3. Decreased atrial compliance (restrictive myopathy)	
Prominent x descent	Cardiac tamponade			
Prominent y descent	1. Constrictive pericarditis	2. Restrictive myopathy	3. Tricuspid regurgitation	
Blunted x descent	1. Atrial fibrillation	2. Right atrial ischemia		
Blunted y descent	1. Tamponade	2. Right ventricular ischemia	3. Tricuspid stenosis	
Miscellaneous				
Kussmaul sign (*inspiratory increase or lack of decline of right atrial pressure*)	1. Constrictive pericarditis	2. Right ventricular ischemia		
Equalization of mean RA, RV diastolic, PA diastolic, PWCP, and pericardial pressures (≤5 mmHg)	Cardiac tamponade			
M or W pattern	1. RV ischemia	2. Pericardial constriction	3. Congestive heart failure	
Ventricularization of RA pressure	Severe tricuspid regurgitation			
Sawtooth pattern	Atrial flutter			
Dissociation between pressure recording and intracardiac electrocardiogram	Ebstein's anomaly			
Selected abnormal left atrial pressure waveforms				
Elevated a wave	1. Mitral stenosis	2. Decreased ventricular compliance: ventricular failure, aortic stenosis, systemic hypertension		
Cannon a wave	A-V asynchrony, e.g., (1) complete heart block, (2) premature ventricular contraction, (3) ventricular tachycardia, (4) ventricular pacemaker			
Absent a wave	1. Atrial fibrillation or standstill	2. Atrial flutter		
Elevated v wave	1. Mitral regurgitation	2. Left ventricular failure	3. Decreased atrial compliance (restrictive myopathy)	
Prominent x descent	Cardiac tamponade			
Prominent y descent	1. Constrictive pericarditis	2. Restrictive myopathy	3. Mitral regurgitation	
Blunted x descent	1. Atrial fibrillation	2. Left atrial ischemia		
Blunted y descent	1. Cardiac tamponade	2. Left ventricular ischemia	3. Mitral stenosis	
Ventricular pressure waveforms				
Dip and plateau in diastolic pressure waveforms	1. Constrictive and restrictive cardiomyopathy	2. Ventricular ischemia	3. Acute dilatation associated with tricuspid regurgitation, mitral regurgitation	
Aortic pressure waveforms				
Widened pulse pressure	1. Systemic hypertension	2. Aortic regurgitation	3. Significant patent ductus arteriosus	4. Ruptured sinus of Valsalva aneurysm
Narrow pulse pressure	1. Tamponade	2. Congestive heart failure	3. Cardiogenic shock	4. Aortic stenosis
Pulsus bisferiens	1. Aortic insufficiency	2. Obstructive hypertrophic cardiomyopathy		
Pulsus paradoxus	1. Tamponade	2. COPD	3. Pulmonary embolus	
Pulsus alternans	1. Congestive heart failure	2. Cardiomyopathy		
Pulsus parvus et tardus	Aortic stenosis			
Spike-and-dome pattern	Obstructive hypertrophic cardiomyopathy			

measuring the expiratory oxygen concentration and by knowing the concentration of oxygen in room air, the quantity of oxygen consumed over time could be determined. Currently, measurement of the expired oxygen concentration is

quantified by using a polarograph. This device can be connected to the patient by use of a plastic hood or by a mouthpiece and tubing.

The advantage of the Fick method is that it is the most accurate method in patients with low cardiac output and thus is preferred over the thermodilution method in these circumstances. It is also independent of the factors that affect curve shape and cause errors in thermodilution cardiac output (e.g., tricuspid regurgitation). The Fick method suffers primarily from the difficulty in obtaining accurate oxygen consumption measurements and the inability to obtain a steady state under certain conditions. Because the method assumes mean flow over a period of time, it is not suitable during rapid changes in flow. Also, the patient cannot receive supplemental oxygen during blood sample collection. In patients with significant mitral or aortic regurgitation, the Fick cardiac output should not be used.

Many laboratories use an "assumed" Fick method in which the oxygen consumption index is assumed on the basis of the patient's age, gender, and body surface area or an estimate is made (125 ml/m^2) on the basis of body surface area. However, when assumed oxygen consumption, rather than measured oxygen consumption, is used, large errors can occur [43].

Angiographic Cardiac Output

Angiographic stroke volume can be calculated by tracing the end-diastolic and end-systolic images. Stroke volume is the quantity of blood ejected with each beat. End-diastolic volume is the maximum LV volume and occurs immediately before the onset of systole. It occurs immediately after atrial contraction in patients in sinus rhythm. End-systolic volume is the minimum LV volume during the cardiac cycle. Calibration of the images with grids or ventricular phantoms is necessary to obtain accurate ventricular volumes. Angiographic cardiac output and stroke volume are derived from the following equations:

$$\text{Stroke volume} = \text{EDV} - \text{ESV}$$

$$\text{Cardiac output} = \left(\text{EDV} - \text{ESV}\right) \times \text{Heart Rate}$$

where EDV = end-diastolic volume and ESV = end-systolic volume.

The inherent inaccuracies of calibrating angiographic volumes often make this method of measurement unreliable. In cases of valvular regurgitation or atrial fibrillation, angiographic cardiac output does not accurately measure true systemic outputs. However, the angiographic cardiac output is preferred over the Fick or thermodilution output for calculation of stenotic valve areas in patients with significant aortic or mitral regurgitation.

Determination of Vascular Resistance

Vascular resistance calculations are based on the Ohm's law. Determination of the resistance in a vascular bed requires measurement of the mean pressure of the proximal and distal ends of the vascular bed and accurate measurement of cardiac output. Vascular resistance (R) is usually defined in absolute units (dyne-sec $\cdot$ cm^{-5}) and is defined as R = [mean pressure gradient (dyne/cm^2)]/[mean flow (cm^3/s)]. Hybrid units (Wood units) are less often used.

Systemic vascular resistance (SVR) in absolute units is calculated using the following equation:

$$\text{SVR} = \frac{80\left(\text{Ao}_\text{m} - \text{RA}_\text{m}\right)}{Q_\text{s}}$$

where Ao_m and RA_m are the mean pressures (in mmHg) in the aorta and right atrium, respectively, and Q_s is the systemic cardiac output (in l/min). The constant 80 is used to convert units from mmHg/l/min (Wood units) to the absolute resistance units dyne-sec $\cdot$ cm^{-5}. If the right atrial pressure is not known, the term RA_m can be dropped, and the resulting value is called the total peripheral resistance (TPR):

$$\text{TPR} = \frac{80\left(\text{Ao}_\text{m}\right)}{Q_\text{s}}$$

Similarly, the pulmonary vascular resistance (PVR) is derived from the following equation:

$$\text{PVR} = \frac{80\left(\text{PA}_\text{m} - \text{LA}_\text{m}\right)}{Q_\text{p}}$$

where PA_m and LA_m are the mean pulmonary artery and mean left atrial pressures, respectively, and Q_p is the pulmonary blood flow. Mean pulmonary capillary wedge pressure is commonly substituted for mean left atrial pressure if the latter has not been measured directly, although errors can occur because of this substitution. In the absence of an intracardiac shunt, Q_p is equal to the systemic cardiac output. Normal values are listed in Table 11.3.

Elevated resistances in the systemic and pulmonary circuits may represent reversible abnormalities or may be permanent owing to irreversible anatomical changes. In several clinical situations, such as congestive heart failure, valvular heart disease, primary pulmonary hypertension, and congenital heart disease with intracardiac shunting, determination of whether elevated SVR or PVR can be lowered transiently in the catheterization laboratory may provide important insights into potential management strategies. Interventions that may be used in the laboratory for this purpose include administration of vasodilating drugs (e.g., sodium nitroprusside), exercise,

and (in patients with pulmonary hypertension) nitric oxide inhalation or intravenous epoprostenol (Flolan), a pulmonary and systemic vasodilator.

Evaluation of Valvular Stenosis

Determining the severity of valvular stenosis on the basis of the pressure gradient and flow across the valve is one of the most important aspects of evaluation of patients with valvular heart disease. In many patients, the magnitude of the pressure gradient alone is sufficient to distinguish clinically significant from insignificant valvular stenosis.

Determination of Pressure Gradients

Aortic Stenosis

In patients with aortic stenosis, the transvalvular pressure gradient is best measured with a catheter in the left ventricle and another in the proximal aorta. Although it is convenient to measure the gradient between the left ventricle and the femoral artery, downstream augmentation of the pressure signal and delay in pressure transmission between the proximal aorta and femoral artery may alter the pressure waveform substantially and introduce errors into the measured gradient [40].

LV–femoral artery pressure gradients may suffice in many patients as an estimate of the severity of aortic stenosis to confirm the presence of a severely stenotic valve. If the side port of the arterial introducing sheath is used to monitor femoral pressure, the inner diameter of the sheath should be at least 1F size larger than the outer diameter of the LV catheter.

The operator should obtain simultaneous ascending aortic and femoral artery pressures in order to verify similarity between the two sites. The LV–femoral artery pressure gradient may not always be relied on in the calculation of valve orifice area in patients with moderate valve gradients. A careful single catheter pullback from left ventricle to aorta is often preferable to simultaneous measurement of LV and femoral artery pressures.

A single catheter with distal and proximal lumen or a micromanometer catheter with distal and proximal transducers is preferable for simultaneous measurement of LV pressure and central aortic pressure. Another method is to use long arterial catheters, in the aorta and the second in the left ventricle.

The mean pressure gradient across the aortic valve is determined by planimetry of the area separating the LV and aortic pressures using multiple beats (Fig. 11.7), and it is this gradient that is applied to calculation of the valve orifice area. The peak-to-peak gradient, measured as the difference between peak LV pressure and peak aortic pressure, is commonly used to quantify the valve gradient because this measurement is rapidly obtained and can be estimated visually. However, there is no physiological basis for the peak-to-peak gradient because the maximum LV and aortic pressures rarely occur simultaneously. The peak-to-peak gradient measured in the catheterization laboratory is generally lower than the peak instantaneous gradient measured in the echocardiography laboratory. This is because the peak instantaneous gradient represents the maximum pressure difference between the left ventricle and aorta when measured simultaneously. This maximum pressure difference occurs on the upslope of the aortic pressure tracing (Fig. 11.7). Mean aortic transvalvular gradient and aortic valve area are well correlated with both techniques [6]. In patients with low-gradient, low-output aortic stenosis, pharmacologic maneuvers can be helpful (see section "Pharmacologic Maneuvers").

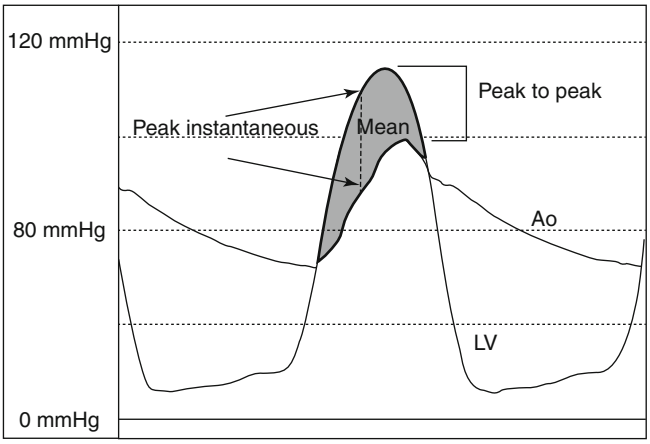

Fig. 11.7 Various methods of describing an aortic transvalvular gradient. The peak-to-peak gradient is the difference between the maximal pressure in the aorta (*Ao*) and the maximal left ventricle (*LV*) pressure. The peak instantaneous gradient is the maximal pressure difference between the Ao and LV when the pressures are measured in the same moment (usually during early systole). The mean gradient (*shaded area*) is the integral of the pressure difference between the LV and Ao during systole

Mitral Stenosis

In patients with mitral stenosis, the most accurate means of determining the mitral valve gradient is measurement of left atrial pressure using the transseptal technique with simultaneous measurement of LV pressure and with planimetry of the area bounded by the LV and left atrial pressures in diastole using several cardiac cycles (Fig. 11.8). The pulmonary capillary wedge pressure is usually substituted for the left atrial pressure, as the pulmonary wedge pressure is more readily obtained. The pulmonary wedge pressure tracing must be realigned with the LV tracing for accurate mean

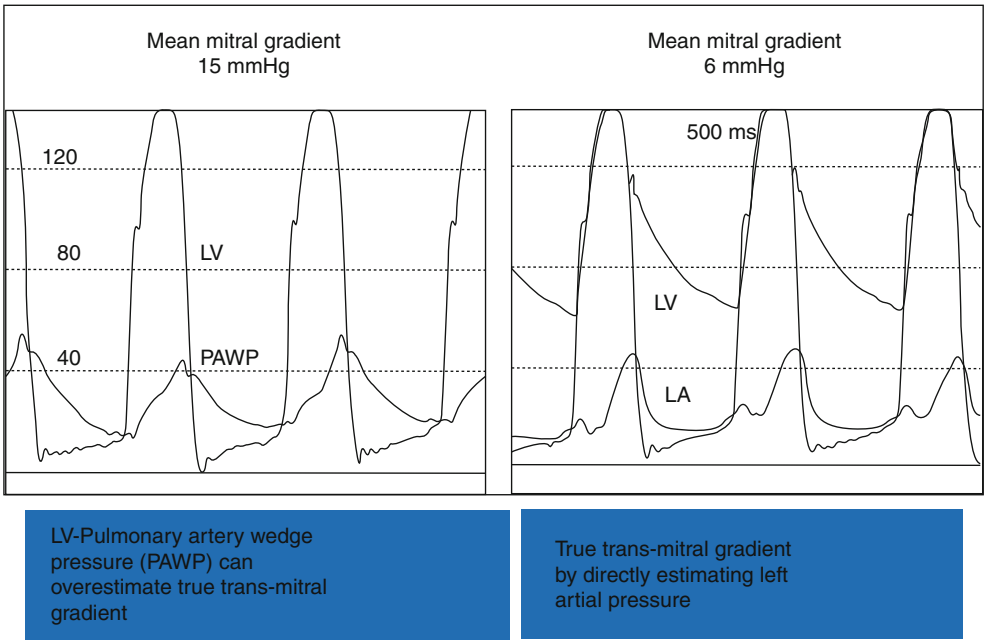

Fig. 11.8 Pressure gradient in a patient with mitral stenosis. The pressure in the left atrium (*LA*) exceeds the pressure in the left ventricle (*LV*) during diastole, producing a diastolic pressure gradient

gradient determination. Although it has been generally accepted that pulmonary capillary wedge pressure is a satisfactory estimate of left atrial pressure, studies indicate that the pulmonary wedge pressure may systematically overestimate the left atrial pressure by 2–3 mmHg, thereby increasing the measured mitral valve gradient [39]. Improperly wedged catheters, resulting in damped pulmonary artery pressure recordings, further overestimate the severity of mitral stenosis. If there is doubt about accurate positioning of the catheter in the wedge position, the position can be confirmed by slow withdrawal of blood for oximetric analysis. Oxygen saturation equal to that of the systemic circulation confirms the wedge position.

Right-Sided Valvular Stenosis

In pulmonic stenosis, the valve gradient is obtained by a catheter pullback from the pulmonary artery to the right ventricle or by placing separate catheters in the right ventricle and pulmonary artery. Multi-lumen catheters can also be used for simultaneous pressure recordings. Tricuspid valve gradients should be assessed with simultaneous recording of right atrial and right ventricular pressures.

Calculation of Stenotic Valve Orifice Areas

The stenotic orifice area is determined from the pressure gradient and cardiac output using the formula developed by Gorlin and Gorlin from the fundamental hydraulic relationships linking the area of an orifice to the flow and pressure drop across the orifice. Flow (F) and orifice area (A) are related by the fundamental formula:

$$F = cAV$$

where V is velocity of flow and c is a constant accounting for central streaming of fluid through an orifice, which tends to reduce the effective orifice size. Hence,

$$A = \frac{F}{cV}$$

Velocity is related to the pressure gradient through the relation $V = k\left(2g\Delta P\right)^{1/2}$, where k is a constant accounting for frictional energy loss, g is the acceleration due to gravity (980 cm/s^2), and ΔP is the mean pressure gradient (mm Hg). Substituting for V in the orifice area equation and combining c and k into one constant C,

$$A = \frac{F}{44.3C\sqrt{\left(\Delta P\right)}}$$

Gorlin and Gorlin determined the value of the constant C by comparing the calculated valve area with actual valve area measured at autopsy or at surgery in 11 mitral valves. The maximal discrepancy between the actual mitral valve area and calculated values was only 0.2 cm^2 when the constant 0.85 was used. No data were obtained for aortic valves, a limitation noted by the Gorlins, and a constant of 1.0 was assumed.

Because flow across the aortic valve occurs only in systole, the flow value for calculating aortic valve area is the cardiac output in milliliters per minute divided by the systolic ejection period (SEP) in seconds per beat times the heart rate (HR) in

beats per minute. The systolic ejection period is defined from aortic valve opening to closure. Hence, the aortic valve area is calculated from the Gorlin formula using the following equation:

$$\text{AVA}\left(\text{cm}^2\right)=\frac{\text{Cardiac Output}\left(\text{l}/\text{min}\right)1{,}000}{44.3\cdot\sqrt{\text{Mean Gradient}\left(\text{mmHg}\right)\text{HR}\cdot\text{SEP}}}$$

Similarly, as mitral flow occurs only in diastole, the cardiac output is corrected for the diastolic filling period (DFP) in seconds per beat in the equation for mitral valve area, where the diastolic filling period is defined from mitral valve opening to mitral valve closure:

$$\text{MVA}\left(\text{cm}^2\right)=\frac{\text{Cardiac Output}\left(\text{l}/\text{min}\right)1{,}000}{37.7\cdot\sqrt{\text{Mean Gradient}\left(\text{mmHg}\right)\text{HR}\cdot\text{DFP}}}$$

The normal aortic valve area is 2.6–3.5 cm^2 in adults. Valve areas of less than 1.0 cm^2 represent severe aortic stenosis. The normal mitral valve area is 4–6 cm^2, and severe mitral stenosis is present with valve areas less than 1.0 cm^2.

The calculated valve area is often crucial in management decisions for patients with aortic stenosis or mitral stenosis. Hence, it is essential that accurate and simultaneous pressure gradient and cardiac output determinations be made, especially in patients with borderline or low-pressure gradients.

There are limitations of the Gorlin-derived orifice area. As the square root of the mean gradient is used in the Gorlin formula, the valve area calculation is more strongly influenced by the cardiac output than the pressure gradient. Thus, errors in measuring cardiac output may have profound effects on the calculated valve area, particularly in patients with low cardiac outputs, in whom the calculated valve area is often of greatest importance.

As noted previously, the thermodilution technique may provide inaccurate cardiac output data when cardiac output is reduced or when concomitant aortic, mitral, or tricuspid regurgitation is present. Thus, the Fick method of determining cardiac output is the most accurate for assessing cardiac output, especially in low-output states. In patients with mixed valvular disease (stenosis and regurgitation) of the same valve, the use of forward flow as determined by the Fick method or thermodilution technique overestimates the severity of the valvular stenosis. This overestimation occurs because the Gorlin formula depends on total forward flow across the stenotic valve, not net forward flow. If valvular regurgitation is present, the angiographic cardiac output is the most appropriate measure of flow. If both aortic and mitral regurgitation are present, flow across a single valve cannot be determined and neither aortic valve area nor mitral valve area can be assessed accurately.

Other potential errors and limitations are inherent in the use of the Gorlin formula, related both to inaccuracies in measurement of valve gradients and to more fundamental issues regarding the validity of the assumptions underlying the formula. In low-output states, the Gorlin formula may systematically predict smaller valve areas than are actually present. Several lines of evidence indicate that the aortic valve area from the Gorlin formula increases with increases in cardiac output. Although this may represent an actual greater opening of stenotic valves by the higher proximal opening pressures that result from increases in transvalvular flow, the flow dependence of the calculated valve area may also reflect inherent errors in the assumptions underlying the Gorlin formula, particularly with respect to the aortic valve.

The increase in Gorlin valve area with increases in transvalvular flow is not associated with alterations in direct planimetry of the aortic valve area by transesophageal echocardiography [44]. This suggests that flow-related variation in the Gorlin aortic valve area is due to disproportional flow dependence of the formula and not a true change in the valve area [6].

An alternative simplified formula (the Hakki formula) for determining valve areas has been proposed. The effects of the systolic ejection period and the diastolic filling period are relatively constant at normal heart rates, and these terms can be eliminated from the equation. This assumes that $(\text{HR}\cdot\text{SEP}\cdot 44.3)\approx 1{,}000$ in most circumstances. In this modified approach, the aortic valve area can be quickly estimated from the following formula:

$$\text{AVA}\left(\text{cm}^2\right)=\frac{\text{Cardiac Output}\left(\text{L}/\text{Min}\right)}{\sqrt{\text{Peak to Peak or Mean Gradient}\left(\text{mmHg}\right)}}$$

Use of either the mean aortic transvalvular gradient or peak-to-peak gradient produces similar correlation with the Gorlin formula.

Patients with low-output, low-gradient aortic stenosis remain a challenge for accurate determination of valve area either by cardiac catheterization or echocardiography. Whether afterload mismatch or intrinsic contractility dysfunction is the primary problem in ventricular impairment can be difficult to ascertain. Thus, the use of pharmacologic stress with low-dose dobutamine infusion has been advocated to distinguish moderate from severe aortic stenosis [45–47]. The concept is that patients without true anatomic severe aortic stenosis will have an increase in valve areas with little change in transvalvular gradient [6]. If dobutamine increases the AVA>0.2 cm^2 with no change in gradient, it is

likely that the baseline evaluation overestimated the severity of aortic stenosis [6]. It has also been shown that patients who increase stroke volume by <20 % lack contractile reserve and have a poor prognosis with either medical or surgical therapy [46].

Despite theoretical limitations, the Gorlin formula has proved to be a reliable clinical determination for evaluating patients with suspected aortic stenosis.

Measurement of Intraventricular Pressure Gradients

The demonstration of an intracavitary pressure gradient is among the most interesting yet challenging aspects of diagnostic catheterization. Simultaneous pressure measurements are obtained in either the central aorta or femoral artery and from within the ventricular cavity. Pullback of a multipurpose end-hole catheter from the ventricular apex to a posterior position just beneath the aortic valve demonstrates an intracavitary gradient. An erroneous intracavitary gradient may be seen if the catheter becomes entrapped by the hypertrophic myocardium.

The intracavitary gradient is distinguished from aortic valvular stenosis by the loss of the aortic–LV gradient when the catheter is still within the left ventricle yet proximal to the myocardial obstruction. In addition, careful analysis of the upstroke of the aortic pressure waveform distinguishes a valvular from a subvalvular stenosis, as the aortic pressure waveform demonstrates a slow upstroke in aortic stenosis. Other methods for localizing intracavitary gradients include the use of a dual-lumen catheter, a double-sensor micromanometer catheter, or placement of an end-hole catheter in the LV outflow tract, while a transseptal catheter is advanced into the left ventricle, with pressure measured simultaneously. An intracavitary gradient may be increased by various provocative maneuvers including the Valsalva maneuver, inhalation of amyl nitrate, introduction of a premature ventricular beat, or isoproterenol infusion (see section "Physiological and Pharmacological Maneuvers").

Assessment of Valvular Regurgitation

The severity of valvular regurgitation is generally graded by visual assessment, although calculation of the regurgitant fraction is used occasionally. According to ACC/AHA guidelines, hemodynamic evaluation of either regurgitant aortic or mitral regurgitant lesions is recommended as a class I indication when pulmonary artery pressure is disproportionate to the severity of regurgitation assessed noninvasively, or when there is a discrepancy between clinical and noninvasive findings [6]. Exercise with right-heart hemodynamic assessment including pulmonary artery, pulmonary capillary wedge pressure, and cardiac output may also provide useful information.

Visual Assessment of Regulation

Valvular regurgitation may be assessed visually by determining the relative amount of radiographic contrast medium that opacifies the chamber proximal to its injection. The estimation of regurgitation depends on the regurgitant volume as well as the size and contractility of the proximal chamber. The original classification scheme devised by Sellers and colleagues remains the standard in most catheterization laboratories:

+ Minimal regurgitant jet seen. Clears rapidly from proximal chamber with each beat.

++ Moderate opacification of proximal chamber, clearing with subsequent beats.

+++ Intense opacification of proximal chamber, becoming equal to that of the distal chamber.

++++ Intense opacification of proximal chamber, becoming more dense than that of the distal chamber. Opacification often persists over the entire series of images obtained.

Regurgitant Fraction

A gross estimate of the degree of valvular regurgitation may be obtained by determining the regurgitant fraction (RF). The difference between the angiographic stroke volume and the forward stroke volume can be defined as the regurgitant stroke volume:

$$\text{Regurgitant stroke volume} = \text{angiographic stroke volume} - \text{forward stroke volume}$$

The RF is that portion of the angiographic stroke volume that does not contribute to the net cardiac output. Forward stroke volume is the cardiac output determined by the Fick or thermodilution method divided by the heart rate. Thermodilution cardiac output cannot be used if there is significant concomitant tricuspid regurgitation.

Compared to visual interpretation, 1+ regurgitation is roughly equivalent to an RF less than or equal to 20 %, 2+ regurgitation to an RF of 21–40 %, 3+ to an RF of 41–60 %, and 4+ to an RF of more than 60 %.

The assumption underlying the determination of RF is that the angiographic and forward cardiac outputs are accurate and comparable, a state requiring similar heart rates, stable hemodynamic states between measurements, and only a single regurgitant valve. Given these conditions, the equation yields only a gross approximation of regurgitant flow.

Shunt Determinations

Normally, pulmonary blood flow and systemic blood flow are equal. With an abnormal communication between intracardiac chambers or great vessels, blood flow is shunted either from the systemic circulation to the pulmonary circulation (left-to-right shunt), from the pulmonary circulation to the systemic circulation (right-to-left shunt), or in both directions (bidirectional shunt). The most commonly used method for shunt deterioration in the cardiac catheterization laboratory is the oximetric method. Although many shunts are suspected before cardiac catheterization, physicians performing the procedure should be vigilant in determining the cause of unexpected findings. For example, an unexplained pulmonary artery oxygen saturation exceeding 80 % should raise the operator's suspicion of a left-to-right shunt, whereas unexplained arterial desaturation (<93 %) may indicate a right-to-left shunt. Arterial desaturation commonly results from alveolar hypoventilation and associated "physiological shunting," the causes of which include oversedation from premedication, pulmonary disease, pulmonary venous congestion, pulmonary edema, and cardiogenic shock. If arterial desaturation persists after the patient takes several deep breaths or after administration of 100 % oxygen, a right-to-left shunt is likely.

Oximetric Method

The oximetric method is based on blood sampling from various cardiac chambers for the determination of oxygen saturation. A left-to-right shunt is detected when a significant increase in blood oxygen saturation is found between two right-sided vessels or chambers.

A screening oxygen saturation measurement for any left-to-right shunt is often performed with right-heart catheterization by sampling blood in the SVC and the pulmonary artery. If the difference in oxygen saturation between these samples is 8 % or more, a left-to-right shunt may be present, and an oximetry "run" should be performed. This run includes obtaining blood samples from all right-sided locations including the SVC, IVC, right atrium, right ventricle, and pulmonary artery. In cases of interatrial or interventricular shunts, it is recommended to obtain multiple samples from the high, middle, and low right atrium or the right ventricular inflow tract, apex, and outflow tract in order to localize the level of the shunt. One may miss a small left-to-right shunt using the right atrium for screening purposes rather than the SVC because of incomplete mixing of blood in the right atrium, which receives blood from the IVC, SVC, and coronary sinus. Oxygen saturation in the IVC is higher than in the SVC because the kidneys use less oxygen relative to their blood flow than do other organs, whereas coronary sinus blood has very low oxygen saturation. Mixed venous saturation is most accurately measured in the pulmonary artery after complete mixing has occurred or can be calculated using IVC+SVC samples (see section "Shunt Quantification").

A full saturation run involves obtaining samples from the high and low IVC; high and low SVC; high, middle, and low right atrium; right ventricular inflow and outflow tracts and midcavity; main pulmonary artery; left or right pulmonary artery; pulmonary vein and left atrium if possible; left ventricle; and distal aorta. When a right-to-left shunt must be localized, oxygen saturation samples must be taken from the pulmonary veins, left atrium, left ventricle, and aorta. Although the major weakness of the oxygen step-up method is its lack of sensitivity, clinically significant shunts are generally detected by this technique. Obtaining multiple samples from each chamber can improve sampling error and variability. Another method of oximetric determination of intracardiac shunts uses a balloon-tipped fiberoptic catheter that allows continuous registration of oxygen saturation as it is withdrawn from the pulmonary artery through the right-heart chambers into the SVC and IVC.

Shunt Quantification

The principles used to determine Fick cardiac output are also used to quantify intracardiac shunts. To determine the size of a left-to-right shunt, pulmonary blood flow (PBF) and systemic blood flow (SBF) determinations are required. PBF is simply oxygen consumption divided by the difference in oxygen content across the pulmonary bed, whereas SBF is oxygen consumption divided by the difference in oxygen content across the systemic bed. The effective blood flow (EBF) is the fraction of mixed venous return received by the lungs without contamination by the shunt flow. In the absence of a shunt, PBF, SBF, and EBF all are equal. These equations are as follows:

$$\mathrm{PBF} = \frac{\mathrm{O_2\ consumption\ (ml/min)}}{(\mathrm{PvO_2} - \mathrm{PaO_2})}$$

$$\mathrm{SBF} = \frac{\mathrm{O_2\ consumption\ (ml/min)}}{(\mathrm{SaO_2} - \mathrm{MvO_2})}$$

$$\mathrm{EPF} = \frac{\mathrm{O_2\ consumption\ (ml/min)}}{(\mathrm{PvO_2} - \mathrm{MvO_2})}$$

where PvO_2, PaO_2, SaO_2, and MvO_2 are the oxygen contents (in milliliters of oxygen per liter of blood) of pulmonary venous, pulmonary arterial, systemic arterial,

and mixed venous bloods, respectively. The oxygen content is determined as outlined in the section on Fick cardiac output.

If a pulmonary vein is not sampled, systemic arterial oxygen content may be substituted, assuming systemic arterial saturation is 95 % or more. As discussed earlier, if systemic arterial saturation is less than 93 %, a right-to-left shunt may be present. If arterial desaturation is present but not secondary to a right-to-left shunt, systemic arterial oxygen content is used. If a right-to-left shunt is present, pulmonary venous oxygen content is calculated as 98 % of the oxygen capacity.

The mixed venous oxygen content is the average oxygen content of the blood in the chamber proximal to the shunt. When assessing a left-to-right shunt at the level of the right atrium, one must calculate mixed venous oxygen content on the basis of the contributing blood flow from the IVC, SVC, and coronary sinus. The most common method used is the Flamm formula:

$$\mathrm{MvO_2} = \frac{3(\text{SVC O}_2\text{ content}) + 1(\text{IVC O}_2\text{ content})}{4}$$

Assuming conservation of mass, the size of a left-to-right shunt, when there is no associated right-to-left shunt, is simply

$$\mathrm{L} \rightarrow \mathrm{R\ shunt} = \mathrm{PBF} - \mathrm{SBF}$$

When there is evidence of a right-to-left shunt in addition to a left-to-right shunt, the approximate left-to-right shunt size is

$$\mathrm{L} \rightarrow \mathrm{R\ shunt} = \mathrm{PBF} - \mathrm{EBF}$$

and the approximate right-to-left shunt size is

$$\mathrm{R} \rightarrow \mathrm{L\ shunt} = \mathrm{SBF} - \mathrm{EBF}$$

The flow ratio PBF/SBF (or Q_p/Q_s) is used clinically to determine the significance of the shunt. A ratio of less than 1.5 indicates a small left-to-right shunt, and a ratio of 1.5 to 2.0, a moderate-sized shunt. A ratio of 2.0 or more indicates a large left-to-right shunt and generally requires percutaneous or surgical repair to prevent future pulmonary and/or right ventricular complications. A flow ratio of less than 1.0 indicates a net right-to-left shunt. If oxygen consumption is not measured, the pulmonic/systemic blood flow ratio may be calculated as follows:

$$\frac{Q_p}{Q_s} = \frac{\mathrm{PBF}}{\mathrm{SBF}} = \frac{(\mathrm{SaO_2} - \mathrm{MvO_2})}{(\mathrm{PvO_2} - \mathrm{PaO_2})}$$

where SaO_2, MvO_2, PvO_2, and PaO_2 are systemic arterial, mixed venous, pulmonary venous, and pulmonary arterial blood oxygen saturations, respectively.

Indicator-Dilution Method

Although the indicator-dilution method is more sensitive than the oximetric method in detection of small shunts, it cannot be used to localize the level of a left-to-right shunt. An indicator such as indocyanine green dye is injected into a proximal chamber while a sample is taken from a distal chamber using a densitometer, and the density of dye is displayed over time. To detect a left-to-right shunt, dye is injected into the pulmonary artery and sampling is performed in a systemic artery. Presence of a shunt is indicated by early recirculation of the dye on the down slope of the curve.

Physiological and Pharmacological Maneuvers

Potentially significant cardiac abnormalities may be absent in the resting condition but may be unmasked by stress. Therefore, if the physician performing a cardiac catheterization procedure cannot elucidate the cause of a patient's symptoms at rest, various physiological and pharmacological maneuvers can be considered.

Physiological Stress

Various physiological stresses alter the severity of obstruction in hypertrophic cardiomyopathy. The Valsalva maneuver (forcible expiration against a closed glottis) increases the systolic subaortic pressure gradient in the strain phase, during which there is a decrease in venous return and decreased LV volume. This maneuver is also abnormal in patients with congestive heart failure. Another useful maneuver in patients with hypertrophic obstructive cardiomyopathy is the introduction of a premature ventricular beat (Brockenbrough maneuver, Fig. 11.9). Premature ventricular contractions normally increase the pulse pressure of the subsequent ventricular beat. In obstructive hypertrophic cardiomyopathy, the outflow gradient is increased during the postpremature beat with a decrease in the pulse pressure of the aortic contour. A premature ventricular beat may also accentuate the spike-and-dome configuration of the aortic pressure waveform.

Rapid volume loading may reveal occult pericardial constriction, when atrial and ventricular filling pressures are relatively normal under baseline conditions owing to hypovolemia, and can help distinguish pericardial constriction from myocardial restriction. The Kussmaul sign occurs in

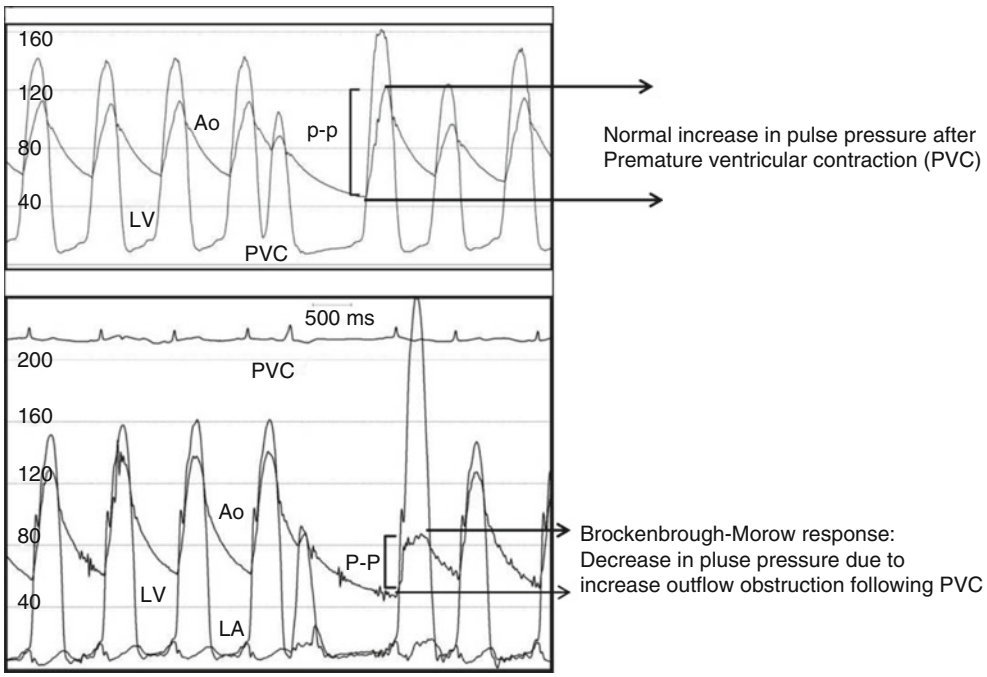

Fig. 11.9 The Brockenbrough–Morrow maneuver showing decrease in pulse pressure following a premature ventricular contraction which results in increased left ventricular outflow obstruction

pericardial constriction. It is demonstrated when, with inspiration, mean right atrial pressure fails to decrease or actually increases in relation to impaired right ventricular filling. The ratio of right ventricular to LV systolic pressure–time area during inspiration compared to expiration is called the systolic area index [48]. This is a measure of enhanced ventricular interdependence (Fig. 11.10) [48]. The index is significantly higher in those with proven constrictive pericarditis compared to restrictive cardiomyopathy (1.4 ± 0.2 vs. 0.92 ± 0.019, $p < 0.0001$) with a sensitivity of 97 % and predicted accuracy of 100 % for identifying constriction [48].

Pharmacological Maneuvers

Dobutamine infusion during cardiac catheterization is indicated in patients with low-flow, low-gradient aortic stenosis [47]. In patients with a mean gradient <30 mmHg, low cardiac output, and low ejection fraction (<40 %), the Gorlin formula may not reflect the true valve area. Provocation with dobutamine infusion can assist in distinguishing intrinsic contractile dysfunction versus afterload mismatch from valvular stenosis. Up to one third of patients with low-output severe aortic stenosis as calculated by the Gorlin formula may have pseudosevere AS [49].

Resting hemodynamics including transvalvular gradient, cardiac output, and aortic valve area should be determined. Dobutamine is infused at 5 μg/kg/min and increased by 3–10 μg/kg/min every 5 min with a maximum of 40 μg/kg/min, mean gradient >40 mmHg, 50 % increase in the cardiac output, or heart rate >140 beats/min. Patients with a final aortic valve area <1.2 cm^2 and mean gradient >30 mmHg are considered to have severe aortic stenosis [45].

Nitric oxide is an endothelial-derived vasodilator with selective pulmonary vasodilator properties that is useful in evaluating patients with pulmonary hypertension. Inhaled NO is rapidly inactivated in contrast to intravenous vasodilator that can cause severe systemic hypotension [50]. It has been well established that lowering of pulmonary artery pressure with vasodilators predicts a favorable clinical outcome.

Inhaled NO can safely and effectively assess the capacity of a patient for pulmonary vasodilator response without causing systemic hypotension. It can accurately predict a response to subsequent medical therapy [50, 51]. Doses of 10, 20, 40, or 80 parts per million can be tested over 5–10 min intervals with serial sampling of mean pulmonary artery pressure, calculation of PVR, and cardiac output. The definition of an acute response that may warrant initiation of long-term therapy with oral calcium channel blockers is a decrease in the mean pulmonary artery pressure of at least 10 mmHg to an absolute mean pulmonary artery pressure of less than 40 mmHg without a decrease in cardiac output.

Sodium nitroprusside infusion may improve the cardiac output and filling pressures in patients with dilated cardiomyopathies and in patients with mitral regurgitation by lowering SVR and PVR. A favorable response to sodium nitroprusside infusion may predict a good clinical outcome.

Agents that increase SVR, such as phenylephrine, reduce the gradient in obstructive hypertrophic cardiomyopathy. This can be used to improve acute systemic hypertension in patients with hypertrophic cardiomyopathy.

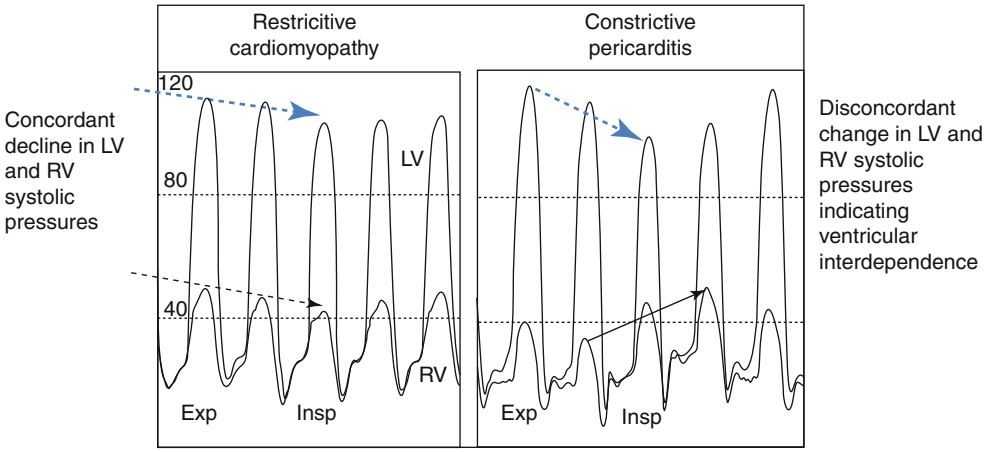

Fig. 11.10 LV and RV pressure traces from two patients during expiration and inspiration. Note that both patients have early rapid filling and elevation and end equalization of the left ventricular (*LV*) and right ventricular (*RV*) pressures at end expiration. (*Left panel*) A patient with restrictive myocardial disease. During inspiration there is a concordant decrease in the RV and LV systolic pressures. (*Right panel*) A patient with constrictive pericarditis showing a discordant change in RV and LV systolic pressures with inspiration and expiration

Isoproterenol infusion may be used to simulate supine dynamic exercise, although untoward side effects limit its applicability. This drug's positive inotropic and chronotropic effects can increase the gradient in obstructive hypertrophic cardiomyopathy and mitral stenosis. Nitroglycerin and amyl nitrate decrease preload and accentuate the systolic gradient in patients with obstructive hypertrophic cardiomyopathy. Amyl nitrate is generally inhaled, and its onset and offset of action are very rapid.

Complications Associated with Cardiac Catheterization

Major complications are uncommon (<2 %) after coronary arteriography (Table 11.5) and include death (0.10–0.14 %), myocardial infarction (0.06–0.07 %), contrast agent reactions (0.23 %), stroke (0.07–0.14 %), and local vascular complications (0.24–1 %). The potential risk of major complications during cardiac catheterization is often related to comorbid disease. The use of low-osmolar and iso-osmolar contrast media [52, 53], lower profile diagnostic catheters, reduced anticoagulation, and extensive operator experience has reduced the incidence of complications. Several large studies provide insight into the incidence of major events and delineate cohorts of patients that are at increased risk Table 11.5 [1, 54–56, 58].

Death related to diagnostic cardiac catheterization occurs in 0.08–0.75 % of patients, depending on the population studied. Data from the Society for Cardiac Angiography identified subsets of patients with an increased mortality rate [1, 55]. In an analysis of 58,332 patients, multivariate predictors of significant complications were moribund status, advanced New York Heart Association functional class, hypotension, shock, aortic valve disease, renal insufficiency, unstable angina, mitral valve disease, acute myocardial infarction within 24 h, congestive heart failure, and cardiomyopathy (Table 11.6) [1, 54, 58]. The risk of any complication during cardiac catheterization is further increased in octogenarians. Although the overall mortality is approximately 0.8 % in this cohort, the risk of nonfatal major complications, which are primarily peripheral vascular, is approximately 5 %.

The risk of myocardial infarction varies from 0.03 to 0.06 %, significant bradyarrhythmias or tachyarrhythmias from 0.56 to 1.3 % [55], and neurological complications from 0.03 to 0.2 % [57]. One study utilizing serial cranial magnetic resonance imaging demonstrated a 22 % incidence of focal acute cerebral embolic events following retrograde crossing of stenotic aortic valves, and 3 % of patients demonstrated clinically apparent neurological deficits [54]. However,

Table 11.5 Risk of cardiac catheterization and coronary angiography

Complication	Percentage
Mortality	0.11
Myocardial infarction	0.05
Cerebrovascular accident	0.07
Arrhythmia	0.38
Vascular complications	0.43
Contrast reaction	0.37
Hemodynamic complications	0.26
Perforation of heart chamber	0.28
Other complications	0.28
Total of major complications	1.70
Mortality	0.11
$N = 59{,}792$ patients	

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Table 11.6 Multivariate predictors of major complications of coronary angiography

Moribund	10.22
Shock	6.52
Acute MI <24 h	4.03
Renal insufficiency	3.30
Cardiomyopathy	3.29
Aortic valve disease	2.72
Mitral valve disease	2.33
Heart failure	2.33
New York Heart Association Functional	
Class I	1.00
Class II	1.15
Class III	1.32
Class IV	1.52
Hypertension	1.45
Unstable angina	1.42
Outpatient/inpatient	0.63

Reprinted from Scanlon et al. [1]. With permission from Elsevier
MI myocardial infarction

this study is in contradistinction to previously published large clinical series and requires additional validation.

Stroke can either be periprocedural in the lab or within a few hours after the procedure. Whether the mechanism is different is unclear. Stroke may develop from embolization of atherosclerotic debris into the cerebral circulation or embolization of clot that formed on the injection catheters, particularly in patients with prior CABG who have a diseased ascending aorta. Stroke should be distinguished from other conditions including seizure, migraine, hypoglycemia, or encephalopathy. The standard stroke management with a multidisciplinary team is important to improve prognosis. Predictors of stroke include diabetes mellitus, hypertension, prior stroke, and renal failure. The procedure length, contrast volume, urgent indications, and use of intra-aortic balloon pumps are known to increase the risk of stroke [57].

The most common complication is arterial access site bleeding and is usually manifested by minor oozing or small hematomas. The incidence of major vascular complications has a slightly higher frequency when the Sones brachial approach is used. The incidence of major vascular complications has decreased over the last decade and is currently reported as approximately 0.20 %. Major vascular complications include occlusion requiring arterial repair or thrombectomy, retroperitoneal bleeding, hematoma formation, pseudoaneurysm, arteriovenous fistula formation, and infection. In a patient with unexplained hypotension, or back pain, retroperitoneal hematoma should be suspected. Evaluation should include serial complete blood count determinations, evaluation of anticoagulation status, and either CT or ultrasound evaluation of the groin, pelvis, and abdomen. The risk of requiring surgical repair for vascular injury is related to advanced age, congestive heart failure, and larger body surface area. With ultrasound guidance, many pseudoaneurysms can be successfully treated percutaneously with directed infusion of thrombin, and surgical repair can often be avoided.

The proper management of the arterial sheath is important in avoiding complications. Since dwell times correlate with hematoma formation, all sheaths should be removed as soon as possible with an ACT <170. Frequent blood pressure and pulse monitoring is essential.

Systemic complications can vary from mild vasovagal responses to severe vagal reactions that lead to prolonged hypotension. Minor complications occur in approximately 4 % of patients undergoing routine cardiac catheterization [1, 55]. The most common untoward effects are transient hypotension and brief episodes of angina lasting less than 10 min.

Hives can occur but are less commonly observed with low-osmolar contrast and with intra-arterial administration. They are readily treated with intravenous corticosteroids and diphenhydramine. Rarely, anaphylactoid complications are observed. These are also treated with intravenous corticosteroid and diphenhydramine. Epinephrine is administered in severe reactions; the dilution of 0.1 mg/ml is administered at 1.4 mcg/min over 5 min.

The most common complications of right-heart catheterization are nonsustained atrial and ventricular arrhythmias. Major complications associated with right-heart catheterization are infrequent. These include pulmonary infarction, pulmonary artery or right ventricular perforation, and infection.

Recent series have shown no increase and, in one study, a decline in the major complication rates associated with coronary arteriography, despite increased morbidity of patients and higher lesion complexity [55, 56].

Minor complications are also uncommon (<2 %) after coronary arteriography. Air embolus is rare (0.1 %) during diagnostic coronary arteriography and is generally preventable with meticulous flushing and elimination of air within the manifold [59]. If an air embolus and air lock do occur, 100 % oxygen should be administered, which allows resorption of smaller amounts of air within 2–4 min. Larger air emboli have been treated with direct aspiration of air from the coronary artery. Ventricular arrhythmias associated with air embolus can be treated with lidocaine and direct-current cardioversion. Reduced anterograde flow, also called no reflow, occurs in 0.17 % of cases, primarily attributable to air embolism, spasm, or dissection. Cholesterol embolization is also uncommon but may occur with catheter manipulation in a diffusely diseased abdominal or thoracic aorta. Nerve pain after diagnostic catheterization is infrequent and generally resolves spontaneously. Although lactic acidosis may develop after coronary angiography in diabetic patients taking metformin, this complication has been minimized with metformin discontinuation before the administration of contrast material

and withholding of metformin after coronary arteriography until renal function has recovered [13]. The presence of chronic kidney disease is also an important predictor of prognosis in patients undergoing coronary angiography [16].

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Nuclear Imaging in Cardiovascular Medicine

12

Diwakar Jain and Barry L. Zaret

Introduction

Nuclear imaging harnesses the unique properties of radiopharmaceuticals in allowing us to noninvasively image physiological, biochemical, and molecular phenomena, anatomical structures, and various physiological spaces and biochemical compartments in patients [1]. Nuclear imaging techniques play an important role in the noninvasive evaluation of patients with established or suspected coronary artery disease (CAD). A number of different radiopharmaceuticals and scintigraphic imaging techniques are available for obtaining important diagnostic and prognostic information about myocardial perfusion, metabolism, cardiac function, and myocardial necrosis in patients with cardiovascular disorders. This chapter briefly describes various cardiac nuclear imaging techniques, radiopharmaceuticals, instrumentation and their applications in clinical practice, and the recent developments in this field.

The following is a list of nuclear imaging techniques used in cardiovascular medicine:

I. Myocardial perfusion imaging: SPECT and PET perfusion imaging
II. Cardiac function imaging: left and right ventricular function imaging
III. Myocardial metabolic imaging
IV. New emerging molecular imaging techniques:
   (a) Myocardial ischemia imaging
   (b) Cardiac adrenergic neuronal imaging
   (c) Angiogenesis and stem cell and gene therapy imaging
   (d) Atheroma and vascular remodeling imaging

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Myocardial Perfusion Imaging

Of various techniques in nuclear cardiology, myocardial perfusion imaging is by far the most widely used technique. CAD is characterized by atheromatous luminal narrowing of the coronary arteries. This complex process evolves slowly over several decades. Symptoms occur relatively late in the course of disease and appear only after significant luminal narrowing of coronary arteries has already occurred. Coronary arterial narrowing interferes with myocardial perfusion downstream. With partial narrowing of the lumen, myocardial perfusion may be normal at rest but fails to increase appropriately during physical exertion or pharmacological vasodilation. This results in regional flow heterogeneity, which can be imaged by injecting radiotracers that are extracted by the myocardium, proportional to the regional blood flow.

Radiotracers

Thallium-201

Thallium-201 (^{201}Tl) is the conventional perfusion tracer. ^{201}Tl behaves like a potassium analog and enters the myocytes through Na^+/K^+ ATPase channels. Two to three mCi of ^{201}Tl is injected intravenously at peak exercise or during pharmacological stress. Approximately 2–4 % of the injected dose of ^{201}Tl goes to the myocardium. Myocardial uptake is proportional to the regional blood flow. Cardiac imaging is started soon after completion of stress. Myocardial segments perfused by narrowed coronary arteries or with scarring due to prior myocardial infarction show diminished tracer uptake on stress images. ^{201}Tl shows a continuous redistribution after initial myocardial extraction. Stress images are followed by redistribution images 3–4 h later. Perfusion abnormality due to ischemia reverses on redistribution images whereas that due to scarring remains unchanged. Segments characterized by scar and ischemia show partial reversibility of the perfusion abnormality. Stress ^{201}Tl imaging has a

C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_12,

sensitivity of nearly 85–90 % and a specificity of 80 % or above for the detection of CAD [2]. However, redistribution of ^{201}Tl is somewhat unreliable and unpredictable. In a significant proportion of defects due to ischemia, ^{201}Tl redistribution may be incomplete and ischemia may be underestimated [3]. A number of different strategies have been proposed for overcoming this limitation [4]. A second injection of ^{201}Tl at rest, either on the same day or on a separate day, overcomes this limitation in selected cases [4, 5]. However, a routine second injection of ^{201}Tl to all patients irrespective of the presence or absence of perfusion abnormalities on the stress images is unnecessary and results in excessive radiation exposure and is inadvisable [6]. Other limitations of ^{201}Tl include its long physical half-life (3 days), which limits the dose that can be used safely without causing undue radiation exposure to the patients, and low-energy photons (69–83 KeV), which are prone to attenuation by the thoracic wall and the soft tissue lying anterior to the heart. Attenuation artifacts can be particularly troublesome in obese patients and in women. Due to these limitations, ^{201}Tl has largely been replaced by technetium-99m tracers. However, recent disruption in supplies of technetium-99m has delayed ^{201}Tl from moving into oblivion. ^{201}Tl is currently used for the detection of myocardial viability, as will be discussed later. Dual-isotope perfusion imaging, where ^{201}Tl was used for rest perfusion imaging and a ^{99m}Tc-labeled perfusion tracer was used for stress perfusion imaging, is generally considered to be unacceptable these days, except for special circumstances, because the radiation exposure from this protocol is unacceptably high [6].

Technetium-99m-Labeled Tracers

^{99m}Tc has a shorter half-life (approx. 6 h) and emits slightly higher-energy photons (140 KeV), and its chemical structure allows its incorporation into a number of different chemicals or ligands, which can be used for studying the anatomy, perfusion, and metabolism of various organs. ^{99m}Tc-labeled agents can be used in much higher doses than ^{201}Tl and provide better-quality images. Two agents, sestamibi (Cardiolite™, Lantheus, North Billerica, MA) and tetrofosmin (Myoview™, GE Healthcare, Princeton, NJ), are FDA-approved agents in current clinical use [7–9]. These are lipophilic cationic agents, which are taken up by the myocardium because of their lipophilicity and positive charge. Their myocardial uptake is not mediated by Na^+/K^+ ATPase pump. In the myocytes, they are localized mainly in the mitochondria. These agents are tightly bound to the myocardium and show little or no clearance or redistribution from the myocardium after initial cardiac uptake [7].

The mechanism of tissue clearance of ^{99m}Tc-sestamibi has recently been elucidated [10]. ^{99m}Tc-sestamibi is a substrate for P-glycoproteins, which belong to a large group of cell membrane transporters. Whereas these transporters are abundantly expressed in the liver, intestinal mucosa, and several other organs, they are not expressed in the myocardium [10]. A lack of these transporters in the myocardium explains a relative lack of clearance of ^{99m}Tc-sestamibi from the myocardium, despite a rapid clearance from other organs. With the use of cationic ^{99m}Tc perfusion tracers, two separate injections are required for stress and rest imaging. The perfusion images are gated to the electrocardiogram. This provides information about left and right ventricular function and wall motion.

However, both ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin suffer from several limitations: liver and gastrointestinal uptake, which can degrade the image quality and produce artifacts, and relatively low first-pass myocardial extraction, which can potentially result in an underestimation of myocardial ischemia, particularly in myocardial segments perfused by coronary arteries with lower grade of narrowing. An ideal ^{99m}Tc myocardial perfusion tracer should have minimal or no hepatic and gastrointestinal uptake and should have a high first-pass myocardial extraction that linearly tracks the myocardial blood flow over a wide range.

Instrumentation

Nuclear imaging is carried out using gamma cameras, which convert gamma rays emitted by the radiotracers into electronic signals to image various organ systems in the body. Conventional gamma cameras consist of a large sodium-iodide crystal as a scintillator, which converts gamma rays into specs of visible light. This light is amplified by an array of photomultiplier tubes and then converted into electronic signals. A collimator comprising of a sheet of heavy metals such as lead or tungsten with holes in it covers the imaging surface of the scintillating crystal. A collimator permits only gamma rays traveling in a particular direction to pass through it to the scintillating crystal and absorbs the remaining rays or scattered rays, and thus, various organ systems can be imaged. Planar imaging was used in the past, but this has now been replaced with single-photon emission computed tomography (SPECT) imaging. Planar imaging was limited to the acquisition of images in anterior, left anterior oblique, and left lateral views, whereas SPECT imaging provides a series of cross-sectional images of the heart in multiple axes. SPECT imaging allows a better anatomic delineation of the perfusion abnormalities and a better angiographic correlation than planar imaging. For SPECT imaging, 32–64 images are acquired in a 180–360° orbit around the heart. These images are processed in a manner similar to that for CT images using filtered back projection or iterative reconstruction so that the left ventricular myocardium is displayed in a series of slices of varying thickness (Figs. 12.1, 12.2, 12.3, and 12.4). SPECT cameras

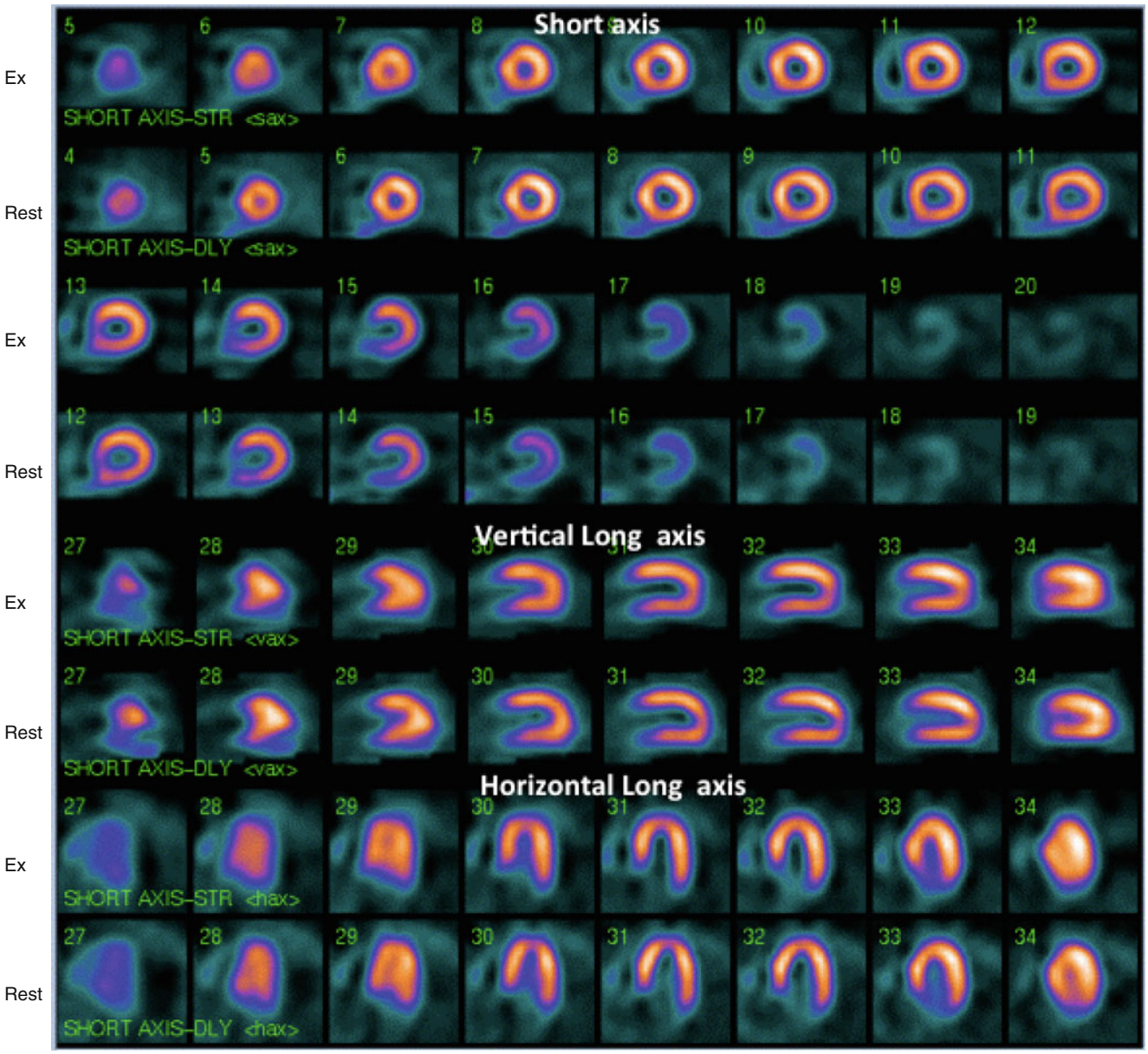

Fig. 12.1 Exercise (*Ex*) and rest ^{99m}Tc-tetrofosmin SPECT images of a 51-year-old man with end-stage renal disease and hypertension, who underwent Ex-rest myocardial perfusion imaging as a part of cardiac evaluation prior to renal transplant. He had no symptoms of CAD. He exercised for 12 min using Bruce protocol and had no chest pain or ST segment depression. He attained age-predicted maximum heart rate. Ex and corresponding rest perfusion images in short axis (*top four rows*) and vertical (*rows 5 and 6*) and horizontal (*rows 7 and 8*) long axes are shown. There is no perfusion abnormality on the Ex-rest images, and left ventricular ejection fraction was 58 % on gated SPECT images. He underwent renal transplant 6 months later with uneventful perioperative course

are available with single, double, or triple heads. For cardiac SPECT imaging, double-head cameras have become the standard imaging equipment. SPECT images are gated with ECG (gated SPECT) to assess left ventricular wall motion, thickening, and ejection fraction from the same study. Thus, simultaneous assessment of myocardial perfusion and function can be carried out from a single study. Since myocardial ischemia and left ventricular function are the two most important determinants of optimal therapy and short-term as well as long-term prognosis, gated SPECT perfusion imaging is currently the single most powerful diagnostic and prognostic modality in cardiovascular medicine.

Soft tissue attenuation continues to be a major source of artifacts in myocardial perfusion imaging. As soft tissue attenuation is nonuniform and varies from patient to patient, a relatively sophisticated approach is required for its correction. Attenuation correction is carried out with the use of a simultaneously acquired transmission map using an external source of radiation such as gadolinium or a low-dose CT

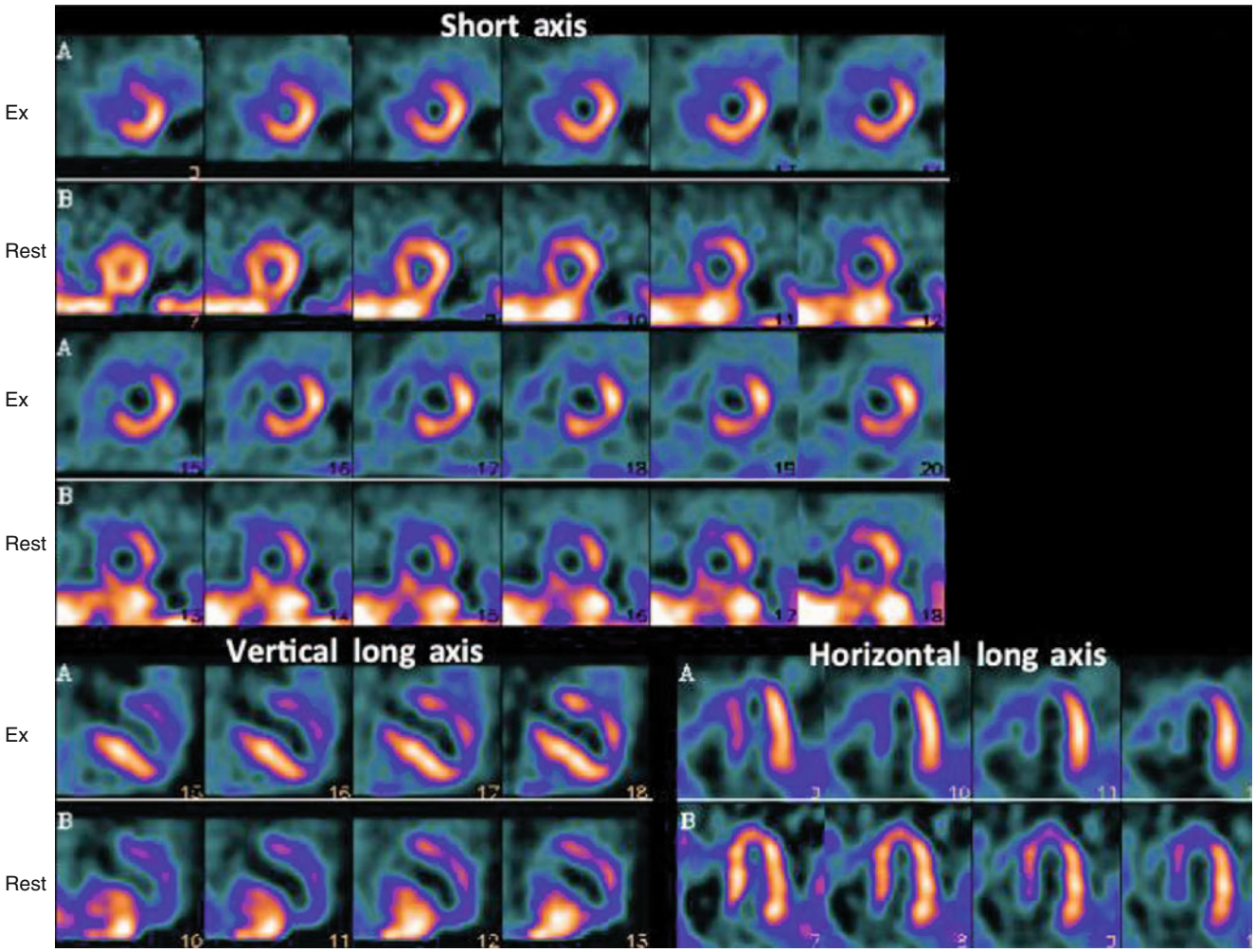

Fig. 12.2 Ex and rest ^{99m}Tc-tetrofosmin SPECT images of a 41-year-old man who presented to the emergency department with chest pain, which had resolved by the time he presented to the hospital. He has no history of CAD. He had history of hyperlipidemia and hypertension and strong family history of CAD. He ruled out for acute myocardial infarction and underwent Ex-rest perfusion imaging. He exercised for 10 min on Bruce protocol. His heart rate increased from 71 to 124 beats per minute and BP from 110/78 to 146/84 mm of Hg. He developed severe chest pain and 1 mm ST elevation in precordial leads and 1 mm ST depression in the inferior leads. The ECG change took over 5 min to return to baseline. There is a large area of perfusion abnormality involving the anterior wall, septum, and apex, which is reversible on rest imaging. There is transient left ventricular dilation on the stress images. Gated SPECT images showed akinesia of the anterior wall, septum, and apex, which normalized on the rest images. Left ventricular ejection fraction was 38 % on the stress images but was normal at 56 % on the rest images. Coronary angiography revealed long 95 % narrowing of the LAD, 80 % proximal narrowing of the RCA, and multiple 60–80 narrowings in the left circumflex coronary artery. He underwent coronary artery bypass surgery

imaging. A three-dimensional attenuation map is created from these transmission images or CT images for pixel-by-pixel correction of the attenuation [11, 12]. CT-based attenuation correction is more reliable than previous generation of external line source-based attenuation correction. Another potential advantage of CT-based attenuation correction is the possibility of scoring coronary calcium from the CT images [13]. Coronary calcium scoring may provide additional prognostic information in selected patient populations.

Recently, several new advances have been made in gamma-camera design. Newer solid-state cameras using cadmium-zinc telluride crystals have significantly higher efficiency for the detection of gamma rays compared to the traditional gamma cameras using sodium-iodide crystal and photomultiplier tubes [12]. These systems directly convert gamma rays into an electronic impulse and have much higher photon flux and efficiency for imaging. These systems are less bulky and lighter, improve the quality of images, and significantly cut down the image acquisition time. Alternatively, the dose of radiotracers can be reduced significantly, while maintaining the image quality. These solid-state cameras are likely to replace conventional sodium-iodide crystal-based cameras in the coming years.

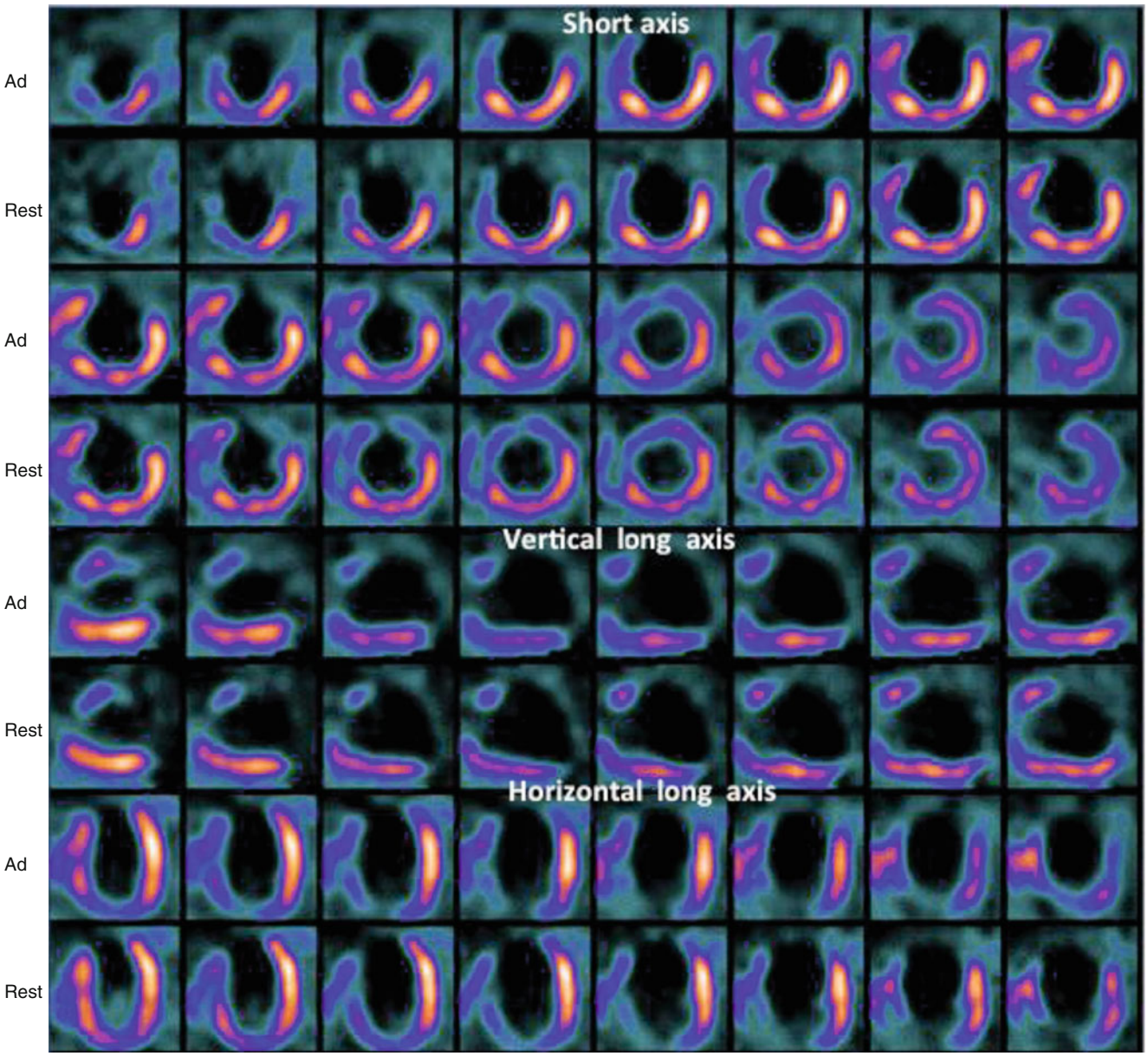

Fig. 12.3 Adenosine stress (*Ad*) and rest ^{99m}Tc-sestamibi SPECT images of a 55-year-old man with long-standing history of CAD. He suffered from a large anterior wall myocardial infarction at the age of 36 years. He suffered from multiple myocardial infarction since then and has undergone multiple revascularization procedures. He developed progressively worsening heart failure despite maximum medical therapy. Ad and rest images show a markedly enlarged left ventricle with a very large dense scar involving the anterior wall, septum, apex, and distal part of the inferior wall. On gated SPECT images, the apex was dyskinetic, anterior wall and septum and inferior wall were akinetic, and the remaining left ventricle was severely hypokinetic and global ejection fraction was severely impaired at 11 %. He underwent heart transplantation because of progressively worsening heart failure

Choice of Stress

Exercise

Exercise is by far the preferred method of stress testing. Information about exercise capacity, changes in heart rate and blood pressure, adverse symptoms such as chest pain, undue fatigue, and electrocardiographic changes such as the magnitude and duration of ST segment depression and arrhythmias provides important and independent prognostic information. The radiotracer is injected close to the peak exercise, and exercise is continued for another 2 min to allow radiotracer extraction by the myocardium at peak exercise. It is important for the patients to reach an adequate workload, which can be judged from the peak heart

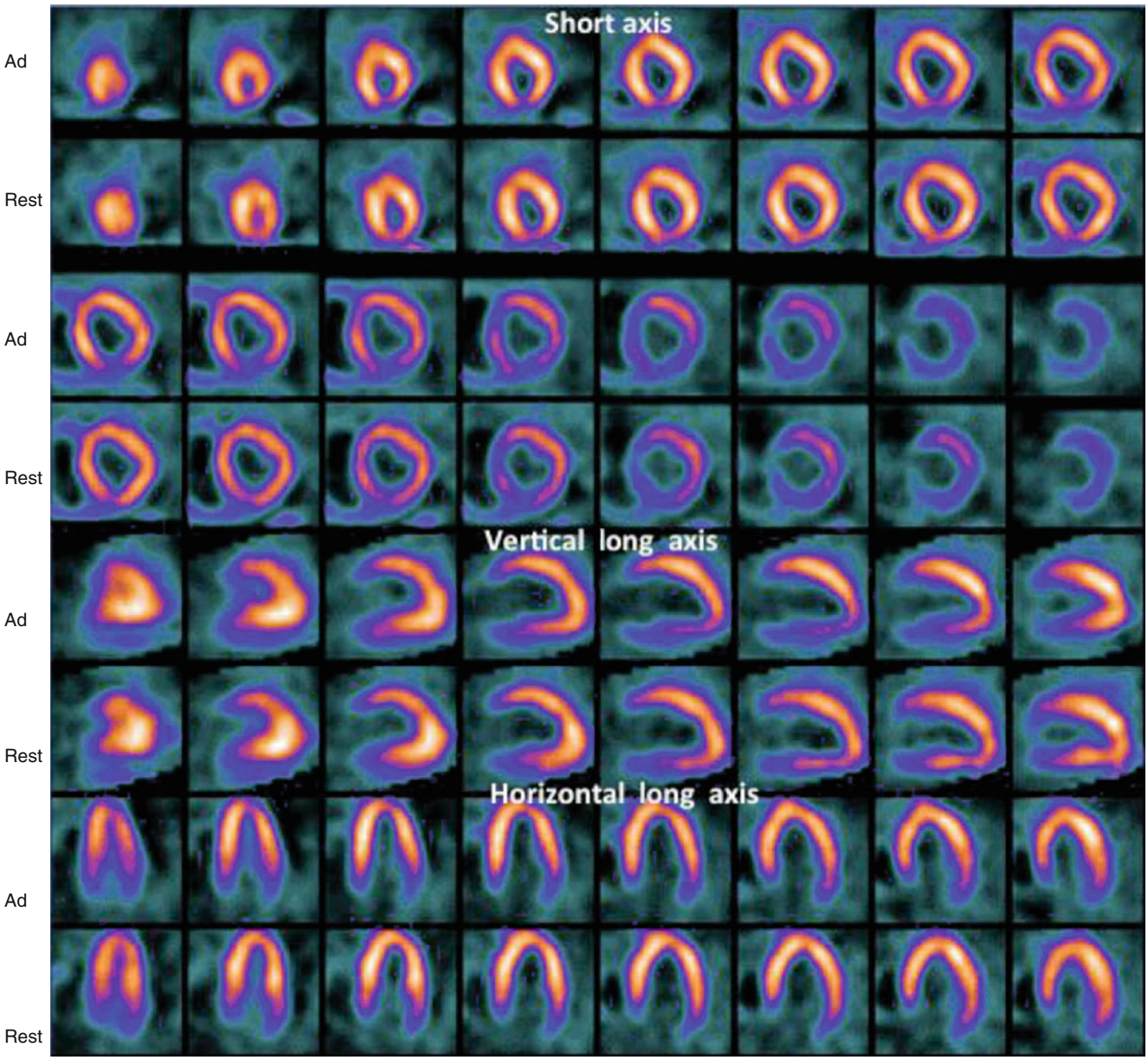

Fig. 12.4 Adenosine stress and rest perfusion images of a 48-year-old male with long history of hypertension, heavy alcohol abuse, smoking, and atrial fibrillation. He was admitted with worsening heart failure after an alcohol binge. After initial stabilization, he underwent adenosine and rest perfusion imaging. He has no chest pain or ST depression. There is no perfusion abnormality. But the LV is markedly enlarged, hypertrophied, and severely hypokinetic on gated SPECT images with an ejection fraction of 28 %. This patient has non-ischemic cardiomyopathy

rate, product of the heart rate, and blood pressure at peak exercise (peak double product) or oxygen consumption at peak exercise. A peak heart rate above 85 % of the age-predicted maximum heart rate or a double product >25 K is used to determine the adequacy of the exercise level. However, with changing demographic patterns, an increasing proportion of patients requiring stress testing are unable to exercise to an adequate workload and require pharmacological stress testing either alone or in conjunction with low-level exercise.

Pharmacological Stress

In patients who are unable to exercise or unable to reach an adequate workload due to noncardiac limitations (peripheral vascular disease, musculoskeletal disorders, or pulmonary disease), pharmacological stress should be used. Dipyridamole, adenosine (Adenoscan®, Astellas Pharma, Deerfield, IL), and regadenoson (Lexiscan™, Astellas Pharma, Deerfield, IL) are the most widely used agents for this purpose [14–18]. Following intravenous administration, these agents cause marked coronary vasodilation and can

increase myocardial blood flow three to four times the resting flow. However, blood flow increase is blunted in myocardial segments perfused by narrowed coronary arteries. This produces flow heterogeneity and results in apparent perfusion abnormalities. True ischemia is rare and occurs in patients with severe CAD where collateral circulation contributes significantly toward myocardial perfusion, and these vasodilators may induce a coronary steal in such cases. At a cellular level, dipyridamole acts by inhibiting the intracellular uptake of adenosine. Thus, adenosine is more directly acting than dipyridamole and has more predictable effect on the coronary blood flow. In a small percentage of patients, the standard dose of dipyridamole (0.56 mg/kg given over 4 min) may not result in maximum coronary vasodilation and may thus result in underestimation of CAD [16]. Dipyridamole is a long-acting agent, and its pharmacological effects persist for more than 30 min, which poses a challenge in those with significant dipyridamole-induced side effects and often requires longer monitoring and reversal of dipyridamole with intravenous aminophylline [16]. Due to these limitations, dipyridamole has largely been replaced by adenosine and regadenoson for pharmacological stress.

Adenosine has an extremely short half-life of less than 10 s and requires an infusion pump for its administration at a steady rate. This is administered at a dose of 0.14 mg/kg/min for 5–6 min. The radiotracer is injected at midpoint of adenosine infusion. Side effects are very common with adenosine infusion but generally are minor and self-limiting in nature. The most common side effects are nausea, headache, flushing of face, and hypotension. Transient high-grade AV block or symptomatic hypotension occurs in 5–7 % of patients with adenosine infusion. These side effects are generally self-terminating on completion of infusion and only rarely require premature discontinuation of adenosine infusion. Chest pain occurs in approximately 25 % of cases but is not specific for myocardial ischemia. The exact mechanism of dipyridamole- or adenosine-induced chest pain is not clear; perhaps, they act directly on the pain receptors. ST segment depression occurs rarely, but if it occurs, it is indicative of severe CAD. If possible, adenosine infusion should be combined with low-level exercise [15, 18]. This reduces adverse effects such as hypotension, nausea, and flushing and also reduces radiotracer uptake in the liver and other splanchnic organs, which improves the image quality. Addition of low-level exercise to adenosine infusion also improves the sensitivity and specificity for the detection of coronary artery disease [15]. Theophylline derivatives, including caffeine, act as antagonists of dipyridamole and adenosine at a cellular level and should be stopped prior to performing dipyridamole or adenosine stress perfusion imaging. Aminophylline can be given intravenously if the side effects of dipyridamole are persistent and bothersome to the patient. Because of the extremely short half-life, side effects of adenosine generally disappear with the discontinuation of its infusion, and aminophylline is only very rarely required. Figure 12.3 is an example of adenosine stress and rest ^{99m}Tc-sestamibi study.

Apart from coronary vasodilation, adenosine also results in systemic vasodilation and slowing of conduction in the AV node, which are undesirable side effects for pharmacological stress testing. There are four different kinds of adenosine receptors: A1, A2a, A2b, and A3. Adenosine acts on all four receptor types. A1 receptors are present in AV node and adenosine causes AV nodal block. A2 receptors are present in arterioles: A2a receptors are present in coronary vessels and A2b in systemic vessels. Adenosine results in coronary as well as systemic vasodilation. A3 receptors are present in lungs, bronchioles, and several other tissues. Adenosine can result in bronchospasm in patients with history of bronchial asthma or chronic obstructive pulmonary disease. A number of adenosine analogs, which are highly selective for adenosine receptors in coronary vessels (adenosine A2a receptor agonists), are under development for pharmacological stress perfusion imaging [17, 19, 20]. Of these, regadenoson (Lexiscan™, Astellas Pharma, Deerfield, IL) got FDA approval for pharmacological stress in 2008. Another two agents apadenoson and binodenoson are under clinical development. Unlike adenosine, regadenoson does not require intravenous infusion and is given as a fixed-dose bolus injection over 10 s. The diagnostic information provided by regadenoson is similar to that of adenosine, but adverse effects are fewer and less intense compared to adenosine [17, 19]. Because of ease of administration and fixed dose for all patients, regadenoson is gradually replacing all other pharmacological stress agents in clinical practice. Recent studies have shown that regadenoson is well tolerated in patients with history of bronchial asthma and COPD and renal insufficiency [21, 22]. Ingestion of caffeine-containing food and beverages prior to vasodilator stress testing can result in underestimation of ischemia, and therefore, patients need to be instructed to withhold all caffeine-containing food and beverages for at least 12 h prior to regadenoson stress testing. This poses logistical challenges in scheduling patients for stress testing, who may have inadvertently consumed caffeine in the preceding hours. It has recently been proposed that unlike dipyridamole or adenosine, regadenoson is less likely to be affected by small quantities of caffeine consumption [23]. However, recently concluded phase III-b study indicates that administration of 200 or 400 mg or oral caffeine 90 min prior to regadenoson stress testing did result in underestimation of ischemia compared to baseline regadenoson study [24]. Therefore, caffeine should be withheld for at least 12 h prior to any vasodilator stress testing.

Intravenous dobutamine can also be used for stress imaging [25]. This acts by increasing the heart rate and myocardial contractility and oxygen demand. Adenosine or

regadenoson are preferable over dobutamine because of a greater increase in myocardial blood flow and flow heterogeneity with these agents. Dobutamine is generally used in patients where dipyridamole or adenosine is contraindicated, such as in patients with severe bronchopulmonary disease or congestive heart failure or in those where theophylline cannot be stopped. Dobutamine is administered as infusion starting at 10 μg/kg/min and increased by 10 μg/kg/min every 3 min until a maximum dose of 40 μg/kg/min is reached, target heart rate is achieved, or adverse symptoms or evidence of ischemia develops. In those who fail to achieve target heart rate at maximum dobutamine dose, atropine in 0.5–1.0 mg dose can be injected intravenously [25, 26]. Side effects with dobutamine are common and are of particularly of concern in elderly and sick patients and in those with impaired left ventricular function and with history of significant atrial or ventricular arrhythmias [26]. Since regadenoson is well tolerated in patients with bronchial asthma and COPD [21], dobutamine use is declining for pharmacological stress perfusion imaging.

Interpretation of Perfusion Images

Interpretation of myocardial perfusion images requires experience and skill and an adequate understanding of the cardiac physiology, pathology, and applied physics, as well as awareness of the possible sources of artifacts. Perfusion images are prone to artifacts due to attenuation from structures overlying the heart or in proximity to the heart. The diaphragm and liver can attenuate the inferior wall. In women, breast can cause attenuation. Proximity of the liver to the inferior wall of the heart is also an important source of artifacts. Tracer activity in the liver can result in artifactually higher counts in the inferior wall due to scattered counts. Conversely, during image reconstruction, over-subtraction of counts from the structures in close proximity of the hot liver can result in artifactually lower counts in the inferior wall. SPECT imaging is also prone to a variety of other artifacts, such as patient motion during imaging and tracer activity in the gut and other subdiaphragmatic structures. ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin result in high activity in the liver, gall bladder, and gut, particularly in the rest and pharmacological stress images. Sometimes bowel loops with significant radiotracer activity may overlap the heart, which can substantially degrade the image quality and in the worst scenario can render the images uninterpretable. If bowel loops with radioactivity are noticed to overlap the heart during image acquisition, the image acquisition should be aborted and recommenced after repositioning the patient a few minutes later. Administration of fatty food prior to imaging does not enhance clearance of radiotracer from the liver. On the other hand, this can increase the amount of radioactivity in the gut because of dumping of gall bladder activity in the gut. Artifacts can also appear during various stages of image acquisition and data processing due to technical and equipment-related issues. Strict and rigorous quality control of gamma camera is mandatory for avoiding technical artifacts. A meticulous effort is required to prevent false interpretation of the images due to these artifacts [27, 28].

A number of techniques are used for correcting attenuation artifacts during SPECT imaging. Attenuation is nonuniform, being dependent on the density and thickness of the tissue around the heart. A three-dimensional spatial map of attenuation coefficients using an external radiation transmission source or CT is obtained. These attenuation maps are unique for each patient and are used for correcting the emission images [11]. Imaging patients in the prone position can also help in the differentiation of attenuation artifacts from true perfusion abnormalities in the inferior wall. However, prone imaging does not replace standard supine imaging. Prone images are acquired in addition to the standard supine images. This increases the time required to image the patients.

The perfusion images can be interpreted visually. However, quantitative analysis of the images is more reliable. Subtle abnormalities can better be appreciated with quantitative analysis. Quantitative analysis can be performed using a simple circumferential analysis program or with the use of a polar map. The distribution of counts in the patients' images is compared with a database derived from the normal subjects of the same gender. To obtain a circumferential profile, a region of interest is drawn around the cardiac contour, the myocardium is divided into 36 radial sectors, and the counts in these sectors are plotted and compared with the normal database. In a polar plot, the short-axis myocardial slices from SPECT images are displayed as a series of concentric rings in a single display. These rings are displayed on a color scale and compared with gender-based normal database so that the myocardial segments with abnormally low radiotracer uptake are shown in a different color from the normal myocardium. Quantitative analysis can also provide an estimate of the extent or severity of myocardial ischemia, which is important if serial studies are used to follow the disease progress. Quantitative analysis also minimizes the intra- and interobserver variability of the image interpretation [27].

A systematic approach is required for a comprehensive interpretation of myocardial perfusion studies [29]. The raw images should be examined to look for any potential sources of artifacts and overall image quality. Sometimes important extra-cardiac abnormalities, such as tumors in

lungs, mediastinum, or breasts or pleural effusion, can be detected on raw images.

Gastrointestinal abnormalities such as hiatal hernias or ascites can also be observed on raw images. Many times, these abnormalities are detected for the first time as unexpected incidental findings during perfusion imaging but nevertheless are important for the management of the patients (Figs. 12.5 and 12.6) [30, 31]. The patient's gender, body weight, and body habitus, the radiopharmaceutical used and its dose, the interval between tracer injection and imaging, and the type of stress used should be taken into consideration while viewing the raw images. With ^{201}Tl, the lung fields should be examined for any evidence of increased lung tracer uptake on stress images, which is an indicator of high-risk study. The processed images should be interpreted qualitatively as well as quantitatively. Clinical history, pretest likelihood of CAD, details of stress testing, and electrocardiographic changes should be taken into consideration while performing the final interpretation. The report should be comprehensive and succinct and clearly concluded whether abnormal or normal, and if abnormal, the extent, location, and nature of abnormality should be adequately described [28, 29].

Clinical Applications of Myocardial Perfusion Imaging

Detection of Coronary Artery Disease

Myocardial perfusion imaging is useful for establishing the diagnosis of CAD in patients presenting with chest pain or in those with a high clinical suspicion of CAD because of the presence of one or more risk factors for CAD. This is an important noninvasive test for identifying patients who should be considered for further invasive studies. Addition of myocardial perfusion imaging to exercise ECG increases the sensitivity as well as specificity of the test for the detection of CAD. The sensitivity and specificity of exercise ECG alone are 50–60 and 60 %, respectively, for the detection of

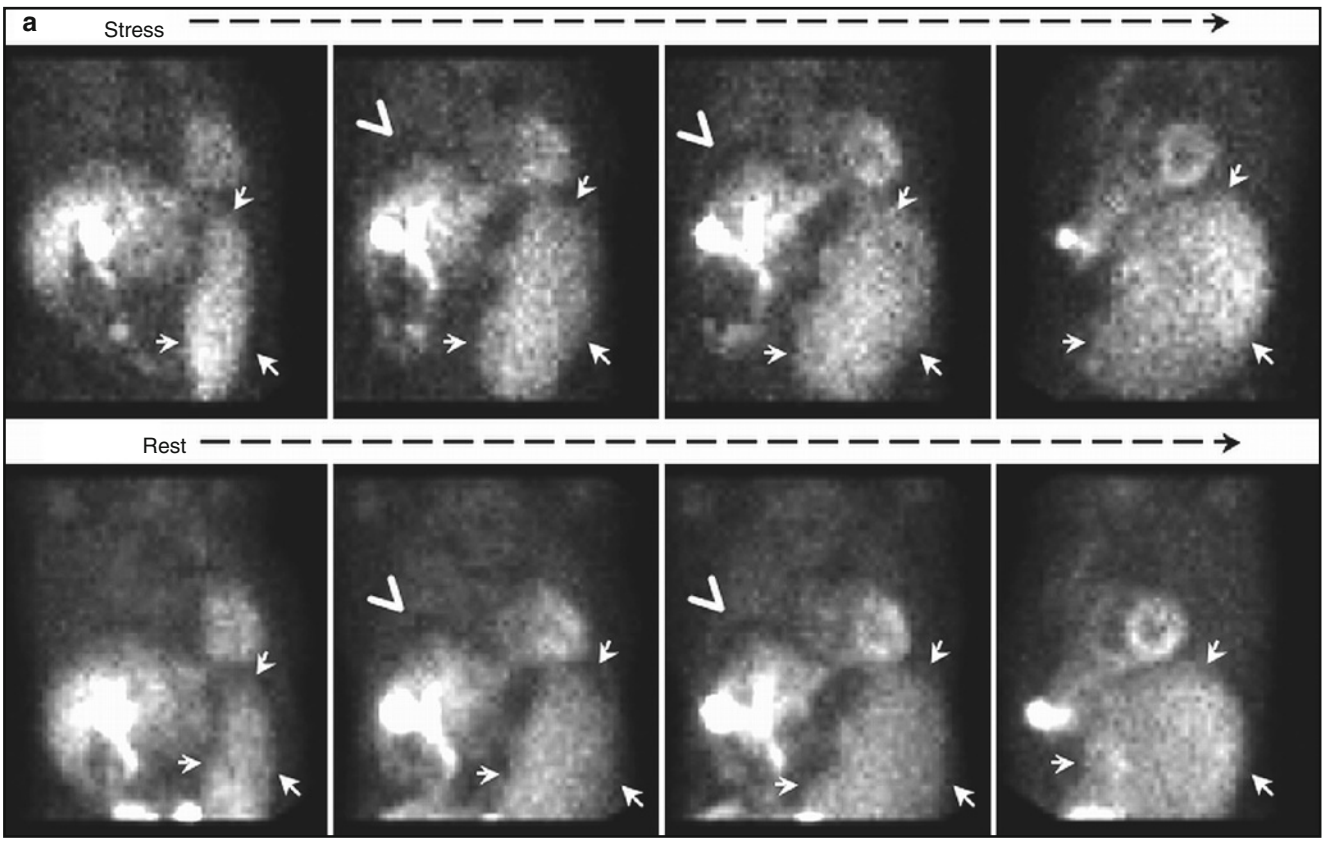

Fig. 12.5 (**a**) Representative frames from Ad stress and rest SPECT images of an 82-year-old woman who underwent this study as a part of preoperative cardiac evaluation prior to abdominal surgery. The raw images reveal massive splenomegaly (*small arrows*) and ascites (*large arrow heads*). The patient had history of agnogenic myeloid metaplasia and portal hypertension. (**b**) CT of the abdomen and pelvis with contrast showed massive splenomegaly (*S*) (24 × 20 × 11 cm), ascites (*black arrows*), massively dilated portal (*Pv*) and splenic veins (*Sv*), and esophageal and splenic varices (*white arrows*) (*L* liver, *A* aorta)

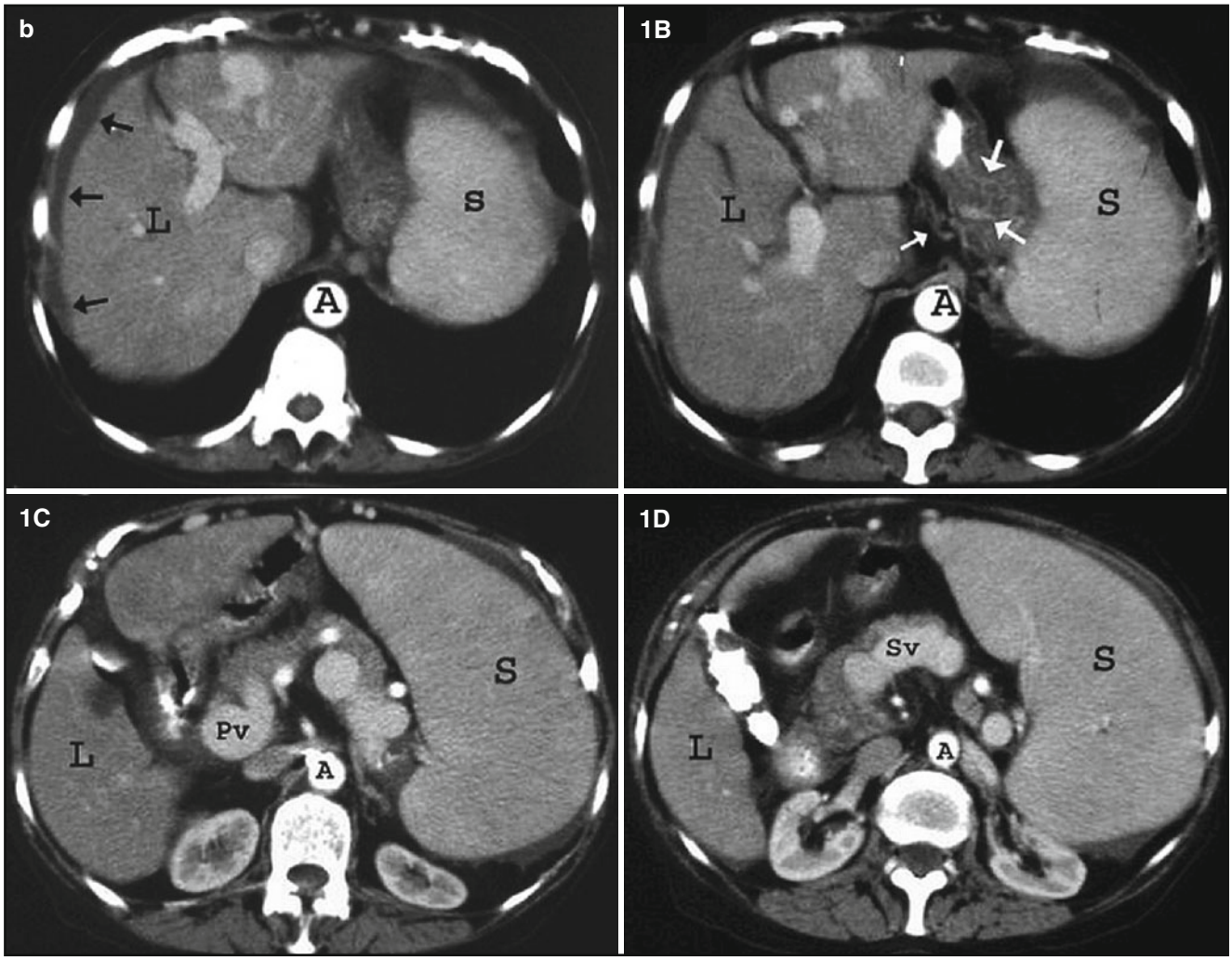

Fig. 12.5 (continued)

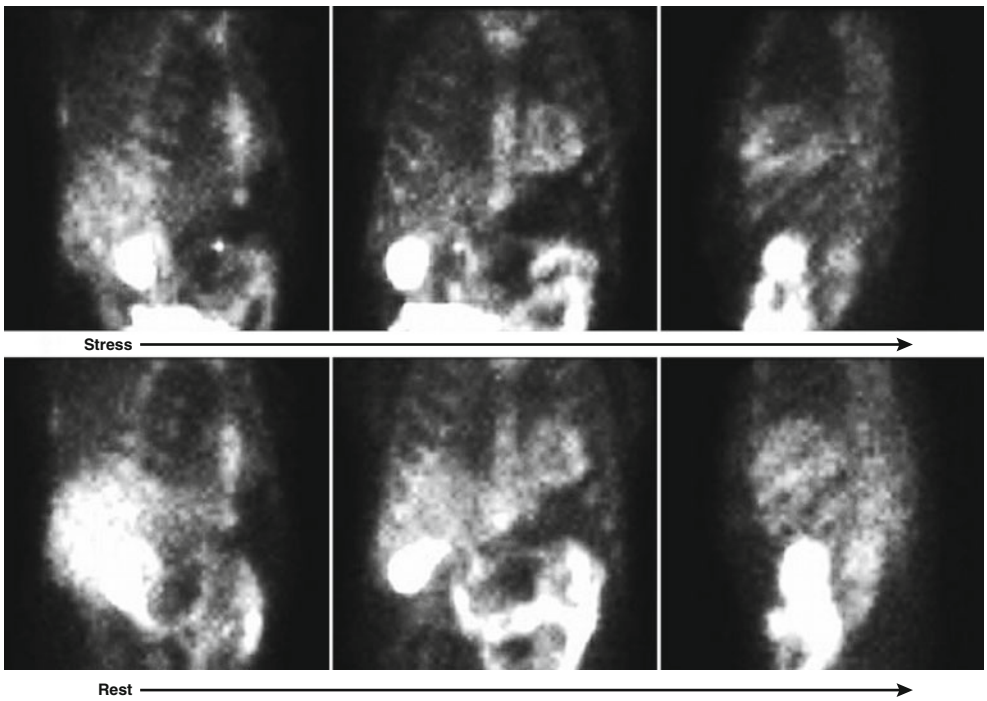

Fig. 12.6 Representative frames of Ad stress and rest raw rotating images of a patient with known CAD and worsening angina pectoris showing marked tracer uptake in ribs, sternum, vertebrae, and scapulae on both stress and rest images. The patient turned out to have multiple myeloma with severe pancytopenia (Reprinted from Gowda et al. [30] with permission from Springer Science+Business Media)

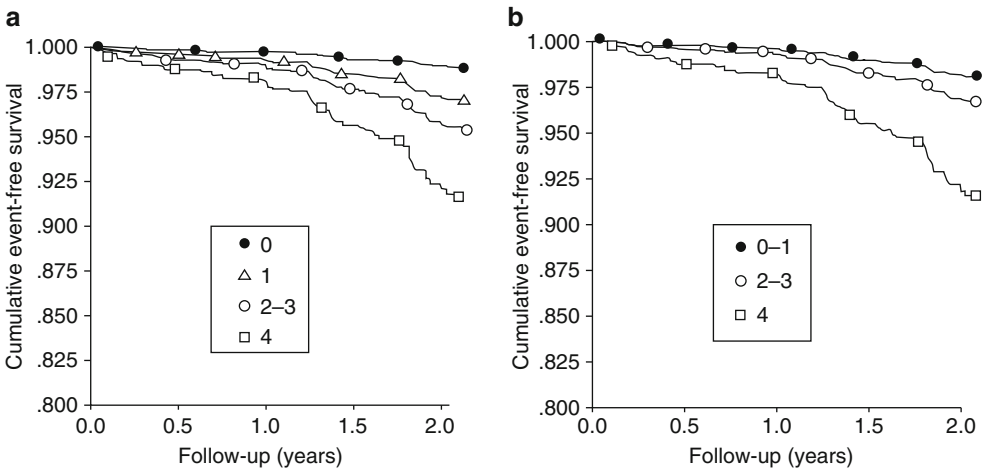

Fig. 12.7 Cumulative 2-year event-free survival stratified by defect extent and severity score (**a**) and reversibility score (**b**), $p<0.001$ for each (Reprinted from Thomas et al. [36] with permission from Elsevier)

CAD, whereas myocardial perfusion imaging has a sensitivity of 85–90 % and specificity of 90 % or above for the detection of CAD. Myocardial perfusion imaging has a particular advantage over exercise ECG in patients with left ventricular hypertrophy, left bundle branch block (LBBB), therapy with digoxin, and other abnormalities interfering with proper interpretation of ST segment changes on exercise.

Myocardial perfusion imaging is an important and cost-effective gatekeeper for the identification of patients who should undergo further invasive cardiac workup. In a study involving more than 4,000 patients who underwent stress myocardial perfusion imaging for the evaluation of CAD, the subsequent cardiac catheterization rates over a mean follow-up period of 9 months were 32 % in those with reversible perfusion abnormality and only 3.5 % in those without reversible perfusion abnormality [32]. Furthermore, in the reversible perfusion abnormality group, cardiac catheterization rate was 60 % in those with high-risk studies (reversible perfusion abnormality of the left anterior descending coronary artery territory, multiple areas of ischemia, or increased lung tracer uptake), compared with 9 % in the remaining patients with reversible perfusion abnormalities. The findings on myocardial perfusion imaging were far more predictive of subsequent cardiac catheterization than clinical and treadmill exercise ECG variables alone or in combination, indicating the important role of stress myocardial perfusion imaging for initial evaluation of patients with suspected CAD.

Risk Stratification of Patients with CAD

Information about the severity, location, and extent of myocardial ischemia is useful for risk stratification of patients with known CAD [33]. Large areas or multiple areas of perfusion abnormality identify patients at high risk for cardiovascular events on follow-up. Increased lung tracer uptake and transient left ventricular dilation on stress images are indicative of severe CAD and are predictive of poor prognosis. Both of these findings are due to a transient left ventricular dysfunction during stress. The magnitude of ST depression on symptom-limited exercise testing does not correlate with the extent of ischemia on perfusion imaging [34]. The quantitative extent and severity of myocardial ischemia determined from stress-rest perfusion imaging correlates with the subsequent occurrence of unstable angina, acute myocardial infarction, and cardiac death. Of various clinical and laboratory variables including electrocardiographic and coronary angiographic variables, myocardial perfusion imaging provides the most powerful prognostic information in all groups of patients with CAD. Based on the quantitative extent and severity of perfusion abnormalities on stress perfusion images and the extent of reversibility on stress-rest perfusion imaging, patients with CAD can be categorized into low- to high-risk categories for the occurrence of adverse cardiac events on follow-up (Fig. 12.7) [35, 36]. Patients with a negative myocardial perfusion study have an excellent prognosis; several large clinical studies have shown these patients to have a less than 0.6 % annual cardiac event rate [35, 36]. A normal myocardial perfusion imaging study, even in the presence of angiographically documented CAD, is associated with an excellent long-term prognosis and a very low incidence of cardiac events on follow-up [35].

Post-Myocardial-Infarction Evaluation

Sub-maximum stress perfusion imaging is an established technique for risk stratification of patients with uncomplicated myocardial infarction prior to hospital discharge [37]. Patients with fixed defects have a low incidence of adverse cardiac events, whereas those with reversible defects have a higher incidence of adverse cardiac events. This test can be used to identify patients with recent myocardial infarction who can benefit from cardiac catheterization and revascularization. With the current practice of the routine use of revascularization with percutaneous interventions in patients with acute myocardial infarction and unstable angina, predischarge stress perfusion imaging is rarely needed these days. However, stress perfusion imaging plays an important role in

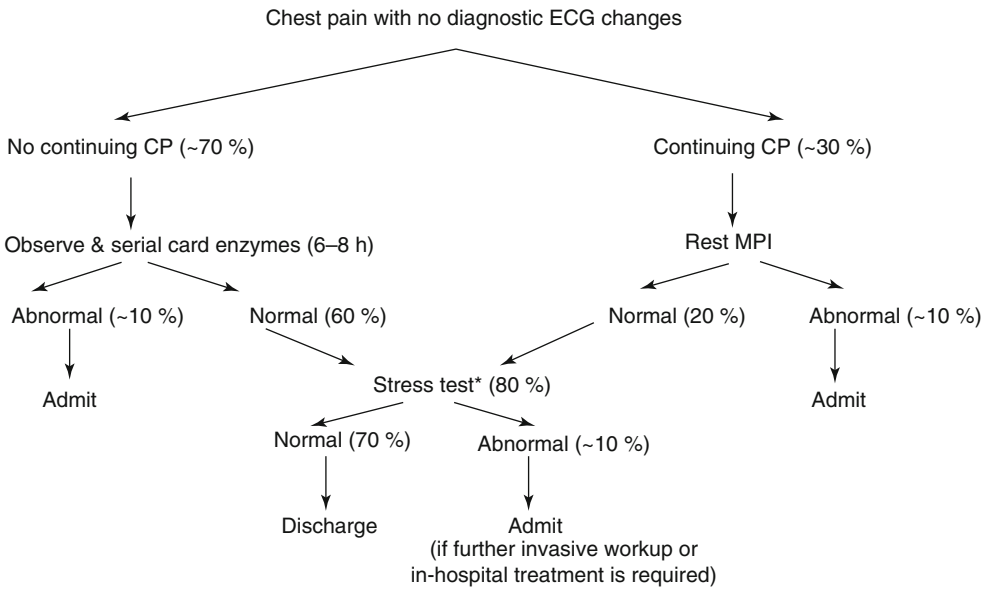

Fig. 12.8 A schematic representation of the proposed algorithm for early triaging of patients presenting with acute chest pain using myocardial perfusion imaging

determining the need of subsequent revascularization in the presence of additional noncritical coronary lesions of unclear significance and in patients with recurrence of symptoms of chest pain following revascularization for acute myocardial infarction [38]. Myocardial perfusion imaging is very helpful for long-term follow-up of patients undergoing revascularization for acute myocardial infarction.

Triaging of Patients with Chest Pain of Uncertain Origin

With greater public education and awareness for presenting immediately to the nearest emergency department in case of chest pain or any other symptoms suspicious of an acute myocardial infarction, a large number of patients with chest pain are seen in the emergency departments these days. Acute chest pain is the second most common condition seen in emergency departments in the USA [39–41]. In the USA, six to eight million patient visits for chest pain occur annually to the emergency department. Fewer than 15 % of these patients turn out to have acute coronary syndrome. On the other hand, a small but significant proportion of patients with acute coronary syndrome may have only atypical symptoms with no overt electrocardiographic or biochemical abnormalities at presentation, which may prompt an early but inappropriate discharge from the emergency department with a mistaken conclusion of noncardiac chest pain. Most large emergency departments now have a dedicated chest pain center or institutional protocols for an effective, reliable, and prompt triage of patients with chest pain. A combination of serial electrocardiograms, cardiac enzymes, and noninvasive cardiac imaging is used for triaging these patients [39–43]. Resting and stress myocardial perfusion imaging can be used quite effectively in chest pain centers. Despite an upfront cost associated with instrumentation and training of personnel and recurring cost associated with each study, an appropriate use of myocardial perfusion imaging in emergency departments is associated with significant reductions in the time required to arrive at a definitive diagnosis, hospital admission rate, average hospital stay, and overall per-patient cost [40–43]. The presence of resting perfusion abnormalities in patients with chest pain in the absence of prior myocardial infarction is indicative of an acute coronary syndrome and warrants admission to the coronary care unit and appropriate treatment. Absence of perfusion abnormalities points more toward a noncardiac cause of chest pain. Patients with negative resting perfusion images can further undergo stress perfusion imaging within a short period of time to detect the presence of exercise-induced myocardial ischemia [41, 42]. Figure 12.8 shows a proposed scheme for the utilization of myocardial perfusion imaging in chest pain centers [43], and Fig. 12.9 shows rest perfusion images of a patient who presented with atypical chest pain and turned out to have severe CAD. Figure 12.2 shows stress-rest perfusion images of a patients presenting with chest pain, who ruled out for acute myocardial infarction but turned out to have severe multi-vessel CAD. Currently, there is a great interest in rapid triaging of patients presenting to the emergency department with chest pain but no overt evidence of acute coronary syndrome. Whereas several different imaging modalities are available and have shown some promise for this role, nuclear imaging using a judicious combination of rest imaging, rest-stress imaging, or stress imaging alone remains the most readily available, cost-effective, and relatively simple technique for this purpose [44, 45]. The information provided by nuclear imaging is not only useful for safely discharging patients from the emergency department but is also critically important for arriving at a definitive diagnosis and for guiding long-term

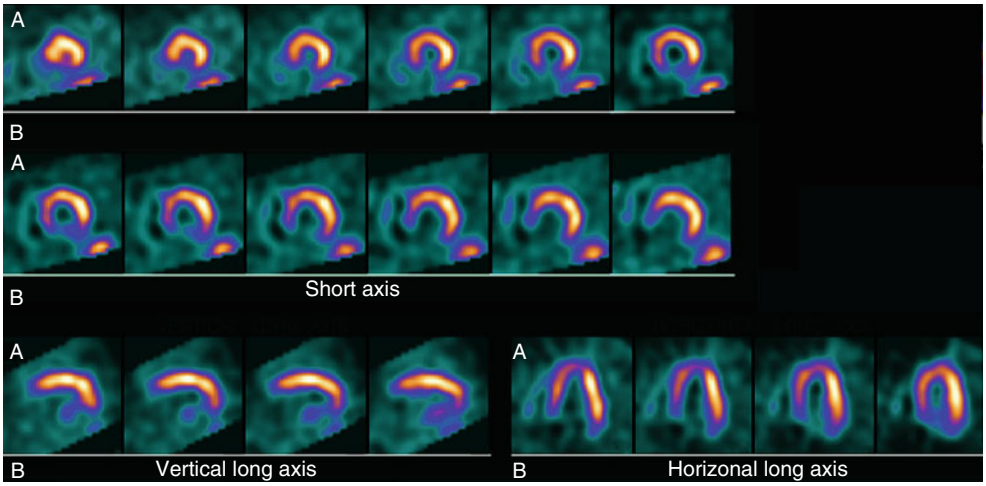

Fig. 12.9 Rest myocardial perfusion images of 43-year-old male patient with multiple risk factors for CAD, who presented with atypical chest pain and no electrocardiographic changes or increase in cardiac enzymes. The patient had no history of prior myocardial infarction. There is a large area of perfusion abnormality involving the inferior and inferoseptal walls. Coronary angiography showed completely occluded RCA with a large thrombus and 90 % narrowing of the LCx. There was a significant reduction of the perfusion abnormality following immediate revascularization the RCA and LCx

management and follow-up plan and for providing long-term prognostication of these patients [41, 43].

Risk Stratification Prior to Noncardiac Surgery

Adverse cardiac events are important cause of morbidity and mortality following noncardiac surgery, particularly in elderly patients and in those with known CAD or with risk factors for CAD [46, 47]. Appropriate use of nuclear imaging techniques can significantly lower the incidence of this complication. The frequency of occurrence of adverse cardiac events in the perioperative period depends on a number of factors: the prevalence and severity of CAD and left ventricular dysfunction in this patient population and the nature and severity of hemodynamic stress during the perioperative period. Patients with a high prevalence of CAD, either symptomatic or occult, and with impaired left ventricular function are particularly vulnerable to cardiac events. Prolonged vascular surgery involving cross-clamping of the aorta, major shifts between intravascular and extravascular fluid compartments, and hypotension impose significant stress on the cardiovascular system and can result in arrhythmias, pulmonary edema, or myocardial infarction in the perioperative period in patients with CAD. Patients with peripheral vascular disease have a high prevalence of CAD and are at a high risk of perioperative cardiac events. Even after peripheral vascular surgery, these patients continue to have very high morbidity and mortality due to cardiac events. A number of studies have established the role of pharmacological stress perfusion imaging for identifying patients at high risk for perioperative cardiac events [46, 47]. Adenosine and regadenoson are particularly suitable because of the inability of these patients to exercise. Abnormalities on stress perfusion imaging are predictive not only of perioperative morbidity and mortality but also of long-term mortality and morbidity [47]. The current ACC/AHA guidelines for preoperative risk stratification take into consideration the presence of CAD or CAD risk factors, functional capacity, and the nature and risk of the surgical procedure [47]. Myocardial perfusion imaging is useful in patients with risk factors for CAD and impaired functional capacity and in those undergoing relative high-risk surgery. Patients with no risk factors of CAD and good functional capacity and those undergoing relative low- to intermediate-risk surgical procedure do not warrant routine preoperative myocardial perfusion imaging. Similarly patients undergoing emergent or life-saving surgery also do not warrant preoperative myocardial perfusion imaging. Optimization of their hemodynamic status in the perioperative period is probably the most effective approach in these patients. However, following recovery from successful surgery, many of these patients may require consideration for myocardial perfusion imaging for long-term management if they have multiple CAD risk factors and impaired functional capacity.

Detection of Myocardial Viability

The impairment in left ventricular function and regional wall motion abnormalities in many patients with CAD may be reversible to varying extents with proper utilization of revascularization procedures [3, 48–50]. This can result in improvement in left ventricular function and symptoms of heart failure, as well as prognosis, and can potentially avoid or delay the need for cardiac transplantation in some patients with advanced heart failure. However, identification and differentiation of this viable but dysfunctional myocardium with a potential for recovery in contractility and left

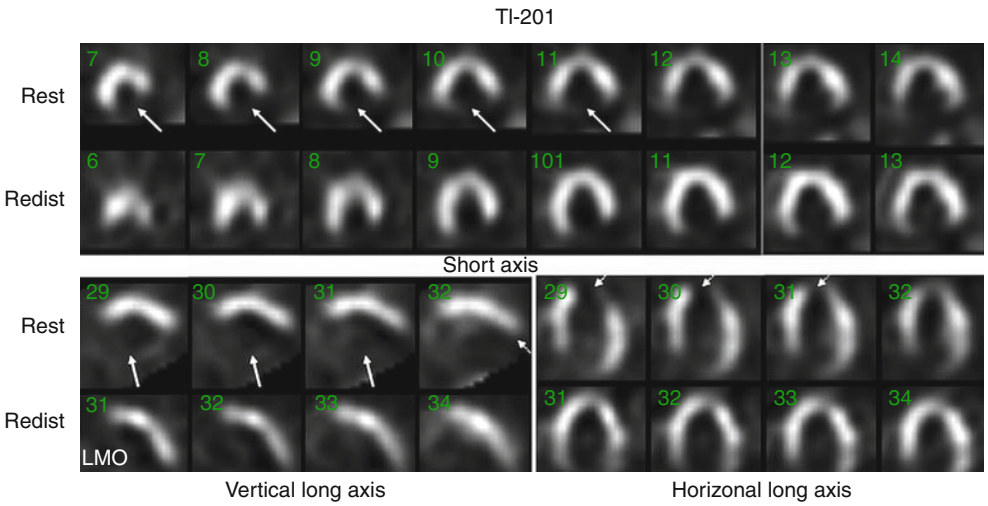

Fig. 12.10 Rest and 4-h redistribution ^{201}Tl images of a patient with old myocardial infarction and congestive heart failure. The left ventricle is enlarged with a large dense scar involving the inferior and lateral walls with no viability (*solid arrows*). There is apical reversible perfusion abnormality indicating viability (*dotted arrows*). The anterior wall and septum are normally perfused at rest indicating preserved viability. The inferior and lateral walls are akinetic, and the remaining ventricle is hypokinetic on gated SPECT with an LVEF of 21 %. LAD had 70 % proximal lesion and RCA had 100 % occlusion. Based on the presence of viability in the anterior wall, septum, and apex, the LAD was revascularized

ventricular dynamics from the irreversibly scarred myocardium with no potential for recovery in function pose a major challenge in current practice of cardiology [51, 52]. Symptoms, clinical examination, electrocardiogram, and conventional techniques for functional assessment are often not helpful. A number of techniques such as dobutamine echocardiography and magnetic resonance imaging have been employed with varying success, but nuclear imaging techniques, conventional perfusion imaging, and positron emission tomography have played a crucial role in this field [3]. A brief episode of myocardial ischemia may result in regional wall motion abnormalities, which may persist for a variable period of time even after the restoration of perfusion. This is called as stunned myocardium. This myocardium is characterized by wall motion abnormalities but preserved perfusion and metabolism. Wall motion abnormality recovers spontaneously over time without any intervention. Myocardium with chronic low flow but without any necrosis is called as hibernating myocardium. This myocardium is characterized by reduced perfusion, impaired resting wall motion, but preserved metabolic activity, improvement in wall motion with low-dose dobutamine administration, and restoration of contractility after revascularization. This myocardium needs to be differentiated from scarred myocardium, which also has impaired perfusion and wall motion at rest, but shows no improvement in contractility with low-dose dobutamine, has no evidence of metabolic activity, and shows no change in wall motion with revascularization. Myocardial uptake and retention or washout of perfusion tracers is dependent on the structural and metabolic integrity of the myocytes. Rest-redistribution ^{201}Tl imaging can be used for the detection of myocardial viability. Presence of significant myocardial uptake on quantitative analysis (≥50 % uptake compared to the normal myocardial segments) or redistribution on delayed imaging is indicative of myocardial viability and predictive of functional improvement after revascularization in abnormal myocardial segments [48] (Fig. 12.10). Resting ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin can also provide information about myocardial viability using a quantitative approach. Similar to ^{201}Tl, ≥50 % uptake of ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin in abnormal myocardial segments is predictive of myocardial viability [49].

Nitrate administration prior to the injection of myocardial perfusion tracers has shown a promising role for the detection of myocardial viability. Viable myocardial segments with resting hypoperfusion show an improvement in perfusion following nitrate administration; this change is predictive of functional improvement after revascularization [50]. PET imaging techniques for myocardial viability are based on the demonstration of metabolic activity in the dysfunctional myocardial segments. PET permits imaging of myocardial metabolism at rest and under different physiological conditions. Myocardium has very high energy requirement, which is derived from the metabolism of free fatty acids and glucose. Free fatty acids are the preferred substrate in normally perfused myocardium. However, in the presence of ischemia, such as in hibernating myocardium, anaerobic glycolysis is the predominant source of energy production. Anaerobic glycolysis is very inefficient

Table 12.1 Indications of myocardial perfusion imaging and the most appropriate imaging technique(s) and radiotracer(s)

Indication	Imaging technique(s)	Radiotracer(s)
Detection of CAD	Gated stress[a]-rest SPECT	^{99m}Tc tracers
Risk stratification of patients with known CAD	Gated stress[a]-rest SPECT	^{99m}Tc tracers
Post-myocardial-infarction evaluation	Gated stress[a]-rest SPECT	^{99m}Tc tracers
Patients with acute chest pain of uncertain origin	Gated rest SPECT (stress SPECT with normal rest SPECT)	^{99m}Tc tracers
Evaluation prior to noncardiac surgery	Gated pharmacological stress-rest SPECT	^{99m}Tc tracers
Detection of myocardial viability	Rest-redistribution SPECT/gated rest SPECT (preferably with nitrates)	^{201}Tl/^{99m}Tc tracers
Congestive heart failure	Rest/redistribution-stress SPECT	^{201}Tl/^{99m}Tc tracers

^{99m}Tc tracers, ^{99m}Tc-sestamibi, or ^{99m}Tc-tetrofosmin

[a]Exercise is the preferred stress modality. Choose pharmacological stress for those unable to exercise to an adequate workload

in ATP production and requires a very large amount of glucose for meeting the energy demand. Therefore, hibernating myocardium is characterized by a profound increase in glycolytic activity despite a reduction in perfusion. Glucose uptake and initial steps involved in glycolysis can be imaged by ^{18}F-fluorodeoxyglucose (^{18}FDG), a PET tracer. Myocardial flow-metabolic mismatch is the hallmark of myocardial viability on PET imaging. This will be discussed further in a later section of this chapter. A proper evaluation of myocardial viability requires an adequate understanding of coronary physiology, pathology, and metabolism and a thoughtful integration of pertinent clinical information and angiographic data with the nuclear imaging data [51, 52].

Evaluation of Patients with Congestive Heart Failure

Currently, there are more than 4.5 million patients with congestive heart failure in the United States, and more than 500,000 new patients are diagnosed with congestive heart failure every year. A detailed and often expensive workup is required to determine its etiology, assess its severity, and optimize its treatment. Myocardial perfusion imaging can be used to differentiate between ischemic and non-ischemic cardiomyopathy and for the assessment of left and right ventricular function (Figs. 12.3 and 12.4). This is highly cost-effective and can potentially avoid invasive tests in a substantial proportion of patients with heart failure. In patients with ischemic cardiomyopathy, perfusion imaging can be used quite effectively for the detection of myocardial viability, which may warrant a consideration for revascularization. Furthermore, as described below, nuclear imaging techniques can be used for an accurate, reliable, and highly reproducible serial assessment of left ventricular and right ventricular function in these patients. This is critical because an appropriate use of angiotensin-converting enzyme inhibitors and β-blockers can result in an improvement in left ventricular function in a significant proportion of patients with congestive heart failure.

Table 12.1 provides a summary of the indications of myocardial perfusion imaging and the optimal imaging techniques and radiotracers for each indication.

Assessment of Left and Right Ventricular Function

Although a number of techniques such as echocardiography, contrast ventriculography, and magnetic resonance imaging can be used for the assessment of the right and left ventricular function, yet, nuclear imaging techniques offer a distinct advantage in several clinical situations. With nuclear imaging techniques, ventricular function can be assessed by first-pass imaging, equilibrium radionuclide angiocardiography, or gated SPECT imaging.

First-Pass Imaging

First-pass imaging is done by dynamic imaging of the passage of radioactivity from the superior vena cava to the right heart, to the lungs, and then to the left heart after injecting a bolus of radiotracer into the peripheral vein. Right and left ventricular ejection fraction can be calculated from these data. ^{99m}Tc-labeled myocardial perfusion imaging agents permit dynamic first-pass imaging during the injection of these agents either at rest or during exercise. Thus, information about perfusion and function can be obtained from the same injection of radiopharmaceutical [53]. The complex geometry of the right ventricle makes it somewhat difficult to visualize and study its function by conventional imaging techniques. However, first-pass imaging permits a clearer visualization of the right ventricle, unobstructed by other chambers of the heart, and a reliable and objective assessment of right ventricular ejection fraction. With greater recognition of pulmonary hypertension and availability of effective therapies for this condition, first-pass imaging can play an important role in evaluation and monitoring of therapy in patients with pulmonary hypertension.

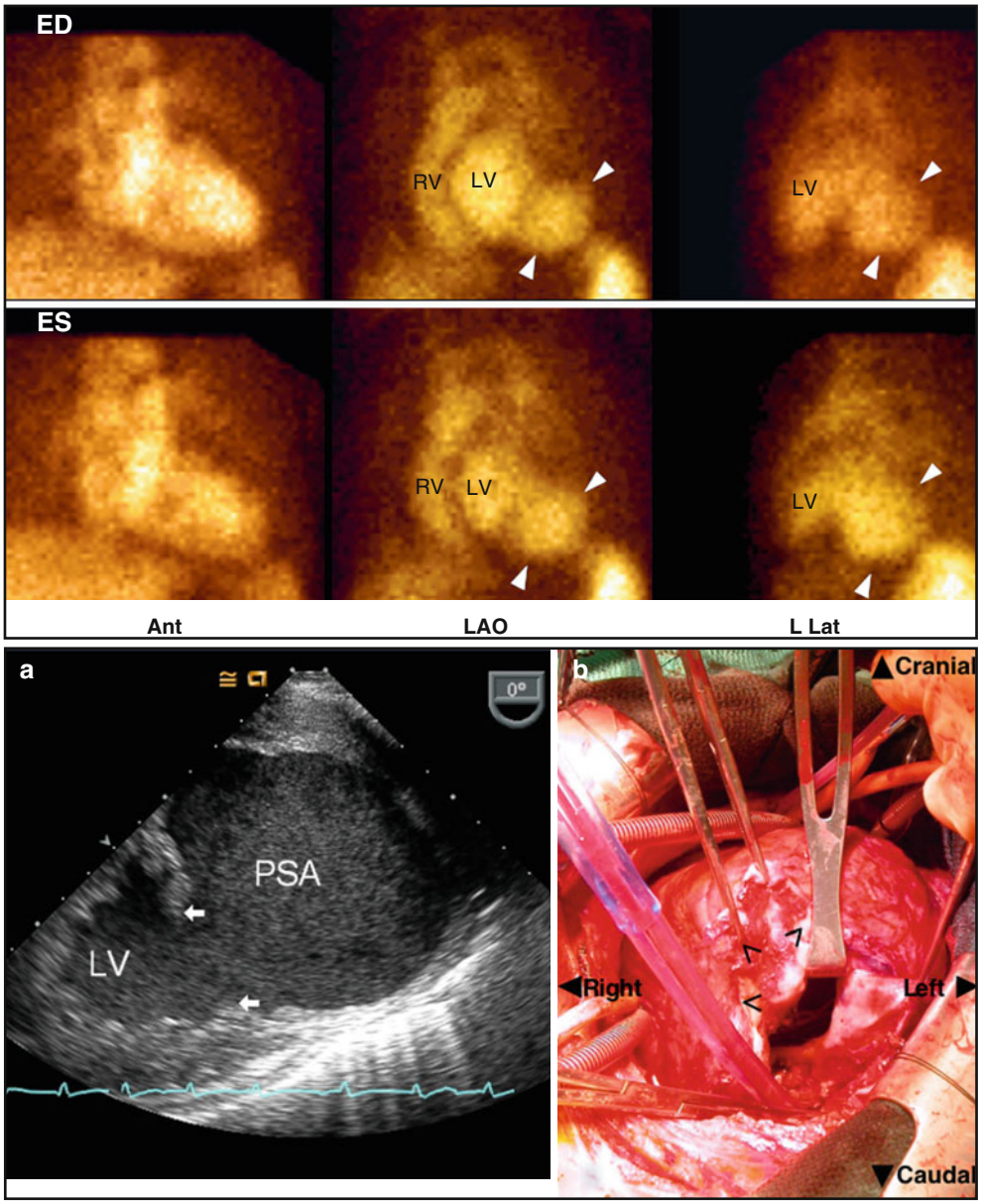

Fig. 12.11 (**a**) End-diastolic (*ED*) and end-systolic (*ES*) frames of equilibrium radionuclide angiocardiography images in three standard planar views (*ANT* anterior, *LAO* left anterior oblique, *L Lat* left lateral) of a 47-year-old male who presented with worsening heart failure following a myocardial infarction. There is a large pseudoaneurysm involving the basal part of inferolateral wall (*arrowheads*). (**b**) Transesophageal echocardiogram shows rupture in the basal lateral wall in *panel a* (*solid arrows*). *Panel b* shows the rupture in lateral wall from the opened pseudoaneurysmal sac (*arrowheads*) during surgery

Equilibrium Radionuclide Angiocardiography

Equilibrium radionuclide angiocardiography (ERNA), also commonly known as multigated acquisition (MUGA), is performed by blood pool labeling with ^{99m}Tc-pertechnetate. ^{99m}Tc-pertechnetate, when injected after the administration of pyrophosphate, binds to red blood cells. The ECG-gated images of the heart are acquired in three standard views (anterior, left anterior oblique, and left lateral) to assess right and left ventricular wall motion and to calculate left ventricular ejection fraction. A time activity curve reflecting the temporal changes in left ventricular volumes during the cardiac cycle can also be obtained from these images. From this curve, left ventricular ejection fraction can be calculated. The slopes of this curve during rapid ejection phase in systole and during the rapid filling phase in diastole provide the peak ejection and peak filling rates. Left ventricular ejection fraction (LVEF) is the most widely used index of left ventricular function. SPECT imaging can also be used with equilibrium radionuclide angiocardiography. This may provide a more detailed assessment of the regional left and right ventricular function. However, SPECT-ERNA imaging has not gained wide clinical acceptance, and planar ERNA still remains the standard test in clinical practice (Fig. 12.11). ERNA provides a quantitative, objective, and highly reproducible estimate of left ventricular ejection fraction. Left ventricular ejection fraction is obtained from the background-corrected end-diastolic and end-systolic counts from automated regions drawn around the left ventricle. The assessment of left ventricular ejection fraction from ERNA is independent of the geometry

of the left ventricle and does not require any geographical assumptions used by all other imaging modalities. Furthermore, patients with difficult echogenic windows still yield good quality ERNA images. ERNA remains somewhat underutilized in clinical practice. ERNA should be preferred over other modalities in patients where a precise and objective assessment of left ventricular ejection fraction has important implications for therapy planning such as in patients under consideration for implantable cardiac defibrillators for primary prevention of sudden cardiac death.

Gated SPECT Imaging

ECG-gated SPECT perfusion imaging is the most widely used technique for determining the left ventricular ejection fraction. This is readily accomplished during the performance of SPECT imaging without incurring any additional costs or increasing the imaging time. Gated SPECT imaging has become the standard technique for myocardial perfusion imaging, and information about left ventricular volume, ejection fraction, and wall motion is routinely available from these studies. Conventionally, gated SPECT perfusion imaging is acquired using 8 frames per cardiac cycle. However, with the availability and use of current generation of gamma cameras and image acquisition algorithms, which yield higher counts, 16-frame gating can readily be accomplished.

In patients with CAD, left ventricular ejection fraction is an important determinant of long-term prognosis [54]. Measurement of left ventricular ejection fraction also has important therapeutic implications in patients with CAD. Progressive spontaneous deterioration of LVEF occurs in patients with moderately impaired LVEF (EF < 40 %) due to ventricular remodeling. This process can be arrested by appropriate use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and aldosterone antagonists [55].

Serial LVEF monitoring is also useful for the prevention of overt heart failure in cancer patients undergoing chemotherapy with anthracyclines. Congestive heart failure is the most significant complication of doxorubicin and other anthracycline derivatives. However, anthracycline-induced congestive heart failure is preceded by a progressive deterioration in left ventricular function, which in the initial stages is asymptomatic, but nevertheless provides an opportunity for the prevention of overt heart failure by discontinuation of anthracyclines at an early stage with only a subclinical left ventricular dysfunction. This requires a highly reliable, reproducible, and accurate technique for the serial monitoring of left ventricular function. Because of its high reproducibility and accuracy, ERNA is ideal for detecting changes in left ventricular ejection fraction at an early stage during the course of doxorubicin chemotherapy. In contrast, echocardiography provides an approximation of left ventricular ejection fraction, which is suboptimal for detecting early changes in left ventricular ejection fraction on serial studies. With the appropriate use of guidelines for performing serial ERNA in various subsets of patients, it is possible to reduce the incidence of doxorubicin-induced congestive heart failure from 20 to 2–3 % [56–59].

Exercise ERNA

ERNA can also be carried out during exercise. This has been used for the detection of CAD in the past. A drop in left ventricular ejection fraction of 5 % or more compared to the pre-exercise ejection fraction and/or appearance of new wall motion abnormalities during exercise is indicative of the presence of CAD [60]. However, the sensitivity and specificity both are relatively suboptimal. With the widespread use of myocardial perfusion imaging, exercise ERNA is not used these days for detecting CAD. Exercise perfusion imaging has better sensitivity and specificity and provides more quantitative information about the presence, location, and severity of CAD. Perfusion-based imaging techniques are preferable and more reliable than wall motion-based imaging techniques for the detection and quantification of CAD.

Ambulatory Left Ventricular Function Monitoring

This technique is unique for nuclear imaging of the heart. A combination of equilibrium radionuclide angiocardiography with Holter monitoring has resulted in a device for the continuous ambulatory monitoring of left ventricular function over several hours [61]. A miniature radiation detector is positioned on the chest after blood pool labeling with ^{99m}Tc-pertechnetate, which monitors and records the left ventricular blood pool activity on a modified Holter monitor. This technique has been used for studying the effects of interventions such as mental stress on left ventricular function and for detecting spontaneous changes in left ventricular function in patients with CAD [62]. Mental-stress-induced left ventricular dysfunction is predictive of adverse cardiac events in patients with chronic stable angina [63]. Mental-stress-positive patients had a threefold higher incidence of adverse cardiac events over 1 year compared with mental-stress-negative patients [63]. Several subsequent studies have confirmed the adverse prognostic implications of mental-stress-induced changes in left ventricular wall motion or ejection fraction [64, 65]. This is an important technique for noninvasively studying complex phenomena pertaining to behavior, mental stress, and abnormal

coronary vasoreactivity and long-term outcome in a broad cross section of patients with CAD and for evaluating the impact of conventional and nonconventional therapeutic interventions in this patient population.

Myocardial Necrosis and Apoptosis Imaging

^{99m}Tc-pyrophosphate was used for imaging acute myocardial necrosis in the 1970s and 1980s. However, due to several technical drawbacks, this is not in clinical use any more. Indium-111 (^{111}In)-labeled Fab fraction of antibody against cardiac myosin (^{111}In-antimyosin) (Centocor Inc., Malvern, PA) is highly selective for imaging the necrotic myocardium. This has high sensitivity and specificity for diagnosing acute myocardial infarction [66]. However, slow blood pool clearance, and slow localization in the necrotic myocardium, and a delay of 24–48 h between tracer injection and imaging significantly limit its clinical utility. ^{111}In-antimyosin is more useful for diagnosing acute myocarditis and cardiac transplant rejection [67, 68]. These conditions are characterized by a diffuse myocardial uptake of ^{111}In-antimyosin. Currently, ^{111}In-antimyosin is no longer commercially available in the USA because of limited demand.

The ^{99m}Tc-labeled agents ^{99m}Tc-glucarate and ^{99m}Tc-annexin V are also infarct-avid agents [69–71]. Glucaric acid is a simple 6-carbon dicarboxylic acid sugar that can be labeled with ^{99m}Tc. This localizes in the infarcted myocardium as early as 3–4 h after its injection. ^{99m}Tc-annexin is a normally circulating protein, which binds to the outer membrane of the cells undergoing apoptosis or necrosis. This agent has been used extensively for imaging apoptosis in tumors and in myocardium under various pathological conditions. Apart from imaging apoptotic myocardium, this also binds to acutely necrotic myocardium and has been used for imaging acute myocardial infarction [70]. However, with the wider availability of reliable and simpler biochemical markers of acute myocardial injury and because of the need to intervene early, acute myocardial infarction imaging is unlikely to gain a wide acceptance in clinical practice. ^{99m}Tc-annexin has also been used for imaging myocardial apoptosis in patients with cardiac transplant rejection and in experimental animal studies to image myocardial apoptosis [72, 73].

Positron Emission Tomography

Positron emission tomography (PET) is an integral part of nuclear medicine. However, because of different instrumentation used and unique properties of radiotracers used, PET imaging warrants a separate discussion. Positron emission tomography (PET) involves the use of positron-emitting isotopes (^{11}C, ^{18}F, ^{13}N, ^{15}O, ^{82}Rb, ^{68}Ga, ^{67}Cu). These radiotracers decay by converting a proton into a neutron while ejecting a positron from their nucleus. Upon coming in contact with an electron, positron disintegrates into two γ rays each with 511 KeV energy released at 180°, which can be detected as coincident photons by an array of detectors placed around the patient. These detectors employ different scintillators such as bismuth germanate (BGO), gadolinium oxo-orthosilicate (GSO), or lutetium oxo-orthosilicate (LSO), which are much denser than sodium iodide scintillator used by regular gamma cameras and are more efficient in absorbing high-energy photons. PET images are of very high technical quality and are less vulnerable to artifacts, which are inherent in SPECT imaging. PET tracers have a relatively short half-life and require an on-site cyclotron for their production. ^{82}Rb is produced from a ^{82}Sr/^{82}Rb generator and ^{68}Ga is produced from ^{68}Ge/^{68}Ga generator. These generators contain a column of parent radioisotope bathed in saline, which decays into daughter PET radioisotope, which is released into the surrounding saline and can readily be eluted. Generator-produced radiotracers make it possible to performing PET imaging without the need for an on-site cyclotron. PET traces can readily be incorporated into a number of metabolic substrates such as deoxyglucose, free fatty acids, acetate, sympathomimetic amines, peptides, and proteins and are useful for studying the perfusion, metabolism, adrenergic neuronal activity, and various cell membrane receptors of the myocardium and other organs [74–81]. ^{15}O-water, ^{13}N-ammonia, and ^{82}Rb can be used for myocardial perfusion imaging. A major advantage of PET perfusion imaging is that, apart from a qualitative assessment, an accurate quantitative assessment of the regional myocardial blood flow per gram of myocardial tissue at rest and under various physiological conditions can be carried out [81]. Thus, myocardial flow reserve can be studied by PET imaging. This is particularly useful in detecting patients with multi-vessel CAD and diffuse endothelial dysfunction and for studying microvascular function [77, 81, 82]. Currently ^{18}F-flurpiridaz, a new ^{18}F-based perfusion tracer, is undergoing clinical evaluation for myocardial perfusion imaging. The preliminary results are encouraging (Fig. 12.12) [78–80, 83]. Availability of an ^{18}F-based myocardial perfusion tracer would permit PET myocardial perfusion imaging without the need for on-site cyclotron or generator.

^{18}F-fluorodeoxyglucose (^{18}FDG) imaging is useful for studying myocardial viability. Chronically ischemic but viable myocardial segments are characterized by a preferential uptake of ^{18}FDG that is disproportionately higher compared to the regional perfusion [77]. This is the classical paradigm for viability with PET imaging. However, ^{18}FDG imaging for viability requires a strict control of metabolic milieu and is of limited value in patients with diabetes or recent myocardial infarction.

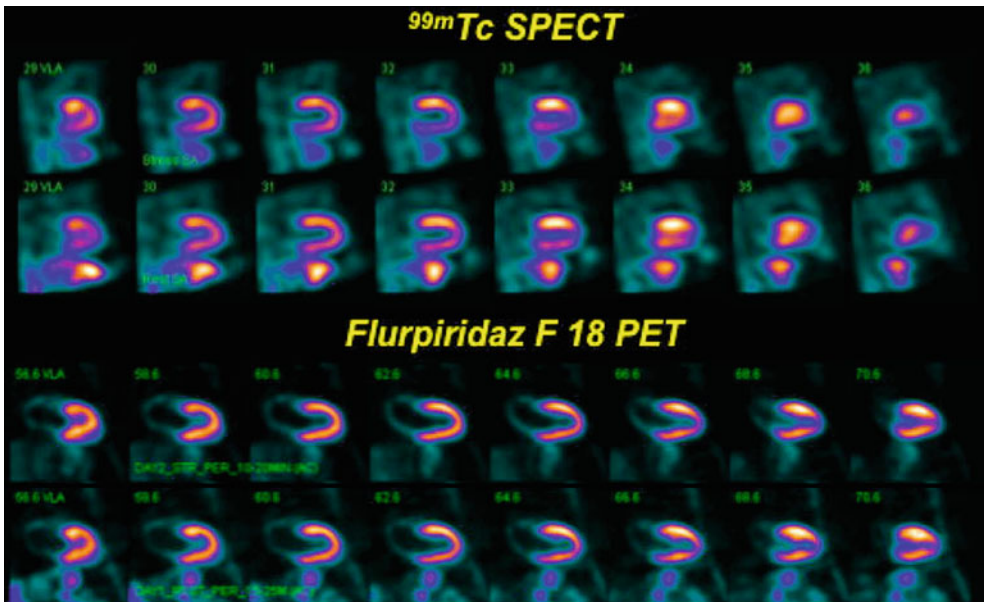

Fig. 12.12 Stress-rest vertical long-axis myocardial perfusion images of a patient with low likelihood of CAD. *Top two rows* show ^{99m}Tc SPECT images and the *bottom two rows* show ^{18}F-flurpiridaz PET images. ^{18}F-flurpiridaz images are unequivocally normal, whereas ^{99m}Tc SPECT images show inferior and apical perfusion abnormality, which is attributable to attenuation artifact but, nevertheless, can be misinterpreted as real perfusion abnormality (Reprinted from Maddahi [83] with permission from Springer Science+Business Media)

^{18}FDG imaging has also been used for imaging atherosclerosis in aorta and other vascular systems [84, 85]. The presence of macrophages and other inflammatory cells in atheromatous plaques result in increased regional ^{18}FDG uptake, which can be imaged using PET-CT imaging. Whereas abnormal vascular uptake can readily be seen in aorta, carotid arteries, and other large vessels, imaging coronary atheroma still remains somewhat challenging given the motion of coronary arteries during cardiac cycle and relative small size of these lesions [85]. Recently ^{18}F-sodium fluoride, a bone imaging PET agent, has been used for imaging coronary arterial calcification [86]. Interestingly, a significant discrepancy has been found in the extent of coronary calcification seen on ^{18}F-sodium fluoride PET imaging and cardiac CT imaging. However, the clinical utility of this technique remains unclear at this point.

PET cameras are significantly more expensive than SPECT cameras and the upfront cost of installing a PET imaging laboratory is significantly more than a conventional SPECT imaging laboratory. However, with the recent growth of PET imaging in oncology, PET imaging is more readily available for cardiovascular imaging and is likely to grow rapidly in near future.

^{18}FDG imaging has also been carried out using conventional SPECT cameras after making alterations in the scintillation crystals and collimators [75]. Dual-head cameras with thicker scintillation crystals have also be been used in coincidence imaging mode, similar to standard PET imaging. Alternatively, a high-energy collimator can also be used for standard SPECT imaging of ^{18}FDG. However, these modified imaging systems do not match the quality of standard PET imaging. These systems have a very low sensitivity for capturing PET photons and have lower spatial resolution compared to standard PET imaging systems. Due to these limitations, these SPECT cameras have fallen out of use for PET imaging.

Appropriate Use Criteria

The successful use of nuclear cardiovascular imaging in clinical practice has resulted in an explosive growth in the total number of studies being performed in the USA over the last several years. This has resulted in concerns about increased and excessive radiation exposure to our patients as well as increasing healthcare costs [87–90]. These concerns are currently being dealt with at several levels. Firstly, with the use of newer generation of solid-state cameras and technical advances in image acquisition and processing, cardiac imaging can be performed successfully using only a fraction of the conventional radiotracer doses [6, 12, 87]. These newer cameras are gradually replacing the conventional cameras. Secondly, there is renewed emphasis on performing stress imaging first and limiting rest imaging to only those with any abnormality on stress images [6, 87]. This is particularly attractive in patients with low to intermediate pretest probability of CAD, such as patients presenting to the emergency department with chest pain, but no electrocardiographic or enzymatic evidence of acute coronary syndrome. Several studies have observed 80–90 % normal perfusion studies in this patient population [45]. At the same time there is also emphasis on responsible use of myocardial perfusion studies in clinical practice. American College of Cardiology, American Society of Nuclear Cardiology, and several other professional organizations have spearheaded a campaign for establishing "appropriate use criteria" for

myocardial perfusion imaging [90]. According to these criteria, patients with no risk factors or symptoms of CAD should not undergo myocardial perfusion imaging. There is no clinical utility of performing routine yearly stress perfusion imaging in patients with CAD, who have undergone revascularization and are currently asymptomatic. Also myocardial perfusion imaging is not indicated as a part of preoperative cardiovascular evaluation of younger patients, those with good functional capacity, and patients undergoing low- or intermediate-risk elective noncardiac surgery. Implementation of these appropriate use criteria has resulted in a reversal of the trend for total number of myocardial perfusion imaging studies being performed on annual basis in the USA.

Molecular Cardiovascular Imaging

Several new nuclear cardiovascular imaging techniques are under development. These techniques provide a unique opportunity to gain insight into complex metabolic, biochemical, enzymatic, and immunological phenomena at a cellular and molecular level by imaging under various physiological conditions. This field is growing rapidly and parallels advancements in our understanding of the pathological, biochemical, and molecular basis of cardiovascular disease and advances in imaging sciences. Techniques are under development for imaging myocardial metabolism, atheroma, angiogenesis, vascular remodeling, and stem cell and gene therapy. A brief description of these imaging techniques is as follows.

Direct Myocardial Ischemia Imaging

Myocardial ischemia results in an immediate and profound metabolic shift. There is a suppression of fatty acid uptake and metabolism and a substantial increase in glucose uptake with the onset of myocardial ischemia. Under fasting conditions, the normal myocardium preferentially utilizes free fatty acids for energy production. Furthermore, with exercise, circulating catecholamines increase and there is further increase in the levels of free fatty acids. Therefore, during exercise under fasting conditions, the predominant source of energy production in the normal myocardium is free fatty acids. However, glycolysis is the predominant source of energy production in the ischemic myocardium. Glycolysis is a relatively inefficient mode of ATP production, and large quantities of glucose are required to sustain the ischemic myocardium by glycolysis. This is mediated by immediate translocation of glucose transporters (GLUTs) from the cytosol to the cell membrane. Once translocated to the cell membrane, GLUTs remain there for several hours even after a relatively brief episode of ischemia. Therefore, myocardial ischemia results in immediate increase in glucose uptake by the ischemic myocardium, and the signature of myocardial ischemia persists for several hours after an episode of ischemia. This provides a strong rationale for the use of radiolabeled glucose for direct imaging of myocardial ischemia. Since ^{18}FDG tracks the initial cellular uptake and phosphorylation of glucose in the cells, this agent can be used for directly imaging exercise-induced myocardial ischemia [91–97]. A preliminary study by He, Jain, and colleagues has shown a remarkable potential of exercise ^{18}FDG imaging for the detection and quantification of CAD. Whereas the overall sensitivity of exercise ^{18}FDG and exercise-rest ^{99m}Tc-sestamibi imaging was similar for the detection of CAD (91 % vs. 82 %, p = ns), the sensitivity of ^{18}FDG was significantly higher than that of exercise-rest perfusion imaging for the detection of individual vessels with ≥50 % luminal narrowing (67 % vs. 49 %, $p < 0.01$). Figures 12.13 and 12.14 show exercise ^{18}FDG and exercise-rest perfusion images of patients with CAD. In another study by the same group, patients with CAD underwent exercise perfusion and ^{18}FDG imaging and rest perfusion and ^{18}FDG imaging 24 h apart. In over two thirds of myocardial segments with ischemia, increased ^{18}FDG was seen only on exercise images, which normalized on rest images 24 h later (Fig. 12.15). In a small proportion of cases, faint ^{18}FDG uptake persisted on rest images 24 h later. The latter category of patients had more severe CAD and developed ischemia at a relatively lower workload compared to the former group of patients. These data indicate the potential superiority of direct ischemia imaging over conventional myocardial perfusion imaging for the detection and risk stratification of patients with CAD. These studies also highlight the strength of molecular nuclear imaging. Nuclear imaging techniques can image biochemical and molecular phenomena in intact human, which cannot be accomplished by any other imaging modality. Clearly further large-scale studies are warranted to explore this concept further.

Cardiac Adrenergic Neuronal Imaging

Metaiodobenzylguanidine (MIBG) labeled with iodine-123 (^{123}I-MIBG) and parafluorobenzylguanidine labeled with ^{18}F can be used for imaging cardiac sympathetic neuronal activity [98–100]. In patients with congestive heart failure, there is activation of the sympathetic activity, and the extent of sympathetic activation correlates negatively with the prognosis of these patients. Cardiac uptake of ^{123}I-MIBG is reduced in patients with congestive heart failure and

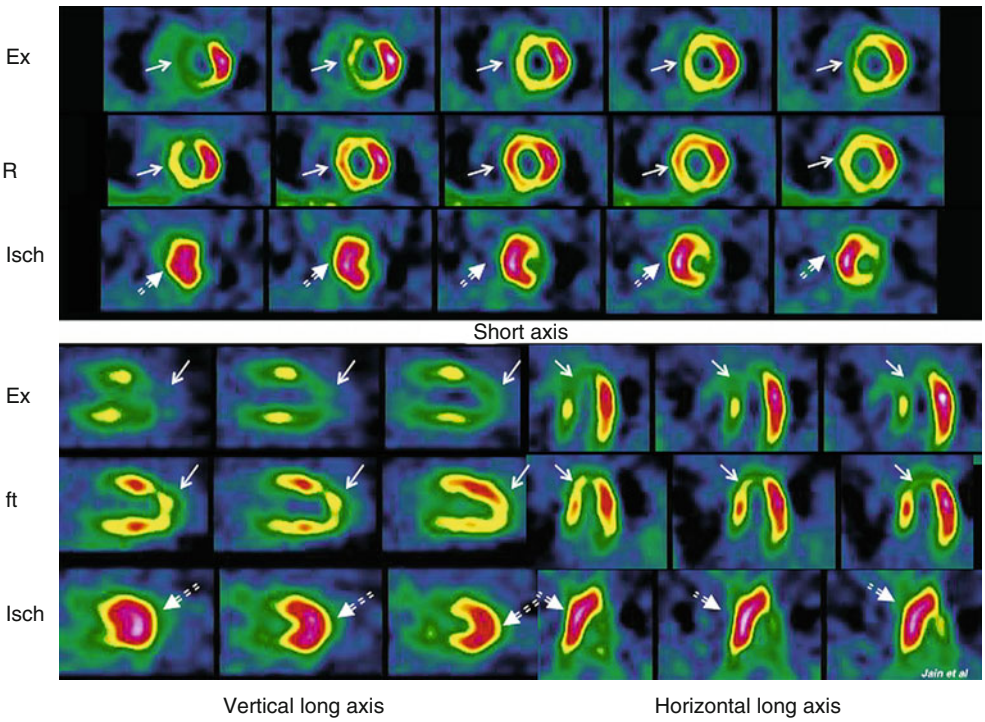

Fig. 12.13 Exercise (*Ex*) and rest (*R*) ^{99m}Tc-sestamibi and exercise ^{18}FDG (*Isch*) images of a 67-year-old man with angina and no prior myocardial infarction. There is a large area of partially reversible perfusion abnormality involving the septum, anterior wall, and apex (*small arrows*). Intense ^{18}FDG uptake is present in these areas (*solid arrowheads*). Coronary angiography showed 90 % stenosis of the left anterior descending coronary artery and a 60 % stenosis of the left circumflex artery (Reprinted from He et al. [92] with permission from Wolter Kluwers Health)

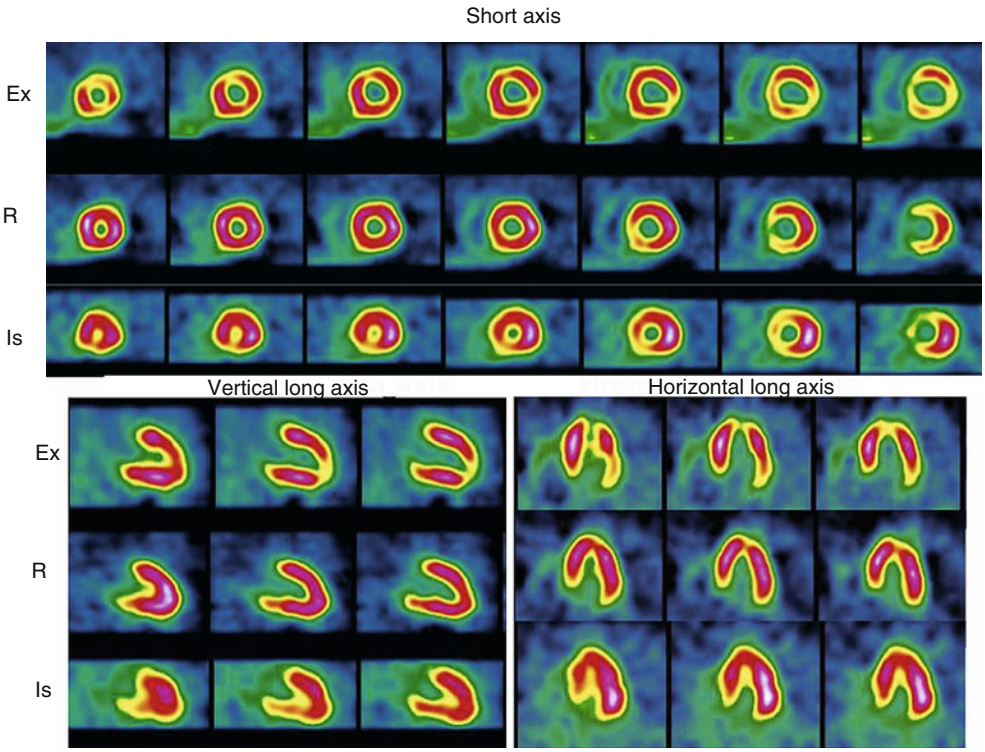

Fig. 12.14 Ex-rest ^{99m}Tc-sestamibi and exercise ^{18}FDG ischemia images of a 56-year-old male with angina and no prior myocardial infarction. There is ischemia involving the anterior wall, lateral wall, and apex. There is intense ^{18}FDG uptake in anterior wall, septum, apex, lateral wall, and contiguous inferior wall. Coronary angiography revealed 80 % narrowing of the left anterior descending and 100 % narrowing of the left circumflex coronary arteries (Reprinted from Jain and He [95] with permission from Springer Science+Business Media)

correlates inversely with the severity and prognosis of heart failure. This technique has the potential for further risk stratification of patients with heart failure and selecting the optimal therapeutic strategies for these patients (Fig. 12.16).

Free Fatty Acid Imaging

^{123}I-labeled fatty acids such as iodophenylpentadecanoic acid (IPPA) and 15-(*p*-iodophenyl) 3R, S-methylpentadecanoic acid (BMIPP) have been used for studying regional myocardial

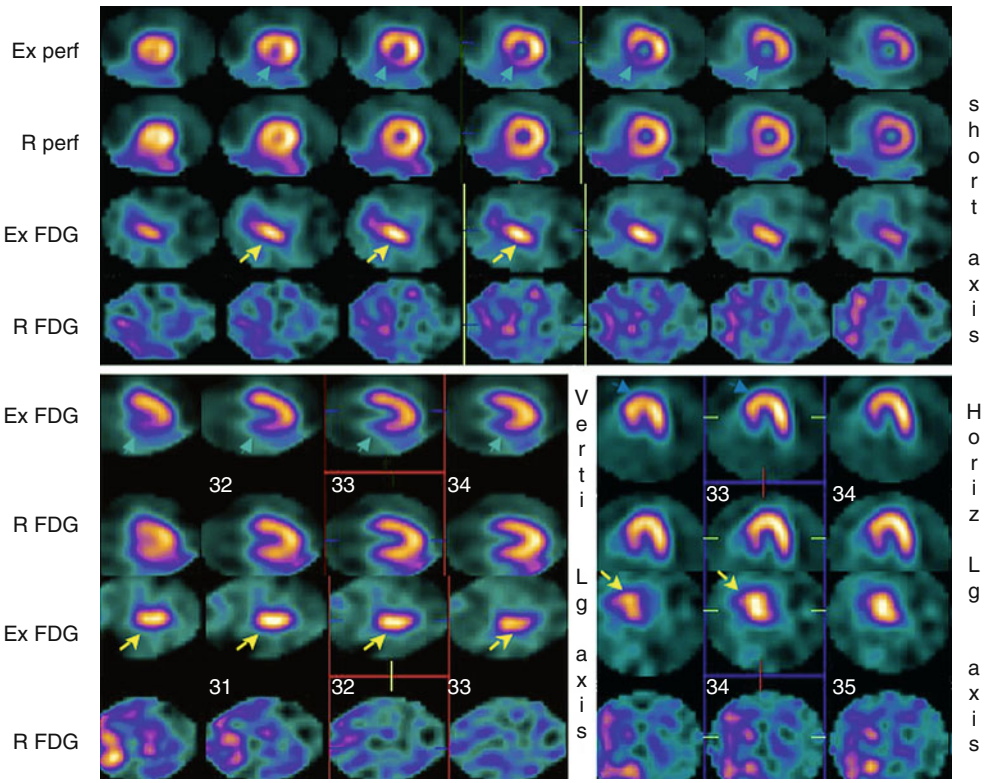

Fig. 12.15 Exercise (*Ex*) and rest (*R*) ^{99m}Tc-sestamibi perfusion (*Perf*) and ^{18}FDG images of a 49-year-old male with exertional angina, in short axis and vertical and horizontal long axes. There is exercise-induced perfusion abnormality in the posterior septum and inferior wall, which is reversible on the rest images. There is intense ^{18}FDG uptake on the exercise images (*yellow arrows*) in the corresponding segments, which is not present in the rest images. This patient had 85 % stenosis of the right coronary artery (Reprinted from Dou et al. [94]. With permission from the Society of Nuclear Medicine)

fatty acid metabolism. This is useful in studying the extent of myocardial viability and is also undergoing evaluation as a possible ischemia memory marker [101].

Angiogenesis, Gene Therapy, Stem Cell Therapy, and Vascular Remodeling Imaging

Several complex biological phenomena such as angiogenesis, gene therapy, stem cell therapy, and vascular remodeling have been imaged using radiolabeled molecular probes in experimental studies [102–104]. These probes are developed based upon the identification of molecular targets, which are selectively and abundantly expressed in tissues or organs with these phenomena. These molecular targets are enzymes, peptides, or cell surface receptors or transporters or their degradation products, which are uniquely expressed under these conditions. Next step is the identification or production of exogenous molecules with high affinity for the target molecules, such as monoclonal antibodies against these molecules, peptides, or other ligands, which can be radiolabeled with suitable SPECT or PET tracers. Because of its superior resolution and image quality and versatility of PET tracers, PET imaging is highly promising for the development of next generation of molecular imaging agents. Furthermore, hybrid imaging, which combines SPECT or PET imaging with CT imaging, provides a unique opportunity to precisely localize and quantify uptake of molecular imaging tracers to the sites of angiogenesis, stem cell engraftment, or gene expression. These radiolabeled tracers or probes can be used for imaging these phenomena in intact animals and man. For angiogenesis, radiolabeled VEGF (vascular endothelial growth factor) or $\alpha_v\beta_3$ integrins have been used successfully [102, 103]. In the future, it may become possible to radiolabel various adhesion molecules, interleukins, and other mediators of endothelial dysfunction, intimal injury, and atherogenesis in experimental models. This is likely to emerge as an interesting approach for understanding the pathophysiology of endothelial dysfunction, intimal injury, and atherosclerosis.

Conclusion

Radionuclide imaging techniques have greatly enhanced our understanding of cardiovascular physiology and pathology. These techniques have played a crucial role in the evaluation of patients with definite or suspected CAD and for optimal and cost-effective utilization of various therapeutic options. Myocardial perfusion imaging is the most important and most widely used nuclear imaging technique. This provides important diagnostic and very powerful prognostic information in males as well as in females and in all subsets of the patient population:

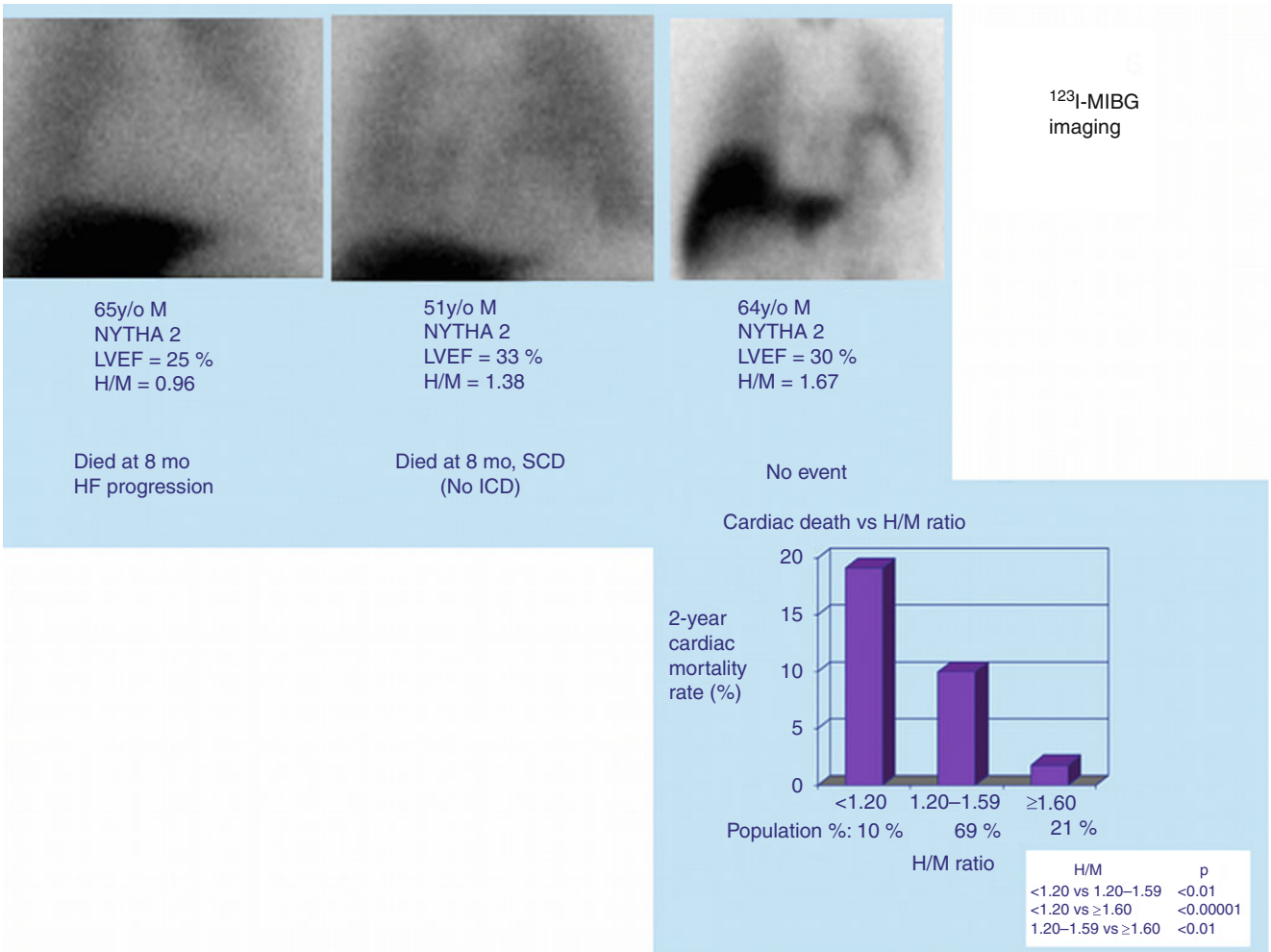

Fig. 12.16 Planar anterior view of ^{123}I-MIBG images of three different patients with heart failure in NYHA class II. All three patients had very similar LVEF. However, myocardial MIBG uptake (as indicated by heart to mediastinal ratios) is very different in these patients. The patient with normal lung to mediastinal ratio had an excellent outcome, whereas the remaining two patients with low heart to mediastinal ratio had poor outcome. The inset shows 2-year mortality in patients with heart failure categorized based upon heart to mediastinal ratios of ^{123}I-MIBG. Patients with lowest ratios had over six times mortality compared to patients with preserved heart to mediastinal ratios (Image courtesy of Arnold Jacobson, MD)

suspected CAD, known CAD, and following acute myocardial infarction. New PET and SPECT molecular imaging techniques, hybrid imaging, radiopharmaceuticals, and imaging paradigms are emerging to meet the challenge of changing practice of cardiovascular medicine and to gain further insight into the molecular basis of disease process.

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Cardiovascular Magnetic Resonance and Multidetector Computed Tomography

13

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Introduction

There have been considerable advances in cardiovascular cross-sectional imaging techniques. These include cardiovascular magnetic resonance (CMR) and multidetector computed tomography (MDCT) imaging. These technologies complement each other by allowing highly accurate and reproducible assessment of cardiac and vascular morphology and function.

Magnetic resonance (MR) provides the basis for and the newest of the imaging technologies. While magnetic resonance generates images with high resolution and high contrast without the need for contrast agent administration, most magnetic resonance systems available today must be gated to acquire high-quality images that demonstrate cardiac contraction. Newer systems, only recently available, allow acquisition of images at high speed, obviating the need for electrocardiographic synchronization. However, at present, gated studies offer superior resolution and image contrast, but either gated or "real-time" magnetic resonance images are optimally suited to visualize the heart and its contractile function. Magnetic resonance angiography (MRA) is excellent for rapidly evaluating the aorta and the peripheral arteries and can be acquired and displayed in 2-D and 3-D. MRI can precisely characterize cardiac function and quantify ventricular volumes, right and left ventricular ejection fraction, and left ventricular mass and can quantify pressure gradients across stenotic valves, regurgitant fractions, and shunt fractions in patients with intracardiac shunts. Valve morphology and area can also be evaluated and the severity of valvular stenosis quantified. Cardiac MR is also useful for identifying cardiac masses, pericardial abnormities, and congenital heart disease. In certain disease states, such as myocardial infarction and cardiomyopathies, the resolution of MRI is further improved by the addition of extrinsic contrast agents. Cardiac MRI is also very useful in assessing paramagnetic contrast agents that cause a reduction in the T1 relaxation time leading to increased signal intensity on T1-weighted images and are typically small molecular weight compounds containing as their active elements gadolinium, manganese, or iron. All of these elements have unpaired electron spins in their outer shells and long relaxivities. Magnetic resonance spectroscopy (MRS) allows assessment of the metabolic responses of the myocardium most commonly by using the proton (H-1) and the phosphorus-31 (P-31) spectra. Phosphorus-31 spectroscopy can assess the conversion of energy through oxidative phosphorylation during myocardial work by evaluating high-energy phosphate. Proton MRS of the heart, despite high sensitivity of the proton metabolites, has not been readily applicable for clinical utility due to technical challenges including signal suppression of the huge water resonance peak and identification of the methyl and methylene group of the lipid.

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_13,

Magnetic Resonance Imaging

Principle of Nuclear Magnetic Resonance

When an atomic nucleus contains an odd number of subatomic particles (i.e., protons plus neutrons), it possesses a property known as "spin." The nucleus can be imagined to spin around its axis in a manner similar to the rotation of the earth. When electrical charges (in this case, the atomic nucleus) move, a magnetic field is generated. Intrinsic magnetic fields of atomic nuclei can interact with externally applied magnetic fields. Sensitive atomic nuclei placed within an extrinsic magnetic field will align either *with* or *against* that field. Quantum mechanical considerations dictate that for any macroscopic amount of material, slightly more nuclei will align with the field than will be antialigned. Thus, material placed in an external magnetic field will attain a bulk magnetic field strength. Stronger fields generate higher numbers of nuclei that preferentially align. If the nucleus is disturbed—for example, by applying a radio frequency (RF) field—it will displace from alignment with the extrinsic magnetic field. When the RF energy is terminated, the disturbed nuclei continue to precess. *Precession* is the relatively slow "wobbling" phenomenon that is observed with a child's spinning top or a gyroscope. In a similar manner, nuclei with intrinsic "spin" and a magnetic moment will precess in an external magnetic field. The frequency of precession depends on the strength of the magnetic field (B_0) and the nuclear characteristics (gyromagnetic ratio, γ) of a given element. The RF field has to be applied at the precession frequency (i.e., at the resonance frequency for the system, which is also known as the Larmor frequency). The phenomenon of nuclear MR (NMR) is manifested when a substance with magnetically sensitive nuclei (e.g., the nucleus of hydrogen-1 [proton], phosphorus-31, fluorine-19, or sodium-23) that is placed in a strong magnetic field is momentarily pulsed with RF energy at the resonance frequency. The nuclei of all these atoms are naturally abundant and stable (i.e., not radioactive). While virtually all MR images are derived from the hydrogen nucleus (ubiquitous in water), researchers have created cardiac images of less-abundant signal sources, such as the natural sodium-23 distribution. During the process of free precession (i.e., after termination of the RF field), nuclei give off a detectable signal. This RF signal is detected by a conducting coil placed close to the sample [1].

The units of magnetic field strength are the gauss (G) and the tesla (T). The strength of the earth's magnetic field is on the order of 0.5 G. A typical commercial MR system useful for cardiovascular studies has a field strength of 15,000–30,000 G. It is customary to express field strength with NMR in tesla units (1 T = 10,000 G). Thus, 15,000 G is equivalent to 1.5 T.

Importance of Radio Waves or Radio Frequency

RF pulses are delivered at the resonant or Larmor frequency:

$$\omega = \gamma B_0$$

For protons, γ= 42.58 MHz/T. Typical spin-echo pulses reorient the net magnetism of the nuclear spins by 90 or 180°. Faster and newer imaging techniques used for cardiovascular MR apply pulses of short duration, with net spin reorientation of less than 90°. Following the RF pulse, the net magnetization precesses at the Larmor frequency. As individual spins precess, they emit an RF signal, which is detected by an RF coil. The frequency of these radio waves is characteristic for a given atomic nucleus and is affected by the chemical milieu. The detected radio waves are digitized and converted into signal peaks, or spectra, by application of the mathematical process known as *Fourier transformation*. The chemical milieu can cause the location of a resonance peak in the spectra to appear at a slightly different position than indicated by the field strength, B_0, a phenomenon known as chemical shift. Thus, the three phosphorus peaks of adenosine triphosphate (ATP) are located in different spectral frequencies on phosphorus-31 spectrum, and the hydrogen peak of water and of fat are in different spectral frequencies in the proton spectrum.

The intrinsic magnetic field produced by the tissue will gradually reorient and realign with the extrinsic field after perturbation by the RF pulse and is said to *relax*. There are two relaxation times: T1 (or spin–lattice relaxation), which is related to the time required for the net magnetization of the sample to realign with the main magnetic field by 63 % (i.e., $1 - 1/e$), and T2 (or spin-spin relaxation time), which is related to the time required for spins that were originally in phase with the applied RF pulse to lose phase coherence by 63 % (i.e., $1 - 1/e$). The concentration of the nuclei (spin density) and the relaxation times T1 and T2 determine the magnitude of a peak in the spectrum or the intensity of a pixel in an image. Other variables that affect signal intensity are motion, flow, chemical shift, and magnetic susceptibility. Previously, image contrast was derived from a "weighting" toward one of these parameters, for example, a T1-weighted image was obtained using a high RF flip angle and a rapid repetition such that only spins with very short T1 relaxation substantially contributed to the image signal. There is a growing trend to obtain images in which these spin characteristics are quantitatively represented. Typically this involves "mapping" out the exponential character of the T1 or T2 relaxation curves. When applied to cardiac tissue, due to the heart motion, these techniques tend to be either time-consuming or of limiter accuracy. However, the importance of quantitative parameter imaging is likely to increase as time goes on.

Whereas spectroscopy utilizes differences in chemical shift of each metabolite in a uniform magnetic field, imaging

utilizes externally applied magnetic field gradients. The key to imaging is to vary the magnetic field strength as a function of spatial location. This is accomplished by applying a linear magnetic gradient along each axis in which spatial differentiation is required. Each gradient either adds to or subtracts from the main magnetic field, producing a continuous variation in resonance frequency along the sample. Application of the Fourier transform to signals acquired in the presence of linear gradients directly translates this range of frequency information into spatial intensity data and forms the basis of imaging and angiography. Control of the gradients allows slice selection to be achieved in any orientation.

Instrumentation for Magnetic Resonance Studies

A CMR system consists of a large (typically cylindrical) superconducting magnet, an RF coil that fits within the bore of the magnet; RF receiver coils, gradient coils that generate the magnetic fields needed to create images; and an image-processing computer (Fig. 13.1). The large magnet contains multiple coils of niobium titanium, which has essentially no resistance to electrical current when it is supercooled. Such supercooling takes place when the coils in the magnet are bathed in liquid helium at 4 °K or −269 °C. While permanent, "open" magnets are also available for CMR, high-field superconducting magnets are preferable for the resolution and speed required for cardiac applications. The imaging gradient coils are located within the magnet bore and are used to vary the magnetic field in a precisely controlled manner. They introduce controlled variations in magnetic field related to the position of an organ or a portion of an organ within the magnet. Having the ability to rapidly switch the gradient coils on and off allows rapid acquisition of cardiovascular images. The cylindrical body RF coil also fits concentrically within the bore of a cylindrical magnet and transmits the radio waves needed to create a spectrum or an image. A smaller multielement coil placed over the heart or vascular bed of interest is used to receive the RF signal with high sensitivity (the combination of receiver element and sampling hardware is referred to as a "channel"). There are so-called parallel imaging techniques that utilize the independence of the multiple channels to speed up the image acquisition at the expense of losing signal to noise. Naturally, coordination of this complex system requires extensive computer control of the gradient and RF amplifiers and the vast array of associated electronic components. Typically, an operator's console is placed in a room adjacent to the scan room, allowing visual contact with the patient environment via a window. The console provides a convenient means to alter the acquisition methods, RF pulse sequence, and view selection.

A spin-echo image of the heart typically is acquired with high spatial resolution in which moving blood appears as a signal void or as a "dark-blood" region. A gradient-echo pulse sequence typically generates images at higher speed and with "bright blood." The dark-blood approach is ideal for assessing cardiac morphology, whereas the bright-blood approach is appropriate for assessing ventricular function. When turbulence occurs in the bloodstream, bright-blood images demonstrate a localized reduction in brightness directly associated with the turbulence. For example, the jet associated with mitral or aortic regurgitation is visualized as a dark region against otherwise bright blood, owing to signal dephasing. Newer systems have higher-speed imaging capabilities such as "echo planar" and spiral imaging, which are capable of generating an image in under 30 ms, but presently, these images are of generally low resolution. Both dark-blood and bright-blood imaging can be performed with cardiac gating to freeze heart motion at certain phases in the cardiac cycle, thus allowing higher-resolution images to be acquired, but at the expense of increased scan time. Typically, in cardiac gated sequences, 20–30 frames representing the cardiac cycle are acquired. In general, cardiac cine sequences are based on bright-blood gradient recalled echo (GRE) approaches, or a variant termed steady-state-free precession (SSFP). In this way both regional and global ventricular performance can be evaluated. A typical GRE sequence requires 10–15 s acquisition time and can be acquired within a breath hold. Using GRE methods, a series of images can be acquired throughout the cardiac cycle and then assembled in sequence in the computer as a cine loop that can be replayed repeatedly to allow evaluation of wall motion (Fig. 13.2).

Since its introduction into routine clinical practice, steady-state-free precession (SSFP) imaging has evolved in a number of different forms that efficiently combine the gradient and spin-echo components to increase blood signal contrast. These approaches, variously and imaginatively termed FIESTA, true FISP, balanced FFE, and others, have resulted in excellent blood-myocardial contrast, almost independently of blood flow characteristics. Both dark-blood and bright-blood imaging sequences are performed in conjunction with cardiac gating to effectively freeze the motion of the heart at distinct phases within the cardiac cycle.

Older CMR systems have rather long cylindrical magnets. Some patients (as many as 5 %) are unable to tolerate such an enclosure due to claustrophobia. Anxious patients can be given a mild sedative such as benzodiazepine. Most modem systems have shorter magnet length and a wider bore and are thus more "patient friendly." Again, even on newer systems the gradients can be quite noisy. This is especially true for the fast imaging sequences used in cardiovascular MR. Earplugs are always required to protect the patient from noise-related hearing damage. Newer systems incorporate substantial sound dampening to isolate the gradient vibrations from the system, thus reducing noise to some extent. An intercom system is used to maintain verbal contact

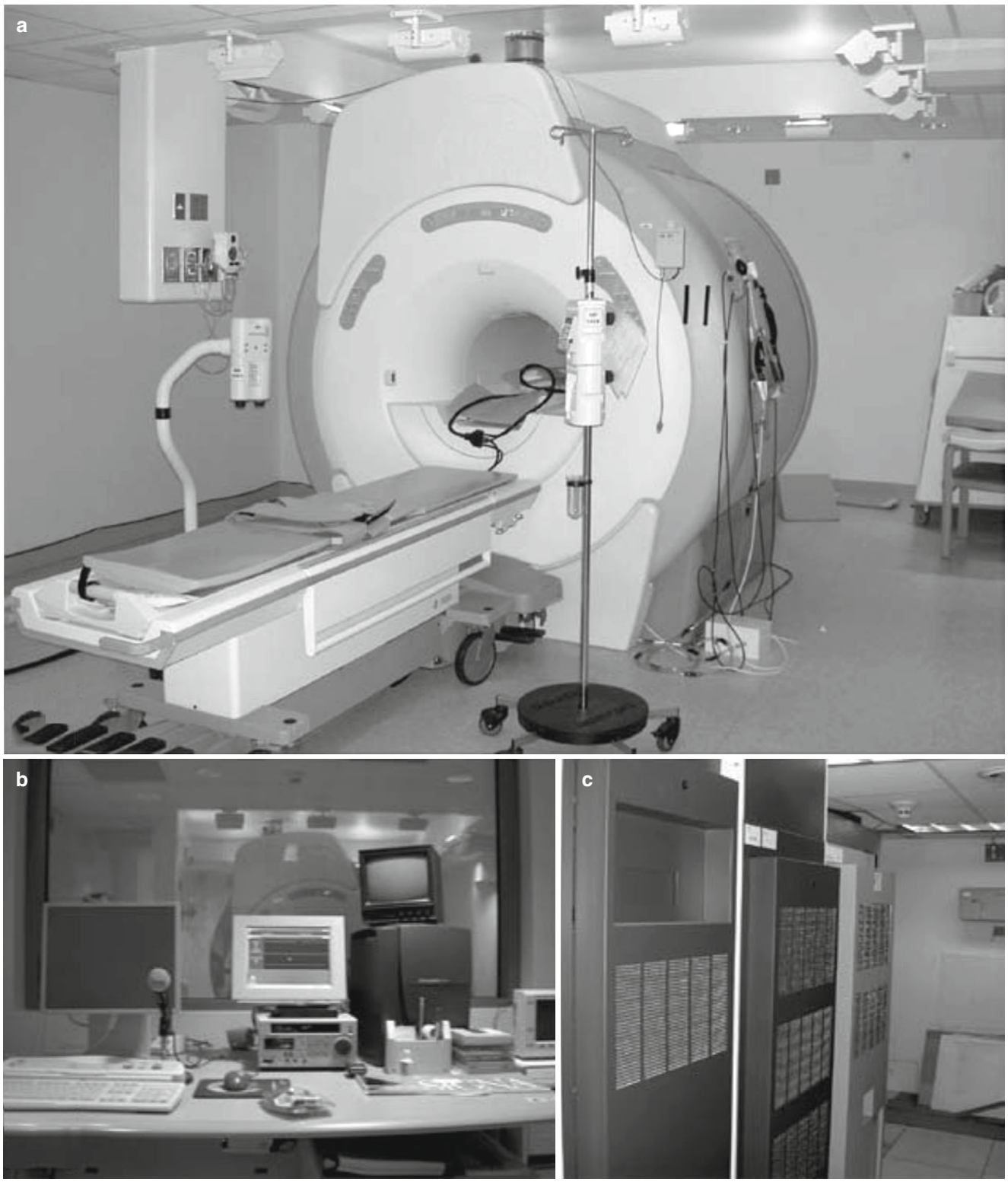


Fig. 13.1 Composite photograph of major components of a typical MRI system. (**a**) Scanner magnet and patient table; the table accommodates patient entry, exit, and positioning within the magnet bore. (**b**) Operator's console, which is remote from the scanner, allows control of scanner functions and incorporates an image and physiologic data viewing station. (**c**) Bulky hardware to power the scanner is typically located in a separate room; components include gradient and RF power units and the controlling computer

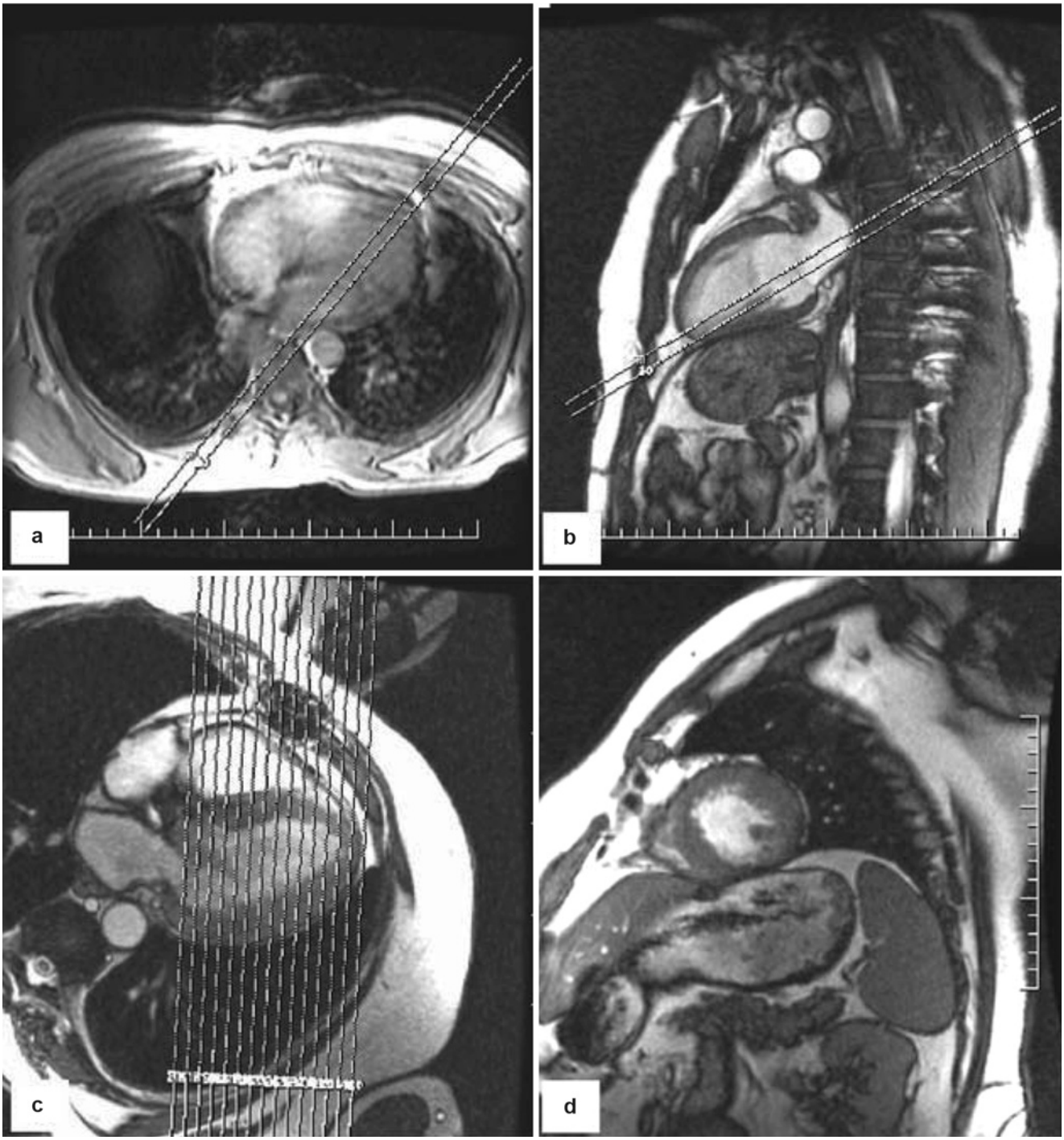


Fig. 13.2 Sequence of scans required to obtain standard cardiac views. (**a**) A noncardiac-triggered spin-echo transverse scout is obtained and is used to plan the two-chamber view. (**b**) The two-chamber view of the left ventricle is in turn used to plan the four-chamber view. (**c**) The four-chamber view is in turn used to plan the multiple-slice short-axis views. (**d**) A short-axis view of the left and right ventricles. Views (**b** and **d**) were obtained in cine mode using steady-state free precession imaging

between system operator and patient. This is important, to inform the patient of important events during the examination such as table movements, injections of contrast agents, or stress agents. Verbal communication is especially important to direct the patient with the appropriate timing for breath holding during image acquisition. Special MR-compatible (e.g., nonmagnetic) systems are required for physiological monitoring of the patient during an examination. This is especially important if the patient receives pharmacological stress while within the bore of the magnet.

While a uniform body coil is required to optimally transmit RF energy into the body, the most important characteristic for signal reception is maximization of the signal-to-noise ratio. This can be accomplished by positioning a receiver coil system on the body's surface. A typical reception system consists of a number of separate coils that are essentially positioned or wrapped around the thorax (for cardiac imaging). This composite coil is made up of a number of smaller sub coils, each requiring its own signal reception electronics, and is referred to as a phased array system (the number of coil elements relating directly to the number of channels). Importantly, recent advances have allowed reduction in scan time by separately processing the signal from each coil in parallel, to essentially construct a separate part of each full image. These parallel imaging approaches cause a slight reduction in signal-to-noise ratio, but typically can reduce the scan time by factors of 2 or 4. These approaches are generically known under various trade names including ASSET, SMASH, and SENSE.

In addition to the inherent contrast produced by each imaging sequence, it is possible to augment contrast by means of "spin preparation pulses." Preparation pulses are typically applied to produce contrast dependent on the T1 relaxation process. At 1.5 T the T1 value of myocardium (water signal) is approximately 850 ms, while that of fat tissue is about 300 ms. Application of an RF pulse to invert the spin system will initially invert both the water and fat signals. However, as the spin system relaxes to its equilibrium condition, the fat signal relaxes faster than the water signal. By carefully selecting the time following the inversion pulse at which to perform the imaging sequence, it is possible to "null" either the fat or the water signal. The process of inverting the signal and waiting for it to partially recover before performing imaging is referred to as "inversion recovery" (IR).

Currently, there is some debate concerning the utility of higher-field imaging systems (e.g., 3 T systems) for cardiac imaging purposes. The potential advantage is that the SNR is higher, but the downside is that RF energy is higher (leading to heating) and sources of artifact are higher (related to the susceptibility/inhomogeneity introduced by the high magnetic field). At the time of writing, there is no clear indication for cardiac imaging and higher fields.

Further, it is possible to alter the T1 of tissue by administration of a contrast agent. These nonionic agents typically contain a gadolinium chelate, which, when it comes in close contact with tissue, effectively reduces the tissue's T1 by introducing a highly localized, randomly varying, magnetic field gradient. Contrast agents have application areas varying from allowing visualization of myocardial perfusion, imaging the vasculature, differentiating between masses, and identifying viable and nonviable myocardium with high accuracy.

Current Applications

CMR and MRA are excellent for assessing both cardiac morphology and function. CMR has the unique ability to acquire images of the heart in any tomographic plane that is preselected by the operator at the console. However, it is customary to acquire imaging planes through the vertical long axis (two-chamber view), the horizontal long axis (four-chamber view), and the short axis (Fig. 13.2). At the present time, magnetic resonance imaging and angiography are excellent for assessing global and regional left and right ventricular size and performance; for evaluating the abnormal morphology and physiology found in congenital heart disease, including intra- or extracardiac shunt quantification; for characterizing myocardial tissue, such as in arrhythmogenic right ventricular cardiomyopathy; for assessing myocardial wall thickness and ventricular volumes and geometries in the cardiomyopathies and in valvular heart disease, particularly to interrogate velocities; for the assessment of the pericardium, particularly differentiation of constrictive pericarditis from restrictive myocardial disease; for cardiac/paracardiac masses; for comprehensive evaluation of aortic dissection and aortic aneurysms; and for assessment of the larger arterial branches from the aorta such as the carotids, the renals, the iliofemorals, and more recently, the coronary arteries with and without contrast. CMR has been demonstrated to be clinically effective in myocardial perfusion and is considered to be the gold standard for myocardial viability.

Cardiac chamber size, myocardial wall thickness, and mass are readily assessed from CMR images. Chamber morphology, orientation, and relationships to the great vessels and viscera are easily assessed. In addition, atrioventricular, venoatrial, and ventriculoarterial connections can readily be defined and evaluated in terms of anatomy and hemodynamics. Three-dimensional contrast-enhanced cardiac views can be rotated and viewed from any orientation. Such capability is ideal for assessing complex congenital heart disease.

Many of the current applications of EBCT and MDCT are similar to those described for CMR but also include assessment of the presence, extent, and location of calcified and noncalcified coronary artery plaque.

- Global and regional left and right ventricular function
- Assessing myocardial wall thickness and ventricular volumes and cardiomyopathies
- Assessment of coronary artery anatomy and stenosis
- Assessment of coronary calcium to detect atherosclerosis
- Assessment of myocardial ischemia and infarction
- Assessment of aorta and the larger arterial branches
- Comprehensive evaluation of aortic dissection and aortic aneurysms
- Evaluating congenital heart disease, anatomy, and conduit patency
- Assessing cardiac and paracardiac masses
- Assessing the pericardium and pericardial effusion or constriction

Table 13.1 CMR EBCT and MDCT: respective clinical applications

	MRI	EBCT and MDCT
Cardiac morphology	Excellent intrinsic soft tissue and blood contrast allows delineation of anatomic features with good resolution. No external contrast required	Requires administration of contrast agent to delineate blood pool features, but provides good anatomic depiction
Ventricular (and other chamber) function	Excellent temporal and spatial resolution with any orientation allows optimal evaluation of contractile function; RF tags provide further delineation of regional wall function	Requires contrast agent to distinguish blood pool, limited angulation available, but 3-D images can be generated with good resolution
Coronary anatomy	Breath-hold techniques allow coronary artery location to be traced to origin	Contrast techniques allow coronary artery trajectory to be traced to origin
Myocardial perfusion	Myocardial perfusion, in later stages of development	Myocardial perfusion by tracking a bolus of radiopaque contrast
Pericardial disease	Allows differentiation between restrictive and constrictive disease (i.e., generally, myocardial vs. pericardial). MR is a "gold standard" for assessing pericardial thickness. Able to determine physiologic significance, even in absence of thickened pericardium	MDCT is able to distinguish between myocardium and pericardium similar to CMR
Valvular assessment	Can assess valve function, visualize turbulent flow, and approximate the severity of regurgitation and stenosis	Unable to visualize turbulence, must rely on ancillary data (quantifying differences in stroke volumes between LV and RV)
Metallic artifacts	Signal void	Streak artifacts
Cardiac masses	Can be easily detected as filling deficits within the cardiac blood pool, important role for T1 and T2 tissue characterization	Can be identified after a contrast bolus
Contrast agent	Chelates of gadolinium and dysprosium with no known adverse effects	Iodinated contrast—many adverse side effects: renal failure, anaphylaxis, or pulmonary edema
Angiography of the arterial system:	No need for contrast agent although early data suggests contrast markedly shortens acquisition time and further increases resolution	Radiopaque iodinated contrast agent required
Aorta	++++	+++
Aortic arch	++++	+++
Carotid and cerebral arteries	++++	++
Peripheral arteries and veins	++++	+++
Coronary calcification	Not well visualized; calcium has little CMR signal due to its solid state	Easily visualized without contrast administration
High-energy phosphate metabolism	Yes	No
	No	Yes

Table 13.1 contrasts/compares these technologies in their respective applications.

Ventricular Function Chamber Size and Wall Thickness

CMR Techniques

Global and regional right and left ventricular function can be assessed using cine GRE, SSFP, or other rapid acquisition sequences such as echo planar imaging [2]. Ventricular volumes can be measured at end-diastole and end-systole using traditional area-length approaches from the long-axis images or using Simpson's rule with serial short-axis images [3]. Simpson's rule is the common method of computing volumes of continuous objects by summing the areas of cross sections obtained at a discrete number of points. While most current techniques acquire contiguous slices, gaps between sampled cross sections are treated as if they were represented by the average of the nearest cross-sectional views. In essence, the area is found by summing each cross-sectional area and multiplying it by the sum of the slice thickness and the interslice gap. Stroke volume and ejection fraction can be readily determined from the end-systolic and end-diastolic volumes. In addition to the geometrically simple left ventricle, the more irregularly shaped right ventricle can also be studied using a Simpson's rule approach with serial short-axis views from base to apex. The three-dimensional coverage of CMR images makes possible calculation of highly accurate right ventricular volumes and ejection fractions [4]. By evaluating size, shape, and the regional contractile ability of the left ventricle, lesions such as ventricular aneurysm and pseudoaneurysm, dilated and hypertrophic cardiomyopathy, myocardial thinning, and remodeling can readily and comprehensively be evaluated. CMR is the most reliable means for assessing right and left ventricular

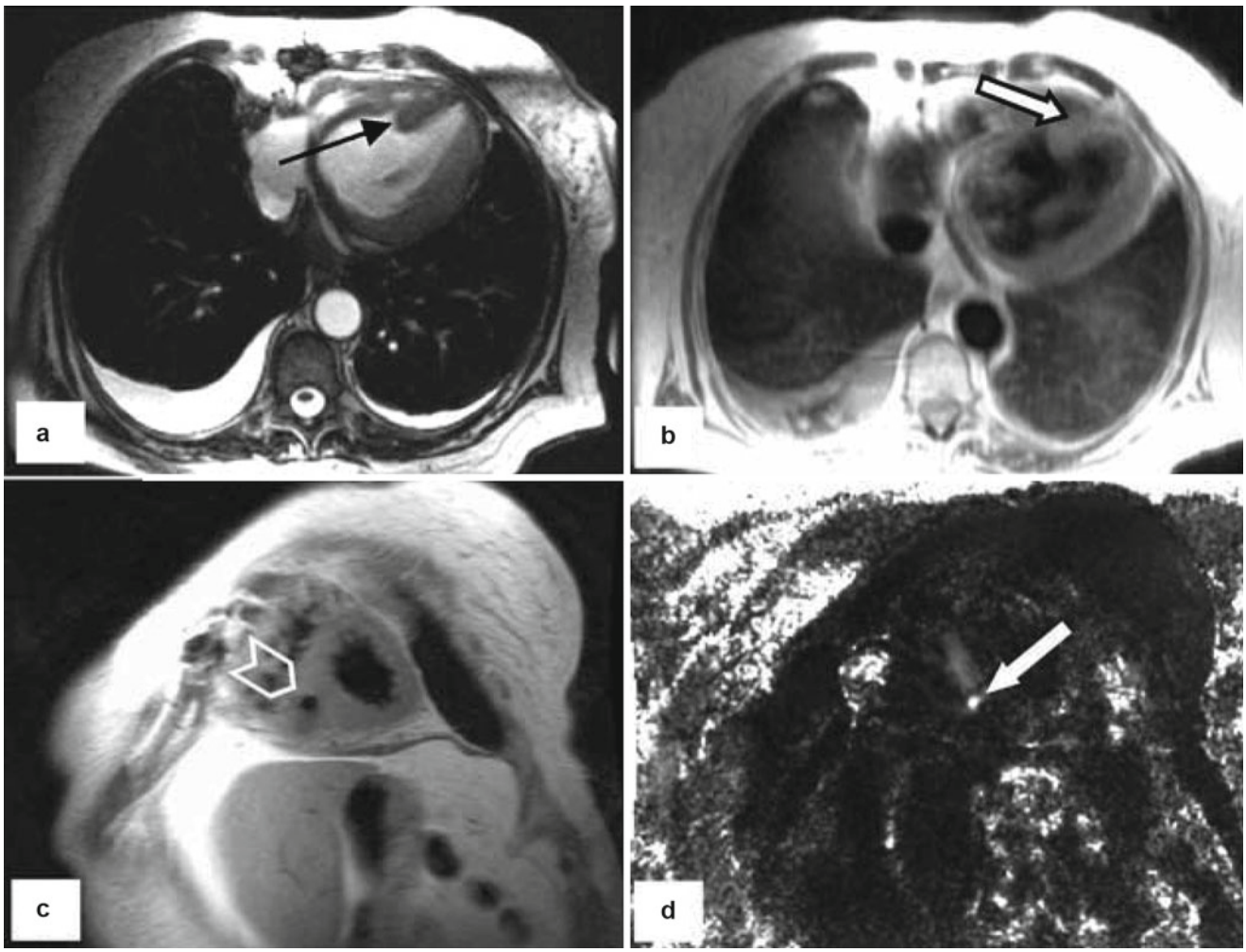


Fig. 13.3 A 54-year-old female with progressive dyspnea 6 month following an anterior septal MI. A murmur was heard prompting an MRI evaluation. (**a**) A septal defect in the interventricular myocardium is seen (*arrow*). (**b**) The high-velocity flow between the LV and RV was diagnostic of a post-infarct VSD (*arrow*). (**c**) Selective breath-hold imaging reveals the distinct septal hole (*arrow*), allowing for measurement. (**d**) Phase velocity imaging allowed quantitation of the Qp:Qs of 2.2, primarily left to right. As the patient was turned down for surgical repair, she underwent compassionate use of the nonsurgical ASD closure device for the VSD (*arrow*)

function. Since the myocardium is clearly visualized, it is easy to measure wall thickness and to evaluate wall thickening [5]. Furthermore, global and regional myocardial mass can be measured [6].

In addition to functional evaluation with conventional contrast imaging, other methods specific to cardiovascular MR studies are available: phase velocity mapping and RF tagging. Phase velocity mapping is analogous to Doppler echocardiography. In phase velocity mapping, the phase of each pixel in the MR image is related to the voxel's velocity. Unlike Doppler echocardiography, it is not dependent on exact angulation, and it measures velocity and flow accurately in two and as many as three dimensions. Phase velocity mapping has a plethora of applications, including blood flow visualization and determination of stroke volume and cardiac output at the aortic valve and in evaluating ventricular septal defects (Fig. 13.3). Shunt flow may be evaluated by comparing aortic flow to pulmonary artery flow. RF tagging provides CMR with a unique ability to more precisely evaluate regional myocardial function [7]. By using the appropriate perpendicular saturation band pulse sequence, dark lines in a regular crisscross pattern can be applied to the myocardium at the time of the ECG R wave. Since these lines move with the myocardium, intrinsic motion can be visualized to assess true function without the confounding effect of myocardial through-plane motion [8] or remote muscle influences (tethering). Furthermore, changes in distance between intersections of RF grid lines can be tracked and regional strains, indices of rotation, and translation amounts calculated. Unlike tracking of material markers, RF tagging does not impede or influence myocardial dynamics, and it is completely noninvasive.

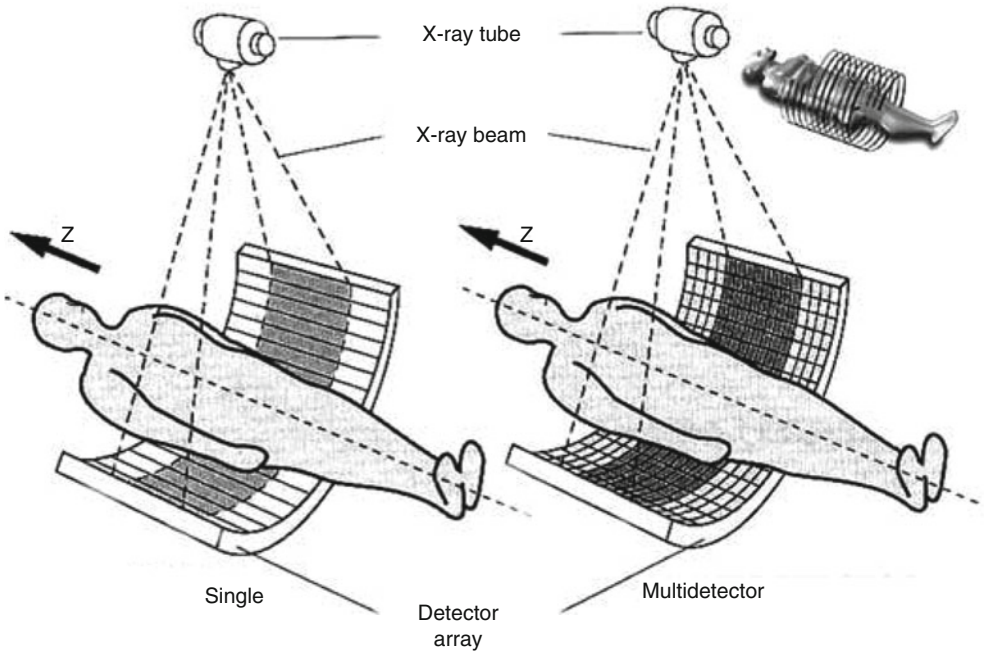


Fig. 13.4 Multidetector CT. Comparison of single-slice and multidetector CT. Multidetector CT uses an array of detectors to improve resolution (smaller pixels) and temporal (more slices) coverage of the heart and great vessels. Cardiac CT has shown continued improvement as detector arrays have increased from 1 to 2, 4, 8, 16, 40, and 64

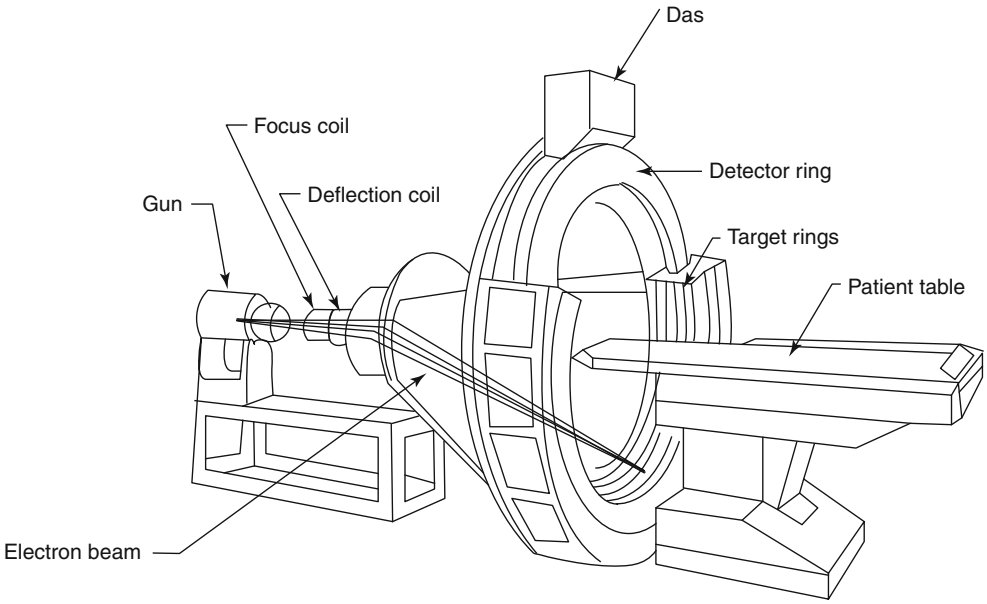


Fig. 13.5 Diagrammatic display of an electron beam computed tomographic imaging system (Courtesy of GE Healthcare)

Computed Tomography

The main type of CT systems used for cardiovascular diagnosis is multidetector CT (MDCT). MDCT devices use a slip ring, continuously rotating X-ray source, and circular arrays of stationary detectors (Fig. 13.4). MDCT is performed with the table continuously in motion during scanning, generating multiple (4, 8, 16, 32, 64, 125, 256 up to 320) spiral slices per 250–400 ms revolution, with excellent ($<0.5 \times 0.5 \times 0.5$ mm^3) spatial resolution. MDCT cardiac acquisitions must be ECG-triggered and coupled with a breath hold between 1 and 10 s. Partial rotational data may be subsegmentally reconstructed to produce cardiac images with an effective temporal resolution for MDCT images from 50 to 200 ms (Fig. 13.5).

Cardiovascular CT spatial resolution is considerably better than MR. Single-source MDCT is difficult to perform effectively in patients with a heart rate over 90 beats/min. Heart rate reduction using a β-blocker such as propranolol (20–40 mg) or metoprolol (50–100 mg) prior to MDCT for coronary artery examinations is desirable [9]. Currently available MDCT techniques allow for better control of the X-ray tube output to reduce radiation exposure. However, MDCT does not spare the radiation exposure compared to angiography. When angiographic intervention procedures are performed, they generate considerably more radiation exposure for patients and personnel [10, 11].

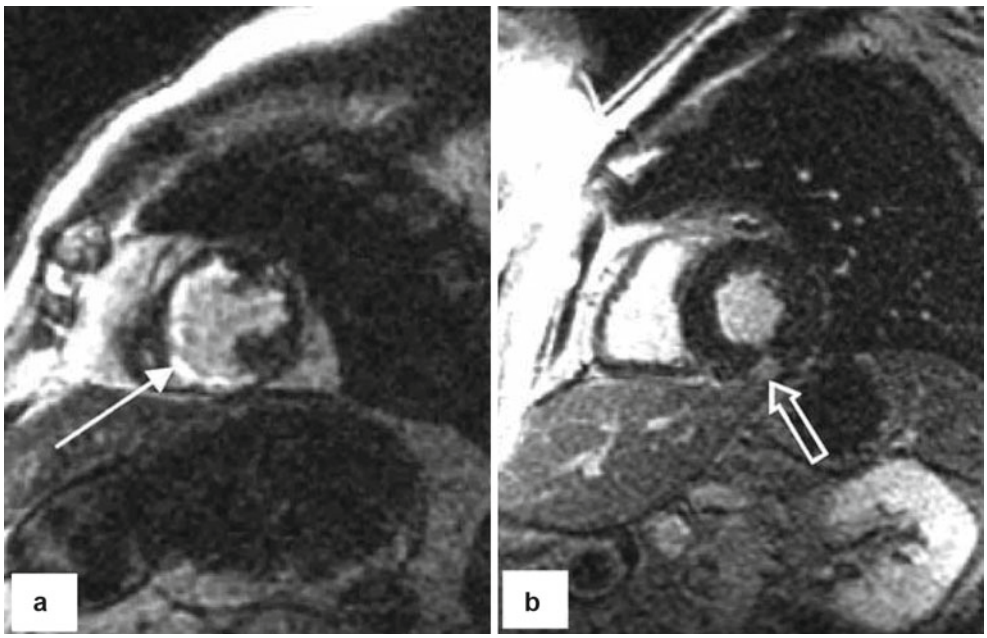


Fig. 13.6 A paramagnetic agent (gadolinium DTPA) was infused and the delayed enhancement image seen here acquired after a delay of 15 min. The accumulation of gadolinium is seen (*arrows*) indicating distribution of necrotic myocardium. (**a**) A large region is affected. (**b**) A small region is affected in a patient with equivocal troponin I (7 ng/dL). The latter patient underwent cardiac catheterization, demonstrating a left circumflex distal marginal occlusion

Because the relative radiographic densities of the myocardium and the blood pool are nearly identical, other than for the evaluation of coronary artery calcification, there is an absolute need to administer iodinated radiopaque contrast medium with CT [12]. Some patients may be allergic to radiopaque contrast media, and administration of contrast medium could precipitate renal failure in patients with borderline renal function or idiosyncratically in those with normal function. Finally, the osmotic load required to generate important diagnostic information could precipitate an episode of pulmonary edema in patients with congestive heart failure. The use of low-osmolality nonionic contrast agents is required in such patients but does not reduce the incidence of renal impairment.

CT Methods

A number of recent studies have described the use of MDCT to assess right and left ventricular function. These are typically acquired in a continuous series over several heartbeats, a process known as retrospective acquisition. After intravenous administration of radiopaque contrast medium, serial images depict the cardiac chambers with good contrast between ventricular wall and ventricular blood pool. From such an acquisition, left and right ventricular volume and ejection fraction can accurately be determined. Like CMR, MDCT provides a means of evaluating heart function, including chamber volumes, ejection fraction, and myocardial mass. Unlike CMR, it is essential to use radiopaque contrast medium to define the endocardial borders of the cardiac chambers. High-resolution images can be generated that allow precise measurement of regional and global ventricular function at the expense of higher doses of effective radiation compared to prospectively ECG-triggered MDCT acquisition. As with CMR, a series of short-axis ventricular slices can be reconstructed from the volumetric data and ventricular volumes calculated. These slices can sample 10–20 or more images throughout the cardiac cycle depending on the baseline heart rate and temporal resolution of the CT scanning hardware. With a modification of Simpson's rule, ventricular volume and mass can be determined. Studies in both laboratory animals and humans demonstrate the reliability of left ventricular volume and mass determination using MDCT. Similar results have been demonstrated previously using EBCT.

Ischemic Heart Disease

Since CMR and MDCT can reliably evaluate the function of both ventricles by examining volumetric changes and changes in myocardial thickness during systole and diastole, they can be used to demonstrate regional wall motion abnormalities [13]. Using gadolinium MR contrast agents, one can see delayed hyperenhancement of the infarcted myocardium (Fig. 13.6) [14, 15]. Unlike nuclear or echocardiographic techniques, this seems to be a unique phenomenon of CMR and presently is the subject of intense research. Specifically, the extent of delayed enhancement, or "transmurality," has been shown to be predictive of functional recovery after appropriate revascularization. Further prognostic value can be attained by the evaluation of microvascular obstruction within

a prior myocardial infarction, a process also known as "no reflow" on traditional coronary angiography [16] (Fig. 13.7).

Myocardial *ischemia* can be diagnosed by comparing resting images obtained at rest to images acquired after approaches that increase myocardial blood flow, such as handgrip, pharmacologic infusion of dobutamine or of a vasodilator agent, or even exercise using specialized equipment [17]. Coronary vasodilator agents such as regadenoson, adenosine, and dipyridamole may be infused during contrast-enhanced CMR perfusion studies to demonstrate reduced dynamic enhancement in territories served by stenotic coronary arteries (Fig. 13.8) [18]. The imaging and physiologic principles are similar to those of radionuclide or "nuclear" perfusion stress testing [19, 20].

Using CMR cine, one sees deterioration in left ventricular myocardial contraction with higher doses of dobutamine in segments supplied by coronary arteries with significant stenoses. Myocardial *viability* can also be assessed through a phenomenon termed "contractile reserve" when dobutamine stress CMR is used to enhance poorly contracting myocardial segments. One would see improvement in wall motion with low-dose dobutamine but deterioration of the wall motion of the same segments at higher doses due to ischemia, that is, the biphasic response, in the presence of viable but hypocontractile myocardium.

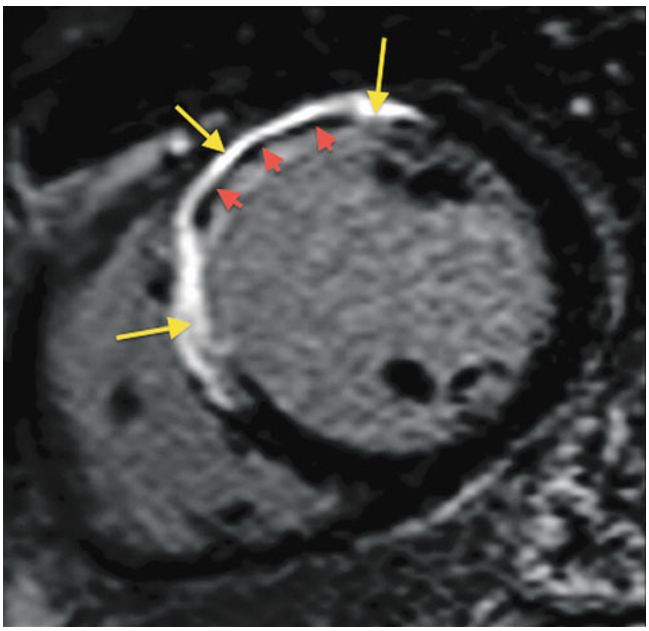


Fig. 13.7 Delayed enhancement image in a short-axis view of the mid-left ventricular cavity demonstrating transmural delayed gadolinium enhancement in the anterior and anteroseptal walls consistent with a left anterior descending coronary artery myocardial infarction (*yellow arrows*). The area of reduced signal within the core of the infarct represents microvascular obstruction, analogous as "no reflow" on coronary angiography (*red arrows*)

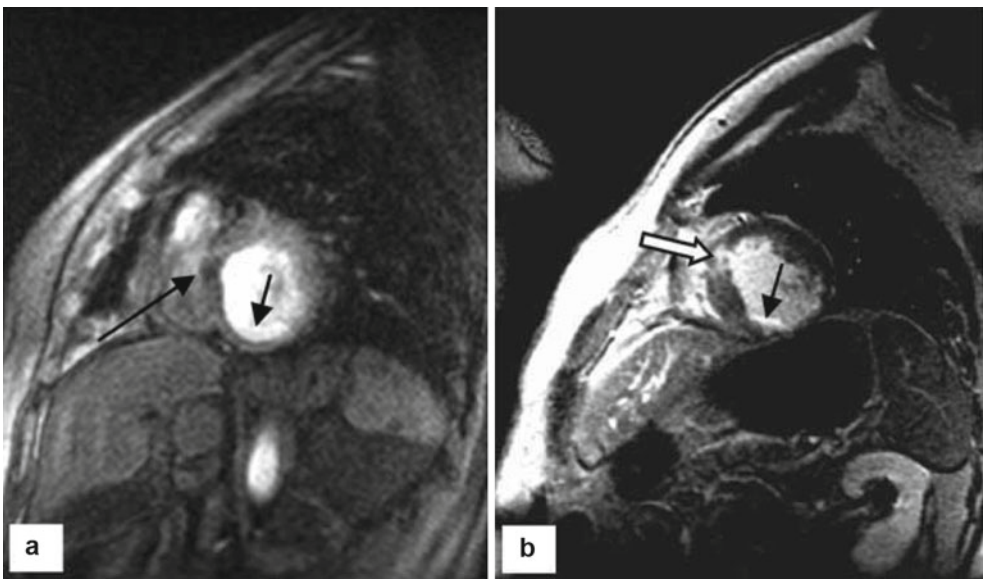


Fig. 13.8 (**a**) FSGRE image of a short-axis slice demonstrating the concept of first-pass perfusion using gadolinium. The *large arrow* indicates a focal hypoenhanced near-transmural anteroseptal lesion, representing the relative lack of gadolinium's T1 effect in poorly perfused myocardium (low signal) as compared to the otherwise normally perfused myocardium (higher signal). The *small arrow* points to a small endocardial lesion missed by nuclear imaging due to its 1–2 mm thickness, well below the 10–13 mm resolution required for radionuclide-based techniques. (**b**) A unique property of CMR, using this technique, is the relative late (5–20 min) effect that contrast provides to highlight necrotic (scarred) myocardium, *outlined arrow*. As shown in the *small arrow*, an even smaller endocardial scar can be seen, partially encircling the inferior/inferior lateral wall. This technique, referred to as "delayed hyperenhancement," is now demonstrated to be the reference standard for interrogation of myocardial viability

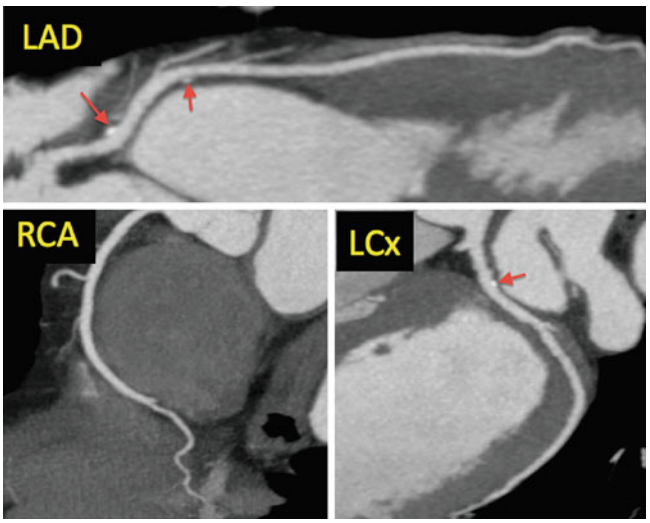


Fig. 13.9 Coronary CT angiogram depicting mild, non-obstructive calcified plaque in the proximal and mid-LAD and proximal LCx (*red arrows*). The RCA and PDA appear widely patent and are free of coronary atherosclerosis. *LAD* left anterior descending coronary artery, *LCx* left circumflex coronary artery, *RCA* right coronary artery, *PDA* posterior descending coronary artery

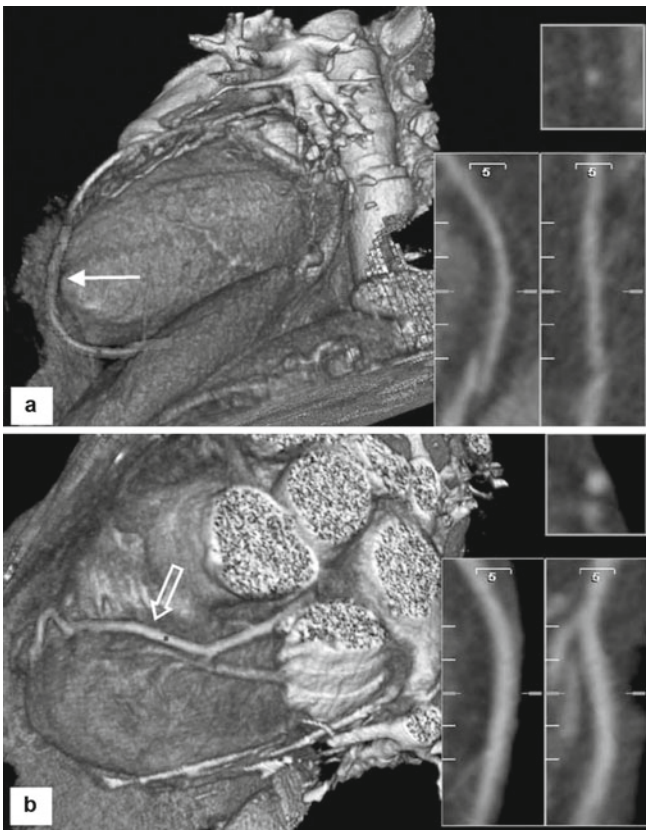


Fig. 13.10 Images obtained using MDCT processed to highlight the LAD and epicardium. (**a**) Distal view (*arrow*) and (**b**) the proximal section (*arrow*). Inserted views depict orthogonal views of the highlighted sections

CT approaches to myocardial perfusion can be applied to semiquantitatively assess perfusion levels [21]. By analyzing the myocardium as the contrast agents perfuse it, it is possible to calculate regional perfusion using automated software evaluation of myocardial segments similar to that currently performed by nuclear perfusion studies. CT perfusion with vasodilator stress has been shown to be feasible and safe and have good correlation to SPECT and CMR perfusion [22–24].

Coronary Artery Imaging

In many instances, visualization of the coronary arteries is required, and substantial progress in both techniques, but particularly MDCT has been made toward this goal during the past decade.

Currently, MDCT is able to routinely visualize normal coronary arteries using multidetector technology (initially attempted with 16 and 32 slice systems) and more recently using 64, 128, 256, and 320 slice detector systems. Rapid advancements in this field coupled with advanced acquisition techniques have led to the widespread adoption of MDCT as the gold standard noninvasive evaluation of coronary artery disease. Several multisite studies have demonstrated the overall very high negative predictive value (>99 %) of this technique in individuals with low to intermediate likelihood of coronary disease. An example of a coronary CT angiogram with mild, non-obstructive calcified plaque (red arrows) in the proximal LAD and LCx is shown in Fig. 13.9 (LAD, left anterior descending; LCx, left circumflex; RCA, right coronary artery). Exciting new developments in this field include the ability to integrate flow information through computational fluid dynamics, permitting noninvasive evaluation of fractional flow reserve (FFR-CT). Limitations to MDCT still include contrast requirements, the need to administer β-blockers to reduce the heart rate to approximately 60 beats/min, and radiation doses. Improvements in spatial resolution may allow reductions in contrast dosage (Fig. 13.10b) [25]. Through various radiation dose-lowering techniques such as reduced tube voltage, greater use of prospective ECG-triggering, and iterative reconstruction, effective radiation doses have seen a dramatic decline since the introduction of 64-slice MDCT technology in 2004.

Using the latest instrumentation and MR techniques, imaging the proximal coronary trunks and some more distal segments of the coronary arteries is feasible. It has been shown to be more accurate for the delineation of anomalous coronary arteries than X-ray angiography (Fig. 13.11). Limitations of coronary MRA include long acquisition times (typically upward of 10 min), motion artifacts, and the intrinsic temporal and spatial resolution limits of the CMR system. Certainly, more investigation is needed to refine coronary MRA for it to be adopted in a widespread fashion. Such additions as the use

of a blood pool contrast agent might improve the sensitivity and specificity as compared with catheter coronary angiography. A few investigators have evaluated the potential for CMR to characterize coronary arterial plaque. Clinical determination of plaque vulnerability may be within the realm of possibility for this versatile technology.

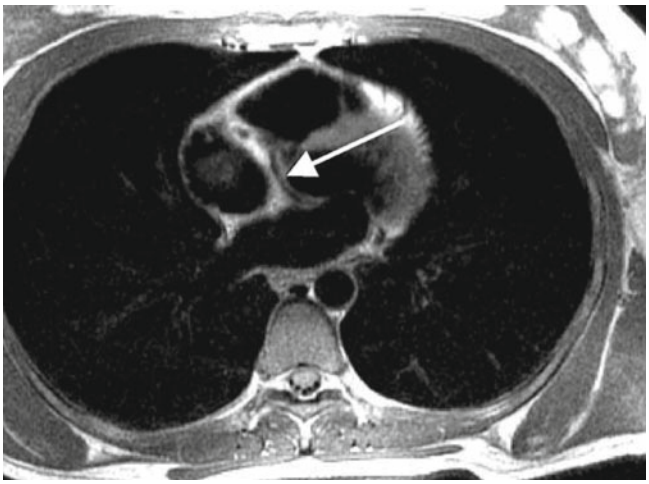


Fig. 13.11 This 45-year-old patient presented with chest pain, underwent X-ray coronary angiography, and was found to have an anomalous left circumflex arising off the right coronary sinus. Regarding the question as to trajectory, the catheterization results were equivocal, prompting a cardiac MRI. This double-inversion recovery image was acquired in a breath-hold manner without administration of contrast, clearly demonstrating the benign nature of this anomaly. The vessel travels posterior to the aortic root (*arrow*) as the great majority, if not all, of anomalous left circumflex vessels do

Coronary Calcium

Both MDCT and EBCT detect coronary artery calcification, as direct evidence of coronary atherosclerosis [26]. In view of the high speed of EBCT acquisition, the coronary arteries are virtually "frozen" in space, and the extent of calcification can be accurately assessed (Fig. 13.12). MDCT also can provide relatively fast imaging, but with 50–200 ms acquisitions, the blurring effect due to cardiac motion could be problematic, although less so with modern 64-slice or greater systems (Fig. 13.13). Because of the widespread availability of MDCT scanners, in contrast to EBCT scanners, it is important to note that MDCT provides coronary artery calcification scoring comparable to that of EBCT. Use of coronary artery calcification as a predictor of functionally significant coronary artery disease remains controversial [27], especially in younger individuals who have predominantly noncalcified plaque. It clearly indicates the presence and burden of atherosclerosis but not its physiologic significance. Proponents of the application of EBCT maintain that it should become a routine study for coronary risk assessment [28]. Others suggest that plaque rupture, a common cause of coronary occlusion, is related to the lipid constituents of plaque (invisible to X-rays), but not to the amount of calcium. At present, the value of the EBCT coronary calcium score is uncertain, and it does not supplant current clinical methodologies, although it does provide another, albeit expensive, means for risk assessment [29]. The most recent 2007 ACC/AHA Consensus Document supports the role of CT coronary calcium measurement in asymptomatic patients with intermediate coronary heart disease risk, that is, those at 10–20 % 10-year risk

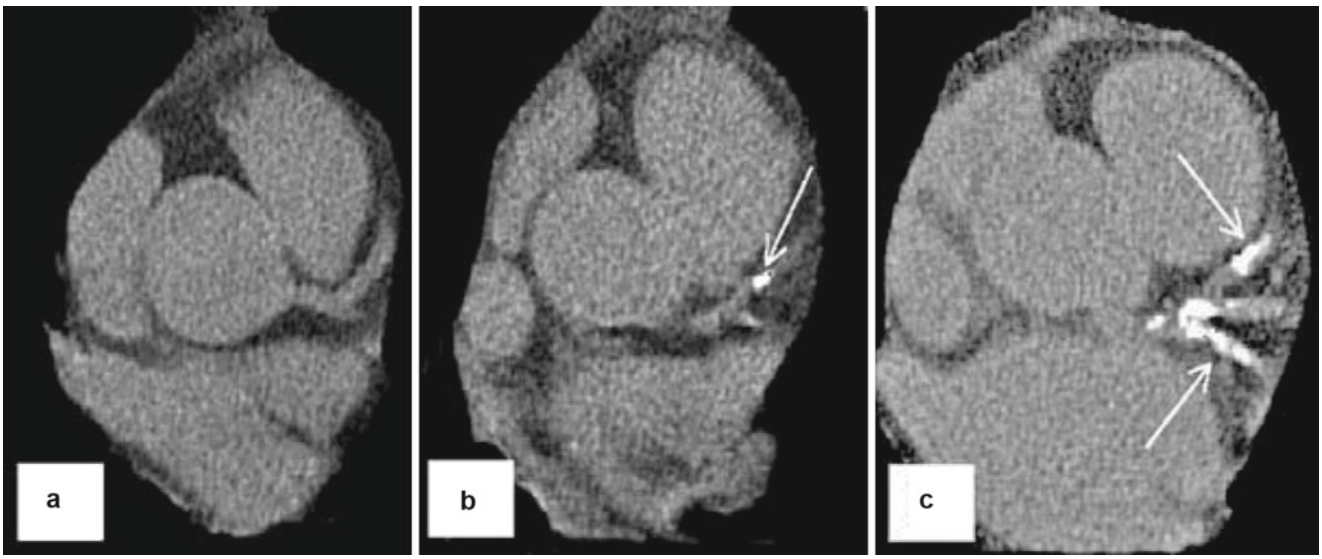


Fig. 13.12 Examples of progressive coronary artery calcification (**a–c**) depicting increasing signal as the intraluminal calcium burden rises. Formal calcium scores can be derived using the Agaston algorithm from the scans quantifying the signal from the calcium. Although calcium is a well-accepted marker for atherosclerosis, the direct relation between calcium and prediction of clinical events is less well established (Courtesy of GE Healthcare). *Arrows* represent calcified coronary artery plaque

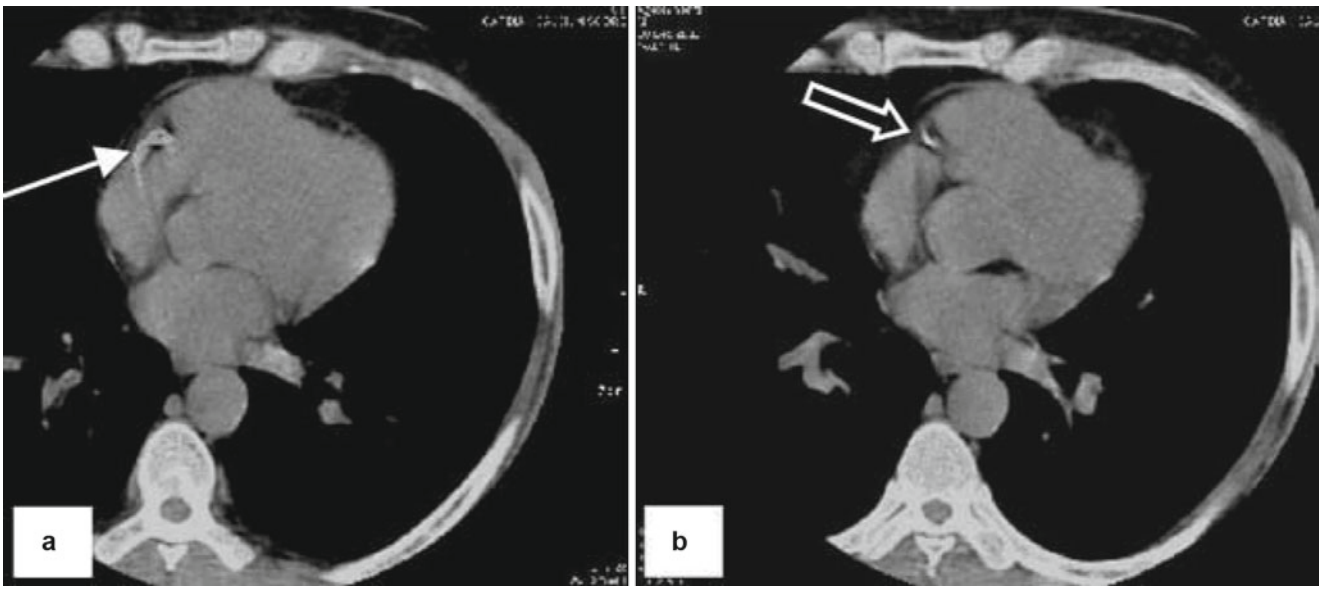


Fig. 13.13 Examples of low levels of coronary artery calcification (*arrows*, **a–b**) visualized as increased signal as the intraluminal calcium burden rises

of death or myocardial infarction (class IIb recommendation, level of evidence B) [30]. Further data will be required to determine its actual utility [31].

Cardiomyopathies

With dilated and valvular cardiomyopathy (either acquired or of congenital origin), one might expect to find both left and right ventricular involvement and homogeneously depressed left ventricular wall motion (Fig. 13.14). Hemochromatosis, an infiltrative cardiomyopathy whereby iron accumulates in the myocardium, can be readily diagnosed by CMR. The iron that is localized in the myocardium and the liver generates a characteristic signal dropout pattern so that the liver and, in part, the myocardium demonstrate very low signal. In *sarcoidosis*, one can visualize the granulomatous infiltrates with delayed gadolinium enhancement that may lead to ventricular dysfunction as well as local inflammation.

One cardiomyopathy that may be well characterized by CMR is arrhythmogenic myocardial dysplasia. In this condition, which is associated with life-threatening ventricular arrhythmias, the right ventricle is involved with fat infiltration and myocardial thinning. The fatty infiltrate shows up as a bright signal on black-blood spin-echo CMR (in about half of these patients) and regional wall motion dysfunction (in most patients) on gradient-echo or SSFP images, combined with signal nulling on T2-weighted images, confirming the presence of intramyocardial fat deposits (or transformation) (Fig. 13.15). Morphologic imaging can also be accomplished with CT [32].

Hypertrophic cardiomyopathy (HCM) is a genetic cardiomyopathy that causes myocardial hypertrophy in a variety of patterns. The hypertrophy can be readily imaged and quantified with CMR imaging. One particular type of HCM that can be challenging to detect with standard echocardiography is apical variant HCM (aka "Yamaguchi's disease") [33] (Fig. 13.16). CMR may avoid this problem because it is less operator dependent, is not subject to acoustic-window limitations, and has multiplanar capability and displays excellent soft-tissue contrast.

Finally, cardiac amyloidosis has several characteristic patterns of delayed gadolinium enhancement on CMR imaging studies and can be readily identified. Interestingly, the development of myocardial gadolinium deposition predates any clinical manifestation and thus permits identification even in asymptomatic individuals.

Fig. 13.15 A 34-year-old woman presenting with several episodes of syncope and near syncope before a catheter-based electrophysiological study. The patient's risk was stratified using CMR. (**a**) A four-chamber view with *arrow* pointing to a mid-systolic asynergic, tardykinetic zone of the right ventricle free wall with thinning, meeting two major working group classifications for arrhythmogenic right ventricular dysplasia (ARVD). The third classification (out of four) is met in (**b**) as shown by a triple-inversion recovery sequence, a unique sequence to magnetic resonance, that takes advantages of the faster relaxation of fat compared to protein. This T2-weighted image provides insight into specific tissue characteristics, which is another important property of CMR. Note the subtle but evidence of fat within the myocardium corresponding to the asynergic zone. The fat signal of the breast tissue is similar to that within the affected RV free wall (*arrow*). The patient was referred to the NIH-sponsored ARVD trial and likely for defibrillator placement, the current standard for treatment

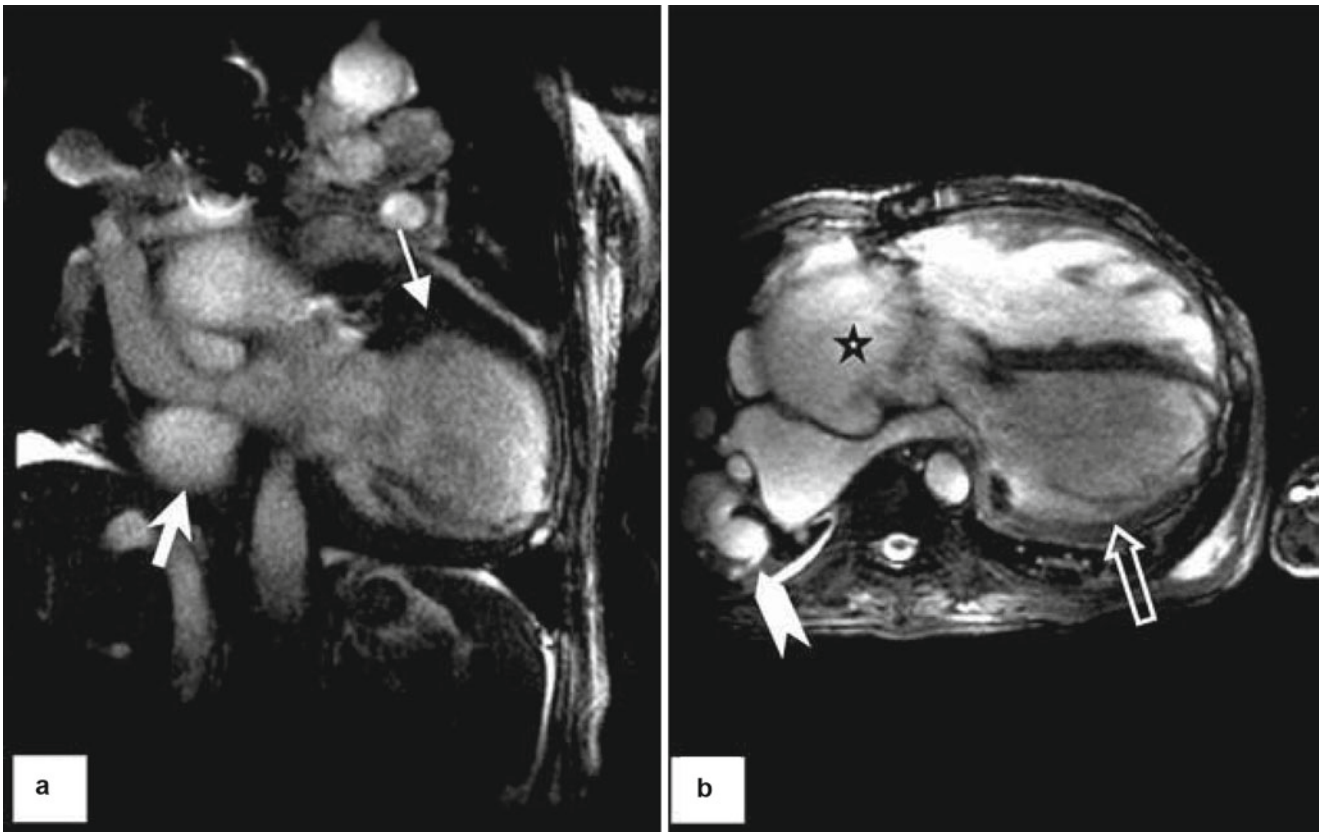
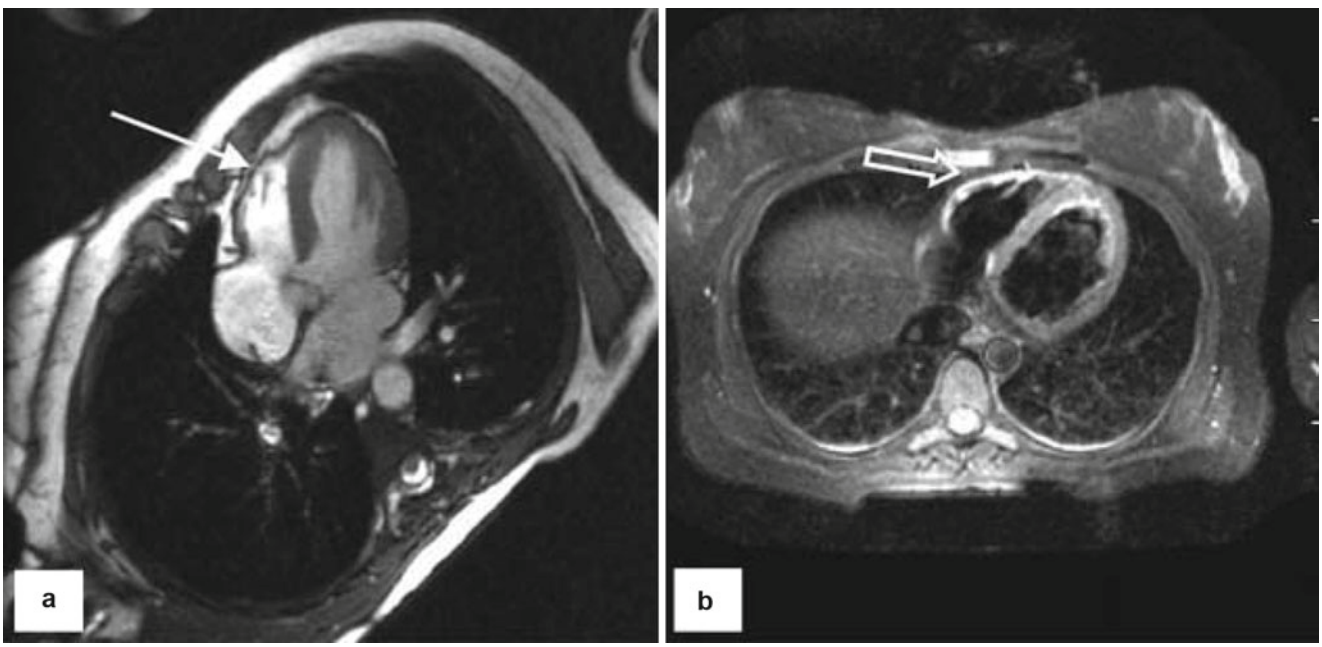


Fig. 13.14 A 32-year-old female presented 25 year after repair of tetralogy of Fallot. (**a**) The LV was dilated (*small arrow*), measuring 100 mm × 53 mm with a markedly compressed LA (*large arrow*). (**b**) Note the enlarged right ventricle, left ventricle (*open arrow*), and the RA/LA, as well as small aortobronchiolar communications to augment pulmonic flow (*chevron*). The enlarged aortic root (*star*) is probably related to late correction and high early childhood systemic flow due to redirection of pulmonic flow. Poor migration of neural crest cells with their elastin, forming progenitor cells, has been implicated in the aortic root and ascending aortic dilation, as seen in this patient who was shown to have a small contained aortic dissection (not shown)



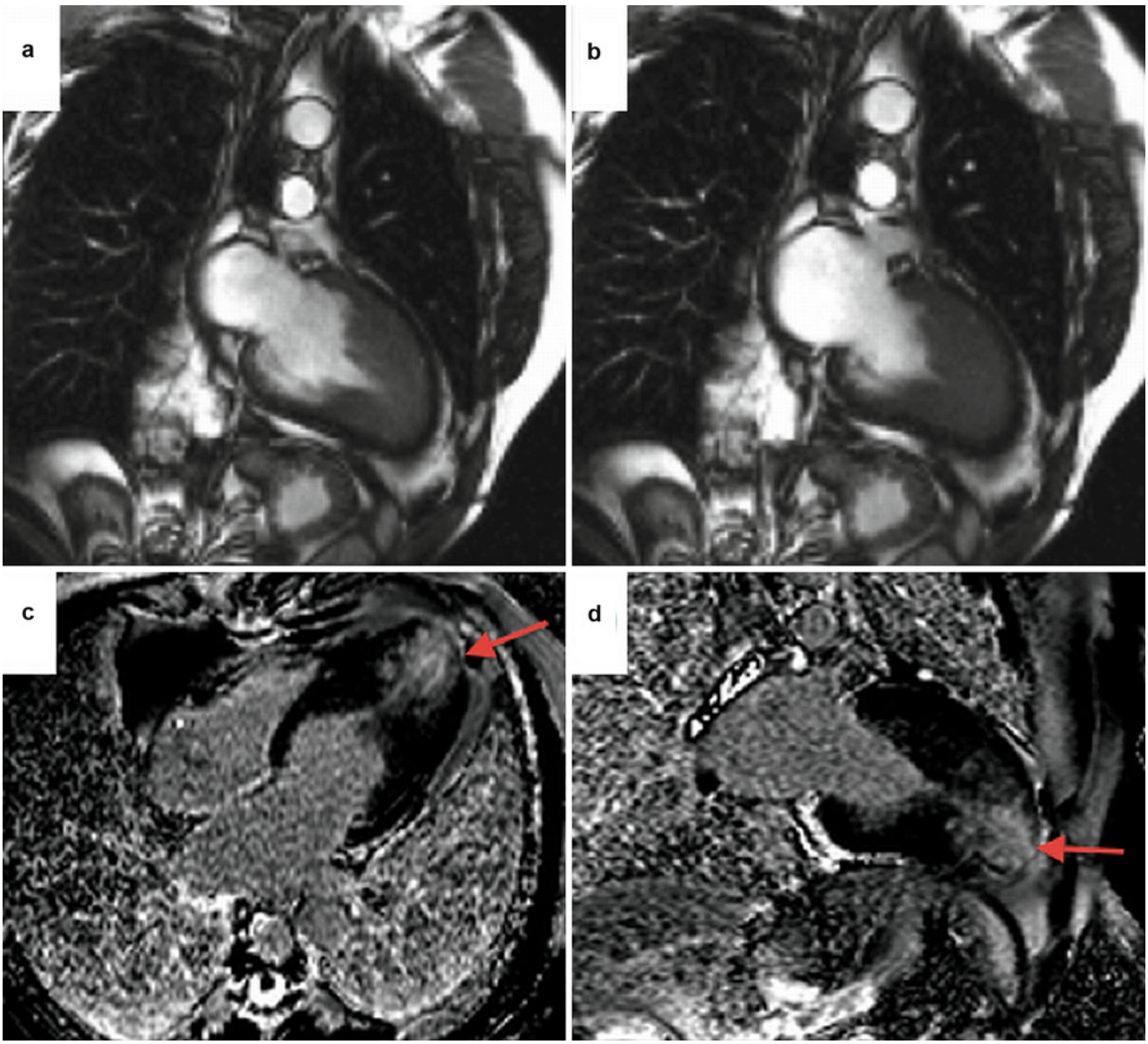


Fig. 13.16 A 42-year-old man presented with suspicion of apical hypertrophy on an echocardiogram. (**a**) SSFP cine sequence at end-diastole demonstrates apical hypertrophy and a "spade-shaped" ventricle, (**b**) SSFP cine at systole, and (**c** and **d**) phase sensitive inversion recovery delayed enhancement sequence showing marked apical enhancement (*red arrows*) consistent with apical variant of hypertrophic cardiomyopathy

Aortic and Peripheral Vascular Imaging

MRA offers excellent noninvasive imaging of the aorta, pulmonary arteries and veins, cerebral vasculature, and the iliofemoral arterial system. Satisfactory visualization of the lower extremity runoff vessels is routinely achievable. Because signal can be generated through the motion of blood, MRA may not require any contrast agent administration for many of these examinations. MR contrast agents have an excellent safety profile and are safe to use in patients with renal failure. The osmotic load is less than that of iodinated contrast agents. Intravenous contrast-enhanced MRA is routinely used for examinations of the aorta, pulmonary vessels, carotid arteries, renal arteries, and arteries of the lower extremity but can be performed in their entirety without contrast through time-of-flight approaches.

MRA of the aorta is considered to have equivalent sensitivity but superior specificity to transesophageal echocardiography or multislice contrast-enhanced CT for the evaluation of aortic aneurysms and aortic dissection. In dissection, intimal flaps and entry site can be identified, allowing for identification of the true and false lumen, differentiation between blood flow and clot in the false lumen, and involvement of branch vessels (Fig. 13.17). The critical distinction

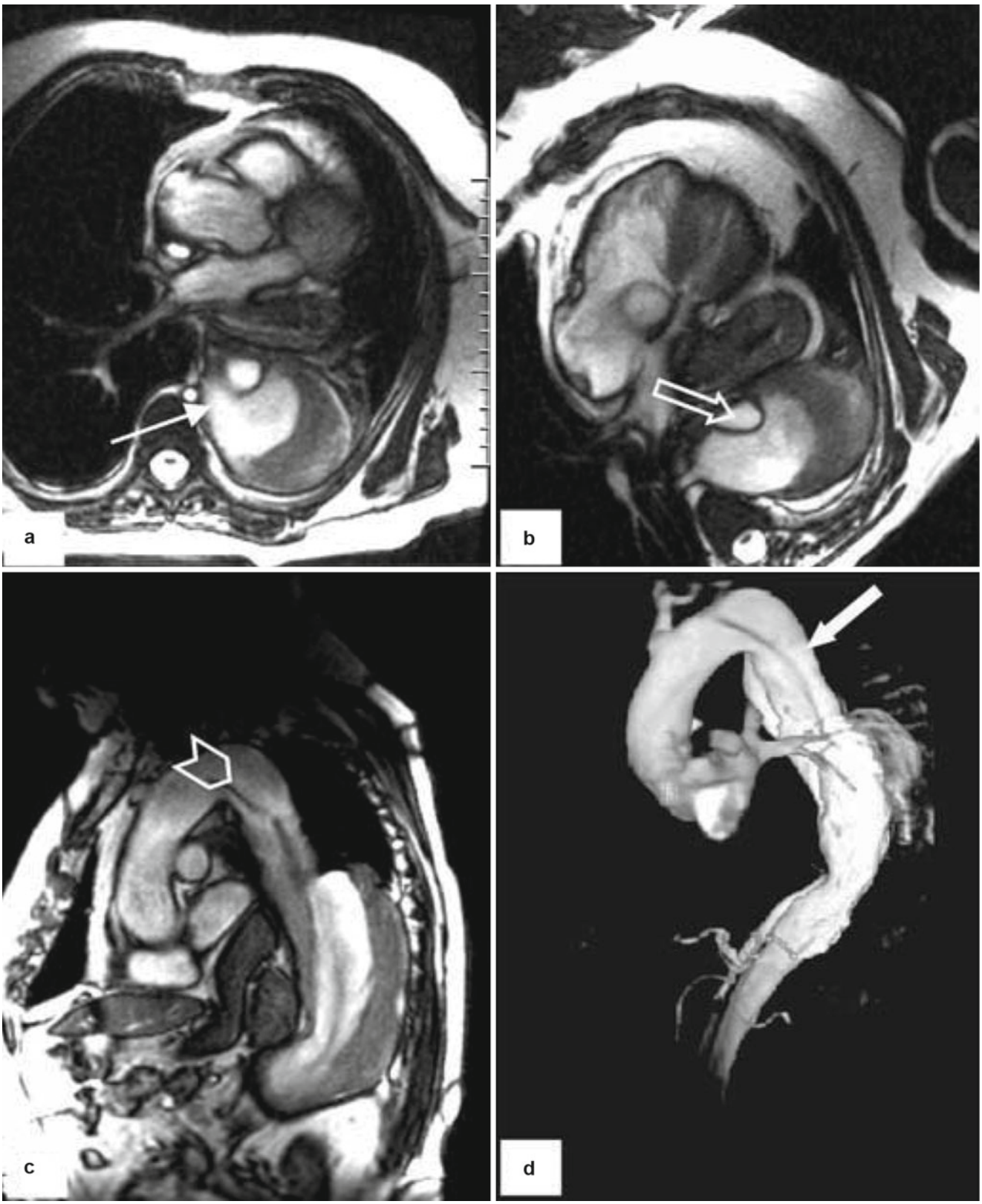


Fig. 13.17 Dissection and thrombus is visible in the false lumen. Multiple views of a type B descending aortic dissection are shown. (**a**) A SSFP axial slice depicts flow in the false lumen (*arrow*). (**b**) The partially thrombosed false lumen can be seen to the right (dark) and the true lumen is seen to the left (*arrow*). (**c**) The high descending aortic origination of intimal flap is seen (*chevron*). (**d**) A 3-D surface rendering of an MRA acquired in 22 s with gadolinium demonstrates the intimal flap (*arrow* indicates false lumen). Note the tiny true lumen in the abdominal aorta. The images demonstrate a "clean" dissection of the aorta with the true lumen supplying the right renal artery and the false lumen supplying the left renal artery

between DeBakey dissection type 1 or 2 and type 3 lesions is readily made with MR. Congenital anomalies of the aorta can also be identified, such as coarctation, arch interruption, and transposition. Imaging the cerebral arterial supply, including the carotid and vertebral arteries, has become routine in clinical practice, supplanting X-ray angiography.

The thoracic and abdominal aorta can readily be evaluated using MDCT after a bolus injection of radiopaque contrast medium. Aortic aneurysms and dissections are detected and assessed. Where CMR is not available, MDCT, EBCT, or TEE are preferred for diagnostic assessment. Like CMR, CT methods are useful for visualizing the intimal flap and for determining the extent of branch vessel involvement. CMR and CT are useful for differentiating between aortic aneurysm with mural thrombus and dissection with thrombus in the false lumen.

Both MDCT and EBCT have been used to visualize the renal arteries in the evaluation of hypertensive patients with suspected renal artery stenosis. Using contrast enhancement patterns, kidney volumes (both cortical and medullary) can be determined. High-speed CT provides a means of examining renal blood flow and excretion. Branch vessels from the aorta can also be well visualized, including the carotids and vertebral arteries, the trifurcation, the celiac, the superior and inferior mesenteric, the brachiocephalic, the iliofemoral, and the popliteal arteries. CMR is the preferred technique in the majority of patients, especially if there is evidence for renal compromise. One caveat to this rule is when severe baseline chronic kidney disease is present (estimated glomerular filtration rate <30 mL/min). In this situation administration of gadolinium chelates has been reported to rarely lead to nephrogenic systemic fibrosis, a chronic, progressive, and debilitating condition associated with cutaneous, subcutaneous, and joint thickening and fibrosis with resultant disability and immobility [34].

Pulmonary Arteries

Pulmonary emboli have been reliably identified using MDCT, which requires breath holding for optimal imaging of the pulmonary arteries. For patients with possible pulmonary embolism, breath holding is a very difficult challenge. EBCT, however, requires no breath holding. Both breath-hold MDCT and non-breath-hold EBCT have been reported to have sensitivity on the order of 85 % and specificity in the low 90 % range, in a select group of patients with intermediate probability of pulmonary embolism by radionuclide ventilation-perfusion scanning. Generally, the combination of ventilation-perfusion scanning followed by CT is the optimal strategy for detecting pulmonary embolism in a minimally invasive way. CT, like MR, is also very useful for the evaluation of pulmonary veins for anomalies and thrombosis. MRI has been used in limited manner for pulmonary embolism evaluation, although is ideal for pulmonary arteriovenous malformations (Fig. 13.18).

Valvular Disease

CMR can demonstrate valve anatomy, leaflet motion, and blood flow. Regurgitant or stenotic valves appear as regions of signal loss, due to the dephasing of spins within the jet of disturbed flow, on bright-blood cine MR images (Fig. 13.19). Regurgitant lesions may be evaluated by the size of the signal void (for a given TE), the volume of the accepting chamber, the time over which the signal void persists, and the size and duration of persistence of the zone of proximal convergence (i.e., the region where blood converges radially toward the valve orifice) [35].

The severity of valve disease may also be quantitatively evaluated with *phase velocity mapping*. This is similar to Doppler echocardiography. Phase velocity images are related to the velocity of spins passing through a given plane. Phase velocity mapping can be used to quantitate the flow rate volume and velocity of the blood. Stenotic valvular lesions are frequently characterized by phase image velocities as high as or even higher than 8 m/s (i.e., any velocity encountered in human valvular heart disease). Using a modified Bernoulli approach, pressure drop in mmHg may be estimated from phase contrast-measured velocities:

$$\text{Pressure drop} = 4 \times \text{velocity}^2$$

Thus, CMR can be used to assess both regurgitant and stenotic valvular disease. However, its ability to directly visualize normal valve tissue and associated abnormalities, such as endocarditis, while improving, may be somewhat limited compared with echocardiography. It is possible, however, to make excellent images of a bicuspid or tricuspid aortic valve.

Cardiac Masses

Clearly, intracardiac masses such as atrial myxomas and atrial and ventricular thrombi can be detected and evaluated by CMR or MDCT. In fact, ventricular thrombi have been shown to be detected with higher sensitivity and specificity by CMR than by TEE. Virtually any tumor within the heart or that compromises atrial or ventricular function can be assessed. Unfortunately, rhabdomyomas and fibromas may not be distinguished from myocardium on CT, since their density is equivalent to that of myocardium. Differential dynamic contrast enhancement may be useful here. However, because of its sensitivity to T1 and T2 parameters, CMR can frequently differentiate tumors from myocardium (Figs. 13.20, 13.21, 13.22, 13.23, 13.24, and 13.25).

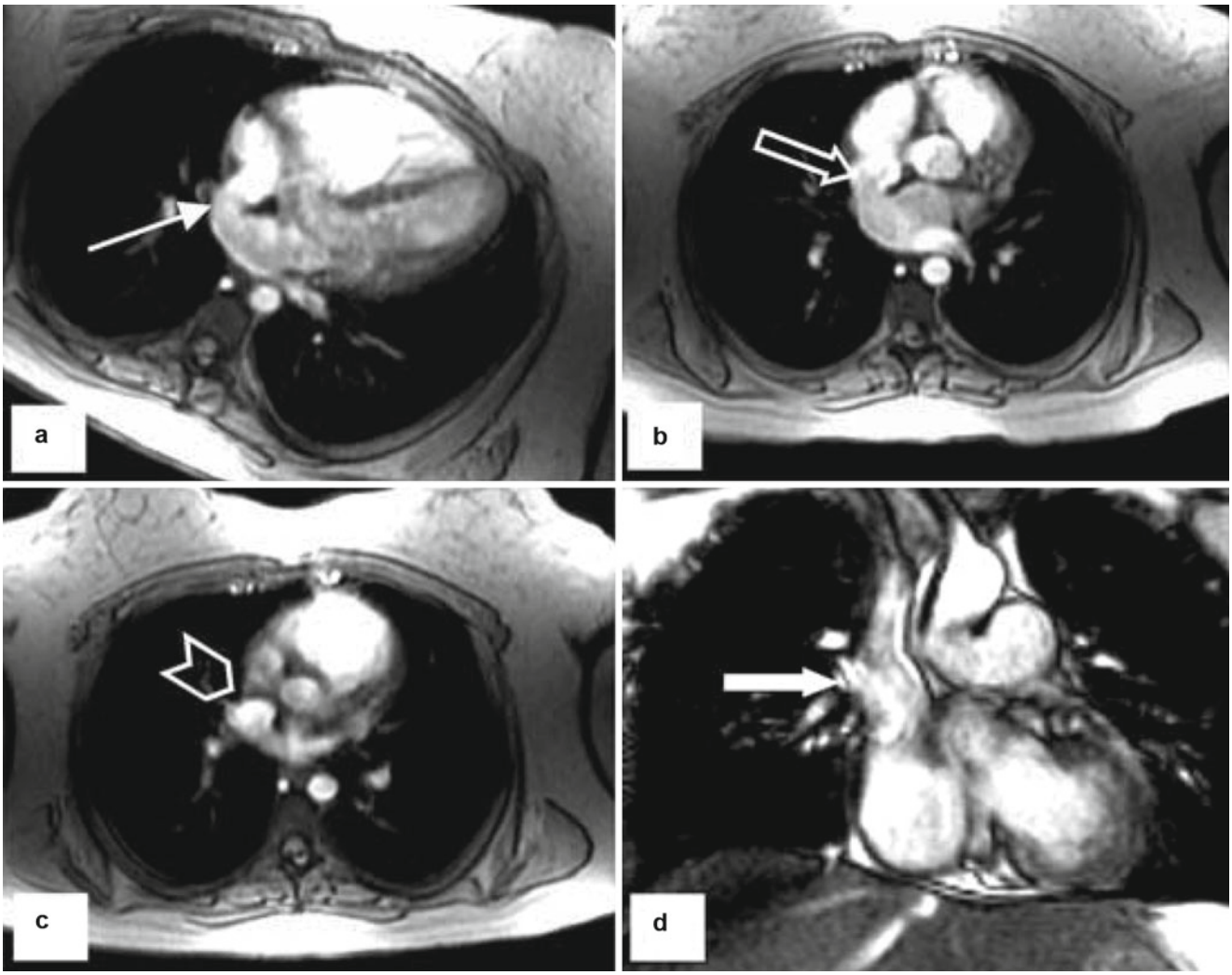


Fig. 13.18 A 24-year-old female presented to the internal medicine clinic for establishment of routine care. A murmur was heard and an echo performed, demonstrating normal LV/RV size, no intracardiac shunt, and an atypical posterior RA signal by color Doppler, prompting a cardiac MRI. (**a**) Demonstrates an absent posterior inner atrial septum with flow saddling between the RA and LA. The "broken ring sign" is present in **b** (*arrow*) demonstrating the classic sinus venosus defect as a defect between junction of the low SVC and high RA, a less common form of an ASD with an obligate anomalous right upper pulmonary vein. (**c**) Demonstrates the defect in the posterior RA (*arrow*). (**d**) Demonstrates the anomalous entry of the right upper pulmonary vein into the SVC/RA junction (*arrow*), confirming, on a second oblique, the presence of the congenital defect. Phase velocity mapping was performed demonstrating a Qp:Qs of 1.7 and a top normal RV size (115 mL) indicating a hemodynamically significant intracardiac shunt, worthy of repair, which was successfully conducted noninvasively

Pericardial Disease

CMR can readily visualize, measure, and characterize (i.e., distinguish transudate from exudate) pericardial effusions. The problem of differentiating between constrictive pericarditis and restrictive cardiomyopathies is made easier by using MR methods, since the pericardium can be visualized and its thickness measured (*see* Fig. 13.23) [36]. Adherence between the visceral and parietal pericardia, the equivalent of surgical visualization of adhesions, is possible employing RF tissue tagging. Under normal circumstances pericardial thickness should not exceed 3 mm. Restrictive left ventricular filling can be demonstrated by volumetric analysis using CMR or by phase velocity mapping. Finally, late gadolinium enhancement of the pericardium is a pathognomonic feature of acute pericarditis (Fig. 13.26).

The pericardium can be visualized by CT techniques as a thin layer, from 1 to 2 mm thick, with density similar to that of myocardium. As with CMR, pericardial thickening can readily be visualized by MDCT and EBCT, although the contrast between pericardium and myocardium may be better on CMR. While pericardial disease should be evaluated by two-dimensional echocardiography and Doppler approaches, both CMR and CT methods are useful for more comprehensive evaluation of patients with possible pericardial disease. CT is clearly the optimal technique to detect pericardial calcification.

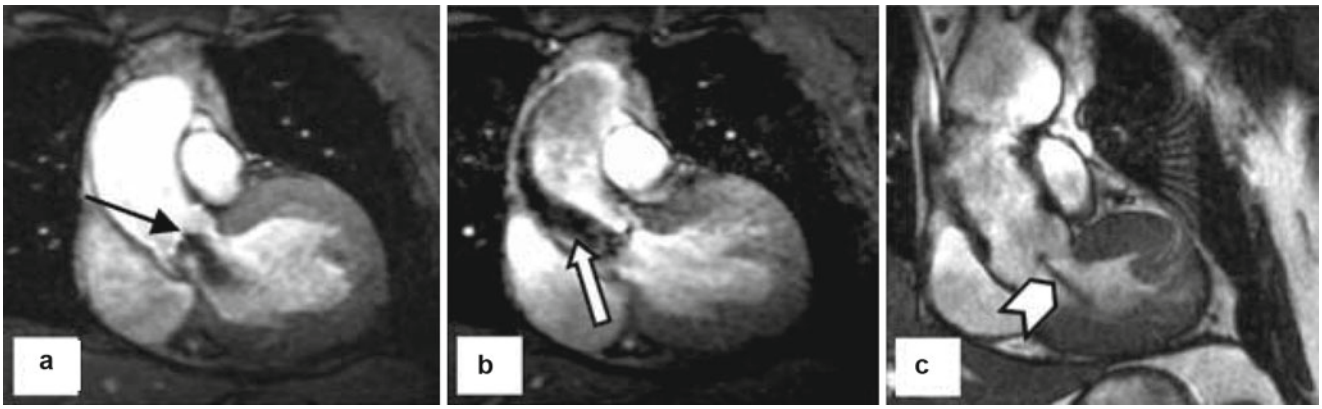
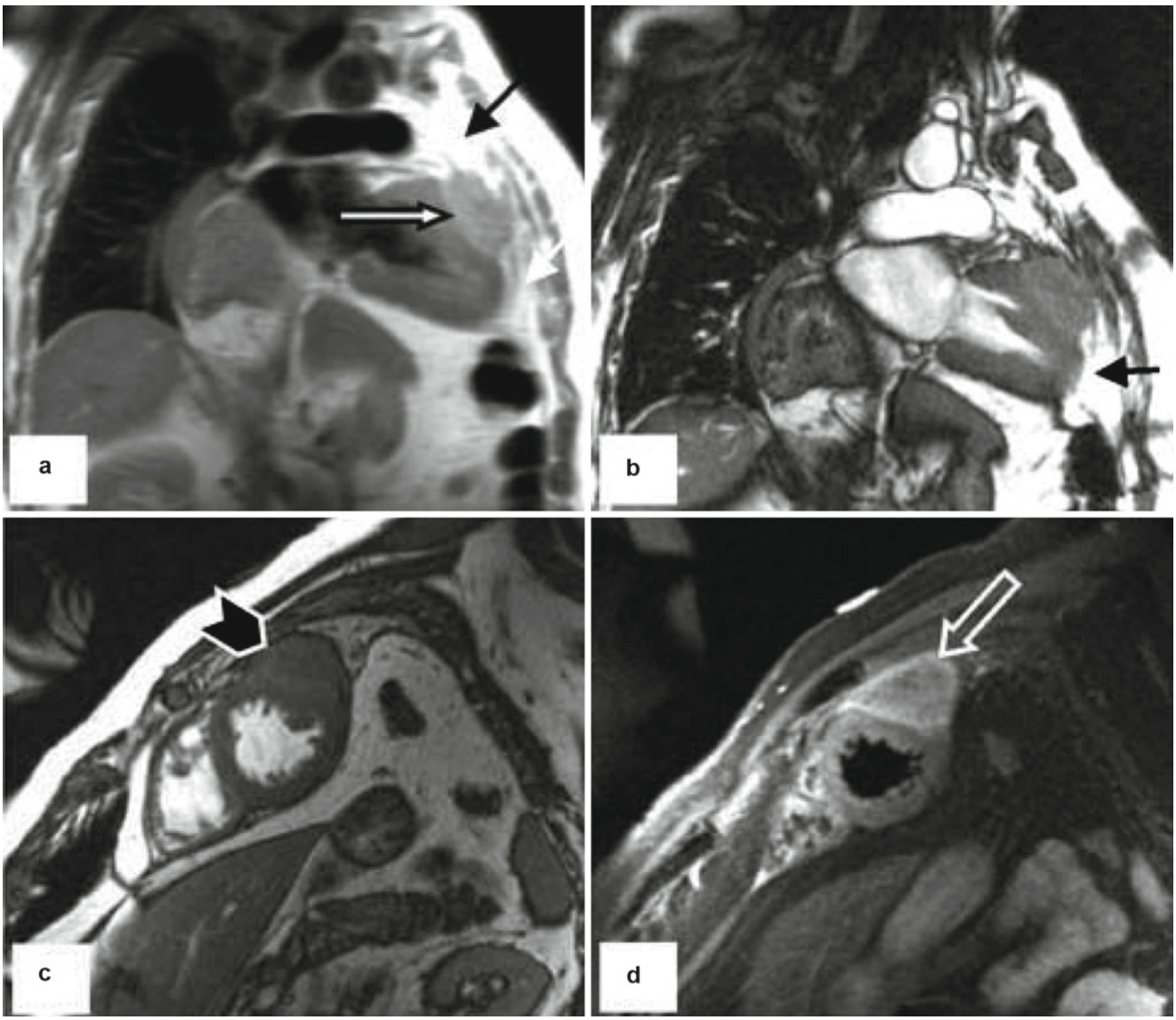


Fig. 13.19 Aortic regurgitation and aortic insufficiency. A 65-year-old male with combined aortic valvular lesions. (**a**) Central aortic regurgitation (*arrow*) and (**b**) the dephasing jet of an aortic stenosis (*arrow*). A moderately thickened, calcified, and restricted aortic leaflet is seen by SSFP imaging. Phase velocity mapping (not shown) quantified mean and peak gradient of 45–87 mmHg, respectively, confirming the diagnosis of severe aortic stenosis with moderate aortic regurgitation. (**c**) A mild jet of aortic regurgitation in another patient with an interposed tube graft (*chevron*)



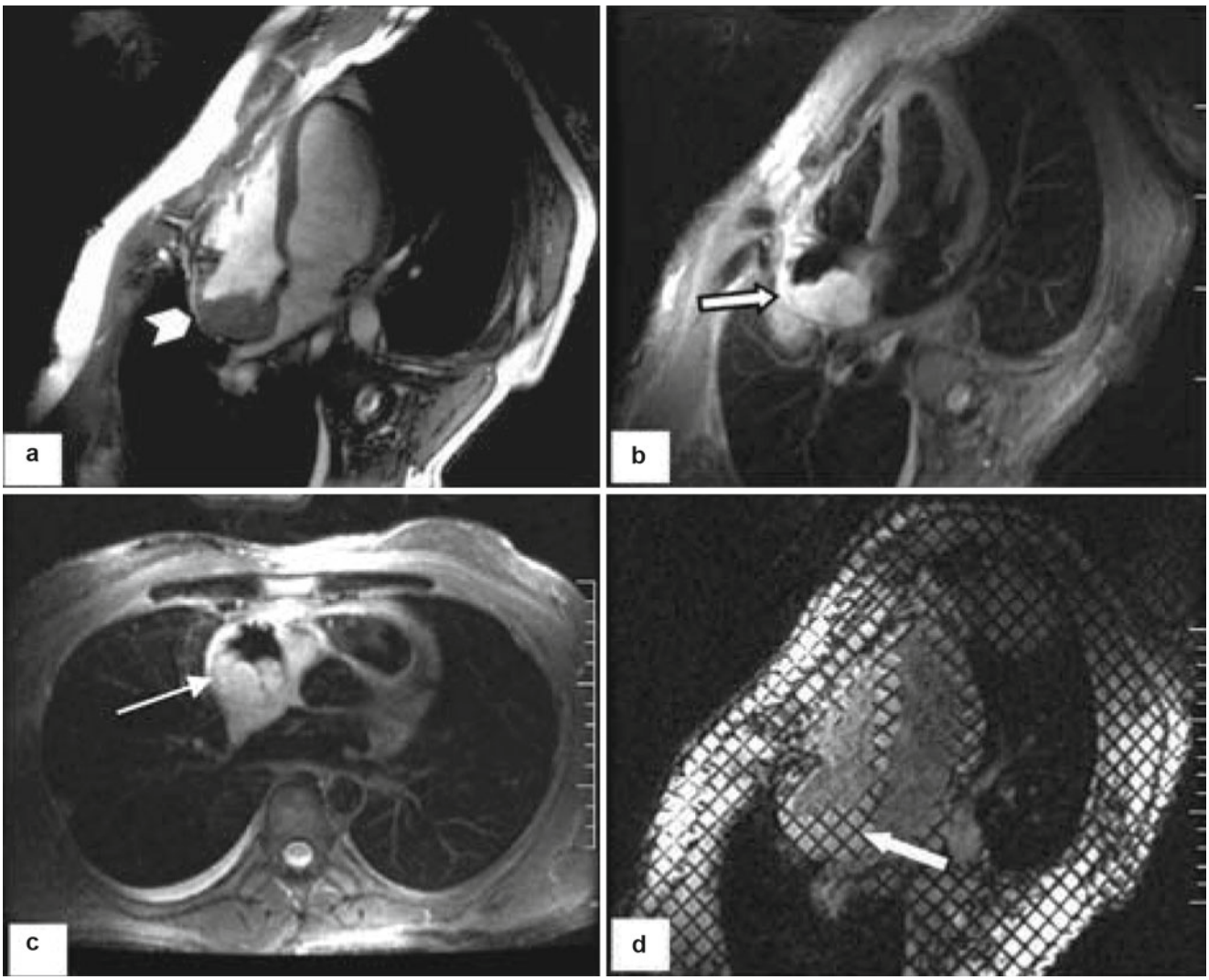


Fig. 13.21 A 39-year-old with chronic cough and fullness in the upper airway for several months presented after a CT scan revealed a mediastinal mass. Mediastinoscopy/biopsy revealed a small-cell carcinoma, but the proximity to the cardiac structures was unclear. The CMR data show that the mediastinal mass has invaded through the pericardium and deep into the right atrium (*arrows*). (**a**) Demonstrates SSFP (**b**) and (**c**) T2 weighting shows the extracardiac mass and (**c**) shows the multilobed nature of the invading mass. (**d**) RF tissue tagging demonstrates the mechanical properties of the mass and the interrelationship to the myocardium

Future Applications

We are far from exhausting the potential of MR and CT methods in applications to the cardiovascular system. As noted, it is now possible to obtain reasonable-quality images of the proximal coronary arteries. There is substantial work in progress to generate myocardial perfusion images using a bolus injection of gadolinium chelate at rest and with vasodilator stress using dipyridamole, adenosine, or regadenoson. This has provided accuracies similar to those obtained with

Fig. 13.20 A 73-year-old male who presented with several months of progressive chest discomfort was eventually diagnosed with small-cell carcinoma and underwent resection. He returned 8 month later for follow-up. A CT scan demonstrated a mass adjacent to the heart but was unable to distinguish invasion. (**a**) Demonstrates the large anterior oval mass (*large arrow*). The pericardium is clearly breached (*small arrows* **a–b**). (**c**) SSFP imaging demonstrated a loss of epicardial/mass continuity with penetration through the pericardium observed (*chevron*). (**d**) Late enhancement of the lesion (*arrow*) and the LV epicardial effacement. The CMR images demonstrated pericardial breaching and loss of epicardial border, and other images (not shown) depicted clear epicardial invasion, including tagged images portraying dyssynchronous motion of the tumor with impairment of the epicardial fibers, confirming lack of a separating surgical plane. The patient was deemed not a surgical candidate due to invasion, the high complexity, and risk of surgical resection

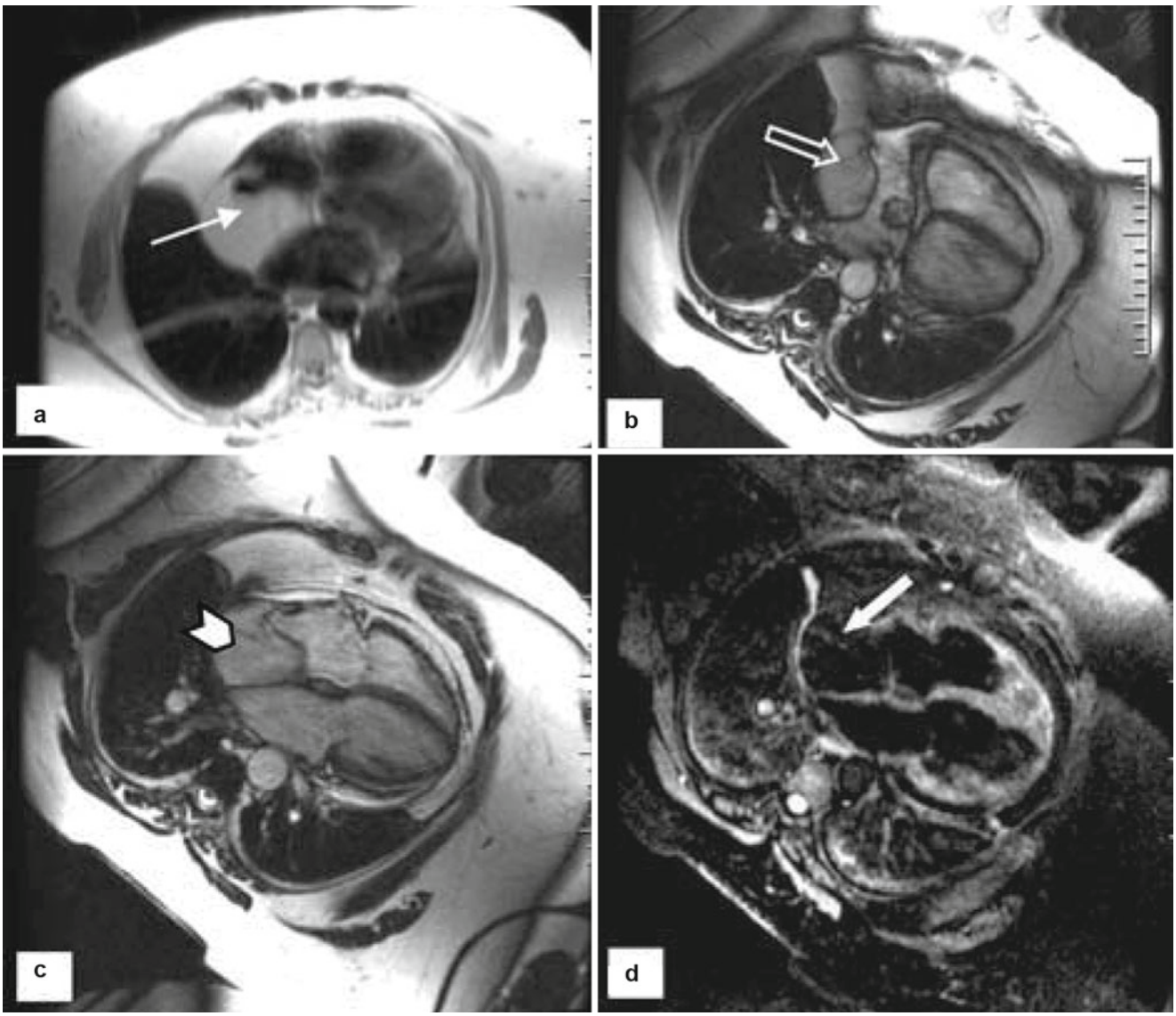


Fig. 13.22 A 65-year-old female presented with shortness of breath and mild SVC syndrome and was shown to have a mass on CT involving the right atrium and confirmed by TEE. For further evaluation, the patient underwent CVMRI. (**a** and **b**) demonstrate a large homogeneous mass occupying a large segment of the RA as well as considerable anterior mediastinal extrapericardial tissue, all bright on spin-echo imaging (proton density weighted). (**c**) An SSFP sequence demonstrated the obliteration of the posterior RA. Not shown is the near obliteration of the SVC. (**d**) The benign pathology of this presentation in this obese patient is confirmed by the T2-weighted image demonstrating uniform nulling of the tissue, which is diagnostic of a large fatty lipoma. Note the capsule surrounding the mass, which is a characteristic feature, differentiating it from lipomatous inner atrial hypertrophy. Diet and weight loss with exercise were recommended as an interim solution to forestall surgical resection for this otherwise benign lipoma with nonneoplastic but "malignant" features

the radiopharmaceuticals ^{201}Tl thallous chloride and ^{99m}Tc sestamibi or similar technetium-labeled compounds. CMR gadolinium perfusion may also have a role in identifying myocarditis (Fig. 13.27) or pericarditis and is the reference standard now for myocardial viability. MRS is another unique diagnostic modality that can assess myocardial metabolism without the need for ionizing radiation or administration of intravenous tracer or contrast agents. The ultimate potential for clinical application of ^{31}P MRS is the detection of myocardial ischemia using the evaluating the transient imbalance between oxygen supply and demand by measuring high-energy phosphate. Noninvasive MRS has been suggested to be complimentary to myocardial biopsy and has characterized various myocardial pathologies such as cardiac rejection, in vivo differentiation between cardiac rejection and acute myocardial ischemia, evaluation of dilated/hypertrophic cardiomyopathy or valvular disease, and various microvascular diseases [16, 37]. As MR paramagnetic contrast techniques evolve and MR "tracer" approaches using nanotechnology and other approaches

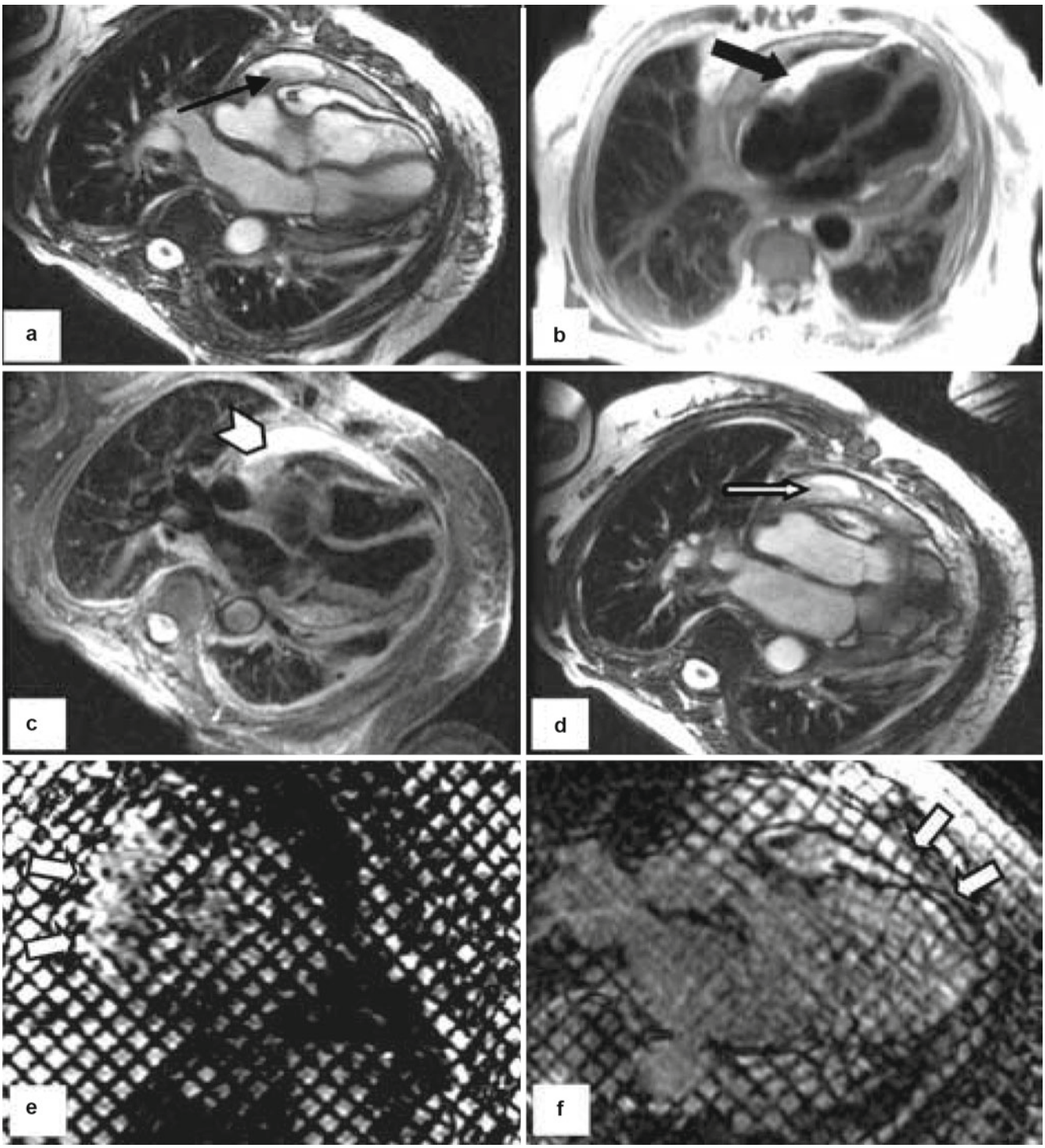


Fig. 13.23 This patient had a restrictive cardiomyopathy. (**a**) Demonstrates a pericardial effusion (*arrow*), which, when combined with (**b–d**), is better described as an effusive-constrictive pericarditis, as evidenced by fibrinous stranding and the densely adherent fibrous nature intermixed with the effusion (*arrows*, **b–d**). Radio frequency tissue tagging (*arrows*, **e**, **f**) demonstrates the adherence between the visceral and parietal pericardia, as evidenced by the absence of slippage and deformation of the *tag lines*, confirming the finding of a constrictive anatomy and physiology that was confirmed at surgery

develop and as the use of systems using higher magnetic fields progress, the opportunity for further creative applications of CMR will expand. Furthermore, CT applications have improved substantially, since the development of 64-slice MDCT and more advanced CT systems with up to 320-slice capability. Further development of CT stress perfusion and fractional flow reserve methods (FFR-CT) will take CT from its present status of anatomic imaging to the

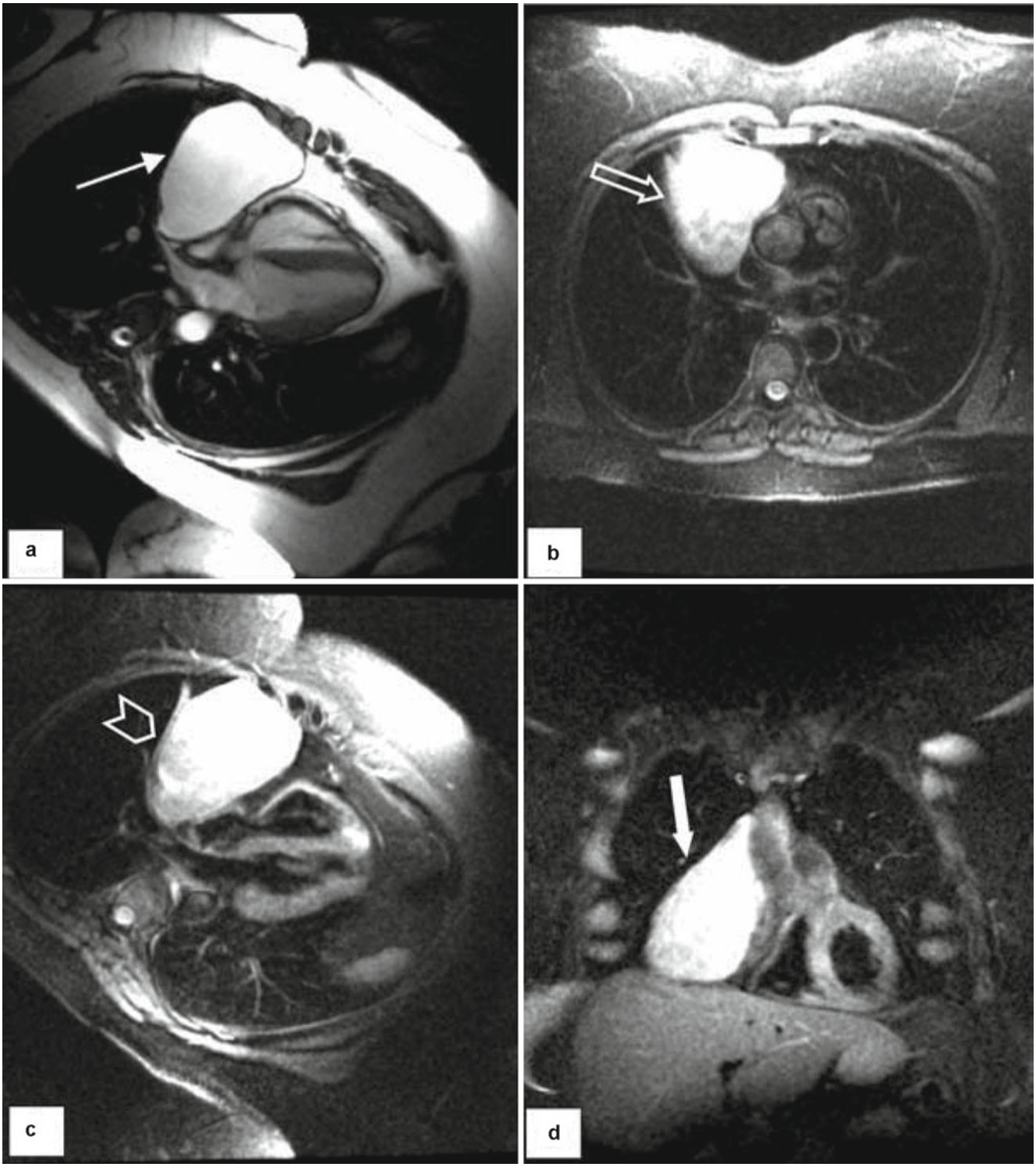


Fig. 13.24 A 45-year-old female was followed for several years by CT and TEE for this right-sided homogeneous, well-circumscribed, and encapsulated mass (*arrows*, **a**–**d**). (**a**) The bright signal characteristic on T1 imaging is seen and in (**b**) the lack of nulling on T2 imaging, consistent with its cystic nature (**c** and **d**). In (**c** and **d**) note the proper nulling of epicardial fat adjacent to mass (*chevron*). Tissue characteristics, as well as the anatomic position, make this mass pathognomonic for a pericardial cyst, which is large but benign

additional ability to add physiologic information. As such, CT could provide information complementary to that of CMR. Nonetheless, the advantage of CMR as a methodology that, like ultrasound, has no ionizing radiation gives CMR a remarkable advantage as an overall imaging modality. Ultimately, appropriate use and new applications of these remarkable two advanced imaging technologies will solidify their place in the armamentarium of the clinician.

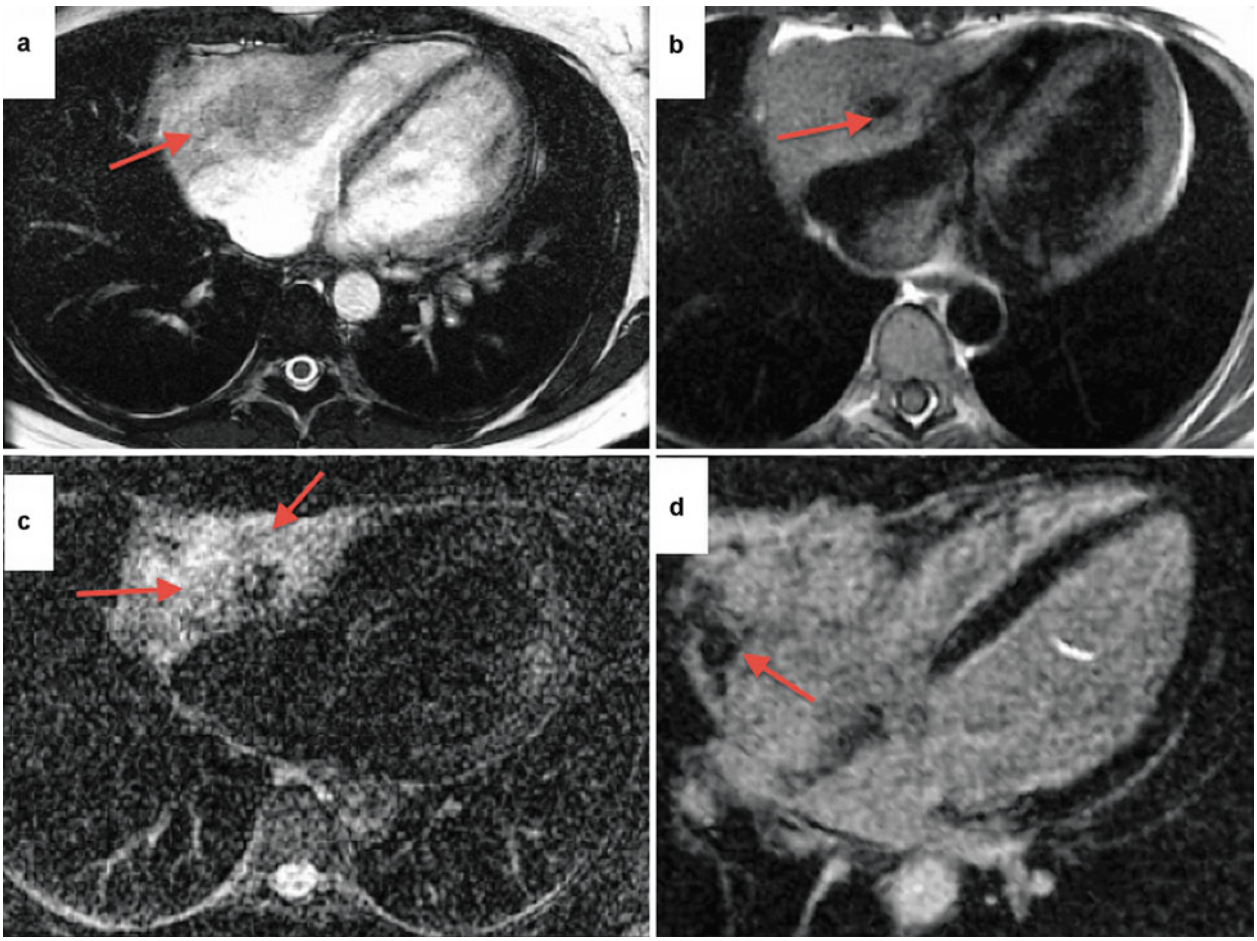


Fig. 13.25 A 40-year-old female with atypical chest pain and non-sustained ventricular tachycardia underwent CMR for evaluation of a right atrioventricular groove mass. (**a**) Axial SSFP cine showing a large heterogeneous mass invading the right atrium and ventricle (*arrow*). (**b**) Axial T1-weighted DIR fast spin echo depicting a void (*arrow*) within the mass thought to be the encased and dilated right coronary artery. (**c**) Axial T2-weighted image showing high water signal within the mass consistent with a highly vascular malignancy (*arrow*). (**d**) Four-chamber delayed enhancement showing area of nulling within the mass thought to be necrotic material or thrombus (*arrow*). The tumor was biopsied and histology revealed a primary cardiac angiosarcoma

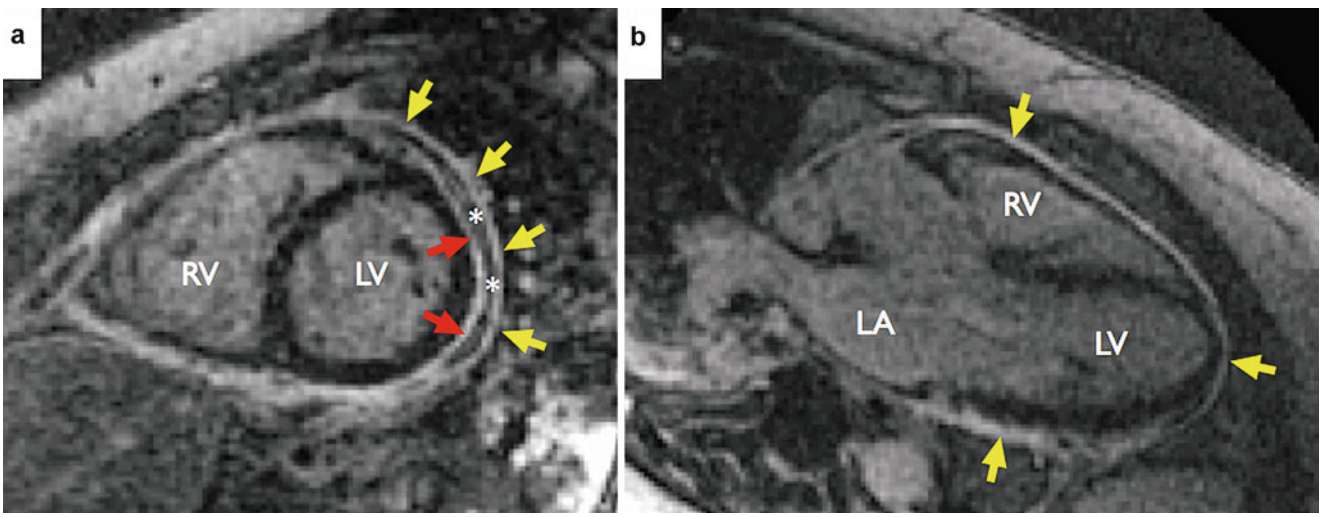


Fig. 13.26 Delayed enhancement images in mid-level short-axis (**a**), three-chamber (**b**), two-chamber (**c**), and four-chamber (**d**) orientations. These images demonstrate delayed enhancement of the parietal pericardium (*yellow arrows*), visceral pericardium (*red arrows*), and a small pericardial effusion (*asterisks*) consistent with acute pericarditis

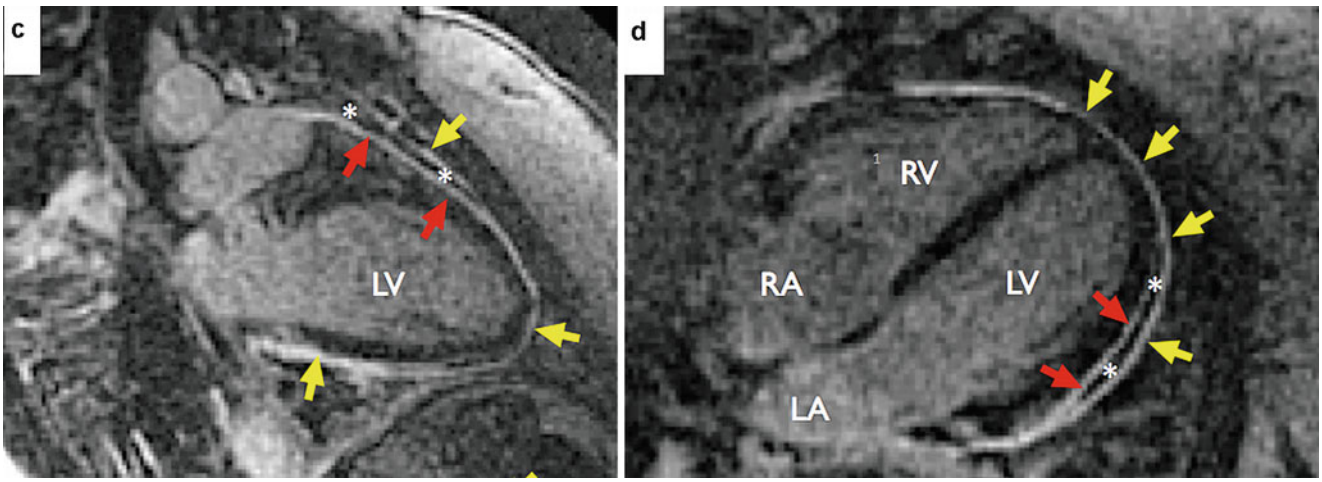


Fig. 13.26 (continued)

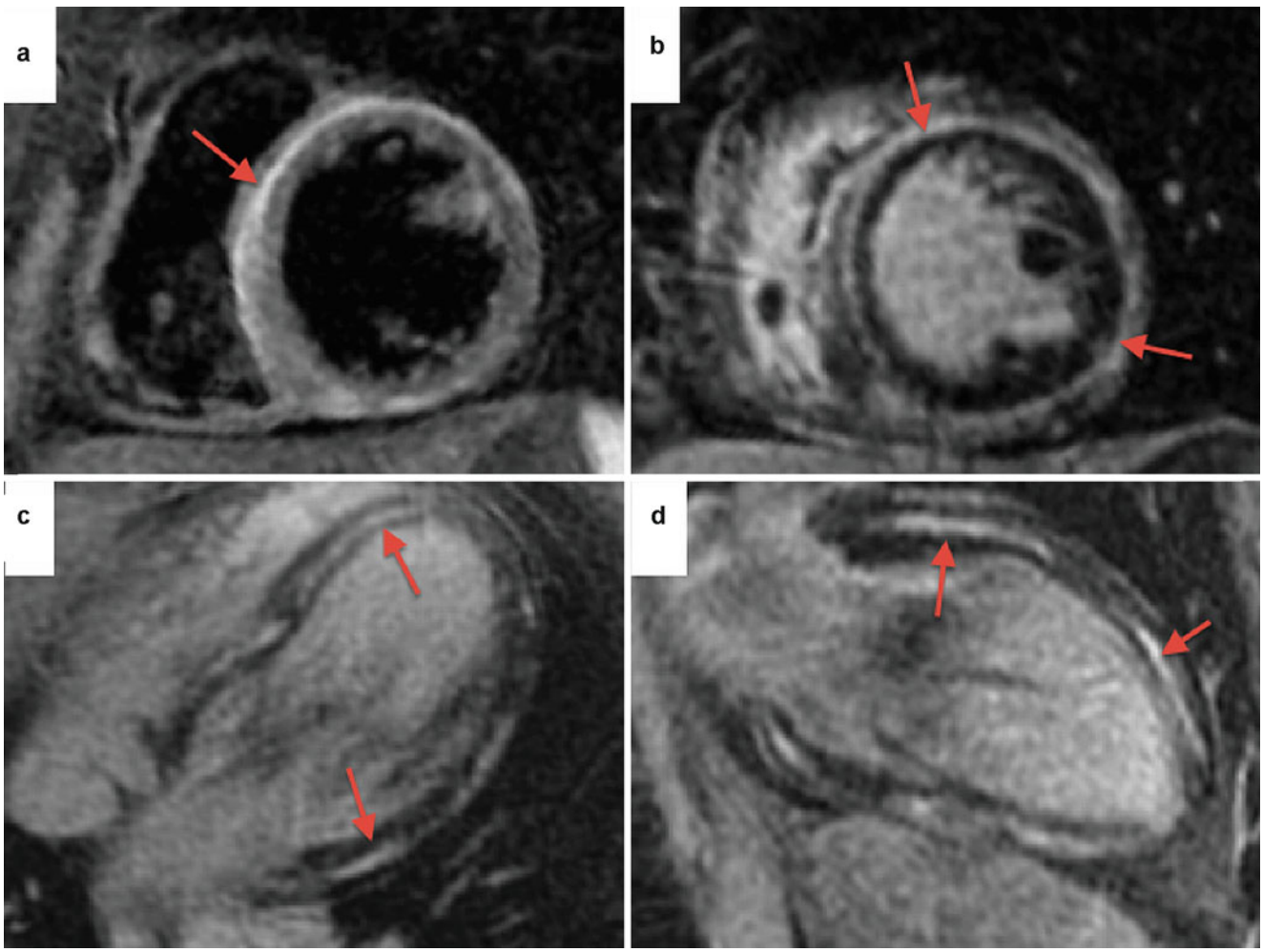


Fig. 13.27 An 18-year-old female was admitted with severe chest pain and elevated serum troponin and normal coronary arteries by angiography. (**a**) Short-axis T2-weighted inversion recovery sequence showing near-circumferential signal increase consistent with myocardial edema (*red arrows*, **a**–**d**). (**b**) Short-axis delayed enhancement sequence at a similar ventricular level to (**a**) showing circumferential mid-wall enhancement typical for acute myocarditis. Four-chamber (**c**) and two-chamber (**d**) delayed enhancement sequence showing patchy areas of mid-wall and epicardial enhancement

Conclusions

Cardiac MR and CT (Table 13.1) have been available for clinical use since the early 1980s. Advances in both have been achieved throughout the years. CMR has proven to be the more versatile, owing to its ability to use a number of contrast mechanisms, whereas CT methods rely only on X-ray attenuation. Both technologies have substantial clinical utility, however, and can often be used for similar diagnostic applications. When a facility has only CMR or CT, it may be possible to use that modality as the primary diagnostic study. If the advances of the past decade are any indication, both techniques are poised for substantial breakthroughs in cardiovascular imaging for improving speed, resolution, and diagnostic accuracy.

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Choosing Appropriate Imaging Techniques

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Introduction

Cardiac imaging is an important component in the comprehensive evaluation of a patient. Imaging modalities most commonly employed include chest roentgenography, echocardiography, computed tomography, cardiac angiography, magnetic resonance imaging, and radionuclide imaging. Appropriate decision making requires a basic knowledge of the advantages and disadvantages of each imaging modality, as well as indications and contraindications, cost, and potential radiation exposure. In this chapter, we will review the basic fundamentals of the most common cardiac imaging tests and lay a framework to help the clinician in selecting the most appropriate test.

Coronary Artery Disease

The stepwise approach to imaging in coronary artery disease (CAD) depends largely on the clinician's initial impression of the pretest probability of the presence of disease, which is assessed from the patient's clinical history, cardiovascular risk factor profile, physical exam, and EKG. In addition, imaging strategies will also vary based on either an acute or chronic presentation.

Imaging modalities in CAD either offer an anatomic evaluation through direct visualization of the coronary artery lumen or allow indirect assessment of the significance of coronary stenoses based on a functional evaluation through rest and stress myocardial perfusion and/or systolic function in territories supplied by a stenosed artery. Knowledge of left ventricular systolic function and ejection fraction is a key component of the evaluation of patients with suspected or confirmed CAD, since subsequent management is often impacted by LVEF. Therefore, an ideal imaging test for CAD would provide an accurate assessment of LVEF as well. Myocardial perfusion imaging with gated single-photon emission computed tomography (SPECT), stress echocardiography, and magnetic resonance imaging provide simultaneous accurate noninvasive assessment of coronary stenoses and LVEF.

A Paradigm Shift

Direct imaging of coronary arteries previously focused exclusively on the detection of lumenal stenosis of greater than 50–70 %, so-called flow-limiting stenosis. These lesions were thought to be the most significant culprits leading to acute myocardial infarction and its sequelae. However, there has been a critical paradigm shift in recent years. Atherosclerosis is an inflammatory process that begins with intimal thickening and accumulation of oxidized lipid in the arterial wall. This thickening can progress to form a lipid-rich necrotic core encapsulated by fibrous tissue, also known as a fibroatheroma. As the necrotic core increases in size, this will develop into a thin-cap fibroatheroma, also referred to as a *vulnerable plaque.* Although considerable controversy exists over the importance of vulnerable plaque in acute coronary syndrome, previously most acute coronary syndromes were thought to be a result from rupture of non-stenotic soft lipid-laden plaques which allows blood to come in contact with highly thrombogenic material in the necrotic core leading to acute thrombosis.

However, a large percentage of acute coronary syndromes are attributable to lesions with <50 % luminal stenosis, which may not be detectable by traditional coronary imaging techniques, which rely on either visible luminal encroachment by a stenotic plaque or their hemodynamic impact. For assessment of "global plaque burden" and extent of atherosclerotic

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_14,

disease that can develop into these high-risk nonstenotic plaques, other modalities, including measurement of serum inflammatory markers (i.e., C-reactive protein), carotid intimal medial thickness (IMT), ankle-brachial index (ABI), and plaque tissue characterization with cardiac magnetic resonance imaging (CMR), have been advocated. The ultimate utility of these newer tests for diagnosing atherosclerosis will be determined by their ability to provide the clinician with incremental risk-stratifying information above and beyond existing standard clinical risk assessment tools (e.g., the Framingham risk score).

Chronic CAD

Suspected Chronic CAD

The suspicion of the presence of chronic atherosclerosis is raised either by symptoms (i.e., chest pain or its equivalent, which may be dyspnea with exertion, jaw pain, etc.) or suspected high likelihood in the presence of multiple traditional coronary risk factors in the absence of symptoms. In the case of a symptomatic patient, a search for flow-limiting endolumenal stenoses begins with history and physical examination accompanied by a 12-lead ECG, paying special attention for the presence or absence of pathologic Q waves or ST segment deviation.

According to Bayes' theorem, the clinician's pretest suspicion for the presence or absence of a disease will determine the posttest likelihood and will only be affected by a test result in proportion to that test's sensitivity and specificity. Thus, in patients with pretest likelihood of CAD at the two ends of the likelihood spectrum, low (i.e., 0–20 % chance of CAD) or high (80–100 % likelihood), cardiac imaging is unlikely to change management. Therefore, if the clinical suspicion for obstructive CAD is low based on a patient's clinical risk profile, extensive testing beyond history, physical, and ECG is rarely warranted. Conversely, in a patient with multiple typical cardiac risk factors and a history of typical angina, proceeding directly to the "gold standard" test of coronary angiography is reasonable and likely cost-effective.

The algorithm for evaluating patients in the intermediate likelihood category is often the most challenging. One must decide whether to proceed with standard treadmill stress 12-lead electrocardiography or to pursue more in-depth imaging with either a radionuclide perfusion study or stress echocardiography. Coronary CT and MRI also have the potential to provide accurate detail of coronary anatomy, although at significantly higher cost.

Because of its reliance on the insensitive phenomenon of surface ECG ST segment deviations for detection of myocardial ischemia, treadmill ECG should be reserved for patients in whom pretest suspicion is low to assess functional capacity or to clarify atypical symptoms. False-positive and false-negative tests are relatively common. However, in a patient in whom the question of CAD is raised by exercise-induced chest pain or dyspnea, a treadmill ECG can reproduce the symptoms and assess overall functional capacity and anginal threshold in tandem with diagnostic ECG changes.

When the pretest suspicion is intermediate or high-intermediate, an accurate test for obstructive CAD is appropriate. The two most common modalities are indirect assessments: myocardial perfusion imaging provides information on relative coronary flow based on regional uptake of a radionuclide-labeled perfusion agent, and stress echocardiography, which requires induction of myocardial ischemia and consequent regional ventricular systolic dysfunction to provide inferences about the presence and location of obstructive CAD. Cardiac CT, MRI, and PET imaging have also emerged as useful tools in the assessment of ischemic heart disease. The indications and limitations for these different modalities will be reviewed here.

Table 14.1 Risk-based approach to suspected CAD based on results of ^{99m}Tc-sestamibi myocardial perfusion with gated SPECT or stress echo [1]

Normal: Very low risk for cardiac death, low risk for MI
Reassurance
Risk factor (RFM) modification
Mildly abnormal: low risk for cardiac death, intermediate risk for MI
Antianginal therapy
Aggressive risk factor modification (RFM)
Catheterization if symptoms refractory to therapy
Moderately–severely abnormal: intermediate to high risk for cardiac death or MI
Cardiac catheterization
RFM

Adapted from Gibbons et al. [2]. With permission from Wolters Kluwer Health

Radionuclide Perfusion Imaging and Stress Echocardiography

Some fundamental principles guide the decision to pursue either radionuclide perfusion imaging or stress echocardiography and whether these tests should accompany either exercise or pharmacologic "stress" with dobutamine or by pharmacologic vasodilation with adenosine or Persantine (*see* Table 14.1).

In general, exercise is the preferred mode of stress for patients undergoing an ischemic evaluation, typically with the Bruce or modified Bruce protocol, among patients who are able to achieve an adequate workload defined as 85 % of maximum predicted heart rate. An exercise treadmill test (ETT) is the initial test of choice for patients with suspected

cardiovascular disease. Not only is it safe and inexpensive, since it simulates their daily activity, stress EKG also provides important information regarding patient symptoms, hemodynamic response to exercise, as well as prognostic information. Several well-validated nomograms and criteria (i.e., the Duke treadmill score) exist that can help the clinician accurately estimate subsequent cardiac morbidity and mortality after an ETT. In special circumstances, bicycle exercise can substitute for treadmill exercise. The overall sensitivity and specificity of an exercise treadmill test in an intermediate risk population is estimated to be 68 and 77 %, respectively [1].

However, if the 12-lead ECG ST segment is uninterpretable for ischemia (i.e., due to LVH, LBBB, pacemaker, baseline ST segment depression, digoxin therapy, or hormone therapy) and thus cannot be used as a guide for interpretation and cessation of the treadmill exercise, a stress imaging modality is preferred. Pharmacologic stress imaging should be considered among patients unable to achieve an adequate workload, such as vascular patients, elderly, disabled, or frail patients to increase diagnostic accuracy. The choice between stress echocardiography and myocardial perfusion imaging should be based upon the local availability and expertise of those performing either technique.

Stress echocardiography can evaluate for the presence of coronary disease by demonstrating stress-induced wall motion abnormalities. It offers both an increased sensitivity and specificity when compared to ETT; however, it relies on the ability to obtain high-quality images which can be limited by poor acoustic windows or level of skill of the sonographer. It has the added benefit of providing global assessment of cardiac structure and function and can provide supplemental information including exercise-induced pulmonary pressure elevation or dynamic left ventricular outflow tract obstruction and other potential sources of chest pain or dyspnea such as valvular or pericardial disease. The absence of radiation exposure for this testing modality makes it a preferred choice for young patients or females. Precision microspheres for "contrast" echo can increase the yield of diagnostic studies by enhancing left ventricular border detection.

Current state-of-the-art myocardial perfusion imaging relies on single-photon emission tomography (SPECT) with similar sensitivity and specificity to stress echocardiography for diagnosis of coronary artery disease. This technique utilizes scintillation cameras to collect high-energy photons that are emitted by the patient after injection of a radiopharmaceutical that distributes in proportion to regional myocardial perfusion. The two commonly used isotopes are thallium (T1-201) and technetium-99m (^{99m}Tc) (see Table 14.1). Technetium-based agents include 99m-Tc-sestamibi and 99m-Tc-tetrofosmin and are more commonly used clinically owing to their higher photon energy and shorter half-life. The higher myocardial counts obtained with ^{99m}Tc also allows for gated imaging acquisition which is useful for assessing ventricular function as well. Standard protocols consist of a rest acquisition followed by a post stress acquisition, and perfusion defects are characterized by their type (fixed or reversible) as well as extent and severity. Several advances within nuclear cardiology have resulted in achieving significantly lower radiation exposure to the patient, including the development of CZT cameras as well as stress-only protocols.

Radiation doses can be as low as 4–5 mSv compared to 15 mSv for the standard study. Multiple pharmacologic stress agents are available for use with nuclear imaging including dobutamine as well as vasodilating agents such as adenosine, dipyridamole, or regadenoson and are typically reserved for patients who are unable to perform an adequate level of exercise on the treadmill. For nuclear testing, a pharmacologic vasodilator is the preferred agent and typically results in a three- to fivefold increase in coronary blood flow. The mechanism of action of all three agents is by stimulation of A2A adenosine receptors. Contraindications to use of these agents include bronchospastic airway disease, AV nodal conduction disease, and consumption of caffeine or methylxanthine-containing medications (e.g., theophylline) within 4–6 h prior to testing which blocks adenosine binding and reduces coronary vasodilatation. Dobutamine is the preferred agent of choice for pharmacological stress echocardiography and follows a standard protocol with initial infusion starting at 5 ug/kg/min and increasing to 10, 20, 30, and 40 ug/kg/min, or by increments of 5 ug/kg/min for slower titration, every 3 min until target heart rate response is achieved. As necessary, atropine should be administered in doses of 0.1–0.5 mg as necessary to achieve an adequate chronotropic response workload.

Perhaps most importantly, both stress echocardiography and myocardial perfusion imaging have been shown to provide prognostic information for the patient, with negative predictive value of subsequent MI or cardiac death at 99 and 98 %, respectively [3]. The ACC/AHA published appropriateness criteria for use of stress echocardiography in 2011 and cardiac radionuclide imaging in 2009, which support the use of these two modalities for the diagnosis and risk assessment of coronary artery disease in intermediate and high-risk patient populations.

Computed Tomography and Cardiac Magnetic Resonance

Improvements in cardiovascular imaging technology have increased the number of tools available to physicians for diagnosing the presence and severity of coronary heart

Table 14.2 Comparison of various diagnostic tests for CAD accuracy [3]

Test	Dx	Prog	Avail	Function	Time	Cost
ETT ECG	+	+	+++	–	30 m	+
Stress echo	++	++	++	++	30–60 min	++
Stress MPI	++	+++	++	++	2–4 h	+++
EBCT	+	±	+	±	15 min	++++
PET	+++	++	±	++	1–2 h	++++

Adapted from Gibbons et al. [2]. With permission from Wolters Kluwer Health
Avail availability, *DX* for diagnostic purposes, *ETT ECG* exercise tolerance test electrocardiography, *MPI* myocardial perfusion imaging, *EBCT* electron beam computed tomography, *PET* positron emission tomography, *Prog* provides prognostic information

disease (*see* Table 14.2). While the diagnostic tests described above evaluate for physiologic changes related to decreased coronary flow reserve, cardiac CT provides a purely anatomic evaluation of the coronary circulation. Imaging of the coronary artery is limited by artifacts resulting from patient motion, respiration, and cardiac motion. To improve image quality, patients are often administered beta-blockers to achieve a slow and regular heart rate (typically <65 bpm) as well as sublingual nitroglycerin for vasodilatation. This, coupled with patient cooperation and breath-holding, provides high-resolution images for detailed coronary lumenography.

Initial multidetector CT scanners with 64-channel systems have been replaced by 128-, 256-, and even 320-channel systems which have allowed for faster image acquisition time and shorter breath-holds. To date, several large multicenter studies have demonstrated the diagnostic accuracy of coronary CT angiography using 64-slice MDCT scanners. The US-based ACCURACY trial demonstrated a 95 % sensitivity and 83 % specificity for greater than 50 % stenosis [4]. The international CORE study excluded patients with calcium scores >600 and showed a sensitivity and specificity of 85 and 90 %, respectively [5]. Newer MDCT scanners have incorporated a larger number of detector rows, more sensitive detectors, and dual-source CTs in order to improve image quality and reduce motion artifacts. More recently, the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes) registry demonstrated that, in the absence of known CAD, both nonobstructive and obstructive CAD detected by CCTA were associated with increased risk of mortality while absence of CAD was associated with an excellent outcome [6].

Coronary computed tomography angiography serves as a rapid noninvasive imaging test that with fairly high accuracy that can identify areas of significant coronary artery stenosis. It also has the added benefit of providing information about the presence, distribution, and composition of nonobstructive plaque. According to the most recent appropriate use criteria, cardiac CT angiography is deemed appropriate in the following clinical settings: detection of CAD in symptomatic patients (acute and nonacute presentations), risk assessment in patients with significant family history or intermediate global CHD risk, detection of CAD among patients with newly diagnosed heart failure, and preoperative assessment prior to noncardiac surgery [7]. Other indications include evaluation of coronary anomalies, congenital heart disease, and assessment of coronary stent or bypass graft patency. In most circumstances, a negative coronary CT angiogram rules out the presence of significant obstructive coronary artery disease. This diagnostic strategy is often useful in the emergency department evaluation of acute coronary syndrome in the absence of EKG changes or biomarkers.

Although radiation exposure is an increasing concern among patients, use of higher "slice" MDCT scanners have significantly decreased the radiation exposure per study (8–18 mSv) [8]. Prospective gating has further reduced the effective dose to 2–4 mSv (standard chest radiograph = 0.1 mSv) [9]. Several factors can interfere with the quality of CCTA including tachycardia, arrhythmia, coronary calcification, inability to breath-hold, and presence of intracoronary stents or other metal artifacts. In addition, this modality is contraindicated among patients with IV-contrast allergies or renal dysfunction at high risk for contrast nephropathy.

Detection of coronary artery calcification with either electron beam computed tomography (EBCT) or MDCT has been shown to correlate with the risk of future cardiovascular events as well as the presence of coronary artery stenosis. However, randomized clinical trials have failed to show a significant benefit from instituting pharmacologic therapy among asymptomatic patients based on increased CAC scores [10, 11]. The most recent 2010 ACCF/AHA guidelines recommends against the use of coronary artery calcium scoring among asymptomatic patients with low or high global CHD risk. In patients with intermediate risk profiles, a coronary artery calcium score can provide additional prognostic information and may be appropriate if the result will lead to reclassification to a lower or higher risk group.

Noninvasive imaging of chronic atheromatous plaque at risk for rupture but not hemodynamically significant is currently under investigation, with MRI and CT on the forefront. Current gating techniques, faster imaging sequences combined with breath-holding, are permitting assessment of

Table 14.3 Recommendations for use of radionuclide techniques to assess myocardial viability

Indication	Test	Class	Level of evidence
1. Predicting improvement in regional and global LV function after revascularization	Stress/redistribution/reinjection Tl-201	I	B
	Rest-redistribution imaging	I	B
	Perfusion plus PET FDG imaging	I	B
	Resting sestamibi imaging	I	B
	Gated SPECT sestamibi imaging	IIa	B
	Late Tl-201 redistribution imaging (after stress)	IIb	B
	Dobutamine RNA	IIb	C
	Postexercise RNA	IIb	C
	Postnitroglycerin RNA	IIb	C
2. Predicting improvement in heart failure symptoms after revascularization	Perfusion plus PET FDG imaging	IIa	B
3. Predicting improvement in natural history after revascularization	Tl-201 imaging (rest-redistribution and stress/redistribution/reinjection)	I	B
	Perfusion plus PET FDG imaging	I	B

Adapted from Klocke et al. [12]. With permission from Elsevier
FDG flurodeoxyglucose, *PET* positron emission tomography, *RNA* radionuclide angiography, *SPECT* single-photon emission computed tomography, *T1-201* thallium-201

coronary plaque morphology by CT and MRI in several academic institutions; however, these techniques are not yet ready or available for widespread clinical application. Imaging for the purpose of plaque and tissue characterization remains a research tool. Before plaque morphology determination becomes clinically useful, the benefits of targeting individual high-risk asymptomatic plaques must be further studied. In addition, the predictive accuracy of plaque imaging must be compared with current risk assessment methods, such as the Framingham risk score. Future clinical studies will need to determine if identifying patients with high-risk vulnerable plaques and instituting appropriate therapy improve patient outcome.

Confirmed Chronic CAD

When a patient is known to have coronary atherosclerosis on the basis of prior testing, there are a few specific principles to guide selection of subsequent imaging. Testing in this setting is often performed either to assess a change in patient symptoms (e.g., worsening angina, dyspnea, or functional capacity), to assess the efficacy of pharmacologic therapy, or to guide decisions about possible percutaneous or surgical coronary revascularization. "Routine" imaging with MPI or stress echocardiography is generally not recommended for the asymptomatic patient in the absence of some other clinical indication.

In the case of chronic coronary artery disease with ventricular dysfunction, knowledge of the extent and severity of obstructive coronary artery disease is oftentimes insufficient to guide management of the patient. It has become clear that impaired regional left ventricular systolic function due to coronary heart disease is not always related to myocardial scarring. Although myocardial necrosis is an irreversible process, other causes of left ventricular dysfunction such as stunned or hibernating myocardium can improve with revascularization. The detection of such "viable" myocardium within hypocontractile, hypokinetic, or akinetic segments may affect a physician's decision to recommend coronary revascularization, either percutaneously or surgically (*see* Table 14.3). A substudy of the STICH trial (Surgical Treatment for Ischemic Heart Failure) looked at 601 patients undergoing medical therapy plus CABG versus medical therapy alone and failed to show a significant association between presence of viable myocardium by routine imaging and likelihood of survival; however, results from this study remain controversial [13]. Additional studies are needed to determine whether myocardial viability testing should be routinely performed in this patient population with heart failure and LV systolic dysfunction. The 2009 update to the ACC/AHA guidelines for management of chronic heart failure concludes that it is reasonable to perform myocardial viability testing in patients presenting with heart failure who have known coronary artery disease and no angina [14].

Multiple imaging modalities have been used to assess myocardial viability including dobutamine echocardiography, radionuclide perfusion imaging, cardiac MRI, and PET. The use of radionuclide imaging for viability testing has been well validated and is typically the procedure of choice for this indication. Thallium uptake is dependent on intact cell membranes and thus is seen only in areas of viable myocardium. Several different protocols exist using thallium viability studies, the most common being stress imaging followed by 4-h or late (18–24 h) redistribution imaging. Technetium-based imaging, although once thought to be inferior to thallium for viability studies due to its passive

Table 14.4 Recommendations for emergency department imaging for suspected ACS

Indication	Test	Class	Level of evidence
1. Assessment of myocardial risk in possible ACS patients with nondiagnostic ECG and initial serum markers and enzymes, if available	Rest MPI	I	A
2. Diagnosis of CAD in possible ACS patients with chest pain with nondiagnostic ECG and negative serum markers and enzymes or normal resting scan	Same day rest/stress perfusion imaging	I	B
3. Routine imaging of patients with myocardial ischemia/necrosis already documented clinically by ECG and/or serum markers or enzymes	Rest MPI	III	C

See Fig. 6 of ACC/AHA 2002 guideline update for the management of patients with unstable angina and Non–ST-segment elevation myocardial infarction at http://www.acc.org/clinical/guidelines/unstable/incorporated/figure6.htm and Fig. 1 of ACC/AHA guidelines for the management of patients with acute myocardial infarction at www.acc.org/clinical/guidelines/nov96/1999/jac1716f01.htm
ACS acute coronary syndromes, *CAD* coronary artery disease, *ECG* electrocardiogram, *MPI* myocardial perfusion imaging

myocyte uptake and lack of redistribution, has been shown to provide similar information [15].

PET imaging is considered the gold standard for viability detection; however, its use is limited by expense and availability. PET can differentiate nonviable myocardium from hibernating or stunned myocardium by identifying distinct patterns of perfusion and cellular metabolism. Regions of myocardial dysfunction but normal blood flow and normal/enhanced FDG uptake represents stunned myocardium. Reduced perfusion with normal FDG uptake, also called a PET "mismatch," represents hibernating myocardium, while a reduced perfusion and FDG uptake (PET "match") represents myocardial scar.

In the 2003 guidelines of the ACC/AHA for cardiac radionuclide imaging, all three imaging modalities were recommended for evaluation of myocardial viability (LOE IB) [16].

Dobutamine stress echocardiography has proven utility in detecting regions of viability through the "biphasic" response; a hypo- or noncontractile wall segment that augments with administration of low-dose dobutamine is distinguished from a scar that fails to augment. Cardiac MRI uses delayed gadolinium enhancement imaging to identify areas of myocardial necrosis and scarring [17]; however its use is also limited by availability, high cost, and presence of renal disease.

Acute Coronary Syndromes

Acute coronary syndromes (unstable angina, non-ST elevation, and ST elevation myocardial infarction) typically result from rupture of a lipid-rich coronary plaque. The degree of myocardial ischemia and necrosis relates to the balance between impaired supply of oxygenated blood (i.e., the degree of intracoronary thrombosis, presence of collateral vasculature, ischemic preconditioning) and demand (relating especially to heart rate, blood pressure, wall stress, and systemic oxygenation).

Suspected ACS

Acute coronary syndrome (ACS) is classically caused by atherosclerotic plaque rupture and thrombosis with resultant partial or total occlusion of a coronary artery. ACS represents a spectrum of clinical diagnoses including ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina. The initial evaluation of a patient with suspected acute coronary syndrome depends heavily on clinical history, as well as other objective data including a 12-lead electrocardiogram, physical examination, and cardiac biomarkers (e.g., CK-MB or troponin). Given the life-threatening consequences of ACS, early and rapid triage, diagnosis, and management of these patients is crucial. One of the challenges for the clinician is differentiating chest pain caused by acute coronary syndrome from a multitude of other cardiac and noncardiac causes that can often mimic ACS. Patients with high-risk features, such as positive cardiac biomarkers or significant ST changes on ECG, should undergo aggressive medical management and possible urgent angiography. However, in patients at low to intermediate risk, the absence of both typical ischemic ECG changes and serologic evidence of myocardial injury cannot completely exclude the diagnosis of an ACS, since biomarkers may be normal initially. The clinical history and presenting electrocardiogram also have limited sensitivity and specificity for diagnosis of ACS. For this reason, additional noninvasive testing is often employed for further evaluation of the acute chest pain patient (*see* Table 14.4).

Both rest and stress imaging strategies can be employed in the evaluation of a patient with acute chest pain. Rest echocardiography can detect regional systolic wall motion abnormalities and can be used for diagnosis of acute MI if performed during or soon after onset of symptoms. This has the added advantage of being portable and readily accessible, can be used for rapid triage in the emergency department setting, and is able to detect for other valvular, aortic, or pericardial abnormalities. Acute rest myocardial perfusion imaging has been shown to have a high diagnostic sensitivity

for ischemia in the setting of obstructive coronary artery disease but relies on injection of the radioisotope during or soon after an episode of chest pain (within 2 h). In this scenario, Tc-99 m-labeled tracers should be used rather than thallium which will allow for delayed imaging without significant redistribution. Areas of myocardium that are ischemic will have decreased regional perfusion and thus demonstrate reduced radioactive counts with SPECT imaging.

In the absence of further symptoms and negative cardiac enzymatic evidence of myocardial necrosis, further stress testing can be useful in differentiating cardiac from noncardiac causes of chest pain and can be performed 8–12 h after presentation. As mentioned above, exercise ECG stress testing is the preferred modality as recommended by the ACC/AHA given its cost effectiveness and wide availability. Patients who are able to achieve ≥10 METS during a symptom-limited Bruce or modified Bruce protocol have been shown to have a very low risk of cardiac mortality and nonfatal MI, irrespective of the heart rate, and therefore, myocardial perfusion imaging is likely of little clinical benefit [18, 19]. A commonly employed algorithm in many chest pain centers is to discharge home patients who are able to achieve ≥10 METS during a symptom-limited Bruce or modified Bruce protocol, which has been associated with a very low rate of cardiac associated morbidity or mortality. However, among patients with poor exercise capacity or with an abnormal resting ECG, pharmacologic stress testing with imaging can be performed.

Coronary CTA has also been used to facilitate early triage and diagnosis in patients being evaluated for acute chest pain, and the 2011 ACC/AHA guidelines for evaluation of UA/NSTEMI suggests this as a reasonable alternative to stress testing among patients with low to intermediate pretest probability [20]. This test would be best suited for patients with no history of CAD or MI, who are in normal sinus rhythm, and are able to cooperate with breath-holding. The recent ROMICAT trial demonstrated a 100 % negative predictive value for ACS when no CAD was detected by coronary CTA, although a limited sensitivity (77 %) for detection of ACS in the presence of significant stenosis by coronary CTA [21]. A negative CTA performed in the ER leading to immediate discharge may reduce cost of a hospitalization and subsequent imaging. As mentioned above, this modality has a high sensitivity and high negative predictive value in low and intermediate risk patients, but is limited by only a moderate positive predictive value.

Once the diagnosis of ACS has been made, early risk stratification is important to identify patients who are at the highest risk of subsequent cardiac events and would therefore benefit from more aggressive clinical management. Several risk models have been developed to estimate the probability of adverse outcomes among patients diagnosed with ACS. The 7-point Thrombolysis in Myocardial Infarction (TIMI) risk score is one favored algorithm for risk stratification and is very easy to calculate at the bedside [22]. A high TIMI risk score is associated with increased risk of mortality, new/recurrent MI, or ischemia requiring revascularization, and warrants aggressive medical management with urgent angiography and revascularization as indicated.

Confirmed ACS

When clinical history, physical examination, ECG, and serum markers confirm the diagnosis of ACS, testing may elucidate the extent and severity of atherosclerosis.

According to the 2011 ACC/AHA focused update, any patient with high-risk indicators presenting with unstable angina or acute non-ST elevation MI will likely benefit from an early invasive strategy of aggressive antiplatelet and antithrombotic therapy and cardiac catheterization with an eye toward percutaneous or surgical revascularization as indicated. These high-risk features include recurrent ischemia or chest pain, elevated troponin T or I, ST segment depression, CHF, presumed new MR, high-risk noninvasive testing result, left ventricular ejection fraction less than 40 %, hemodynamic instability, sustained ventricular tachycardia, or prior coronary artery bypass grafting [20]. Patients without any of these high-risk features may be treated with a more conservative approach focused on further risk stratification.

Imaging Acute Complications of ACS

Outcomes have improved significantly among patients with acute MI in the current era of rapid revascularization and aggressive medical management. However, acute complications of acute MI can appear early or late during clinical presentation and include arrhythmia, cardiac rupture (free wall or ventricular septal defect), ischemic mitral regurgitation due to papillary muscle rupture, and cardiogenic shock. Echocardiography is the diagnostic test of choice in this setting because it provides rapid, bedside evaluation of valvular, myocardial, and pericardial function and structure. Moreover, directed Doppler interrogation can provide extensive hemodynamic information, including estimations of right atrial, right ventricular, pulmonary arterial, left atrial, and left ventricular end-diastolic pressures. The speed, accuracy, and portability of 2-D echo and Doppler interrogation have relegated LV angiography and right heart catheterization to a supportive, confirmatory role in most cases.

Valvular and Congenital Heart Disease

The test of choice for diagnosing and following cardiac valvular and congenital structural (i.e., ASD, VSD, coarctation of the aorta, PDA) lesions is transthoracic echocardiography (TTE). When higher-resolution images are needed, or when metallic valvular prostheses or body habitus preclude adequate visualization of intracardiac structures, transesophageal echocardiography (TEE) especially using 3-D imaging frequently provides better definition. Preoperative and intraoperative 3-D TEE can better define valvular pathology and guide appropriate intervention. A combination of M-mode, 2-D gray scale, Doppler, and color flow mapping provides virtually all necessary information to make definitive clinical decisions regarding medical management and the timing and utility of percutaneous or surgical intervention.

In difficult imaging cases by 2-D, (estimated as 10–15 % of all echo studies) when body habitus or breast tissue make ultrasonographic images uninterpretable, the addition of IV precision microspheres, echo contrast agents (gas-containing microspheres of albumin, lipid, or polymer) sufficiently improves the quality of the study. Cardiac catheterization, including right heart catheterization and LV angiography, is primarily relegated to confirm the noninvasive echo-Doppler findings before surgical intervention is contemplated. In cases of congenital heart disease, intracardiac shunts can be visualized with either color Doppler flow mapping or IV contrast and accurately quantified with standard Doppler techniques.

MRI, because its imaging is not limited by ultrasound windows, has assumed an important supporting role in the evaluation of complex valvular disease when echocardiography or right heart catheterization are suboptimal or in conflict. Flow-sensitive MRI techniques provide useful information on valvular pathophysiology as well as perhaps the most accurate assessment of ventricular size and function [23]. However, the gadolinium used for MRI contrast can increase the risk of a rare but serious disorder called nephrogenic systemic fibrosis among patients with renal dysfunction. Subjects with intracardiac devices, valves, and pacemakers and AICDs may be imaged by MRI, but the manufacturer should be contacted for appropriate management. MRI helps delineate extracardiac conduits and intracardiac flow patterns as well as 3-D rendering of cardiac anatomy [24]. Radionuclide studies such as first-pass angiography can also quantify intracardiac shunts in congenital heart disease [25].

3-D echocardiography has the potential to provide important definition of valvular disease and more accurate volumetric information compared to routine 2-D imaging; however, better transducer hardware and automated analysis software must be further developed before it becomes the clinical standard.

More recently, the development of portable hand-carried ultrasound (HCU) machines has proved a useful adjunct to the physical examination. Because of their portability, ease of use, and ability to provide immediate critical information on both myocardial and valvular structure and function, these "echo-stethoscopes" can be used at the "point of care" in the office or ER or in the field by cardiologists, internists, ER physicians, and intensivists.

Infective Endocarditis

Echocardiography plays an important role in the diagnosis, management, and follow-up of suspected or confirmed cases of infective endocarditis (IE). Clinical suspicion for IE may arise from a variety of signs/symptoms including fever associated with a new murmur, bacteremia (especially with virulent pathogens known to cause endocarditis), or embolic disease of unknown etiology. TTE is the recommended initial diagnostic test for a patient with suspected IE, because it is easily accessible, safe, and noninvasive. However, given the much higher sensitivity of TEE for identifying vegetations in IE as well as superior image quality, this is often indicated even when the TTE is normal and may be the first-line test in the evaluation of prosthetic valves. In addition, it is also helpful for the diagnosis of perivalvular involvement (i.e., abscess), assessment of embolic risk, and other complications of IE including leaflet perforation, chordal rupture, and fistula formation. Diagnosis of IE among patients with prosthetic valves often requires the use of TEE, given the acoustic shadowing that often interferes with transthoracic imaging. According to the 2007 ACC/AHA Appropriateness Criteria for Transthoracic and Transesophageal Echocardiography, use of TEE as an initial test may be appropriate for the diagnosis/management of endocarditis with a moderate to high pretest probability or with persistent fever in a patient with an intracardiac device [26].

Pericardial Disease

The pericardium is composed of two components, the visceral and parietal layers, which enclose a pericardial space that typically contains between 15 and 50 ml of pericardial fluid. Several pathologic processes can affect the pericardium including infectious, inflammatory, malignant, traumatic, and iatrogenic. Clinical manifestations of pericardial disease include pericarditis, pericardial effusion without hemodynamic compromise, cardiac tamponade, and constrictive pericarditis. The evaluation of a patient suspected of having pericardial disease is based on clinical history (typical pericardial chest pain), physical examination (pulsus paradoxus, pericardial friction rub, diminished heart sounds,

Kussmaul's sign), ECG (diffuse ST elevations suggestive of pericarditis, electrical alternans suggesting the heart showing the presence of a very large effusion), or X-ray (enlarged cardiac silhouette). Subsequent imaging studies can often provide useful information in the diagnosis and management of pericardial disease.

Transthoracic echocardiography is the recommended test of choice for pericardial disease and can detect and estimate the amount of pericardial fluid, as well as assess for pericardial thickening and nodularity, which may suggest inflammatory, infectious, or malignant process. The absence of a pericardial effusion does not rule out pericarditis; however, the presence of one may support the diagnosis. In cardiac tamponade, the echocardiographic feature most supportive of a clinical diagnosis is demonstration of >25 % variability in transvalvular flow with changes in the respiratory cycle by Doppler imaging. Other signs suggestive of tamponade include right ventricular or atrial collapse during diastole as well as IVC distention. When percutaneous drainage of a pericardial effusion is required, echocardiographic guidance at the bedside or in the cath lab is often used with injection of agitated saline into the pericardial space to confirm proper needle and/or catheter location.

Constrictive pericarditis should be suspected among patients with symptoms of volume overload, fatigue, and dyspnea on exertion, especially in the setting of a previous cardiac surgery, recurrent pericarditis, radiation therapy, renal failure, chest trauma, or infection. However, the differentiation between constrictive pericarditis and restrictive cardiomyopathy is oftentimes challenging even for the experienced clinician. Constrictive pericarditis is typically characterized by pericardial thickening, pericardial calcification, and abnormal diastolic filling that can be detected by M-mode and two-dimensional echocardiography. Doppler echocardiography can also be used to show respiratory-dependent changes in inflow velocity filling patterns across the mitral and tricuspid valves, a sign of ventricular interdependence that is seen in constrictive pericarditis and not restrictive cardiomyopathy [27]. Tissue Doppler imaging at the mitral annulus can also help differentiate constrictive pericarditis, which usually has a prominent E', from restrictive cardiomyopathy, which has a decreased E' velocity.

Cardiac catheterization can be used to confirm the clinical diagnosis of constrictive pericarditis. The most common findings include increased right atrial pressure, a prominent x and y descent of the venous and atrial tracings, equalization of LV and RV diastolic pressure tracings, and "discordant" respiratory variation in the RV-LV pressure tracings. CT and MRI provide supplemental information, including detection of pericardial calcification and accurate measurement of pericardial thickness, respectively [28, 29].

Cardiomyopathies

Cardiomyopathies were previously categorized by the WHO in 1995 by the underlying pathophysiologic mechanism and included dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy. However, as new entities have been discovered, the AHA in 2006 proposed a newer classification system that separates primary cardiomyopathies, which only have cardiac involvement, from secondary cardiomyopathies which have multiorgan involvement [30]. Primary cardiomyopathies were further classified as genetic, acquired, or mixed. Evaluation and diagnosis of cardiomyopathies rely predominantly on two-dimensional and Doppler echocardiography to provide basic anatomic information including ventricular and atrial dimension, ejection fraction, systolic and diastolic function, wall thickness, hemodynamic assessment, and valvular function.

Dilated cardiomyopathy is characterized by increased left ventricular dimension and global left ventricular systolic dysfunction. Abnormal ventricular wall thickening is suggestive of hypertrophic cardiomyopathy; however, this should be distinguished from hypertrophy secondary to hypertension, hypertrophy secondary to aortic stenosis, or infiltrative disease. Restrictive cardiomyopathy is characterized by a restricted diastolic filling pattern with preserved systolic function, normal wall thickness, and biatrial enlargement. The etiology of restrictive cardiomyopathy includes infiltrative disease (i.e., amyloidosis, sarcoidosis), glycogen storage disease, hemochromatosis, and other miscellaneous causes such as radiation or chemotherapy. Endomyocardial biopsy can also be useful in the diagnosis of a suspected infiltrative disease or glycogen storage disease.

In cases where echo data are suboptimal or incomplete, MRI can also accurately assess left and right ventricular systolic function and aid in tissue characterization in cases of cardiomyopathy (i.e., sarcoidosis or amyloidosis). Delayed gadolinium enhancement can identify myocardial scar or fibrosis, distinctive uptake patterns of infiltrative and hypertrophic myopathies, and myocarditis. Unfortunately this technique is still limited by several factors including decreased specificity, poor patient cooperation, presence of metallic implants, and renal dysfunction which may limit the use of gadolinium contrast agents. MUGA (Multi-Gated Acquisition Scan) radionuclide imaging will also provide accurate quantification of both RV and LV function by using volumetric measurements based on actual photon density arising from within the ventricular cavity during diastole and systole rather than on geometric assumptions about ventricular shape (as in echocardiography) or by edge-detection techniques (used in standard gated SPECT imaging). However, due to overlying chambers or septal position, a first-pass nuclear study will separate the ventricles better than standard MUGA.

Right Ventricular Dysfunction

Because of difficulties in assessing right ventricular morphology and systolic function with standard echocardiography due to the irregular geometry of the right ventricle, contrast echo and 3-D echo have improved echo assessment of RV size and function. MRI has an important role in providing accurate assessment of RV structure and function [31], particularly when the diagnosis of arrhythmogenic right ventricular cardiomyopathy is suspected. The most recent criteria for diagnosis of ARVC include parameters for RV volume, regional RV dysfunction, and global RV function [32].

Diastolic Dysfunction

Up to 40 % of patients presenting with dyspnea and symptoms of CHF may have normal LV systolic function. The same techniques used to diagnose and characterize the degree of impairment of ventricular relaxation in restrictive cardiomyopathies are those used in cases of suspected diastolic dysfunction. Restrictive cardiomyopathies are typically characterized by normal left and right ventricular size as well as valvular function on M-mode and two-dimensional echocardiography, features that help exclude a diagnosis of hypertrophic or valvular heart disease. The atria, pulmonary veins, venae cavae, and hepatic veins are all typically dilated, because of increased filling pressures [33].

Four Doppler methods are used to assess LV diastolic compliance: transmitral E/A, pulmonary vein flow, Doppler tissue imaging (DTI), and strain imaging. Doppler tissue imaging of mitral annular motion has been advocated for assessment of restrictive diastolic filling (and diastolic dysfunction) because it is relatively independent of preload conditions. Elevated LV filling pressures (i.e., left atrial pressures) are inferred when E′ (tissue Doppler velocity of the mitral annulus during early diastole) is less than 8 ms and E (i.e., early transmitral flow duration)/E′ is greater than 15 ms [34].

Aortic Disease

Acute aortic syndrome refers to a group of three conditions, including aortic dissection, intramural hematoma, and penetrating atherosclerotic ulcer, that are associated with disruption of the medial layer of the aorta [35]. Aortic dissection is an uncommon but catastrophic illness caused by an intimal tear with propagation of blood between the intimal and medial layers producing a false lumen which can rupture. Acute proximal aortic dissection (proximal to the left subclavian artery) is associated with a very poor prognosis, with estimated overall in-hospital mortality of 27 % [36]. The clinical diagnosis of aortic dissection can be made by the identification of several clinical features including severe chest or abdominal pain, mediastinal widening on chest radiography, and pulse or blood pressure differential. Additional imaging is almost always performed to confirm the diagnosis, as well as to localize the site of tear, identify antegrade or retrograde extension, evaluate for involvement of the coronary arteries, and assess for other complications such as pericardial effusion, aortic regurgitation, or pericardial/pleural hemorrhage. MR imaging has the highest sensitivity and specificity for diagnosis of dissection, followed by TEE. However, TEE is preferable in the unstable patient in the ER or ICU. Computed tomography is the most commonly used initial test for aortic dissection and is likely related to the widespread availability of CT scanners in acute care settings.

The decision on which imaging modality is used can vary depending on the patient's clinical status and availability of the test. For the unstable patient, TEE is the test of choice since it can be performed at the bedside and provides comprehensive evaluation of the thoracic aorta. However, TEE provides limited views at the "blind spot" where acoustic shadowing from the interposed trachea precludes imaging of the proximal portion of the aortic arch. In addition, it requires esophageal intubation and sedation which may be difficult in an unstable patient, and this technique may be unavailable in the emergent setting. MRI is another highly accurate imaging modality for diagnosis of aortic dissection and can provide adequate detail to identify the intimal flap; however, prolonged acquisition times and lack of availability limit its use in the acute setting. MRI is the imaging modality of choice for evaluation of chronic dissection or in the stable patient. CT angiography allows for detailed and rapid imaging of the entire aorta but requires exposure to radiation and IV contrast. In general, CT should be reserved for patients in whom TEE and MRI are unavailable or contraindicated.

For thoracic aortic aneurysms, CT and MRI are the preferred imaging techniques for diagnosis and serial follow-up. It is recommended that these be performed on a yearly basis if there is no significant evidence of enlargement, or every 3–6 months with any significant increase in size. Serial echocardiography can also be performed for follow-up of aortic disease; however, it provides less detail than CT or MRI. Local experience, available technologies, and patient stability will dictate the procedure of choice.

Conclusion

There is no single algorithm for choosing among myriad cardiac imaging tests. However, the clinician can narrow the selection by pairing a working knowledge of the strengths and weaknesses of each test with a narrowly focused clinical question regarding a particular cardiac structure, function, or clinical scenario (*see* Table 14.5).

Table 14.5 Relative utility of imaging methods for specific cardiac disorders

Disorder	CXR	Echo	Angio	Radionuclide	CT	MRI
Ischemic	+	+++	++++	+++	++	++
Valvular	+	++++	++++	+	++	+++
Congenital	++	++++	++++	++	++	++++
Traumatic	++	++++	+++	++	++	+++
Myopathic	+	++++	+++	++	+++	+++
Pericardial	++	++++	++	0	+++	++++
Endocarditis	+	++++	++	0	++	+++
Masses	0	++++	+++	+	++++	++++

Based on data from Skorton et al. [37]

Before any imaging is performed, the clinician should consider how the results are likely to affect patient management and whether the benefits of testing outweigh any potential risks, cost, radiation exposure, or inconvenience. As in all fields of medicine, a stepwise approach to cardiac diagnosis should be followed, from least to most invasive modality.

Suspected or confirmed epicardial coronary artery stenoses are typically evaluated directly by X-ray angiography in settings where revascularization is under consideration or when the pretest likelihood of disease is sufficiently high to warrant bypassing less invasive indirect testing of coronary perfusion (i.e., treadmill stress electrocardiography, stress echocardiography, or myocardial perfusion imaging.) As the pathophysiologic model of acute coronary syndromes continues to evolve, more attention will focus on early detection of nonstenotic but high-risk "vulnerable" atheromatous plaques. CT, cardiac MRI, intravascular ultrasound, and nuclear imaging techniques will continue to evolve for the purpose of coronary plaque characterization and risk stratification.

Myocardial and valvular disorders, including myocardial tissue abnormalities and systolic and diastolic dysfunction, are best imaged by techniques that provide both structural and functional (i.e., hemodynamic) information. While 2-D echocardiography with Doppler imaging is currently the standard for assessing myocardial and valvular function, cardiac MR techniques may develop into a new "gold standard" for measuring systolic function. 3-D echocardiography has great potential but requires better hardware and software development. Invasive measurement of intracardiac pressures by right heart catheterization is reserved for cases in which noninvasive testing yields inconclusive results or results discrepant with clinical findings.

Appropriateness of Use guidelines still present multiple methods to explore the same problem. Thus, clinicians should develop their own cost-effective and time-efficient algorithms based on their clinical evaluation of the patient and the local facilities' technical resources as well as local expertise in acquisition and interpretation of the various techniques.

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Electrophysiology of Cardiac Arrhythmias

15

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Introduction

In order to understand the pathophysiology of cardiac arrhythmias, one must have a grasp of the normal cardiac cycle, which is initiated by electrical events that precede cardiac contraction. Abnormalities in the initiation and propagation of cardiac impulses result in a variety of arrhythmias. The purpose of this chapter is to highlight the cellular mechanisms responsible for normal impulse formation and conduction and to review the clinical consequences when these mechanisms are perturbed.

Cellular Electrophysiology: The Cardiac Action Potential

The cardiac action potential consists of five phases (phases 0 through 4) that are determined by channels that allow ions to flow passively down their electrochemical gradients, as well as by a series of energy-dependent ion pumps. Ion channels are protein "tunnels" that span the cell's lipid membrane. By selectively permitting the passage of specific ions, they maintain the electrochemical cell membrane potential. Flow of a specific ion through a channel is dependent on gating of the channel as well as the electrical and chemical concentration gradients of that particular ion. Ions will flow passively down a chemical gradient if the channel is gated open and will also be drawn toward their opposite charge.

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Sodium (Na^+) and calcium (Ca^{2+}) channels consist of a single α-subunit that contains six hydrophobic transmembrane regions (Fig. 15.1) [1]. The voltage-gated potassium (K^+) channel consists of four identical subunits each containing a six-transmembrane-spanning unit similar to Na^+ and Ca^{2+} channels. The six transmembrane units, S1–S6, form the core of the sodium, calcium, and most potassium channels.

Na^+, K^+, Ca^{2+}, and chloride (Cl^-) are principally responsible for the membrane potential (Fig. 15.2). It is helpful to recall the equilibrium potential of these ions when considering the cardiac action potential (Table 15.1). The positive and negative values reflect the intracellular potential relative to a reference electrode. When a single type of ion channel opens, the membrane potential will approach the equilibrium potential of that ion. Thus, during diastole (phase 4), the cell membrane is impermeable to Na^+. However, K^+ diffuses freely out of the cell until the concentration gradient is balanced by the negative intracellular potential that attracts K^+. This balance represents the potassium electrochemical equilibrium potential (E_K). During phase 0, when the cell membrane is freely permeable to Na^+, the membrane potential approaches +50 mV (Fig. 15.3) [2]. Typically, more than one channel type is open at a time. The resulting membrane potential is determined by the balance of the competing currents.

Phase 0 marks the initiation of the action potential. Nodal cells are characterized by an influx of Ca^{2+}, while atrial, ventricular, and His–Purkinje cells depend on an influx of Na^+. Initiation of each cardiac cycle is dependent on membrane depolarization initiated at the sinus node. In nodal cells, the pacemaker current, I_f, initiates each cycle. I_f is activated by the polarization of phase 4 and carries a nonselective inward current composed primarily of Na^+ and K^+ ions, as well as a small Ca^{2+} current. I_f causes slow depolarization of the nodal cell membranes during diastole until a threshold for firing is achieved. Following initial local membrane depolarization by I_f, the upstroke of the nodal action potential is completed by a slow inward calcium current. Two types of calcium

C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_15, © Springer Science+Business Media New York 2013

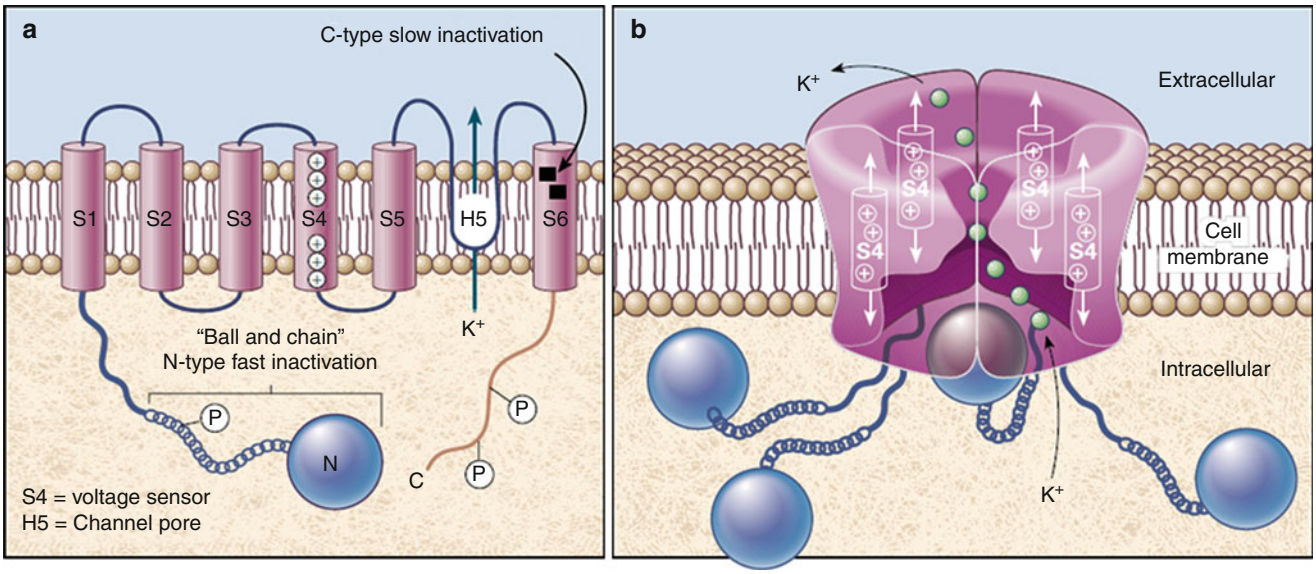

Fig. 15.1 (**a**) Diagram of a subunit containing six transmembrane-spanning motifs, S1 through S6, that forms the core structure of sodium, calcium, and potassium channels. The "ball and chain" structure at the N-terminal of the protein is the region of a potassium channel that participates in N-type "fast inactivation," occluding the permeation pathway. The *circles* containing plus signs in S4, the voltage sensor, are positively charged lysine and arginine residues. Key residues lining the channel pore (H5) are found between S5 and S6. (**b**). Diagram of the four identical subunits of the voltage-gated postassium channel, each containing a six-transmembrane-spanning unit. (Modified from Ackerman and Clapham [1]. With permission from Massachusetts Medical Society)

currents are present: the predominant slowly inactivating, dihydropyridine-sensitive L current (I_{Ca-L}) and the rapidly inactivating T current (I_{Ca-T}; *see* Fig. 15.3 and Table 15.1). Local membrane depolarization is propagated to neighboring cells via gap junction channels.

In "nonpacemaker" tissue, I_f is absent. In these cells, phase 0 is triggered when the cell membrane is depolarized by adjacent cells. Once a sufficient proportion of a cell surface is depolarized and the cell reaches its activation threshold, the permeability of the cell surface membrane to I_{Na} is markedly increased, allowing Na^+ to enter the cell and complete phase 0 depolarization. Blocking this inward current decreases the rate of change of the upstroke of the action potential (dV/dt) and slows conduction velocity.

Phase 1 consists of rapid membrane repolarization. This is achieved by inactivation of the inward Na^+ current and activation of the transient outward current (I_{to}), which is comprised of two currents. I_{to1} is a voltage-activated outward potassium current, and I_{to2} is a calcium-activated chloride current. Phase 2, the plateau phase, may last as long as 100 ms and is characterized by a small change in membrane potential generated by I_{Ca-L}.

Rapid repolarization of the cell occurs during phase 3. I_{Ca-L} is inactivated in a time-dependent fashion, thus decreasing the flow of cations into the cell. Simultaneously, several outward potassium currents, known as the delayed slow (I_{Ks}), rapid (I_{Kr}), and ultrarapid (I_{Kur}) currents, become active. This results in a net outward positive current and a negative transmembrane potential.

Mechanisms of Arrhythmias

Automaticity

Rhythmic (pacemaker) activity is an inherent property of different cell types. There is a normal hierarchy in the frequency of the initiated action potentials, with the sinus node being the dominant pacemaker. Automaticity in the distal conduction system (or working myocardium) may compete with that in the sinus node on the basis of *enhanced normal* or *abnormal* automaticity.

Under pathologic conditions, a decrease in the resting membrane potential may occur, which can lead to spontaneous phase 4 depolarization in all cardiac cells [3]. Abnormal automaticity is defined as spontaneous impulse initiation in cells that are not fully polarized. The disturbances in the normal ionic balance leading to abnormal automaticity may result from perturbations in various currents, e.g., reduction in the inward rectifying current, I_{K1}. During the subacute phase (24–72 h) following coronary occlusion, automatic arrhythmias can arise from the borders of the infarction.

Clinical Correlates

A representative clinical example of an automatic arrhythmia is atrial or ventricular tachycardia that is precipitated by exercise in patients without structural heart disease. These forms of tachycardia are thought to represent adrenergically mediated automaticity, because programmed stimulation can

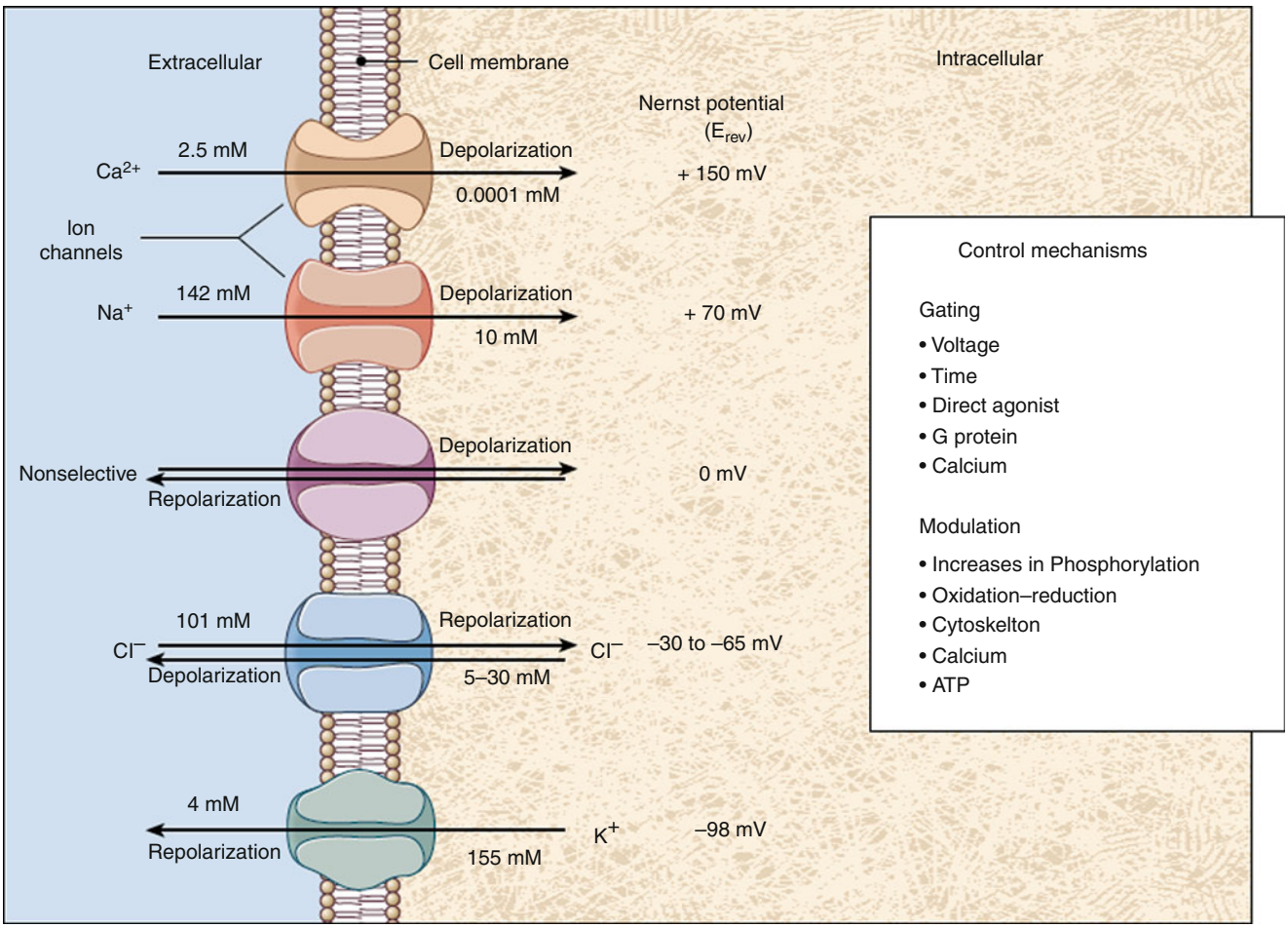

Fig. 15.2 Physiology of ion channels. Five major types of ion channels determine the transmembrane potential of a cell. The ionic gradients across the membrane establish the Nernst potentials (E_{rev}) of the ion-selective channels (approximate values are shown). Under physiologic conditions, calcium and sodium ions flow into the cell and *depolarize* the membrane potential (i.e., they drive the potential toward the values shown for E_{Ca} and E_{Na}), whereas potassium ions flow outward to *repolarize* the cell toward E_K. Nonselective channels and chloride channels drive the potential to intermediate voltages (0 mV and −30 to −65 mV, respectively) (Modified from Ackerman and Clapham [1]. With permission from Massachusetts Medical Society)

neither initiate nor terminate the arrhythmia, whereas the tachycardia can be induced with catecholamine stimulation and is sensitive to β-blockade (Table 15.2) [4, 5].

The cellular mechanism governing automatic arrhythmias and their anatomic substrate is poorly delineated. Catecholamines modulate the rate in automatic cells by increasing cyclic AMP (cAMP) synthesis and alter the kinetics of I_f such that it is activated at less negative membrane potentials [6]. Adenosine appears to attenuate I_f through an inhibition of cAMP synthesis, an antiadrenergic mechanism similar to that mediated by vagal stimulation [7].

Triggered Activity

In cardiac cells, oscillations of membrane potential that occur during or after the action potential are referred to as *afterdepolarizations*. They are generally divided into two subtypes: early and delayed afterdepolarizations (EADs and DADs, respectively; Fig. 15.4). When an afterdepolarization achieves sufficient amplitude and the threshold potential is reached, a new action potential is evoked; this is known as a triggered response. Under appropriate circumstances, this process may become iterative, resulting in a sustained triggered arrhythmia. Triggered activity differs fundamentally from abnormal automaticity in that abnormal automaticity occurs during phase 4 of the action potential and it depends on partial depolarization of the resting membrane potential.

Early Afterdepolarizations and Arrhythmogenesis

An EAD can appear during the plateau phase (phase 2) and/or repolarization (phase 3) of the action potential (Fig. 15.4). Distinction between phase 2 and phase 3 EADs is often based on the takeoff potential of the EAD, e.g., above −35 mV for the phase 2 and below −35 mV for the phase 3 EADs. It is

Table 15.1 Summary of transmembrane currents

Ion (Nernst potential)	Currents	Role in AP
Potassium (−98 mV)	I_f—inward "pacemaker" current (also carried by Na^+)	Activated in nodal tissue polarization of membrane during phase 4
	I_{K1}—inward rectifier responsible for resting membrane potential	Maintains phase 4 resting membrane potential; absent in sinus node
	I_{Kur}—inward ultrarapid rectifier	Minor current of phase 1 repolarization
	I_{Kr}—inward rapid rectifier repolarization	Primary current of rapid phase 3
	I_{Ks}—inward slow rectifier	Contributes to late phase 3 repolarization
	I_{to1} (=I_{Kto1})—transient voltage-sensitive outward current	Activated (by voltage) briefly during phase 1 rapid repolarization
	$I_{K(ACh)}$—outward current	Activated by muscarinic (M_2) receptors via GTP; important in nodal and atrial cells where it may cause hyperpolarization and shortening of action potential duration
	$I_{K(Ado)}$—outward current	Appears identical in function to $I_{K(ACh)}$, but activated by adenosine
	$I_{K(ATP)}$—outward current	Blocked by ATP; activated during hypoxia (when ATP concentration low); shortens action potential during ischemia
Sodium (+70 mV)	I_{Na}—fast inward current carried by Na^+ through a voltage-gated channel	Phase 0
	I_{Ti}—transient inward current	Activated during phase 4 by release of Ca^{2+} from the sarcoplasmic reticulum; contributes to DADs
	$I_{Na\text{-}K\ pump}$—bidirectional current	Pumps 3 Na^+ out for 2 K^+ in producing small rectifier current; when this channel is blocked by digoxin, the Na/Ca exchanger $I_{Na/Ca}$ takes over, resulting in intracellular Ca^{2+} overload
	$I_{Na/Ca}$—outward current	Exchanges 1 Ca^{2+} (into the cell) for 1 Na^+ (out of the cell) during intracellular Na^+ overload; during digoxin toxicity, this may result in intracellular Ca^{2+} overload and triggered arrhythmias
Calcium (+150 mV)	I_{Ca-L}—slow inward calcium current, blocked by dihydro-pyridines	Active during phase 0 in nodal cells, phase 2 of atrial, ventricular, and His–Purkinje cells
	I_{Ca-T}—transient inward current	May contribute to phase 4 depolarization in sinus and His–Purkinje cells
	$I_{Na/Ca}$—inward current	Exchanges 1 Ca^{2+} (out of the cell) for 3 Na^+ (into the cell) during phase 2; during digoxin toxicity, this may result in intracellular Ca^{2+} overload and triggered arrhythmias
Chloride (−30 mV)	I_{Cl}—outward current	Contributes to phase 3 repolarization; activated by adrenergic stimulation
	I_{to2} (= $I_{Cl.Ca}$)—transient (Ca^{2+} activated) outward chloride current	Activated briefly during phase 1 rapid repolarization

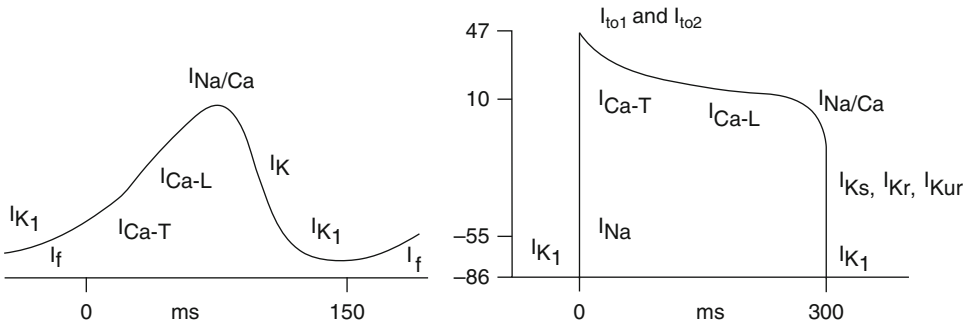

Fig. 15.3 The human cardiac action potential. Principal currents responsible for the sinoatrial nodal (*left*) and ventricular (*right*) action potential (Modified from Ackerman and Clapham [2], pp. 81–301. With permission from Elsevier)

possible for both forms of EADs to appear during the same action potential. A critical prolongation of repolarization, either by a reduction in outward currents, an increase in inward currents, or a combination of the two, is normally required for the manifestation of EAD-induced ectopic activity. EADs are often potentiated by bradycardia or a pause, which further prolongs repolarization, since action potential duration is dependent on the prior diastolic interval.

Clinical Correlates

A wide variety of medications can produce EADs, EAD-related triggered activity, or even a form of polymorphic ventricular tachycardia known as *torsade de pointes* (Fig. 15.5). These agents excessively prolong repolarization and include the Vaughan-Williams class Ia (e.g., quinidine and procainamide) and class III (e.g., sotalol, dofetilide, and ibutilide)

Table 15.2 Electropharmacologic matrix

	Reentry	Automaticity	cAMP-triggered activity
Catecholamine stimulation	Facilitates/no effect	Facilitates	Facilitates
Induction with rapid pacing	Facilitates/no effect	No effect	Facilitates
Overdrive pacing	Terminates/accelerates	Transiently suppresses	Terminates/accelerates
β-blockade	No effect/rarely terminates	Terminates	Terminates
Vagal maneuvers	No effect	Transiently suppresses	Terminates
Calcium channel blockade	No effect[a]	No effect	Terminates
Adenosine	No effect	Transiently suppresses	Terminates

Reprinted from Lerman et al. [4]. With permission from John Wiley & Sons Inc.
Automaticity refers to arrhythmias that arise from spontaneous phase 4 depolarization from nearly fully repolarized cells. Abnormal automaticity (which occurs in cells with resting membrane potentials ≤−60 mV) is not included in this table because it has not conclusively been shown to be a cause of clinical arrhythmias
[a]An exception is intrafascicular reentry, which is sensitive to verapamil

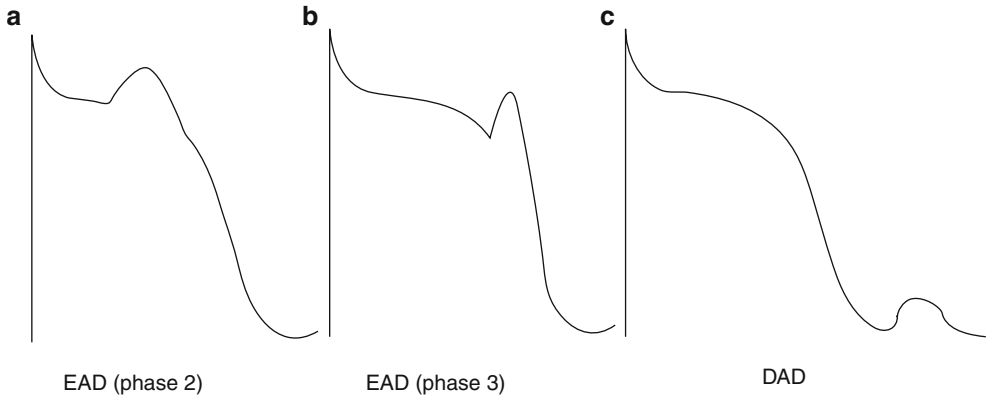

Fig. 15.4 Schematic examples of (**a**) phase 2 early afterdepolarization (*EAD*), (**b**) phase 3 *EAD*, and (**c**) delayed afterdepolarization (*DAD*)

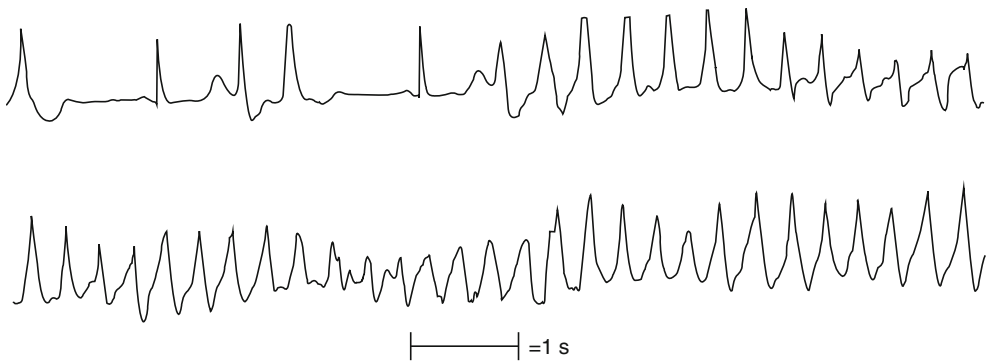

Fig. 15.5 Initiation of torsade de pointes following a "long-short" interval in a patient with long-QT syndrome

antiarrhythmic agents, and a variety of noncardiac drugs, including antibiotics (e.g., erythromycin), pentamidine, and nonsedating antihistamines (e.g., terfenadine and astemizole).

One of the most extensively studied EAD-related arrhythmias is that found in patients with congenital long-QT syndrome (LQTS). Initially thought to be a rare disease (1 per 10,000 births), more recent estimates demonstrate a much higher prevalence (1 per 2,500 births) [8]. LQTS provides an opportunity to examine the effects of ion-channel mutations on structure and function of these channels.

Two distinct phenotypes of congenital long-QT syndrome were initially recognized. In 1957 Jervell and Lange-Nielsen described the autosomal recessive pattern of the congenital long-QT syndrome associated with congenital sensorineural hearing loss and recurrent syncope [9], and in 1963, an autosomal dominant form of the disease manifesting only as QT prolongation was described separately by Romano et al. and Ward [10, 11]. Genotyping has now revealed 13 disease-causing genes for the long-QT syndrome [12].

Certain clinical features appear to be common to most forms of the congenital long-QT syndrome. Most patients will have a corrected QT interval (QTc) of 460 ms or greater [13], although some LQTS patients can have a normal QTc. The standard heart rate correction, according to Bazett's formula, is $QTc = QT/RR^{1/2}$, where RR is the R–R interval expressed in seconds. Initially, a scoring system was developed and was used to assist in the diagnosis of the long-QT syndrome and took into account factors including the QT interval, patient

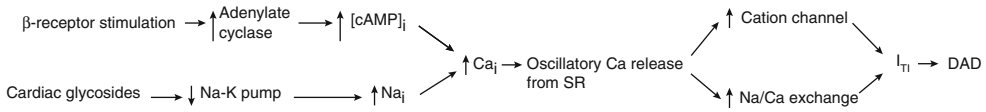

Fig. 15.6 Mechanism of DADs related to catecholamines and digoxin toxicity. Intracellular Ca^{2+} overload triggers I_{Ti}, a depolarizing inward Na^+ current. Ca_i inward Ca^{2+} current, Na_i increased intracellular Na^+ concentration, I_{TI} depolarizing inward Na^+ current, *SR* sarcoplasmic reticulum

symptoms, and family history [14]. The syndrome appears to be equally distributed between men and women.

Genetic testing for LQTS is currently available and is recommended for any patient in whom there is a strong clinical index of suspicion for LQTS (based on clinical history, family history, electrocardiogram, and/or provocative stress testing) or for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval. Furthermore, mutation-specific genetic testing is recommended for family members (and other appropriate relatives) following identification of the LQTS-causing mutation in an index case [15]. Known mutations account for about 75 % of those diagnosed with LQTS. LQT1 accounts for approximately 30–35 % of LQTS cases. The responsible gene is located on the short arm of chromosome 11 and encodes the pore forming the α-subunit (one of the two proteins) that comprise $I_{Ks,}$ the slowly activating delayed rectifier current. The defective I_{Ks} is inactive, thus prolonging repolarization and predisposing to EADs.

Mutations in the gene encoding I_{Kr} (HERG) on chromosome 7, which result in prolonged phase 3 repolarization, appear to be responsible for another autosomal recessive form of the long-QT syndrome, LQT2, and account for another 25–40 % of LQTS patients.

LQT3 has been linked to SCN5A, a gene on chromosome 3 that encodes $I_{Na,}$ the current responsible for phase 0 rapid depolarization. LQT3 results from a sodium channel that fails to inactivate appropriately and is present in 5–10 % of LQTS cases. This mutation causes continued inward sodium current (beyond phase 0) throughout the action potential, thereby prolonging the action potential duration. Mexiletine, a selective Na^+ channel blocker, has been demonstrated to shorten the QTc in affected patients and may therefore have a therapeutic role.

Less common mutations include LQT4 (ankyrin B), located on chromosome 4, which causes disruption in the cellular organization of the Na^+ pump, the Na^+/Ca^{2+} exchanger, and the inositol triphosphate receptor; extrasystoles are caused by altered Ca^{2+} signaling. In addition, the β-subunit of I_{Ks} and I_{Kr} are encoded by KCNE1 and KCNE2 (both on chromosome 21), and mutations in these genes can also result in prolonged QTc due to delayed repolarization (LQT5 and LQT6, respectively). LQT7 is caused by the mutant gene KCNJ2, which decreases the inwardly rectifying K^+ current ($I_{Kir2.1}$).

Mutations in one allele of either the α- or β-subunit of I_{Ks} appear to be phenotypically expressed as the Romano–Ward syndrome. Both subunits have been demonstrated to be present in the stria vascularis of the inner ear in mice. Mutations in both alleles (i.e., homozygotes) for the α- or β-subunit are associated with the Jervell and Lange-Nielsen phenotype.

Delayed Afterdepolarizations and Arrhythmogenesis

Delayed afterdepolarizations (DADs) are oscillations in membrane potential that occur after repolarization and during phase 4 of the action potential. In contrast to automatic rhythms that originate de novo during spontaneous diastolic depolarization, DADs are dependent on the preceding action potential. By definition, they do not occur in the absence of a previous action potential.

During the plateau phase of the normal action potential, Ca^{2+} enters the cell. The increase in intracellular Ca^{2+} triggers release of Ca^{2+} from the sarcoplasmic reticulum (SR); this, in turn, further elevates intracellular calcium and initiates contraction. Relaxation occurs through sequestration of Ca^{2+} by the SR. DADs arise when the cytosol becomes overloaded with Ca^{2+} and triggers I_{Ti}, a transient inward current (Fig. 15.6). I_{Ti} is generated by the Na^+–Ca^{2+} exchanger (I_{NaCa}) and/or a nonspecific Ca^{2+}-activated current [16, 17]. DADs can originate from Purkinje fibers, as well as from myocardial, mitral valve, and coronary sinus tissues. Rapid pacing potentiates DADs because more Na^+ (and Ca^{2+}) enters the cell during rapid depolarization, further loading the cell with Ca^{2+}. Most experimental studies on triggered activity were performed under conditions of digoxin excess. By blocking the Na^+/K^+ pump, digoxin causes increased concentration of intracellular Na^+. The high concentration of Na^+ stimulates the electrogenic Na^+/Ca^{2+} exchanger, which moves Na^+ out of the cell in exchange for allowing Ca^{2+} entry into the cytosol. This results in intracellular Ca^{2+} overload and DADs. β-adrenergic stimulation, the effects of which are mediated by an increase in intracellular cAMP, also provokes delayed afterdepolarizations by increasing the inward Ca^{2+} current.

Clinical Correlates

The prototypical clinical arrhythmia due to cAMP-mediated triggered activity (DAD dependent) is idiopathic ventricular tachycardia arising from the right ventricular outflow tract

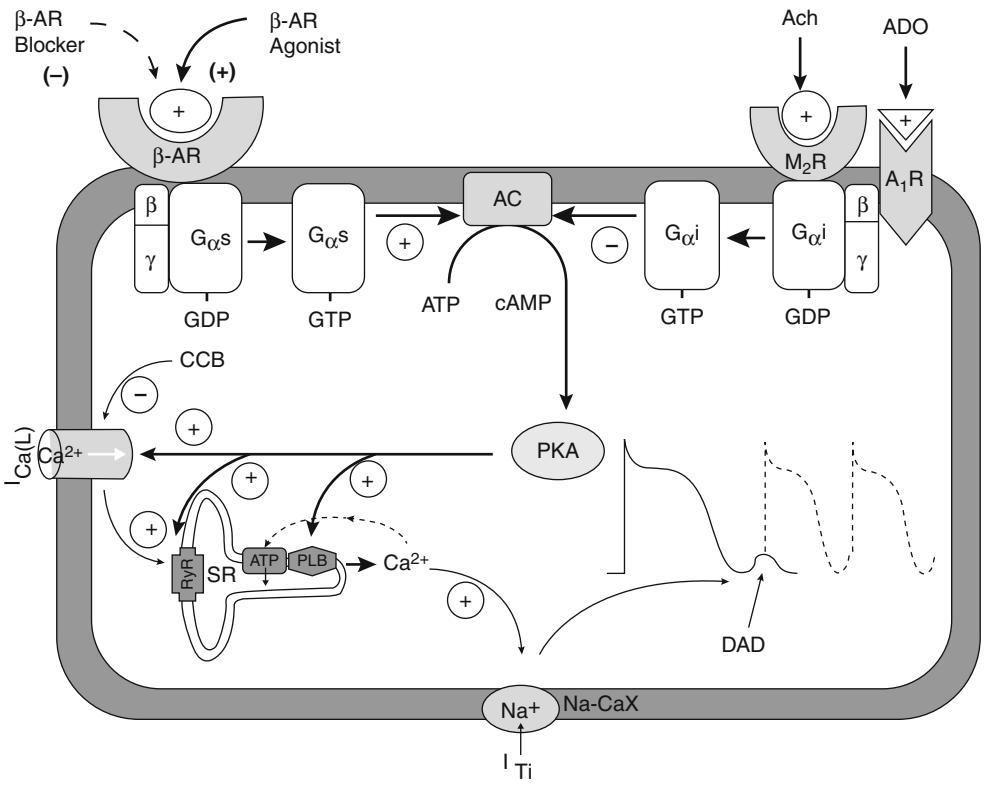

Fig. 15.7 Schematic representation of the cellular model for adenosine. *AC* adenylyl cyclase, *ACh* acetylcholine, *ADO* adenosine, A_1R adenosine A_1 receptor, *ATP* adenosine triphosphate, *β-AR* β-adrenergic receptor, *DAD* delayed afterdepolarization, $G\alpha_i$ inhibitory G protein, $G\alpha_s$ stimulatory G protein, *GDP* guanosine diphosphate, *GTP* guanosine triphosphate, M_2R muscarinic cholinergic receptor, *PKA* protein kinase A, *PLB* phospholamban, *RyR* ryanodine receptor, *SR* sarcoplasmic reticulum, *cAMP* cyclic adenosine monophosphate, I_{Ti} Transient inward current, *CCB* calcium channel blocker

(RVOT) [18] and is usually characterized by paroxysmal stress-induced VT or repetitive monomorphic VT (RMVT) [19, 20]. RMVT occurs during rest and is characterized by frequent ventricular extrasystoles, ventricular couplets, and salvos of nonsustained VT with intervening sinus rhythm. In contrast, paroxysmal stress-induced VT usually occurs during exercise or emotional stress and is a sustained arrhythmia. Common to both groups are the absence of structural heart disease, similar tachycardia morphology (left bundle branch block, inferior axis), and similar site of origin (RVOT), although the tachycardia can occasionally originate from other right ventricular sites as well as the left ventricle, especially from near the left and right coronary cusps of the sinuses of Valsalva [20, 21]. Overlap between these phenotypes of VT can be considerable.

Since activation of adenylyl cyclase and $I_{Ca–L}$ is critical for the development of cAMP-mediated triggered activity, the triggered arrhythmia would be expected to be sensitive to many electrical and pharmacological stimuli, including β-blockade, calcium channel blockade (verapamil), vagal maneuvers, and adenosine (Table 15.2; Fig. 15.7). Termination of VT with adenosine is thought to be a specific response for identifying cAMP-mediated triggered activity due to DADs, since adenosine has no ventricular electrophysiologic effect in the absence of β-adrenergic stimulation and has no effect on digoxin-induced DADs or quinidine-induced EADs. Furthermore, adenosine has no effect on catecholamine-facilitated reentry that is due to structural heart disease [22]. The clinical effects of adenosine and verapamil in a patient with VT attributed to cAMP-mediated triggered activity are shown in Fig. 15.8 [19]. While calcium blockers may be helpful in the cardiac electrophysiology laboratory in determining the mechanism of a specific arrhythmia (Table 15.2), their use is *contraindicated* in the treatment of most clinical forms of ventricular tachycardia.

Another arrhythmia that is likely due to triggered activity and delayed afterdepolarizations is *catecholaminergic polymorphic ventricular tachycardia* (CPVT). CPVT also occurs in patients with no evidence of structural heart disease, who present with a distinctive pattern of stress-related, bidirectional VT, or polymorphic VT. Mutations in the cardiac ryanodine receptor gene (RyR2) and calsequestrin 2 have been linked to CPVT [23–25]. RyR2 is responsible for calcium release from the sarcoplasmic reticulum, in response to calcium entry from the voltage-dependent L-type calcium channels (i.e., calcium-induced calcium release). Calsequestrin provides a calcium reservoir in the sarcoplasmic reticulum and possibly serves as a luminal Ca^{2+} sensor for the ryanodine receptor. Malfunction in either of these genes can result in intracellular calcium overload.

Reentry

The normal cardiac impulse follows a predetermined path. It is initiated at the sinus node and is extinguished after it has

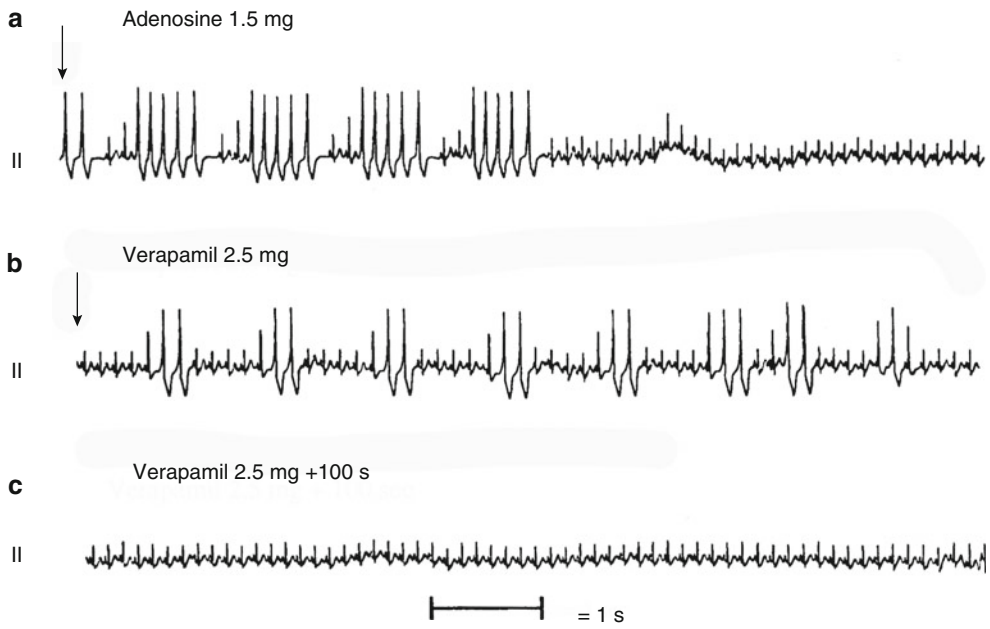

Fig. 15.8 (**a**) ECG recording showing termination of incessant repetitive monomorphic ventricular tachycardia (VT) by adenosine. The *vertical arrow* indicates the completion of adenosine administration and saline flush. (**b**) Administration of verapamil during incessant repetitive monomorphic VT. *Vertical arrow* indicates completion of verapamil infusion. (**c**) Termination of VT 100 s after verapamil administration. Surface lead II is shown (Reprinted from Lerman et al. [19]. With permission from Lippincott Williams & Wilkins)

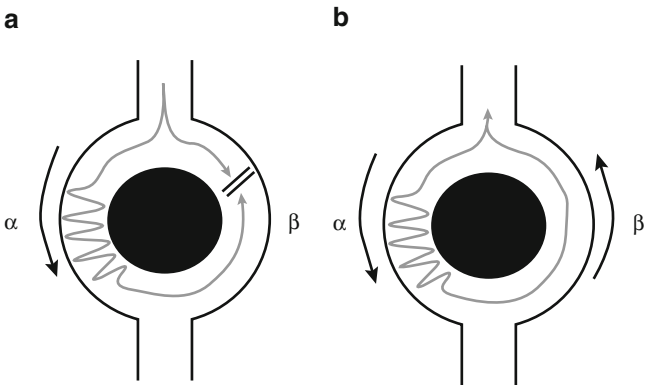

Fig. 15.9 Model of anatomic reentry. The impulse passes through a hypothetical conduit via two pathways, α and β, which meet at a common exit point. (**a**) Since α and β have distinct refractory properties, a hypothetical extrastimulus could be blocked in β pathway and conduct slowly over α pathway and reenter β pathway retrogradely. (**b**) This could result in sustained circus movement (reentry)

activated the ventricles. Reentrant arrhythmias arise when the cardiac impulse circulates around an anatomic or functional obstacle initiating an independent, repetitive rhythm. Reentry may be broadly classified as being either *anatomic* or *functional*.

Anatomic Reentry

In the anatomic model of reentrant arrhythmias, four prerequisites must be met to initiate reentry (Fig. 15.9): (1) a predetermined anatomic circuit must exist; (2) unidirectional block (e.g., in response to an extrastimulus) must occur in one limb of the reentrant circuit; (3) slow conduction in a contiguous pathway of the circuit, allowing recovery of excitability of the previously refractory limb; and (4) the wavelength of the impulse must be shorter than the length of the circuit [26, 27]. An illustration of some of these principles is shown in Fig. 15.9a, where an impulse "blocks" in the β pathway and travels down the α pathway slowly, but not with sufficient delay to allow resolution of refractoriness in the β pathway. Therefore, the retrograde impulse is extinguished. In Fig. 15.9b, conduction proceeds anterogradely down the α pathway and then subsequently retrogradely up the β pathway, which is no longer refractory. This results in reentry.

The concept of wavelength is inherent in the anatomical model of reentry. The leading edge of the wave must encounter excitable tissue in which to propagate. Therefore, the rotation *time* around the reentrant circuit must be longer than the recovery period of all segments of the circuit, and the *length* of the circuit must exceed the product of the conduction velocity and the recovery period of the tissue (Fig. 15.10a). Interruption of the anatomical circuit at any point interrupts reentry.

Functional Reentry

The mechanism of many atrial or ventricular reentrant arrhythmias may be more complex than just anatomical reentry. It has become apparent that reentry may be sustained even in the absence of a specific anatomical circuit and in the absence of abnormal myocardium. This type of reentry is termed *functional*.

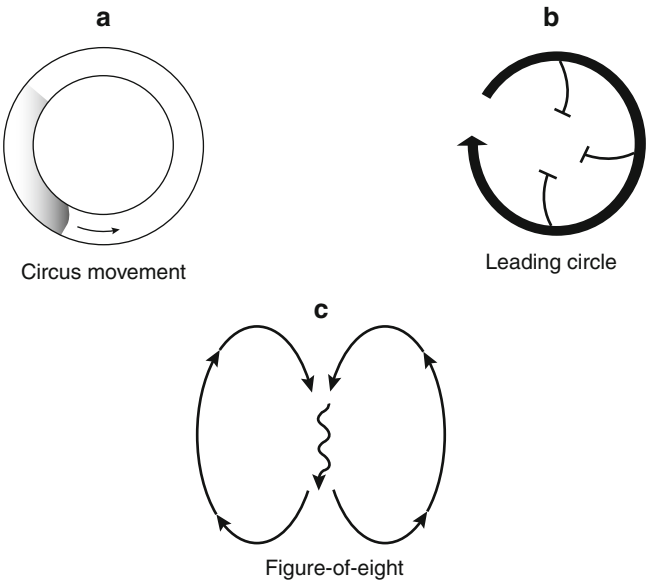

Fig. 15.10 (**a**) Circus movement reentry. The impulse (*gray region*) must be shorter than the entire length of the circuit (*circle*) and travel at a rate slow enough to allow separation of the impulse from its own refractory tail. This interval (depicted as *white*) is called the excitable gap. Reentry will be extinguished if the leading edge of the impulse (*black*) impinges on its tail (*gray*). (**b**) Model of leading circle reentry. Reentry follows the smallest possible circuit with tissue at the vortex remaining unexcitable. No anatomical barrier is present. (**c**) Figure-eight reentry in anisotropic cardiac muscle. Two reentrant circuits rotate in opposite directions sharing a central common pathway

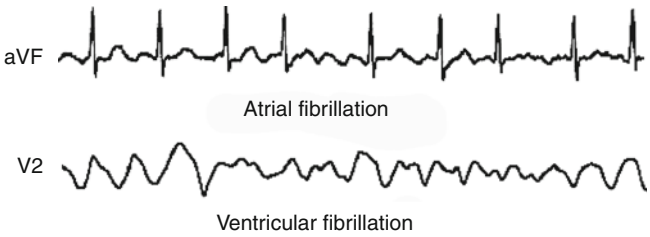

Fig. 15.11 Atrial fibrillation and ventricular fibrillation are examples of clinical arrhythmias that can be caused by spiral wave reentry

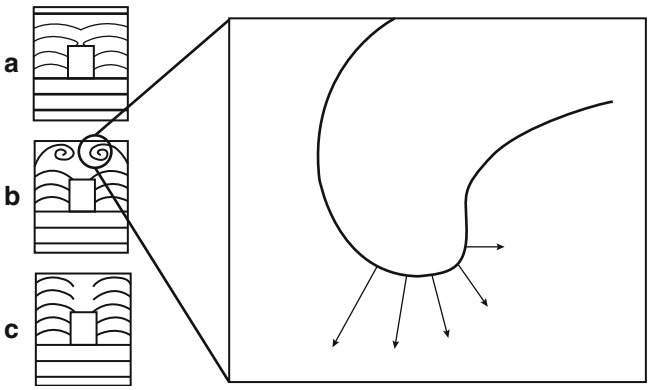

Fig. 15.12 Spiral wave reentry. (**a**) At normal levels of excitability, the wave separates into two daughter waves that circumnavigate the borders of the obstacle and fuse again at the opposite side. No wave break occurs. (**b**) At lower levels of excitability, the broken wave front curves and initiates a pair of counter-rotating spiral waves. The inset depicts propagation velocity along the curved wave front of a spiral wave. The more pronounced the curvature, the slower the conduction velocity (*small arrows*). Toward the periphery, conduction velocity reaches the maximum (*large arrows*). (**c**) Finally, at lower levels of excitability, the broken wave fronts are unable to rotate, propagating decrementally until they disappear (Reprinted from Jalife et al. [26]. With permission from John Wiley & Sons Inc.)

The *leading circle* hypothesis of reentry accounts for reentry in the absence of an anatomic obstacle [26]. Reentry follows the smallest possible circuit with tissue at the vortex remaining unexcitable (Fig. 15.10b). The propagating wave must penetrate tissue that remains relatively refractory. Thus, the circuit is much smaller than the circuit in anatomical reentry and no portion of the circuit is ever fully recovered (i.e., there is no *excitable gap*). It is unclear whether leading circle reentry is responsible for clinical arrhythmias.

Propagation of impulses in cardiac tissue is dependent on myocyte fiber orientation. Cell-to-cell communication depends primarily on gap junction proteins that are unequally distributed along the cell surface. The greater density of gap junction proteins along the longitudinal axis (as compared with the transverse axis) accounts for more rapid conduction in this direction. However, the longitudinal axis is associated with a lower safety factor of conduction (i.e., longer refractory period). The differential conduction properties in the longitudinal and transverse directions provide a substrate for *anisotropic* reentry. Anisotropy may account in part for some arrhythmias in the atria, AV node, and the peri-infarct regions of myocardium [28].

Figure-eight reentry may be considered an "extension" of leading circle reentry (that also incorporates anatomic reentry and anisotropic conduction properties), in which two reentrant circuits rotate in opposite directions in close proximity to one another utilizing a central common pathway (Fig. 15.10c). This mechanism may underlie sustained monomorphic ventricular tachycardia observed in some patients with ischemic heart disease. Unlike other forms of functional reentry, figure-of-eight reentry depends on a central common pathway between the rotating reentrant waves that is delimited by unexcitable tissue. Disruption of this central pathway effectively terminates reentry.

Spiral waves represent the most complex form of functional reentry and are believed to be a possible underlying mechanism for some forms of atrial and ventricular fibrillation (Fig. 15.11). In its simplest form, spiral wave reentry may be depicted as a broken wave front that curls at its broken end and begins to rotate (Fig. 15.12) [26]. The wave propagates through cardiac muscle but is interrupted by an obstacle such as a scar. When the obstacle causes a break in the wave front, several outcomes are possible depending on the excitability of the tissue. When excitability is high after passing the obstacle, the broken ends will fuse rapidly. When excitability is lower, the broken ends cannot fuse but begin to spiral. The trajectory of each point on the wave varies according to the

curvature of the wave: the greater the curvature, the slower the conduction velocity. The variable excitability of cardiac muscle compounds the complexity of propagation. When excitability of the tissue is further reduced, propagation of the wave front is extinguished.

Finally, reentry may occur in a linear circuit in the absence of even a functional loop (Fig. 15.13). An example of this form of reentry, termed *reflection*, may be seen when local injury occurs over a short portion of the His–Purkinje fibers. In this model, reentry occurs over a single pathway and depends on the presence of a region of severely impaired (but not blocked) conduction [26]. The impulse propagates toward the region of depressed conduction, but the damaged cells are incapable of being excited and the action potential is unable to propagate further. However, a small current is generated across these cells, and if the distance across the gap is relatively small, current may reach the distal segment and bring those cells to threshold, where propagation of an action potential can be initiated. If there is sufficient delay in propagation of the current to the distal side of the gap, the distal action potential may be reflected backward across the gap, reinitiating (or reflecting) an action potential.

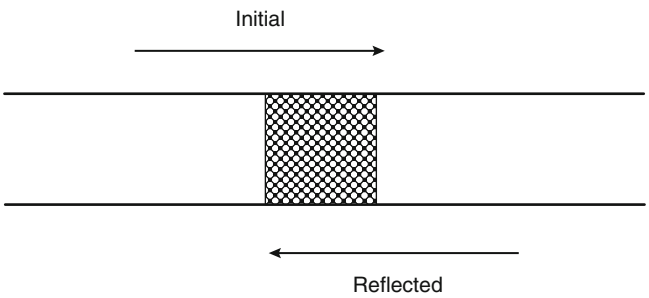

Fig. 15.13 Model of reflection. *See* text for explanation (Reprinted from Jalife et al. [26]. With permission from John Wiley & Sons Inc.)

Clinical Correlates

Most clinical supraventricular and ventricular arrhythmias are due to reentry. In this section, we describe the most common reentrant arrhythmias. The surface electrocardiogram (ECG) provides important clues to the mechanism of reentrant tachycardias (Fig. 15.14). Supraventricular tachycardias due to AV node reentry or an accessory AV pathway will typically have a short RP' interval (i.e., the interval between the P wave on surface ECG and the preceding R wave, denoted as the RP' interval <50 % of the RR interval). Conversely, supraventricular tachycardias such as atrial tachycardias, the atypical form of AV node reentry (discussed below), and the permanent form of junctional reciprocating tachycardia (a reentrant SVT due to a slowly conducting retrograde accessory pathway) typically demonstrate a long RP' interval (<50 % of the RR interval). When evaluating wide complex tachycardia, dissociation of the surface ECG P waves from the QRS complexes supports the diagnosis of ventricular tachycardia (Fig. 15.15). However, a 1:1 relationship between the P waves and QRS complexes may be observed in ventricular tachycardia (with 1:1 retrograde ventricular-to-atrial conduction) or supraventricular tachycardia conducted with a wide QRS complex.

Intra-Atrial Reentry

Intra-atrial reentrant tachycardias comprise a diverse group of arrhythmias. Reentrant arrhythmias may occur anywhere

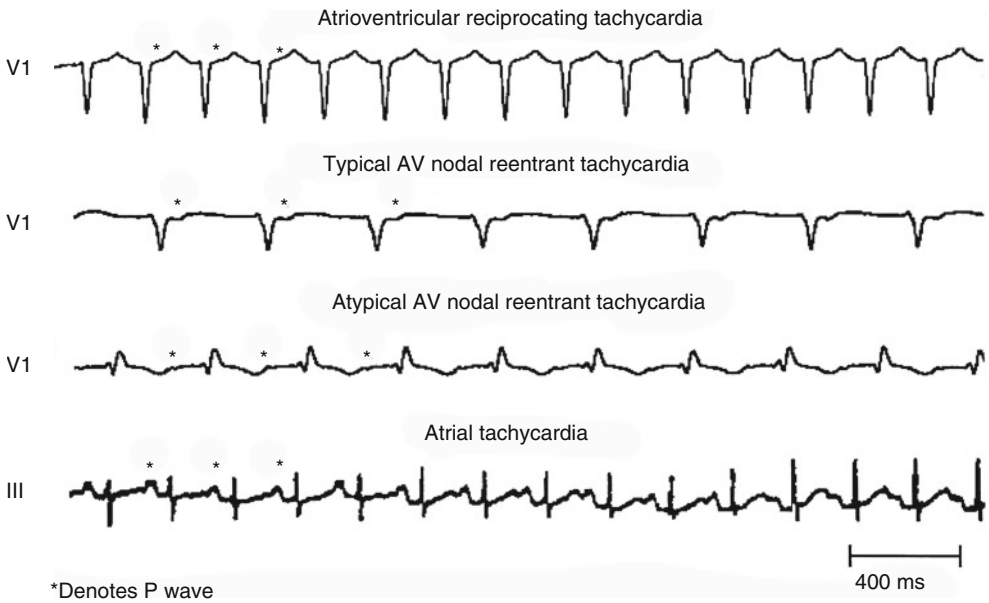

Fig. 15.14 Typical AV nodal reentrant tachycardia demonstrates a short RP' interval on the surface ECG. Similarly, orthodromic atrioventricular reciprocating tachycardia is characterized by a short RP' interval. Atrial tachycardias and atypical AV nodal reentrant tachycardia are characterized by a long RP' interval

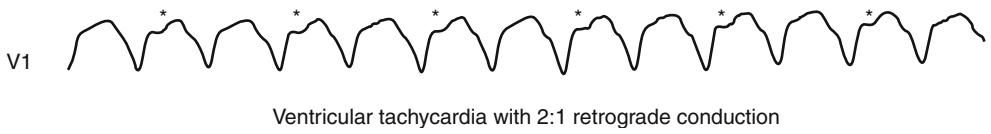

Fig. 15.15 Dissociation of the P waves (denoted with an asterisk, *) from the QRS complexes, or variable retrograde conduction to the atria, strongly supports the diagnostic of ventricular tachycardia. This is demonstrated in the figure. However, a 1:1 relationship of P waves to QRS complexes during a wide complex tachycardia may be due to either ventricular tachycardia with 1:1 retrograde conduction to the atria or a supraventricular tachycardia with 1:1 anterograde conduction to the ventricles in a patient with a preexisting bundle branch block

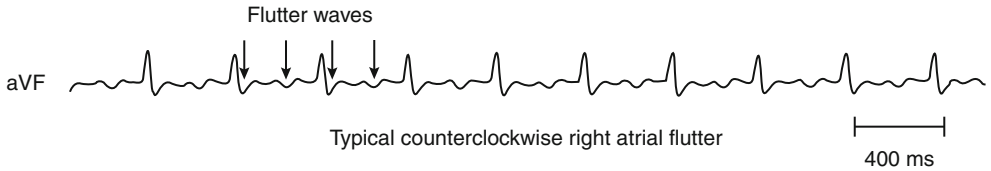

Fig. 15.16 Typical counterclockwise right atrial flutter is often characterized by 2:1 ventricular response and a ventricular rate of 150 beats per minute. Flutter waves on the surface ECG are usually negative in the inferior leads (II, III, aVF), as atrial activation proceeds down the right atrial free wall and up the interatrial septum, activating the interatrial septum and left atrium in a caudal to cranial sequence

in the atria and may affect persons with or without structural heart disease. Because areas of scar tissue typically provide the substrate for reentry, these tachycardias have been called *incisional reentrant tachycardias* [29]. Another common form of intra-atrial reentry is atrial flutter (Fig. 15.16). The "typical" form of atrial flutter occurs at a remarkably consistent rate of 250–300 beats per minute with propagation in counterclockwise fashion around the tricuspid valve annulus, down the free wall of the right atrium, and up the interatrial septum. When conduction proceeds up the interatrial septum, the caudal–cranial activation inscribes the superiorly directed flutter waves (i.e., negative in the inferior leads) observed on the surface ECG. Clockwise right atrial flutter (in the opposite direction) is less common.

Most intra-atrial reentrant tachycardias are not responsive to adenosine, β-blockers, or calcium channel blockers [5]. Over the past decade, electrophysiologists have made substantial progress in mapping and ablating reentrant atrial tachycardias. As with all reentrant arrhythmias, disruption of any part of the circuit will terminate tachycardia. For example, both the typical and atypical forms of flutter depend on a critical isthmus of conduction at the base of the right atrium. Creating a linear ablation lesion extending from the tricuspid valve annulus to the inferior vena cava blocks conduction across this isthmus and effectively eliminates tachycardia.

Atrioventricular (AV) Nodal Reentrant Tachycardia

Excluding atrial flutter and fibrillation, typical AV nodal reentrant tachycardia is the single most common form of supraventricular tachycardia and accounts for nearly 50–60 % of all sustained SVTs in adults [30, 31]. Usually, it presents

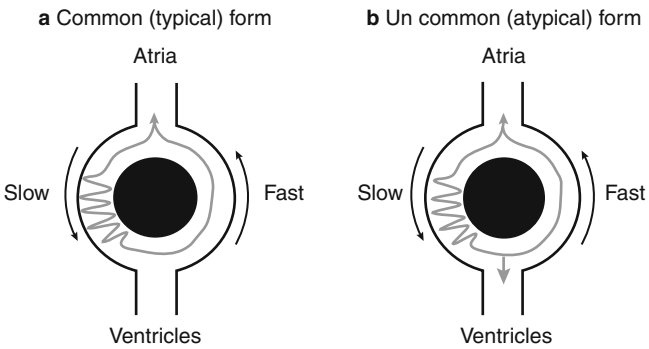

Fig. 15.17 Schematic drawings of AV nodal reentrant tachycardia. Illustrations depict two forms of supraventricular tachycardia due to reentry within the AV node, i.e., typical (**a**) and atypical forms (**b**)

before age 40, with rates typically ranging from 160 to 200 beats per minute but may vary (from 100 to 300 beats per minute). The reentrant circuit is limited to the peri-AV nodal region, with anterograde conduction proceeding over a "slow" pathway and retrograde conduction traversing a "fast" pathway [32]. In the usual case, the fast pathway has a longer refractory period than the slow pathway. Therefore, initiation of reentry occurs when a premature atrial beat blocks in the fast pathway and is conducted over the slow pathway. By the time the impulse reaches the distal portion of the slow pathway, the retrograde fast pathway has regained excitability and is able to conduct the impulse to the atrium, perpetuating the arrhythmia by engaging and activating the slow anterograde pathway. The atypical form of AV nodal reentry activates these limbs in the opposite direction; anterograde conduction proceeds over the fast pathway and retrograde conduction across the slow pathway (Fig. 15.17). As one would predict, the typical form of AV nodal reentry (with retrograde conduction up the fast pathway) is characterized by a short RP'

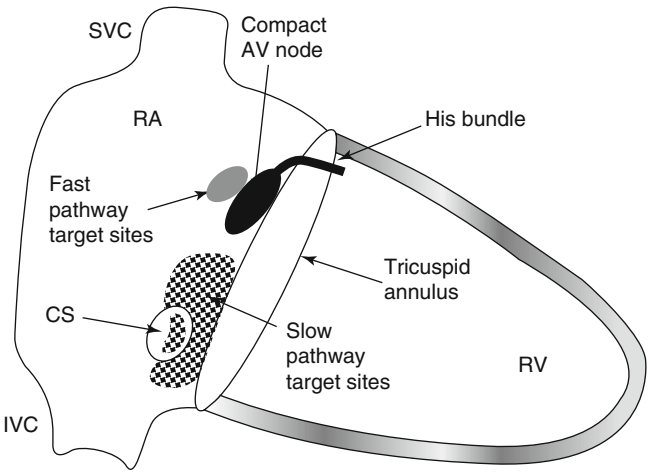

Fig. 15.18 Anatomical positions of slow and fast pathways. The posterior location of the "slow" pathway, remote from the compact AV node, makes it the target of choice for radiofrequency catheter ablation (Reprinted from Kalbfleisch and Morady [36]. With permission from Elsevier)

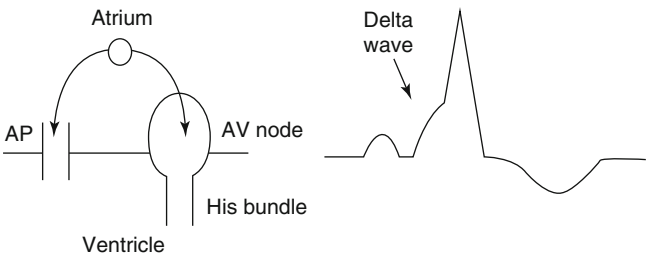

Fig. 15.19 Schematic of Wolff–Parkinson–White syndrome during normal sinus rhythm. Conduction over the accessory pathway (*AP*) activates the ventricle simultaneously with conduction over the AV node. Preexcitation of the ventricles by the accessory pathway creates the delta wave visible on the surface ECG

interval on the surface ECG, while atypical AV nodal reentry inscribes a long RP' interval. An electrophysiologic hallmark of AV nodal reentry is that neither the atria nor ventricles are necessary parts of the reentrant circuit.

Adenosine is effective in terminating reentrant tachycardias that involve the AV node and is mediated by activation of the outward potassium current $I_{K(Ado,\ ACh)}$, which hyperpolarizes the AV node to about −90 mV and abbreviates the action potential. Adenosine can terminate tachycardia in either limb, but it occurs most often in the slow pathway [33, 34]. Vagal maneuvers (carotid sinus massage or Valsalva) also terminate AV nodal-dependent reentry by activating the same outward potassium current $I_{K(Ado,\ ACh)}$.

The slow pathway is located in the region of the posteroseptal space of the interatrial septum and is readily amenable to ablation (>95 % success rate; Fig. 15.18) [35, 36]. This location, remote from the compact AV node, minimizes the chance of AV node damage during ablation. Ablation of the fast pathway also effectively treats AV nodal reentry but carries a relatively high risk of complete heart block.

Atrioventricular Reciprocating Tachycardia

Reentrant arrhythmias utilizing an accessory AV connection comprise the second most common form of regular narrow complex tachycardias (approximately 35 % of SVTs). Accessory pathways are composed of muscular bridges along the tricuspid and mitral valve annuli that provide an abnormal electrical connection between the atria and ventricles. The electrophysiologic properties of most accessory pathways resemble those of normal atrial tissue. Because the resting membrane potential is approximately −90 mV, typically, accessory pathways are insensitive to vagal maneuvers, adenosine, and Ca^{2+} channel blockers.

Most accessory pathways conduct only in one direction—retrogradely from the ventricles to the atria—and are therefore concealed during sinus rhythm. Conversely, accessory pathways with anterograde conduction properties usually result in ventricular preexcitation (known as Wolff–Parkinson–White syndrome). During sinus rhythm, conduction proceeds simultaneously down the AV node and accessory pathway (Fig. 15.19). Preexcitation of the ventricles by the accessory pathway inscribes a delta wave visible on the surface ECG that prolongs the QRS complex. Typically, the PR interval is abbreviated (<120 ms) owing to rapid conduction over the accessory pathway. Orthodromic reciprocating tachycardia (anterograde conduction over the AV node and retrograde conduction across the accessory pathway) accounts for 90 % of reentrant arrhythmias in patients with Wolff–Parkinson–White syndrome. This arrhythmia may degenerate into atrial fibrillation, which may precipitate ventricular fibrillation because of rapid conduction over the accessory pathway. A less common arrhythmia, antidromic reciprocating tachycardia (the anterograde limb being the accessory pathway and the retrograde limb being the AV node), is a regular rhythm and inscribes a wide QRS complex on the surface ECG.

Ventricular Reentrant Arrhythmias

Most ventricular arrhythmias occur in patients with a prior history of myocardial infarction. Experimental evidence suggests that mechanism of the tachycardia may be dependent on the time of the infarct. Within the first 30–60 min (early phase) following an acute myocardial infarction, the intracellular and extracellular milieux appear to favor reentrant ventricular arrhythmias, as does autonomic tone [37]. Automatic idioventricular rhythms, with rates typically between 60 and 120 beats per minute, are usually observed within the first 6–10 h (delayed phase). After the relatively quiescent second phase, the third and final stage of ventricular arrhythmias (late phase) begins within 48–72 h after infarct and is characterized by rapid monomorphic tachycardias, owing to reentry arising in the peri-infarct border zone. Inhomogeneous conduction properties of the peri-infarction tissue create regions of slow and rapid conduction, causing anisotropic and figure-of-eight reentry. The risk of reentrant late-phase ventricular arrhythmias persists indefinitely following myocardial infarction and is thought to account for at least half of all deaths among myocardial infarction survivors. Electrophysiologic studies and endocardial mapping in humans have demonstrated that monomorphic VT that occurs late after a myocardial infarction is caused by areas of slow conduction and diastolic activation. These arrhythmias may be induced or terminated with pacing maneuvers.

Another example of reentrant ventricular tachycardia occurring in patients with heart disease is bundle branch reentrant VT. This example of anatomic reentry is usually observed in patients with diseased His–Purkinje system function, complete or incomplete left bundle branch block during sinus rhythm, and a nonischemic dilated cardiomyopathy. The incidence of bundle branch reentry as the cause of sustained monomorphic ventricular tachycardia ranges from less than 1 to 6 % [38]; this form of VT most often has a left bundle branch block, left superior axis morphology. It is typically initiated by a ventricular premature beat that follows a pause. The premature impulse blocks in the retrograde direction within the right bundle but conducts transseptally to retrogradely activate the left bundle. When the impulse reaches the His bundle, it is able to engage the right bundle in the anterograde direction and then continues back to the left bundle (Fig. 15.20). It is important to recognize this form of tachycardia since it is readily curable by radiofrequency catheter ablation of the right bundle.

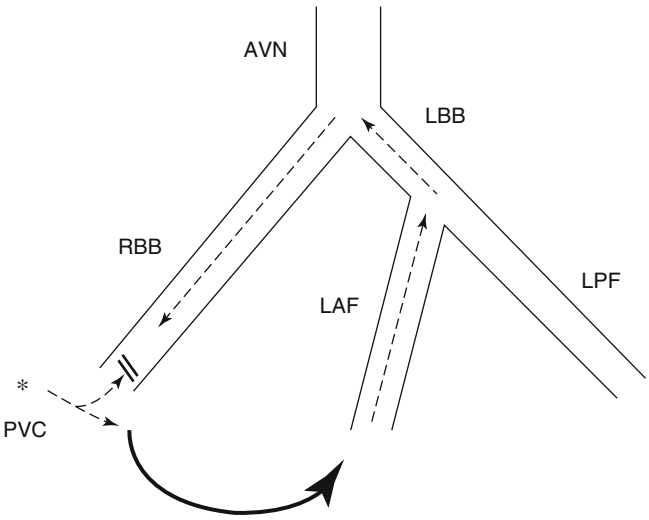

Fig. 15.20 Bundle branch reentry circuit, utilizing the left anterior fascicle (*LAF*) as the retrograde limb of the circuit and the right bundle branch (*RBB*) as the anterograde limb. *AVN* atrioventricular node, *LAF* left anterior fascicle, *LBB* left bundle branch, *LPF* left posterior fascicle, *PVC* premature ventricular complex, *RBB* right bundle branch Asterisk (*) denotes PVC origin

Functional reentry may be responsible for the initiation of ventricular arrhythmias in patients with Brugada syndrome, although some data suggest an alternative mechanism [39]. These patients, first described in 1992 [40], present with an ECG pattern of right bundle branch block, right precordial downsloping ST segment elevation (leads V1–V3) with a normal QTc interval, and have no evidence of structural heart disease. ST segment elevation is due to relatively early epicardial repolarization with respect to the endocardium and results from greater expression I_{to} and I_{ks} in the epicardium. There is evidence that Brugada syndrome is a primary electrical disease, and in some families it has been linked to mutations causing loss of function in a sodium channel (SCN5A) [41]. This results in an outward shift of the balance of current at the end of phase 1 of the action potential, leading to the loss of the action potential dome, preferentially in the epicardial layer. The subsequent abbreviation of the action potential at some epicardial sites leads to the substrate for phase 2 reentry. Phase 2 reentry has been studied in a canine model of simulated ischemia, where loss of epicardial action potential dome (after exposure to a K^+ channel opener) gives rise to ST-segment elevation (Fig. 15.21) [42].

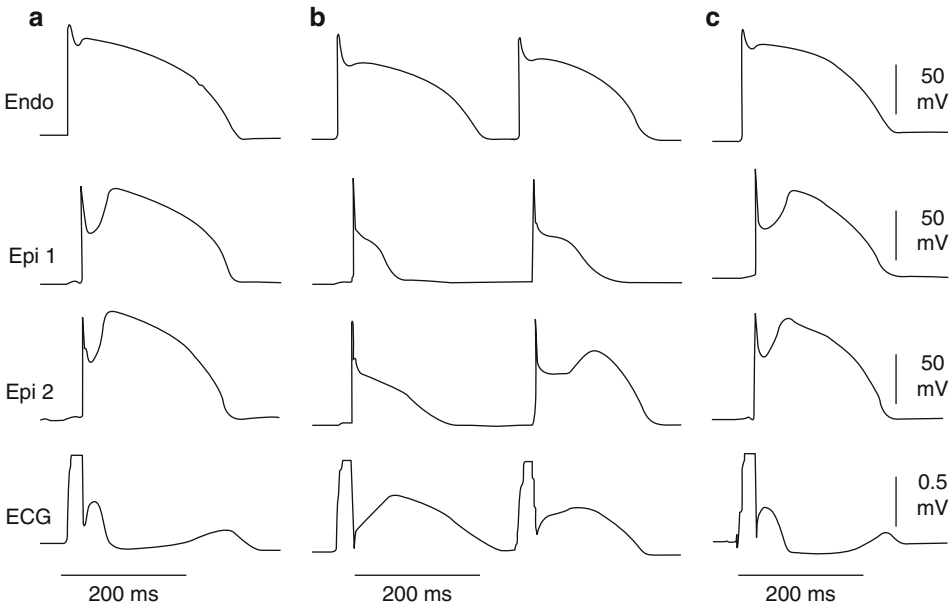

Fig. 15.21 Loss of epicardial AP dome after exposure to K^+ channel opener gives rise to ST-segment elevation in arterially perfused RV wedge preparation. (**a**) Control. (**b**) Pinacidil (causes loss of action potential dome in epicardium and marked abbreviation of the action potential duration, resulting in a transmural voltage gradient). (**c**) Recorded 2 min later in continued presence of pinacidil. *Endo* endocardial layer, *Epi* epicardial layer(s). *ECG* electrocardiogram (Reprinted from Yan and Antzelevitch [42]. With permission from Lippincott Williams & Wilkins)

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Treatment of Cardiac Arrhythmias

16

Suraj Kapa and Francis E. Marchlinski

Introduction

The treatment of cardiac arrhythmias comprises a choice between a broad array of options, ranging from noninvasive pharmacologic means to invasive procedures including cardiac ablation and implantable cardiac devices. The choice and timing of treatment may often vary between patients and depends on the clinician's interpretation of the cause of the patient's arrhythmia, the frequency with which it occurs, and the clinical situation in which it is first diagnosed. For example, an incident episode of atrial fibrillation noted post-cardiac surgery may or may not lead to the addition of medical therapy depending on the duration of the episode and the perceived likelihood of recurrence. Several guideline statements exist regarding the choice of different therapies for different diseases and offer a thought-based structure from which to approach the patient presenting with a cardiac arrhythmia. However, the approach to the patient will always comprise a wide variety of options that may all prove reasonable and thus require decisions based on the patient's unique clinical scenario and consideration of the pathophysiologic mechanisms surrounding the arrhythmia. In this chapter, we focus on the different options for treating cardiac arrhythmias and the mechanisms by which they work, and then offer a disease-based approach in discussing their application to therapy.

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Specific Therapies

Antiarrhythmic Drugs

Antiarrhythmic drugs play an important role in the treatment of all cardiac arrhythmias, both as first- and last-line options depending on the clinical situation. They may be used as primary prevention, as when used prior to and after open heart surgery to prevent atrial fibrillation; secondary suppressive therapy, as in the case of a patient presenting with symptomatic atrial fibrillation in whom the goal is to prevent further episodes; and immediate arrhythmia termination, as with a patient presenting with the acute onset of a reentrant supraventricular tachycardia. The decision on which treatment to use includes considerations of patient comorbidities, pharmacokinetic variables, and the pathophysiology underlying the type of arrhythmia being treated.

Electrophysiologic Effects

The goal of antiarrhythmic drugs is to exert effects on various phases of the action potential to alter cell membrane polarization, thereby changing the likelihood of electrical activation of the cell (Fig. 16.1). Antiarrhythmic drugs are thus classified most commonly in the Vaughan Williams classification, which categorizes agents according to their predominant electrophysiologic effects as recorded from Purkinje fibers during in vitro studies. However, many antiarrhythmic drugs may overlap classes in terms of electrophysiologic effect and also may have metabolites with varying degrees of antiarrhythmic activity.

There are two main mechanisms underlying arrhythmogenesis where antiarrhythmic drugs work – abnormal automaticity and reentry. Automaticity, which mediates arrhythmias such as atrial tachycardia and some ventricular tachycardias, may be suppressed by antiarrhythmic drugs by decreasing the slope of phase 4 depolarization, hyperpolarizing the resting membrane potential, and shifting the threshold

C. Rosendorff (ed.), *Essential Cardiology*,
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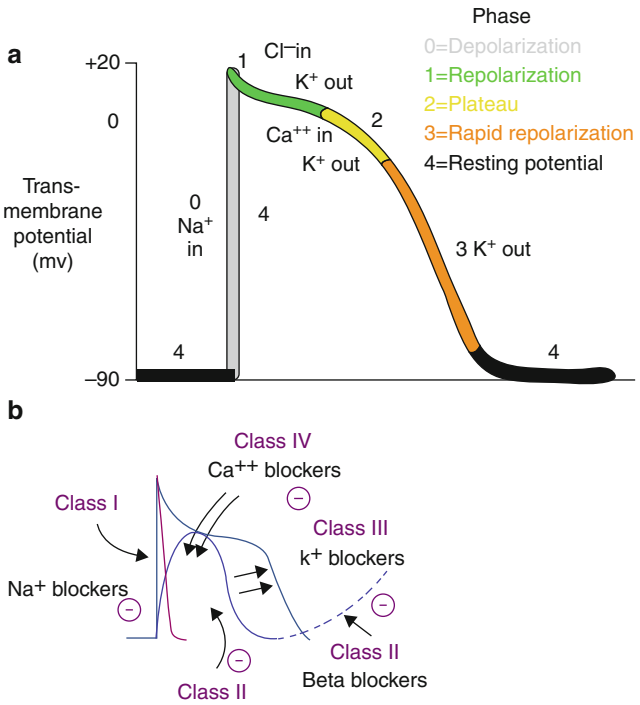

Fig. 16.1 Action potential effects of antiarrhythmic drugs - depicted is the normal action potential and the primary ion fluxes that characterize each phase (**a**). In (**b**) the primary point of action of the different Vaughan Williams classes of antiarrhythmic drugs are shown

voltage to a less negative level. Thus, drugs that affect automaticity may also impact normal pacemaker cells, though they tend to have a relative greater effect on ectopic foci.

Drug treatment of reentry, which mediates scar-related ventricular tachycardia, atrial flutter, atrioventricular (AV) nodal reentry, and AV reentry, involves the alteration of circuit characteristics to affect either refractoriness or conduction of cells comprising the abnormal circuit. Reentrant arrhythmias may be treated by slowing conduction through the circuit, thus abolishing reentry or by increasing refractoriness so that the reentrant wave front impinges on refractory tissue (Fig. 16.2).

Classes of Antiarrhythmic Agents and Specific Drugs

Antiarrhythmic drugs are divided into several classes based on their mechanism of action (Table 16.1). While the classic classification scheme is the Vaughan Williams system, another system, termed the Sicilian Gambit, may also be used. In this latter system, drugs are associated with the ion channels affected, receptors and pumps on which they act, and the relevant areas of cardiac electrophysiology that are affected. Figure 16.3 demonstrates the Sicilian Gambit classification for some common antiarrhythmic drugs. Discussion of specific antiarrhythmic drugs is beyond the

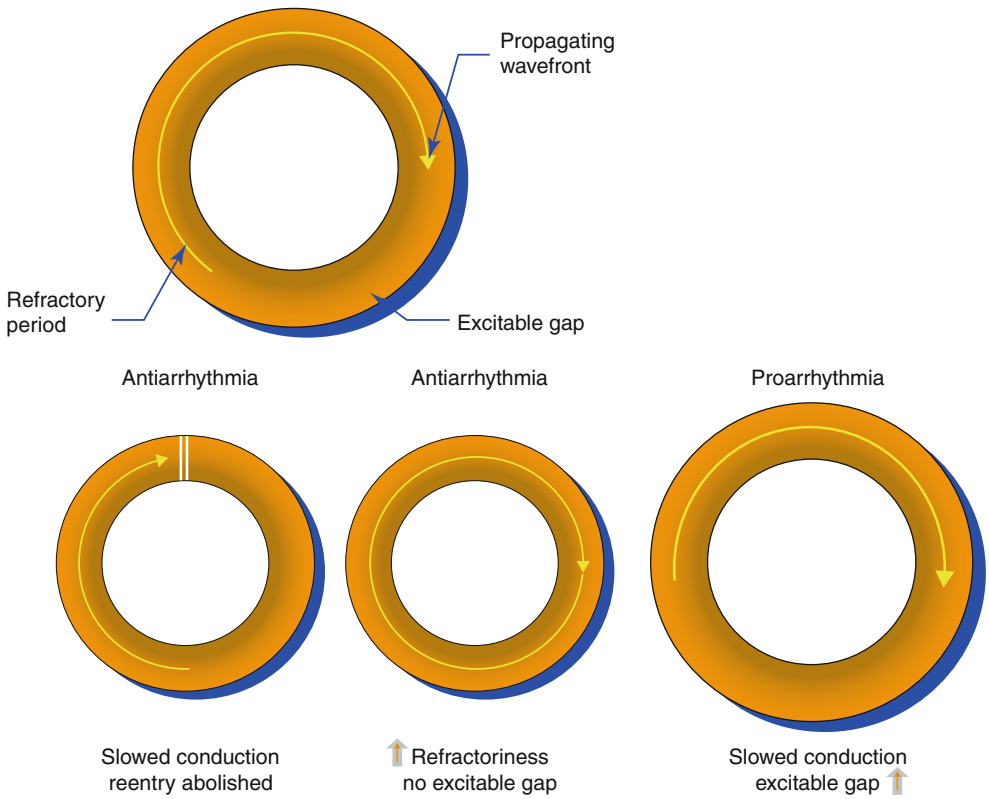

Fig. 16.2 Effects of antiarrhythmic drugs on reentrant circuits – a model of reentry is depicted in (**a**) in which a circuit exists with a critical excitable gap and a region of refractoriness that allows for zones of fast and slow conduction around which a wave front may propagate. Figure (**b**) demonstrates the mechanisms by which antiarrhythmic drugs seek to treat the circuit, either by slowing conduction and thus abolishing the possibility of reentry (*left*) or by increasing refractoriness and thus eliminating the excitable gap (*middle*). However, in some patients, there may be an increase in the size of the excitable gap along with slowing in conduction that may result in a pro-arrhythmic state (*right*)

Table 16.1 Vaughan Williams classification of antiarrhythmic drugs

Class	Mechanism	Drugs
I	Sodium channel blockers	
Ia	Decrease phase 0 upstroke	Disopyramide
	Delay conduction	Quinidine
	Prolong repolarization	Procainamide
Ib	Decrease phase 0 upstroke in abnormal tissue	Lidocaine
	Little phase 0 effect in normal tissue	Mexiletine
	Shorten repolarization or little effect	Tocainide
		Phenytoin
Ic	Decrease phase 0 upstroke	Flecainide
	Slow conduction markedly	Propafenone
	Slight repolarization effect	Moricizine
		Encainide
II	Beta-blockade	Various drugs including metoprolol, propranolol, and esmolol
III	Prolongation of repolarization through potassium channel effects primarily	Amiodarone
		Sotalol
		Ibutilide
		Dofetilide
		Azimilide
		Tedisamil
IV	Calcium channel blockers	Verapamil
		Diltiazem

scope of this chapter and will be discussed below under "Treatment of Specific Arrhythmias".

Class I: Sodium Channel Blockers

Sodium channel blockers decrease the automaticity of cells by decreasing the slope of phase 4 depolarization and thus increasing threshold potential, requiring a greater depolarization to open the sodium channel. The time constant for recovery of the sodium channel from block is used to divide this class into three subclasses and is predictive of the extent to which a drug will decrease conduction velocity through sodium-dependent tissue.

Class Ia

Class Ia antiarrhythmics decrease phase 0 upstroke velocity, delay conduction velocity, and often have some potassium blocking effect, decreasing the outward potassium current and thus increasing the refractory period of cell membranes, thereby prolonging repolarization. Examples include quinidine, procainamide, and disopyramide.

Class Ib

Class Ib antiarrhythmics block sodium channels, which activate during late phase 2 of the action potential, and thus shorten repolarization. Compared to class Ia agents (which

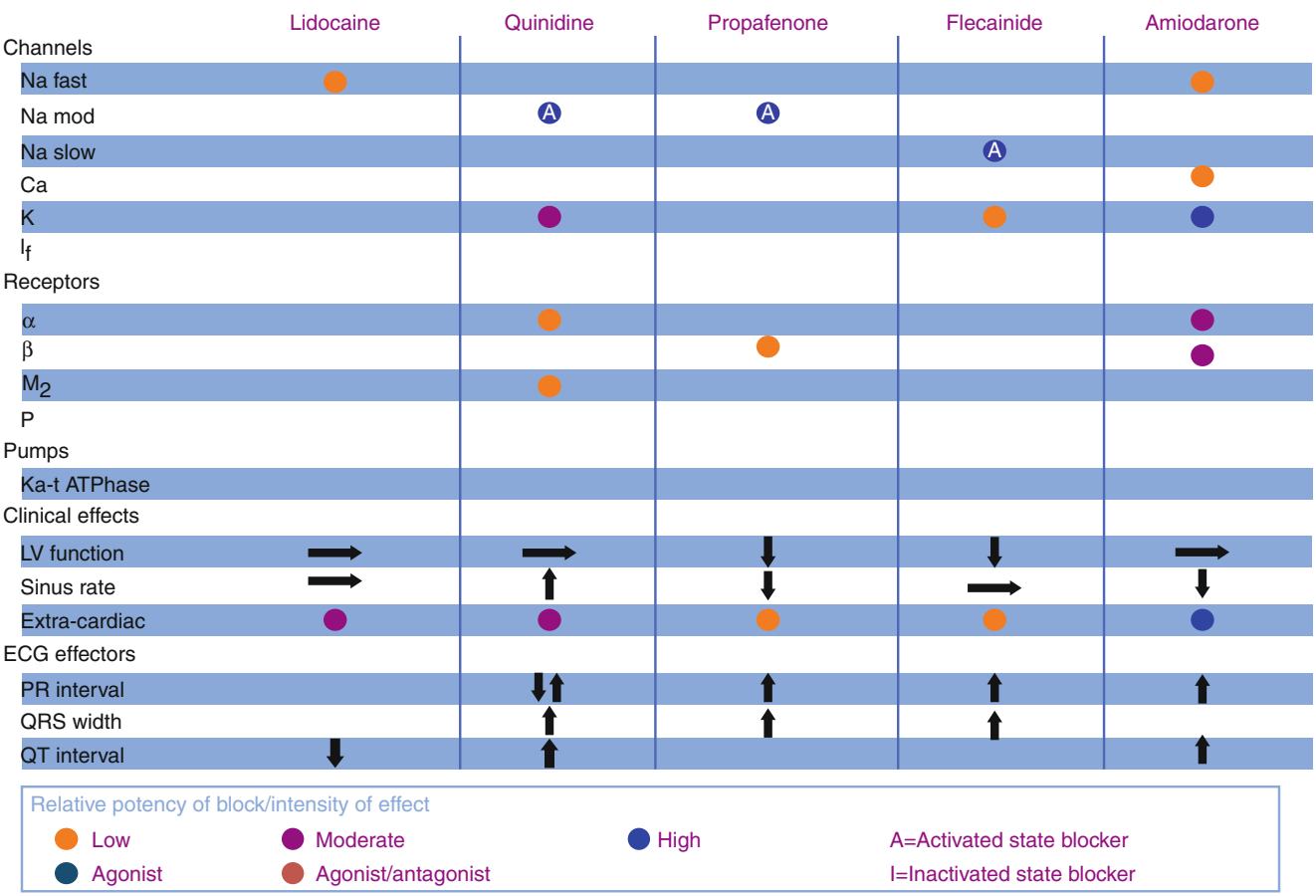

Fig. 16.3 Sicilian Gambit classification of select antiarrhythmic drugs. *F* fast, *M* medium, *S* slow, *Ca* calcium, *K* potassium, *If* funny current, *LV* left ventricle, *PR* PR interval, *QRS* QRS width, *QT* QT interval, *Na-K ATPase* sodium potassium ATPase

bind preferentially to open sodium channels), class Ib agents bind to both open and inactivated sodium channels. Therefore, they are most useful in blocking rapidly driven channels and have little effect on normal cardiac tissue. They are most useful in cases of myocardial ischemia where ischemic myocytes tend to fire more frequently and spend more time in the open state. Examples include lidocaine, mexiletine, tocainide, and phenytoin.

Class Ic

Class Ic antiarrhythmics are potent blockers of the sodium channel and markedly decrease the rate of phase 0 upstroke of ventricular cells. They are useful in the prevention of premature ventricular contractions (PVCs) as well as supraventricular tachycardia (SVT) and atrial fibrillation. However, they can also markedly depress cardiac function and thus should not be used in patients with heart failure [1, 2]. Examples include flecainide, propafenone, and moricizine.

Class II

Class II antiarrhythmics are beta-adrenergic antagonists and inhibit sympathetic input to the sinoatrial (SA) and AV nodes. Antiarrhythmic effects are achieved through two mechanisms: decreasing the rate of phase 4 depolarization (which results in decreased automaticity) and prolonging repolarization (which decreases the incidence of reentry). This leads to negative chronotropic effects which reduce cardiac output and therefore decrease myocardial oxygen demand.

Beta-antagonists are used for treatment of both supraventricular and ventricular arrhythmias and have been shown to reduce mortality after myocardial infarction. Side effects include muscle spasm (bronchospasm, cool extremities, and impotence), bradycardia, decreased cardiac output, hypotension, and depression or insomnia due to CNS penetration of the drug.

Class III

Class III antiarrhythmics block potassium channels, causing a longer plateau phase and prolonging repolarization. This increases the refractory period and decreases the incidence of reentry. However, prolongation of the plateau phase can also increase the chance of early after depolarizations and in rare cases increases the risk of torsade de pointes. Specific examples include amiodarone, sotalol, ibutilide, dofetilide, and dronedarone [3].

Class IV

Class IV agents block calcium channels, acting preferentially on the calcium-channel-dependent SA and AV nodal tissues. These agents have little effect on tissues which are more dependent on fast sodium channels (such as atrial and ventricular muscle). Calcium channel blockers slow the rise of phase 0 of the action potential in the SA and AV nodes (thus slowing conduction velocity) and also prolong AV nodal repolarization (thus increasing the effective refractory period of the AV node). Therefore, these agents are effective in treating AV-nodal-mediated reentrant arrhythmias. They may also suppress some forms of idiopathic ventricular tachycardia (VT) or ventricular arrhythmias associated with coronary artery spasm.

Calcium channel blockers differ in terms of which subtype of voltage-gated channel they preferentially bind to. There are three classes of calcium channel blockers: the dihydropyridines, the benzothiazepines, and the phenylalkylamines. All three classes block L-type calcium channels (responsible largely for myocardial contractility, SA node pacemaker rate, and AV node conduction velocity), but each binds to a different second channel. Toxicities include negative chronotropic and inotropic effects.

Antiarrhythmic Drugs Not in the Vaughan Williams Classification

Adenosine

Adenosine stimulates the P1 class of purinergic receptors and leads to opening of the G protein-coupled potassium channel, thus inhibiting SA nodal, atrial, and AV nodal activation (with the SA node being more sensitive to its effects than the AV node). Adenosine also inhibits cAMP-induced calcium influx and suppresses calcium-dependent action potentials. This drug has an extraordinarily short half-life (less than 10 s). It is useful in the conversion of SVT to normal sinus rhythm (effective in 90 % of cases) and is often used to aid in diagnosis of tachycardia mechanism by slowing AV node conduction. Side effects include headache, flushing, chest pain, and bronchoconstriction, as well as transient arrhythmias at the time of administration.

Digoxin

Digoxin is a cardiac glycoside which selectively inhibits the plasma membrane sodium/potassium pump, leading to decreased expulsion of sodium and increased intracellular sodium concentrations. This in turn leads to a decrease in calcium efflux and increase in calcium influx and a net rise in intracellular calcium, facilitating cardiac contractility. Digoxin at higher doses also inhibits sympathetic outflow, increasing vagal tone. Lastly, digoxin acts directly on the cardiac conduction system, decreasing automaticity of the AV node, prolonging the effective AV nodal refractory period, and slowing AV nodal conduction. Therefore, digoxin is useful in the treatment of atrial fibrillation and other atrial arrhythmias with a rapid ventricular response. However, digoxin toxicity, in addition to causing high-grade AV block, can also enhance automaticity of the infranodal conduction system. Toxicity can thus lead to accelerated idioventricular rhythms or bidirectional VT in addition to AV dissociation.

Digoxin has a narrow therapeutic window and is excreted primarily by the kidneys; therefore, patients with renal

failure often have reduced clearance and increased drug levels. Additionally, hypokalemia increases the myocardial concentration of digoxin, as it has a higher affinity for the phosphorylated sodium/potassium pump, and reduced extracellular potassium levels result in increased sodium pump phosphorylation. Unfortunately, digoxin also interacts with many other drugs, including beta-adrenergic blockers (increased risk of complete heart block through decreased AV nodal conduction), calcium channel blockers (opposed action through decreased cardiac contractility), and potassium-wasting diuretics (which increase affinity of digoxin for the sodium/potassium pump). Administration with verapamil or quinidine, which decreases renal clearance of digoxin, can increase plasma levels. Additionally, antibiotics can often kill enteric bacteria which normally metabolize digoxin.

Toxic digoxin levels can lead to AV nodal block, ventricular ectopy, and junctional or fascicular tachycardias (at levels above 2–3 ng/mL). Treatment in the case of toxicity should include normalization of serum potassium levels, minimizing ventricular arrhythmia potential via treatment with lidocaine, and use of anti-digoxin antibodies.

Catheter-Based Cardiac Ablation

The concept of ablation therapy was first introduced in the late 1970s and first proven in humans in 1981 via studies demonstrating that delivery of high-energy direct current shocks through intracardiac electrodes could produce complete heart block in patients with atrial fibrillation and uncontrolled ventricular rates. This technique evolved over time to the use of high-frequency alternating current, which caused less barotrauma, and ultimately to the use of radiofrequency, which allowed for the creation of small lesions with a high degree of operator control. The goal of catheter-based cardiac ablation is the modification of arrhythmogenic substrate contributing to the genesis and propagation of cardiac arrhythmias. Modern-day ablations are complex, involving the use of advanced mapping techniques, fluoroscopy, technology to control catheter manipulation ranging from specialized sheaths to magnetic navigation systems, and novel energy systems including cryo-based ablation. The most common form of ablation used is radiofrequency energy.

Goals of Ablation

The main goal of ablation is to eliminate the continued abnormal propagation of electrical signals through the heart. This may be achieved by specifically targeting the responsible anatomic structure (e.g., the cavotricuspid isthmus [CTI] in the case of CTI-dependent flutter or an atrial tachycardia focus) or isolating an arrhythmogenic anatomic structure (e.g., creating ablation lesions circumferentially around the pulmonary vein ostia) (Table 16.2). In turn, to determine whether or not adequate ablation has been performed, a variety of stimulatory pacing maneuvers and drug infusions may be used to try and reinduce the arrhythmia. However, depending on the arrhythmia being targeted, non-inducibility at the end of the case and likelihood of long-term cure may or may not be correlated. This is discussed in more detail under the treatment of specific arrhythmia syndromes.

Surgical Ablation

The goal of surgical ablation is similar to that of catheter-based ablation but often involves performing the procedure under bypass in the operating room. The most common currently performed surgical ablation procedure is open surgical MAZE for atrial fibrillation. This procedure may be performed with cryoenergy, radiofrequency energy, or newer techniques such as laser, microwave, or ultrasound. The goal of a surgical MAZE is to isolate the pulmonary veins and effectively "septate" the atria so as to create electrically isolated areas and impair the ability for stimulatory signals that would usually provoke or maintain atrial fibrillation from

Table 16.2 Arrhythmias treated with catheter ablation

Arrhythmia	Target of ablation	Success rate (%)
Arial flutter	Cavotricuspid isthmus	>90
AV nodal reentrant tachycardia (AVNRT)	Slow AV nodal pathway	>98
AV reciprocating tachycardia	Accessory pathway	>98
Atrial fibrillation		
Palliative	AV node	>99
Curative	Pulmonary veins ± linear lesions	>70 (depending on substrate)
Atrial tachycardia	Automatic atrial focus	>80
Sinoatrial reentrant tachycardia	Sinus node	>95
Inappropriate sinus tachycardia	Superior crista terminalis region	>75
Idiopathic ventricular tachycardia	Focus of abnormal automaticity or fascicle	>95
Reentrant ventricular tachycardia	Slow conduction zone in area of scar	~60–70

conducting into the atria. While not as common today, open heart surgery also used to be the principal technique by which accessory pathways were treated prior to the development of more advanced mapping techniques and catheters. In addition, VT ablation may be performed surgically with the primary goal of scar modification, including scar resection in order to remove arrhythmogenic substrate (including subendocardial resection) or ablation of areas of scar (achieved by applying cryo- or laser ablation lesions to a region of visualized scar). The limitation of surgical approaches, however, is the lack of ability to study the electrophysiology during the procedure and, thus, the lack of clear endpoints to determine if sufficient lesion sets have been created or if other arrhythmogenic foci have been missed.

Anticoagulation

Multiple clinical trials and guideline statements support the use of long-term anticoagulation for stroke prevention in high-risk patients with atrial fibrillation or atrial flutter. Anticoagulation options include parenteral (heparin, argatroban), subcutaneous (low molecular weight heparins such as enoxaparin and dalteparin), and oral (warfarin, dabigatran, rivaroxaban) agents, in addition to antiplatelet agents such as aspirin or clopidogrel. The choice of therapy often depends on the patient presentation and the rapidity with which anticoagulant effect needs to be achieved, with parenteral and subcutaneous forms of heparin often used to achieve immediate anticoagulant effect, while transition is made to an oral agent such as warfarin. In this section, we will discuss specific oral anticoagulant options. Their indications for use will be discussed under "Treatment of Specific Arrhythmias".

Oral Agents

Warfarin

Warfarin, a vitamin K antagonist, has been approved for use as a medication since the 1950s. Anticoagulation is achieved by inhibiting vitamin K epoxide reductase, an enzyme that recycles oxidized vitamin K to its reduced form after it has participated in carboxylation of several blood coagulation proteins, including prothrombin and factor VII. When warfarin is initiated, several days are often required before clotting factors disappear in the metabolism and full anticoagulation is achieved. Duration of action of a single dose of warfarin is 2–5 days. The therapeutic effect of warfarin exists within a narrow therapeutic window as dictated by the prothrombin time – international normalized ration (INR), and there is considerable inter- and intra-individual dose variability that may be impacted by a wide range of physiologic (e.g., liver and thyroid function), genetic, and environmental (e.g., diet and other drugs) factors. Thus, regular monitoring of the INR is required to avoid excessive or insufficient anticoagulant effects. However, warfarin's anticoagulant effects may be reversed via a variety of means ranging from administration of vitamin K (which may take several hours) to administration of clotting factors intravenously (which may offer faster reversal).

Dabigatran

Dabigatran is a direct thrombin inhibitor given at a fixed dose twice daily without requiring the need to monitor the INR or other clotting parameters. The drug has limited drug–drug interactions, the most significant of which is with other P glycoprotein pump inhibitors, such as proton pump inhibitors, which may impair absorption, and quinidine, verapamil, or amiodarone, which may impair excretion. The drug also has a short half-life compared with warfarin (12–17 h versus 2–5 days). Its therapeutic effect is also impacted by renal function, requiring dose reductions in patients with acute or chronic renal failure (dialysis may reduce dabigatran levels by as much as 66 % within 2 h). The onset of action of dabigatran is rapid, with full anticoagulant effect being achieved in 2 h. There are no currently available agents capable of reversing the anticoagulant effect of dabigatran. Various assays exist to monitor the degree of anticoagulant effect with dabigatran, such as the ecarin clotting time (ECT) and chromogenic assays, though they are not widely available [4].

Rivaroxaban and Apixaban

Rivaroxaban and apixaban are oral direct factor Xa inhibitors that are oxazolidinone derivatives. These drugs bind to the catalytic/active site of factor X, thus directly interfering with the coagulation cascade. They have predictable pharmacokinetics and allow for fixed dosing. Similar to dabigatran, their half-lives are also under 12 h, and means of reversal of anticoagulant effects are not currently available. Monitoring of the anticoagulant effect of these drugs is possible using anti-factor Xa levels, though these assays are not widely available [4].

Implantable Cardiac Device Therapy

Cardiac devices have evolved since their initial use in the 1950s, including the development of smaller generators, more advanced programming allowing for more physiologic pacing, and improved diagnostic capabilities. Broadly, implantable cardiac devices include pacemakers, defibrillators, and cardiac resynchronization devices. All defibrillators have pacemaker capabilities, though pacemakers do not have the capability to defibrillate.

Generator and Leads

A pacemaker or defibrillator system consists of the lead or leads and the pulse generator to which the lead(s) attach. The generator acts as the central processing unit which is

programmed with certain parameters to deliver therapies in response to preset sensing parameters. The average battery life of a device is dependent on how much it is used, with more frequent use resulting in a shorter battery life. Modern pacemakers will indicate when battery life is being depleted past a certain set threshold called an elective replacement indicator (ERI). Once ERI is reached, the device has several months prior to reaching end of life (EOL). Once the battery is at EOL, depending on the make and model of the device, the response may include stepwise changes in the pacing rate or change of the pacing mode to an asynchronous mode in which the device continuously paces without consideration for the underlying rhythm. Most modern devices will deliver an audible tone when ERI is reached that indicates to the patient that the device requires follow-up.

Leads used for cardiac pacing or defibrillation may be unipolar or bipolar. Unipolar leads include a single cathode at the lead tip with the pacemaker generator acting as the anode. Bipolar leads, however, have both the cathode and anode near the distal end of the lead, with the tip acting as the cathode and the proximal ring acting as the anode. Generally, bipolar leads are preferred because they tend to reduce over-sensing of myopotentials and far-field signals, reduce the frequency of crosstalk, and allow for more pacing configurations including bipolar and unipolar. However, given the greater complexity in design, bipolar leads may have a slightly greater failure rate than unipolar leads, though with modern lead design that difference is small.

A lead may be placed endocardially or epicardially. Endocardial leads are placed via a fluoroscopic approach and can be actively or passively fixated. Passive fixation uses leads with tines or wings at the tips that get trapped in the trabeculae of the right atrium or ventricle. Active fixation involves deployment of a screw into the atrial or ventricular myocardium. Modern endocardial leads are also steroid eluting to diminish the inflammatory reaction at the interface between the electrode and myocardium and thus promote better thresholds and sensing acutely and chronically. Epicardial leads are typically sewn onto the epicardium surgically and are more commonly used for pediatric patients, though may also be used in adult patients in whom endovascular access is not possible or not desired (e.g., in a patient with recurrent infective endocarditis who has pacing needs).

Pacemaker Nomenclature

The nomenclature indicating the pacing mode programmed into a device is defined by a set of standards established in 2002 by the North American Society for Pacing and Electrophysiology and the British Pacing and Electrophysiology Group. The letters used indicate the chambers that are being paced, the chambers that are being sensed, the response to sensing, how the rate is modulated, and whether multisite pacing is used in either or both chambers (Table 16.3). This results in a short three to five letter summary of the pacing mode that defines key aspects of pacemaker programming.

Pacing Modes

The most common pacing modes include AAI or VVI if a single chamber atrial or ventricular pacemaker, respectively, or DDD if the device is dual chamber. One exception is a VDD mode which can be programmed with special types of leads used in patients in whom fewer leads are preferred, and only atrial sensing but not atrial pacing is required (e.g., with a young patient presenting with complete congenital heart block). Another special case is DDI pacing which is often programmed as a "mode switch" from DDD when a patient is in an atrial tachyarrhythmia and tracking of atrial activity is not desired.

In some devices, special modes are available to limit the frequency of ventricular pacing. The reasoning behind these modes is that chronic right ventricular only pacing can be deleterious to cardiac function. However, in some patients, due to prolonged intrinsic AV delay or Wenckebach phenomenon, there may be infrequent loss of AV conduction that is not necessarily pathologic but for which the device would otherwise pace the ventricle. Thus, the device will allow occasional dropped ventricular beats in the interest of encouraging intrinsic conduction through the AV node rather than forced pacing from the device.

In all pacemakers, a lower rate interval is chosen to define what the lowest allowable intrinsic heart rate is before the pacemaker will begin pacing. Several intervals may also be programmed to define how long a device will wait after an atrial stimulus before pacing the ventricle (AV delay) and how long after a ventricular stimulus the device will wait to respond to another sensed atrial stimulus (post-ventricular atrial refractory period, PVARP), which together define the TARP, or total atrial refractory period. The upper

Table 16.3 NASPE/BPEG nomenclature for pacing modes

Category	Chamber paced	Chamber sensed	Response to sensing	Rate modulation	Multisite pacing
Letter	0 = none	0 = none	0 = none	0 = none	0 = none
	A = atrium	A = atrium	T = triggered	R = rate modulation	A = atrium
	V = ventricle	V = ventricle	I = inhibited		V = ventricle
	D = dual (A + V)	D = dual (A + V)	D = dual (T + I)		D = dual (A + V)

tracking rate is the maximum rate at which the device will track atrial stimuli and stimulate the ventricle in a 1:1 fashion.

Rate responsive pacing is an option available in all modern pacemakers which allows pacemakers to respond to external stimuli, usually either via an accelerometer or a minute ventilation sensor, to determine when a patient may require a higher heart rate. Activation of a rate response sensor will augment the paced heart rate accordingly. This is particularly useful in patients with sinus node dysfunction or complete heart block in the setting of permanent atrial fibrillation in whom the native heart rate may not increase with activity, and thus, the pacemaker will need to respond by pacing at a faster rate to respond to increased physiologic demand.

Defibrillators

Implantable cardioverter defibrillators (ICDs) include all the same functions as a pacemaker with the addition of the ability to deliver rapid burst pacing or single or multiple electrical shocks to the heart in order to terminate a sensed ventricular tachyarrhythmia. ICD generators have several differences from those of pacemakers and are also larger. ICD leads are also inherently different, including either a single or dual coils located along the length of the lead. The coils dictate the path the energy delivered will take during defibrillation (whether between the coil and the generator or between coils). The reason for using different potential defibrillation paths is that different shock polarities may have differing likelihood of defibrillation success.

Prior to defibrillation, however, most ICDs are programmed to deliver at least one if not several rounds of ATP, or antitachycardia pacing. The goal of ATP is to terminate the ventricular arrhythmia without having to deliver a potentially painful ICD shock. ATP consists of delivering a prespecified number of paced beats at a rate a certain percentage faster than the sensed rate of the arrhythmia. Frequently, one or more rounds of ATP will terminate the tachycardia without need for a shock, and particularly with ventricular tachyarrhythmias at lower rates which may be hemodynamically tolerated, several rounds of ATP will be offered prior to delivering the first ICD shock.

Given the increased morbidity and mortality associated with both appropriate and inappropriate ICD shocks, the goal of programming in ICDs is to limit the need for shocks by programming ATP while also trying to optimize the ability of the device to discriminate VT from SVT. Various programming options, including discriminators used to differentiate the two types of arrhythmia based on morphologic similarity of ventricular signals to those in sinus, the rapidity of onset of the arrhythmia, and the regularity of the ventricular rate, can be used to help avoid inappropriate shocks.

Implantation Considerations

The decision to implant requires close consideration of periprocedural risks (Table 16.4) as well as understanding of appropriate device programming. Implantation requires use of fluoroscopy to determine lead placement and sterile conditions to avoid risk of infection. Patients will generally stay in the hospital overnight to rule out pneumothorax (if the axillary or subclavian vein is accessed via percutaneous stick), to evaluate the incision site for hematoma, and to evaluate device function to ensure that the lead has not migrated or dislodged. It may take as long as 4–6 weeks after initial implant before leads have fibrosed into the myocardium and, thus, the potential for lead dislodgement or migration exists for several weeks after initial implant.

External Direct Current Cardioversion

External direct current cardioversion is a mainstay of the acute treatment of both stable and unstable arrhythmias. The goal of cardioversion is to immediately return a patient back to a normal rhythm by applying a prespecified amount of electric energy to the heart. Electrical energy may be applied in a synchronized or asynchronous fashion through a set of two pads placed in either the anteroposterior or anterolateral positions on the patient's chest. Generally, asynchronous shocks are used to treat polymorphic ventricular arrhythmias, while synchronous shocks are used to treat supraventricular arrhythmias. A synchronous shock allows the automatic

Table 16.4 Complications associated with pacemaker and ICD implantation

Complication	Treatment
Lead complication	
Acute perforation	Reposition the lead, monitor for pericardial effusion, rarely pericardiocentesis or surgery
Dislodgement of lead	Repositioning of the lead
Infection	Antibiotics, usually requires explantation and implantation of new system on opposite side
Venous thrombosis	Anticoagulation or venoplasty, rarely thrombolysis if superior vena cava syndrome presence
Pocket complication	
Pocket hematoma	Observation, rarely open evacuation if large, consider pressure dressing
Infection	Antibiotics, usually requires explantation and implantation of new system on opposite side
Erosion	Treat as infection if pacemaker system has eroded through the skin, if not can relocate pocket
Pacemaker migration	No treatment if no associated discomfort, rarely requires revision of skin pocket

external defibrillator (AED) to deliver a shock at a specific point in the cardiac cycle corresponding to the R wave of the QRS complex on the ECG, thus preventing delivery of a shock during the relative refractory period of the cardiac cycle, which may rarely induce ventricular fibrillation. Asynchronous shocks are applied when a patient is hemodynamically unstable or unconscious and the patient is either in a disorganized ventricular tachyarrhythmia or the rhythm is not readily identifiable at the time of clinical evaluation. While immediate cardioversion in the unstable, unconscious patient is necessary if hemodynamic instability is felt to be secondary to the clinical arrhythmia, if a patient is awake and alert and not decompensated hemodynamically, care should always be taken to fully sedate the patient given the discomfort associated with cardioversion. Most modern-day AEDs are biphasic, giving two sequential lower energy shocks of 120–200 J with each shock moving in an opposite polarity between the AED pads. These types of AEDs have proven more effective in clinical trials with a reduced rate of complications compared with monophasic devices which deliver the entire amount of prespecified energy in one shock. If initial attempt at defibrillation fails to terminate an arrhythmia, higher energy or two sets of pads with two AEDs may be used. The keys to efficacy of cardioversion include contact of the pads with the skin and use of a sufficiently high energy to affect the heart.

Wearable External Defibrillators

Wearable external defibrillators allow patients to receive the benefit of arrhythmia monitoring and defibrillation at home when they either cannot receive ICDs for other reasons, such as resolving bloodstream infection, or do not yet meet criteria for ICD implantation but are nevertheless considered high risk for sudden death. These defibrillators are vests sized to the patient and worn continuously while the patient is not in a monitored setting. They detect when the ventricular rate exceeds a prespecified threshold and then deliver a shock to try and restore normal rhythm. Multiple shocks can be delivered by the same vest in succession. The vest alerts the patient prior to delivering the shock in case of inappropriate detection or if the patient is still conscious so that they may manually abort the shock. Clinical trials have suggested that the vest is safe and effective in preventing sudden death in patients who are at high risk [5].

Temporary Pacing

Temporary cardiac pacing may be required in the setting of sustained symptomatic or hemodynamically untolerated bradyarrhythmias. In addition, in cases of potentially unstable rhythms, such as Mobitz II block or paroxysmal AV block, temporary pacing may be required to avoid the sudden loss of conduction in the absence of a stable underlying escape rhythm. The options for temporary pacing include leads placed either transvenously or epicardially or transcutaneous pacing with pads placed over the thorax. Transvenously placed leads are the most commonly used in acute scenarios requiring potentially long periods of pacing and may be placed at the bedside though are ideally placed under fluoroscopy. Placement is similar to that of a Swan–Ganz catheter, with use of an introducer placed ideally in the right internal jugular or left subclavian vein and then a pacing wire introduced into the heart. If placed at the bedside without fluoroscopy, balloon-tipped "floating" catheters should be used to reduce the risk of perforation. If balloon-tipped catheters are not available, placement of the pacing catheter under ECG guidance while delivering a pacing stimulus through the wire is a possible alternative in emergent situations. In certain cases, such as after prior mechanical tricuspid valve replacement, crossing the tricuspid valve may not be feasible, and thus, coronary sinus cannulation may be used to attain ventricular capture, though higher pacing outputs may be needed. Coronary sinus cannulation should not be attempted without fluoroscopy. In certain cases where a "temporary" externalized wire is being used for longer periods of pacing due to inability to place a permanent pacemaker (e.g., due to active infection), a permanent pacemaker wire may be placed via an introducer and fixed to ventricular muscle using either an active or passive mechanism. The proximal tip of the wire which is normally attached to the pacemaker generator may then be attached to a temporary pacing box via an adapter. This externalized permanent pacemaker wire allows for a more stable wire position until a fully internalized permanent pacemaker system can be placed.

Temporary epicardial pacing is most often used after cardiac surgery, with leads fixed to atrial and/or ventricular epicardial surfaces and the tips of the wires externalized through the skin. These wires can be removed by applying gentle traction without need for another thoracotomy but will often migrate over the course of several days resulting in eventual loss of capture.

Transcutaneous pacing may be performed using the AED previously described. This technique is often the fastest way of achieving pacing in emergent situations. However, capture may only occur in 60–80 % of patients, and substantial discomfort may be experienced by the unsedated patient. Pads may be placed prophylactically such that, were conduction to be lost, pacing can immediately be started until more definitive measures can be instituted. Because the large pacing artifact from transcutaneous pacing may obscure ECG on telemetry, palpation of the pulse during pacing should be performed to confirm capture.

Evolving Therapeutic Options

There are several therapeutic options that present intriguing options to the treatment of cardiac arrhythmias but are either not yet in widespread clinical use, pending regulatory approval, have not been well studied to date in clinical trials, or are still in experimental phases with only potential benefits. These therapies may serve either as adjuncts to the aforementioned categories of more established therapies or as alternative future means of managing patients.

Subcutaneous ICDs

Subcutaneous ICDs which consist of parasternal, subcutaneous electrodes and generators have been demonstrated in clinical trials to be safe and effective in terminating clinical arrhythmias [6]. They eliminate the need for venous access in patients who do not require a system with both pacing and defibrillation capacity while providing the benefit of an implantable device that can terminate a ventricular tachyarrhythmia. The limitation of these devices is the lack of ability to pace, thus requiring defibrillation to terminate a ventricular tachyarrhythmia which can be painful in the case of a hemodynamically tolerated arrhythmia that may not have resulted in syncope or sudden death. However, brief post-shock pacing for about 30 s is offered by current models of these devices. Thus, in the case of patients with rapid, hemodynamically untolerated ventricular arrhythmias in the absence of any pacing needs and in whom transvenous leads are not desired, subcutaneous ICDs may offer a reasonable alternative.

Left Atrial Appendage Occlusion Devices

The location of greatest concern for thrombus formation in atrial fibrillation is the left atrial appendage. As a result, exclusion of thrombus in this region while on therapeutic anticoagulation is considered sufficient to proceed with cardioversion in patients presenting with atrial fibrillation of unknown duration (see later under "Treatment of Specific Arrhythmias"). However, for patients with concerns regarding taking long-term anticoagulation, left atrial appendage occlusion devices may offer an alternative means by which to prevent thromboembolic stroke. One randomized controlled trial has suggested that a left atrial appendage occlusion device has similar rates of prevention against stroke when compared with warfarin [7]. These devices may be placed minimally invasively via a venous or epicardial approach and occlude the left atrial appendage orifice, eliminating flow into the appendage and thus limiting the possibility of thrombus formation that can later embolize. Several other devices are under investigation, though clarification of indications for and approval of these devices is still pending.

The Choice of Therapy and Assessment of Therapeutic Effect

As with any disease process, the diagnosis and management of a patient presenting with an arrhythmia requires a full evaluation of the patient, their symptoms, the clinical impact of the arrhythmia, and the setting in which their arrhythmia occurs. For example, the acute treatment of a patient presenting with ventricular fibrillation due to an acute coronary occlusion will require emergent defibrillation, but may not require addition of any additional long-term therapy once the coronary occlusion is successfully treated and if cardiac function improves. Furthermore, a single asymptomatic episode of an atrial tachyarrhythmia noted in the hospital during another acute illness may not require additional therapy if no further recurrences are seen in the ambulatory setting. However, even asymptomatic arrhythmias, such as frequent premature ventricular contractions (PVCs), atrial fibrillation, or atrial tachycardia, may result in negative functional effects (e.g., a depression in left ventricular ejection fraction) that may benefit from suppression or elimination of the clinical arrhythmia. Determining the setting in which the arrhythmia arises, whether a fully reversible arrhythmogenic cause is identifiable, and the clinical relevance of the arrhythmia in terms of symptoms or other negative pathophysiologic effects is key to developing an effective treatment plan.

In certain cases, for example, septic shock, thyroid storm, or drug overdose (e.g., with digoxin), arrhythmias may occur that may or may not recur clinically upon withdrawal of the underlying cause. However, in some patients, presentation with an arrhythmia, such as atrial fibrillation, during another illness may represent the first clinical presentation of an arrhythmia that may have been previously present or for which the substrate exists that was not previously recognized. Furthermore, the clinical manifestation of an arrhythmia due to another cause, such as ventricular fibrillation at the time of myocardial infarction, may portend the possibility of future clinical arrhythmias due to the creation of new arrhythmogenic substrate. Thus, the choice of treatment is dynamic and requires a focus not just on the initial treatment plan but on future risk stratification and follow-up to determine whether a change in therapies may be required.

With any arrhythmia, treatment first needs to be divided into acute and long-term goals. Acute treatment may be considered any intervention done at the bedside to immediately terminate an arrhythmia. Long-term treatment includes instituting specific drugs or referring for invasive therapies such as ablation in the interests of suppression or cure. Decisions regarding the long-term management of arrhythmia patients may occur within hours to days of initial presentation or months to years later.

Once initial treatment decisions are made, consideration of how to determine efficacy of the decided-on therapy is

required. For example, if an antiarrhythmic drug is initiated or an ablation is performed, parameters need to be identified that will allow one to decide whether the therapy was effective. In the case of symptomatic arrhythmias, this may take the role of simply following the patient for symptom recurrence. However, in many patients, symptoms may be nonspecific, or arrhythmias that may result in sudden death or other negative pathophysiologic effects may be otherwise asymptomatic. Thus, symptoms alone may not be an effective means by which to monitor for whether or not treatment was effective in all patients. Other options to monitor for treatment effect include a variety of rhythm monitoring devices, which include implantable loop recorders which continuously record patients' heart rhythms for years and external ambulatory electrocardiographic monitors which can be worn for days to weeks, though are cumbersome to use. The monitoring of arrhythmias is an integral part of treatment planning since adequate cure or suppression cannot always be determined with routine clinical follow-up alone, and treatment decisions depend on understanding the outcome of prior therapies.

Treatment of Specific Arrhythmias

Bradyarrhythmias

The treatment of clinically significant bradyarrhythmias is focused on trying to maintain an adequate ventricular rate, whether by pacing the atria or the ventricles. When clinically evaluating the patient presenting with a bradyarrhythmia, the primary goal preceding choice of treatment is recognizing (1) whether or not the bradyarrhythmia is a primary phenomenon (i.e., due to a disturbance in normal electrophysiology) or a secondary phenomenon (i.e., due to a drug or another clinical event that may induce a slow heart rhythm and is readily reversible), (2) whether or not the patient has symptoms attributable to the slow heart rate, and (3) how urgent treatment of the arrhythmia is.

The clinical presentation of a bradyarrhythmia may range from exercise intolerance in the setting of sinus node dysfunction to syncope with complete loss of consciousness in the case of paroxysmal AV block. Furthermore, sometimes a heart rate that is reasonable for one patient may be excessively low for another patient depending on the clinical situation. For example, a well-trained athlete may have sinus bradycardia in the 40s without any ill effects, while a patient with a severely depressed left ventricular ejection fraction may have a heart rate in the 40s and decompensate due to the attendant decrease in cardiac output. Finally, the urgency of initiating therapy in specific cases needs to be considered, since in some patients, such as those presenting with type 2 second-degree AV block, the presence of a reasonable underlying escape may not be predictable and so the initiation of pacing therapy via temporary wires, prophylactically placed pads, or a permanent pacemaker may be warranted shortly after recognition of the clinical problem.

The other key issue related to bradyarrhythmias is whether or not treatment is needed based on the reversibility of the condition. In some cases, for example, beta-blocker overdose, temporary pacing or use of a sympathomimetic drug such as isoproterenol until the offending drug washes out may be sufficient. Similarly, in patients with a recent large, inferior myocardial infarction, presentation with complete heart block is not uncommon, and normal rhythm may be restored upon reperfusion. However, in other cases a primary cause for the bradyarrhythmia may be identified and may not be able to be withdrawn, and thus, alternative therapies such as a permanent pacemaker may be required.

The treatment of symptomatic bradyarrhythmias for which there is no reversible underlying cause is usually pacing. In some cases, such as after heart transplantation (see later in the text), pharmacologic agents such as isoproterenol or theophylline may be used to augment the heart rate. However, these interventions are considered temporary and are used in hopes that underlying nodal activity or conduction may recover with time. Thus, consideration needs to be given to the physiologic setting, the time period over which one feels comfortable waiting to determine if the condition reverses, and the ultimate best choice of therapy.

Sinus Node Dysfunction

The hallmark of sinus node dysfunction is chronotropic incompetence resulting in inappropriate heart rate during rest or stress. This may take a variety of forms including a normal resting heart rate with inappropriate heart rate response to exercise, sinus pauses due to sudden arrest of nodal activity, or sinus pauses due to a prolonged recovery time when another extra-nodal rhythm that has been suppressing the sinus node (e.g., atrial fibrillation or atrial tachycardia) suddenly stops. In some cases, such as poorly rate controlled atrial fibrillation, treatments such as beta-blockers which are needed to manage the heart rate also may suppress sinus node activity when the patient is not in atrial fibrillation, and thus, the offending agent cannot be withdrawn because of medical necessity to treat the other condition (Fig. 16.4).

There is no clear cutoff regarding heart rate or duration of a pause that can guide decision on whether pacing therapy needs to be offered. Rather, the presence of symptoms or negative physiologic effects attributable to sinus node dysfunction is considered the mainstay in deciding when therapy is needed. If a patient is symptomatic or if sinus bradycardia limits the ability to institute therapies felt to be needed for another medical problem (like poorly rate controlled atrial fibrillation), then pacing therapy may be appropriate.

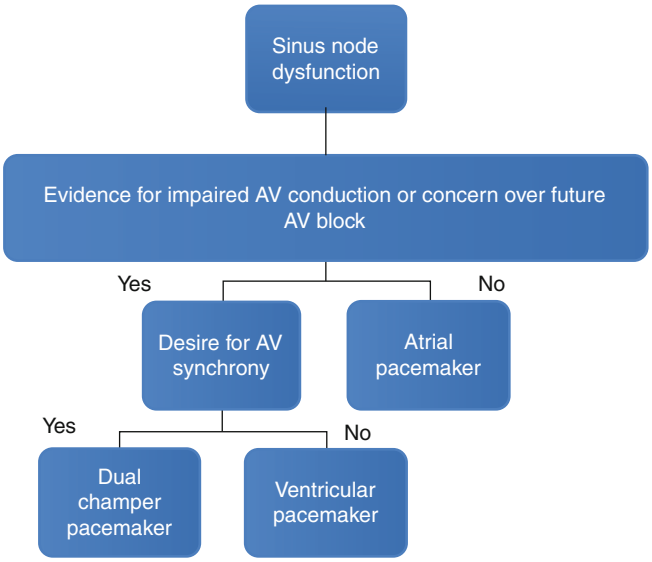

Fig. 16.4 Algorithm regarding decision on pacing in sinus node dysfunction – shown is an algorithm to help determine the type of pacemaker to implant when referred a patient with symptomatic sinus node dysfunction

Acutely, intervention for sinus node dysfunction is rarely needed. Low resting sinus rates are not fatal. It is also rare for a patient to have no underlying sinus rhythm in the setting of a history of paroxysmal atrial fibrillation, though if rate control agents have been aggressively uptitrated, it is possible that a prolonged period of asystole until the sinus node has recovered may occur. If the heart rate needs to be augmented acutely, isoproterenol may be used. However, concomitant drops in blood pressure may limit its use. If support of the ventricular rate is needed because of hemodynamic decompensation due to the low heart rate or due to concern for further periods of asystole in the setting of recurrent atrial tachyarrhythmias, then a temporary pacing wire may be placed. A temporary wire may also be placed when a permanent pacemaker is undesirable due to active infection or other medical comorbidities make recovery from the acute situation unlikely. Ultimately, however, the treatment of choice is placement of a permanent pacemaker. Summarized in Table 16.5 are the guidelines from the ACC/AHA regarding use of pacing in patients presenting with bradyarrhythmias [8]. Consideration may be given to placement of an atria-only pacing system, though generally a dual chamber pacemaker will be placed in cases of sinus node dysfunction due to the possibility of AV node disease that can occur with time in patients with an already diseased SA node.

Atrioventricular and Interventricular Conduction Defects

The pathophysiology of AV conduction defects is discussed elsewhere. Decision to treat AV conduction defects and the acuity with which therapy needs to be instituted depends on the type of defect seen and the clinical situation. As with sinus node dysfunction, even low-grade AV block (i.e., first-degree AV block or type 1 second-degree AV block) may require pacing therapy if symptomatic. First-degree AV block is rarely symptomatic, though if the PR interval is sufficiently prolonged, a pacemaker syndrome-like phenomenon may occur where the patient experiences simultaneous atrial and ventricular activation. Type 1 second-degree AV block (Wenckebach) may also be symptomatic, though the degree of symptoms may depend on the heart rate given that AV conduction tends to delay more with higher rates. Generally, use of isoproterenol may improve conduction across the AV node but will also increase the sinus rate, and thus, response may not be predictable. Furthermore, temporary pacing is rarely required given that both first-degree AV block and type 1 second-degree AV block are not fatal, and the main reason for therapy is associated symptoms.

Type 2 second-degree AV block is a more serious condition often requiring more aggressive management. Patients may present with a history of syncope. The diagnosis requires close attention to episodes of "missed beats" seen on electrocardiographic monitoring to determine whether they represent blocked premature extrasystoles or intermittent loss of conduction below the AV node. If type 2 second-degree AV block is diagnosed, then this suggests a potentially critical condition given the level of disease involves the His–Purkinje system, and thus, the likelihood of the patient having an underlying ventricular escape rhythm is not predictable. Thus, consideration may be given to either placing transcutaneous pads that can be used to deliver pacing therapy should AV conduction suddenly be lost or to placing a temporary pacing wire. Caution should be used with the latter given that if a patient has an underlying left bundle branch block, placement of a temporary pacing wire into the right ventricle without fluoroscopic guidance may "bump" the right bundle and produce complete heart block. Placement of a dual chamber permanent pacemaker should be performed as soon as appropriate resources are available. The use of isoproterenol in this condition is not indicated given the level of disease is below the AV node, and thus, accelerating the sinus rate and AV conduction may actually result in a greater likelihood of arrest of conduction than would be the case in a patient with type 1 second-degree AV block.

Complete heart block often but does not always require urgent placement of a temporary wire. If a patient has a reliable and reasonably fast junctional or ventricular escape in the setting of complete heart block, it may be reasonable to defer placement of a temporary wire or use of transcutaneous pacing until a permanent pacemaker can be placed. Given that symptoms may be due to either loss of atrioventricular synchrony or to the low ventricular rate, consideration needs to be given to which one is mediating the patient's symptoms since a temporary pacing wire or pacing pads will only

Table 16.5 Indications for permanent pacing with sinus node dysfunction and atrioventricular block

Class	Indications
Sinus node dysfunction	
I	1. Documented symptomatic bradycardia including frequent sinus pauses that produce symptoms
	2. Symptomatic chronotropic incompetence
	3. Symptomatic sinus bradycardia that results from required drug therapy for other medical conditions
IIa	1. Heart rate less than 40 when a clear association between significant symptoms consistent with bradycardia and presence of bradycardia has not been documented
	2. Syncope of unexplained origin when clinically significant abnormalities of sinus node function are discovered or provoked in electrophysiological studies
IIb	1. Minimally symptomatic patients with chronic heart rate less than 40 while awake
III	1. Asymptomatic patients
	2. Patients for whom the symptoms suggestive of bradycardia have been clearly documented to occur in the absence of bradycardia
	3. Symptomatic bradycardia due to nonessential drug therapy
Atrioventricular (AV) block	
I	1. Third-degree and advanced second-degree AV block at with bradycardia with symptoms or ventricular arrhythmias presumed due to AV block
	2. Third-degree and advanced second-degree AV block with arrhythmias and other medical conditions that require drug therapy that results in symptomatic bradycardia
	3. Third-degree and advanced second-degree AV block in awake, symptom-free patients in sinus rhythm with documented periods of asystole ≥3.0 s or any escape rate less than 40 or with an escape rhythm that is below the AV node
	4. Third-degree and advanced second-degree AV block in awake, symptom-free patients with atrial fibrillation and bradycardia with one or more pauses of at least 5 s or longer
	5. Third-degree and advanced second-degree AV block after catheter ablation of the AV junction
	6. Third-degree and advanced second-degree AV block associated with postoperative AV block that is not expected to resolve after cardiac surgery
	7. Third-degree and advanced second-degree AV block associated with neuromuscular disease with or without symptoms
	8. Second-degree AV block with associated symptomatic bradycardia regardless of type or site of block
	9. Asymptomatic persistent third-degree AV block with average awake ventricular rates of 40 or faster if cardiomegaly or LV dysfunction present or if site of block is below the AV node
	10. Second- or third-degree AV block during exercise in the absence of myocardial ischemia
IIa	1. Persistent third-degree AV block with an escape rate greater than 40 in asymptomatic adult patients without cardiomegaly
	2. Asymptomatic second-degree AV block at intra- or infra-His levels found at electrophysiological study
	3. First- or second-degree AV block with symptoms similar to those of pacemaker syndrome or hemodynamic compromise
	4. Asymptomatic type II second-degree AV block with a narrow QRS. When type II second-degree AV block occurs with a wide QRS, including isolated right bundle branch block, pacing becomes a class I recommendation
IIb	1. Neuromuscular diseases with or without symptoms because progression of AV conduction disease is unpredictable
	2. AV block in the setting of drug use and/or drug toxicity when the block is expected to recur even after the drug is withdrawn
III	1. Asymptomatic first-degree AV block
	2. Asymptomatic type I second-degree AV block at the supra-His (AV node) level or that which is not known to be intra- or infra-Hisian
	3. AV block that is expected to resolve and is unlikely to recur (e.g., drug toxicity, Lyme disease, transient increases in vagal tone or during hypoxia in sleep apnea syndrome in the absence of symptoms)

support the ventricular rate but not restore AV synchrony. If there is hemodynamic compromise due to complete heart block and a low escape rate, placement of transcutaneous pads and, once the option is available, placement of a temporary wire should be performed. The mainstay of therapy is ultimately placement of a permanent pacemaker to restore AV synchrony (Fig. 16.5).

In patients referred for complete heart block after open heart surgery, conduction may return as late as 5–7 days postoperatively, and thus, time to allow for return of conduction should be given prior to referring for a pacemaker. The likelihood of need for a pacemaker is greatest with aortic valve replacement in the setting of preexisting right bundle branch block or in the case of surgical replacement of multiple valves or redo valve surgery. When episodes of complete heart block are interspersed with periods of normal conduction, this suggests higher grade conduction system disease that is unlikely to recover regardless of the number of days postoperatively. Patients leaving the operating room will often have temporary epicardial wires in place, and care of these patients should include daily underlying rhythm and threshold checks on the temporary pacing wires to ensure that temporary pacing is not suddenly lost in the absence of an underlying rhythm. If epicardial wires lose capture and

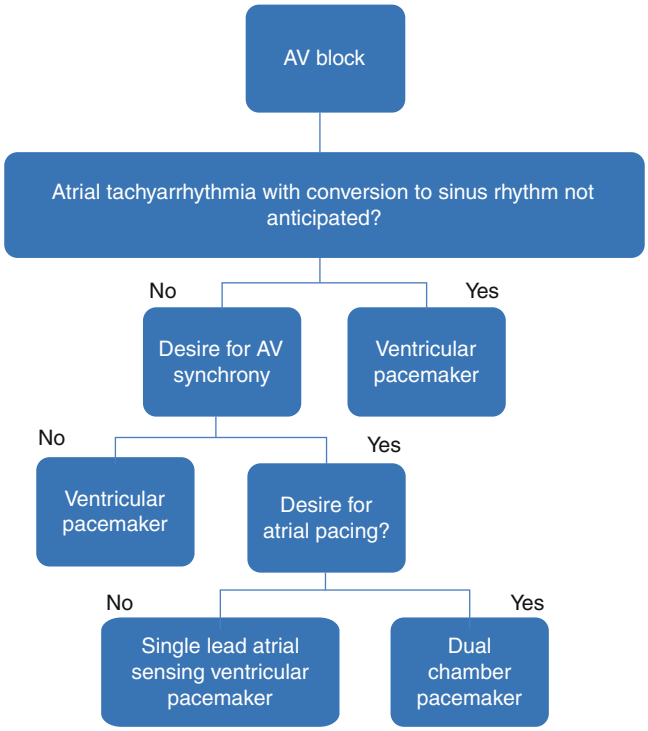

Fig. 16.5 Algorithm regarding decision on pacing in AV block – shown is an algorithm for decision making regarding the type of pacemaker to implant when a patient is referred for AV block

there is not a stable underlying rhythm, emergent transcutaneous pacing or placement of a bedside temporary pacing wire may be necessary. In patients after minimally invasive trans-aortic valve intervention (TAVI), there is a moderate risk of complete heart block, particularly in the setting of previously existing conduction disease, and it is unlikely that normal conduction will return more than one to days postoperatively. Thus, post-TAVI it is reasonable to consider pacemaker placement sooner than in the general postsurgical population [9].

Some patients may present with a history of syncope and paroxysmal AV block, or phase IV block. This unique phenomenon can be unpredictable, and thus, patients presenting with paroxysmal AV block in the absence of a ventricular escape should have temporary pacing, either via prophylactically placed pads or a temporary wire, implemented immediately.

The decision on whether a dual chamber or single ventricular chamber system is warranted in the setting of AV conduction disease depends on the underlying atrial rhythm. Placing a single ventricular chamber pacemaker is reasonable in patients with permanent atrial fibrillation in whom restoration of sinus rhythm is not expected. However, in patients in whom sinus rhythm is expected to return, placement of a dual chamber pacemaker to maintain atrioventricular synchrony is preferred.

Special Cases

Chronic Bifascicular Block

Chronic bifascicular block, in which right bundle branch block is associated with either left anterior or left posterior fascicular block, has a relatively higher frequency of progression to complete heart block. In asymptomatic patients with only first-degree AV block but no additional evidence of higher levels of block, pacemaker implantation is not indicated. However, in certain cases, even in the absence of type II second-degree AV block or complete heart block, permanent pacemaker insertion may be considered.

Cardiac Transplantation

After cardiac transplantation, sinus node dysfunction in the donor heart is possible. Typically, after transplantation, native atrial rates are expected to be in the 90s or greater. However, some patients may have sinus node dysfunction, possibly due to ischemia of the sinus node or prolonged sinus node recovery, and in these patients it is reasonable to consider implantation of a pacemaker. Furthermore, if there is relative bradycardia (i.e., a heart rate that is not considered sufficient for the patient's physiologic state) that may hinder rehabilitation or discharge from the hospital, pacemaker insertion may also be considered. Oftentimes, in the absence of higher degree block, a week or longer may be permitted to await sinus node recovery. It is reasonable to consider an atrial-only pacemaker in these patients particularly given a higher infection risk while on immunosuppressive agents.

Bradycardia-Dependent Ventricular Tachycardia

In the setting of pauses, even in the absence of QT prolongation, intervening ventricular escape beats may induce a ventricular tachyarrhythmia. Bradycardia- or pause-dependent VT is treated with placement of a pacemaker in order to avoid further bradycardia or pauses, since these are considered to be the etiology of the ventricular tachyarrhythmia.

Supraventricular Tachyarrhythmias

For purposes of this section, all organized SVTs will be considered together, while atrial fibrillation will be considered in a separate section. SVTs include any tachyarrhythmia in which the atrium plays a primary role in driving the tachycardia. We will also consider AV reentrant tachycardias mediated by accessory pathways in this section.

SVTs may include atrial tachycardias, caused by either automatic foci or micro-reentrant circuits; atrial flutter, caused by macro-reentrant circuits involving the atria; AV nodal reentrant tachycardia (AVNRT); and accessory pathway-mediated tachycardias, or so-called AV reentrant

tachycardias. The substrate and pathophysiology of these arrhythmias is discussed elsewhere. Guidelines have been published regarding the treatment of these arrhythmias and will be summarized here [10]. The decision to treat an SVT is often a patient-specific one, based on their tolerance of drugs, how effective drugs are in managing the arrhythmia, and how likely catheter ablation is felt to be effective.

When a patient presents with a new diagnosis of SVT, obtaining a history regarding how the tachycardia initiates and terminates is important to help distinguish the mechanism. For example, predictable termination with vagal maneuvers may suggest AVNRT. Furthermore, close evaluation for the presence of any structural heart disease or electrocardiographic abnormalities may help distinguish the presence of an antegradely conducting accessory pathway or suggest the possibility of a more complex arrhythmia substrate. Obtaining 12-lead electrocardiographic tracings of the tachycardia, of adenosine challenge during tachycardia, and/or of the initiation and termination of the tachycardia may further assist in guiding discussion regarding the most likely tachycardia mechanism and the next best steps in treatment.

Options regarding drug therapy are varied and depend on the presumed mechanism of the tachycardia. For example, for AV node-dependent tachycardias, AV nodal blocking drugs should be the preferred choice. However, if there is evidence of preexcitation and the patient is not felt to be a reasonable ablation candidate, classes Ia, Ic, and III agents that will prolong the refractory period of the accessory pathway are reasonable options. Use of more powerful classes Ia, Ic, and III agents should be made based on the patient's ability to tolerate beta-blockers or calcium channel blockers alone, the frequency of symptoms, and after full consideration regarding invasive and noninvasive options. Patients should understand that the prognosis associated with SVTs is usually benign, though in rare cases (e.g., accessory pathway-mediated tachycardias with associated atrial fibrillation and/or a history of syncope) there is the potential for sudden death.

When a decision is made to pursue catheter ablation for a SVT, the definitive diagnosis is usually made at the time of ablation. An electrophysiology study is always performed at the beginning of the case to confirm the tachycardia mechanism and to ensure that no other tachyarrhythmias exist that may be causing the patient's symptoms. Depending on the results of the diagnostic maneuvers, a decision to treat can be made at the time of the study based on the anticipated complexity of the ablation and previous discussions with the patient regarding the procedure. For example, given the relative increased complexity of left-sided ablations in which anticoagulation and a transeptal approach may be needed, some patients would prefer to only treat a tachycardia if it clearly originates in the right atrium.

Acute Treatment of the Patient Presenting with an SVT

When a patient presents to the emergency room or office setting with a SVT, the goal is severalfold – to determine the mechanism, terminate the tachycardia, and improve symptoms. If the patient is hemodynamically compromised, immediate synchronized cardioversion with an AED should be performed. However, if the patient is symptomatic but otherwise hemodynamically stable, initial evaluation should include a 12-lead electrocardiogram followed by immediate institution of therapy which can include carotid sinus massage, having the patient perform a Valsalva maneuver, or giving intravenous adenosine. Carotid sinus massage should only be performed in the absence of carotid bruits given the rare possibility of carotid dissection. During performance of these maneuvers, leaving the patient hooked up to a continuously running 12-lead electrocardiogram may help in diagnosing the mechanism of the arrhythmia. Use of vagal maneuvers will generally terminate AV-node-dependent tachycardias, while atrial tachycardias are rarely terminated in this way. Adenosine is usually used as the parenteral drug of choice in this setting given that it is short-acting and has an almost immediate effect. However, if adenosine is not immediately available, it is reasonable to use verapamil, beta-blockers, or other agents.

Adenosine may not only serve to terminate the tachycardia for AV-dependent tachycardias but also to evaluate the source of the tachycardia in atrial tachycardias and atrial flutters. By slowing AV conduction, atrial activity may be more easily seen with fewer interspersed ventricular complexes such that morphologic evaluation can help diagnose the location of the circuit or abnormal focus mediating the arrhythmia.

Accessory pathway-mediated tachycardias in the setting of atrial fibrillation present a unique clinical situation with danger of degenerating into ventricular fibrillation. The rapid depolarization of ventricular myocytes via atrial fibrillation signals bombarding a rapidly conducting accessory pathway can result in a polymorphic appearing irregular tachycardia that is often very fast. This rhythm may degenerate into ventricular fibrillation, particularly if the shortest coupling interval (the distance between QRS complexes) is less than 250 ms. The preferred drug for termination in this case is procainamide. Electrical cardioversion may also be used.

AV Nodal Reentrant Tachycardia

AVNRT is the most common form of paroxysmal SVT. The region responsible for propagation of AVNRT is where atrial conduction pathways insert into the AV node. These conduction pathways may be divided into fast and slow conduction pathways based on differing refractory and conduction properties. The fast pathway is typically located anteriorly and superiorly on the interatrial septum, while the slow

pathway is located more inferiorly and posteriorly along the tricuspid annulus near the coronary sinus os. During electrophysiology study, the presence of a critical delay in AV conduction, indicative of a "jump" in conduction from the fast pathway to the slow pathway, is a characteristic finding suggestive of AVNRT. The presence of this "jump" may precede the onset of AVNRT.

The decision to ablate AVNRT is made on the basis of the presence of associated symptoms. Prior to ablation, it is reasonable to advise patients on the use of AV nodal blocking agents such as beta-blockers or calcium channel blockers to prevent the tachycardia or on the use of vagal maneuvers such as Valsalva to try and terminate the tachycardia when it starts. However, some patients may prefer an ablative approach which has curative success rates greater than 95 %. There is a small risk associated with ablation of injuring the His bundle resulting in complete heart block requiring pacemaker implantation and of injury to the heart wall resulting in perforation and cardiac tamponade, though these risks are rare.

Once confirmed, ablation is usually targeted at the slow pathway, especially given the proximity of the fast pathway to the His bundle and the consequent risk of causing heart block. Given the relative proximity of the His bundle to the region being ablated, a catheter is typically left in the region of the His bundle so that continuous recording may be made of His electrograms. Onset of an accelerated junctional rhythm during ablation is one sign that suggests successful targeting of the slow pathway. Once the slow pathway is ablated, repeat attempts at stimulation with and without isoproterenol infusion are performed to attempt to initiate the tachycardia. The persistent evidence of single "echo" beats, or reentrant beats that may suggest continued functional presence of a slow pathway with altered conduction, is associated with a good prognosis.

Accessory Pathway-Mediated Tachycardias

The presence of preexcitation on a baseline electrocardiogram may not necessarily suggest that an accessory pathway participates in SVT. It is estimated that as many as 70 % of asymptomatic patients with evidence of preexcitation on electrocardiogram (ECG) do not have an inducible accessory pathway-mediated tachycardia during electrophysiology study. The reason for this may have to do with pathway characteristics including its ability to conduct rapidly both antegrade and retrograde. Most patients presenting with preexcitation in the absence of symptoms suggestive of SVT will likely need no further treatment. The caveat to this is that in several reported series, up to 20 % of patients suffering accessory pathway-associated cardiac arrest report no symptoms relatable to an SVT prior to their arrest [10]. This raises the concern that in some asymptomatic patients with evidence of preexcitation, even in the absence of symptoms to suggest an SVT, there may be an increased risk of sudden death. However, performing electrophysiology studies or targeting these pathways in all asymptomatic patients is not cost-effective and likely does not offer a favorable risk-benefit profile. Thus, additional studies such as treadmill stress tests to determine the health of antegrade conduction across the pathway, ambulatory monitoring, and discussion with the patient should be considered before referring for invasive therapy.

In the case of SVT mediated by an accessory pathway, considerations need to include whether the patient is symptomatic, how frequently their symptoms arise, and whether or not there is any history of atrial fibrillation. There is some evidence that atrial fibrillation may exist as a secondary phenomenon due to AV reentry, possibly due to atrial pressure and volume changes as well as heightened sympathetic tone. Generally patients who experience ventricular fibrillation due to the presence of an accessory pathway will also have atrial fibrillation causing rapid activation of the ventricle at short coupling intervals across the pathway.

Management acutely depends on the patient's symptoms and determination of whether the tachycardia is orthodromic or antidromic. Antidromic AV reentrant tachycardia typically has a wider QRS complex than sinus rhythm given the ventricle is activated from the accessory pathway. In the case of orthodromic AV reentry, vagal maneuvers and injection of adenosine may be attempted to terminate conduction across the antegrade limb (the AV node). In the presence of atrial fibrillation and an accessory pathway, however, cardioversion is the safest way to restore sinus rhythm, though procainamide may also be used. Generally, any medication that blocks the AV node should be avoided in patients with an antegradely conducting accessory pathway who presents in atrial fibrillation because these drugs can increase the risk of cardiac arrest.

While drug therapy can be attempted in patients with AV reentrant tachycardia, the high cure rate and low risk of complications associated with catheter ablation make it the mainstay of therapy. Patients are generally young when they present, and the prospect of lifelong drug therapy may not be palatable to all patients. Furthermore, beta-blockers and other AV nodal blockers are not necessarily as effective as antiarrhythmic drugs such as flecainide, propafenone, or sotalol, and antiarrhythmic drugs carry additional risks.

Ablation should be recommended in all patients who present with cardiac arrest due to ventricular fibrillation presumed due to an accessory pathway, when rapid atrial fibrillation with associated preexcitation is present and when there is recurrent SVT with significant associated symptoms, particularly if the antegrade conduction across the pathway is fast (i.e., a cycle length less than 250 ms between QRS complexes) [10]. The target of ablation is the insertion of the pathway in either the atrium or ventricle. If the pathway is

right sided, catheters are inserted via the femoral veins. However, if left sided, the pathway may be targeted via a retrograde aortic or transeptal approach. Mapping is performed during the study to identify the location of the bypass tract, and sometimes high-frequency potentials (pathway potentials) may be seen in the area of the insertion of the accessory pathway. The presence of multiple accessory pathways or insertion of the pathway near sensitive anatomic structures can make ablation difficult. Furthermore, if the pathway is contained within significant epicardial fat, endocardial ablation may be insufficient to eliminate the pathway. Rarely, surgery may be needed for successful ablation.

Sinus Tachycardia

Sinus tachycardia is almost always a physiologic response to an underlying stressor, and treatment should be aimed at relieving the underlying cause. However, in rare cases, patients may have inappropriate sinus tachycardia with associated symptoms, and pharmacologic or ablative treatment may be indicated. Beta-blockers are the initial drug of choice, and verapamil may also be used. Ablation for inappropriate sinus tachycardia may be considered, though elimination of inappropriate sinus tachycardia via destruction of sinus nodal tissue can be difficult because there is no discrete site of origin of inappropriate sinus tachycardia [11]. Rather, inappropriate sinus tachycardia likely represents enhanced responsiveness to normal stimulation throughout the SA nodal apparatus. Ablation may be complicated by stenosis of the superior vena cava/right atrial junction due to the extent of ablation needed and by chronotropic incompetence resulting in the need for pacemaker insertion.

Inappropriate sinus tachycardia should be considered separately from sinus node reentry which is a different phenomenon characterized by an area of micro-reentry in the vicinity of the sinus node leading to an arrhythmia with characteristics similar to that of other reentrant tachycardias. Sinus node reentry is more amenable to catheter ablation with a >95 % likelihood of success, as contrasted with inappropriate sinus tachycardia.

Atrial Tachycardia

Atrial tachycardias may be considered micro-reentrant or as emanating from a single repetitively firing automatic focus. An underlying cause for the tachycardia should be investigated since it is possible that regular atrial tachycardias may occur during acute illness and their treatment may require no more than resolution of the acute illness. Multifocal atrial tachycardia is not targeted with ablation but rather with medications, such as calcium channel blockers, particularly given its common coexistence with chronic obstructive pulmonary disease. If a regular atrial tachycardia is present, consideration can be given to drug therapy or to pursuing ablation. Medications including beta-blockers and classes Ia, Ic, and III antiarrhythmics are reasonable options to try and maintain sinus rhythm. Digoxin and calcium channel blockers may also be used for ventricular rate control by causing AV nodal blockade.

If the diagnosis of atrial tachycardia is unclear or if ablation is considered because of intolerance to or lack of desire to try medications, electrophysiology study and ablation is reasonable. The likelihood of success often depends on the complexity of the substrate being dealt with – more structurally abnormal hearts may have either multiple tachycardia foci or concomitant atrial fibrillation. Success rates for focal atrial tachycardia ablation have been reported in the >90 % range. The ablation of atrial tachycardias in the setting of prior ablation performed for atrial fibrillation will be considered separately under "Atrial Fibrillation."

Atrial Flutter

Atrial flutter is a broad term used to denote any macro-reentrant atrial tachyarrhythmia. The most common type of atrial flutter is "typical" atrial flutter or cavotricuspid isthmus (CTI)-dependent flutter. This type of flutter was first described over a century ago and involves a critical area of slow conduction in the posterior right atrium. The activation wave typically propagates counterclockwise through the right atrium, though clockwise CTI-dependent flutter is also seen. The critical isthmus consists of a region in the low right atrium between the Eustachian valve at the anterior rim of the inferior vena cava extending to the tricuspid annulus. Ventricular rate control using AV nodal blocking agents with CTI-dependent flutter is often difficult, and antiarrhythmic drugs have poor efficacy in suppressing the arrhythmia, with studies suggesting a <50 % success rate. Synchronized cardioversion is reasonable to perform if the patient is hemodynamically unstable, has poorly controlled ventricular rates, or is symptomatic. However, atrial flutter has an associated risk of intracardiac thrombus formation, and the same criteria for anticoagulation should be used as for those patients with atrial fibrillation (see later in text). Generally, if a patient has been in atrial flutter for more than 48 h and has not been therapeutically anticoagulated, a transesophageal echocardiogram should be performed prior to any attempt at cardioversion. Furthermore, anticoagulation will often need to be continued for at least 4 weeks after cardioversion.

Therapy for CTI-dependent flutter usually involves ablation because there is a clear anatomic substrate with well-defined landmarks that results in a high (>95 %) success rate. A series of ablation lesions extending from the tricuspid annulus to the inferior vena cava comprises the ablation line. By creating a line of block across this isthmus, which also serves as the critical slow zone of the flutter circuit, the flutter circuit may be effectively interrupted. Bidirectional block across the line is evaluated after completion of ablation to ensure adequate ablation has been performed. Some patients

(20–30 %) may also go on to develop atrial fibrillation over follow-up [12]. Many patients with coexisting atrial fibrillation and CTI-dependent atrial flutter will have both arrhythmias targeted at the time of ablation.

Atypical flutter refers to any atrial flutter that is not CTI-dependent and can include right- and left-sided flutter circuits. Sometimes it is not possible to differentiate CTI-dependent from atypical flutter on a surface electrocardiogram, and as a result, electrophysiologic mapping is required prior to making a definitive diagnosis. Unlike CTI-dependent flutter, the critical isthmus may be broader than the cavotricuspid isthmus, as with flutter involving the mitral annulus, potentially making ablation more complex. Furthermore, atypical flutters are often related to prior ablation procedures (e.g., atrial fibrillation ablation) or surgery. Atriotomy scars are one classic surgical site that may serve as the area around which a flutter circuit revolves. Similar to CTI-dependent flutter, the response to medication in terms of arrhythmia suppression and ventricular rate control is highly variable, though synchronized cardioversion does serve a role for the acute termination of the arrhythmia. Patients often do require anticoagulation similar to CTI-dependent flutter for stroke prophylaxis. Catheter ablation is reasonable to consider in these patients and involves mapping of the flutter circuit and creating a line between two fixed points (e.g., between the atriotomy scar and the inferior vena cava) in order to cut off the circuit. Success rates with atypical flutter ablation, however, are lower than with CTI-dependent flutter and often depend on the complexity of the substrate, with more complex patients such as those who have had multiple prior ablations or have complex congenital heart disease being less likely to have a successful ablation.

Atrial Fibrillation

Atrial fibrillation is often a difficult arrhythmia to treat. It can manifest unpredictably and be mediated by other clinical syndromes (e.g., hyperthyroidism), acute stress (e.g., cardiac surgery or severe infectious states), or excess intake of alcohol or sympathomimetic agents. Even when arising in the setting of another clinical situation, atrial fibrillation may not always be "reversible" upon withdrawal of the stimulus. Namely, it is possible that introduction of the stimulus merely uncovered already existent substrate for the arrhythmia and that future episodes of atrial fibrillation are possible. Unfortunately, few prediction models exist to risk stratify which patients will have recurrence of atrial fibrillation after a single episode that occurs in another clinical setting. Thus, the treatment of a patient presenting with atrial fibrillation is dynamic and often involves the introduction and withdrawal of the same or different rate control and antiarrhythmic drugs over months to years after initial presentation in addition to the use of ambulatory monitors to evaluate whether the arrhythmia is controlled. Unfortunately, symptoms do not always correlate with arrhythmia occurrence, and thus, rate and rhythm checks using patient-performed pulse checks or electrocardiographic monitoring are needed to determine whether a given therapy is effective in preventing further recurrences.

The hallmark of treatment in atrial fibrillation consists of managing the arrhythmia and preventing thromboembolic sequelae, specifically stroke [13, 14]. Managing the arrhythmia may take on either a rate or rhythm control strategy. The choice of strategy often depends on the individual, their symptoms from atrial fibrillation, and their comorbidities. Whether a rate control strategy, in which AV nodal blockers such as beta-blockers, calcium channel blockers, or digoxin are used, or a rhythm control strategy, in which antiarrhythmic drugs or ablation are used, is chosen, the ultimate goal is to manage symptoms associated with atrial fibrillation while also preventing long-term sequelae from un-rate controlled atrial fibrillation, such as a tachycardia-induced cardiomyopathy.

In addition to management of the arrhythmia, consideration needs to be made into thromboembolic risk. Several studies have supported a role for anticoagulation in the prevention of stroke associated with atrial fibrillation. There is a 1.8-fold increase in mortality in patients with atrial fibrillation-related than non-atrial fibrillation-related stroke, likely due to the fact that such strokes more often suffer hemorrhagic transformation and are often larger in size. Thus, risk stratification scores, including the $CHADS_2$ and CHA_2DS_2-VASc scores, have been developed to stratify stroke risk to determine the relative benefit of anticoagulation beyond aspirin.

Anticoagulation

The decision on whether or not to anticoagulate a patient with atrial fibrillation depends on determining the risk–benefit for prevention of stroke. The risk of stroke is attributable to the relatively disorganized rhythm in the upper chambers of the heart leading to sludging of blood, particularly in the left atrial appendage. If a thrombus organizes in this region of the heart, it has potential to embolize resulting in stroke or other arterial embolic events. Thus, the goal of anticoagulation is generally either to treat an already present thrombus or to prevent formation of one.

The decision on whether or not to anticoagulate is dependent on calculation of a risk score. The $CHADS_2$ and CHA_2DS_2-VASc scores (Table 16.6) are used to help determine what the risk of stroke is in a given patient. Generally the higher the score, the more likely the patient is to be at risk of stroke [15]. Table 16.7 summarizes the per year risk of stroke associated with atrial fibrillation according to the $CHADS_2$ score. A score of 2 or higher on either scoring

Table 16.6 Scoring systems used to help determine anticoagulation use in atrial fibrillation

Scoring system	Components
Stroke risk	
$CHADS_2$	6 total points
	Congestive heart failure – 1 point
	Hypertension or treated hypertension on medication – 1 point
	Age ≥75 years – 1 point
	Diabetes mellitus – 1 point
	Prior stroke or TIA – 2 points
CHA_2DS_2-VASc	9 total points
	Congestive heart failure – 1 point
	Hypertension or treated hypertension on medication – 1 point
	Age ≥75 years – 2 points
	Diabetes mellitus – 1 point
	Prior stroke or TIA or thromboembolism – 2 points
	Vascular disease (e.g., peripheral arterial disease, myocardial infarction) – 1 point
	Age 65–74 years – 1 point
	Female gender – 1 point
Bleeding risk	
$HEMORR_2HAGES$	12 total points
	Hepatic or renal disease – 1 point
	Ethanol abuse – 1 point
	Malignancy – 1 point
	Older (age ≥75 years) – 1 point
	Reduced platelet count or function – 1 point
	Prior bleed – 2 points
	Hypertension (uncontrolled) – 1 point
	Anemia – 1 point
	Genetic factors – 1 point
	Excessive fall risk – 1 point
	Stroke history – 1 point
HAS-BLED	9 total points
	Hypertension (uncontrolled) – 1 point
	Renal disease (dialysis, transplant, or Cr >2.6) – 1 point
	Liver disease (cirrhosis, bilirubin >2 times normal, AST/ALT >3 times normal) – 1 point
	Stroke history – 1 point
	Prior major bleeding or predisposition to bleeding – 1 point
	Labile INR (unstable/high INRs, <60 % time in therapeutic range) – 1 point
	Age ≥65 – 1 point
	Medication usage predisposing to bleeding (antiplatelets, NSAIDs) – 1 point
	Alcohol usage history – 1 point

system is used to indicate that a patient would definitely benefit from anticoagulation beyond aspirin alone. A score of 0 is used to state that aspirin alone is sufficient therapy. It is important to recognize that atrial fibrillation conveys

Table 16.7 Stroke risk in atrial fibrillation by $CHADS_2$ score

$CHADS_2$ score	Stroke risk (%)
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2

an increased stroke risk even when $CHADS_2$ or CHA_2DS_2-VASc is 0. However, this risk is counterbalanced by hemorrhagic risk associated with oral anticoagulants, which may be guided by risk scores for bleeding including the $HEMORR_2HAGES$ score and HAS-BLED score (Table 16.6) [16, 17].

Thus, the decision to anticoagulate requires a careful balance between both stroke risk and bleeding risk. In patients who have no contraindications to full anticoagulation, sometimes brief periods of anticoagulation after performing either ablation or cardioversion may be used. For example, low-risk patients for stroke who have had >48 h of atrial fibrillation and undergo cardioversion are at increased risk of thromboembolic phenomena within the first several weeks post-cardioversion while atrial contraction recovers. Thus, even in the absence of significant risk factors for stroke, anticoagulation will be prescribed for at least 4 weeks. Similarly, after ablation, given the extensive scarring created in the left atrium and in order to give atrial contraction to recover, anticoagulation may be prescribed for at least 4 weeks in the absence of stroke risk factors. However, if a patient has had a single <48 h episode of atrial fibrillation, especially if considered a secondary phenomenon (e.g., due to alcohol intoxication), and no other risk factors exist for stroke, then consideration may be given to cardioversion without initiation of anticoagulation.

Rate Versus Rhythm Control Strategies

The decision on whether to pursue rate or rhythm control in atrial fibrillation may be difficult. Early clinical trials, such as the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial, suggested that there was no significant difference between rate and rhythm control strategies in terms of survival advantage, with the advantage of rate control including avoidance of the side effects of antiarrhythmic drugs [18]. However, more recent sub-analyses of AFFIRM and other trials suggest that those patients who do maintain sinus rhythm may fare better than those who do not maintain sinus rhythm [19]. The limitation of prior trials comparing rate and rhythm control strategies is that the differences between a rhythm or rate control approach did not take into account whether or not the patient actually

maintained sinus rhythm in the strategy to which they were randomized. Thus, it is possible that patients who are successfully rhythm controlled may fare differently than those who are not.

The decision to pursue rhythm control, whether with antiarrhythmic drugs or catheter ablation, requires consideration of the patient's symptoms and whether or not they are a candidate for anticoagulation since even pharmacologic cardioversion of atrial fibrillation that has been present for >48 h carries an associated increased risk of stroke due to atrial stunning after return to sinus rhythm. Some patients are symptomatic even when their heart rate is well controlled in atrial fibrillation, may have infrequent paroxysms or have difficulty with further uptitration of rate control agents, and thus may opt for a rhythm control approach regardless. Rhythm control is usually coupled with rate control drugs in case patients have recurrence of atrial fibrillation in spite of antiarrhythmic drugs or ablation.

Rate Control

Beta-blockers are most commonly used for rate control given the high incidence of heart failure associated with atrial fibrillation. However, sometimes a combination of multiple classes of drugs is needed because of difficult to control rates. The heart rate goal depends on the patient and needs to take into account the heart rate when the patient is active as well as at rest. Though the heart rate may be well controlled at rest, it may become significantly higher during even routine daily activities. Thus, having the patient ambulate is important to assess the efficacy of the rate control regimen. One study looking at strict (heart rate less than 80 at rest and less than 110 with moderate exercise) versus lenient (heart rate less than 110 with rest or moderate exercise) rate control strategies suggested no difference between the two in terms of patient outcomes and that lenient rate control was easier to achieve [20]. Monitoring for LV dysfunction in patients with lenient rate control remains important.

Another more invasive rate control strategy may be used in patients in whom rhythm control is not considered an option or is ineffective and in whom heart rates are poorly controlled. This strategy involves ablation in the region of the compact AV node by the His bundle to create complete heart block with placement of a permanent pacemaker. Long-term outcome studies of patients who undergo AV node or His bundle ablation and pacemaker implantation suggest favorable outcomes with no change in cardiac performance and better control of symptoms and quality of life (though decision to refer was partly based on prior resistance to or intolerance of drug therapy) [21]. The type of pacemaker used can be either a single chamber ventricular (in the case of permanent atrial fibrillation) or dual chamber atrial plus ventricular (if the patient has periods of sinus rhythm along with atrial fibrillation) systems. If the patient meets criteria, a biventricular system to avoid negative effects of chronic dyssynchrony may be implanted given they will be 100 % pacemaker dependent.

Rhythm Control

Rhythm control includes the performance of electrical cardioversion to convert patients back to sinus rhythm, use of antiarrhythmic drugs, and performance of either catheter or surgical ablation to maintain sinus rhythm. Any attempt at converting a patient back to sinus rhythm should be preceded by an assessment of stroke risk. Namely, prolonged (>48 h) episodes of atrial fibrillation in the absence of anticoagulation ought to be approached with performance of a transesophageal echocardiogram and initiation of anticoagulation prior to performing cardioversion or starting an antiarrhythmic drug.

Electrical cardioversion works in >99 % of patients to regain sinus rhythm. In some patients, however, restoration of sinus rhythm may only be brief (termed early recurrence of atrial fibrillation, or ERAF). Furthermore, some patients, especially in the setting of prolonged episodes of atrial fibrillation, may have a prolonged pause or sinus bradycardia following cardioversion owing to chronic suppression of the sinus node. In the case of ERAF, options may include initiation of an antiarrhythmic drug or, if the patient is already on one, changing to a different antiarrhythmic drug prior to repeat attempt at cardioversion. ERAF may also prompt a clinician to choose a rate control approach over rhythm control given that these patients may be more refractory to maintaining sinus rhythm.

Antiarrhythmic drug options are several and need to take into account patient comorbidities and age. In the absence of structural heart disease, flecainide and propafenone are reasonable options. Both these drugs are also capable of quickly cardioverting an acute paroxysm of atrial fibrillation and, in certain patients, are prescribed as a "pill in the pocket" approach to be used only at the time of an atrial fibrillation recurrence. However, if there is heart disease present, including significant left ventricular hypertrophy, class III antiarrhythmics, including amiodarone, dofetilide, dronedarone, and sotalol, are considered safer. Sotalol is generally not used in the setting of heart failure given potential negative inotropic effects, and dronedarone has been associated with increased morbidity and mortality in patients with heart failure. Both sotalol and dofetilide require inpatient monitoring of the QT interval and may not be used if the patient has an excessively prolonged QT interval at baseline. Dronedarone may not be as effective as other agents in maintaining sinus rhythm, though its side effect profile is better than amiodarone. The use of amiodarone is generally reserved for refractory or older patients given the multiple potential side effects. Figure 16.6 presents an algorithmic approach by

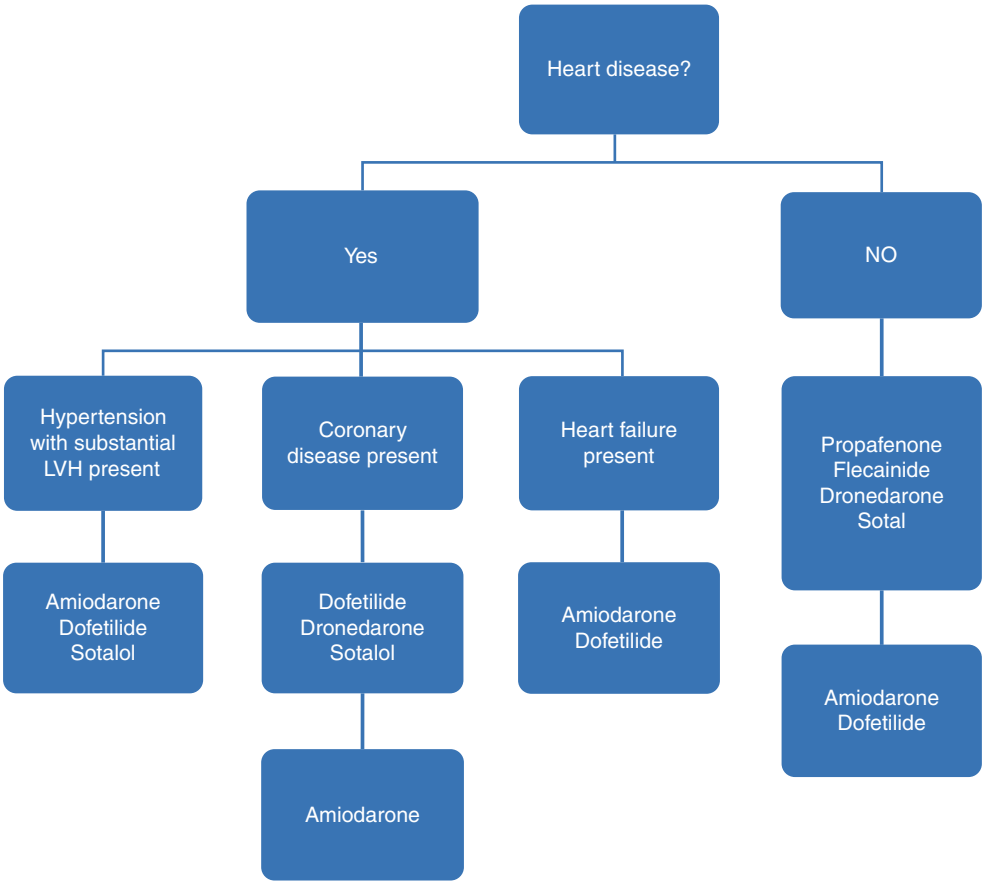

Fig. 16.6 Algorithm for decision making on antiarrhythmic drug choice for the maintenance of sinus rhythm – shown is an algorithmic approach to deciding on antiarrhythmic drug initiation in patients presenting with atrial fibrillation. The choice of drug is largely guided by the presence and type of heart disease (Adapted from Wann et al. [14].With permission from WolterKluwers Health)

which to consider the initiation of different antiarrhythmic drugs in atrial fibrillation.

Ablation

Ablation for atrial fibrillation targeting the atria and aimed at eliminating atrial fibrillation is generally considered after a patient has failed at least one antiarrhythmic drug. Drug failure includes either inability to effectively maintain sinus rhythm or intolerance of the medication. Atrial fibrillation ablation is primarily focused on eliminating the principal drivers for the onset and propagation of atrial fibrillation. Clinical trials have demonstrated that the pulmonary veins are key to the pathogenesis of atrial fibrillation in many patients and that isolation of the muscle fibers extending into these veins via the creation of a set of lesions encircling all four veins may effectively eliminate atrial fibrillation during long-term follow-up. If other arrhythmias coexist with atrial fibrillation, such as CTI-dependent flutter or AVNRT, ablation may be targeted at these arrhythmias at the same time. Different approaches exist to performing catheter ablation for atrial fibrillation, though all generally involve isolation of the pulmonary veins. Other approaches involve creating ablation lesions in other areas of the atria to create other lines of block or targeting of complex-fractionated electrograms which may mark ganglia involved with the perpetuation of atrial fibrillation. The cure rate after a first procedure is estimated around 70–80 %, with paroxysmal patients being more likely to be successful after a one-time procedure than persistent patients. After a second procedure, the likelihood of cure increases accordingly to as high as 90 % and so on with each subsequent procedure.

The most concerning risks during atrial fibrillation ablation include (1) bleeding due to high-dose anticoagulation being used during the procedure, risk of perforation, and resultant cardiac tamponade, especially at the time of transeptal puncture, and (2) stroke both during and after the procedure. Even in the absence of intracardiac thrombus prior to the procedure, post-procedural stroke is possible due to the extensive ablation performed and the need to stop anticoagulation after the procedure for a period of time to remove the sheaths and obtain hemostasis. Thus, close monitoring for at least one night in the hospital after ablation is generally preferred, and most procedures are now performed during ongoing warfarin therapy with little enhanced risk of bleeding and further reduction on stroke risk.

After ablation is performed, antiarrhythmic drugs may be continued for at least the first 6 weeks. The reason for this period of antiarrhythmic drug continuation is that some patients may experience arrhythmia recurrence immediately after the procedure during a period termed the “blanking

period" [22]. Arrhythmias recurring during this period do not necessarily predict future recurrence. In many patients the arrhythmia may spontaneously resolve, and thus, it is frequently desirable in the absence of significant symptoms to determine if spontaneous abatement will occur. Recurrent arrhythmias during this period that do not resolve on their own may be managed with cardioversion or adjustment in antiarrhythmic regimen.

In patients who are not atrial fibrillation-free off antiarrhythmic medications after ablation, better control with antiarrhythmics that did not work prior to ablation may be seen. Patients may also experience fewer symptoms related to atrial fibrillation or more infrequent paroxysms. Persistent patients who undergo ablation may sometimes become paroxysmal afterwards. Thus, some patients who are not necessarily "cured" of their arrhythmia may find that it is better controlled.

Special Considerations When Managing the Patient with Atrial Fibrillation

Most decision making regarding the management of a patient presenting with atrial fibrillation revolves around the frequency of the episodes, the clinical situation in which they arise, and the associated symptoms. For example, atrial fibrillation is common after major cardiac, thoracic, or gastrointestinal surgery, though its presence does not necessarily predict future recurrence. Furthermore, patients with atrial fibrillation associated with alcohol intoxication may never have another recurrence. Other secondary causes, such as hyperthyroidism, should also be evaluated for and treated. Sometimes a short term of antiarrhythmic drugs and anticoagulation may be used when atrial fibrillation occurs as a presumed secondary phenomenon with eventual withdrawal of the medications once the underlying process is reversed.

Assuming there are no readily reversible secondary causes of atrial fibrillation, the management is often guided by the type of atrial fibrillation – paroxysmal, persistent, or permanent. Paroxysmal atrial fibrillation, in which patients spontaneously convert without need for cardioversion, is usually considered more easily managed with antiarrhythmic drugs and to have a better cure rate with catheter ablation. Persistent atrial fibrillation, in which patients do not convert out of atrial fibrillation on their own but consistently require cardioversion, whether pharmacologic or electrical, has a poorer cure rate with catheter ablation. Long-standing or "permanent" atrial fibrillation, in which restoration of sinus rhythm even with attempts at cardioversion is not possible and antiarrhythmic drugs have failed, is generally managed with rate control alone. However, more recent experience with catheter ablation therapy in this setting is indeed promising and making "permanent" a misnomer that should not be applied to atrial fibrillation [23]. Selected patients who are not appropriate candidates for primary ablative therapy and who have poorly controlled ventricular rates with maximum medical therapy can undergo AV node ablation and pacemaker implantation.

One special consideration in patients presenting with atrial fibrillation is that of tachycardia–bradycardia syndrome. Patients may have symptomatic pauses in atrial fibrillation with periodic low rates and high rates, or when they convert spontaneously back into sinus rhythm, they may be symptomatic due to conversion pauses that occur while the sinus node recovers. Sinus bradycardia after termination of atrial fibrillation may be in part induced by the rate control agents used during atrial fibrillation, though these drugs are needed to control the ventricular rate in the case of another arrhythmia recurrence. In such cases, consideration for a more aggressive rhythm control approach using ablative therapy or for pacemaker insertion to maintain heart rate during periods of bradycardia is appropriate.

Ventricular Arrhythmias

The management of ventricular arrhythmias has significantly evolved over the last decade [24–26]. Ventricular arrhythmias for which patients may be referred for electrophysiologic evaluation include frequent PVCs or nonsustained VT, sustained VT, and ventricular fibrillation (VF). Oftentimes the latter two are recognized in the context of aborted sudden cardiac arrest and less often on ambulatory ECG monitoring. The management of these arrhythmias needs to take into account the underlying substrate which, in turn, correlates with the likelihood of efficacy with any particular treatment.

As with any other arrhythmia, a full assessment for a reversible cause at the time of presentation should be made. The most common reversible cause sought in a patient presenting with very rapid VT or more commonly VF is acute myocardial infarction. A ventricular tachyarrhythmia that occurs in the setting of an acute coronary occlusion may not recur should the coronary occlusion be successfully treated. In turn, if a patient's risk for ventricular tachyarrhythmias is attributable to heart failure, it is possible that aggressive treatment aimed at maintaining euvolemia and optimizing heart failure symptoms could also reduce the risk but importantly not eliminate the potential for the ventricular arrhythmia.

In this section, we will focus on pharmacologic and invasive approaches to the management of ventricular arrhythmias that occur outside the setting of clear reversible causes, such as electrolyte disturbances, myocardial ischemia or infarction, or use of other drugs that can cause ventricular arrhythmias (e.g., digoxin).

Premature Ventricular Contractions

Premature ventricular contractions (PVCs) have recently come to be recognized as potentially pathologic in some patients. PVCs may be idiopathic, as in the case of outflow

tract-related PVCs, or associated with myocardial scarring both in the presence and absence of clinically significant heart failure. Historically, PVCs were only targeted when frequent and causing symptoms such as palpitations, chest tightness, or dyspnea and if refractory to medical therapy such as beta-blockers. However, recent studies suggest that frequent PVCs (>24 % of heart beats over a 24-h period) may cause a depression in cardiac function (i.e., PVC-induced cardiomyopathy) [27, 28]. Suppression or ablation of these PVCs, in turn, may lead to recovery of function. In addition, frequent PVCs in the setting of heart failure may be deleterious, especially in the setting of biventricular pacing when PVCs may decrease the overall frequency of biventricular pacing and thus counteract attempts at achieving ventricular synchrony. Thus, the decision to treat PVCs may be based on symptoms, due to presence of a PVC-induced cardiomyopathy or due to interference with the clinical efficacy of other treatments, such as biventricular pacing.

The success of any individual treatment depends on the clinical context in which it is introduced. For example, ablation of idiopathic PVCs (e.g., outflow tract PVCs) has a >95 % likelihood of success, while success rates for ablating PVCs in patients with more complex substrates (e.g., congenital heart disease, prior infarction) may vary depending on the substrate and the experience of the center Thus, the clinical context needs to be taken into account.

The pharmacologic treatment of choice for symptomatic PVCs is beta-blockers given that PVCs are often sympathetically stimulated. Antiarrhythmic drugs may also be used if beta-blockers are ineffective or their use is not desired. The treatment chosen ultimately depends on the setting in which the PVCs occur, patient symptoms, and patient preference.

Idiopathic PVCs

Idiopathic PVCs are not associated with sudden death but can cause symptoms or, in rare cases, a PVC-induced cardiomyopathy. The definition of idiopathic PVCs is that they exist in the absence of structural heart disease. Initial treatment is generally with beta-blockers. However, patients are often intolerant of beta-blockers, wish to not take medication lifelong, or continue to have symptoms on medications. In this case, ablation is a highly successful option with a >95 % success rate at terminating the PVCs. The success of mapping to target the origin of the PVC, whether in the right or left ventricular outflow tract, the fascicles, or elsewhere has improved with increased understanding of morphologic criteria for identifying the origin of the PVC and high-fidelity mapping and imaging systems to visualize the heart during ablation.

PVCs with Heart Failure

If a patient presents with frequent PVCs and a reduced ejection fraction in the absence of coronary disease sufficient to explain the depressed ventricular function, it may not be possible to determine if the PVCs exist in the setting of a cardiomyopathy or if the PVCs may be contributing to the cardiomyopathy. Thus, the decision on treatment is often tailored to the presumptive cause. If the cardiomyopathy is felt to arise first and the patient is decompensated, treatment of the heart failure is appropriate to evaluate whether or not the PVC burden improves. However, if the patient is well compensated, it is reasonable to consider electrophysiology study and targeted ablation or antiarrhythmic drug therapy. Beta-blockers may be used, though are typically avoided if the patient is in decompensated heart failure and their titration may be limited by blood pressure. If the PVC burden is excessive and is interfering with biventricular pacing or felt to be contributing to further heart failure decompensation, it is reasonable to initiate an antiarrhythmic drug such as amiodarone or dofetilide. All other antiarrhythmic drugs are potentially deleterious in the setting of heart failure.

Ventricular Tachyarrhythmias

Initial treatment of a patient presenting with a ventricular tachyarrhythmia needs to be aimed at stabilizing the patient. If the patient is hemodynamically stable, obtaining a 12-lead electrocardiogram while using medications to try and terminate the tachycardia such as amiodarone, lidocaine, or beta-blockers is reasonable. If these do not work, electrical cardioversion may be performed once the patient has been properly sedated. However, if the patient is hemodynamically unstable, then they require emergent cardioversion/defibrillation. If the patient already has an ICD and personnel with the proper equipment and skill are available, it is reasonable to try and terminate the tachycardia manually using the ICD, either via forced delivery of increasingly aggressive cycles of ATP or with an internally delivered shock.

After the patient stabilizes, investigation for secondary causes should be performed. While monomorphic VT is generally not associated with ischemia or acute infarction, performing an ischemic evaluation is reasonable. If the patient presents with polymorphic VT or VF, initial evaluation should almost always include cardiac catheterization. In addition to this, evaluating for secondary causes, including drug effect (e.g., digoxin or cocaine), electrolyte abnormalities, and thyroid function is reasonable.

Once the patient has been stabilized and other secondary causes are ruled out, then a decision regarding additional therapy needs to be made. These may include referral for ablation, initiation of antiarrhythmic drug therapy, implantation of an ICD, or deferral of any therapy if it is felt that the underlying cause has been addressed and there is possibility of sufficient recovery as to no longer place the patient at high risk.

Primary Prevention ICDs

Primary prevention against sudden death is reasonable in certain patients based on results of clinical trials including the Multicenter Automatic Defibrillator Implantation Trials (MADIT) I and II, the Multicenter Unsustained Tachycardia Trial (MUSTT), and the Sudden Cardiac Death Heart Failure Trial (SCD-HeFT) [8]. Table 16.8 summarizes indications for ICD implantation for populations with no prior history of sudden death or sustained ventricular tachyarrhythmias but who are considered high risk [8]. These populations generally include those with reduced left ventricular ejection fractions (≤35 %) or with other disease processes that may increase proclivity towards ventricular tachyarrhythmias (e.g., sarcoidosis, arrhythmogenic right ventricular dysplasia, hypertrophic cardiomyopathy, long QT, or Brugada syndrome). Patients with a family history of sudden death in primary relatives, with reduced ejection fractions, or with electrocardiographic abnormalities including prolongation of the baseline QT interval or a Brugada pattern should be referred to an electrophysiology center for evaluation for possible ICD implantation. While current risk stratification tools are excellent at discriminating those at risk for sudden death, the majority of patients who will experience sudden death are still not covered within all the subgroups that are known to be high risk, and all people with high-risk

Table 16.8 Primary and secondary indications for ICD implantation

Class	Indication
I	Survivors of cardiac arrest due to ventricular fibrillation (VF) or hemodynamically unstable sustained ventricular tachycardia (VT) after evaluation to define the cause of the event and to exclude any completely reversible causes
	Patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable
	Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced during electrophysiology study
	Patients with left ventricular ejection fraction (LVEF) ≤35 % due to prior myocardial infarction (MI) who are at least 40 days post-MI and are functional class II or III
	Patients with nonischemic dilated cardiomyopathy who have an LVEF ≤35 % who are functional class II or III
	Patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF ≤30 %, and are functional class I
	Patients with nonsustained VT due to prior MI, LVEF ≤40 %, and inducible VF or sustained VT at electrophysiologic study
IIa	Patients with unexplained syncope, significant LV dysfunction, and nonischemic dilated cardiomyopathy
	Patients with sustained VT and normal or near normal left ventricular function
	Patients with hypertrophic cardiomyopathy who have one or more major risk factors for sudden cardiac death
	Prevention of sudden cardiac death in patients with arrhythmogenic right ventricular cardiomyopathy who have one or more risk factors
	To reduce sudden cardiac death risk in patients with long QT syndrome who are experiencing syncope and/or VT while receiving beta-blockers
	Non-hospitalized patients awaiting transplantation
	Patients with Brugada syndrome who have had syncope
	Patients with Brugada syndrome who have documented VT that has not resulted in cardiac arrest
	Patients with catecholaminergic polymorphic VT who have had syncope and/or documented sustained VT while receiving beta-blockers
	Patients with cardiac sarcoidosis, giant cell myocarditis, or Chagas' disease
IIb	Patients with nonischemic heart disease who have an LVEF ≤35 % and are functional class I
	Patients with long QT syndrome and risk factors for sudden cardiac death
	Patients with syncope and advanced structural heart disease in whom thorough invasive and noninvasive investigations have failed to define a cause
	Patients with a familial cardiomyopathy associated with sudden death
	Patients with LV non-compaction
III	Patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year, even if they meet ICD implantation criteria above
	Patients with incessant VT or VF
	Significant psychiatric illness since they may be aggravated by device implant or if illness precludes systematic follow-up
	Class IV patients with drug-refractory congestive heart failure who are not candidates for transplant or cardiac resynchronization
	Syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias and without structural heart disease
	When VT or VF is amenable to surgical or catheter ablation (e.g., arrhythmias associated with the Wolff–Parkinson–White syndrome, RV or LV outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease)
	VT or VF due to a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, or trauma)

Adapted Epstein et al. [29]. With permission from Wolter Kluwers Health

features will not necessarily go on to have a ventricular tachyarrhythmia. However, at least in the heart failure population and other groups with genetic channelopathies or infiltrative/inflammatory cardiac processes, ICD therapy is beneficial in terms of overall risk–benefit for preventing sudden death, even when taking into account cost of the device and risks associated with the procedure.

The exception to the role for placing ICDs for reduced ejection fractions is immediately after myocardial infarction or revascularization. The Coronary Artery Bypass Graft-Patch Trial (CABG-Patch) demonstrated no benefit to ICD implantation immediately after revascularization in the setting of an ejection fraction ≤35 % and an abnormal signal-averaged ECG. In turn, several trials have now shown that, even with a reduced ejection fraction after myocardial infarction, though the risk of sudden death is presumed to be increased in the periinfarction period, there is no benefit to ICD implantation in the first 40 days, primarily related to an increased rate of non-arrhythmic deaths in patients receiving ICDs (Table 16.9). Thus, the decision to place a primary prevention ICD after a myocardial infarction is usually deferred for 40 days after myocardial infarction and for 90 days after recent revascularization for ischemic cardiomyopathy, during which period the patient is followed for improvement in the ejection fraction.

In patients presenting with a new diagnosis of heart failure unrelated to ischemia, ICD implantation is often deferred because cardiac function may improve on guideline-directed heart failure therapy. Thus, even in the setting of a reduced ejection fraction, regardless of whether or not the patient had a recent myocardial infarction, decision may be made to defer ICD therapy, though these patients are still at high risk of sudden arrhythmic death should their heart function not improve. Antiarrhythmic drugs have not been shown to be beneficial as primary prevention against sudden death in these patients, likely due in part to potential pro-arrhythmic effects. Wearable external defibrillators have proven beneficial in these patients as a bridge to ICD therapy for prevention of sudden death related to ventricular tachyarrhythmias.

Secondary Prevention ICDs

Secondary prevention ICDs are placed when a patient presents with syncope or cardiac arrest due to a presumed ventricular tachyarrhythmia, whether VT or VF. Table 16.8 summarizes the indications for ICD implantation for primary and secondary prevention [8]. In the case of patients with clear idiopathic VT that has a high likelihood of cure with ablation, ICD is not indicated. However, idiopathic VT is unlikely to be associated with true syncope or cardiac arrest, and thus, other etiologies or other coexisting cardiac disease should be considered if a patient has idiopathic VT and syncope.

Monomorphic Ventricular Tachycardia

Ventricular tachycardia (VT) always needs to be considered within the context of the underlying substrate. Monomorphic VT may be idiopathic, occur in the setting of a nonischemic, inflammatory, or infiltrative cardiomyopathy or occur secondary to scar from prior infarction. The most common cause of monomorphic VT is scar related to prior infarct. The treatment of patients presenting with monomorphic VT may include either antiarrhythmic drug therapy or ablation. Table 16.10 lists indications for VT ablation [24–26].

Idiopathic VT

Idiopathic VTs, such as those related to the left or right ventricular outflow tract, fascicles, or papillary muscles, are

Table 16.9 Randomized trials evaluating the role of ICDs early after myocardial infarction

Trial	Number patients	Inclusion criteria	Mean follow-up (months)	Arrhythmic death (%)			Non-arrhythmic death (%)			Overall mortality (%)		
				ICD	Control	*p*-value	ICD	Control	*p*-value	ICD	Control	*p*-value
DINAMIT	674	EF≤35 %, HR≥80 bpm or HRV≥70 ms	30	4	8.5	0.009	15	8.5	0.020	19	17	0.66
BEST+ICD	143	EF≤35 %, PVCs≥10/h, EPS-guided ICD implantation	18	7.5	11.0	0.400	4	12.5	NS	20	29.5	0.20
IRIS	898	Criteria 1: EF≤40 % with HR≥90; criteria 2: NSVT≥150 bpm	37	6	13.0	0.049	15	9.0	0.001	26	26	0.78

All ICDs in all three trials were placed within 40 days after myocardial infarction for the inclusion criteria listed. *HRV* heart rate variability, *EF* ejection fraction, *HR* heart rate, *NSVT* nonsustained ventricular tachycardia, *ICD* implantable cardioverter defibrillator, *DINAMIT* the defibrillator in acute myocardial infarction trial, *BEST+ICD* beta-blocker strategy plus implantable cardioverter defibrillator trial, *IRIS* immediate risk stratification improves survival trial

Table 16.10 Consensus guidelines for VT ablation

Class	Indication
Idiopathic ventricular tachycardia and premature ventricular contractions	
I	Symptomatic VT or PVC of right ventricular origin unresponsive to medical therapy with beta-blockers and calcium channel blockers
	Symptomatic VT or PVC of left ventricular fascicular or endocardial origin remote from the aortic sinus of Valsalva unresponsive to medical therapy with beta-blockers and calcium channel blockers
	Symptomatic or asymptomatic VT/or VC of right ventricular or left ventricular origin thought to be causing cardiomyopathy and unresponsive to medical therapy
IIa	Asymptomatic sustained VT of right ventricular origin unresponsive to medical therapy
IIb	Symptomatic VT or PVC originating from uncommon left ventricular sites (aortic sinus of Valsalva, epicardium) that are unresponsive to medical therapy including class I/III agents
	Asymptomatic sustained VT of left ventricular origin unresponsive to medical therapy
III	Asymptomatic PVC of right or left ventricular origin not thought to be causing cardiomyopathy
Nonischemic VT or VF	
I	Sustained monomorphic VT in patients at low risk of sudden death when drug therapy is not effective, not tolerated, or not preferred
	Bundle branch reentrant VT
	Adjunctive treatment for VT storm in patients with an ICD
	Accessory pathway ablation in VF caused by preexcited AF in WPW syndrome
IIa	Symptomatic nonsustained VT in patients at low risk of sudden death when drug therapy is not effective, not tolerated, or not preferred
	Frequency symptomatic PVC in patients at low risk of sudden death when drug therapy is not effective, not tolerated, or not preferred
	Ablation of accessory pathway to prevent VF in symptomatic patients with WPW syndrome in whom the refractory period of the accessory pathway is less than 240 ms
IIb	Ablation of Purkinje fiber potentials in VT/VF storm consistently triggered by ectopics of a similar morphology
	Ablation of asymptomatic PVC to avoid or treat tachycardia-induced cardiomyopathy
III	Ablation of asymptomatic and infrequent PVC is not indicated
Ischemic ventricular tachycardia	
I	Patients after myocardial infarction with an ICD who present with repetitive monomorphic VT that leads to multiple shocks or who present with drug-refractory incessant VT or "electrical storms" that cannot be avoided despite adequate reprogramming of the antitachycardia pacing mode and that cannot be prevented by beta-blocker and/or antiarrhythmic drug therapy or when patients are intolerant of these drugs
	Patients after myocardial infarction with an ICD who present with repetitive sustained VT, which made mandatory the therapy with antiarrhythmic drugs that decreased the rate of VT below an acceptable intervention rate into the range of exercise-induced sinus rhythm despite concomitant beta-blocker therapy
	Patients with bundle branch reentry after myocardial infarction
IIa	Patients after myocardial infarction with an ICD who present with infrequent monomorphic VT that have been terminated successfully by more than one electrical shock that most probably cannot be avoided in the long-term future despite adequate reprogramming of the antitachycardia pacing mode and where it is difficult to predict whether future events can be avoided by beta-blocker and/or antiarrhythmic drug therapy or when patients are not willing to take long-term drugs the efficacy of which cannot be predicted beforehand
IIb	As the sole procedure, that is, without an ICD, in patients after myocardial infarction who have relatively well-preserved LV function (above 35–40 %) and in whom VT is monomorphic, relatively slow, and well tolerated, who are considered to have a good long-term prognosis, and who are either drug resistant, do not tolerate an antiarrhythmic drug, or do not accept long-term therapy
	Patients after myocardial infarction who present with frequent self-terminating monomorphic VT that may cause shock intervention by the ICD that potentially cannot be avoided by changing the intervention rate of the ICD
	Patients with markedly reduced longevity and comorbidities (e.g., heart failure, reduced renal function) where VT can either not be prevented by antiarrhythmic drug therapy or drugs have not been tolerated and where an ICD would not be indicated due to the overall condition of the patient)
	Patients with more than one intervention of the ICD by a shock that is causing severe anxiety and psychological distress

unlikely to be associated with sudden death, particularly in the absence of structural heart disease. Treatment may consist of beta-blockers or, in the case of fascicular tachycardias, calcium channel blockers such as verapamil. Most of these VTs are automatic, and ablation is >95 % effective in curing idiopathic VT when performed in experienced centers. Thus, it is reasonable to consider VT ablation in patients initially presenting with presumed idiopathic VT.

Monomorphic VT Associated with Prior Infarction

Monomorphic VT associated with prior myocardial infarction is not uncommon. Generally, patients will present with ICD therapies, including ATP or ICD shock. However, even in the absence of primary prevention indications, the presence of scar may serve as the substrate for the pathogenesis of VT. Patients may present with sudden death or, rarely, hemodynamically tolerated VT localizable to the area of scar. The primary mechanism of VT is reentry. Rarely, patients may present with bundle branch reentry VT that is easily targeted in the area of the right bundle branch, though other circuits for scar-related VT may coexist.

Treatment of the patient presenting with monomorphic VT in the setting of prior infarction should be aimed at treating heart failure exacerbation if present, implantation of an ICD for secondary prevention if the patient does not already have one, and decision regarding need for further therapy to treat the arrhythmia. An ischemia evaluation is reasonable in these patients, though ischemia does not precipitate monomorphic VT and thus should not be considered the cause of VT.

A single episode of monomorphic VT seen clinically or on ICD interrogation in the setting of a reduced ejection fraction may prompt no treatment (a watch-and-see approach to evaluate for recurrence), initiation of antiarrhythmic drugs as suppressive therapy, or referral for ablation. Amiodarone is often the drug of choice in these patients and has the greatest efficacy for suppressing further episodes of VT, though sotalol (in the absence of significant heart failure symptoms), quinidine, dofetilide, and mexiletine are reasonable options as well. Beta-blockers should also be initiated as tolerated. Trials have been performed on the utility of antiarrhythmic drugs and of early ablation in the setting of patients presenting with either single episodes or multiple episodes of infarct-related VT. These trials support a role for considering early ablation in these patients, which is typically aimed at either modification of the scar or targeting of the specific arrhythmia if it is hemodynamically tolerated and thus amenable to mapping and more precise localization.

The patient presenting with recurrent ICD therapies (whether ATP or ICD shocks) over the course of months to years or electrical storm (multiple ICD shocks within a short period of time) may also be considered for antiarrhythmic drug therapy or ablation. The likelihood of success of ablation as a primary modality often relates to the number of different morphologies of VT present and the complexity of the substrate. If all VTs are of a single morphology, there is likely one primary circuit. However, if several different VTs exist, their circuits may share a common substrate but exit at different points requiring more extensive ablation or emanate from multiple different sites.

Catheter ablation in ischemic monomorphic VT is aimed at targeting the primary circuit responsible for the VT, if possible, and the area of scar which serves as the substrate for reentry. This involves mapping of the heart including definition of areas of scar using voltage mapping followed by attempts at initiation of the VT and mapping during the VT, if possible. Sometimes multiple VTs may be induced, and then a substrate modification approach alone may be used (Fig. 16.7). At the termination of the case, attempts at reinducing VT are used to determine the likelihood of success of the ablation procedure. Successful endpoints may include the inability to induce any VT or the inability to induce any VT at the same cycle length or slower than the clinical VT. The results of substrate-based ablative therapy for ventricular tachycardia

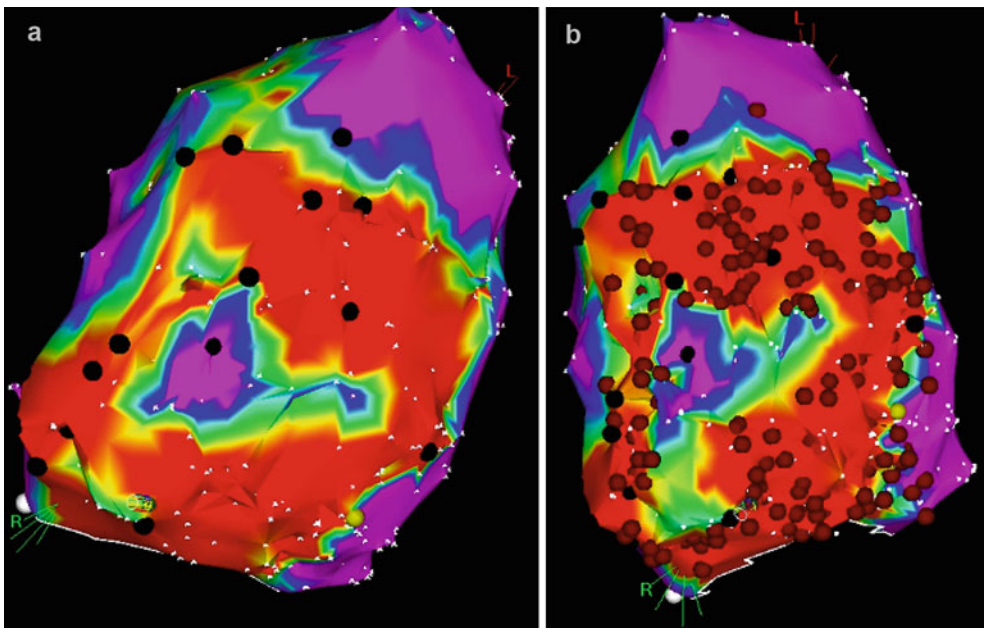

Fig. 16.7 Example of ischemic ventricular tachycardia map and substrate ablation – shown is the bipolar voltage map (**a**) from a patient with a history of an inferior wall myocardial infarction. The *red* indicates areas of scar with the *purple* representing areas of healthy myocardium. *Intermediate* colors at the borders represent the border zone of the scar. The heart is seen from a left anterior oblique inferior view. The *black dots* are areas of late potentials. Figure (**b**) shows the final map with the ablation lesions. The red dots represent ablation lesions. A substrate modification approach was used given the VT was not hemodynamically tolerated ablation lesions were applied throughout the region of scar. VT was not inducible at the end of the procedure

have been excellent. Most patients experience good arrhythmia control with elimination of the risk of "VT storm" and reduction or elimination of antiarrhythmic drug therapy [30].

Some patients may have scar not amenable to endocardial ablation alone. Epicardial ablation, in which the pericardial space is accessed via a subxiphoid approach, may be required. Epicardial scar as a substrate for VT is most common in patients with nonischemic right or left ventricular cardiomyopathy. Other options for ablation include alcohol ablation (instilling alcohol into a coronary artery to ablate a region of myocardium) and surgical ablation, including substrate modification using cryoablation in patients with nonischemic cardiomyopathy and subendocardial resection from the edges of aneurysm or scar.

VT Associated with Other Structural Heart Disease

Monomorphic VT may occur secondary to a variety of other disease processes, including arrhythmogenic right ventricular dysplasia, sarcoidosis, and other nonischemic cardiomyopathies. Similar to the approach with patients with ischemic scar, in addition to ensuring that patients have an ICD, therapy may be aimed at either suppression using antiarrhythmic drugs or more permanent elimination via ablation. Antiarrhythmic drug choices are similar to those used in ischemic VT and include beta-blockers, amiodarone, mexiletine, dofetilide, sotalol (if significant heart failure symptoms are not present), and quinidine. As indicated, ablation in patients with nonischemic causes of VT more often requires an epicardial approach than with ischemic VT, though an endocardial approach is still typically attempted first. Successful ablation in patients with sarcoid and arrhythmogenic right ventricular dysplasia may stave off recurrence of ventricular arrhythmia for years, thus avoiding the potential for ICD shocks and need for antiarrhythmic drug therapy.

Polymorphic Ventricular Tachycardia and Ventricular Fibrillation

Polymorphic VT and VF should always prompt evaluation for a secondary cause, in particular ischemia. Rarely, coronary vasospasm may induce VF, and in the case of patients who have no other identifiable cause, provocative maneuvers in the catheterization lab to evaluate for coronary vasospasm may be reasonable. If no ischemia is present and other secondary causes such as drugs and severe electrolyte abnormalities have been ruled out, an ICD should be placed for secondary prevention. In addition to ICD implantation, consideration should also be given to other causes such as PVC-induced VF. In this clinical entity, an irritable ectopic ventricular focus may trigger VF when timed perfectly against the normal cardiac cycle. This may be evident on electrocardiographic monitoring or on ICD electrograms as a single morphology PVC that precedes the onset of episodes of VF. In this special situation, ablation targeted at the PVC is reasonable. However, many cases of polymorphic VT or VF that occur in the absence of ischemia may not have a clear etiology. If ventricular tachyarrhythmias recur resulting in ICD therapies, it is reasonable to start an antiarrhythmic drug in addition to beta-blockers if the patient is not already taking them.

Summary

The clinical management of the arrhythmia patient requires an intimate understanding of pathophysiology. Consideration of symptoms and the natural history of different arrhythmias needs to be made whenever prescribing treatment. Furthermore, for many patients, both pharmacologic and invasive options may exist for long-term management. Advances in ablation offer improving success with regards to the curative treatment of arrhythmias. In turn, while antiarrhythmic drug therapy can be complex and have a wide array of side effects, it remains an important part of the management of patients, particularly in the setting of more complex arrhythmias such as atrial fibrillation or ventricular tachyarrhythmias. Ultimately, the goals of care and risks and benefits of different approaches need to be considered carefully with each patient when establishing a treatment plan.

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Syncope

17

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Introduction

Syncope is a syndrome in which a relatively brief and self-limited period of loss of consciousness is triggered by transient insufficiency of oxygen delivery to the brain [1, 2]. By far, the most common cause of syncope is spontaneously reversible systemic hypotension leading to insufficient cerebral blood flow; however, rare events such as acute hypoxemia (e.g., aircraft decompression at altitude) may also cause syncope. In the absence of complete loss of consciousness, the individual is considered to have experienced a near-faint or near-syncope (sometimes the term "presyncope" is used).

Syncope falls within a larger set of conditions in which there is real or apparent transient loss of consciousness (TLOC). However, not all TLOC is syncope. Thus, a TLOC episode should not be considered syncope if a medical intervention is required to reverse the loss of consciousness (e.g., glucose administration for hypoglycemia). Similarly, if cerebral dysfunction is not due to insufficient cerebral nutrient flow, the loss of consciousness or apparent loss of consciousness should not be termed syncope (e.g., concussion, epilepsy). Finally, many patients complain of less-specific symptoms such as "dizziness" or "lightheadedness." More often than not, these latter symptoms are not related to syncope either clinically or pathophysiologically but nevertheless often find their way into the "syncope clinic" and require evaluation.

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A wide range of conditions may be responsible for initiating syncope; in many instances, the trigger is relatively benign (e.g., upright posture or emotional upset or pain causing a vasovagal faint), but in other situations, the trigger for the faint may have more serious implications (e.g., ventricular tachyarrhythmias). In any case, whether the underlying problem is "innocent" or potentially life-threatening, syncope may lead to physical injury, accidents that put the affected individual and others at risk, and economic loss. Consequently, the management goals must be to first identify the specific causes(s) of the faint(s) and thereafter, based upon this knowledge, develop a treatment plan designed to prevent recurrences [1].

This chapter focuses principally on clinical management (diagnosis and treatment) of syncope. Whenever possible, the recommendations provided here are adapted from the European Society of Cardiology Syncope Task Force guidelines [1].

Classification and Etiology

Establishing the cause (or causes) of syncope is crucial in order to assess prognosis and provide an effective treatment strategy [1–3]. Unfortunately, however, the diagnostic evaluation of these patients is often challenging. In part, the difficulty is due to the fact that most syncope patients have returned to their usual state of health by the time they are first seen by medical practitioners. Consequently, the physician usually has little to find on initial examination, and whatever is found can only be inferentially linked to the apparent collapse. The result is that syncope patients are commonly admitted to the hospital and undergo expensive investigations, many of which are unnecessary and ultimately do not provide a definite diagnosis. The development of specialized syncope evaluation clinics and the publication of diagnosis and treatment guidelines may play an important role in improving care of these patients [1].

C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_17, © Springer Science+Business Media New York 2013

Table 17.1 Classification of syncope

Neurally mediated reflex syncopal syndromes
Vasovagal syncope (common faint)
Carotid sinus syncope
Situational syncope
Acute hemorrhage
Cough, sneeze
Gastrointestinal stimulation (e.g., swallow, defecation, and visceral pain)
Micturition (postmicturition)
Postexercise
Other (e.g., brass instrument playing, weightlifting, and postprandial)
Glossopharyngeal and trigeminal neuralgia
Orthostatic syncope
Primary autonomic failure syndromes (e.g., pure autonomic failure, multiple system atrophy, Parkinson's disease with autonomic failure)
Secondary autonomic failure syndromes (e.g., diabetic neuropathy, amyloid neuropathy, drugs, alcohol)
Volume depletion (e.g., hemorrhage, diarrhea, Addison's disease)
Cardiac arrhythmias as primary cause
Sinus node dysfunction (including bradycardia/tachycardia syndrome)
Atrioventricular conduction system disease
Paroxysmal supraventricular and ventricular tachycardias
Inherited syndromes (e.g., long QT syndrome and Brugada syndrome)
Implanted device (pacemaker and ICD) malfunction
Drug-induced proarrhythmias
Structural cardiac or cardiopulmonary disease
Cardiac valvular disease
Acute myocardial infarction/ischemia
Obstructive hypertrophic cardiomyopathy
Atrial myxoma
Acute aortic dissection
Pericardial disease/tamponade
Pulmonary embolus/pulmonary hypertension
Cerebrovascular
Vascular steal syndromes

Table 17.1 summarizes the most important causes of syncope, and a brief overview of the principal diagnostic categories is provided here.

- Neurally mediated syncope (also termed neural reflex syncope) comprises a number of related clinical conditions (Table 17.1), the best known of which is the common or vasovagal syncope. Other forms of neural reflex syncope include carotid sinus syndrome or syncope triggered by micturition or defecation. Swallowing or coughing may also trigger a reflex syncope; in the case of cough-induced syncope, hypotension induced by cough-related mechanics (i.e., transient obstruction of venous return) may also contribute to the faint (Fig. 17.1).
- Orthostatic (postural) syncope is very common. It is usually associated with movement from lying or sitting to a standing position. Most often, postural faints tend to occur a few moments after arising, especially if the affected individual has walked a short distance. Many healthy individuals experience a minor form of this syncope when they need to support themselves momentarily just after standing up (Fig. 17.2). The most dramatic postural syncope occurs in older frail individuals, particularly in the presence of autonomic failure (e.g., diabetes or certain nervous system diseases) or persons who are dehydrated (e.g., from hot environments or inadequate fluid intake). Certain commonly prescribed medications that inhibit the autonomic nervous system and/or reduce blood volume (e.g., β-adrenergic blockers, diuretics, antihypertensives, or vasodilators) may predispose to postural syncope.
- Cardiac arrhythmias may cause syncope if the heart rate is either too slow or too fast to permit maintenance of an adequate systemic arterial pressure. Bradycardia, such as sinus pauses or high-grade AV block, or asystole at the termination of an atrial tachyarrhythmia, is the most common cause of syncope in this section (Fig. 17.3). Occasionally, however, syncope of this type also occurs at the onset of an episode of paroxysmal ventricular or

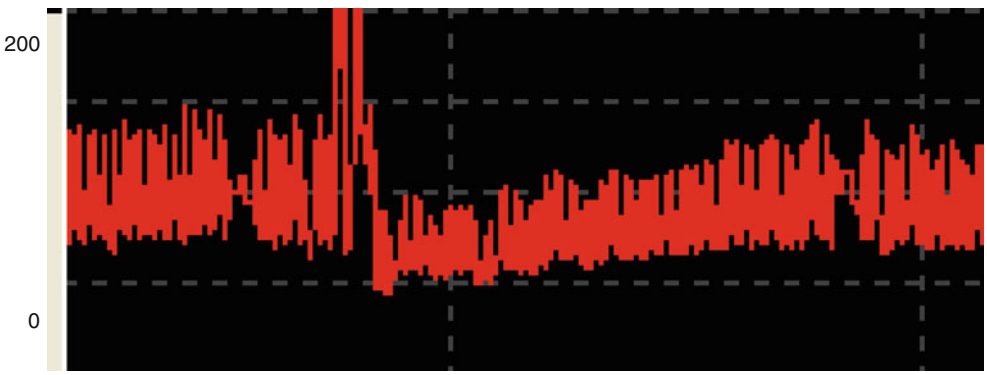

Fig. 17.1 Recording illustrating noninvasive blood pressure recording during and after a brief cough (spike in trace). The arterial pressure declined abruptly and remained below control value for >30 s. Patient was seated during this test

supraventricular tachycardias. Neurally mediated hypotension plays an important role in these patients. Individuals with underlying heart disease (e.g., previous myocardial infarction or valvular heart disease) or disturbances of autonomic nervous system responsiveness are at greatest risk for arrhythmia-related syncope. Patients suspected of ventricular tachycardia-induced syncope should receive prompt referral for cardiac electrophysiological evaluation due to high risk of sudden cardiac death [4].

- Structural cardiopulmonary diseases (such as acute myocardial infarction or pulmonary embolism) are relatively infrequent causes of syncope. Neurally mediated reflexes as well as the direct hemodynamic impact of the acute disease process are the important underlying mechanisms.
- Cerebrovascular disease is almost never the cause of a true syncope [1, 2, 5]. A rare exception may be vertebrobasilar transient ischemic attack (TIA), but this condition is very rare and is usually accompanied by other symptoms suggesting a posterior cerebral circulation problem such as vertigo. Subclavian steal (evidenced by blood pressure difference of >20 mmHg between arms) is another example in this class.
- Conditions that mimic syncope (Table 17.2) are included primarily because they often are mislabeled as syncope and thereby cause diagnostic confusion. In the absence of the essential mechanism of syncope (transient global cerebral hypoperfusion), a real or apparent episode of loss of consciousness should not be diagnosed as syncope. The most common conditions in this category include seizures, sleep disturbances, cataplexy, accidental falls, and some psychiatric conditions (e.g., anxiety attacks and hysterical reactions).

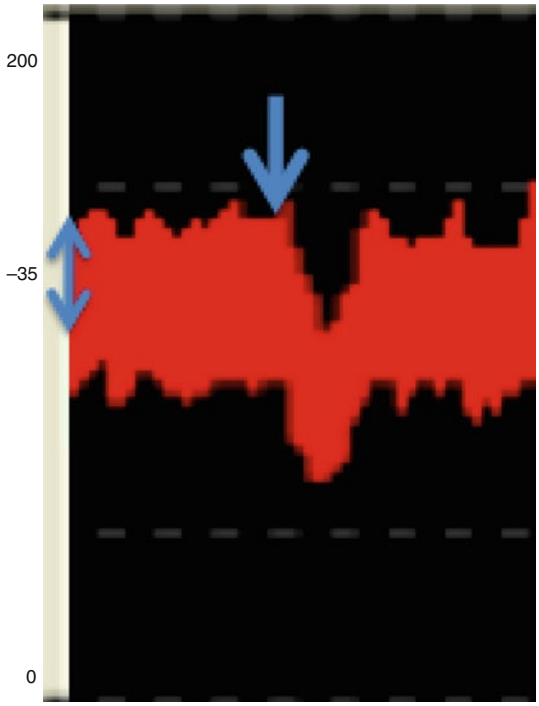

Fig. 17.2 Immediate orthostatic hypotension (OH) syncope: graphic representation of a prompt drop in blood pressure occurring in a patient who complained of near-faints immediately upon arising from seated or supine position. Systolic and diastolic pressure on a beat-by-beat basis is illustrated at very slow recording speed. The *top blue arrow* indicates when the patient stands up from a seated position. The recording obtained by a noninvasive technique (Finometer®) reveals an approximate immediate 35 mmHg drop of arterial pressure. The pressure drop is brief (about 10 s duration) and then recovers promptly. The patient complained of feeling "lightheaded" for a few seconds after standing

Epidemiology, Recurrence, and Prognosis

The reported prevalence of syncope varies from 15 to 25 % in different populations. The highest frequency of worrisome causes of syncope occurs in patients with cardiovascular comorbidity and older patients in institutional care settings. Younger, otherwise well individuals, tend to have more benign forms of syncope, particularly vasovagal faints (however, one should not rely on all faints in young persons being

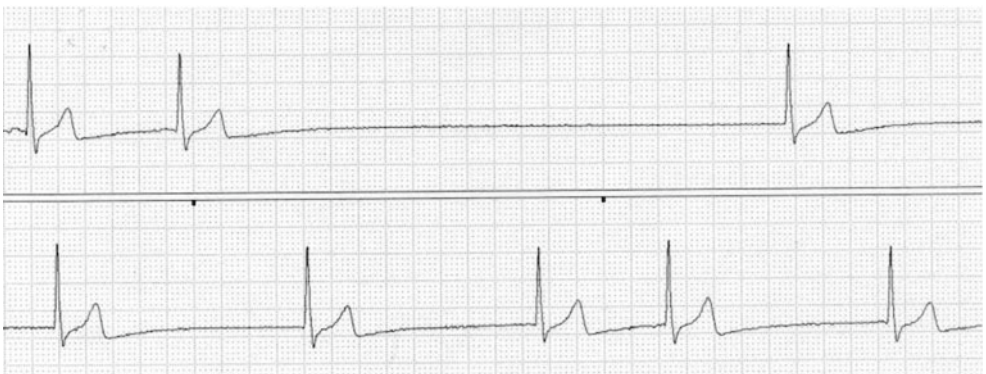

Fig. 17.3 Continuous ECG monitor strip revealing marked bradycardia in a patient who presented with syncope. The patient had not been taking any medications. Cardiac pacing was indicated

innocent in nature). Recent surveys indicate that syncope accounts for approximately 1 % of emergency department visits in Europe [6, 7] and from 1 to 6 % of general hospital admissions in the USA [8–11].

A rough sense of the "burden" of syncope in various population subsets can be derived from the literature. Thus, the Framingham Study reported occurrence of at least one syncope event in approximately 3 % of men and 3.5 % of women [12] in a relatively broad-based free-living population studied over an approximate 26-year follow-up. The first syncope occurred at an average age of 52 years (range 17–78 years) for men and 50 years (range 13–87 years) for women. Further, while syncope occurred at virtually all ages, syncope burden tended to increase with advancing age from 8/1,000 person exams in the 35–44-year-old age group to approximately 40/1,000 person exams in the ≥75-year-old age group. In more selected populations, syncope has been estimated to occur in 15 % of children <18 years of age, 25 % of young military population, and in up to 23 % of a nursing home population >70 years of age [9, 10, 12–18]. However, with respect to the elderly patient, the reported frequency may well be an underestimate since many of these individuals exhibit various degrees of cognitive impairment that may affect memory of events, and up to 20 % of these individuals are believed to be amnestic for such episodes (i.e., retrograde amnesia) and often when queried will deny that they ever lost consciousness. Eyewitness accounts then become crucial.

Two reports provide an assessment of syncope burden among free-living persons, although they tend to focus on younger individuals. Ganzeboom et al. [17] surveyed medical students in the Netherlands and found that 39 % had fainted at least once by about age 25 (women, 47 % vs. men, 24 %). A report from the University of Calgary indicated that the likelihood of at least one faint was 37 % by age 60, and almost all first spells occurred by age 40 [19]. Combined, these studies suggest that 40 % of people faint at least once in their lives.

In terms of the causes of syncope, as noted earlier, younger patients without structural heart disease predominantly exhibit neurally mediated reflex faints and especially vasovagal syncope. However, one should remain alert to the so-called channelopathies in such patients (e.g., long QT syndrome, Brugada syndrome). While these are relatively rare, they are being recognized with increasing frequency and have a worrisome prognosis; some remain as yet unidentified from a genetic perspective but nevertheless can cause life-threatening arrhythmias (Fig. 17.4). Among patients with known structural heart disease (i.e., coronary artery disease, valvular disease, cardiomyopathies, and consequences of hypertension) and elderly individuals, there is increased concern for more worrisome causes of syncope (e.g., cardiac arrhythmias, orthostatic faints due to primary neurologic disease). Mortality is a greater concern in these patients than among individuals with no structural disease; however, the primary mortality "driver" is the severity of the heart disease rather than the syncope itself. Furthermore, whatever the cause of syncope, older patients with faints are at increased risk of serious injury.

Ungar et al. [20], in an assessment of 242 patients aged 65–98 years, found that the combination of neural reflex and orthostatic faints accounted for 67 % of diagnoses. Vasovagal, situational, and carotid sinus syndrome (CSS) (i.e., the neurally mediated reflex faints) made up 62 % of cases in patients ≤75 years of age and 36 % in patients >75 years. More recently, Anapalahan and Gibson reported observations in 200 patients ≥65 years of age who presented to the ED due to unexplained or accidental falls. Their findings indicated that approximately 25 % of unexplained falls were due to neurally mediated reflex syncope [21]. Overall, in a broad examination of the literature, the ESC syncope task force found that orthostatic faints (OH) and CSS were particularly prevalent in older patients. In the case of OH, age-related neurological

Table 17.2 Causes of conditions commonly misdiagnosed as syncope

Disorders with impairment or loss of consciousness
Metabolic disorders (e.g., hypoglycemia, hypoxia, and hyperventilation with hypocapnia)
Epilepsy
Intoxication (drugs and alcohol)
Vertebrobasilar transient ischemic attack
Disorders resembling syncope without loss of consciousness
Cataplexy
Drop attacks
Psychogenic pseudosyncope
Transient ischemic attacks of carotid artery origin

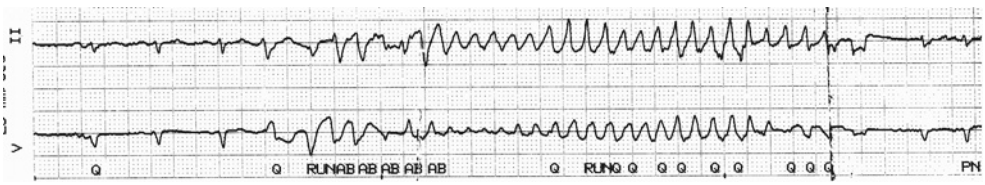

Fig. 17.4 ECG monitor strip revealing nonsustained polymorphous VT in a patient who presented with recurrent syncope. Although the tachycardia resembles torsades, the patient did not have evident LQTS and the onset was not of the "long-short" form. Correction of electrolyte disturbance (marked hypokalemia) appeared to resolve the problem, but an ICD was placed as well

causes contribute to syncope susceptibility, but drug-induced OH is also a very important consideration. CSS accounts for 20 % of syncope in older individuals with vasovagal syncope amounting to a further 15 %. Finally, although less frequent, cardiac causes become more frequent with increasing age and concomitant prevalence of structural heart disease [1].

In economic terms, the Ambulatory and Hospital Care Statistics Branch of the Centers for Disease Control and Prevention's National Center for Health Statistics provides periodically on its website (http://www.cdc.gov/nchs/ahcd.htm) nationally representative data on ambulatory care visits to hospital EDs in the USA. Statistics are presented on selected hospital, patient, and visit characteristics based on data collected in the National Hospital Ambulatory Medical Care Survey (NHAMCS). NHAMCS is a national probability survey of ED visits and outpatient departments of nonfederal short stay and general hospitals in the USA. However, as in any survey, results are subject to sampling errors, processing errors, and biases due to nonresponse/incomplete response. The NHAMCS in 2006 noted that primary diagnosis of "Syncope and Collapse" (ICD-9; 780.2) had increased from approximately 887,000 ED visits in 2001 to greater than 1,125,000 ED visits in 2006. In 2008, syncope and collapse remained in the top 10 reasons for ED visits for both men and women. On the other hand, "syncope and collapse" listed among all US hospital discharge diagnoses in the 2006 National Hospital Discharge Survey remained relatively constant over this same time period, 405,000 in 2001 and 411,000 in 2006. This suggests, perhaps, that ED physicians are becoming less hesitant to have such patients evaluated on an outpatient basis.

Recurrences

One-third of syncope patients have symptom recurrences by 3 years of follow-up [1, 8]. The majority of these recurrences occur within the first 2 years. Predictors of recurrence include a history of recurrent syncope at the time of presentation (i.e., recurrences, at least statistically, tend to lead to more future recurrences), age less than 45 years, or a psychiatric diagnosis. After positive tilt-table testing, patients with more than six syncopal spells have a risk of recurrence of >50 % over 2 years. Additionally, in a more recent analysis which mainly included a young referral-based population, the history of syncope in the past year was shown to better predict recurrent syncope than was a history of syncope in the more distant past [22].

Quality of Life (QoL)

The social impact of TLOC/syncope is important. Syncope may result in injury and recurrent syncope is associated with fractures and soft tissue injury in >10 % of fainters [23]. Fortunately, syncope while driving is thought to be a rare cause of motor vehicle accidents; sleep deprivation and intoxication are much more important. On the other hand, falls as a result of syncope are important. There is a marked negative relationship between the frequency of symptomatic episodes and overall perception of health [24]. Functional disturbance may also make these individuals more prone to injury.

Apart from physical injury, patients with recurrent syncope may develop moderate to severe functional incapacity similar to those associated with chronic disease states. Impairment is particularly evident in domains such as mobility, usual activities, self-care, pain and discomfort, and anxiety and depression. By way of example, Santhouse et al. [25] compared psychiatric assessment and quality of life (QoL) measures in 52 syncope patients, 96 patients with epilepsy, and 100 healthy controls. The syncope and epilepsy groups did not differ substantially in terms of psychiatric and QoL findings, but both manifested greater anxiety and depression and reduced QoL compared to controls.

Prognosis

Many syncopal patients, especially young healthy individuals with a normal ECG and without heart disease, have an excellent prognosis. Most of these individuals have one of the neurally mediated syncope syndromes. While injury and QoL issues may be important considerations, mortality risk is generally not. However, the prognosis of syncope is not always benign, especially in the presence of cardiac diseases or channelopathies.

Four risk factors favoring cardiac causes of syncope or death are age >45 years, history of congestive heart failure, history of ventricular arrhythmias, and abnormal ECG (other than nonspecific ST changes). Arrhythmias or death within 1 year occurred in 4–7 % of patients without any risk factors and progressively increased from 58 to 80 % in patients with three or more factors. The 1-year mortality of patients with cardiac syncope is consistently higher (18–33 %) than patients with noncardiac causes (0–12 %) or unexplained syncope (6 %). The 1-year sudden death rate is 24 % in patients with a cardiac cause compared with 3 % in the other two groups [7, 8, 26, 27].

The presence and severity of coexisting structural heart disease are the most important predictors of mortality risk in syncope patients. Thus, among individuals with cardiac syncope (i.e., primary cardiac arrhythmia, an ischemic episode, or severe valvular heart disease), the 1-year mortality is high (ranging between 18 and 33 %) compared to that for patients with either noncardiac (including "vasovagal") causes of syncope (0–12 %) or unexplained syncope. The risk of death differences is even more striking when considering "sudden

cardiac death" events; the 1-year incidence of sudden death is approximately 24 % in patients with a cardiac cause versus about 3 % in the other two groups [8, 12]. Although patients with cardiac syncope have higher mortality rates compared with those of noncardiac or unknown causes, cardiac syncope patients do not as a rule always exhibit a higher mortality compared with matched controls having similar degrees of heart disease [28–32]. There are, however, some important exceptions to this rule. These include severe aortic stenosis (average survival without valve replacement of 2 years), hypertrophic cardiomyopathy in which syncope at diagnosis is a predictor of increased sudden death risk, and possibly patients with heart failure and severe left ventricular dysfunction as described by Olshansky et al. [32].

As suggested earlier, the mortality risk associated with syncope in the setting of one of the channelopathies (e.g., Brugada syndrome, long QT syndrome) or in the presence of arrhythmogenic right ventricular dysplasia (ARVD) may reasonably be considered to fall into this exception as well, if the syncope is known to be due to ventricular tachyarrhythmias. However, apart from LQTS, prognostic implications of syncope in other channelopathies are less well settled. In regard to LQTS, one large prospective observational trial [33] in >800 patients, cardiovascular endpoints including apparent syncope, cardiac arrest and sudden death occurred in 23 % of patients. Syncope was associated with a fivefold increased risk of cardiac arrest or sudden death, but it was not a sensitive indicator of death risk. Conversely, in a multicenter study [34], 40 % of 220 Brugada patients implanted with an ICD had a history of syncope, but the patients with syncope were not at a higher risk of appropriate ICD discharge than those who had been asymptomatic. Similarly, in a large meta-analysis [35] encompassing 1,140 patients (262 of them [23 %] with a history of syncope), the patients with syncope had the same risk of ventricular tachyarrhythmias as those who had been without syncope and significantly lower than those presenting with documented cardiac arrest.

Pathophysiology and Clinical Presentation

As noted already, transient global cerebral hypoperfusion is the sine qua non of syncope pathophysiology [1, 2]. In the vast majority of cases, diminished cerebral perfusion is due to a transient fall in systemic blood pressure. Acute hypoxemia, such as might occur with abrupt high altitude aircraft decompression, could also be the culprit, but fortunately this mechanism is very rare.

Cerebral blood flow is normally autoregulated within a relatively wide range of systemic blood pressures. A decrease in systolic blood pressure to 60 mmHg or less usually leads to syncope (Fig. 17.5). Consequently, the integrity of cerebral nutrient flow is ultimately dependent on mechanisms

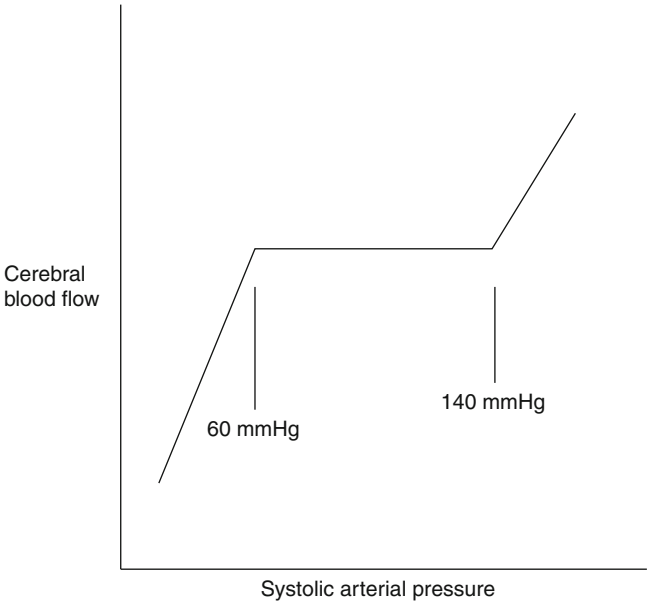

Fig. 17.5 Graph illustrating the manner in which cerebral blood flow is autoregulated over a wide range of systemic pressures under normal conditions. On this graph, cerebral blood flow (*y*-axis) remains relatively constant over the arterial pressure range (*x*-axis) 60–140 mmHg. Only at lower or higher pressures is flow pressure-dependent. Disease states, such as diabetes or hypertension, may move the "autoregulated" zone to higher pressures. In such cases, affected individuals may be even more predisposed to faints

that maintain systemic pressure. The most important of these factors are:

- Baroreflexes and autonomic adjustment in blood pressure, cardiac contractility, and heart rate
- Intravascular volume regulation, incorporating renal and hormonal influences to maintain central blood volume

Transient failure of the protective mechanisms that govern cerebral blood flow may be due to various factors, including diseases that result in primary or secondary autonomic failure, vasodilator drugs, diuretics, dehydration, or hemorrhage. Any of these may reduce systemic blood pressure below the autoregulatory range and thereby trigger a syncopal episode.

Orthostatic blood pressure adjustment is crucial for permitting humans to operate in the upright posture and not be recurrently subjected to gravitationally induced drops in cerebral blood flow that could initiate syncope. Moving from the supine to the erect posture initiates a large gravitational shift of blood away from the chest to the venous capacitance system below the diaphragm [1, 36]. This shift is estimated to total 500–1,000 ml of blood and largely occurs in the first 10 s of standing. With prolonged standing (within 10 min), the high capillary transmural pressure in dependent parts of the body causes a filtration of protein-free fluid into the interstitial spaces. As a consequence of this gravitationally induced blood pooling and superimposed decline in plasma

volume, the return of venous blood to the heart is reduced, resulting in rapid diminution of cardiac filling pressure and decrease in stroke volume. Reflex-induced increase in heart rate is the immediate response to maintain cardiac output. However, vasoconstriction and subsequent neuroendocrine system adjustment are important to compensate for reduced effective blood volume. Intra-abdominal vasoconstriction may be particularly crucial as the splanchnic bed is very large and compliant and can provide a substantial reservoir for vascular volume leaving the thorax.

In many forms of syncope, impaired vasoconstriction is a key factor leading to systemic hypotension. Similarly, reduced skeletal muscle pump activity due to prolonged quiet upright posture may be an additional important contributor as well. On the other hand, certain physiological maneuvers may help prevent hypotension [37]. Physical movement and leg crossing enhance muscle pump activity, supine posture reduces gravitational demands on vascular constriction, and increased "respiratory pump" activity may increase venous return. In fact, enhancement of respiratory pump activity appears to be a promising means for reducing susceptibility to excessive orthostatic hypotension.

Loss of postural tone is an inevitable consequence of loss of consciousness. If the affected individual is not restrained, he or she will slump to a gravitationally neutral position (e.g., fall to the ground). Sometimes, nonskeletal muscles may be affected, resulting in loss of bladder (common) or bowel (rare) control. On occasion, patients may have jerky movements after onset of loss of consciousness; because of these muscle movements, true syncope may be mistaken for a seizure disorder or "fit" by untrained witnesses.

Risk Stratification: In-Hospital Versus Out-of-Hospital Evaluation of Syncope

In-hospital evaluation of patients with syncope may be a necessity in certain cases. Unfortunately, many more patients are admitted than is probably necessary. Furthermore, most hospital facilities are inadequately equipped and organized to manage these patients optimally. The development of an organized multidisciplinary group of physicians (e.g., cardiologists, neurologists, and psychiatrists) may be warranted in order to provide a more efficient approach to the problem. In certain hospitals, this type of organized approach is incorporated within a "syncope clinic" or "syncope unit." Syncope units offer the potential for improving the accuracy and cost-effectiveness of syncope evaluation and treatment.

The ineffectiveness of conventional approaches to evaluation of the suspected syncope patient is widely recognized [38–40] and has been highlighted by two major studies from Italy, OESIL, and EGSYS [41, 42]. Both illustrated the inefficiency of the standard approach. Further, in each case, a follow-up study (OESIL-2, EGSYS-2) demonstrated that a more standardized guideline-based care pathway (such as could be provided in a structured multidisciplinary syncope management units [SMU] as recommended by the ESC syncope task force) significantly improved diagnostic yield and reduced hospital admissions, resource consumption, and overall costs [43–45]. Two different models of syncope facilities have been developed, one primarily centered within emergency departments (ED) [44] and the other within the cardiology or medicine department [46]. A prospective trial conducted by Mitro et al. [47] looked at the diagnostic yield of standardized work up based on European society of cardiology guidelines. A total of 501 patients with mean age of 65 years were evaluated. Evaluation started with history, physical examination, and ECG; further diagnostic testing was ordered only if the diagnosis was not clear from initial evaluation. The study showed that this approach was successful in determining the etiology of syncope in 89 % of patients.

The SMU operating primarily within an ED usually has risk stratification as its principal goal; that is, identifying those individuals who can be sent for outpatient assessment versus those needing hospital admission. In this regard, the prospective single-center SEEDS study [44] evaluated the hypothesis that a designated syncope unit in the ED improves diagnostic yield and reduces hospital admission for patients with syncope who were considered to be at intermediate risk for an adverse cardiovascular outcome. Patients were randomly allocated to one or other of two treatment arms: syncope unit evaluation or standard care. The study enrolled 103 individuals, with 51 patients randomized to SMU care. Comparing SMU versus standard care patients, a presumptive diagnosis was established in 34 (67 %) and 5 (10 %) patients, respectively, and hospital admission was required for 22 (43 %) and 51 (98 %) patients, respectively. The SMU care pathway reduced total patient-hospital days from 140 to 64. Thus, the SMU appeared to improve diagnostic yield and cost-effectiveness of care significantly. The findings in a more recent trial by Fedorowski et al. [48] further supported the fact that adherence to systematic approach to unexplained syncopal attacks based on the European Society of Cardiology guidelines would improve the diagnostic and therapeutic outcomes.

In another ED-based study, a previously developed rule set (the so-called San Francisco Syncope Rule) was applied [45]. This strategy combined the presence of any of the following observations to risk stratify patients: an abnormal ECG, symptoms of shortness of breath, a hematocrit <30 %, systolic blood pressure <90 mmHg, or a history of congestive heart failure. The rule was 98 % sensitive and 56 % specific to predict serious outcomes within the next 7 days. Serious outcomes were defined as death, myocardial infarction, arrhythmia, pulmonary embolism, stroke, subarachnoid bleed, significant hemorrhage, or any condition resulting in a

return ED visit and hospitalization. However, in one external validation cohort [49], the San Francisco Syncope Rule had a lower sensitivity and specificity (89 and 42 %).

The SMU model adopted in some Italian hospitals is a functional or "virtual" unit managed inside the department of cardiology. Where appropriate, patients are jointly managed with other specialists. The patients may be referred to the unit from any of several sites, including the ED, in-patient services, or outpatient clinics. Patients referred to such units typically are given higher priority for diagnostic tests that the unit's physicians may deem to be needed.

In the context of the more structured approach to the syncope evaluation, EGSYS-2 [41] provided a prospective, controlled, multicenter study designed to determine if a "standardized" method of care is superior to the usual care [49]. There were 929 patients in the usual care pathway and 745 patients in the standardized care group. At the end of the evaluation, the standardized care group had a lower hospitalization rate (39 % vs. 47 %), 11 % shorter in-hospital stay (7.2 ± 5.7 vs. 8.1 ± 5.9 days), and 26 % fewer tests performed per patient (median 2.5 vs. 3.4). Additionally, standardized care patients had 75 % fewer discharges with "unexplained syncope" (standardized, 5 % vs. usual care, 20 %). The mean cost per patient was 19 % lower (€1,127 vs. 1,394), and the mean cost per diagnosis was 29 % lower (€1,240 vs. 1,753) in the standardized care group.

SMUs of the type discussed here, while strongly advocated by the ESC syncope task force [1], are only infrequently found in either North America or Europe. In 2005, a survey of US and Canadian medical centers revealed that only 4 of 28 reporting centers (4/28, 14 %) had organized an SMU [50]. Of the centers with an SMU, the unit was described as a "physical space" in one case and as a "virtual unit" (i.e., not a defined physical entity) in the others.

Among the various "risk factors" that have been proposed in the several "risk stratification" schemes that have been published, two factors seem to have been consistently identified as indicators supporting a recommendation for hospitalization. Specifically, most schemes agree that the presence of underlying structural heart disease and/or abnormalities of the baseline ECG are important indicators favoring admission [51].

Hospitalization is strongly recommended for patients suspected of cardiac syncope or who have markers indicative of increased risk of sudden cardiac death (e.g., ischemic heart disease with reduced ejection fraction). A less frequent, but crucial, prognostic marker is the family history of sudden death, as certain malignant ventricular arrhythmias can have a genetic basis (e.g., long QT syndrome, Brugada syndrome, familial cardiomyopathies). The Rose study did show that serious cardiovascular outcomes are more likely to occur in the first month after syncope. The study however had several limitations [52].

Suspected neurally mediated syncope, especially in patients without evidence of cardiac disease, does not usually need in-hospital evaluation. In essence, for those cases in whom risk of death is thought to be low and there is low likelihood of harm to the public health, there is little need for hospitalization. However, cautionary advice regarding avoidance of unnecessary driving and risky occupational and/or a vocational exposure should be provided, as further outpatient evaluation is needed before a final diagnosis and appropriate treatment can be established.

Strategy for Syncope Evaluation

Figure 17.6 provides an overview of a recommended approach to the assessment of a patient who presents with TLOC/collapse based on the ESC syncope task force guidelines [1].

The "initial evaluation" of a patient presenting with transient loss of consciousness (TLOC) and in whom syncope is considered to be a possibility consists of careful medical history, physical examination including orthostatic blood pressure measurements, and 12-lead ECG. In selected cases, the initial evaluation may also include echocardiography and neurological evaluation. The point at this stage is to ascertain whether the reported loss of consciousness episode(s) was in fact true syncope. In order to achieve this goal in a cost-effective manner, the assessment of these patients must be both well organized and thorough and at the same time avoid excessive application of inappropriate tests. As experience is gained, the number of tests needed to assure a correct diagnosis will diminish.

Initial Evaluation: The History

The story provided by the patient and witnesses very often reveals the most likely cause of TLOC and provides a means of guiding any necessary subsequent evaluation. Three key questions are:

1. Is loss of consciousness attributable to syncope or other causes, including accidental falls?
2. Is heart disease present or absent?
3. Are there important clinical features in the history that suggest the diagnosis, or at a minimum whether the TLOC was real and in fact "syncope?"

Assuming that TLOC was indeed "syncope," the absence of signs (including echocardiographic assessment in many cases) of suspected or overt heart disease largely excludes a cardiac cause; but there are several important exceptions including those in which syncope is:

- Accompanied by palpitations, which could be due to paroxysmal tachycardia (especially paroxysmal supraventricular tachycardia)

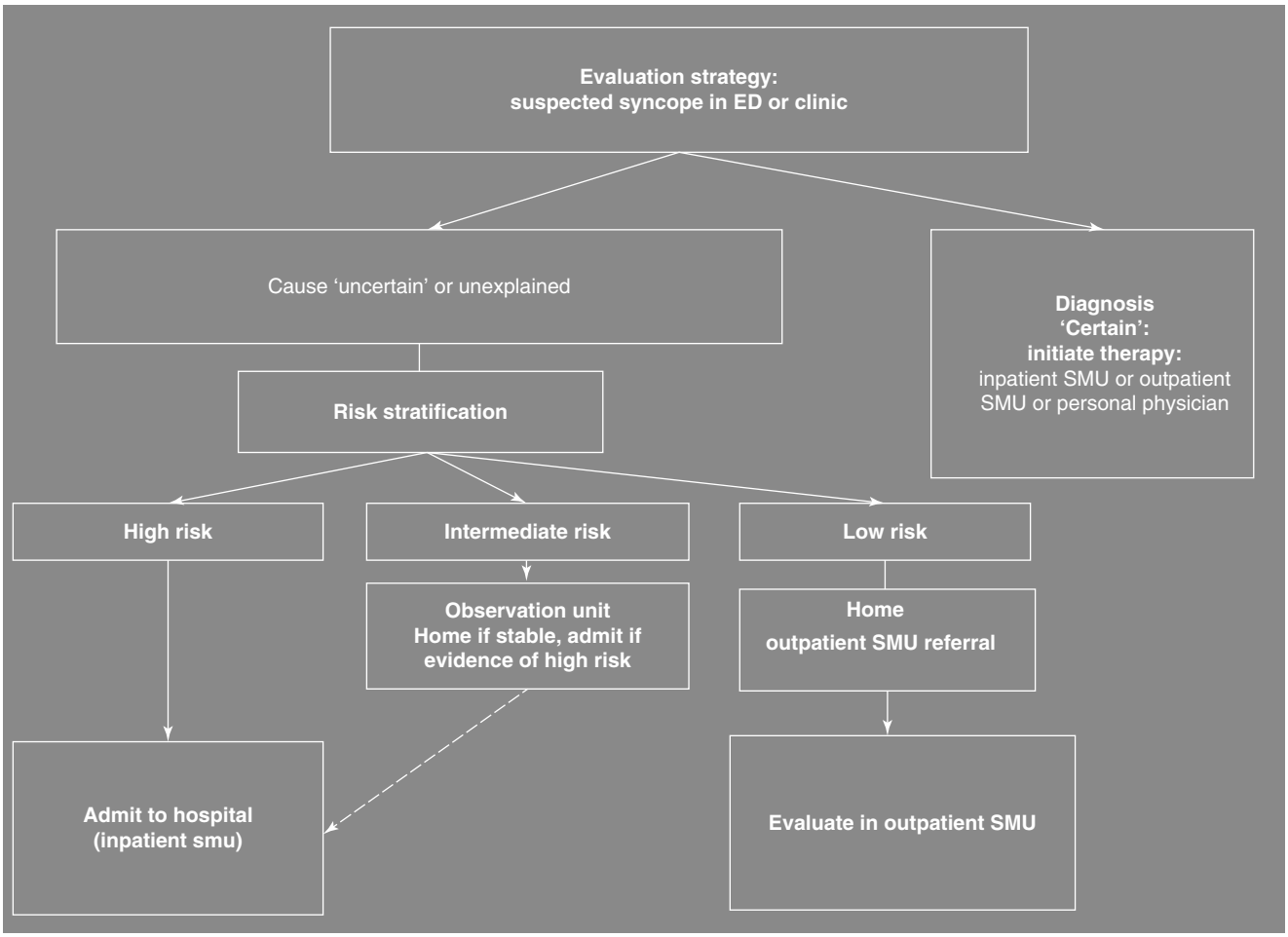

Fig. 17.6 Evaluation strategy for patients with presumed syncope coming to emergency department (ED) or clinic. The approach is patterned after that recommended by the ESC Syncope practice guidelines [1, 34]

- Associated with ECG findings suggesting a channelopathy (e.g., LQTS, Brugada syndrome), preexcitation syndrome, or conduction system disease
- Marked by a strong family history of premature death

Conversely, although evidence indicating presence of heart disease at initial evaluation is a strong predictor of a cardiac cause of syncope, its specificity is low; about half of patients with heart disease have a noncardiac cause of syncope. For instance, Alboni et al. [53] found that heart disease was an independent predictor of cardiac cause of syncope, with a sensitivity of 95 % and a specificity of 45 %; by contrast, the absence of heart disease allowed exclusion of a cardiac cause of syncope in 97 % of the patients.

In terms of taking the medical history, the details surrounding symptom events, if documented carefully, may be valuable in terms of determining a "certain" or at least "suspected" diagnosis. In this regard, witnesses can be extremely valuable for filling in items that the patient may not recall. Key features to consider include:

- Characterize situations in which TLOC tends to occur

  Position (supine, sitting, or standing), activity (at rest, exercise, or postprandial period), abrupt neck movements, voiding or defecation, cough or swallowing, crowded or warm places, prolonged standing, or psychological stress (fear, intense pain, or emotional upset)
- Define prodrome ("warning") symptoms

  Are symptoms associated with nausea, vomiting, feeling of cold, sweating, visual aura, pain in neck or shoulders, blurred vision, or palpitations?
- Document eyewitness observations

  The manner of the "fall" should be recorded (abrupt fall with possibility of injury or purposeful avoidance of injury) along with noting, skin color changes, duration of syncope, breathing pattern, physical movements (e.g., tonic-clonic or myoclonic movements), incontinence, or tongue biting. In particular, try to determine whether "jerky" muscular movements began before loss of consciousness (more typical of epilepsy) or afterward (more consistent with a faint).
- Document symptoms after syncope

Fatigue, confusion, palpitations, headache, nausea, vomiting, sweating, feeling of cold, muscle aches, skin color, injury, or chest pain. Inability to stand up without triggering another episode may suggest neurally mediated reflex syncope.

- Characterize risk for syncope recurrence and/or life-threatening consequences

  Family history of syncope, sudden death, or known genetically transmitted conditions (e.g., long QT syndrome, Brugada syndrome, arrhythmogenic ventricular dysplasia). Fainter's medical history of structural cardiac disease (e.g., prior myocardial infarction, valvular heart disease, congenital conditions, and previous cardiac surgery), neurological conditions (e.g., Parkinson's disease, epilepsy, migraine), metabolic/intoxication disorders (e.g., diabetes and alcoholism), or drug abuse (e.g., cocaine).
- Identify prescribed medications predisposing to syncope

  Drugs known to predispose to syncope include antihypertensives, antianginal drugs, antidepressant agents, antiarrhythmics, diuretics, or any QT-prolonging agents. Has there been any recent dosing change? Have any new drugs been added?

Initial Evaluation: Physical Findings

As noted earlier, most "presumed syncope" patients have fully recovered by the time they are first seen by a medical practitioner. Consequently, the relation between physical finding abnormalities (if any) and the cause of syncope is at best inferential in most cases.

Physical findings that may help to establish a basis for syncope include orthostatic blood pressure changes, cardiovascular abnormalities, response to carotid sinus message, and (less frequently) persistent neurological signs. Carotid sinus massage is a recommended diagnostic step during the physical examination, especially in the older person (>60 years). ECG, echocardiogram, chest X-ray, and blood count may also be reasonably incorporated.

Important cardiovascular findings that may lead to a suspected cause of syncope include differences in blood pressure in each arm, pathological cardiac and vascular murmurs, signs of pulmonary embolism, aortic stenosis, hypertrophic cardiomyopathy, myxoma, or aortic dissection. Signs of focal neurological lesions, such as hemiparesis, dysarthria, diplopia, and vertigo or signs of Parkinsonism are suggestive of, but not diagnostic of, a neurological cause of impairment of consciousness. In most cases, these patients did not suffer from a true syncope, but may have collapsed in association with instability triggered by an acute neurological event; they should be referred for neurological evaluation.

Outcomes of Initial Evaluation

For purposes of the following discussion, we assume that TLOC was indeed due to true syncope (Fig. 17.6). In this case, the outcome of the initial evaluation may be identification of a "certain" basis for symptoms, or a less confident "suspected" basis for symptoms, or symptoms may remain of an entirely unexplained cause. The appropriate subsequent strategy varies depending on which of these categories the physician finds him/herself.

Diagnosis Is "Certain"

A number of conditions can be clearly identified with sufficient confidence by careful initial evaluation alone. In such cases, no further testing is required. Examples include:

- "Classic" vasovagal syncope in which precipitating events such as fear, blood draw, severe pain, or emotional distress are associated with typical prodromal symptoms.
- Situational syncope that occurs during or immediately after certain circumstances, such as emptying the bladder, coughing, or swallowing.
- Postural ("orthostatic") syncope in which there is documentation of orthostatic hypotension associated with syncope or presyncope.
- Presence on routine ECG of a severe abnormality (preferably with concomitant symptoms), such as asystolic pauses >6 s, Mobitz II second-degree AV block, or complete or high-grade AV block. However, it is very rare for such findings to be obtained during a routine ECG; longer-term monitoring is most often needed.

Diagnosis Is Suspected but Not Certain

In patients with a suspected diagnosis for the cause of syncope after initial evaluation, carefully selected "confirmatory" testing (such as long-term ECG monitoring [by mobile cardiac outpatient telemetry (MCOT) or an implanted loop recorder (ILR)], tilt-table testing, and/or electrophysiological study) is necessary. In these cases, diagnostic testing should first be restricted to evaluation of the suspected diagnosis and expanded only if that diagnosis does not prove to be satisfactory. A "shotgun" approach is discouraged as both being ineffective in most cases and costly.

Unexplained Diagnosis

In these cases, the strategy for subsequent assessment varies according to the severity and frequency of the episodes and the presence or absence of heart disease.

- Patients without evidence of structural heart disease: the majority of patients with single or rare syncope episodes in this category probably have one or other of the neurally mediated syncopes. In such cases, tilt-table testing and carotid sinus massage should be undertaken if not already done. It should be noted, however, that tilt tests are

generally of value only in unmasking susceptibility to vasovagal faints and the test has poor sensitivity. Similarly, carotid sinus massage exhibits strong specificity but limited sensitivity. Psychiatric illness (leading to pseudosyncope) should be considered for patients without structural heart disease and with a normal ECG, especially if the history suggests numerous syncope episodes (e.g., many episodes each week).

- Patients with structural heart disease: In patients with structural heart disease or who have an abnormal ECG, cardiac evaluation is recommended at this stage. This should consist of echocardiogram, stress testing if deemed appropriate, prolonged ambulatory ECG monitoring (including early use of ILRs), and if needed invasive electrophysiological study (EPS). For patients with palpitations associated with syncope, ambulatory ECG monitoring (including ILRs) is especially valuable. In almost every case, these patients should be referred to a specialist in the evaluation of syncope or a syncope diagnostic center.

Diagnostic Yield of the Initial Evaluation

Pooled data from population-based studies indicate that the history and physical examination identify a potential cause of syncope in approximately 50 % of the patients [49, 54–56]. Reflex syncope (vasovagal, situational) accounts for approximately 75 % of diagnoses at initial evaluation. The diagnostic yield of standard ECG obtained in the emergency department is, on average, 6 % and accounts for about the half of total diagnoses of cardiac syncope. In-hospital (telemetry) monitoring is helpful in a minority of selected high-risk patients [55].

Routine blood tests rarely yield diagnostically useful information. In selected syncope cases, they can confirm a clinical suspicion of acute anemia, acute myocardial infarction, or pulmonary embolism. Very rarely such tests may yield other non-syncope diagnoses such as hypoglycemia and intoxications.

Specific Causes of Syncope

Neurally Mediated Reflex Syncope

The best known and most frequently occurring forms of the neurally mediated reflex faints are vasovagal syncope and carotid sinus syndrome. Situational syncope (e.g., postmicturition syncope, defecation syncope, swallow syncope, cough syncope, etc.) is also encountered from time to time, but in these cases, the history is generally sufficient to establish the diagnosis.

Tilt-table testing, carotid sinus massage, the Valsalva maneuver, active standing test, cold pressor test, and cough test are occasionally used for assessment of patients with suspected reflex syncope [1, 57]. However, except for tilt-testing for possible vasovagal faints and carotid massage in suspected carotid sinus syndrome (CSS), the clinical value of other tests is unclear, and they play little role in clinical evaluation.

In terms of other tests, the previously used eyeball compression test is now strongly discouraged. Neurological studies (head MRI or CT scans, as well as electroencephalograms [EEGs]) are often ordered by physicians for syncope evaluation, but usually contribute little to the diagnosis, especially in the case of neural reflex syncope [1]. The adenosine triphosphate (ATP) test remains a controversial topic [58, 59]. It may have a role to play in the older fainter, where neural reflex mechanisms may be relevant but are as difficult to unmask. ATP-induced pauses >6–10 s, even if interrupted by escape beats, are defined as abnormal [58, 59]. The ATP test is contraindicated in patients with asthma.

Vasovagal Syncope

Vasovagal syncope usually starts in younger individuals (often adolescence) and is generally unassociated with cardiovascular or neurological diseases. A weak family history may be present. In essence, isolated vasovagal syncope should not be regarded as a disease, but rather as a relatively frequent transient aberration of normal physiology [1]. It may affect sporadically 10–20 % of the general population during their life. Furthermore, isolated vasovagal syncope in the young should be distinguished from those forms, usually with an atypical presentation, that start in older age and which are often associated with cardiovascular or neurological disorders, and other dysautonomic disturbances such as carotid sinus hypersensitivity, postprandial hypotension, and symptoms of autonomic dysfunction. In these latter cases, the reflex syncope appears as an expression of a pathological process, mainly related to impairment of the autonomic nervous system to activate compensatory reflexes; the result may be considered an overlap with autonomic failure [60, 61].

Vasovagal syncope may be triggered in a variety of ways, including unpleasant sights, pain, extreme emotion, and prolonged standing. However, not infrequently the precise trigger for a given symptomatic event remains unknown.

Autonomic activation (e.g., flushing and sweating) in the premonitory phase strongly suggests a vasovagal origin. Typical presentations occur in about 40 % of presumed vasovagal syncope, but increasingly less often as patients' age. A head-up tilt-table test is often used to confirm the diagnosis and is the only laboratory test deemed useful in diagnosing vasovagal syncope.

As a rule, the first step of the head-up tilt-table test is a "passive" head-up tilt at 70° during which the patient is supported by a footplate and gently applied body straps for a period of 20–45 min [62]. If needed, tilt-testing in conjunction with a drug challenge (e.g., isoproterenol or nitroglycerin)

may be employed. This is particularly pertinent if a short passive phase is used (i.e., 20–30 min). Until recently, the most frequently used provocative drug was isoproterenol, usually given in escalating doses from 1 to 3 μg/min. However, nitroglycerin intravenously or sublingually has gained favor, in part because it expedites the procedure without adversely affecting diagnostic utility.

The head-up tilt-table test in a drug-free state appears to discriminate well between symptomatic patients and asymptomatic control subjects. The false-positive rate of the tilt test is approximately 10 %. Test sensitivity appears to be increased with the use of pharmacologic provocation (isoproterenol or nitroglycerin), but at the cost of reduced specificity. For patients without severe structural heart disease, a positive tilt-table test (especially if it reproduces the patient's spontaneous symptoms) can be considered diagnostic. On the other hand, for patients with significant structural heart disease, other more serious causes of syncope must be excluded prior to relying on a positive tilt-test result. For the most part, the head-up tilt test is not to be relied on for predicting treatment outcomes [1]. However, recent findings from the ISSUE 2 registry suggest that in older fainters, the development of prolonged asystole during tilt-testing may correlate well with spontaneous bradycardia detected by ILR [63]. Based on this observation, and findings from the ISSUE 3 randomized controlled trial, it is possible that pacemaker therapy may someday once again be considered for older patients with asystole during tilt-table testing [63].

In the vast majority of cases of vasovagal syncope, patients principally require reassurance and education regarding the nature of the condition. In patients with multiple recurrent syncopes, initial advice should include review of the types of environments in which syncope is more common (e.g., hot, crowded, and emotionally upsetting situations) and provide insight into the typical warning symptoms (e.g., hot/cold feeling, sweaty, clammy, nauseated), which may permit many individuals to recognize and respond to an impending episode and thereby avert the faint. Thus, avoiding venipuncture may be desirable when possible, but psychological therapy (systematic desensitization) may be necessary. Additional common sense measures, such as keeping well hydrated and avoiding prolonged exposure to upright posture and/or hot confining environments, should also be discussed.

"Volume expanders" or moderate exercise training appear to be among the safest initial approaches [1, 64]. "Tilt-training" (progressively lengthening periods of enforced upright posture) and certain physical maneuvers (leg crossing and arm tugging) upon onset of premonitory symptoms may be helpful [37].

Many drugs have been used in the treatment of vasovagal syncope (such as β-blockers, disopyramide, scopolamine, clonidine, theophylline, fludrocortisone, ephedrine, etilefrine, midodrine, clonidine, and serotonin inhibitors). While the results have often been satisfactory in uncontrolled trials, placebo-controlled prospective trials have been unable to show a benefit for most of these drugs [1]. The principal exception is midodrine, a vasoconstrictor agent [65, 66]. The ultimate role of cardiac pacing for vasovagal syncope remains controversial. As noted above, cardiac pacing may be useful in selected older patients in whom a prolonged asystole has been documented [63].

Carotid Sinus Syndrome (CSS)

CSS is generally most prevalent in older males and is often associated with concomitant atherosclerotic disease. Spontaneous CSS accounts for about 1 % of all causes of syncope and may be defined as syncope that seems to occur in close relationship with accidental mechanical manipulation of the neck. It is presumed that the basis for the faint is mediated through the carotid sinus baroreceptors, but disturbances of neck proprioception may contribute. In any case, diagnostic testing requires that symptoms be reproduced by carotid sinus massage (CSM). Induced carotid sinus syndrome is diagnosed when patients are found to have an abnormal response to carotid sinus massage and an otherwise negative workup for syncope. Thus, diagnosis of the induced form does not require the "classic" history. However, the positive predictive value of diagnostic CSM testing is clearly reduced in this scenario [1, 67, 68].

CSS may be diagnosed when CSM reproduces symptoms in conjunction with a period of asystole, paroxysmal AV block, and/or a marked drop (usually >50 mmHg systolic) in systemic arterial pressure. In many instances, the most convincing results from carotid sinus massage are obtained when massage is undertaken in the upright position. In the absence of a history of spontaneous syncope, the exaggerated response, which is defined as carotid sinus hypersensitivity, must be distinguished from carotid sinus syndrome. The main complications of CSM are neurological (0.01–0.14 %) [69, 70]. CSM should not be performed in patients with TIAs or strokes within the past 3 months or in patients with carotid bruits (unless carotid Doppler studies convincingly exclude significant carotid artery narrowing) [1].

Two approaches to CSM have been advocated. The first method is probably the most widely used. CSM is performed for no more than 5 s in the supine position. A positive response has traditionally been defined as a ventricular pause ≥ 3 s (but more recently > 6 s is considered more specific) and/or a fall of systolic blood pressure ≥50 mmHg [1]. The estimated positive rate is 35 %. Abnormal responses can also be observed in subjects without syncope. The diagnosis may be missed in about one-third of cases if only supine massage is performed [71]. The second method requires reproduction of spontaneous symptoms during CSM for 10 s in both supine and upright positions. A positive response was observed in 49 % of patients with syncope of uncertain ori-

gin and in 60 % of elderly patients with syncope and sinus bradycardia, but only in 4 % of patients without syncope. The eliciting of symptoms is probably the more useful endpoint for evaluation of carotid sinus syndrome.

Treatment of CSS is guided by the results of CSM (i.e., relative importance of cardioinhibitory vs. vasodepressor responses). Cardiac pacing appears to be beneficial and is acknowledged to be the treatment of choice when marked bradycardia has been documented (usually defined as a CSM-induced pause >3–5 s). Judicious use of vasoconstrictors (e.g., midodrine) may be needed for patients in whom the vasodepressor aspect of the reflex is prominent. However, inasmuch as many of the affected patients are older and also have hypertension as a comorbidity, the impact of vasoactive agents must be monitored carefully.

Situational Faints

Situational faints encompass a wide range of clinical scenarios. Each is characterized by the specific clinical circumstances surrounding (and presumably triggering) the event. Thus, cough syncope, micturition syncope, and swallow syncope are examples of situational faints (Table 17.1). Recognition of these conditions clearly depends on the careful taking of the medical history. Thereafter, treatment relies heavily on avoidance of triggering circumstances, or at least reducing the risk associated with the circumstance. By way of example, males are encouraged to sit while voiding, especially if the bladder is very full or if they have recently consumed a significant amount of alcohol.

Orthostatic Hypotension

Orthostatic syncope can be diagnosed when there is documentation of posturally induced hypotension associated with syncope or presyncope. For the diagnosis of orthostatic hypotension, arterial blood pressure must be measured when the patient adopts the standing position after at least 5 min of lying supine. For practical purposes, orthostatic hypotension is often defined as a decline in systolic blood pressure of at least 30 mmHg within 3 min of assuming a standing posture, regardless of whether or not symptoms occur. If the patient cannot tolerate standing for this period, the lowest systolic blood pressure during the upright position should be recorded.

Identification of an underlying cardiovascular, neurological, or pharmacological etiology is of particular importance for patients with orthostatic hypotension. At the outset, it is important to identify nonneurogenic reversible causes of orthostatic hypotension, such as volume depletion, effect of medications (common), and effect of comorbidities (e.g., diabetes and alcohol and more rarely adrenal insufficiency). The most frequent drugs associated with orthostatic syncope are vasodilators and diuretics. Alcohol can be associated with orthostatic syncope, because it not only causes orthostatic intolerance but also can induce autonomic and somatic neuropathy. Elimination of the responsible drug or offending agent is usually sufficient to improve symptoms.

In some cases, the cause of orthostatic hypotension proves to be a primary neurological disorder. Parkinsonism is probably the most frequently diagnosed. Pure autonomic failure is also observed from time to time. Although cure may not be possible, a precise diagnosis can lead to initiation of treatment that may provide substantial symptom relief.

The initial treatment for patients with orthostatic syncope includes education regarding factors that can aggravate or provoke hypotension upon assuming the upright posture. These include avoiding sudden head-up postural change, especially in the morning after being in bed all night or standing still for a prolonged period of time. Other important considerations that may predispose to orthostatic hypotension are high environmental temperature (including hot baths, showers, and saunas leading to vasodilation), large meals (especially with refined carbohydrates), and severe exertion.

Patients with orthostatic hypotension should be encouraged to increase dietary salt and volume intake to the extent possible if there are no contraindications (i.e., hypertension). In some cases, sleeping with the head of the bed elevated by 8–10 in. or 20–25 cm may improve symptoms by subjecting the patient to gravitational stress at night (and possibly reducing renal filtration to diminish morning dehydration). Certain physical counter-maneuvers, such as leg crossing, squatting, bending forward, arm tugging, and other measures, may be useful to combat orthostatic hypotension.

When physical maneuvers alone are not sufficiently effective, pharmacological interventions may be warranted. Fludrocortisone and midodrine are probably the most commonly used drugs for orthostatic hypotension. Fludrocortisone is a synthetic mineralocorticoid with minimal glucocorticoid effect for expansion of intravascular and extravascular body fluid. The starting dose is usually 0.1 mg once a day and then increased by 0.1 mg at 1–2-weeks intervals up to 0.3 mg daily, if needed. The pressor action is not immediate and takes some days to be manifest, and the full effect requires a high dietary salt intake. A weight gain of 2–3 kg is a reasonably good clue for adequate volume expansion. Mild dependent edema can be expected. Patients on fludrocortisone may develop hypokalemia within 2 weeks, and potassium supplements are advised. Midodrine is a prodrug that is converted to its active metabolite, desglymidodrine, after absorption. It acts on α-adrenoreceptors to cause constriction of both arterial resistance and venous capacitance vessels. Midodrine is administered in doses of 2.5–10 mg, three times daily. Midodrine is of particular value in patients with severe postural hypotension and in those with autonomic failure [72]. For patients with hypertension, supine hypertension is a potential problem during treatment of orthostatic

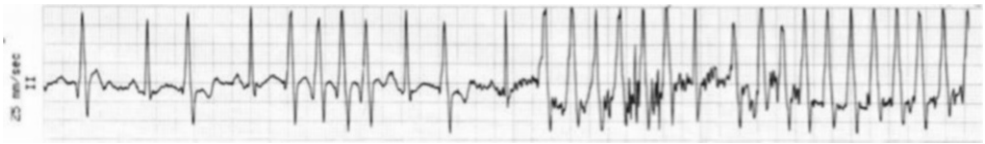

Fig. 17.7 Recordings from a 28-year-old female without significant past medical history who presented to the emergency room with recurrent syncope. Recurrent episodes of wide QRS complex tachycardia associated presyncope/syncope were documented by telemetry. Orthodromic AV reentry tachycardia was easily induced during electrophysiological study. This tachycardia tended to degenerate into atrial fibrillation with a rapid ventricular response and ultimately on one occasion into ventricular fibrillation. A left anterior lateral accessory pathway was successfully ablated. The patient has remained symptom-free thereafter

hypotension. Better control of hypertension may improve orthostatic hypotension in some patients. In others, it may be necessary to accept higher resting blood pressures than would normally be considered desirable.

Cardiac Arrhythmias as Primary Cause of Syncope

Both brady- and tachycardias can cause syncope. Patients with syncope associated with cardiac arrhythmias or who are thought to be at increased risk of sudden cardiac death (e.g., severe underlying structural heart disease) are most appropriately evaluated by a cardiac electrophysiologist.

Bradyarrhythmias

Sinus node dysfunction leading to syncope is best established when symptoms are clearly correlated with sinoatrial bradycardia (occasionally a long pause following termination of an atrial tachycardia) using an event recorder or an implanted loop recorder. In absence of such correlation, severe sinus bradycardia lower than 40 beats/min or sinus pauses longer than 3 s are highly suggestive of symptomatic sinus node disease. Aggravation of bradycardia by drug treatment often unmasks sick sinus syndrome. A pacemaker, preferably an atrial-based pacing system with a rate-adaptive sensor, is usually required for treatment.

Chronic or paroxysmal atrioventricular (AV) block can be the cause of syncopal episodes. Bradycardia due to intermittent AV block is among the more important causes of syncope during prolonged monitoring. The presence of Mobitz II type second-degree AV block, third-degree AV block, or alternating left and right bundle branch block can reasonably be considered as being diagnostic of a bradycardic cause of syncope. In unsure cases, event monitor, electrophysiological assessment AV conduction with and without pharmacological challenge and induction tachycardias may be warranted. A prolonged recording period (5–10 months duration is often needed using an insertable loop recorder, ILR) is sometimes required to detect correlation between arrhythmia (often paroxysmal AV block) and syncope in difficult cases.

Tachyarrhythmias

Supraventricular tachycardias (SVT) are not often the cause of syncope (Fig. 17.7). However, lightheadedness and syncope may occur at the onset of episodes of tachycardia before vascular compensation occurs or as the result of prolonged bradycardia at the termination of an episode. Patients with preexcitation syndrome (e.g., Wolff-Parkinson-White [WPW] syndrome) may also be at risk of sudden cardiac death. Radiofrequency catheter ablation is the treatment of choice for SVTs in most patients. Atrial flutter and fibrillation may cause syncope in patients with structural heart disease or dehydration. A pacemaker may be needed for syncope associated with asystolic pause at termination of supraventricular tachyarrhythmias.

Ventricular tachycardias (VT) most often occur in patients with structural heart disease, especially ischemic heart disease and dilated cardiomyopathies. However, approximately 10–15 % of VT patients have no overt structural heart disease.

VT Associated with Ischemic Heart Disease or Dilated Cardiomyopathies

Ventricular tachyarrhythmias have been reported to be responsible for syncope in up to 20 % of patients referred for electrophysiologic assessment (Fig. 17.8). Tachycardia rate, status of left ventricular function, and the efficiency of peripheral vascular constriction determine whether the arrhythmia will induce syncopal symptoms. ICDs are the mainstay of treatment of VT associated with structural heart diseases. Currently, pharmacological therapy and transcatheter ablation are considered principally as adjunctive measures. Treatment of nonsustained VT in the presence of syncope is a controversial topic. In essence, syncope associated with nonsustained VT and diminished LV function warrants ICD therapy. However, ICD might not prevent faints due to the delay in detection and charge of the ICD capacitor. Antiarrhythmic drugs and/or ablation may be considered in this setting when indicated.

Idiopathic Ventricular Tachycardias and Syncope

Idiopathic right ventricular outflow tract tachycardia (RVOT) is the most frequent type of idiopathic VT (Fig. 17.9). It

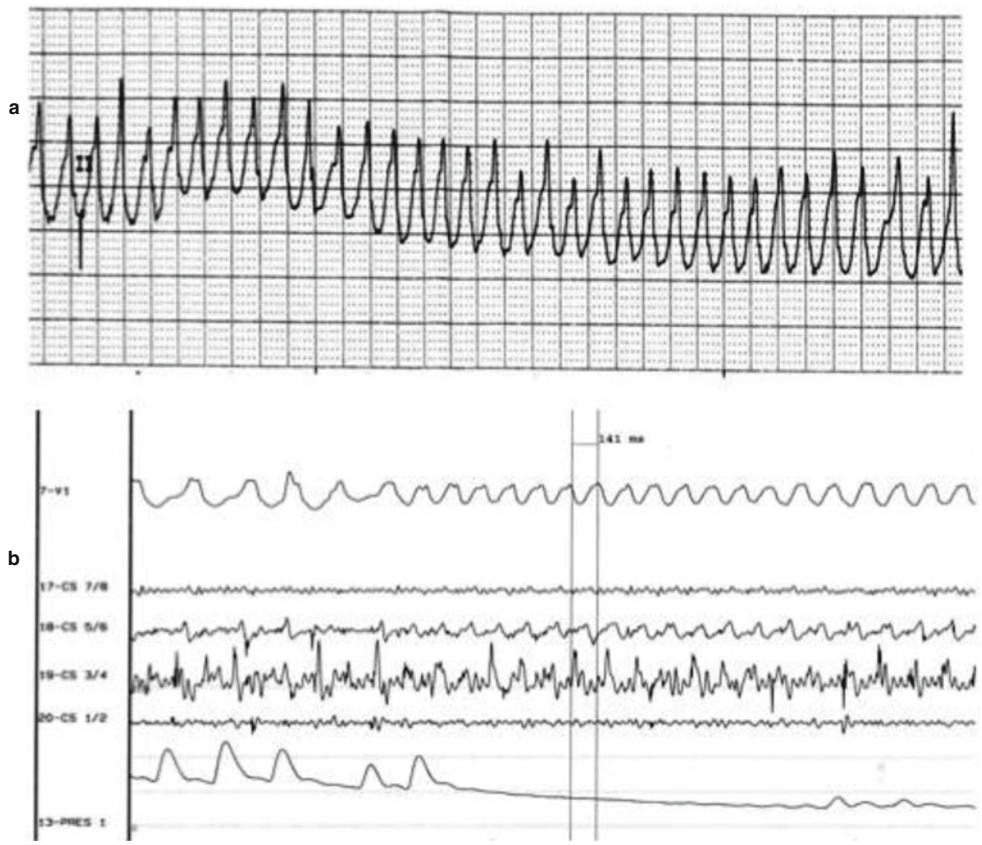

Fig. 17.8 Findings from a 52-year-old male with a history of myocardial infarction and angina who presented for evaluation of recurrent syncope. Echocardiogram showed low-normal left ventricular function. Telemetry recordings in hospital revealed multiple episodes of a very rapid but self-limited wide QRS tachycardia (panel **a**). The arrhythmia was associated with syncope, but without any other symptoms, such as palpitations. Electrophysiologic study confirmed a scar-related ventricular tachycardia with marked hypotension. The tachycardia was successfully ablated using an EnSite® balloon mapping method (panel **b**)

represents approx 80 % of all idiopathic VTs and about 10 % of all patients who are evaluated for VTs. Syncope is not an uncommon presentation (23–58 %). The major differential diagnostic concern is VT due to arrhythmogenic RV cardiomyopathy.

Some patients with a clinically normal heart may nonetheless present with idiopathic left ventricular VTs. For the most part, these come from the left ventricular outflow tract or of presumed fascicular origin. These idiopathic VTs can be mapped and ablated in most cases; ablation is generally the most effective therapy. Pharmacological treatment, including class I and III drugs, β-blockers, calcium channel blockers, and adenosine, may be effective in these patients. However, drug-related side effects are a common problem.

Less Common Arrhythmic Causes

Other, less common, arrhythmic causes of syncope include arrhythmogenic right ventricular cardiomyopathy (formerly "dysplasia"), long QT syndromes, Brugada syndrome, and hypertrophic cardiomyopathy. These conditions are crucial to recognize and are best referred to specialized centers for management, as they are often associated with increased risk of sudden cardiac death.

Structural Cardiac and Cardiopulmonary Causes of Syncope

The most common causes of syncope as a result of structural cardiac and pulmonary disease are listed in Table 17.1. In these cases, syncope occurs as either a direct result of the structural disturbance or as a consequence of a neural reflex disturbance triggered by the heart condition. Thus, syncope in acute myocardial infarction or severe aortic stenosis may be due to a diminution of cardiac output in some cases. Alternatively, neural reflex vasodilation may be triggered and cause hypotension. Probably both mechanisms most often participate. In any event, treatment is best directed at amelioration of the specific structural lesion and its consequences.

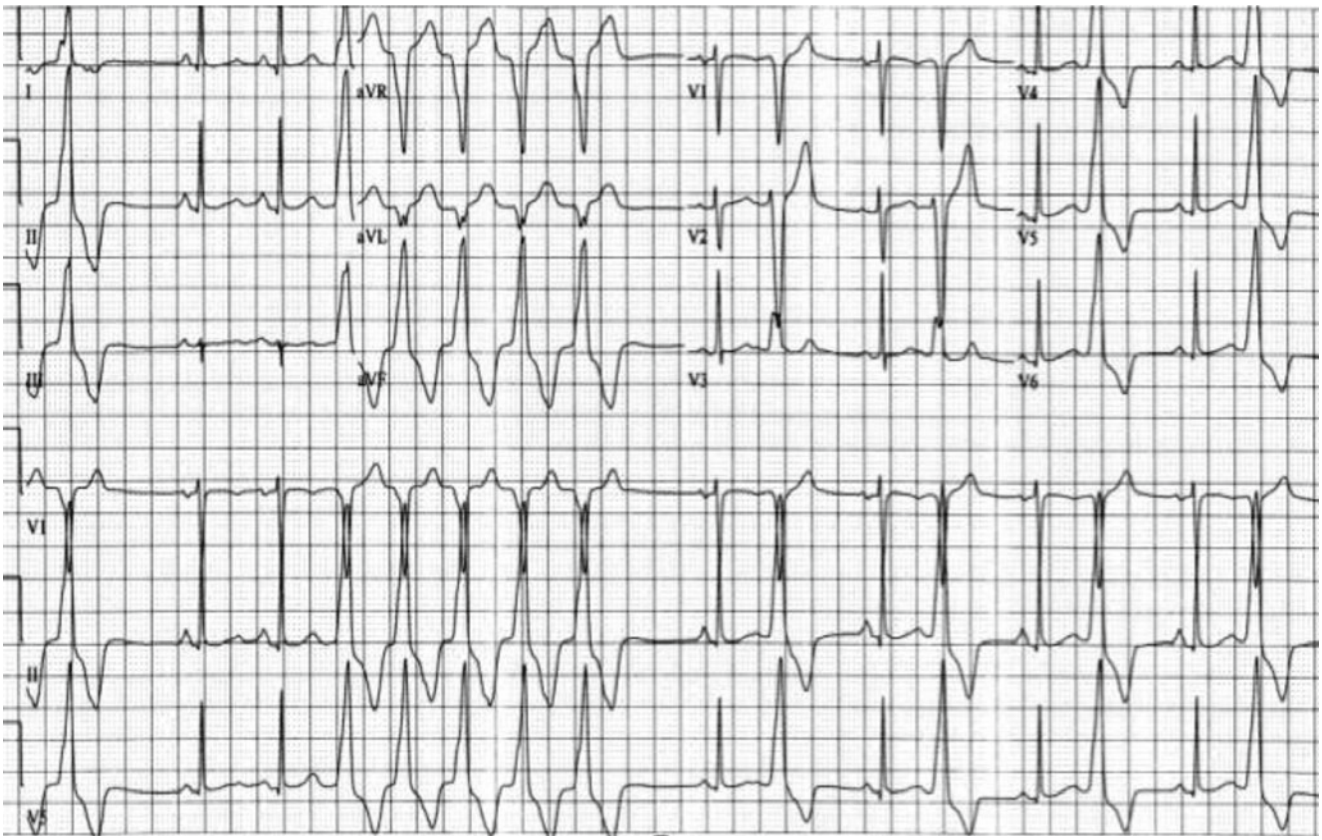

Fig. 17.9 Recordings obtained in a 36-year-old male with a clinically normal heart who presented for evaluation of recurrent syncope. A Holter monitor recording showed frequent ventricular ectopic beats and nonsustained ventricular tachycardia, which correlated well with his symptoms. The morphology of these ventricular ectopic beats on 12-lead ECG was consistent with RVOT origin. He underwent electrophysiological study, and his ventricular arrhythmias were successfully ablated

In patients with cardiac disease such as hypertrophic cardiomyopathy (HCM) [73] or aortic stenosis [74], either SVT or VT may cause cardiac syncope. The rapid rates can preclude adequate venous filling in a stiff ventricle, while abnormal excitation (especially in VT) may aggravate any tendency outflow tract obstruction. However, neurally mediated reflex hypotension may also contribute; the triggers are believed to come from the heart itself, presumably via excessive stretch on ventricular and atrial mechanoreceptors. Finally, potentially certain anatomic variations may increase susceptibility to syncope or near-syncope, although the evidence is not robust. For example, Moon et al. [75] suggest that a smaller left atrial volume may predispose to vasovagal syncope, while a more significant reduction in the end diastolic volume was noted in patients with history of vasovagal syncope when compared to normal subjects [76].

Cerebrovascular Causes of Syncope

In general, cerebrovascular diseases are rarely the cause of true syncope. Neurological causes are even less frequent. As a result, tests looking for these diseases are hardly ever of value in the early assessment of the syncope patient. Conditions that may reasonably be considered include:

1. Subclavian steal
2. Migraine
3. Primary autonomic failure
4. Parkinson's disease

On the other hand, transient ischemic attacks (TIAs) and epilepsy are not part of the differential diagnosis. TIAs do not cause loss of consciousness as a rule, with an exceedingly rare exception being vertebral-basilar TIAs. Epilepsy is not a form of syncope, but must be considered in the differential diagnosis of transient loss of consciousness (see next section).

Conditions That Mimic Syncope

Certain medical conditions (Table 17.2) may cause a real or apparent loss of consciousness that might appear to be syncope, but that is in fact not true syncope. Whether conditions listed below actually "mimic" syncope depends largely on the quality of the account of the events obtained by the

Table 17.3 Clinical features distinguishing syncope from seizures

Clinical findings that suggest the diagnosis	Seizure likely	Syncope likely
Findings during loss of consciousness (as observed by an eyewitness)	Tonic-clonic movements are usually prolonged and their onset coincides with loss of consciousness	Jerky movements are always of short duration (<15 s) and start after loss of consciousness
	Hemilateral clonic movement	
	Clear automatisms such as chewing or lip-smacking or frothing at the mouth	
	Tongue biting	
Symptoms before the event	Blue face	Nausea, vomiting, abdominal discomfort, feeling of cold, sweating (neurally mediated)
	Aura (such as funny smell)	
	"Pins and needles"	
Symptoms after the event	Prolonged confusion	Usually short duration
	Aching muscles	Nausea, vomiting, and pallor (neurally mediated)
	Incontinence	Usually no confusion
	Injury	Fatigue (vasovagal faint)
	Headache	
	Sleepiness	

physician; that is, if a very detailed and comprehensive description of the collapse event can be obtained (usually from witnesses), it may be possible to eliminate "syncope" as a concern and focus on the true cause of TLOC.

Epilepsy

Table 17.3 summarizes the main differences between syncope and epilepsy. Perhaps the aspect of greatest importance is abnormal motor activity. In syncope, it is not uncommon for patients to exhibit jerky movements of the arms and legs for a brief period of time. Not infrequently, nonexpert bystanders misinterpret these movements as being indicative of a "seizure." However, the jerky movements during syncope differ from those accompanying a grand mal epileptic seizure:

1. They are briefer in syncope patients.
2. They occur after the loss of consciousness has set in.
3. They are less coarse.
4. They do not have the "tonic-clonic" features of a true grand mal epileptic seizure.

Cataplexy

Cataplexy refers to loss of muscle tone, often associated with emotional lability. In contrast to vasovagal syncope, triggers such as pain, fear, and anxiety are not important. Startle or laughing may provoke cataplexy. Partial attacks are more common (dropping of the jaw and sagging or nodding of the head). Complete attacks look like syncope in that the victim is unable to respond at all, although he or she is completely conscious and aware of what is going on. Narcolepsy is diagnosed based on the narcolepsy tetrad:

1. Excessive daytime somnolence
2. Cataplexy
3. Hypnogogic hallucination
4. Sleep paralysis (a condition of feeling paralyzed and/or unable to speak that may occur between sleep stages either when falling asleep or when awakening)

Psychogenic Pseudosyncope

The diagnosis of a psychiatric origin for an apparent (not "true") episode of loss of consciousness relies on careful exclusion of other causes of syncope. In psychogenic pseudosyncope, there is no change in blood pressure or heart rate. Further, psychogenic pseudosyncope is often characterized by a frequency of symptoms far in excess of what might be expected for a "true" fainter. Indeed, there are "too many" episodes to be believable. Psychiatric assessment is especially recommended for patients with frequent pseudosyncope and recurrences in conjunction with multiple other somatic complaints and medical concern for stress, anxiety, and possibly other psychiatric disorders. However, a specific neurological diagnosis should be made if any signs of autonomic failure or neurological disease are detected. An implantable loop recorder (ILR) may be needed to rule out arrhythmias in some patients.

Hyperventilation

Hyperventilation simply refers to breathing more than metabolic requirements demand. This leads to a series of physiological events, including hypocapnia, constriction of cerebral vessels, and reduced cerebral blood flow. As such, the act of hyperventilation could lead to syncope. However, this is probably exceedingly rare. Lightheadedness and tingling fingers or toes may, with good reason, be seen as physiological manifestations of overbreathing and are the more common manifestation of hyperventilation syndrome.

Syncope in Psychiatric Patients

Nonpsychiatrists may tend to label complaints of patients with a psychiatric history as "psychogenic." The three psychiatric disorders most likely to lead to symptoms mimicking syncope are conversion reactions, factitious disorders, and malingering. However, other psychiatry patients with "major" psychiatric conditions such as bipolar disorder, depression, and schizophrenia take medications that can cause autonomic failure leading to syncope or other syncope-prone conditions such as long QT syndrome. The main culprits are phenothiazines, tricyclic antidepressives, and monoamine oxidase inhibitors.

Drop Attacks

The term "drop attack" refers to a phenomenon in which there is a very short-lasting spell in which the affected individual suddenly falls without any apparent or recollected warning. These attacks tend to occur in middle-aged people, especially women. Usually the events are too brief for patients to be certain whether there was any loss of consciousness, but most likely loss of consciousness may have been incomplete. Commonly, the victim remembers hitting the ground, often experiencing some degree of minor physical injury. History-taking is crucial, particularly in terms of documenting that the patient recalls falling and usually denies any loss of consciousness. Although "drop attacks" may be a specific but poorly understood clinical entity, it is likely that many instances are in fact due to near-syncope or brief true syncope of conventional etiologies (particularly orthostatic hypotension).

Summary

Syncope is a very common problem in daily practice. The physician's key tasks are first to establish a confident causal diagnosis and then provide appropriate advice to the patient regarding treatment and prognosis. In order to be successful, it is important to develop an organized approach to the assessment of the syncope patient, keeping in mind which of the many possible causes is most likely in a given clinical setting. The initial patient evaluation, particularly a detailed medical history, is the key to finding the most likely diagnosis. Based on findings from this initial step, subsequent carefully selected diagnostic tests can be chosen to confirm the clinical suspicion. Unselected random screening tests for syncope are not cost-effective and should be avoided.

Acknowledgment The authors would like to express their appreciation to Wendy Markuson and Barry L. S. Detloff for assistance with preparation of the manuscript. The authors are grateful for the philanthropic support provided by the 'Earl E Bakken family fund' to the Minnesota Medical Foundation in support of heart-brain studies.

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Pathophysiology of Heart Failure

18

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Introduction

Heart failure is a clinical syndrome initiated by abnormal function of the heart. One of the earliest terms used to describe heart failure syndrome was "hydrops," which has its origins in the observation that salt and water retention was a common feature of the condition. Despite this obvious systemic manifestation, heart failure was still considered primarily a disease of the heart until relatively recently. It is now realized that heart failure is a multisystem disorder, with abnormalities of the heart, vasculature, skeletal muscle, kidneys, and respiratory control combining with various neurohormonal derangements to produce the heart failure syndrome. Of particular importance has been the idea that many of the compensatory mechanisms designed to overcome the initial insult to the heart are the same processes that set in motion a variety of detrimental consequences for cardiac function, gradually worsening the heart failure syndrome further. Our increasing understanding of these concepts has resulted in a rapid advancement in drug development and many new therapeutic targets continue to emerge. In this chapter we summarize the pathophysiology of heart failure, beginning with the specific insults that initiate heart failure and continuing with a discussion of the body's responses to such insults, and how compensatory mechanisms ultimately cause further deterioration in cardiac function.

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Definitions and Terminology

Various attempts at defining and classifying heart failure have been proposed; these are summarized in Tables 18.1 and 18.2, respectively. Many definitions are unsatisfactory because they emphasize particular pathological or clinical features. Definitions based on clinical criteria are limited as observations can vary over time, with the level of exercise, or with transient comorbidity, and in response to treatment. Likewise our emerging understanding of heart failure pathophysiology indicates that specific biochemical, anatomical, or physiological features do not occur in isolation and cannot fully explain the heart failure syndrome on their own. Our definition of "a clinical syndrome caused by an abnormality of the heart and recognized by a characteristic pattern of hemodynamic, renal, neural, and hormonal responses" [1] is a useful one, as it recognizes that an abnormality of the heart is the origin of heart failure but that systemic responses to the cardiac dysfunction are important in further defining its pathophysiology and clinical manifestations.

Nevertheless this definition would have limitations in epidemiological data collection where more objective and measurable criteria are needed to define heart failure. In this respect the European Society of Cardiology guidelines [2] are more useful, as they require heart failure to be based on a clinical diagnosis whereby symptoms and signs of heart failure have been observed, where a demonstrable abnormality of the heart is present, and where, preferably, there is a favorable response to treatment. Terms such as forward versus backward failure and right-sided versus left-sided failure have confused generations of students, and although they may be a useful clinical shorthand, they are often misleading or based on outdated concepts.

Diastolic Versus Systolic Dysfunction

"Diastolic" heart failure has emerged as a distinct clinical entity and is characterized by clinical features suggestive of

†deceased

C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_18, © Springer Science+Business Media New York 2013

Table 18.1 Some definitions of heart failure

Lewis 1933	A condition in which the heart fails to discharge its contents adequately
Wood 1950	A state in which the heart fails to maintain an adequate circulation for the needs of the body despite a satisfactory filling pressure
Braunwald 1980	A pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolising tissues
Poole-Wilson 1985	A clinical syndrome caused by an abnormality of the heart and recognised by a characteristic pattern of haemodynamic, renal, neural and hormonal responses
Harris 1987	A syndrome which arises when the heart is chronically unable to maintain an appropriately high blood pressure without support
Cohn 1988	A syndrome in which cardiac dysfunction is associated with reduced exercise tolerance, a high incidence of ventricular arrhythmias and shortened life expectancy
Denolin 1993	Heart failure is the state of any heart disease in which, despite adequate ventricular filling, the heart's output is decreased or in which the heart is unable to pump blood at a rate adequate for satisfying the requirements of the tissues with function parameters remaining within normal limits
Lenfant 1994	The principal functions of the heart are to accept blood from the venous system, deliver it to the lungs where it is oxygenated (aerated), and pump the oxygenated blood to all body tissues. Heart failure occurs when these functions are disturbed substantially
Jackson 2000	A multisystem disorder characterized by abnormalities of cardiac, skeletal muscle, and renal function, stimulation of the sympathetic nervous system and a complex pattern of neurohormonal changes
Jessup and Brozena 2003	A clinical syndrome…the final pathway for myriad diseases that affect the heart

Table 18.2 Classification schemes for heart failure

Acute vs. Chronic
Clinical classification based on the duration of symptoms and speed of onset
High output vs. Low output
Pathophysiological classification based on whether increased circulatory or metabolic demands exceed the capacity of a normal functioning heart (high-output failure) or whether a poorly functioning heart is unable to meet the normal circulatory and metabolic demands of the body (low-output failure)
Forward vs. Backward
Clinical classification based on whether the predominant features are those directly relating to a poor cardiac output, such as hypotension and poor peripheral perfusion (forward failure), or those of systemic and pulmonary venous congestion (backward failure)
Right sided vs. Left sided
A clinical classification that recognizes that specific causes have an impact primarily on either the left- or right-sided cardiac chambers and produce a characteristic cluster of clinical features, namely, abdominal discomfort and peripheral edema (right-sided failure) and dyspnea, hypotension, and poor peripheral perfusion (left-sided failure)
Diastolic vs. Systolic
Pathophysiological classification based on whether the primary cardiac abnormality is reduced ventricular contractile force generation during systole or impaired chamber filling resistance and ventricular relaxation during diastole

heart failure but with minimal or no systolic dysfunction. Diastolic heart failure may occur in up to 50 % of patients with heart failure and is associated with the older age, female gender, arterial hypertension, obesity, diabetes mellitus, and the presence of concentric left ventricular hypertrophy [3]. It can be defined as heart failure due to increased resistance in diastolic filling of the heart and is usually given as a diagnosis of exclusion when clinical features are suggestive and other pathology and systolic dysfunction have been excluded [4]. More recently, the terms "heart failure with preserved systolic function" (HFPEF) or "heart failure with normal systolic function" (HFNEF) have been used to describe the clinical syndrome of heart failure that arises when systolic function of the heart is maintained, recognizing that definitive diagnosis of diastolic abnormality is often difficult or not attempted [5]. Although evidence-based data are lacking on the application of standard heart failure therapy to isolated diastolic dysfunction, its identification is still important as an appreciation of its underlying pathology would suggest specific treatment options that reduce ventricular load, slow heart rate, and increase ventricular filling time are most likely to be of benefit. Due to the overlap between diastolic and systolic heart failure in terms of etiology and pathophysiology, we will not consider diastolic heart failure separately at this stage; rather, throughout this chapter we will highlight particular pathophysiological aspects that are of relevance to diastolic dysfunction.

Etiology

The etiology of heart failure represents the specific underlying insult to the heart that initiates a decline in cardiac performance. Many of the pathological and clinical features of heart failure occur whatever the specific underlying etiology. Nevertheless the underlying etiology is still important, as it may influence the nature and speed of heart failure progression over time, and if still active may suggest particular therapeutic options in the overall management strategies of patients. For these reasons the diagnosis of heart failure on its own is always inadequate without a further search to

identify the underlying cause [2]. Diagnosis may be aided by a pattern of clinical and investigative findings that are particular to a specific etiology. In contrast, the initial pathological insult may have been a transient event many months or years before, in which case the search for its identification may prove extremely difficult. This highlights the concept that heart failure can persist and indeed worsen long after the initial insult to the heart has occurred as a result of various compensatory mechanisms that are designed to overcome the initial insult in the first place but eventually become harmful and disadvantageous if chronically activated. When considering causes it is also important to bear in mind the nature of the population in question; for example, hypertension and coronary artery disease are responsible for most heart failure in highly developed countries today, whereas valvular disease and the manifestations of infection or nutritional deficiency are much more important causes worldwide due to their higher relative prevalence in poor countries [6]. The general causes of heart failure are listed in Table 18.3.

Table 18.3 Causes of heart failure: general classification

Coronary artery disease
Intrinsic myocardial disease
Dilated cardiomyopathy
Hypertrophic cardiomyopathy
Restrictive cardiomyopathy
Arrhythmogenic right ventricular cardiomyopathy
Valvular heart disease
Congenital
Age-related/calcific
Infective endocarditis
Immunological (e.g., rheumatic fever)
Collagen disease (e.g., Marfan's syndrome)
Neoplastic (metastases, carcinoid syndrome)
Congenital heart disease
Hypertension
Systemic and pulmonary
Arrhythmias and cardiac conduction disturbances
Tachyarrhythmias
Bradyarrhythmias
Intraventricular conduction disturbance
High-output cardiac failure
Anemia
Thyrotoxicosis
Pregnancy
Arteriovenous fistula
Liver cirrhosis
Paget's disease
Renal cell carcinoma
Pericardial disease
Constrictive pericarditis
Pericardial effusion with tamponade

Coronary Artery Disease

Coronary artery disease is the single most common cause of heart failure in highly developed countries [7, 8]. However, many of the risk factors for coronary artery disease, such as hypertension and diabetes, are also independent risk factors for the development of heart failure, irrespective of whether coronary artery disease is present or not. Myocardial ischemia may produce altered functional states within the myocardium known as hibernation, stunning, and ischemic preconditioning. However, it is primarily within the context of myocardial ischemia and infarction that coronary artery disease manifests as heart failure. The outcomes of coronary artery disease on the myocardium are summarized in Table 18.4.

Hypertension

Hypertension is the second major cause of heart failure in highly developed countries and often coexists with coronary artery disease [8]. Hypertension is particularly associated with heart failure in specific populations, including women, diabetics, and people of African origin [6]. Furthermore, its causal role in the development of left ventricular hypertrophy makes it a very important etiologic factor in the development of "diastolic" heart failure.

Cardiomyopathy

The term *cardiomyopathy* is widely used in the context of heart failure and, at its most basic level, can be defined as a disease process involving cardiac muscle. It is traditionally reserved for intrinsic cardiac muscle disease in the absence of coronary artery disease, hypertension, valvular, congenital, and pericardial heart disease. Cardiomyopathy can be divided on descriptive terms into several functional categories: dilated, hypertrophic, restrictive, and arrhythmogenic right ventricular [9].

Dilated cardiomyopathy (Table 18.5) can be defined as heart muscle disease in which the predominant abnormality is dilation of the left ventricle (with or without right ventricular dilation). It is the end result of numerous pathological insults on the heart, although in many cases it is idiopathic, in the sense that the cause is unknown. Recent work suggests that familial disease accounts for over a third of cases [9]. It is the most common form of cardiomyopathy, highlighting the fact that the final response of the heart to sustained injury is a global chamber remodeling resulting in a globular heart with thinned walls, decreased systolic function, and functional valvular regurgitation.

Hypertrophic cardiomyopathy is characterized by hypertrophy of a nondilated left and/or right ventricle. It is a term usually applied to situations in which hypertrophy of the ventricles

Table 18.4 Outcomes of coronary artery disease on myocardial function

Acute ischemia
Atheromatous plaque rupture and thrombosis formation
Impaired resting and exercise myocardial contractility
Chronic ischemia
Stable atheromatous plaque disease with flow limitation on exercise/stress
Impaired contractility during exacerbations
Potential to initiate ischemic preconditioning
Myocardial infarction
Prolonged vessel occlusion with irreversible myocardial damage
Impaired contractility due to replacement of muscle with scar tissue
Cardiogenic shock, ventricular septal rupture, and acute mitral regurgitation cause life-threatening left ventricular dysfunction
Stunning
Transient and reversible contractile dysfunction following ischemia, despite restored coronary flow
Hibernation
Persistent but potentially reversible contractile dysfunction due to episodes of reduced coronary perfusion and/or limited coronary reserve
Ischemic preconditioning
Resistance of myocardium to sustained ischemia, conferred by transient sublethal periods of ischemia
Potential for subsequent infarct size reduction
Reduced demand for ATP under ischemic conditions

Table 18.5 Causes of dilated cardiomyopathy

Genetic
Gene defects: mutations in genes that encode a wide variety of cellular compartments and pathways, including nuclear envelope, contractile apparatus, Z-disc and costamere, gene transcription and splicing machinery, and calcium handling
Mitochondrial myopathies
Arrhythmogenic right ventricular dysplasia (chiefly desmosomal protein gene defects)
Infection
Viral (e.g., coxsackievirus, HIV)
Bacterial (e.g., *Clostridium diphtheriae* exotoxin)
Protozoal (e.g., trypanosomiasis)
Parasitic (e.g., schistosomiasis, trichinosis)
Rickettsiae (e.g., epidemic typhus-induced myocarditis)
Spirochetes (e.g., Lyme disease)
Drugs and toxins
Heavy metal (e.g., cobalt, mercury, lead)
Alcohol and recreational drugs (e.g., cocaine)
Carbon monoxide poisoning
Cytotoxic drugs (e.g., bleomycin, doxorubicin, busulfan, adriamycin)
Antimicrobial drugs (e.g., chloroquine, zidovudine)
Antipsychotic drugs (e.g., clozapine, haloperidol, risperidone)
Pregnancy (peripartum cardiomyopathy)
Nutritional deficiency
Keshan disease (selenium)
Beri-beri (thiamine)
Pellagra (niacin)
Kwashiorkor (generalized protein/energy malnutrition)
Storage disease
Hemochromatosis
Refsum's disease
Fabry's disease
Autoimmune/vasculitides
Systemic lupus erythematosus
Polyarteritis nodosa
Rheumatoid arthritis
Churg–Strauss disease
Endocrine
Diabetes mellitus
Myxoedema and thyrotoxicosis
Acromegaly
Pheochromocytoma

occurs in the absence of an identified systemic or cardiac stimulus such as hypertension or aortic stenosis. The classic form of familial hypertrophic cardiomyopathy is an autosomal dominant disorder characterized by asymmetrical septal hypertrophy and, in severe cases, symptoms of aortic outflow tract obstruction. Many genetic defects within sarcomeric proteins, such as β-myosin heavy chain, troponin, and tropomyosin, have been identified in familial hypertrophic cardiomyopathy [9], with mutations in one of nine genes in up to two-thirds of patients with hypertrophic cardiomyopathy [10].

Restrictive cardiomyopathy is characterized by a stiff, noncompliant ventricle with abnormal ventricular filling. It is especially associated with diastolic dysfunction and is associated with a diverse range of conditions associated with fibrosis or infiltration of the heart such as endomyocardial fibrosis, hypereosinophilic syndromes, sarcoidosis, amyloidosis, radiation, and neoplastic disease. Restrictive cardiomyopathy is rare in highly developed countries and is seen more commonly in the developing world, primarily due to its association with tropical parasitic infection and eosinophilia.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a familial cardiomyopathy, typically autosomal dominant, in 50 % of cases [9]. The main feature is fibrofatty replacement of the myocardium of the right, and sometimes the left, ventricle, with a susceptibility to ventricular arrhythmia. The majority of mutations associated with this specific cardiomyopathy are in genes that encode desmosomal proteins, thus compromising cell-to-cell adhesion at intercalated discs and gap-junction function.

The Failing Heart: From Organ to Molecule

In response to cardiac injury, mechanisms are activated that compensate for depressed cardiac performance, and these attempt to restore both cardiac output and tissue perfusion to

normal. Many of these responses take place within the heart; these intrinsic cardiac responses to injury occur at the gross anatomical, cellular, molecular, and genetic levels. Although these responses to injury occur initially as a mechanism to augment cardiac function, many subsequently become detrimental to ongoing cardiac function if allowed to continue (Table 18.6). This concept of secondary injury mechanisms, distinct from the initial insult to the heart, is outlined in Fig. 18.1, which summarizes our current understanding of the major pathophysiological processes involved in heart failure syndrome.

Ventricular Chamber Size, Shape, and Remodeling

All four cardiac chambers possess the capacity to alter their size and shape in response to acute or chronic injury and changes in hemodynamic load and wall stress. Changes in chamber geometry may occur rapidly over a period of hours and days, for example, following myocardial infarction. Alternatively they may occur gradually over many months by a process known as remodeling [11]. Remodeling is influenced, at least initially, by the underlying etiology of the primary cardiac injury process, although ultimately a grossly dilated spherical heart chamber phenotype occurs if resolution or death does not intervene in the interim period.

Table 18.6 Abnormalities of the failing heart

Macroscopic
Loss of muscle mass
Alteration in chamber size and shape (dilation and/or hypertrophy)
Incoordinate contraction and abnormal timing of contraction
Microscopic
Myocyte changes (cell thinning, lengthening, hypertrophy, necrosis, apoptosis)
Disorganized muscle fiber orientation and myocyte slippage
Extracellular matrix inflammatory cell infiltrate, fibroblast expansion, and fibrosis
Intracellular
Disorganized cytoskeleton
Impaired cell-to-cell communication (gap junctions)
Contractile protein structural and functional derangements
Deranged excitation–contraction coupling and calcium homeostasis
Reduced efficiency of intracellular signal transduction pathways
Altered energy metabolism
Regression to dedifferentiated "fetal" gene expression pattern

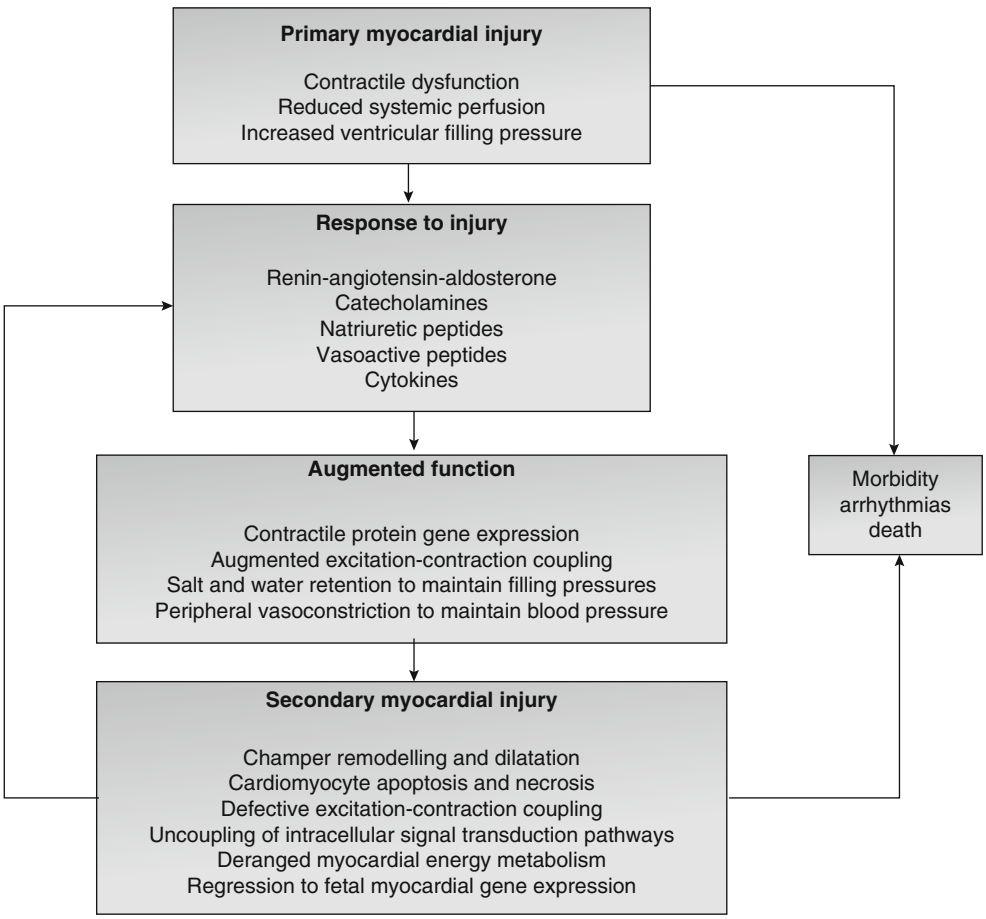

Fig. 18.1 Primary and secondary injury mechanisms in heart failure pathophysiology. Primary injury to the myocardium occurs and is followed by various responses that augment cardiac performance. Subsequent detrimental responses eventually predominate which themselves worsen cardiac function, even if the initial cause of injury has resolved, resulting in an ever-worsening cycle of deterioration. Once critical thresholds of damage are exceeded, either as a result of primary or secondary injury mechanisms, heart failure becomes clinically apparent

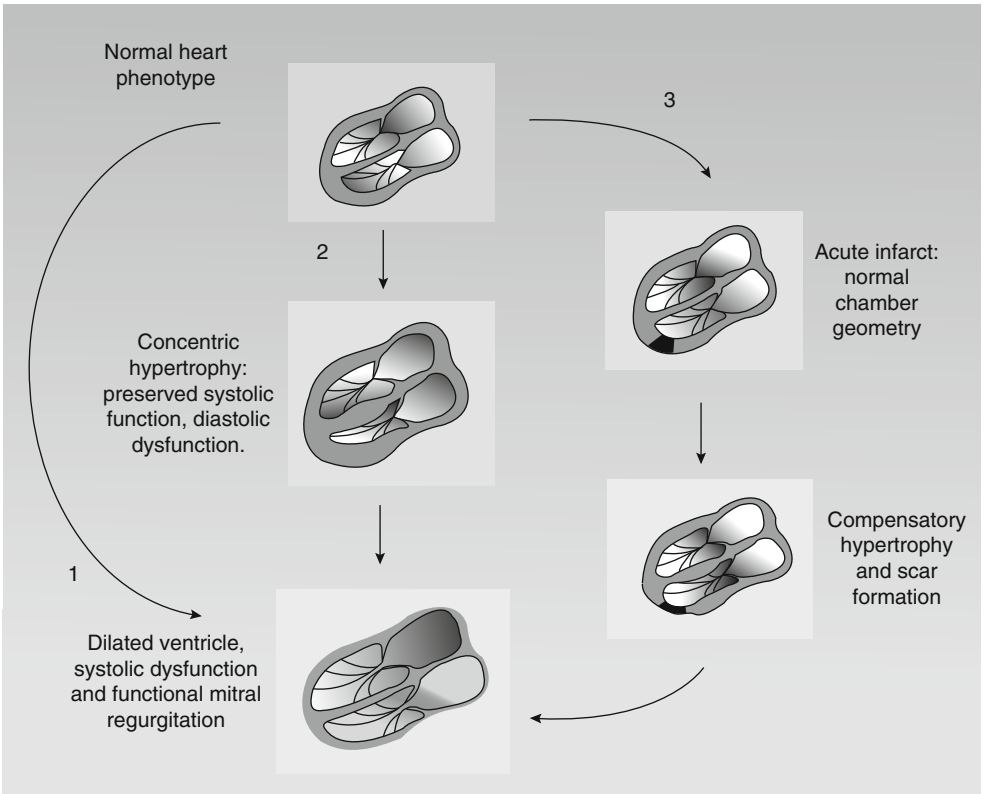

Fig. 18.2 Patterns of ventricular remodeling. (*1*) Intrinsic myocardial disease leads to a dilated ventricle, systolic dysfunction, and disruption of the mitral/tricuspid valve apparatus. (*2*) Concentric left ventricular hypertrophy leads to initially preserved systolic function, diastolic dysfunction, and left ventricular outflow tract obstruction. Progression may eventually lead to chamber dilation and systolic dysfunction. (*3*) Myocardial infarction leads to scar formation and wall thinning, with compensatory hypertrophy in remaining viable muscle as an attempt to alleviate abnormal loading on chamber and elevated wall stress. Progression may eventually lead to chamber dilation and systolic dysfunction

Remodeling is associated with worsening cardiac function, yet it occurs initially as an adaptive response that counteracts abnormal wall stresses and hemodynamic load forces placed on the heart chambers. It is an important clinical process, as it is readily identifiable with cardiac imaging techniques and is associated with an increased mortality secondary to end-stage contractile failure or complications such as myocardial rupture and intracardiac thrombus formation. Several patterns of remodeling are recognized; these are summarized in Fig. 18.2.

The most common pattern of remodeling in the context of chronic heart failure is the dilated cardiomyopathy phenotype, either occurring *de novo* due to intrinsic myocardial disease, secondary to chronic volume overload on the ventricles, or finally as the ultimate outcome of other remodeling patterns when end-stage heart failure approaches. At the macroscopic level there is an increase in chamber size and a thinning of the ventricular wall dimensions, resulting in an enlarged globular heart. This phenotype is associated with reduced systolic function and functional mitral/tricuspid regurgitation and often coexists with intraventricular conduction abnormalities such as bundle branch block. Such bundle branch block (typically left bundle) is characterized by regional differences in loading and contractile work, with differences in regional myocardial blood flow and oxygen consumption. Disparities in wall stiffening that generate dyssynchronous motion are most apparent in early systole during isovolumic contraction and late systole as one region enters relaxation while the other is still contracting [12]. This leads to mechanical inefficiency, exacerbated by functional mitral regurgitation caused by a delay in the rise of LV intracavitary pressure and discoordinate papillary muscle contraction. Resynchronization therapy can improve mechanical efficiency and reduce functional mitral regurgitation, without increasing myocardial oxygen requirements [13], and is associated with morbidity and mortality benefits in clinical practice [14].

A second pattern of remodeling is concentric hypertrophy caused by pressure overload on the ventricles. This produces a stiff noncompliant ventricle with impaired relaxation as the primary problem, with systolic function initially preserved. This remodeling response is common in "diastolic" heart failure and is most commonly associated with hypertensive heart disease and other causes of pressure overload. Progressive dilation may eventually follow and although this will ultimately lead to thinning of the ventricular wall the presence of chamber dilation and myocardial wall hypertrophy are not mutually exclusive and often coexist.

A third pattern is focal myocardial injury, most commonly encountered in acute myocardial infarction. This results in an initial remodeling process at the site of injury and its boundaries, which takes the form of a destruction of normal myocardial architecture and its eventual replacement by scar tissue. It may also initiate changes in ventricular wall stress and loading throughout the affected heart chamber, resulting in compensatory hypertrophy and a progressive global

dilation if the initial infarct insult was of sufficient magnitude. The appearance of the remodeling phenomenon and its partial reversal with modern treatment is useful in the clinical management of patients as it can readily be observed on serial noninvasive imaging. At the pathological level, however, it simply represents the phenotypic manifestation of underlying processes occurring within the myocardium at the cellular, molecular, and genetic levels.

Cardiomyocyte Plasticity in Heart Failure

Individual myocyte responses seen in heart failure comprise alterations in cell size, shape, and number. Increases in myocyte number were previously thought to be impossible, with cardiomyocytes believed to be terminally differentiated cells, incapable of reentering the cell cycle and undergoing further division. In fact there is now a growing body of evidence that indicates that cardiomyocyte cell division does occur in the heart but is not common [15]. It is estimated that without this phenomenon the observed rates of cell death in the normal heart are such that by early adult life the myocardium and myocyte population present at birth would have totally disappeared [16]. Mitosis has long been observed in cardiomyocytes but without subsequent cytokinesis, suggesting that cardiomyocyte mitosis simply resulted in the development of polyploidy and multinucleated cells rather than an expansion in total cell number. Evidence that cardiomyocytes can regenerate and actually do undergo division has now been widely published. One hypothesis is that whereas the majority of cardiomyocytes are terminally differentiated and possess no regenerative capacity, a small number of precursor cells do exist, and these retain the ability to divide and form mature cardiomyocytes. It is unclear whether these cells are a specific population of myocytes present within the myocardium from birth or whether they represent a population of circulating stem cells capable of differentiating into numerous specialized tissue types upon appropriate stimulus. Evidence for the latter is supported by observations in male patients who receive a female donor heart at transplantation. Subsequent analysis of these hearts reveals the presence of numerous myocytes possessing the Y chromosome, raising the possibility that a circulating male stem cell migrates into the female donor myocardium and differentiates into a mature functioning myocyte. After bone marrow transplants from male donors, female recipients have Y-chromosome-positive mature cardiomyocytes, suggesting that the circulating stem cells originate in the bone marrow. What remains to be established is the functional significance of such observations; at present the widely held consensus is that any compensatory response to augment cardiac performance is primarily via hypertrophy of preexisting cells rather than by division and expansion of the cell population. Regenerative therapies aim to restore the physiological cellular composition of the diseased heart by manipulating the cell cycle of differentiated cells, activation of resident cardiac progenitor cells, or the transplantation of exogenous cells [17].

Cardiomyocyte hypertrophy represents an increase in intracellular volume, enlarging the cell primarily in its transverse diameter. It is most readily demonstrated in response to situations of pressure overload, such as hypertension, and occurs without any significant increase in cell length along the longitudinal axis. Cellular hypertrophy occurs to a certain extent in most remodeling processes, including dilated cardiomyopathy. The most obvious change in cardiomyocyte hypertrophy is an increase in contractile protein content and sarcomere number, but nuclear polyploidy also occurs and hypertrophied cardiomyocytes may be heavily multinucleated. In familial hypertrophic cardiomyopathy, there is often considerable loss of normal cellular architecture, termed myocyte disarray. When hypertrophy occurs as a secondary phenomenon, however, the underlying cellular architecture is, in comparison, relatively well maintained. The mechanisms underlying the cardiomyocyte hypertrophy response involve a complex interaction between extrinsic stimuli and growth factors, intracellular amplification cascades, and transcription factors (Fig. 18.3).

Cellular elongation along the longitudinal axis is the primary response in dilated cardiomyopathy. This response is also mediated at a cellular level by altered gene expression that affects both the cytoskeleton and contractile protein components of the cell. Extrinsic factors such as changes in the cellular and matrix components of the myocardial interstitium may also contribute to cardiomyocyte shape change and elongation. In fact, myocyte elongation alone cannot in itself account for the macroscopic increase in chamber size seen in dilated cardiomyopathy. This state of affairs can be accommodated only if there is a degree of myocyte slippage between adjacent muscle fibers that are normally closely apposed.

In addition to the structural changes in cellular architecture described above, there is also evidence that functional connections between adjacent cardiomyocytes are defective in heart failure. Adjacent cardiomyocytes are functionally connected with one another at the level of the gap junction, a set of transmembrane channels that link adjoining myocytes and mediate electrical coupling and communication. Individual gap-junction proteins are called *connexins*; these are assembled in a hexamer configuration termed a *connexon*. In addition to alterations in the absolute number and distribution of connexons in heart failure, the expression pattern of individual connexin isoforms is also altered by heart failure [18]. Connexin-43 is the most widely expressed and important connexin in normal human hearts, but in heart failure its expression is significantly reduced relative to other

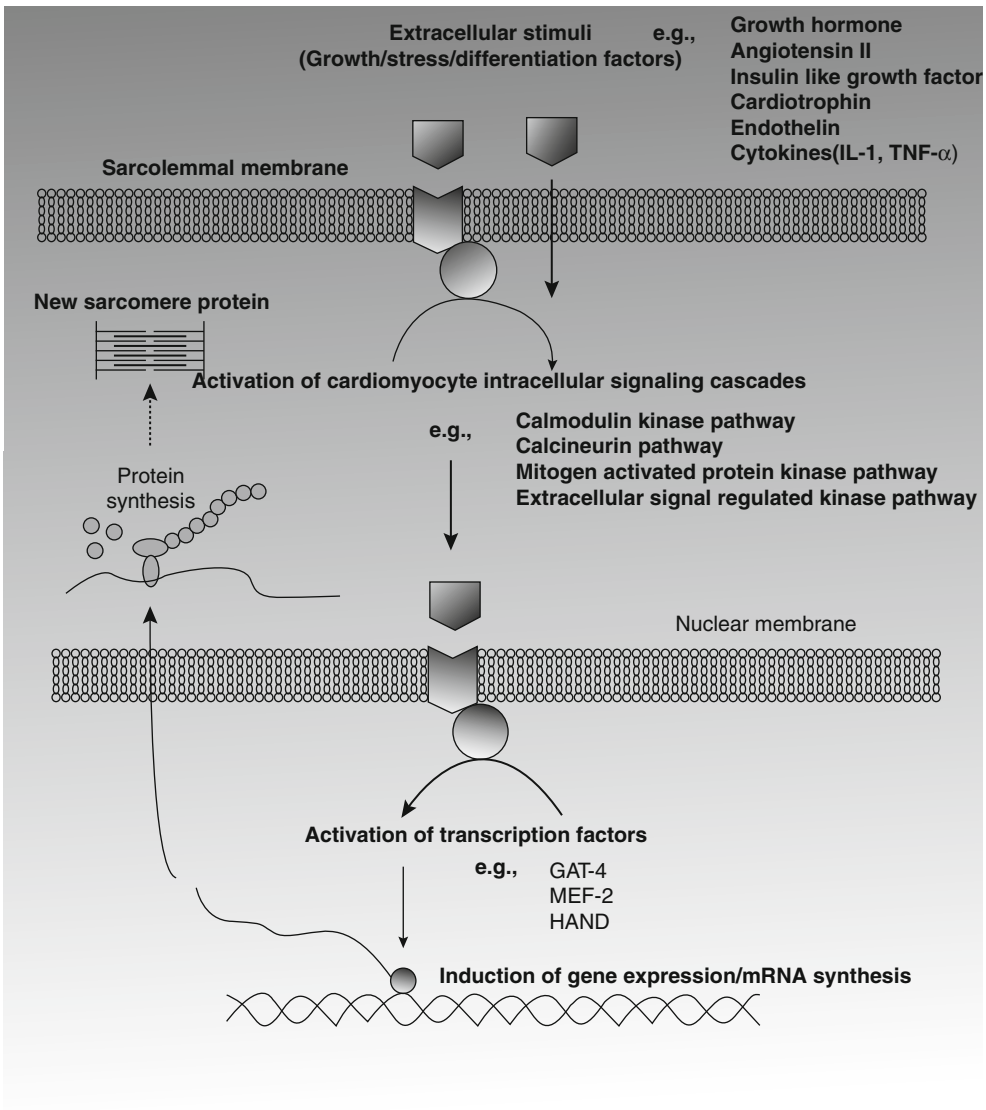

Fig. 18.3 Pathways of altered cardiomyocyte gene expression. Multiple extrinsic stimuli activate intracellular pathways that induce cardiomyocyte gene expression and protein synthesis. Early gene expression comprises specific regulator genes that control cell growth and differentiation, such as *c-myc*, *c-fos*, and *c-jun*. Increased sarcomere protein synthesis can be detected within 6 h of expression induction. Within 24 h increases in sarcomere number and cell size are demonstrable

isoforms. This may disrupt the electrical coupling that facilitates synchronized contraction and may predispose to the electrical instability that precipitates arrhythmias.

Cardiac cell loss is a key feature of both primary and secondary injury mechanisms in the failing heart and occurs via necrosis or apoptosis. Necrosis is most commonly seen in the context of myocardial infarction. Such acute necrosis allows no time for the development of compensatory hypertrophy in remaining viable cells, and if a critical mass of myocardium is lost (~40 % or above), cardiogenic shock and death will quickly ensue. Gradual cell loss through necrosis is much better tolerated and is seen throughout the heart at the microscopic level in most underlying conditions causing chronic heart failure. It is an unregulated process characterized by cell swelling and its eventual fragmentation in response to oxidative stress and the actions of destructive enzymes. Necrotic cells also initiate an inflammatory response and eventually lead to fibrosis, features not seen in myocyte apoptosis.

Apoptosis is characterized by cell shrinkage, the condensation of nuclear chromatin, and the disintegration of cytoplasmic and nuclear contents into discrete vesicles that are phagocytosed by neighboring cells without associated inflammation or any change in the microscopic morphology of the myocardium. It is a normal physiological process during cardiac development but is now recognized as a phenomenon induced by ischemia, infarction, and various systemic responses in heart failure [19]. Apoptosis depends on the activation of intracellular enzymatic cascades, such as the caspase pathway, which eventually leads to the fragmentation of cytoplasmic proteins and nuclear material. Cardiomyocyte apoptosis may sometimes be cut short by inhibition of the activated caspase pathways at the point where nuclear fragmentation begins. These cells retain their nuclear integrity and survive but will have suffered irreversible damage to cytoplasmic metabolic pathways and contractile proteins such that they can no longer function as a

Table 18.7 Composition and function of myocardial interstitium

Cellular
Fibroblasts, mast cells, macrophages, plasma cells
Extracellular matrix
Proteins (e.g., collagen, elastin, reticulin)
Ground substance (e.g., glycosaminoglycans, glycoproteins)
Tissue fluid
Blood vessels
Nerve endings
Lymphatics
Function
Transmit force
Maintain alignment of myocytes and muscle fibers
Prevent overdistension of myocardium
Support and attachment to intracellular cytoskeleton
Store energy in systole (contribute to relaxation)
Repair of myocardial damage
Vehicle for movement and migration of immunocompetent cells
Medium for exchange of nutrients, signaling molecules, and metabolic wastes

competent cardiomyocytes. This process has been called "apoptosis interruptus" and the nonfunctioning cells that remain are appropriately named "zombie myocytes" [20]. Many factors have been shown to initiate apoptosis in heart failure, such as hypoxia, nitric oxide, cytokines, angiotensin II, and catecholaminergic signaling pathways. However, the functional relevance of apoptosis in heart failure and whether it represents a beneficial or harmful aspect of the remodeling process remains unclear. To date experimental caspase blockade and inhibition of apoptosis in animal models of heart failure has not yielded dramatic improvements in myocardial function.

Interstitium and Myocardial Fibrosis in Heart Failure

The myocardial interstitium is made up of various components and has an important structural and supportive role in the normal heart, as outlined in Table 18.7. Ventricular remodeling is facilitated by changes in the composition and function of various interstitial components. Ultimately these changes manifest as an increase in myocardial fibrosis if they are allowed to continue unopposed for any length of time; indeed, in certain disease states such as arrhythmogenic right ventricular dysplasia, fibrosis may be the most prominent microscopic abnormality. The increased myocardial fibrosis in heart failure is associated with an increase of the interstitial fibroblast population. These cells proliferate and undergo differentiation into an active phenotype known as a myofibroblast. Myofibroblasts produce various extracellular matrix proteins, along with a variety of autocrine and paracrine signaling molecules, cytokines, and enzymes. The proportion of total ventricular weight that is due to collagen fibers can increase from insignificant levels in the normal heart to anything approaching 25 % in established heart failure. Excess collagen deposition initially leads to an impairment of diastolic relaxation and increased stiffness of ventricular chambers. As deposition continues, systolic function is also compromised.

The turnover of collagen in the heart is governed by the activity of extracellular matrix metalloproteinases (MMPs), a family of proteolytic enzymes responsible for the degradation of various extracellular matrix proteins. In various models of heart failure, the activity of MMPs has been shown to be dysregulated [21]. Isoforms such as MMP-13 are expressed at very low levels in normal hearts and substantially upregulated in heart failure, whereas MMPs expressed in the normal heart are downregulated in heart failure. Furthermore, the normal regulators of MMP activity, known as the tissue inhibitors of the MMPs (TIMPs), are upregulated in heart failure, and these MMP inhibitors contribute to the overall defective turnover and accumulation of collagen seen in the failing heart. Increased MMP activity is associated with a weakening of the interstitial support network and a net loss of collagen. Paradoxically a reduction in activity of specific MMP isoforms also weakens the interstitial support network because without the normal physiological repair and reabsorption of damaged collagen fibrils, the strength and structural integrity of the extracellular matrix will gradually worsen over time despite an absolute increase in content. Weakened extracellular matrix support and increased fibrosis result in myocyte slippage and ventricular chamber dilation, but hypertrophied myocardium also demonstrates increased fibrosis tissue deposition between muscle fibers on specific staining. Many stimulants of collagen synthesis and turnover (and ultimately increased myocardial fibrosis) are known, including cytokines, catecholamines, oxidative stress, angiotensin II, and aldosterone. The importance of myocardial fibrosis in heart failure pathophysiology is demonstrated by the observation that much of the beneficial effect of aldosterone-antagonist drug therapy in heart failure appears to be secondary to an inhibitory effect on its fibrosis-inducing properties.

Excitation–Contraction Coupling in Heart Failure

Cardiac excitation–contraction (EC) coupling is the process whereby myocyte electrical depolarization acts as the stimulus for a coordinated movement of Ca^{2+} in the cell to bring about contraction. It is a highly efficient amplification system and its modulation is one of the primary mechanisms whereby the inotropic state of the heart can be increased in response to injury.

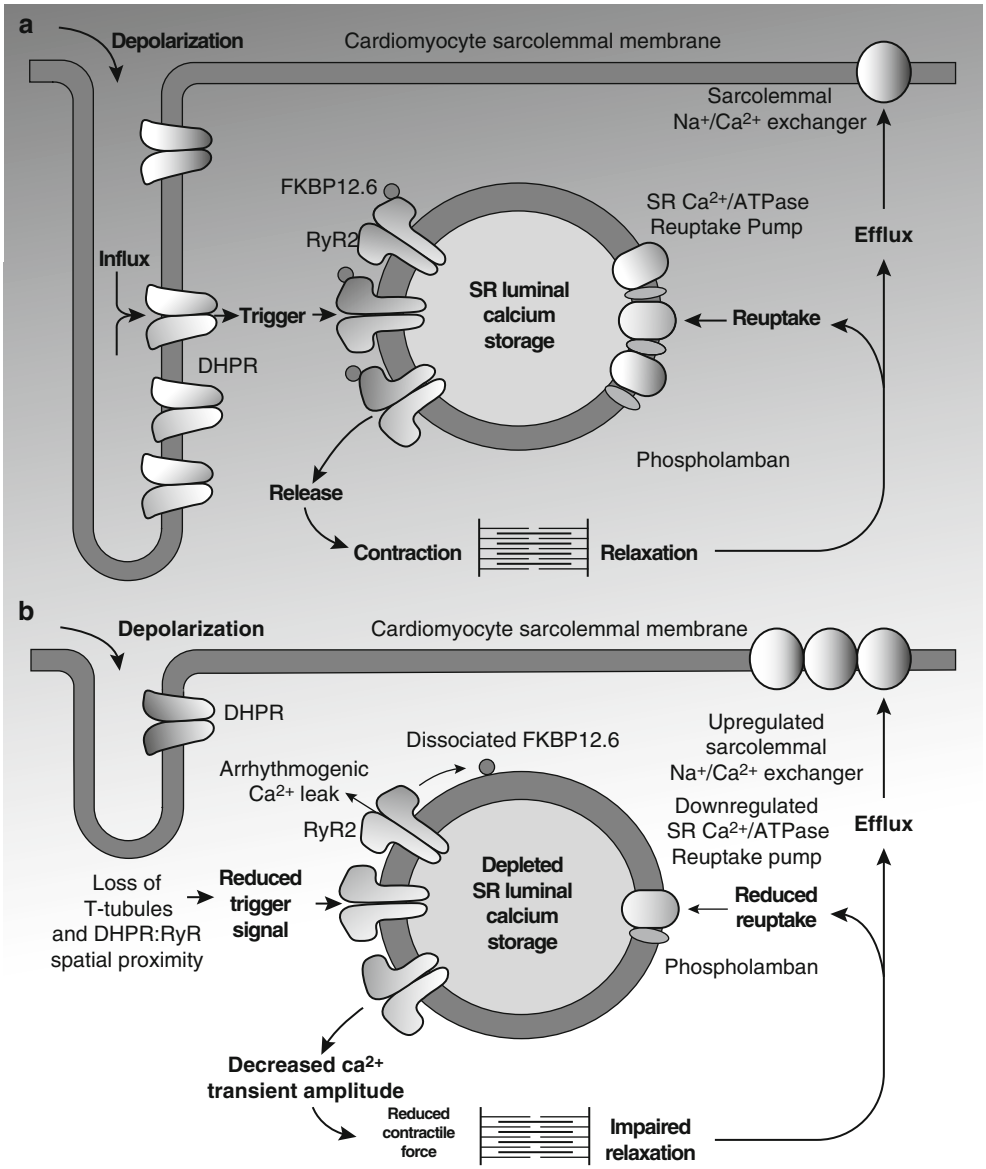

Fig. 18.4 Cardiac excitation–contraction coupling. Cardiac EC coupling and intracellular calcium movement. (**a**) Normal cardiac EC coupling; (**b**) abnormalities of cardiac EC coupling in heart failure. The movement of calcium is shown in *bold text/arrows*. *See* text for further description and abbreviations

The major components of cardiac EC coupling are outlined in Fig. 18.4a [22]. When the myocyte depolarizes, extracellular Ca^{2+} enters the cell through the L-type, voltage-dependent (dihydropyridine [DHPR]-sensitive) Ca^{2+} channel, a phenomenon represented by the phase 2 plateau of the cardiac action potential. This inward Ca^{2+} current is, on its own, insufficient to bring about the required conformational change in troponin needed for contraction to occur. Additional Ca^{2+} is required; this is obtained from a pool of stored Ca^{2+} within the myocyte sarcoplasmic reticulum (SR). The initial inward movement of Ca^{2+} acts as an amplification signal for the release of this storage pool of Ca^{2+}, through an SR membrane ion channel known as the cardiac ryanodine receptor (RyR-isoform 2). Individual populations of RyR2 localize in areas of the SR membrane that are adjacent to DHPR channels deep within the T-tubule invaginations of the outer sarcolemma membrane. Influx of Ca^{2+} through the DHPR activates its associated local RyR2 population causing a synchronized release of Ca^{2+} known as a Ca^{2+} *spark*. The synchronized release of Ca^{2+} from RyR2 is facilitated by the coupled gating of adjacent RyR2 channels, a property mediated by the RyR2-associated regulatory protein FKBP 12.6 [23]. The synchronized release of multiple Ca^{2+} sparks throughout the cell following depolarization creates a global intracellular Ca^{2+} transient of sufficient magnitude to bring about contraction. Conversely, diastole and myocyte relaxation results from closure of RyR2 and the rapid removal of cytosolic Ca^{2+}, either by reuptake into the SR through the SR Ca^{2+}/ATPase pump (SERCA) or by its efflux out of the cell through the sarcolemmal Na^{+}/Ca^{2+} exchanger (NCX).

As an early response in heart failure β-adrenergic receptor-mediated intracellular signaling pathways mediate

phosphorylation of individual EC coupling components, which increases the efficiency of both systolic and diastolic components of the process. Despite these initial beneficial improvements in EC coupling efficiency, ongoing intracellular signaling eventually leads to a blunting of β-adrenergic-mediated compensatory mechanisms. Downregulation of β-adrenergic receptors contributes to this but specific molecular targets such as RyR2, NCX, and DHPR become "hyperphosphorylated." Not only does this render these components incapable of further augmentation in function, but it is also now apparent that hyperphosphorylation of EC coupling molecular targets has detrimental effects. The consequences of RyR2 hyperphosphorylation are the most extensively studied [24] and include dissociation of FKBP12.6, a loss of coupled RyR2 gating, and a diastolic release of SR Ca^{2+}. These effects may in turn lower SR Ca^{2+} stores and precipitate proarrhythmogenic delayed afterdepolarizations. Interestingly, β-blockers in heart failure reverse RyR2 hyperphosphorylation and their action on RyR2 may be one mechanism by which their beneficial effects in heart failure are mediated [25].

Studies of EC coupling in heart failure have consistently demonstrated a reduction in the SR storage pool of Ca^{2+}. This leads to a reduced amplitude of the systolic intracellular Ca^{2+} transient that initiates contraction. As a result, contractile force is reduced. SERCA is significantly downregulated in heart failure, and this will prevent adequate loading and replenishment of SR Ca^{2+} stores [26]. Ca^{2+} availability may also be worsened by an upregulation of NCX, which leads to the removal of Ca^{2+} from the cell. Downregulation of SERCA, preventing the removal of cytosolic Ca^{2+} back into the SR at the end of systole, impairs relaxation as it leads to a prolongation of the systolic Ca^{2+} transient duration and is likely to contribute to the specific pathophysiology of diastolic dysfunction. The close structural and functional relationship between DHPR and RyR2 at the base of sarcolemmal T-tubule invaginations may also be disrupted in heart failure. T-tubules run deep within the cell and bring the outer depolarizing sarcolemmal membrane into close contact with the intracellular machinery of EC coupling. Isolated cardiomyocytes from failing hearts consistently demonstrate a loss of the T-tubule network, which would also be expected to impair efficient EC coupling and contribute to contractile dysfunction [27]. Detrimental consequences of EC coupling in heart failure are outlined in Fig. 18.4b.

Myocardial Energy Metabolism and Oxidative Stress in Heart Failure

Normal cardiac function depends on the adequate delivery of oxygen and energy substrate to the cell for the production of ATP via aerobic respiration. Under normal circumstances the delivery of energy substrate into the mitochondrial oxidative phosphorylation pathways is preferentially through the β-oxidation of fatty acids (>60 %) with glucose utilization via the glycolysis pathway less important (<40 %). A further important pathway in the heart is the phosphocreatine/creatine kinase pathway, which provides a high-energy phosphate store within the myocardium and is responsible for the translocation of high-energy phosphate from mitochondria to the myofibril myosin ATPase.

In situations of ischemia and tissue hypoxia, glycolysis becomes a more important source of energy substrate supply, a phenomenon that can precipitate lactic acidosis. In various models of heart failure numerous qualitative and quantitative changes have been identified within the enzymes and cofactors of the myocardial energy metabolism pathways [28]. The importance of many of these observations is unclear, and it remains speculative as to whether they have a causal role or contribute significantly to the pathophysiology of heart failure. In specific diseases that involve some of these components, such as the mitochondrial myopathies and Refsum's disease, cardiomyopathy can certainly develop as a clinical feature. A further consistent observation in heart failure is a reduction in the levels and activity of both phosphocreatine and creatine kinase, an observation that may contribute to a reduction in myocardial energy reserve [29]. Rather less consistent, however, are the experimental data concerning the levels of myocardial ATP within the failing heart with reductions, increases, and unchanged levels all reported.

Free radicals, such as the superoxide anion and hydroxyl radical, are transiently generated within the heart during normal myocardial energy metabolism. Fortunately any potential for these to cause significant damage is offset by the presence of highly efficient free-radical scavengers such as superoxide dismutase and catalase. In heart failure free-radical generation is increased via several mechanisms leading to damage and impairment of cardiac structure and function, a phenomenon termed oxidative stress [30]. Furthermore, scavenger systems may become downregulated and less efficient at removing harmful free radicals before damage occurs. This may also be of importance and has been shown to cause dilated cardiomyopathy in experimental models [31]. A summary of the important mediators and effects of myocardial oxidative stress is outlined in Table 18.8. The possible role of oxidative stress in heart failure has led to the development of various antioxidant therapies as potential treatment strategies. Unfortunately initial trials have not shown benefit; nevertheless, several drugs used successfully in heart failure, such as angiotensin-converting enzyme inhibitors and the β-blocker carvedilol, are known to have antioxidant properties, which may in part contribute to their beneficial actions.

Table 18.8 Oxidative stress in heart failure

Initiating mechanisms of oxidative stress
Tissue hypoxia and reperfusion injury
Angiotensin II and aldosterone
Cytokines
Catecholamines
Prostaglandins
Endothelin
Manifestations of oxidative stress
Biological membrane damage (lipid peroxidation)
"Uncoupling" of excitation–contraction coupling pathways
Activation of matrix metalloproteinases and collagen/elastin fiber damage
Induced apoptosis
Induced fetal gene expression pattern
Direct mitochondrial DNA damage
Reduced high-energy phosphate availability
Consequences
Contractile dysfunction
Endothelial dysfunction
Chamber remodeling

Contractile Protein Dysfunction in Heart Failure

The molecular and cellular physiology of cardiac contraction and the various sarcomere proteins is outlined in Chap. 2. The importance of contractile proteins in cardiac function is demonstrated by the observation that mutations in both myosin and actin have been identified in many of the familial cardiomyopathy syndromes; for example, classical autosomal dominant hypertrophic cardiomyopathy commonly occurs secondary to mutations in the β-myosin heavy chain (MHC) gene. In all forms of heart failure, however, altered expression of completely normal contractile protein genes and other proteins involved in their regulation also occurs and may contribute to contractile dysfunction in heart failure. Expression of fetal isoforms of troponin T and myosin light change (MLC) I have been demonstrated in heart failure; however, one of the most consistent and important abnormalities in heart failure is an upregulation of β-MHC expression and a reduction in α-MHC expression, confirmed at both the mRNA and protein levels. This altered MHC isoform expression pattern is detected in failing myocardium before chamber remodeling occurs; the consequences of it are an absolute reduction in total myosin levels and a reduction in myosin ATPase activity, both of which will lead to systolic dysfunction [32].

Systemic Responses to Heart Failure

A variety of systemic responses occur within the body as a result of impaired cardiac function. Better understanding of these has led to advances in heart failure therapeutics. The majority of systemic responses to heart failure occur as compensatory mechanisms and produce short-term improvements in various parameters of cardiac performance. This situation cannot be maintained indefinitely, though, and their continued activation eventually results in further cardiac damage.

Activation of the Sympathetic Nervous System

The release of norepinephrine from sympathetic nerves and epinephrine from the adrenal medulla is one of the first responses to worsening cardiac function. This is largely because one of the most rapid and effective mechanisms to improve contractile performance is via catecholamine-mediated intracellular signal transduction pathways that improve the efficiency of myocardial excitation–contraction coupling and contractile protein function. Increased sympathetic nervous system (SNS) activity is initiated by low- and high-pressure sensory baroreceptors within the vasculature, which respond to falling cardiac output and blood pressure.

As an early compensatory mechanism this activity produces numerous positive benefits within the heart, kidneys, and vasculature that improve cardiac output. Ongoing activation eventually produces a drop-off in beneficial effect because of adrenergic receptor downregulation and a maximizing of intracellular signaling pathway effecter mechanisms. Continued activation sees the appearance of additional deleterious responses that actually begin to worsen cardiac performance. These contrasting short- and long-term actions of catecholamines in the heart are summarized in Table 18.9.

Cardiomyocytes contain various classes of adrenergic receptors, the number and function of which are known to change in heart failure. The properties of human cardiac adrenergic receptors in both the normal and failing heart are summarized in Table 18.10. In addition to changes in receptor expression, myocardial catecholamine responses in heart failure are modified by various mechanisms [32]. Upregulation of β-adrenergic receptor kinase-1 (β-ARK-1) activity results in receptor phosphorylation, a primary mechanism to uncouple the receptor from its intracellular signal transduction pathway. There is also increased activity of inhibitor G proteins (G_i), decreased catalytic activity of adenylate cyclase, and reduced availability of intracellular cyclic AMP, all of which will curtail the activity of β-adrenergic intracellular signaling pathways. A summary of myocardial responses to β-adrenergic receptors in heart failure is outlined in Fig. 18.5. The initial beneficial and subsequent harmful responses of the SNS and catecholamines in heart failure are clearly demonstrated by the use of catecholaminergic-based positive inotropic drugs and β-blockers in heart failure. In acute heart failure, positive inotropic drugs produce

Table 18.9 Short- and long-term effects of catecholamines in heart failure

Cardiac:	*Short term:*
	Increased intrinsic inotropic properties
	Increased chronotropic response
	Induced gene expression to initiate hypertrophy phenotype
	Long term:
	Increased energy expenditure and oxygen consumption
	Ischemia and reactive oxygen species generation (oxidative stress)
	Deranged excitation–contraction coupling and calcium homeostasis
	Myocyte apoptosis and necrosis
	Interstitial fibrosis induction
	Chamber remodeling
Renal:	*Short term:*
	Increased tubular reabsorption of sodium and water (independently and via induction of renin–angiotensin–aldosterone system), which augments preload and maintains ventricular filling pressures
	Long term:
	Ventricular chamber remodeling in response to chronic increases in hemodynamic load
Vasculature:	*Short term:*
	Vasoconstriction to maintain peripheral blood pressure and organ perfusion
	Long term:
	Smooth muscle hypertrophy and reduced vessel compliance

Table 18.10 Adrenergic receptors in the heart

Alpha-1
Postsynaptic G protein-coupled receptor, secondary messenger effects via phospholipase C and inositol-1,4,5-triphosphate
15 % of total adrenoceptor population in normal heart, but up to 50 % of total population in heart failure
Activates sarcolemmal voltage-dependent Ca^{2+} channels, Na^{2+}/H^{+} exchanger, Na^{2+}/K^{+}/ATPase and delayed rectifier K^{+} current. Also induces hypertrophic phenotype and increase myofilament calcium sensitivity
Alpha-2
Presynaptic receptor that regulates postsynaptic norephedrine release during enhanced sympathetic activity. Small population in human heart
Beta-1
Most abundant cardiac adrenoceptor, 70 % of total β-adrenoceptor population in normal heart, down regulated and uncoupled from signal transduction pathways in heart failure
Postsynaptic G protein-coupled receptor, secondary messenger effects via adenylate cyclase, cAMP, and protein kinase A-mediated phosphorylation
Augments myocardial inotropy and chronotropic response
Beta-2
30 % of total β-adrenoceptor population in normal human heart
Postsynaptic G protein-coupled receptor, secondary messenger effects as β1
Augments myocardial inotropy and chronotropic response
Downregulated to a lesser extent than β1 receptors in heart failure
Uncoupled from signal transduction pathways in heart failure
Beta-3
Postsynaptic receptor, coupled to inhibitory G proteins that have negative inotropic properties
Not downregulated in heart failure
Beta-4
Increasing evidence for existence, cardiostimulatory effects similar to β1/β2
Significance in normal and failing heart unknown

short-term improvements in various hemodynamic parameters. Their long-term use and ongoing β-adrenergic receptor activation lead to ever-decreasing beneficial effects and an eventual increase in morbidity and mortality. Conversely, whereas β-blocking drugs have a deleterious effect on cardiac contraction in acute heart failure, they have been shown to bring dramatic improvement in chronic heart failure, where it is the harmful adrenergic responses that predominate.

Activation of the Renin–Angiotensin–Aldosterone System

Activation of the renin–angiotensin–aldosterone system (RAAS), as outlined in Fig. 18.6, is a key feature of the systemic response to heart failure. The initial effects of RAAS activation help maintain systemic blood pressure (through peripheral vasoconstriction) and cardiac output (through salt and water retention and maintained ventricular filling pressures). Unfortunately efforts to maintain ventricular filling pressure will eventually become more and more ineffective at supporting cardiac output (classical Starling's law of the heart). Angiotensin II, in addition to being a potent vasoconstrictor and activator of the SNS, has many other direct effects on both the heart and vasculature [33]. It is known to contribute directly to cardiac chamber remodeling through inducing defective collagen deposition, myocyte hypertrophy, and apoptosis. It also acts as the primary stimulus for aldosterone release from the adrenal cortex, a potent mineralocorticoid hormone that induces sodium retention within the renal distal tubule at the expense of potassium and hydrogen ions. It has been observed, however, that the beneficial effects of aldosterone blockade in heart failure are much greater than could be explained by inhibition of this effect alone; recent work has revealed aldosterone to be an important mediator of numerous harmful responses in heart failure. Aldosterone is a potent inducer of both vascular and myocardial inflammation and is known to promote the recruitment of inflammatory mediator cells from the circulation to vascular and myocardial tissue [34]. Cyclooxygenase

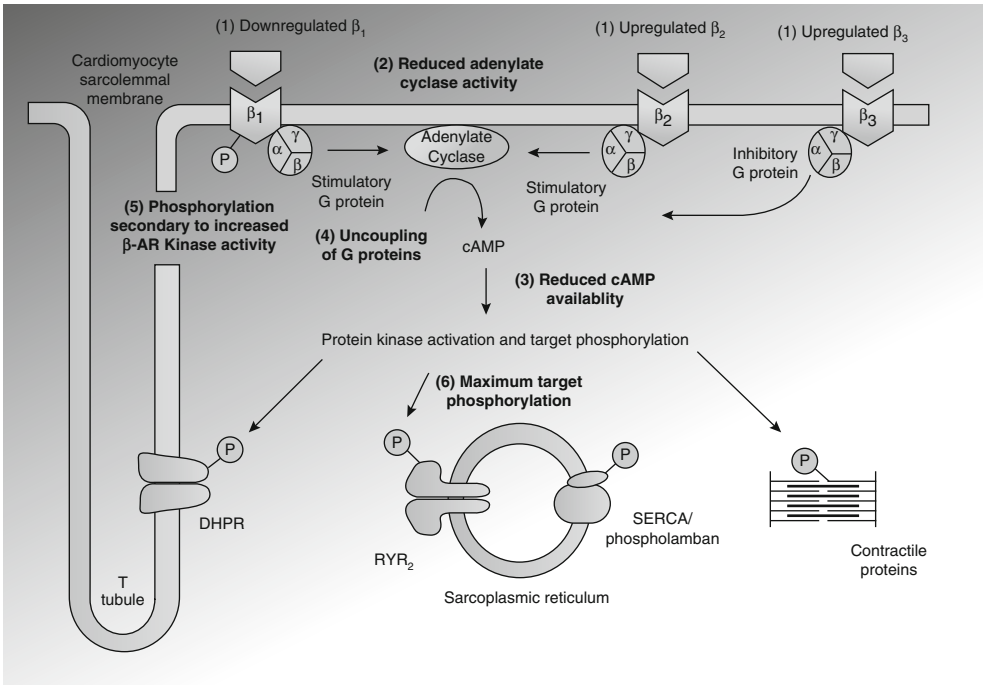

Fig. 18.5 β-Adrenergic receptor activation in heart failure. Normal β-adrenergic receptor signal transduction pathways activate protein kinase A and cause target protein phosphorylation, which enhances contractile function. Alterations in heart failure (*1–6*) are shown in bold (for abbreviations *see* main text): (*1*) Reduction in β1 receptor expression leading to a relative increase in β2 and the inhibitory β3 receptor as a proportion of total β-adrenergic receptor numbers. (*2*) Reduced adenylate cyclase activity. (*3*) Reduced cAMP availability. (*4*) Uncoupling of stimulatory G proteins. (*5*) Increased phosphorylation of β-adrenergic receptors uncouples receptor from signal transduction pathway. (*6*) Target molecules are phosphorylated to full stoichiometry with no further augmentation of function possible

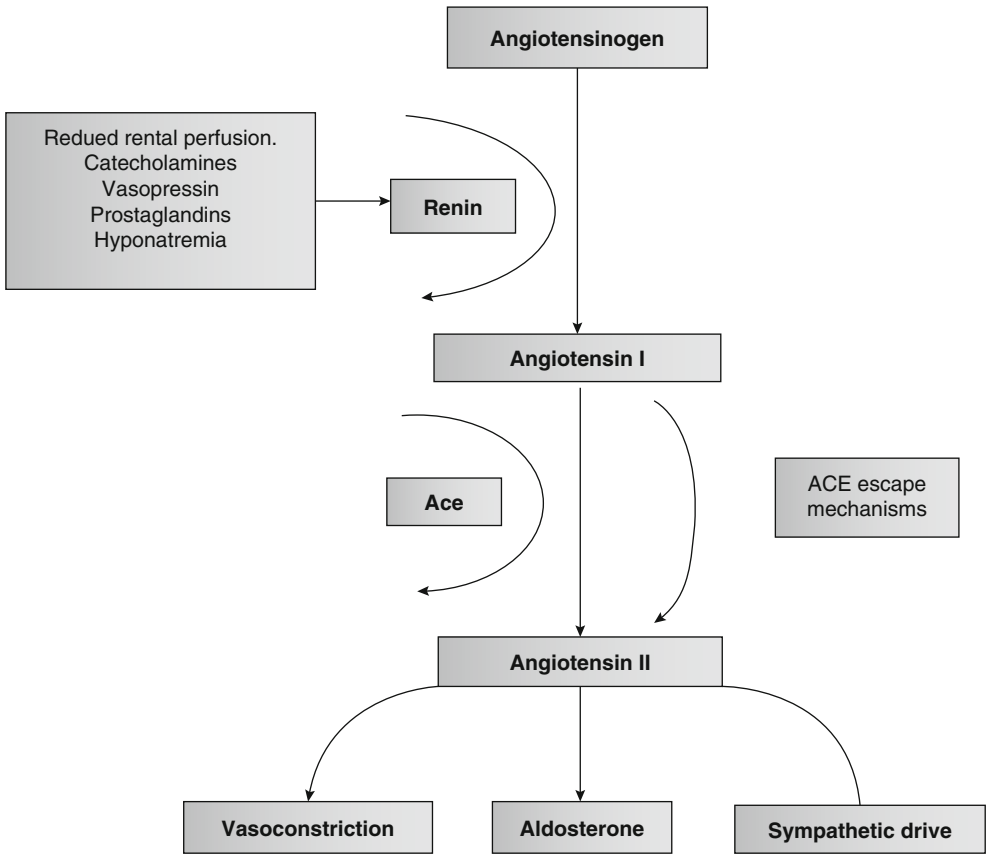

Fig. 18.6 The renin–angiotensin–aldosterone system. In heart failure the kidneys release renin in response to various stimuli. Circulating angiotensinogen (produced in the liver, vasculature, and CNS) is converted into angiotensin I by renin and subsequently into angiotensin II via angiotensin-converting enzyme in the lungs and vasculature. Angiotensin II has diverse actions throughout the body (*see* text). Note the presence of angiotensin-converting enzyme escape mechanisms, alternative pathways for the production of angiotensin II that become significant in the presence of ACE inhibitor treatment

Table 18.11 The actions and consequences of aldosterone

Distal tubule sodium and water retention in exchange for potassium and hydrogen ions
Increased ventricular filling pressures and peripheral edema
Hypokalemia, hypomagnesemia, alkalosis, and arrhythmias
Deranged collagen and extracellular matrix turnover in vasculature and heart
Reduced ventricular and vascular compliance
Chamber remodeling and dilation secondary to fibrosis
Blunted baroreceptor responses and reduced vagal tone
Loss of normal heart rate variability
Reactive oxygen-derived free-radical generation
Necrosis, inflammation, and eventual fibrosis
Recruitment of inflammatory mediator cells
Release of various proinflammatory mediator and cytokines, eventual fibrosis
Proatherosclerotic effect in vasculature
Endothelial vasomotor dysfunction
Reduced nitric oxide availability
Impaired vessel relaxation

2 and osteopontin are two of the main cited proinflammatory mediators released in response to aldosterone [35]; it also directly induces NADPH oxidase within the vasculature, which in turn is a major source of superoxide anions and a cause of oxidative stress-induced inflammation [36]. Animal model experiments designed to look at the specific actions of aldosterone show inflammatory cell infiltrates, ischemia, and patchy necrosis throughout the heart and vasculature, effects that are removed by the addition of specific aldosterone-antagonist agents. In addition aldosterone has a direct effect on the turnover and composition of extracellular matrix proteins such as collagen [37]; this effect, in conjunction with its proinflammatory action, makes aldosterone a potent cause of fibrosis in the vasculature and heart of individuals with chronic heart failure [38]. The actions of aldosterone and their sequelae are outlined in Table 18.11.

Peripheral Vascular Responses to Heart Failure

The vasculature is an important organ for modifying the response to worsening cardiac function; indeed, increased systemic vascular resistance is a cardinal feature of heart failure. This is an initial beneficial response maintaining left ventricular afterload, peripheral blood pressure, and vital organ perfusion. Persistent systemic vascular resistance eventually becomes a maladaptive response and contributes to a decrease in cardiac performance. SNS activation on vascular α_1-adrenoceptors and the direct actions of angiotensin II are one component of vasoconstriction. The vasculature also exerts local control over smooth muscle tone through the relative production of endothelin (a potent vasoconstrictor peptide) and nitric oxide (a potent vasodilator). In heart failure the balance is tipped firmly in the direction of endothelin and subsequent vasoconstriction. Indeed, plasma endothelin levels are elevated in heart failure and correlate closely to prognosis and reduced cardiac performance [30]. This mismatch is caused partly by increased production of vascular endothelin but also by a reduced bioavailability of nitric oxide, which is rapidly scavenged by reactive oxygen anions produced under mechanisms of oxidative stress. Endothelin has also been shown to promote fibrosis and collagen accumulation in the heart [39] and promotes the retention of sodium within the kidney. Vascular remodeling, such as smooth muscle hypertrophy and hyperplasia, secondary to the effects of various mediators also adversely affects vascular function by reducing vessel wall compliance.

Cytokine Activation in Heart Failure

Cytokines are a diverse group of proinflammatory peptides secreted by various tissues and cell types. Cytokine activation is a well-recognized feature of chronic heart failure, and increased levels of inflammatory markers, such as C-reactive protein, are correlated closely to severity of heart failure and prognosis [40]. Indeed, activation of cytokine responses is detectable prior to the onset of symptomatic heart failure and predicts subsequent development of clinical heart failure [41]. A diverse range of cytokines are activated in heart failure, including TNF-α, interleukin-1, and interleukin-6 [42]. Peripheral blood leukocytes are known to migrate into the myocardium during heart failure, where they take on an enhanced cytokine production capacity. Furthermore, cardiomyocytes and myocardial fibroblasts are themselves induced to synthesize specific cytokines in heart failure through altered gene expression [43]. Cytokines are released locally within the heart in response to ventricular wall stress and from various other tissues in response to hypoperfusion, hypoxia, congestion, and oxidative stress [44]. They have various local effects on the heart as outlined in Table 18.12. In addition they have a range of systemic metabolic and immunological actions, particularly on skeletal muscle, where they induce wasting and impaired contraction. The systemic action of cytokines may underlie the cardiac cachexia syndrome in severe chronic heart failure, similar to their causative role in cancer cachexia syndrome [45].

Natriuretic Peptide Response in Heart Failure

The natriuretic peptides are a group of small peptides released by the heart in response to wall stretch when there is circulatory volume expansion in heart failure. Atrial natriuretic peptide (ANP) is secreted from both the atria and ventricles. It is secreted at low levels in normal hearts but levels rise dramatically in heart failure. Even more sensitive as a marker

Table 18.12 Cytokines in heart failure

Inflammatory mediators known to be elevated in heart failure
Interleukin-1, 6, 8, 10
Interferon-γ
Tumor necrosis factor α
Soluble CD14 receptor
Soluble tumor necrosis factor receptors 1 and 2
Intracellular adhesion molecule 1
Leukocyte adhesion molecule 1
Effects of cytokine activation
Reactive oxygen-derived free-radical generation
Induction of fetal gene expression pattern
Hypertrophy and contractile protein synthesis
Chamber remodeling and dilation
Left ventricular dysfunction
Pulmonary edema
Anorexia and cachexia
Reduced skeletal muscle blood flow
Endothelial dysfunction
Cardiomyocyte apoptosis

of myocardial dysfunction is its counterpart, B-type natriuretic peptide (BNP). Natriuretic peptides act on the kidney tubule, where they promote a natriuresis, and also on the peripheral vasculature, where they produce vasodilation. In this way they are seen as direct antagonists of the actions of angiotensin II, aldosterone, and catecholamines. Natriuretic peptides also inhibit endothelin secretion and may also protect against collagen accumulation, fibrosis, and ventricular remodeling [46]. Unfortunately the characteristic progressive decline in heart failure suggests that their beneficial actions fail to compensate for RAAS activation. Indeed it has been suggested that this failure of natriuretic activity is itself a manifestation of heart failure in that poorly functioning myocytes are unable to release biologically active peptides due to a failure of intracellular enzymatic cleavage of the expressed propeptide [47]. Increasing attention in clinical practice is being given to the role of natriuretic peptides as diagnostic and prognostic tools in heart failure [2, 48], as BNP and its precursors (pro-BNP/N-pro-BNP) have good diagnostic utility for heart failure, and high plasma concentrations have consistently been shown to be strongly associated with a poor prognosis [49]. Furthermore, in view of the above beneficial effects, research is also focusing on their role as a therapeutic target, either by enzymatic inhibition to prevent their breakdown or via the administration of synthetic natriuretic peptides.

Skeletal Muscle Dysfunction in Heart Failure

A consistent finding of established heart failure is fatigue and reduced exercise tolerance in excess of that expected from cardiac pump dysfunction alone. It is known that exercise capacity correlates poorly with left ventricular function in chronic heart failure. Furthermore, skeletal muscle wasting is a key feature of cardiac cachexia syndrome in heart failure, of which the above symptoms are a key component. Attention has recently been given to identifying specific aspects of skeletal muscle dysfunction in heart failure. Activation of immunological cells and the increased levels of circulating cytokines are believed to play an important role in much the same way as they are implicated in cancer cachexia [45]. The improvements in skeletal muscle performance seen from exercise training schemes in heart failure patients are associated with a reduction in skeletal muscle cytokine content and attenuation of reactive oxygen species generation, both of which appear to contribute to a skeletal muscle chronic inflammatory process in heart failure [50]. More recently defects in the skeletal muscle ryanodine receptor (RyR1) have also been identified in heart failure, similar to those present in the cardiac ryanodine receptor (RyR2) [51]. Hyperphosphorylation of RyR1 in heart failure impairs contraction as it reduces the overall efficiency of EC coupling, suggesting that heart failure induces a generalized EC coupling myopathy that impairs both cardiac and skeletal muscle function.

Anemia in Heart Failure

Anemia is a common comorbidity in patients with heart failure. It affects more than a third of patients. Anemia is associated with a worse prognosis – with even small reductions in hemoglobin concentrations associated with worse outcomes [52]. The cause of anemia is multifactorial: often renal dysfunction and neurohormonal and proinflammatory cytokine activation contribute to an "anemia of chronic disease," with erythropoietin resistance and defective iron utilization [53]. Under normal conditions, reduced tissue oxygenation due to chronic anemia would lead to a compensatory erythropoieses, but this is defective in heart failure. Hemodynamic responses to reduced tissue oxygenation are complex but include vasodilatation and an increased cardiac output. This may have deleterious long-term consequences. Increasingly, iron deficiency per se, in the absence of frank anemia, is recognized as having a metabolic impact [54]. The treatment of iron deficiency and anemia in heart failure is currently being examined in a number of randomized clinical trials of both intravenous iron and erythropoietin [55].

Sleep-Disordered Breathing in Heart Failure

Many patients with heart failure have sleep-disordered breathing, with frequent apneas, either obstructive (with occlusion of the upper airway) or central (loss of respiratory

drive). Recent estimates suggest that at least 50 % of patients will have abnormal breathing during sleep, with an increasing proportion of respiratory events being central as the severity of the syndrome increases [56]. Interestingly, heart failure patients with such sleep-disordered breathing are less likely to report daytime somnolence than those without heart failure, perhaps due to the alerting influence of increased sympathetic drive found in heart failure.

Sleep-disordered breathing is associated with recurrent hypoxemia and reoxygenation stress, hypercapnia, intrathoracic pressure changes, frequent arousals from sleep, endothelial dysfunction, inflammation, a hypercoagulable state, metabolic dysregulation, and increased sympathetic nervous system activity [56]. During apneas, patients with heart failure show a large reduction in cardiac output and stroke volume, due to a combination of increased left ventricular afterload and decreased preload [57]. Central sleep apnea and hypopnea is associated with less hemodynamic consequences but still result in recurrent hypoxemia, intrathoracic pressure changes, and frequent arousals. It is unclear whether the presence of central sleep apnea and its severity merely reflects the severity of the heart failure syndrome, or whether it is important in accelerating further decline in cardiac function. Those with sleep-disordered breathing (whether obstructive or central) appear to have a worse prognosis than those with a similar severity of heart failure but with no sleep-disordered breathing [58, 59]. There is evidence that positive airway pressure support by mask for obstructive sleep apnea in heart failure can improve daytime somnolence, improve quality of life, and improve left ventricular function [56]. Although there is some evidence that such therapy can also improve left ventricular function and reduce circulating noradrenaline concentrations in central sleep apnea, the only large randomized trial to date reported no reduction in mortality or heart failure hospitalization risk [60]. Further larger randomized studies are ongoing and will help to determine whether central sleep apnea is a reversible risk factor or merely a marker of the severity of the heart failure syndrome.

Pathological and Clinical Decline in Heart Failure: A Final Integrated Viewpoint

The pathophysiological changes outlined in this chapter reflect our current understanding of the syndrome of heart failure and the rationale behind many of the currently available therapeutic strategies. It is always important to remember, however, that every case of heart failure, regardless of the specific cause, represents an individual patient whose functional capacity and quality of life are impaired. It is usual to think of the clinical manifestations of heart failure, outlined in Table 18.13, as simply reflective of an impaired ventricular ejection fraction. Objective cardiac measurements, however, often correlate poorly with the clinical manifestations of the heart failure syndrome and often fail to take into account the impact of secondary consequences and complications such as increased infection risk, anemia, hypoalbuminemia, atrial fibrillation, thromboembolism, and depression. Furthermore, clinical features of heart failure may only indirectly reflect contractile dysfunction. For example, dyspnea may be secondary to both diaphragmatic weakness (skeletal muscle myopathy) and reduced lung compliance (lymphatic distension). In general, the syndrome of heart failure comprises a gradual decline in cardiac function, which may be asymptomatic for a considerable period until a critical threshold is passed at which clinical manifestations occur. This may be relatively late in the overall decline of cardiac function and usually represents the beginning of a more rapid decline manifested by worsening symptoms and eventually resulting in death. Depending on etiology this decline may be stepwise, as in myocardial infarction, or progressive, as in hypertensive heart disease. Furthermore, at any stage sudden cardiac death may occur secondary to arrhythmia.

Table 18.13 Clinical manifestations of heart failure

Symptoms
Fatigue
Dyspnea (exertional, orthopnea, paroxysmal nocturnal)
Swelling (limbs, abdomen)
Signs
Tachycardia
Hypotension
Jugular venous elevation
Abnormal hepatojugular reflex
Abnormal apex beat (displaced, sustained, dyskinetic)
Third heart sound
Inspiratory crepitations on lung auscultation
Edema (peripheral and peritoneal)
Cold peripheries and poor pulses

Heart failure remains one of the most pressing medical problems and is a significant health care burden in developed countries. The initial adaptive physiological responses provide short-term improvements in cardiac performance and were ideally suited to our previous hunter-gatherer lifestyles, where the fight-or-flight response either would result in swift evasion of a life-threatening situation or would be insufficient, resulting in death. The fact that they would result in maladaptive responses if made to continue for any length of time was largely irrelevant in evolutionary terms. There has been little time for physiological mechanisms to develop that can offer a more sustained and long-term compensation for impaired cardiac performance, yet this is what our extended life spans and successes in therapeutics are now demanding. Our increasing understanding of heart

failure pathophysiology and recent therapeutic advances have allowed us to address this imbalance to a certain extent and partially overcome the maladaptive consequences of our responses to heart failure. Despite this, further improvements are still needed if we are to adequately tackle the increasing burden of heart failure in society and reduce mortality rates, which are still worse than those of many common cancers. Whatever the next major advance in heart failure therapeutics is, there is no doubt that its development will stem from our increasing understanding of the complex heart failure syndrome and its underlying pathophysiology.

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Treatment of Congestive Heart Failure

19

Stephen S. Gottlieb

The goals of heart failure treatment include both symptomatic improvement and prolongation of life. These goals are not necessarily concordant. Related to this problem is the observation that the acute actions of an intervention may be very different than the chronic effects. When treating heart failure, therefore, one must understand the immediate and long-term desires of a particular patient and the immediate and long-term consequences of one's therapy. The result is an uncomfortable use of acute treatments known to have adverse consequences when given for a prolonged period and chronic treatments which are counterintuitive. Fortunately, however, congestive heart failure has been well investigated with multiple large studies demonstrating the multiple consequences of many of our standard interventions.

Initial Work-Up

The terms systolic dysfunction and congestive heart failure are often inappropriately used interchangeably; half of the patients with heart failure do not have systolic dysfunction. Since treatment of systolic dysfunction is different than treatment of other causes of heart failure, an assessment of left ventricular function is essential when a patient presents with heart failure. If systolic dysfunction is the cause of the heart failure, proper treatment can be tailored based upon the results of well-controlled studies (most studies of heart failure limit themselves to this defined group of patients). For patients with heart failure without systolic dysfunction, however, few studies provide guidance. The rest of this chapter refers to patients with systolic dysfunction unless stated otherwise.

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Determining Whether Dyspnea Is CHF

The initial diagnostic dilemma in many patients with dyspnea is whether the symptoms are of cardiac or pulmonary causes. If pulmonary function tests are abnormal and there is left ventricular dysfunction, it may be difficult to determine the etiology of the symptoms. Physical findings, such as wheezing, may be nonspecific. Certainly, rales, orthopnea, and paroxysmal nocturnal dyspnea suggest a cardiac origin and chronic hypoxia suggests a pulmonary cause, but fluid overload could be secondary to either right- or left-sided failure. Even experienced clinicians are often fooled.

Measurement of brain natriuretic peptide may be helpful in determining whether dyspnea is from heart failure. Indeed, in a large study, it was better than emergency room physicians [1]. A level below 100 is good negative predictor. However, BNP concentrations may be elevated in right-sided failure from pulmonary emboli or other sources of hypertension and should never be relied upon alone to make the diagnosis. A right heart catheterization may be needed in patients in whom questions remain.

Similarly, it may be difficult to determine if dyspnea in a patient with heart failure is secondary to deconditioning or continued volume overload and poor cardiac function. The role of BNP in these patients is not well defined. Proper treatment may depend on the results of a right heart catheterization. Often, it is felt that such intervention is only needed for patients with severe symptoms. However, it is more likely to affect treatment when there is a question as to the cause of the patient's symptoms.

Reversible Causes of Systolic Dysfunction

In addition to assessing cardiac function, initial evaluation often includes eliminating the possibility of reversible causes of systolic dysfunction. Ischemic heart disease is always a possibility to be considered, and the perceived risk of atherosclerosis should determine which tests, if any, are needed to

C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_19, © Springer Science+Business Media New York 2013

rule out coronary artery disease. Although many cardiologists perform a cardiac catheterization on every patient with heart failure, a young patient without risk factors or clinical suggestion of ischemia can probably be assessed by an exercise tolerance test. This is especially true if another cause, such as ethanol abuse, can be identified. Similarly, a patient without ischemic symptoms who is not a surgical candidate need not undergo a catheterization. It is not clear when revascularization is necessary, however; a recent study showed no improvement in total mortality with revascularization in patients with stable coronary artery disease (mild or no symptoms) and an ejection fraction less than 35 % [2]. This decision must be made taking into account multiple clinical factors.

An echocardiogram should be helpful for ascertaining some causes of heart failure, such as valvular disease. The importance of mitral regurgitation, however, may be difficult to evaluate. Mitral regurgitation is common in patients with dilated ventricles, and it may be impossible to determine if the valvular disease is primary or secondary. In the setting of poor contractility, however, surgical correction of either primary or secondary mitral regurgitation is accompanied by high risk. While there are increasing numbers of surgeons willing to undertake mitral valve repair or replacement, the proper role of mitral valve surgery in patients with poor systolic function remains uncertain.

The possibility that nonischemic cardiomyopathy is caused by thyroid abnormalities, hemochromatosis, or complications of HIV infection can usually be eliminated simply by blood tests. Treatment of these disorders is straightforward, but resultant cardiomyopathies may persist despite treatment of the underlying problem. Nutritional abnormalities and ethanol abuse should also be considered as potential causes of a reversible cardiomyopathy.

There are increasing data that sleep apnea can lead to cardiac dysfunction and worsening heart failure. Conversely, heart failure can cause disturbances in sleep patterns. While the interaction is complicated and incompletely understood, physicians should consider sleep apnea as a possible cause of chronic dyspnea in patients with heart failure.

Myocardial Biopsies

The detection of myocarditis rarely affects treatment. Since there is no randomized support for the use of immunosuppressive therapy and this treatment entails considerable risk, immunosuppressive therapy is controversial and not prescribed by most clinicians. Thus, a diagnosis of myocarditis usually does not affect treatment. However, a diagnosis of myocarditis might have prognostic implications by suggesting potential rapid changes (either positive or negative) in condition. If a patient's expected prognosis will impact the clinical management, a myocardial biopsy might be indicated.

When a clinical suspicion exists for a reversible disease which can be diagnosed by a myocardial biopsy (such as sarcoidosis, hemochromatosis, or amyloidosis) and treatment would be affected, a biopsy is indicated. A biopsy may also diagnose giant cell myocarditis, a rare entity which is generally felt to have a poor prognosis. Since immunosuppression may be considered for these patients, a biopsy could be appropriate in a patient with recent onset of symptoms, a rapid downhill course, and no obvious cause of heart failure. Many of these diagnoses can also be suggested by cardiovascular magnetic resonance imaging with gadolinium enhancement.

Follow-Up Assessments of Cardiac Function

Once the etiology of the heart failure is determined, further assessments are only needed when there are questions as to the patient's status. Thus, repeat echocardiograms or gated blood pool scans are rarely needed if a patient has known systolic dysfunction and continued symptoms. A slight increase or decrease in ejection fraction will add little to a physician's clinical judgment and should not be the basis of a change in therapy. Occasionally, a repeat assessment is needed to rule out the possibility of normalization of cardiac function (at which point treatment might be cautiously withdrawn) or a marked deterioration in function.

Diuretics (Table 19.1)

Diuretic medications remain the primary treatment for the acute symptomatic relief of patients with congestive heart failure. They lead to rapid and dramatic improvements in patients with exacerbations or newly diagnosed disease. In addition, they are needed for relief of chronic symptoms. However, potential long-term adverse consequences mandate that they not be the only treatment for patients with systolic dysfunction.

Fluid Restriction

The best means of keeping patients euvolemic would be the avoidance of the causes of fluid and sodium retention. Reducing sodium intake can decrease the need for high doses of diuretics and should be encouraged in all patients, but fluid restriction is rarely beneficial. While the hyponatremia and fluid overload associated with congestive heart failure makes fluid restriction appealing, such an approach is rarely successful. First, the drive to drink water is strong, and it is virtually impossible to successfully fluid restrict a patient. Second, diuresis can be successful without fluid restriction.

Table 19.1 Comparison of diuretic medications, listed according to site of action

Diuretic	$FENa^+$ (Max) (%)	Dosage (mg/day)	Onset of action		Action duration		Peak oral	Comments
			Oral (h)	IV (min)	Oral (h)	IV (h)	Effect (h)	
Ascending loop of Henle								
Furosemide	20–25	40–400	1	5	6	2–3	1–3	
Bumetanide	20–25	1–5	0.5	5	6	2–3	1–3	
Torsemide	20–25	10–200	1	10	6–8	6–8	1–3	
Ethacrynic acid	20–25	50–100	0.5	5	6–8	3	2	High ototoxicity risk, but (unlike other loop diuretics) can use in sulfa allergic pts
Early distal tubule								
Metolazone	5–8	2.5–20	1	–	12–24	–	2–4	Greatest potential for potassium loss; also slight actions in proximal tubule
Chlorthalidone	5–10	25–200	2	–	24–48	–	6	Ineffective when GFR < 30
Hydrochlorothiazide	5–8	25–100	2	–	12	–	4	Ineffective when GFR < 30
Chlorothiazide	5–8	500–1,000	1	15–30	8	–	4	Ineffective when GFR < 30
Late distal tubule								
Spironolactone	2	50–400	48–72	–	48–72	–	1–2 days	Efficacy dependent upon aldosterone presence
Triamterene	2	75–300	2	–	12–16	–	6–8	
Amiloride	2	5–10	2	–	24	–	6–16	
Proximal tubule								
Acetazolamide	4	250–375	1	30–60	8	3–4	2–4	Efficacy limited by metabolic acidosis it causes

Adapted from Gottlieb [3]. With permission from Lippincott Williams & Wilkins
$FENa^+$ (Max, %) maximal natriuretic effect (maximum fractional excretion of filtered sodium)

Third, chronic hyponatremia rarely causes problems, and excessive hyponatremia can be successfully treated by modifying the diuretic regimen. In patients with congestive heart failure, only the combination of diuresis and ACE inhibition has been demonstrated to reverse hyponatremia. It is therefore not surprising that the overwhelming majority of patients with heart failure need diuretic medications. When medication is needed for diuresis, loop diuretics are generally used. When blood pressure control is the goal and renal function is adequate, thiazides might be preferred.

Extent of Diuresis

The most common clinical problem related to diuretics is underutilization of the drugs. Hospitalized patients who are treated for pulmonary edema are often discharged with marked fluid overload and prescribed doses of diuretics inadequate to continue diuresis. Such patients frequently return to the hospital because of repeat exacerbations. The absence of rales should therefore not be taken as evidence of adequate diuresis. Rather, assessment of total body fluid (using peripheral edema, ascites, and sacral edema as guides) is easy and can indicate the need for more diuresis. While right heart catheterization is not routinely necessary [4], it is clear that adequate diuresis is essential and should be guided by clinical endpoints. A recent study demonstrated that the means of giving diuretics is less important than how much is given. In an acute setting, intravenous infusions or bolus administration led to similar outcomes [5].

A common problem preventing the proper utilization of diuretic medications is fear of using elevated doses. Patients with severe heart failure and evidence of renal dysfunction often need doses perceived as extremely high; daily dosing with 200 mg of furosemide is not uncommon. Despite the frequent need for high concentrations of diuretics, intravenous administration of furosemide is not necessarily needed in order to achieve a clinically important diuresis. Oral regimens may be successful even in markedly fluid overloaded individuals. This is important, as successful outpatient diuresis can save money, prevent iatrogenic complications, and improve a patient's quality of life. However, outpatient diuresis mandates close follow-up to ensure success and prevent deadly electrolyte abnormalities. Although the data suggest that a trial of oral diuretics should be given in most edematous patients, there are patients in whom intravenous

administration will be necessary. When immediate diuresis is necessary because of severe decompensation and pulmonary edema, the more rapid onset of intravenous diuretics may be essential.

Diuretic Combinations

It is often difficult to get effective diuresis in patients with severe heart failure. The physiologic stimulus to retain fluid may be strong enough to overwhelm the diuretic actions of any single agent. Thus, potent diuretics (such as the loop diuretics) may be rendered ineffective by distal reabsorption. In contrast, the agents which act distally, such as the potassium sparing agents, may not be potent enough to yield the desired results. In such patients, the synergistic effects of combining diuretics can have many beneficial consequences.

The combination of loop diuretics and metolazone has proven to be particularly potent [6]. With the combined use of these agents, effective diuresis may be produced in patients who have been resistant to other interventions. However, it may take days to see the results of the addition of metolazone because of the pharmacokinetics of the drug. It is also important to realize that the hypokalemia which results from the combined use of loop diuretics and metolazone may be severe; serum potassium concentrations need to be watched especially carefully in these patients. The other useful method of combining diuretics is to add a potassium sparing agent to the diuretic regimen. Not only does this potentiate the diuretic actions of the original regimen, but it also prevents extreme potassium loss and simplifies electrolyte management.

Spironolactone is not a potent diuretic, but the Randomized Aldactone Evaluation Study (RALES) showed improvement in survival in patients with severe heart failure who received relatively small doses of spironolactone [7] and the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial showed improvement in people with mild heart failure who received eplerenone [8]. The mechanism by which aldosterone antagonists work is uncertain. Spironolactone conserves potassium and magnesium and can be synergistic when combined with other diuretic medications. However, other effects of spironolactone may be even more important and need further investigation. For example, spironolactone may affect fibrosis formation in hearts of patients with cardiomyopathy and may exert direct effects on the sodium-potassium pump. Eplerenone, a more selective aldosterone antagonist without the side effect of gynecomastia, has been shown to be effective in patients with heart failure and an acute myocardial infarction and can be used when spironolactone has been found to cause gynecomastia.

Refractory Patients

In some patients, inotropic therapy may be required to produce acute diuresis. Agents such as dobutamine and milrinone often lead to diuresis in patients with worsening renal function secondary to cardiac dysfunction. Routine use of inotropic therapy in hospitalized patients, however, was not shown to be beneficial, and inotropes should be reserved for patients who are refractory to treatment [9].

Nesiritide is a vasodilator which is approved for the acute treatment of congestive heart failure [10]. It is a vasodilator which lowers cardiac filling pressures. However, the definitive Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial showed no changes in outcome (particularly mortality or renal function) with the use of the drug in any patient subgroup [11]. Therefore, there are few circumstances in which its use appears worthwhile.

Vasopressin antagonists can theoretically lead to free water removal. While its effect on reversing hyponatremia is proven, the clinical utility in patients with heart failure is still uncertain. Routine use, however, has been shown to be ineffective.

When all else fails, ultrafiltration may improve the fluid status of a patient. It reliably leads to fluid removal, but there is no evidence that its renal effects are any different than diuresis. A controlled trial demonstrated long-term benefit, but this may be secondary to more fluid removal in the ultrafiltration group rather than any other effect [12].

Since improving the volume status is so important for treating the symptoms of congestive heart failure, chronic dialysis can be considered for volume control, not just renal failure. Some patients will develop renal failure when euvolemic, with renal function maintained only with fluid overload. Since dialysis can lead to marked improvements in quality of life in such patients, its use is appropriate if agreed to by the patient.

Adverse Effects

There is no doubt that diuretics, though essential for symptomatic relief and decreasing cardiac distension, exert adverse consequences; electrolyte depletion, neurohormonal activation, and renal failure can ensue. While potentially harmful, these side effects can be overcome with other interventions. For example, the use of ACE inhibitors and spironolactone can prevent potassium and magnesium depletion. In the rare instances when it is necessary, potassium replacements can also be given.

Diuretics lead to activation of the renin-angiotensin, sympathetic, and other neurohormonal systems, with potential immediate and long-term repercussions which are discussed

below. However, these problems should not prevent adequate use of diuretic medications; these actions can generally be blocked with ACE inhibitors, beta-blockers, and aldosterone antagonists.

The physician must always be alert when combining agents with opposing actions. Treatment of congestive heart failure usually includes both potassium wasting and potassium sparing agents. The results may be unpredictable, and patients need to be followed carefully to ensure neither hypokalemia nor hyperkalemia.

A slight increase in serum creatinine and BUN concentrations should be expected (and tolerated) in order to achieve adequate diuresis. Diuretic-induced increases in serum creatinine concentrations can be worrisome but can usually be resolved by a slower rate of diuresis. It may also be advisable to limit the use of angiotensin-converting enzyme inhibitors while aggressively diuresing a patient. The patients who develop renal failure with ACE inhibition are usually sodium and volume intravascularly deplete [13]. Initiation of ACE inhibitors after the patient is euvolemic may prevent the renal failure which occasionally occurs when ACE inhibitors are prescribed while the patient is being actively diuresed.

ACE Inhibitors and Other Vasodilators

The long-term effects of angiotensin-converting enzyme (ACE) inhibitors on both symptoms and mortality are clear (Table 19.2). Not only has their survival benefit been consistently demonstrated in patients with systolic dysfunction [14, 15], but the use of ACE inhibitors results in increased exercise tolerance, decreased hospitalization rates, and improvements in other indices reflective of symptoms. This information has been well disseminated and the utilization of ACE inhibition is now appropriately widespread. However, concerns remain as to whether these agents are being used in a manner which provides the most benefit.

Dosing

The commonly used dosages of ACE inhibitors are lower than those studied and which demonstrated benefit. Patients in SOLVD reached mean daily enalapril doses of 16.6 mg, and the severely ill CONSENSUS patients received a mean dose of 18.4 mg of this drug. Nevertheless, enalapril and lisinopril (both have equivalent daily dosing) are frequently prescribed as 2.5 or 5 mg daily.

The doses with demonstrated efficacy are also doses which were tolerated in multiple studies of patients who ranged from being severely ill to relatively asymptomatic. It is therefore important to explore the reasons physicians frequently are reluctant to prescribe these doses. Understanding the effects of ACE inhibition and the ways to prevent adverse consequences should lead to more effective use of these agents.

Table 19.2 Therapeutic doses of ACE inhibitors

Captopril	25–50 mg tid
Enalapril	10–20 mg bid
Lisinopril	20–40 mg qd
Monopril	20–40 mg qd
Ramipril	5–10 mg bid
Quinapril	20 mg bid

These are recommendations for final doses, based upon the doses used in heart failure studies

Adverse Effects

Patients with heart failure often have low blood pressures, but the evidence seems clear that asymptomatic hypotension should not limit the use of these agents. Indeed, ACE inhibitors will often not decrease (and may even increase) the blood pressure of patients with heart failure. It should be remembered, however, that blood pressure will decrease when ACE inhibition is combined with intravascular depletion. Thus, patients who do not tolerate these agents when they are being actively diuresed may tolerate them after they have stabilized. A slight liberalization of fluid status might also help patients with symptomatic hypotension when receiving ACE inhibitors.

The other factor which often limits dosing of ACE inhibition is renal dysfunction. Contrary to many physicians' assumptions, preexisting kidney disease does not increase the risk of renal deterioration [16] (Fig. 19.1). ACE inhibitors may cause renal dysfunction in a small percentage of people with any baseline kidney function (especially those

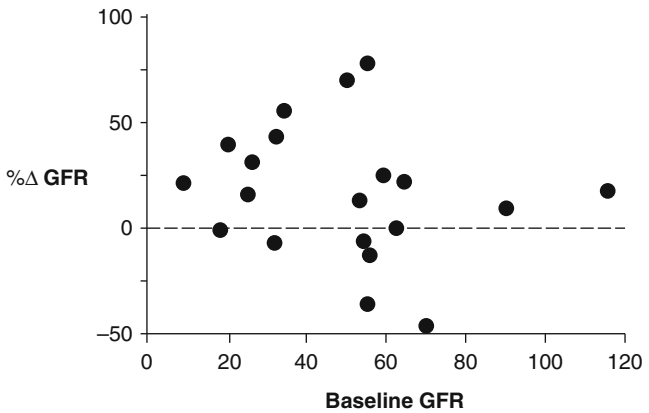

Fig. 19.1 The baseline glomerular filtration rate (*GFR*) as related to the percentage change in GFR after ACE inhibition. There was no relation between baseline renal function and the change in GFR (Reprinted from Gottlieb et al. [16]. With permission from Elsevier)

with renal artery stenosis), and this complication should be carefully looked for in any patient during initiation of ACE inhibition. However, a worsening serum creatinine is usually the result of intravascular depletion, and a change in fluid status will usually permit initiation and upward titration of these agents in patients who at first appear intolerant. Effective ACE inhibition can be achieved in the overwhelming majority of patients.

Hyperkalemia may occur with ACE inhibition. Often this is because of continued potassium supplementation, either by prescription or by ingestion of potassium through salt substitutes or foods rich in potassium. Before blaming and discontinuing the drug, therefore, a careful dietary history must be taken.

Angioedema, neutropenia, and other clear contraindications to ACE inhibitors are infrequent. Other side effects, such as cough and rash, are often ascribed to these agents, even though it may be difficult to differentiate a side effect from a concomitant condition. Furthermore, these conditions are often well tolerated and need not necessarily lead to discontinuation of medications known to be effective. Nevertheless, there are times when these side effects will be severe enough to warrant discontinuation of an ACE inhibitor. At that time other agents can be tried.

Angiotensin II Blockers

Angiotensin II receptor blockers (ARB) have been studied in heart failure and, while not better than ACE inhibitors, appear to be effective [17]. In contrast to ACE inhibitors, which lead to increased bradykinin concentrations in addition to preventing angiotensin II production, the angiotensin II receptor blockers only work on a single system. Bradykinin presumably causes some of the adverse side effects related to ACE inhibitors, such as cough, but may also provide some of the benefits. Thus, an ARB should be prescribed to patients intolerant to the cheaper ACE inhibitors.

The use of ARBs as additive therapy (in addition to ACE inhibitors) has also been evaluated. While one study showed a statistically significant, but modest, benefit [18], a study in patients with a myocardial infarction showed additional adverse effects with no added efficacy [19]. If used, it is important to carefully look for hyperkalemia or harmful renal effects.

Hydralazine and Nitrates

The other treatment choice for ACE intolerant patients is the combination of hydralazine and nitrates. This combination can also be given in addition to ACE inhibitors. It appeared to improve survival in the Vasodilator-Heart Failure Trial (V-HeFT) [20], but was less effective than ACE inhibitors [21]. When studied in African-Americans because of retrospective data suggesting a potential for a better response, it improved survival in patients receiving ACE inhibitors [22]. Because it needs to be given three times per day and can cause headaches, it has not been extensively used. However, it should be considered in patients with continued symptoms. The proven doses are 75 mg tid for hydralazine and 40 mg tid for isosorbide dinitrate.

Nitrates can also be effective for symptomatic relief of patients. The medication should always be prescribed with an appreciation of the tolerance which may develop with its use. Thus, patients should receive nitrates to prevent the most important symptoms. In some patients, a single dose of isosorbide dinitrate (10–40 mg) prior to sleep may prevent orthopnea and paroxysmal nocturnal dyspnea. Others will benefit from longer acting preparations for use prior to activities during the day. Sublingual nitroglycerin can also be helpful prior to unusual exertion. When tailored to the individual patient, nitrates can improve the quality of life.

Calcium Channel Blockers

Most calcium channel blockers have negative inotropic properties and have been shown to have adverse consequences when given to patients with congestive heart failure. The use of these drugs is appealing because of their benefit in treating anginal symptoms, a common condition in patients with heart failure. However, their use in studies following myocardial infarction consistently shows that patients with poor ventricular function have worse survival when given calcium channel blockers. Similarly, studies in patients with heart failure suggest that the older calcium channel blocking agents, such as nifedipine, diltiazem, and verapamil, produce a worse outcome. If needed for treatment of hypertension, amlodipine and felodipine do not have negative inotropic actions and appear safe when used in heart failure patients.

Beta-Blockers

Studies conclusively support the concept that chronic beta-blockade can improve cardiac function, decrease symptoms, and prolong survival [23–25] (Fig. 19.2). The large survival studies have included patients with a wide ranging severity of illness and have demonstrated very consistent improvements in survival of more than 30 %. They are very well tolerated, even in the sickest patients [27, 28]. However, there are still many misconceptions about their actions, and it is important to understand their proper use in patients with heart failure. If used incorrectly, there is no doubt that they

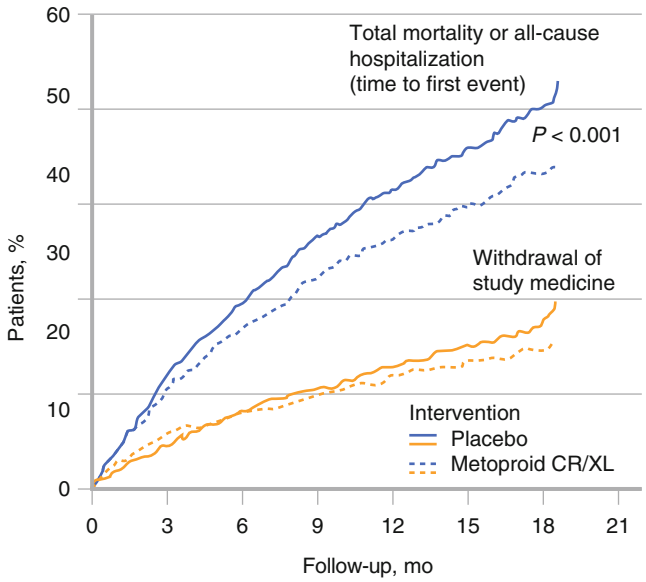

Fig. 19.2 Cumulative percentages for the combined end point of total mortality or heart failure hospitalization (time to first event) from MERIT-HF. Patients who received beta-blockade had a 31 % improvement in hospitalization and mortality rates and less withdrawal from study drug (Adapted from Hjalmarson et al. [26]. With permission from American Medical Association)

can lead to exacerbations of heart failure and death. If used properly, they can have long lasting benefit (Table 19.3).

Beta-blockers should only be given to patients who are euvolemic, optimally treated with other medications, and stable. These agents are properly initiated with slow titration. They are started at minuscule dose (hence the misconception that low-dose beta-blockade is given), but the evidence suggests that the final dose should be higher. Indeed, the MERIT trial gave a final daily dose of 200 mg of metoprolol XL to patients, while initiating treatment with either 12.5 or 25 mg and doubling the dose at weekly or biweekly intervals. Similarly, the carvedilol and bisoprolol studies started treatment with extremely low doses and slowly titrated to effective beta-blocking doses.

The titration of beta-blocking agents should be performed cautiously and carefully. With each increase in dose, patients must be evaluated to ensure safety. For approximately the first month, one is not looking for a positive effect. Rather, the physician is acting to prevent deterioration. Fluid retention may occur, and increased diuretic doses may be temporarily needed. If there is clinical deterioration and evidence of worsening cardiac function, the usual weekly or biweekly titration should be lengthened. Bradycardia or heart block may limit dosing in some patients, and pacemaker placement may be considered.

If the patient deteriorates with initiation of beta-blockade, the dose may have to be decreased. Slower titration can be considered for patients with an initial adverse effect. These caveats refer to all beta-blockers used in patients with heart failure, including carvedilol, metoprolol, and bisoprolol.

Table 19.3 Initiation of beta-blockade in CHF

Stabilize patient with:	
Diuretics	
Maximize ACE inhibition	
Digoxin	
Evaluate	
Euvolemic	
No bradycardia without pacemaker	
No heart block without pacemaker	
Step 1	
Carvedilol:	3.125 mg bid
Metoprolol XL:	12.5 mg qd (can start with step 2 in NYHA class II)
Metoprolol:	6.25 mg bid (can start with step 2 in NYHA class II)
Bisoprolol	1.25 mg qd
Step 2	
Carvedilol:	6.25 mg bid
Metoprolol XL:	25 mg qd
Metoprolol:	12.5 mg bid
Bisoprolol	2.5 mg qd
Step 3	
Carvedilol:	12.5 mg bid
Metoprolol XL:	50 mg qd
Metoprolol:	25 mg bid
Bisoprolol:	3.75 mg qd
Step 4	
Carvedilol:	25 mg bid
Metoprolol XL:	100 mg qd
Metoprolol:	50 mg bid
Bisoprolol:	5 mg qd
Step 5	
Carvedilol:	If weight > 85 kg: 50 mg bid
Metoprolol XL:	150 mg qd (can skip to step 6 if very stable)
Metoprolol:	75 mg bid
Bisoprolol:	7.5 mg qd
Step 6	
Metoprolol XL:	200 mg qd
Metoprolol:	100 mg bid
Bisoprolol:	10 mg qd
Cautions:	
Between each step (every 1–2 weeks):	
If no increased CHF symptoms and no increased weight, proceed to next step	
If no increased symptoms but increased fluid weight, increase diuretics and check patient in 1 week. When back to baseline, proceed to next step	
If increased symptoms and weight, increase diuretics and check patient in 1 week. When back to baseline, proceed to next step	
If slight increase in symptoms and no weight gain, make no change and check patient in 1 week. When back to baseline, proceed to next step	
If marked increase in symptoms, stop drug	
If symptomatic bradycardia, decrease dose of beta-blocker	
If heart block, decrease dose of beta-blocker	
Doses are based on clinical CHF experience with each drug	

Pulmonary disease is not a contraindication to beta-adrenergic blockers. If a patient does not have evidence of reactive airways, beta-blockers are generally well tolerated. Metoprolol succinate is beta-1 selective and might therefore cause less pulmonary constriction.

The consequences of the differences among beta-blockers are controversial. There have been theoretical concerns about beta selectivity, other vasodilatory properties, and even antioxidant effects. Carvedilol, in particular, has vasodilating properties which may be beneficial (for initiation) or harmful (if hypotension is a problem). One study reported improved survival with carvedilol 25 mg bid as compared to short acting metoprolol at 50 mg bid [29]. However, there are questions about using the unproven short acting metoprolol (at a relatively low dose). The only drugs which have been proven to be beneficial are bisoprolol, long-acting metoprolol succinate, and carvedilol. It seems reasonable to use these drugs when possible. While it may be possible that one drug has more of an effect than another, it is clearly far more important to make sure that patients receive beta-blockade at a proven dose than to worry about which drug to give.

Digoxin

The frequency of the use of digoxin varies from nation to nation because of conflicting data as to its efficacy. However, the consequences of using digoxin were clarified by the Digitalis Investigation Group (DIG) in a Veterans Administration study of 6,800 patients with an ejection fraction less than 45 % [30]. There was no effect on mortality in this study, with identical survival curves seen in patients receiving digoxin and those receiving placebo.

Despite the lack of an effect on mortality, the use of digoxin in DIG decreased hospitalization rate by 6 % and the rate of hospitalizations for heart failure by 28 %. This improvement is consistent with previous studies which showed that patients withdrawn from digoxin had more exacerbations of heart failure [31]. The use of digoxin to improve symptoms therefore appears appropriate.

Retrospective analyses of DIG suggest that low concentrations might be more beneficial than higher concentrations. Studies demonstrate that low digoxin concentrations exert beneficial neurohormonal actions. The chronic symptomatic benefit observed with digoxin might be secondary to these effects rather than the positive inotropic effects which occur at higher concentrations. For this reason, the usual dose for patients with heart failure, normal renal function, and without atrial fibrillation is 0.125 mg daily.

While elevated serum digoxin concentrations can support the diagnosis of digoxin toxicity, the routine monitoring of the concentration is expensive and not necessary. It appears wiser to treat patients with doses unlikely to cause toxicity and to only check concentrations when there is a clinical question.

Positive Inotropes

Chronic Use

There are no controlled studies supporting the use of positive inotropes for the chronic treatment of congestive heart failure. Although anecdotal uncontrolled studies suggest that intermittent use of dobutamine or milrinone may be beneficial, controlled studies are lacking or are negative. Furthermore, trials of oral inotropes, such a milrinone [32], have demonstrated increased mortality, especially in the sickest patients. While inotropic therapy is beneficial acutely for patients with decompensated heart failure, its chronic use cannot be justified except in very rare patients with absolutely no other alternative.

The analogy with beta-blockers strongly supports the conclusion that inotropic therapy should only be used acutely. Just as beta-blockers initially have adverse consequences, it is not surprising that catecholamines (such as dobutamine) and phosphodiesterase inhibitors (such as milrinone) may be useful acutely to improve symptoms, increase renal perfusion (and diuresis), and permit time for other treatments to be effective. However, the long-term improvement in contractility and survival seen with beta-blockers suggests that chronic inotropic therapy will lead to decreased contractility, more rapid progression of the disease, and increased mortality. The studies of oral inotropes confirm this conclusion. The chronic effects are opposite to the acute effects.

At present, the use of chronic or intermittent infusion therapy of positive inotropes is inappropriate and not supported by data. It is conceivable that these agents are suitable for occasional patients who are willing to accept long-term risks because of the inability of any other intervention to improve debilitating symptoms. Chronic therapy with inotropic drugs should only be used if both the doctor and patient understand that refractory symptoms might be treated at the cost of more rapid progression of the disease.

Arrhythmias and Electrophysiologic Devices

Implantable Defibrillators

The use of implantable defibrillators in patients with heart failure prevents arrhythmic death, but should be used appropriately. Identification of patients at high risk, in whom defibrillators will prolong life, not dying, will permit cost-effective use of this technology. The Sudden Cardiac Death

in Heart Failure Trial (SCD-HeFT) showed that both ischemic and nonischemic patients with an ejection fraction less than 35 % benefit when given defibrillators [33]. If patients have an expected survival of greater than 1 year, have a low ejection fraction despite chronic therapy, and don't have limiting comorbidities, an ICD is usually recommended.

Amiodarone

Amiodarone did not improve survival in SCD-HeFT. However, it is the only antiarrhythmic agent which appears to be safe in patients with heart failure. It is therefore often used for atrial arrhythmias or to prevent symptomatic ventricular tachycardia. The side effects of amiodarone can be clinically important and difficult to diagnose. Particularly problematic is pulmonary toxicity, both acute and chronic. This may go undiagnosed in patients with heart failure who complain of dyspnea, with devastating results. Pulmonary function tests should be followed at least yearly in patients placed on amiodarone and the diagnosis of pulmonary toxicity should be considered in any patient with worsening symptoms. The physician must also remember to search for other side effects, such as thyroid and dermatologic abnormalities.

Resynchronization Therapy

The idea that the nature of the wave of contraction of each beat might affect cardiac efficiency and output prompted investigation of techniques to initiate contraction more physiologically in heart failure patients with prolonged QRS duration. Studies show that in patients with prolonged QRS duration, placing a left ventricular pacing lead (usually in the coronary sinus) can lead to improvement in cardiac function, symptoms, and survival [34]. Each beat then starts at the apex of the left ventricle, permitting contractions which push the blood forward. This is usually placed as part of a defibrillator. It is proven for symptomatic patients with a depressed ejection fraction and a QRS greater than 150 ms.

Anticoagulation

Warfarin

The use of warfarin, aspirin, and other antiplatelet agents in patients with heart failure has been debated. Clots can form in large poorly contracting ventricles, and there is concern that these clots may embolize, causing cerebrovascular accidents. Unfortunately, the use of anticoagulants in heart failure patients has not been shown to be beneficial. In the largest randomized trials, there was no overall benefit to the use of warfarin [35].

There are other groups of patients in whom anticoagulation is clearly indicated. Patients with atrial fibrillation and cardiac disease, for example, experience decreased events when prescribed effective therapeutic doses of warfarin [36]. Since the atrial fibrillation patients with congestive heart failure are at particularly high risk of embolism, they should be given warfarin unless strong contraindications exist. The warfarin dose should be adjusted so that the INR remains between 2.0 and 3.0. Some of these patients may also be given dabigatran or rivaroxaban.

Aspirin

Even more problematic is the use of aspirin in patients with heart failure. The benefits of aspirin in ischemic heart disease are well documented, and many patients with heart failure receive these agents following myocardial infarctions and other ischemic episodes.

There are suggestions, however, that aspirin might negate some of the beneficial effects of ACE inhibitors. Aspirin can decrease kidney function in heart failure patients in whom renal perfusion may be dependent upon prostaglandins. Other adverse hemodynamic actions can occur because of vasoconstriction. Aspirin also inhibits bradykinin production, antagonizing the effects of ACE inhibitors on bradykinin. The impact of bradykinin in patients with heart failure (and whether it contributes to the beneficial actions of ACE inhibitors) is not known. Thus, whether the actions of aspirin are detrimental in patients with heart failure or patients receiving ACE inhibitors are uncertain.

Theoretical concerns cannot overpower the known marked benefit in patients with previous bypass surgery or myocardial infarction. However, the prophylactic use of aspirin in patients with heart failure but without known ischemic heart disease is inappropriate.

Transplantation

Cardiac transplantation is now a routine and accepted option for patients with severe heart failure refractory to medical therapy. One year survival in many programs approaches 90 %, far superior to the expected prognosis in patients with severe disease. Median survival is more than 10 years. Furthermore, patients can symptomatically improve, returning to work and functioning independently [37]. Ninety percent of patients who survive the initial hospitalization have no activity limitations at 1 year. Considering that these patients were generally New York Heart Association class III and IV prior to transplant, this is a dramatic benefit. These

same patients continue to be impacted by their disease, however; less than 30 % have returned to work full time.

The reason for low employment rates are many, but can be explained in large part by complications of the transplant. Despite improving survival rates, the risks of transplantation remain considerable, with rejection and infectious complications most worrisome for the first year, and coronary artery disease and neoplasms becoming more prevalent with time. Furthermore, important chronic diseases, such as renal failure, hypertension, and diabetes, commonly develop. It is not easy for a patient to undergo a cardiac transplantation.

Considering both the risks and the limited availability of hearts for transplantation, patients with both a very poor prognosis and severe symptoms should be selected for transplantation. While any patient with congestive heart failure is at increased risk of dying, the severity of the disease is directly related to the risk of mortality. For this reason, mortality benefits can only be assumed in the sickest patients. Since a low ejection fraction itself does not portend a particularly poor prognosis, patients with minimal symptoms may not experience an improved chance of survival when transplanted.

It is apparent that only patients with severe symptoms can improve their quality of life with a cardiac transplant. With the morbidity associated with transplantation, some assurance that the patient will benefit is mandatory. Partially for this reason, it is common to objectively evaluate symptoms by performing an exercise test with metabolic monitoring. The peak oxygen consumption gives an excellent documentation of limitation of activity, with low peak oxygen consumption (below approximately 14 ml/kg/min) indicating marked limitation of function. Most normal individuals will have a peak oxygen consumption between 20 and 30 ml/kg/min. When evaluating a patient with heart failure, the physician must also remember that deconditioning can lead to continued symptoms of dyspnea and fatigue. Differentiation of symptoms of heart failure and deconditioning can be extremely difficult, and often only time will make the diagnosis evident.

One needs to continually assess patients with heart failure. Patients who have substantially improved need to be removed from transplant lists, and patients who initially appeared too healthy may have deteriorated. While it may be psychologically difficult to inform a patient that a transplant is no longer needed, transplanting a heart into a healthy patient is of no benefit to anyone.

It is also unwise to transplant patients with a high risk of complications from the procedure [38]. Patients with end organ damage, such as fixed pulmonary hypertension, hepatic failure, renal failure, and peripheral vascular disease, are at high risk. Similarly, because brief episodes of noncompliance can have devastating effects, patients without the social support and ability to carefully follow medical regimens should not be transplanted. Transplantation is miraculous for some patients, but can cause irrevocable harm if used inappropriately.

Mechanical Interventions

Left Ventricular Assist Devices (LVAD)

A mechanical heart substitute which could be permanently implanted (as destination therapy) would be ideal solution for patients with end-stage heart disease; the small supply of hearts available for transplantation and the complications inherent with immunosuppression severely limit the number of patients who can benefit from transplantation. Recent advances in technology, including thrombosis prevention and miniaturization, have brought the possibility of widespread use of ventricular assist devices closer to reality. Indeed, in an extremely high-risk patient population, the outcome of patients who received left ventricular assist devices as destination therapy was better than those who received optimal medical care [39]. However, the complication rate remains high, and the benefit is only proven with the sickest patients.

LVADs are usually placed with an outflow conduit sewn in to the apex of the left ventricle after removal of an adequate size plug. This is connected to the ascending aorta and the LVAD implanted in the abdomen outside of the peritoneum. Ventricular assist devices can permit end organ perfusion in patients whose own hearts are unable to perform adequately.

Improvements in technology have led to LVADs being used as destination (permanent) therapy as well as a bridge to transplantation. They can also be used as a bridge to candidacy to see if the normal cardiac output provided by the device can reverse chronic problems (such as organ failure, anorexia, and muscular weakness) and improve the outcome of transplant surgery when it is ultimately performed.

The initial devices were pulsatile, but recent advances have shown good outcomes with continuous-flow devices [40].

Mitral Valve Repair

Patients with severe heart failure often have marked mitral regurgitation, caused by annular dilatation. The regurgitation can severely exacerbate the underlying problem, causing increased pulmonary pressures and decreased forward flow. If a patient can tolerate the operation, the benefits of surgically decreasing backward flow are obvious.

Such surgery was previously felt to be too high risk in patients with left ventricular dysfunction. Indeed, because the ejection fraction can be markedly increased by mitral regurgitation, the true extent of myocardial dysfunction is difficult

to assess in patients with mitral regurgitation, and patients with extremely poor myocardial function have increased risk of not surviving the surgery or not substantially improving their cardiac performance. However, a few surgeons are now reporting excellent outcomes by correcting mitral regurgitation with mitral annuloplasty, even in patients with severe congestive heart failure and left ventricular dysfunction [41]. The same center, however, reported no improvements in survival with the surgery [42]. The factors which portend a better outcome with this surgery need to be understood before accepting the role of mitral annuloplasty in patients with severe heart failure. Percutaneous modifications of the mitral valve are now being investigated and have the potential (if proven) of decreasing mitral regurgitation and improving symptoms with less risk than surgery.

Monitoring

One of the most important interventions which can be used to treat patients with heart failure is close follow-up and treatment of problems before major decompensations. This is the philosophy behind many nursing interventions being used. Managed care has realized that the prevention of hospitalizations by close follow-up can both save money and make patients feel better.

The optimal means of close follow-up is not known. However, monitoring of weight is particularly useful as fluid retention can be addressed before severe clinical deterioration. Many studies report the benefit of combined interventions; frequent nursing visits, ready access to knowledgeable physicians, education, diet modification, and social work help are often tried in combination [43]. Close follow-up with frequent home nursing visits, transtelephonic monitoring, and heart failure clinics have all been tried and appear to be successful. Personnel used have ranged from qualified nurses with heart failure expertise to lesser-trained individuals asking a few scripted key questions. Most of the controlled studies which show benefit also show increased use of evidence-based medicines and doses. It is possible that the close follow-up leads to more attention to proper medication prescription.

Similarly, using serial measurements of BNP or NT-proBNP has been evaluated and may improve outcomes. As with the use of intensive outpatient care and monitoring, increased use of proven medications appears associated with improved outcomes [44].

Devices which monitor hemodynamics or fluid status have also been evaluated. Some studies suggest that these might permit the addressing of issues before decompensation [45]. However, the data are inconclusive, and hospitalization rate has not been uniformly decreased. When they work, the mechanism by which outcomes are improved remains unclear.

However it is done, addressing fluid overload before it leads to pulmonary edema and ensuring that patients are prescribed medications proven to be beneficial (and are taking these medications) will prevent heart failure exacerbations and hospitalizations.

Exercise

Exercise intolerance is often the result of decreased muscular tone, the result of deconditioning, anorexia, and malnutrition. While the decreased cardiac output and increased ventricular and pulmonary pressures initially limit exercise in patients with heart failure, improvement in cardiac performance does not lead to immediate return of normal capabilities. Indeed, the old philosophy that patients with heart failure should not exercise led to the inability of medically treated patients to improve their functional status. Presently, it is clear that steady exercise will improve muscular (and perhaps vascular) function, leading to a better quality of life.

Many studies have shown that formalized exercise programs lead to increased oxygen consumption and exercise tolerance. Unfortunately, the applicability of these reports is suspect. Motivated young patients are often studied, and compliance of sicker and elderly patients may be different. Furthermore, it is unclear if the cost associated with these programs is necessary. Formal cardiac programs with monitoring instill confidence, but are expensive. In addition, it has never been demonstrated that they improve the safety of exercising. In the largest randomized trial to date, the primary outcome of mortality and hospitalization was not decreased, but symptomatic improvement was seen [46]. Furthermore, exercise was clearly safe.

Another unanswered question is whether exercise must be aerobic. Traditionally, isometric exercise was said to be prohibited for heart failure patients. Physicians were concerned that the increased afterload induced by the exercise would be detrimental. However, this has not been tested. At present, one must conclude that aerobic exercise should be encouraged in whatever setting is possible.

Conclusion

The treatment of congestive heart failure demands close follow-up, attention to detail, and listening to the patient. Fortunately, careful studies (Table 19.4) have guided us to effective treatment of these patients (Table 19.5), and the questions which remain can and must also be addressed in ways leading to evidence-based medicine. Physicians should learn from these studies, treating patients with medicines proven to be effective at doses which are appropriate. The treatments can affect symptoms or mortality, but the physician should understand the impact of any treatment on both.

Table 19.4 Major heart failure survival trials

Acronym	Drug	*N*	Dose goal	% Improvement
Renin-angiotensin-aldosterone axis and vasodilators				
CONSENSUS [15]	Enalapril	253	40 mg	27 %
SOLVD-treatment [14]	Enalapril	2,569	20 mg	16 %
SOLVD-prevention [47]	Enalapril	4,228	20 mg	No effect on mortality, hospitalizations decreased
V-HeFT-II [21]	Hydralazine/ isosorbide dinitrate v. enalapril	804	Enal: 20 mg Hydral: 300 mg Nitrates: 160 mg	28 % improvement with enalapril
V-HeFT [20]	Hydralazine/nitrates v. prazosin v. placebo	642	Hydral: 300 mg Nitrates: 160 mg Prazosin: 20 mg	Improvement with hydralazine/nitrates
A-HEFT	Hydralazine/ isosorbide dinitrate	1,050	Hydralazine 75 mg tid/isosorbide dinitrate 40 mg tid	43 % improvement in survival
CHARM [48]	Candesartan	7,599	32 mg	12 % in combined patient groups: low EF with and without ACE-I, normal EF
RALES [7]	Spironolactone	1,663	25 mg	30 %
EMPHASIS [8]	Eplerenone	2,737	50 mg	37 %-death from CV or hospitalization
Inotropes				
PROMISE [32]	Milrinone	1,088	40 mg	Increased mortality
DIG [30]	Digoxin	6,800	varied	No effect on mortality, hospitalizations decreased
Beta-blockers				
CIBIS-II [23]	Bisoprolol	2,647	10 mg	34 %
MERIT-HF [24]	Metoprolol succinate	3,991	200 mg	34 %
COPERNICUS [25]	Carvedilol	2,289	25 mg bid	35 %
COMET [29]	Carvedilol v. metoprolol tartrate	3,029	Carv: 25 bid Metop: 50 bid	17 % improvement with carvedilol
ICD				23 %-ICD v. placebo
SCD-HeFT [33]	ICD v. amiodarone v. placebo	2,521	Varied	No effect amiodarone v. placebo
Resynchronization				
COMPANION [49]	Resynchronization	813	NA	36 %
RAFT [50]	Resynchronization	1,798	NA	25 % death and hospitalization
Surgery				
STITCH [2]	CABG	1,212	NA	No effect on mortality
LVAD				
REMATCH [39]	LVAD v. medical	129	NA	48 %

Table 19.5 Routine treatment of CHF in 2012

Proven therapy:	
ACE inhibitors	Lisinopril 20–40 mg, captopril 25–50 mg tid, enalapril 10–40 mg bid, or equivalent
ARBs	In patients unable to tolerate ACE inhibitors
Diuretics	Furosemide as needed, or other diuretics
Beta-blockers	Metoprolol XL, carvedilol or bisoprolol
Spironolactone	25 mg if renal function and potassium permit
Resynchronization	Symptomatic with QRS ≥ 150
ICD	If expected prognosis >1 year
May be beneficial in select patients:	
Digoxin	0.125 mg
Warfarin	
Amiodarone	
Aspirin	

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Recommended Readings

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Congenital Heart Disease

20

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Introduction

Congenital heart disease (CHD) is defined as a cardiovascular defect that is present since birth and has an estimated incidence of up to 75/1,000 live births including trivial lesions [1]. Isolated ventricular septal defect (VSD) is one of the most common forms of CHD; approximately 3 % of infants have a tiny muscular VSD with spontaneous closure in 85–90 % of cases by the first year of life [1]. Another 1 % have a bicuspid but non-stenotic aortic valve that seldom causes problems in childhood, but may calcify or degenerate later in life [1] (Table 20.1).

Major chromosomal abnormalities account for 8–13 % of CHD with important implications in prognosis and family counseling [2]. Such an example is the presence of 22q11 deletion in approximately 90 % of patients with DiGeorge syndrome and lesions including Tetralogy of Fallot or VSD, who have a 50 % chance of transmitting the disease to their offsprings [2]. A few congenital anomalies are due to teratogens, such as alcohol, lithium, or retinoic acid, or to single gene defects. However, most cases of non-syndromic CHD are likely to be owing to the complex interplay of genetic aberrations with environmental factors.

Due to medical and surgical advances, 85 % of children born with congenital heart defects now survive into adulthood [3]. Adults with CHD can be divided into those with previous repair or palliation and those with unrepaired defects. While patients with repaired CHD are more likely to have improved outcomes, residual hemodynamic lesions and sequelae from previous interventions, such as scar-related arrhythmias, are frequent. The following sections will provide an introduction to the most prevalent CHD lesions and summarize specific issues which are topical to adult patients with CHD.

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Classification

Congenital heart disease defects can be classified into mild, moderate, or severe with regard to clinical management and appropriate access of patients to tertiary care [4]. A more physiological classification is that of acyanotic CHD, where there is no communication between the systemic and pulmonary circulation or there is a left-to-right shunt, and cyanotic CHD with right-to-left shunting. Finally, a useful approach to accurate description of CHD lesions is "sequential segmental analysis" according to which the heart is broken down into three segments (the atrial chambers, the ventricular mass, and the great arteries; Fig. 20.1) and the relationship between adjacent chambers is described (Table 20.2).

Specific Lesions

Atrial Septal Defect

Atrial septal defect (ASD) is defined as a direct communication between the atrial chambers and can be divided into four morphological types: ostium secundum defect of the oval fossa,

Table 20.1 Incidence of congenital heart disease lesions per 1,000 live births

Lesion	Incidence
Bicuspid aortic valve	9.2
Ventricular septal defect	2.8
Patent ductus arteriosus	0.6
Atrial septal defect	0.6
Pulmonary stenosis	0.5
Aortic coarctation	0.3
Tetralogy of Fallot	0.3
Atrioventricular septal defect	0.3
Transposition of the great arteries	0.3
Aortic valve stenosis	0.2

Modified from Hoffman and Kaplan [1]. With permission from Elsevier

C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_20,

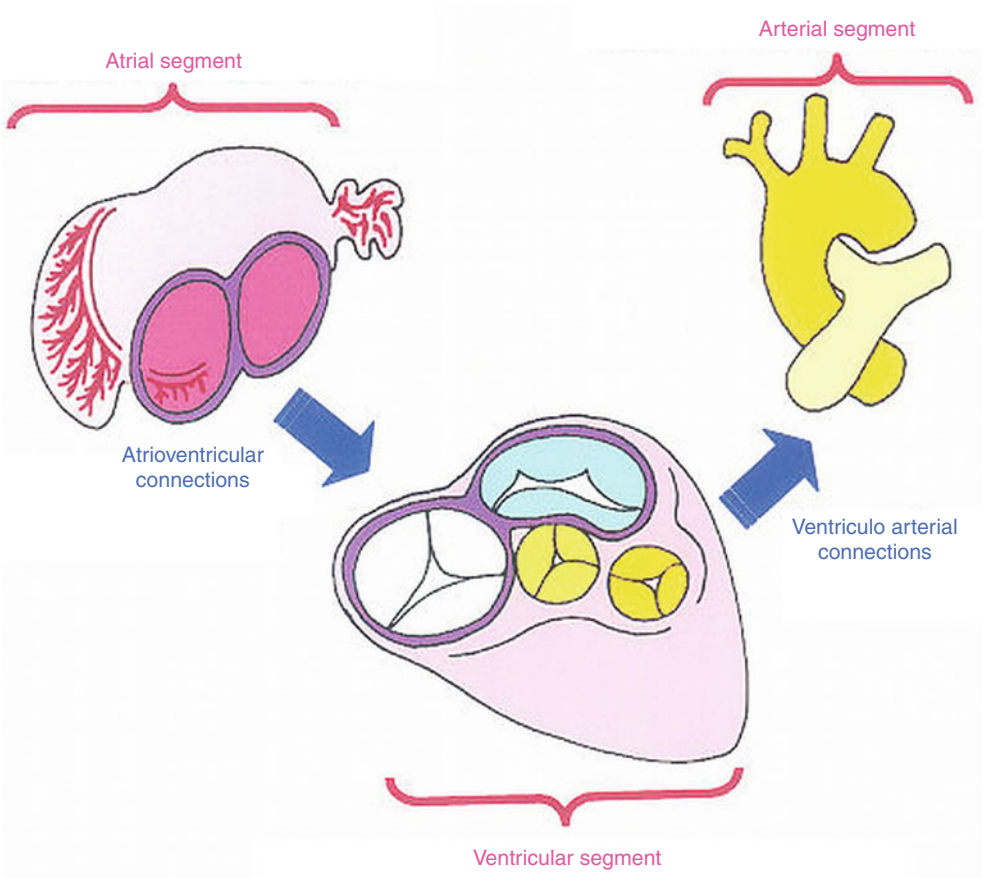

Fig. 20.1 The three segments of the heart used for sequential segmental analysis of congenital heart defects (see Table 20.1) (Image courtesy of S.Y. Ho)

Table 20.2 Sequential segmental analysis of congenital heart disease

1. Arrangement of the atrial chambers (situs)
Situs solitus = morphologically right atrium on the right and morphologically left atrium on the left
Situs inversus = mirror image of the usual arrangement (atria on the wrong sides)
Isomerism = morphological right or left atria bilaterally
2. Atrioventricular (AV) connections
Concordant = appropriate connection of atria to ventricles
Discordant = atria connected to inappropriate ventricles (e.g., right atrium connected to left ventricle)
3. Ventriculoarterial (VA) connections
Concordant = appropriate connection of ventricles to great arteries
Discordant = ventricles connected to inappropriate arteries (e.g., right ventricle connected to aorta)
4. Associated malformations
5. Examples
Atrial septal defect = situs solitus, concordant AV connections, concordant VA connections and atrial septal defect
Complete transposition of the great arteries = situs solitus, concordant AV connections, discordant VA connections

Modified from Ho [5]. With permission from Elsevier

which is the commonest; superior sinus venosus defect overriding the superior vena cava, often associated with partial anomalous pulmonary venous drainage; ostium primum or partial atrioventricular defect, discussed later; and coronary sinus defect, in which there is a deficiency of the wall between the coronary sinus and the left atrium (Fig. 20.2). Left-to-right shunting occurs across an ASD or through anomalous pulmonary veins when the right ventricle becomes more distensible than the left ventricle a few weeks after birth. When pulmonary blood flow (Qp) is more than twice the systemic blood flow (Qs), the right atrium and ventricle are enlarged and hyperactive, with prominent pulsation over the lower left sternal border, and cardiomegaly and increased pulmonary arterial markings on chest X-ray. The relationship between pulmonary and systemic blood flow (Qp/Qs) can be estimated in the catheter laboratory using the Fick principle or noninvasively using cardiac magnetic resonance and echocardiography.

Children with a secundum ASD or partial anomalous pulmonary veins are usually asymptomatic and form one of the largest groups of patients with untreated CHD seen in adult clinics. Adult patients rarely have symptoms before the third or fourth decade of life and may present with exertional dyspnea or palpitations due to atrial tachyarrhythmias. Late complications of unrepaired ASDs include development of right heart failure, atrial flutter or fibrillation, pulmonary hypertension, and paradoxical embolism. Cardinal signs of an ASD on examination include a wide fixed split second heart sound and right ventricular lift. Increased pulmonary

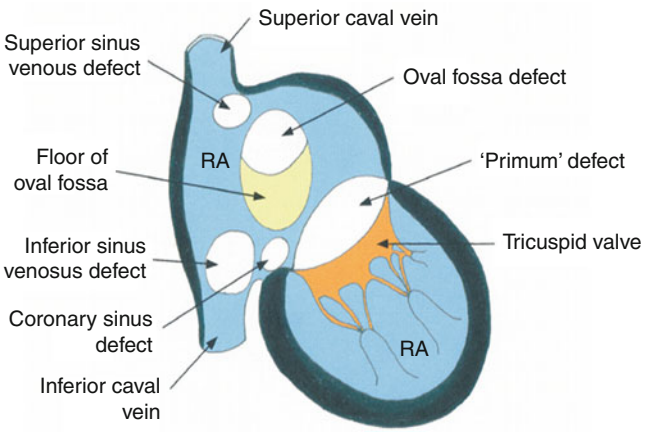

Fig. 20.2 Different types of atrial septal defects (as seen from the right side of the heart)

blood flow may cause a moderately loud pulmonary ejection systolic murmur and a tricuspid mid-diastolic murmur.

The ECG in ASD often shows right-axis (secundum ASD) or superior left-axis (primum ASD) deviation, right atrial enlargement, prolonged PR interval, and right bundle branch block pattern (RBBB). The chest X-ray reveals cardiomegaly (right heart dilation), signs of increased pulmonary blood flow with dilated central pulmonary arteries, and a small aortic knuckle due to persistent low systemic cardiac output. Transthoracic echocardiography is the main diagnostic imaging tool for ASD and demonstrates the location and size of the defect, the direction of the shunt, and a Doppler estimate of the pulmonary artery pressures (PAP). Transesophageal echocardiography (TOE) may be necessary to visualize the pulmonary veins and septal rims of the defect to determine suitability for device closure. Cardiac magnetic resonance imaging (CMR) is useful in the instance of inadequate echocardiographic images and provides information on pulmonary venous anatomy and right ventricular size and function. Diagnostic cardiac catheterization is now rarely performed unless there is suspicion of significant pulmonary arterial hypertension or an indication for assessment of coronary artery disease.

Indications for ASD closure are summarized in Table 20.3; closure of ASDs with right heart dilatation is recommended irrespective of symptoms on the merits of better prognostication. In many centers, percutaneous transcatheter closure has become the recommended treatment for uncomplicated secundum ASDs with suitable anatomy. Surgical closure is required for ostium primum, sinus venosus, and coronary sinus defects. Arrhythmia targeted interventions should be considered at the time of ASD closure, especially in patients older than 40 years who are at a higher risk of developing late atrial flutter or fibrillation following surgical repair [6]. Prophylactic anticoagulation is recommended for 3–6 months following percutaneous closure.

Table 20.3 Indications for closure of atrial septal defect (ASD)

ASD closure	
Indications:	Contraindications:
ASD associated with RA and RV enlargement, irrespective of symptoms	Advanced pulmonary arterial hypertension
Paradoxical embolism	Severe LV dysfunction
Documented orthodeoxia-platypnea	

Abbreviations: *LV* left ventricle, *RA* right atrium, *RV* right ventricle

Ventricular Septal Defect

Ventricular septal defects are divided into (1) perimembranous, (2) muscular, and (3) doubly committed subarterial. Muscular VSDs are bordered completely by myocardium, whereas perimembranous VSDs are partially bordered by the central fibrous body, in continuity between the leaflets of an atrioventricular and an arterial valve. Spontaneous closure of VSDs at both of the above sites is common in childhood. Doubly committed subarterial VSDs are located in the outlet septum in close proximity with the aortic and pulmonary valves. These defects leave the aortic valve cusp (noncoronary or sometimes right coronary cusp) unsupported; the cusp prolapses into the defect and partly occludes it so that the left-to-right shunt is small even if the VSD is large. Progressive aortic regurgitation in this type of VSD is common and replacement of the valve may be needed.

Clinical presentation of a VSD is dependent on the size of the defect, the right and left ventricular pressures, and the pulmonary vascular resistance. Small restrictive VSDs produce a significant pressure gradient between the two ventricles with a small left-to-right shunt ($Qp/Qs < 1.5/1.0$) and no hemodynamic derangement; these defects usually present as systolic murmurs in the absence of symptoms. Moderately restrictive VSDs result in moderate left-to-right shunt ($Qp/Qs = 1.5–2.5/1.0$) with mild to moderate volume overload of the left ventricle; patients with this defect may develop mild congestive heart failure. Finally, large nonrestrictive VSDs ($Qp/Qs > 2.5/1.0$) can lead to Eisenmenger syndrome (discussed later) with progressive pulmonary vascular disease and reversal of the left-to-right shunting.

On examination, a small- or medium-sized VSD has a typical harsh loud systolic murmur, usually pansystolic, obscuring the first heart sound, and heard best at the left lower sternal border. The size of the VSD and the amount of shunting must be judged not on the murmur but on the activity of the heart and precordium. Large nonrestrictive VSDs may produce an apical diastolic rumble of increased mitral flow or signs of pulmonary arterial hypertension (PAH), including a right ventricular heave and a palpable loud P2.

The ECG may reveal left atrial hypertrophy and signs of left ventricular overload in moderate-sized VSDs and signs of right ventricular hypertrophy in large nonrestrictive VSDs with PAH. The chest X-ray in moderate-sized VSDs

Table 20.4 Indications for closure of ventricular septal defect (VSD)

VSD closure	
Indications:	Contraindications:
Left-to-right shunt (Qp:Qs) > 2.0 and evidence of LV volume overload	Pulmonary arterial hypertension
Qp:Qs > 1.5:1 with pulmonary artery pressure < 2/3 of systemic pressure and PVR < 2/3 of systemic vascular resistance	
Qp:Qs > 1.5:1 with LV systolic or diastolic failure	
Previous episode of endocarditis	
Aortic regurgitation	

Abbreviations: *LV* left ventricle, *PVR* pulmonary vascular resistance

shows cardiomegaly (left ventricular dilatation) and pulmonary plethora and in large VSDs with PAH, dilated central pulmonary arteries and right heart enlargement. Transthoracic echocardiography establishes the size, location, and hemodynamic consequences of the defect as well as associated lesions such as aortic regurgitation. Cardiac catheterization can be performed when noninvasive data are inadequate and further information is needed, such as quantification of the shunt and assessment of pulmonary vascular resistance.

Due to spontaneous closure of 70–80 % of VSDs, initial treatment is conservative. Small defects need only prophylaxis against infective endocarditis. Timely surgical closure is required in moderate restrictive and large nonrestrictive defects with a Qp/Qs > 2.0/1.0 and clinical evidence of left ventricular volume overload [4] (Table 20.4). Transcatheter device closure may be considered in selected cases of muscular and perimembranous VSDs. Late complications related to small unoperated VSDs or residual defects following surgery include infective endocarditis, aortic regurgitation secondary to leaflet involvement, and symptomatic arrhythmias [7]. Life expectancy following surgical correction of VSD is close to normal in patients with good left ventricular function prior to surgery.

Atrioventricular Septal Defect

Atrioventricular septal defect (AVSD) comprises a spectrum of abnormalities of the atrioventricular valves (AVV) characterized by the presence of a common atrioventricular junction. In partial AVSD (also known as ostium primum ASD), the right and left AVVs have separate orifices and the ventricular septum is intact. In complete AVSD, there is a contiguous primum ASD and a large VSD, separated only by a common AVV with five leaflets (a trileaflet left and quadrileaflet right AVV). An unwedged position of the aortic valve is also common which results to an elongated left ventricular outflow tract (LVOT) with a risk of subaortic obstruction [8].

The clinical course of patients with partial AVSD is similar to that of secundum ASD with potentially earlier presentation due to development of left AVV regurgitation. The majority of complete AVSDs occur in patients with Down syndrome (>75 %); these patients have large volume loads early in life and develop congestive heart failure and pulmonary vascular disease by a few months after birth. On physical examination, partial AVSDs will have similar signs to ASDs (described above) along with a holosystolic murmur in the instance of significant left AVV regurgitation. Patients with complete AVSDs will be cyanosed and clubbed with a single first heart sound (common AVV) and signs of pulmonary hypertension (discussed later).

Common ECG findings of AVSDs include left-axis deviation and first-degree atrioventricular block due to congenital abnormalities of the conduction system [9]. The chest X-ray will reveal cardiomegaly and increased pulmonary vascular markings. Transthoracic echocardiography can establish an accurate diagnosis with identification of the anatomical defect along with the magnitude of left-to-right shunting and estimation of pulmonary artery pressure. Cardiac catheterization has a limited role in the diagnostic and preoperative evaluation of AVSDs unless there is a need to formally assess the pulmonary vascular resistance and vasoreactivity [4].

Survival without surgery is relatively short [10]. Surgery involves closing the atrial and ventricular defects and repairing the atrioventricular valves. Early surgical repair of complete AVSD is indicated in the absence of irreversible pulmonary hypertension. Late valve problems and even reoperation are relatively common, and complete atrioventricular block may occur. Recurrent left AVV regurgitation is the most common postoperative complication requiring reoperation in 5–10 % of patients [4].

Left Ventricular Outflow Tract Disorders

Left ventricular outflow tract obstruction (LVOTO) is a group of stenotic lesions that can occur at supravalvar, valvar, or subvalvar level. Irrespective of the site of obstruction, significant LVOTO imposes an increase in left ventricular afterload leading to concentric hypertrophy, dilatation, and eventual failure of the left ventricle.

Supravalvar Aortic Stenosis

This is rare and often associated with Williams syndrome (infantile hypercalcemia, mental retardation, elfin facies). The stenosis may be localized or long and diffuse and can extend into the coronary ostia with a worse prognosis in the instance of coronary involvement (Fig. 20.3). Clinical features resemble those of valvar aortic stenosis (described later), but with no ejection click. Frequently, systolic blood pressure is about 15 mmHg higher in the right than in the left arm

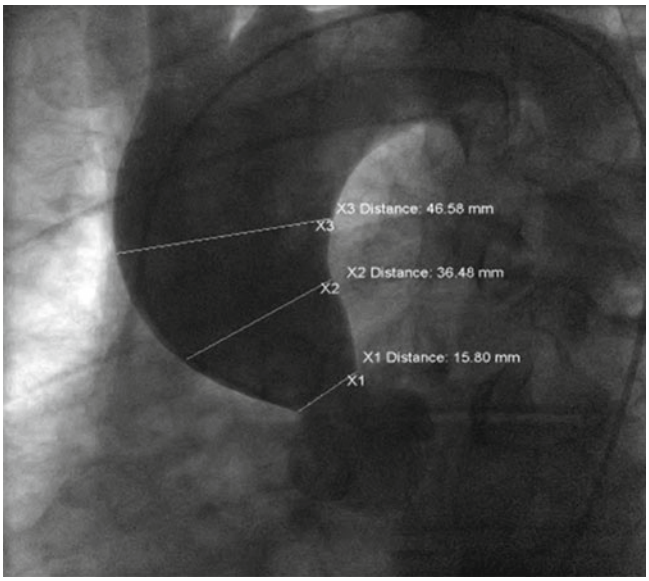

Fig. 20.3 Angiogram of a patient with Williams syndrome. Note marked native supra-aortic valve stenosis with post-stenotic aortic dilatation

because of the direction of the jet coming through the stenosis. Surgical repair is indicated in the presence of a catheter or mean echocardiographic gradient of >50 mmHg. Stenoses of other arteries may occur with Williams syndrome, including the abdominal aorta and peripheral pulmonary arteries.

Valvar Aortic Stenosis and Bicuspid Aortic Valve

Valvar aortic stenosis may occur due to a wide spectrum of congenitally malformed valves, most commonly a bicuspid aortic valve (BAV) comprising of two full-developed leaflets (true BAV) or three leaflets, two of which have been fused together (functional BAV) [11]. Bicuspid aortic valve has a prevalence of 0.5–2 % with a male/female ratio of 3:1 [12]. It is a heritable condition with an incidence of a BAV in approximately 9 % of first-degree relatives of affected individuals. Development of a BAV predisposes to several complications, including valvar dysfunction, infective endocarditis, and structural pathologies of the aortic wall, such as coarctation of the aorta and dilatation of the aortic root. Aortic dilatation in BAV is progressive and may be related to hemodynamic abnormalities or intrinsic structural defects of the aortic wall [12].

Clinical presentation depends on the severity of obstruction and may vary from none to dyspnea, angina, syncope, or chest pain. On examination, there will be an ejection systolic murmur maximal anywhere between the apex and the upper right sternal border and, in the same region, an early systolic ejection click that does not vary with respiration. Left ventricular hypertrophy may be palpable or shown on the electrocardiogram. The chest X-ray may show cardiomegaly and dilatation of the ascending aorta (common with a BAV). Echocardiography is the most effective noninvasive test for identification and quantification of the severity of aortic valve disease and aortic root dilatation. MRI and CT angiography are useful for visualization of the entire thoracic aorta, whereas cardiac catheterization may be needed before aortic valve replacement to determine the presence of coexistent coronary artery disease.

The majority of BAV patients will require valve surgery during their lifetime, predominantly due to significant aortic stenosis in early childhood, aortic regurgitation into adolescence, and calcific valve disease later in adulthood [13]. Intervention on the valve is required for severe aortic stenosis with or without symptoms, and severe aortic regurgitation associated with symptoms, or progressive left ventricular dilatation (LV end-diastolic diameter 4 SDs above normal) [4]. Prophylactic surgery for aortic dilatation is recommended when the ascending aorta diameter is >5.0 cm or when there is progressive dilatation at a rate ≥5 mm/year [4]. Balloon valvotomy is effective if there is minimal aortic incompetence and no significant calcification of the aortic valve. Choice of valve for surgical replacement depends on the patient's lifestyle and includes use of an aortic homograft, a mechanical valve, or the Ross procedure (especially for young women of reproductive age). Lifelong cardiology follow-up is recommended for all patients with aortic valve disease as progressive or recurrent AS, AR, or aortic enlargement (in the presence of a BAV) may occur.

Subaortic Stenosis

Subvalvar LVOTO may develop due to presence of a discrete membranous or fibromuscular ring just below the aortic valve or, less frequently, in relation to a tunnel-like fibromuscular band. The lesion has a male predominance (2:1) and may coexist with other lesions, especially a VSD. There may be mild to moderate aortic incompetence due to valve damage from the high-velocity jet through the stenosis. Clinically these lesions resemble valvar aortic stenosis, and echocardiography is needed to distinguish them. Balloon valvotomy is less useful than in valvar stenosis, and surgical excision may be needed. Indications for surgery include presence of a peak gradient of >50 mmHg or a mean gradient of 30 mmHg on echocardiography or if LVOTO is combined with progressive AR and left ventricular dysfunction or dilatation [4].

Coarctation of the Aorta

This is a localized narrowing of the aorta just beyond the origin of the left subclavian artery with development of an extensive collateral arterial network to supply the lower body. Associated abnormalities include intracranial berry aneurysms, anomalies of the head and neck vessels, VSD, PDA, and Turner syndrome. Multiple left heart lesions, including aortic stenosis and parachute mitral valve, may be

present, whereas a bicuspid aortic valve can be found in up to 85 % of patients. Aneurysm formation is a known clinical feature of the disease and may occur at the site of previous surgical repair or in the proximal ascending aorta [14].

Coarctation of the aorta may present acutely in the neonatal period and early childhood with heart failure or ductal shock following closure of the arterial duct. Milder lesions are frequently missed in childhood and form a large proportion of patients with CHD seen by adult cardiologists. In the latter instance, patients often come to medical attention with systemic hypertension, murmurs, and other related symptoms such as headache, epistaxis, intermittent leg claudication, cerebral vascular accidents (especially subarachnoid hemorrhage), infective endocarditis, rupture of the aorta, or premature coronary artery disease.

Clinical features of the lesion include hypertension in the upper body (blood pressure should be taken in the right arm) with decreased pulses and pressure in the legs; diastolic pressures are often similar in arms and legs, but systolic pressures differ markedly. Most have palpable collateral arteries around the scapula. There is left ventricular hypertrophy clinically and on electrocardiogram, but no T-wave inversion. A systolic or continuous murmur is heard best in the mid-back, and sometimes there is a mid-diastolic rumble at the apex even though there is no mitral stenosis.

On chest X-ray, the ascending aorta is dilated, as is the descending aorta below the constricted site of the coarctation; the hourglass pattern shows a "3" sign on plain X-ray. Confirmation by echocardiography should include demonstration of delayed acceleration of flow in the descending aorta by Doppler study. MRI and computed tomography (CT) angiography are the imaging modalities of choice for evaluation of the lesion pre- and post-repair and when urgent aortic imaging is required in the instance of hemoptysis (suspected aortic dissection or ruptured aneurysm) (Fig. 20.4). Cardiac catheterization is employed for percutaneous intervention and screening for coronary artery disease.

Repair of coarctation may be achieved surgically or percutaneously by angioplasty or stent implantation. Indications for repair include a peak-to-peak coarctation gradient ≥20 mmHg or a peak-to-peak coarctation gradient <20 mmHg in the presence of significant coarctation based on imaging with radiological evidence of significant collateral flow [4]. The choice of catheter versus surgical treatment should be determined jointly by a team of cardiologists, interventionalists, and surgeons specialized in adult CHD. Systemic hypertension, even after adequate repair, is common and should be treated medically.

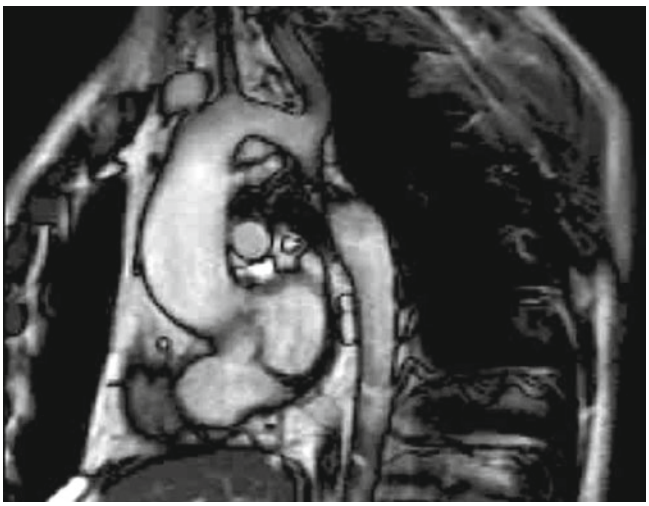

Fig. 20.4 Magnetic resonance imaging of native coarctation of the aorta. Note moderate ascending aortic dilatation secondary to presence of a bicuspid aortic valve. Also marked dilatation of left subclavian artery due to significant collateral blood flow (Image courtesy of PJ Kilner)

Patent Arterial Duct

Patent arterial duct (PDA) is a communication between the proximal left pulmonary artery and the descending aorta distally to the left subclavian artery. This structure is vital in fetal life but may persist postpartum with hemodynamic consequences corresponding to the size of the PDA; small communications can present with a murmur in the absence of symptoms, whereas moderate-large PDAs can lead to left-to-right shunting with excessive pulmonary flow and left heart volume overload.

On clinical examination, there is a continuous "machinery" or "train in a tunnel" murmur heard best below the left clavicle. The size of the PDA and the amount of shunting are diagnosed not from the murmur but from associated features: a big duct has a loud second heart sound, bounding pulses, and left ventricular dilation and hypertrophy on clinical, radiological, electrocardiographic, and echocardiographic examination. Large PDAs can lead to development of Eisenmenger syndrome with absence of murmurs and characteristically differential cyanosis (cyanosis and clubbing of toes but not fingers).

Indications for PDA closure include significant left-to-right shunting and left heart enlargement or prior endarteritis [4]. Closure of the communication is contraindicated in the presence of pulmonary vascular disease. Percutaneous closure at cardiac catheterization by coils or other devices is the preferred method because of its high success and few complications. Surgical closure is reserved for large or distorted defects which are unsuitable for transcatheter closure. Life expectancy after closure is essentially normal with worse prognosis in the instance of pulmonary vascular disease.

Tetralogy of Fallot and Right Ventricular Outflow Tract Disorders

Tetralogy of Fallot (TOF) is the commonest form of cyanotic heart disease, comprised from four features: a large VSD, an

Table 20.5 Late complications following radical repair of Tetralogy of Fallot (TOF)

Late complications after TOF repair
Residual pulmonary regurgitation
Residual RVOT obstruction
Branch pulmonary artery stenosis/hypoplasia
RV dysfunction/RVOT aneurysm
Residual VSD
AR ± aortic root dilatation
LV dysfunction
Endocarditis
Supraventricular arrythmia
Ventricular tachycardia/sudden death
Heart block (uncommon)

overriding aorta, right ventricular outflow tract obstruction from infundibular and/or valvar PS, and right ventricular hypertrophy. Pulmonary artery hypoplasia or stenosis may also be present. The lesion has a wide degree of morphological variation, from mild PS to pulmonary atresia and from minimal degree of aortic override to double-outlet right ventricle (>50 % coming from the RV). Associated cardiac abnormalities include right aortic arch (~25 %), ASD, AVSD, and coronary anomalies, with the left anterior descending coronary artery arising from the right coronary artery and crossing the RV outflow in approximately 3–7 % of patients [4]. Up to 35 % of patients with TOF have a 22q11 deletion; genetic screening should be offered in these patients due to high risk of recurrence of CHD in their offsprings [2].

The clinical presentation of TOF depends on the degree of right ventricular outflow tract (RVOT) obstruction; significant obstruction leads to right-to-left shunting with cyanosis, whereas mild obstruction, the so-called pink tetralogy, may present with dyspnea and minimal cyanosis. The majority of adult patients will have undergone radical repair in childhood and present with symptoms related to late complications (discussed below, see Table 20.5), such as palpitations, syncope, or heart failure. On physical examination, repaired TOF may reveal a right ventricular lift with an ejection systolic murmur of residual RVOT obstruction. A diastolic murmur of pulmonary regurgitation or aortic regurgitation (due to aortic root dilatation) may also be heard. The pulmonary component of the second sound is often not audible.

The electrocardiogram commonly reveals right bundle branch block (RBBB) in patients with previous surgery. The length of QRS reflects the degree of right ventricular dilatation and, when prolonged, is an adverse prognostic marker for sustained ventricular tachycardia and sudden cardiac death [15]. The chest X-ray shows a right-sided aortic arch in ~25 % of patients. Dilatation of the ascending aorta and cardiomegaly from right ventricular enlargement may also be seen. Echocardiography is used following repair to assess the presence of residual pulmonary stenosis or regurgitation, residual VSD, biventricular size and function, the size of the aortic root, and the degree of aortic regurgitation. Magnetic resonance imaging can accurately assess right ventricular size and volumes and with late gadolinium enhancement can identify the presence of ventricular fibrosis, a marker of adverse outcome [16]. Cardiac catheterization is infrequently used but may be used for assessment pulmonary blood flow and resistance and identification of anomalies of the coronary arteries or residual septal defects [4].

Definitive surgical treatment of TOF involves closure of the VSD with a patch and relief of the RVOT obstruction with resection of the hypertrophied infundibular muscle and insertion of an RVOT or transannular patch; a preliminary palliative systemic artery-pulmonary shunt is occasionally needed. Late complications of radical repair are included in Table 20.4; in the instance of transannular patch repair technique, significant pulmonary regurgitation is almost always encountered. Indications for pulmonary valve replacement in the latter instance include the presence of severe pulmonary regurgitation with symptoms or decreased exercise tolerance, RV enlargement/dysfunction, moderate or severe tricuspid regurgitation, or development of clinical arrhythmias (atrial or ventricular). Residual RVOT obstruction can occur at subvalvar, valvar level, or more distally with the following indications for reintervention: peak echocardiography gradient >50 mmHg, RV/LV pressure ratio >7, residual VSD with Qp:Qs > 1.5:1, and severe AR with symptoms or LV enlargement/dysfunction [4]. The proper risk stratification for major cardiac arrhythmias (atrial flutter/fibrillation or sustained VT) remains a matter of debate; high-risk patients for sustained VT and/or sudden death with right ventricular dilatation and QRS duration ≥180 ms will require electrophysiological assessment and are increasingly managed with implantable cardioverter defibrillators [4].

Ebstein's Anomaly of the Tricuspid Valve

Ebstein's anomaly of the tricuspid valve (TV) is defined as an apical displacement of the septal and posterolateral leaflets away from the atrioventricular junction into the right ventricle resulting to "atrialization" of the RV inflow with a smaller functional RV and an enlarged right atrium. The malformed TV can lead to varying degrees of tricuspid regurgitation (TR) exaggerating right heart enlargement. Associated lesions include ASD or patent foramen ovale (up to 94 % of patients) and Wolf-Parkinson-White syndrome, often with multiple accessory atrioventricular pathways [17]. Ebstein's anomaly can also be part of other complex lesions such as congenitally corrected transposition of the great arteries, pulmonary stenosis/atresia, BAV, coarctation, or VSD [17].

Clinical presentation of the lesion depends on its severity and may vary from intrauterine death to manifestation of the disease in late adulthood. Severe Ebstein's anomaly will present in infancy with congestive heart failure and failure to thrive. Adult patients may remain asymptomatic or present with exercise intolerance, palpitations, cyanosis, or

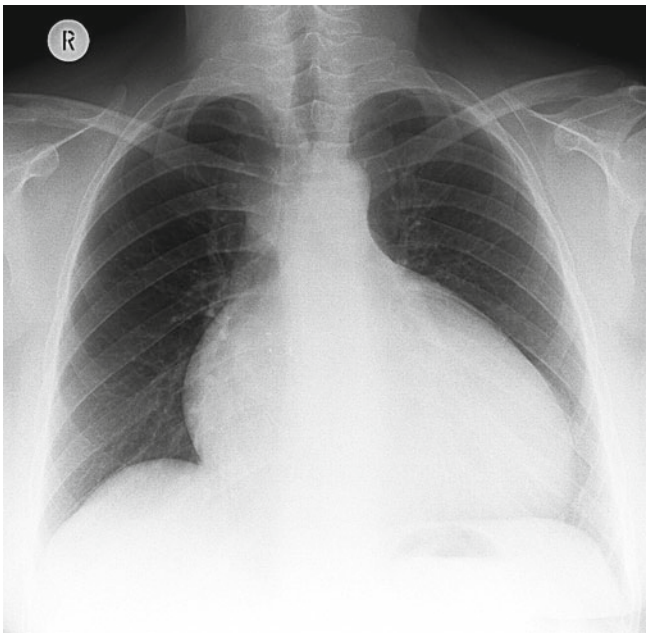

Fig. 20.5 Chest X-ray of a patient with Ebstein's anomaly of the tricuspid valve. Note marked cardiomegaly with globular shape of the cardiac silhouette, small aortic knuckle, and reduced pulmonary vascular markings

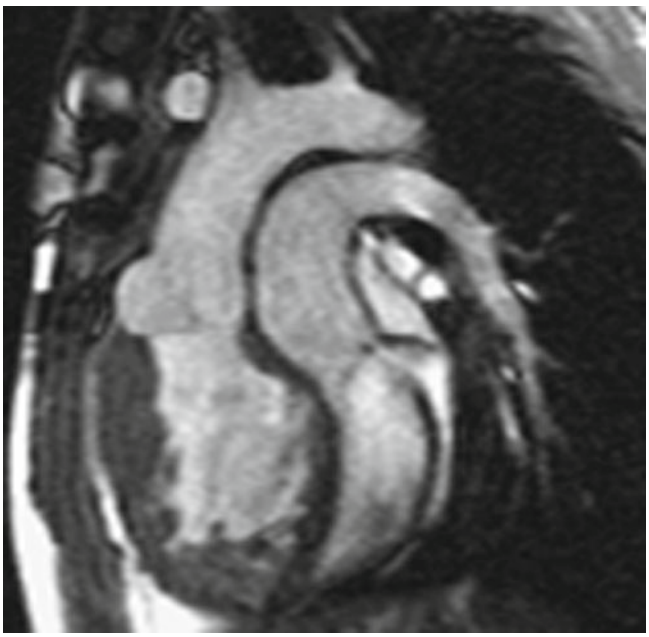

Fig. 20.6 Magnetic resonance imaging of complete transposition of the great arteries. Note anterior aorta arising from a hypertrophied systemic right ventricle and posterior pulmonary artery arising from the left ventricle

paradoxical emboli due to a right-to-left shunt present at atrial level. Physical examination will reveal cyanosis and clubbing in patients with right-to-left shunting. Late signs of Ebstein's anomaly include elevated JVP, hepatomegaly, ascites, and peripheral edema. On auscultation, there will be a widely split S1 and S2 and a holosystolic murmur of TR best heard at the lower left sternal border.

Typical findings of the lesion on electrocardiogram include low QRS voltage, tall P-waves reflective of right atrial enlargement, prolonged PR interval, RBBB, and a delta-wave secondary to an accessory pathway. Supraventricular tachyarrhythmias and atrial fibrillation are frequent in adult patients. The chest X-ray will reveal cardiomegaly due to right heart enlargement with a globular shape of the cardiac silhouette and a small aortic knuckle (Fig. 20.5). Echocardiography can confirm the diagnosis via visualization of apical displacement of the septal leaflet of the TV by >8 mm/m^2 [17].

Surgical procedures for Ebstein's anomaly may involve repair or replacement of the TV, plication of the atrialized portion of the right ventricle, and procedures to ablate arrhythmogenic foci. Indications for intervention include presence of symptoms or deteriorating exercise capacity, significant cyanosis, paradoxical embolism, and progressive right heart enlargement with impaired RV systolic function [4]. Anticoagulation with warfarin is recommended for patients with a history of paradoxical embolism or atrial fibrillation and catheter ablation for treatment of tachyarrhythmias secondary to accessory pathways.

Transposition of the Great Arteries

There are two types of transposition of the great arteries (TGA), complete TGA and congenitally corrected TGA.

Complete Transposition

In complete TGA, there is atrioventricular concordance and ventriculoarterial discordance; in other words, the right atrium connects to the morphological right ventricle which gives rise to the aorta and the left atrium connects to the morphological left ventricle which gives rise to the pulmonary artery (Fig. 20.6). As the systemic and pulmonary circulations run in parallel, complete TGA is incompatible with life unless there is a communication between the two circuits (ASD, VSD, PDA). The lesion is often associated with VSD (~40–45 %), LVOT obstruction (~25 %), and aortic coarctation (~5 %) [18].

Infants with complete TGA become progressively cyanotic as the arterial duct closes and require early surgical intervention. Mortality without intervention reaches 90 % by the first year of life; a few unoperated patients with large VSDs may survive into adulthood and develop Eisenmenger syndrome. Clinical presentation of adult operated patients is related to the type of surgical technique (see below).

Atrial Switch Procedure

This procedure involves redirection of the blood at the atrial level with use of a baffle made of synthetic material or pericardium (Mustard procedure) or atrial flaps (Senning procedure),

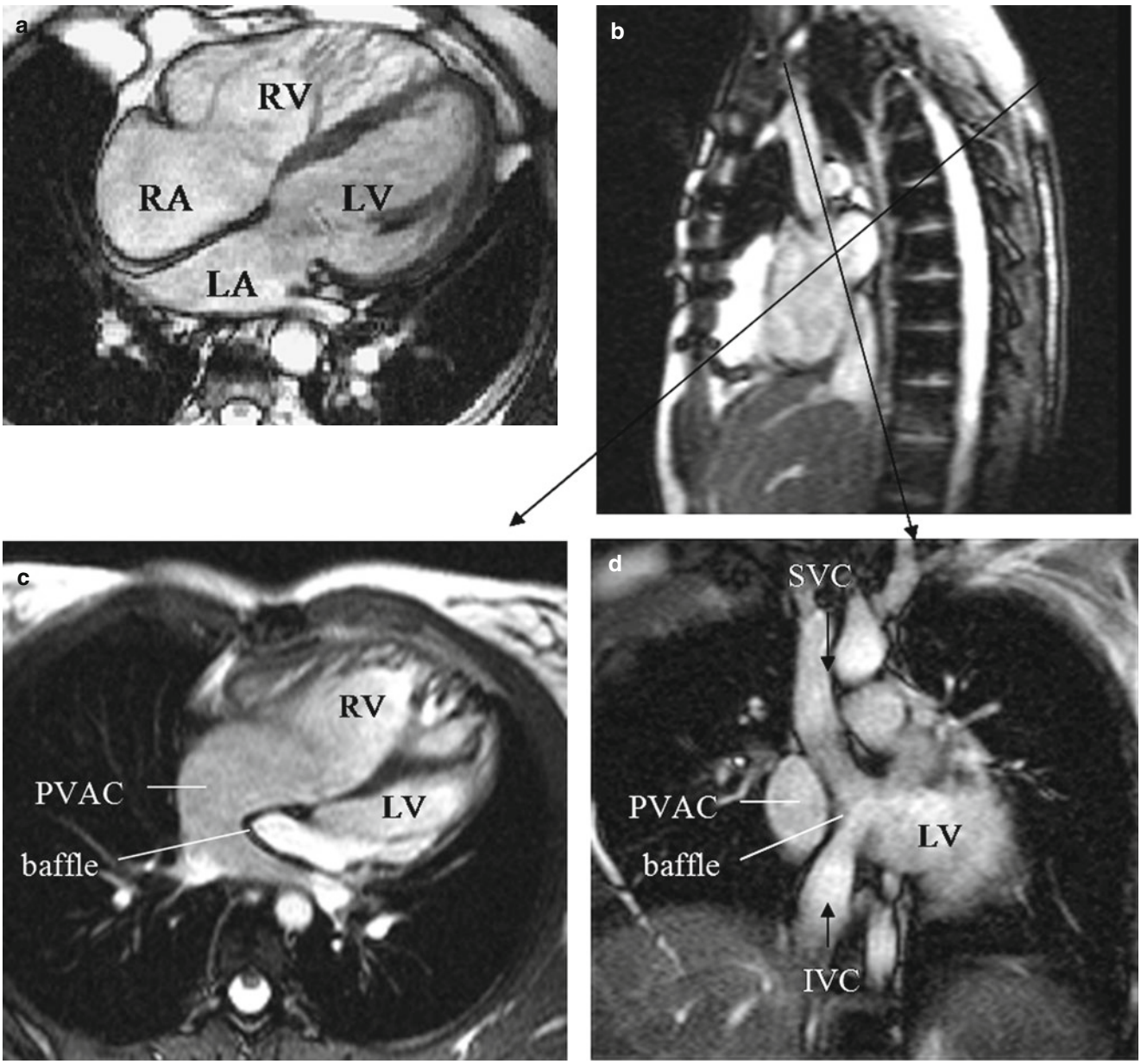

Fig. 20.7 Atrial switch procedure (Mustard) for complete transposition of the great arteries. (**a**) Four-chamber image showing usual atrioventricular connections in a patient with repaired Tetralogy of Fallot. (**b**) A sagittal image though the reconstructed atrial compartments in a patient after Mustard operation. The *black arrows* show the location of: (**c**) an oblique transaxial slice aligned with the pulmonary venous atrial compartment (*PVAC*) and (**d**) an oblique coronal image aligned with superior and inferior vena cava (*SVC* and *IVC*), redirected by the baffle to the left ventricle (*LV*). *LA* left atrium, *RA* right atrium, *RV* right ventricle (Images courtesy of SV Babu-Narayan & PJ Kilner)

achieving a physiological-type repair. The systemic venous return is directed to the left ventricle and thence to the pulmonary artery, and the pulmonary venous return to the right ventricle and thence to the aorta (Fig. 20.7). Common complications of atrial redirection procedures include progressive dysfunction of the right ventricle (which supports the systemic circulation) and high arrhythmic burden due to extensive atrial suture lines. Atrial flutter and fibrillation develops in 14 % of patients and sinus node dysfunction in 48 % [19, 20]. Progressive tricuspid regurgitation is frequent and may require surgical intervention if moderate to severe. Other complications include superior or inferior vena cava pathway obstruction and atrial baffle leak, both of which may require surgical intervention if not amenable to percutaneous repair.

Arterial Switch Procedure

This is an anatomical type repair with redirection of blood flow at the level of the great arteries by switching the

pulmonary artery and aorta, including the coronaries, to their normal position. Arterial switch offers the advantage of a systemic left ventricle. The long-term sequelae of the procedure include development of neoaortic regurgitation, progressive dilatation of the neoaortic root, myocardial ischemia due to stenosis of the coronary ostia, and RVOT obstruction, which is the commonest cause for reoperation.

Rastelli Procedure

This is a procedure used for patients with TGA, pulmonary/subpulmonary stenosis, and a large VSD. Blood flow is redirected at the ventricular level with an intracardiac baffle which tunnels the LV to the aorta via the VSD and with an extracardiac conduit which is placed between the RV and the pulmonary artery. Similarly to arterial switch, this procedure has the advantage of a systemic left ventricle. However, it is not without late complications such as conduit stenosis requiring reoperation and atrial and ventricular arrhythmias.

Congenitally Corrected Transposition

In congenitally corrected TGA (ccTGA), the atrioventricular and ventriculoarterial connections are discordant; the right atrium is connected to the morphological LV and thence to the pulmonary artery and the left atrium is connected to the morphological RV and thence to the aorta. Therefore, in ccTGA, "physiological" correction of the circulation occurs but with presence of a systemic right ventricle. Up to 98 % of patients have associated malformations such as VSD, pulmonary or subpulmonary stenosis, "Ebstein-like" anomalies of the systemic atrioventricular valve, and complete atrioventricular block [21].

Adult patients with isolated ccTGA (~1 %) may remain undiagnosed until late adulthood with usual manifestation of systemic right ventricular failure by the fourth to fifth decade of life and palpitations related to atrial arrhythmias by the sixth decade. Patients with a VSD and pulmonary stenosis will present earlier with cyanosis, congestive heart failure, palpitations, or syncope (due to complete atrioventricular block). On physical examination, there will be a characteristically loud aortic second sound heard best at the upper left sternal border due to the abnormal aortic position (anterior and to the left). Similarly, the abnormal position of the great vessels produces a characteristic straight segment at the left upper heart border on chest X-ray which reflects the ascending aorta. The electrocardiogram can show complete atrioventricular block and prominent Q-waves in the right chest leads, leading often to the mistaken diagnosis of anterior myocardial infarction. Echocardiography can detect the presence of double discordance and associated malformations, whereas MRI can provide an accurate assessment of the systemic right ventricle.

Double-switch procedures, combining an atrial switch with an arterial switch, aim at restoration of the left ventricle in the systemic position and have been performed in infants and young children with encouraging early outcomes [4]. Adult patients usually undergo surgery for significant left atrioventricular valve regurgitation, ideally before deterioration of systemic right ventricular function (EF <45 %). The status of atrioventricular conduction must be monitored regularly as there is a 2 % annual risk of spontaneous heart block [4].

Univentricular Physiology and Fontan Procedure

The term "univentricular heart" describes a variety of rare complex cardiac malformations in which there is a single functional ventricular cavity and biventricular repair is not feasible. Common types of univentricular defects include tricuspid and mitral atresia, double inlet left ventricle, and hypoplastic left heart syndrome. Clinical presentation occurs in infancy with cyanosis due to mixing of systemic and pulmonary blood in a single ventricle. Depending on the underlying anatomy, increased pulmonary blood flow will lead to mild cyanosis and congestive heart failure, whereas decreased pulmonary blood flow will result in profound hypoxemia. Survival without treatment is poor and therapeutic options can only be palliative [22].

A staged approach is taken to achieve a Fontan-type circulation. Initially, palliative procedures are performed in the neonatal period to control pulmonary blood flow, involving either a pulmonary artery band to decrease flow or a systemic to pulmonary artery shunt to increase flow. During the second stage (~4–12 months of age) a bidirectional Glenn shunt is created consisting of an end-to-side anastomosis of the superior vena cava to the top of the right pulmonary artery. The classic Fontan operation, performed in the final stage (18 months to 4 years of age or later), consists of an atriopulmonary connection with anastomosis of the right atrium to the pulmonary artery. However, the current technique of choice is total cavopulmonary connection (TCPC) which can be performed as a single or two-staged procedure and combines a bidirectional Glenn with connection of the inferior vena cava to the pulmonary artery via an intracardiac or extracardiac conduit (Fig. 20.8). A fenestration between the Fontan circuit and the pulmonary atrium is frequently created to prevent excessive elevation of right atrial pressure and improve systemic cardiac output in exchange for a degree of hypoxemia at the immediate postoperative period. The fenestration can be closed at a later stage with a catheter approach.

Clinical presentation of adult patients with Fontan circulation relates to the long-term complications of the procedure, as discussed below. On physical examination there may be cyanosis and clubbing due to presence of a fenestration or collateral vessels. Jugular venous pressure is often elevated. Auscultation will not reveal murmurs but a single second

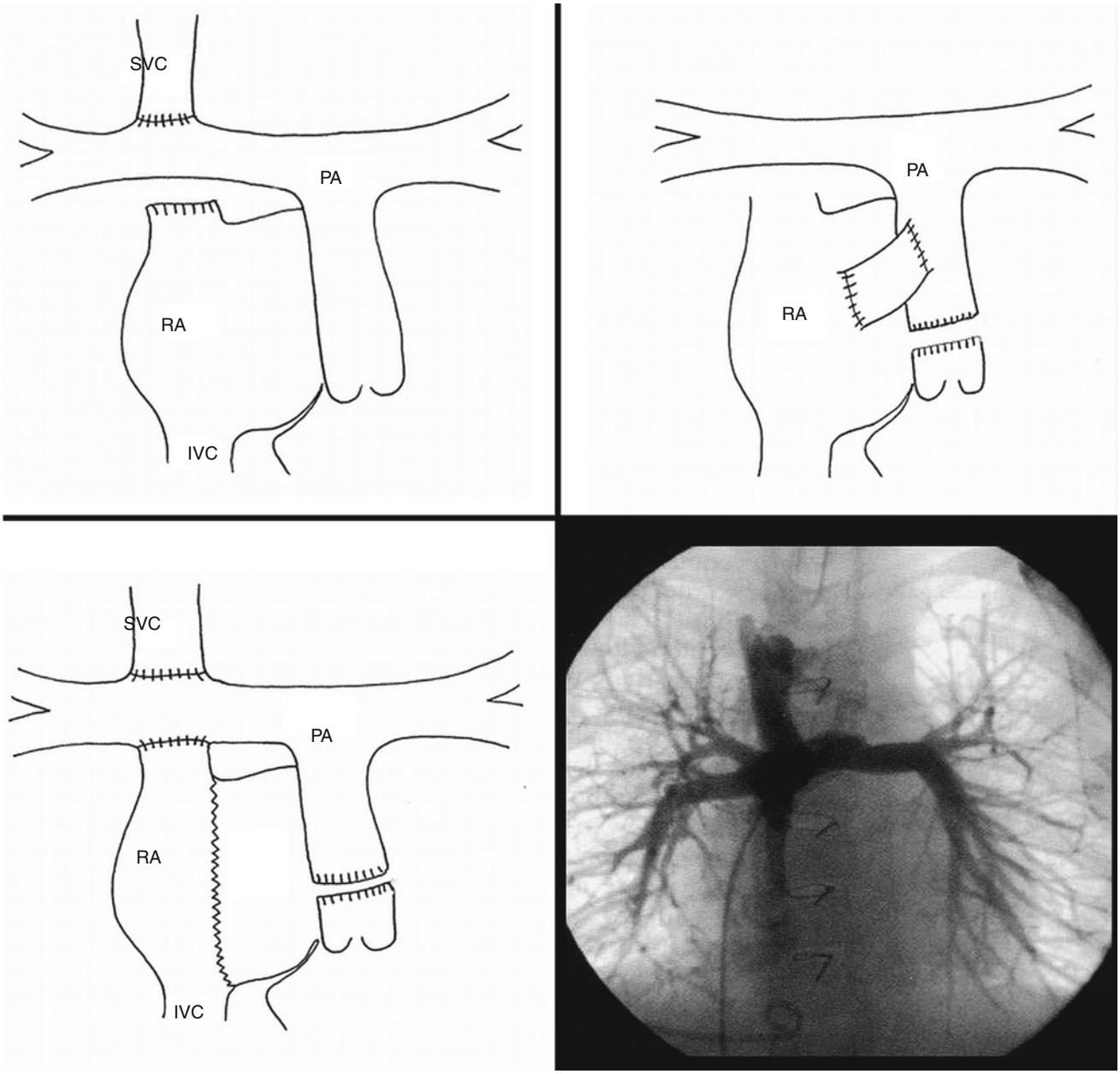

Fig. 20.8 Types of venous anastomoses and Fontan procedures. *Right lower panel* shows an angiogram of a patient with tricuspid atresia and total cavopulmonary connection (lateral tunnel). *IVC* inferior vena cava, *PA* pulmonary artery, *RA* right atrium, *SVC* superior vena cava

heart sound may be heard. The electrocardiogram may reveal intra-atrial reentry tachycardia, sinus node dysfunction, or axis deviation (type depending on the dominant ventricle). The chest X-ray and echocardiographic findings depend on the underlying anatomy. Cardiac MRI is useful for assessment of blood flow in the Fontan circuit.

The modified Fontan procedure with use of intracardiac or extracardiac conduit seems to result in better outcomes and improved survival compared to earlier versions of the technique [23]. However, the complexity of the underlying lesions along with the chronic passive pulmonary blood flow and low cardiac output leads to a number of late complications. Supraventricular tachycardias are an important cause of late morbidity and mortality and should be treated promptly and may require radio-frequency ablation [24]. Underlying hemodynamic lesions precipitating tachyarrhythmias should be excluded [4]. Sinus node dysfunction is common and may require atrial pacing if the atrioventricular node is intact. Intracardiac thrombus formation may occur due to sluggish blood flow in an enlarged right atrium or tachyarrhythmias and will require anticoagulation. Other complications include progressive atrioventricular valve

regurgitation, hepatic congestion, systemic ventricular dysfunction, and obstruction or leaks in the Fontan circuit. Protein losing enteropathy is an additional serious complication of the Fontan physiology with severe protein loss into the intestine due to high mesenteric venous pressure. Clinical manifestations include generalized edema, ascites, pleural effusions, and diarrhea. Reoperation should be considered in patients with failing Fontan circulation and heart transplantation may be an option in the instance of severe ventricular dysfunction or refractory protein-losing enteropathy [4].

Eisenmenger Syndrome

Eisenmenger syndrome is a pathophysiologic condition consisting of PAH with a reversed (right-to-left) central shunt and cyanosis. Patients with Eisenmenger physiology have an uncorrected large communication between the systemic and pulmonary circulations at the atrial, ventricular, or arterial level resulting to high pulmonary blood flow and progressive pulmonary vascular disease. A number of lesions can cause Eisenmenger syndrome, the commonest of which are AVSD, VSD, PDA, and ASD [4]. With large shunts at arterial or ventricular level, the syndrome is frequently established during the first 2 years of life, whereas with shunts at atrial level, pulmonary vascular disease develops later during adult life.

Children with Eisenmenger syndrome may be asymptomatic or present with mild exertional dyspnea. Cyanosis and impaired exercise capacity gradually become more prominent as pulmonary vascular resistance increases and bidirectional shunting develops. Adults with Eisenmenger syndrome may remain clinically stable due to chronic adaptation to their limited exercise capacity with lower activity levels. However, they may also present with symptoms related to complications of the syndrome, such as palpitations, chest pain, edema, syncope, or hemoptysis (discussed later). On clinical examination, there will be central cyanosis and clubbing. Signs of elevated pulmonary vascular pressure include right ventricular heave, loud P2, and occasionally a pulmonary ejection click. Murmurs of pulmonary or tricuspid regurgitation may also be present.

Pulse oximetry should be assessed at least annually in patients with Eisenmenger syndrome [4]. The electrocardiogram may reveal right-axis deviation with signs of right ventricular hypertrophy and right atrial enlargement. The chest X-ray often shows augmented proximal pulmonary arteries andcardiomegaly(rightheartenlargement).Echocardiography will identify the underlying lesion and site of the shunt and estimate pulmonary arterial pressure. MRI is useful for establishment of the diagnosis, while CT can be used to assess the lung parenchyma, aneurysms of the proximal pulmonary arteries, in situ thrombosis, and sites of pulmonary hemorrhage. Cardiac catheterization will establish the diagnosis of Eisenmenger syndrome with potential vasodilator testing or anatomic intervention. Routine laboratory testing is also necessary (see complications) and should include assessment of full blood count, liver function tests, urea, creatinine, electrolytes, uric acid, and iron status (transferrin saturation and ferritin).

Complications of the Eisenmenger syndrome and their management are outlined in Table 20.6. The general care of patients with Eisenmenger syndrome consists of preservation of fluid balance, management of secondary erythrocytosis, appropriate iron supplementation, and abolition of routine phlebotomies. Anticoagulation may be indicated, especially for patients with documented pulmonary thrombosis and embolic phenomena, in the absence of prior severe hemoptysis. Targeted pharmacological therapies have recently become available for patients with PAH and are recommended for symptomatic patients with Eisenmenger syndrome (NYHA functional class ≥ III) [25]. Reparative surgery is indicated only in patients with evidence of pulmonary arterial reactivity and/or at least 1.5:1 left-to-right shunting. Survival of patients with Eisenmenger syndrome has been reported to be 55 % to the age of 50 years, although these data are highly selective as they refer to patients who have survived to adulthood [26].

Issues in Adults with Congenital Heart Disease

Numerous issues should be considered when caring for adult patients with CHD, many of which are unique to this population.

Exercise Intolerance

Exercise intolerance is a common cause of suboptimal quality of life and a strong predictor of outcome in CHD [27]. It may result from a variety of cardiac mechanisms, such as persistent or residual defects, coronary anomalies, and arrhythmias or extracardiac factors including pulmonary parenchymal and vascular disease, cyanosis, and pulmonary arterial hypertension. Subjective evaluation of exercise intolerance using the NYHA classification appears to underestimate the severity of functional impairment in adult CHD [27]. Cardiopulmonary exercise testing is ideally suited for objective evaluation of the cardiovascular, respiratory, and muscular systems and is now becoming part of the routine clinical assessment of adult CHD patients [27]. Echocardiography and MRI are a fundamental part of the long-term follow-up of adult patients, with the latter being particularly suited for assessment of right ventricular function. The primary aim when managing an adult CHD patient with exercise intolerance is to identify and treat residual

Table 20.6 Complications of Eisenmenger syndrome

Complications	Management
Cardiac:	Heart failure: medical treatment (give diuretics with care to avoid dehydration)
Progressive heart failure	Arrhythmias: consider anticoagulation (atrial flutter/fibrillation), give antiarrhythmics (amiodarone), unknown role of implantable defibrillators in this setting
Arrhythmias (supraventricular or ventricular)	Endocarditis: meticulous prophylaxis
Angina	Paradoxical embolism: use air filters on IV lines/infusion pumps with bubble detector
Syncope	Angina: markedly enlarged pulmonary artery aneurysms may rarely cause chest pain by compression of the left main coronary artery
Endocarditis	
Paradoxical embolism	
Progressive pulmonary artery enlargement	
Hematologic:	Hyperviscosity: routine phlebotomy is contraindicated and restricted to patients with hemoglobin >20 g/dL and hematocrit >65 %, associated with severe hyperviscosity symptoms, in the absence of dehydration and iron deficiency
Erythrocytosis	Anemia and dehydration should be avoided and treated promptly
Hyperviscosity syndrome	Iron deficiency: treat with iron supplementation
Iron deficiency	
Neutropenia and thrombocytopenia	
Bleeding disorder	
Pulmonary:	Hemoptysis: chest X-ray and CT scan to determine extent of hemorrhage; embolization of culprit vessels
Hemoptysis	Thrombosis: consider anticoagulation if recurrent events, in the absence of dehydration and iron deficiency
Intrapulmonary bleeding	
Pulmonary artery thrombosis	
Central nervous system:	Stroke: inappropriate repeated phlebotomies increase risk
Stroke/TIA	Cerebral abscess: urgent contrast enhanced CT and blood cultures
Cerebral abscess	
Renal:	Avoid iatrogenic renal dysfunction
Proteinuria and hematuria	
Mildly elevated creatinine	
Progressive renal failure	
Metabolic:	Treat symptomatic hyperuricemia
Hyperuricemia and gout	
Hyperbilirubinemia and gallstones	
Nephrolithiasis	

hemodynamic lesions, especially those potentially amenable to surgical or percutaneous repair.

Arrhythmias

Atrial arrhythmias become more frequent with age, particularly in patients with atrial dilatation (e.g., previous ASD, Ebstein's anomaly) and those with history of surgery involving extensive atrial incisions (e.g., Mustard procedure). Ventricular arrhythmias can also occur in patients with previous ventriculotomy, such as repaired TOF, due to macro-reentrant circuits [28]. Sinus node dysfunction can be present at birth due to congenital abnormalities (e.g., sinus venosus ASD) or following cardiac surgery (e.g., Mustard, Senning, or Fontan procedures) (Fig. 20.9). Atrioventricular block can occur spontaneously in congenital defects with conduction system abnormalities (e.g., AVSD, ccTGA) or postoperatively.

Clinical manifestation of arrhythmias in patients with CHD ranges from absence of symptoms to rapid deterioration or sudden cardiac death. The onset of arrhythmia often reflects hemodynamic abnormalities which require prompt identification and correction with catheter ablation or surgical interventions. Patients with atrial tachycardia will often require long-term anticoagulation to prevent thrombus formation. Antiarrhythmic agents such as amiodarone and beta blockers are commonly used. Pacing for bradyarrhythmias can prove challenging in adults with CHD due to limited access to the heart (e.g., congenital venous anomalies, surgical conduits and baffles). Implantable cardioverter defibrillators (ICD) are increasingly implanted in CHD; indications include patients who survived a cardiac arrest, those with spontaneous ventricular tachycardia (VT) which could not be ablated, and in patients with inducible VT, concomitant unexplained syncope, and impaired right or left ventricular function [29].

Pregnancy

Preconceptual counseling should start in adolescence with timely pre-pregnancy assessment of cardiac status and close follow-up during pregnancy and postpartum. The risk of maternal death is less than 1 % for the majority of parturients with CHD. However, certain conditions are associated with significantly higher risk, such as PAH of any etiology, poor systemic ventricular function, and severe left heart obstructive lesions. Effective contraception is imperative in the latter cases although some women will decide to become pregnant

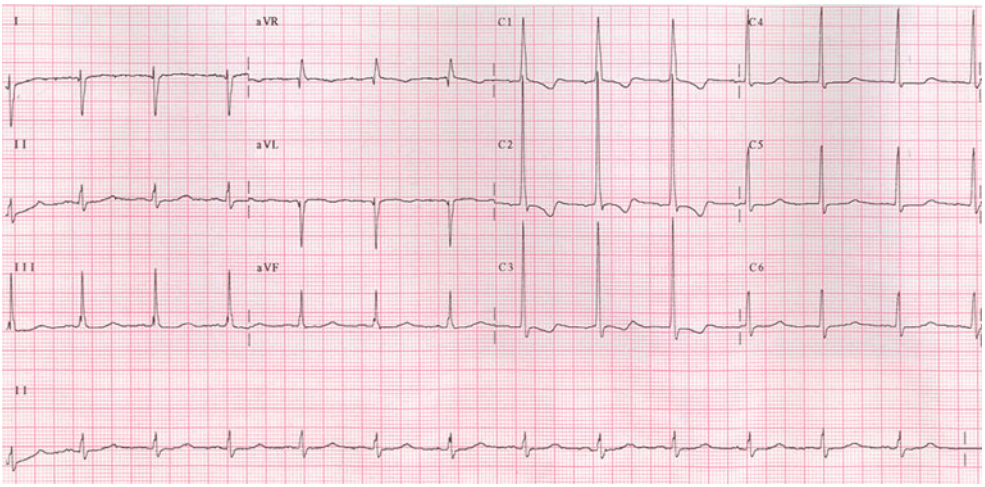

Fig. 20.9 Electrocardiogram of a patient with Mustard procedure for complete transposition of the great arteries. Sinus rhythm with low-amplitude P-waves. Maintenance of sinus rhythm is relatively uncommon in Mustard patients; common rhythms include junctional rhythm and intra-atrial reentrant tachycardia. Note typical findings of marked right-axis deviation and tall dominant R-waves in the anteroseptal chest leads, with T-wave inversion in V1 and V2, reflecting hypertrophy of the systemic right ventricle

regardless of the risks to their health. Minimization of risk by optimization of cardiac function before pregnancy is, thus, essential.

Patients with left-sided obstructive lesions should be identified and offered balloon valvotomy or surgery before pregnancy. Women with lesions associated with aortic root dilatation, such as BAV and aortic coarctation, require careful pregestation assessment of their aortic dimensions and, potentially, elective aortic root replacement. Likewise, women with repaired TOF, pulmonary regurgitation and right ventricular enlargement may be considered for pulmonary valve replacement before pregnancy [30]. Arrhythmia is a common complication during pregnancy; DC cardioversion is safe, whereas antiarrhythmic drug therapy should be used with care [31]. Anticoagulation is an additional issue, especially in parturients with mechanical valves. Low molecular weight heparin can be used during the first trimester, substituted by warfarin during the second and early third trimesters. Warfarin is again replaced by unfractioned heparin at approximately 35 weeks of gestation. Common indications for cardiac intervention during pregnancy include stenotic valve disease, acute dissection of the aorta, pacemaker insertion, and insertion of an inferior vena cava filter.

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Pathogenesis of Atherosclerosis

21

Prediman K. Shah

Introduction

Occlusive arterial conditions include atherosclerosis of native arteries, accelerated atherosclerosis involving vein grafts and arteries of transplanted organs, and restenosis following angioplasty and stenting. Atherosclerotic vascular disease is a leading cause of death and disability throughout the USA and other industrialized nations and consumes enormous fiscal resources. An improved understanding of the pathophysiology of atherosclerosis and thrombosis is likely to lead to improved prevention, diagnosis, and treatment of this common disorder.

Atherosclerosis involves the development of a plaque composed of variable amounts of apo B-100-containing lipoproteins, extracellular matrix (collagen, proteoglycans, glycosaminoglycans), calcium, vascular smooth muscle cells, inflammatory and immune cells (chiefly monocyte-derived macrophages, T lymphocytes, mast cells, dendritic cells), and new blood vessels (angiogenesis) (Fig. 21.1 and Table 21.1). Atherosclerosis represents a chronic inflammatory response to vascular injury triggered by a variety of agents that injure endothelium and promote lipoprotein infiltration, retention, and modification, combined with leukocyte entry, retention, proliferation, and activation [1]. One of the key early steps in atherogenesis is the trapping of apo B-100-containing lipoproteins within the subendothelial matrix due to interaction with proteoglycans that is initially mediated through a charge-based interaction and later from enzymatic modification induced by macrophage-derived enzymes [2–4].

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Sites of Predilection for Atherosclerosis

Atherosclerosis tends to occur at arterial sites characterized by low and oscillatory shear stress, evidence of endothelial activation with expression of proinflammatory genes such as leukocyte adhesion molecules, and increased influx and/or prolonged retention of lipoproteins [5]. Specific arterial sites, such as branches, bifurcations, and curvatures, cause disturbed flow with decreases in shear stress and increased turbulence. Changes in flow alter the expression of shear stress-responsive genes such as intracellular adhesion molecule-1, platelet-derived growth factor B chain, and tissue factor in endothelial cells [6–9]. Recent studies have suggested that athero-promoting flow patterns activate inflammatory and prothrombotic endothelial phenotype by inhibiting a key flow-sensitive transcription factor KLF2 (Kruppel-like factor 2) [10, 11] perhaps accounting for the lipid-rich inflamed phenotype of such plaques in animal models [12, 13]. Proinflammatory priming of atherosclerosis-prone vascular sites in mice is noted even before hyperlipidemia or atherosclerosis is induced [14]. Rolling and adherence of inflammatory cells (monocytes and T cells) occur at these sites as a result of the upregulation of adhesion molecules on both the endothelium and the leukocytes. At these sites, specific molecules form on the endothelium that are responsible for the adherence, migration, and accumulation of monocytes and T cells. Such adhesion molecules, which act as receptors for glycoconjugates and integrins present on monocytes and T cells, include several selectins, intercellular adhesion molecules, and vascular cell adhesion molecules [6–9]. Molecules associated with the migration of leukocytes across the endothelium, such as platelet-endothelial-cell adhesion molecules act in conjunction with chemoattractant molecules generated by the endothelium, smooth muscle, and monocytes – such as monocyte chemotactic protein-1 (MCP-1), osteopontin, and modified low-density lipoprotein (LDL) – to attract monocytes and T cells into the artery [5–9]. Chemokines may be involved in the chemotaxis and accumulation of macrophages in fatty streaks [15].

C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_21, © Springer Science+Business Media New York 2013

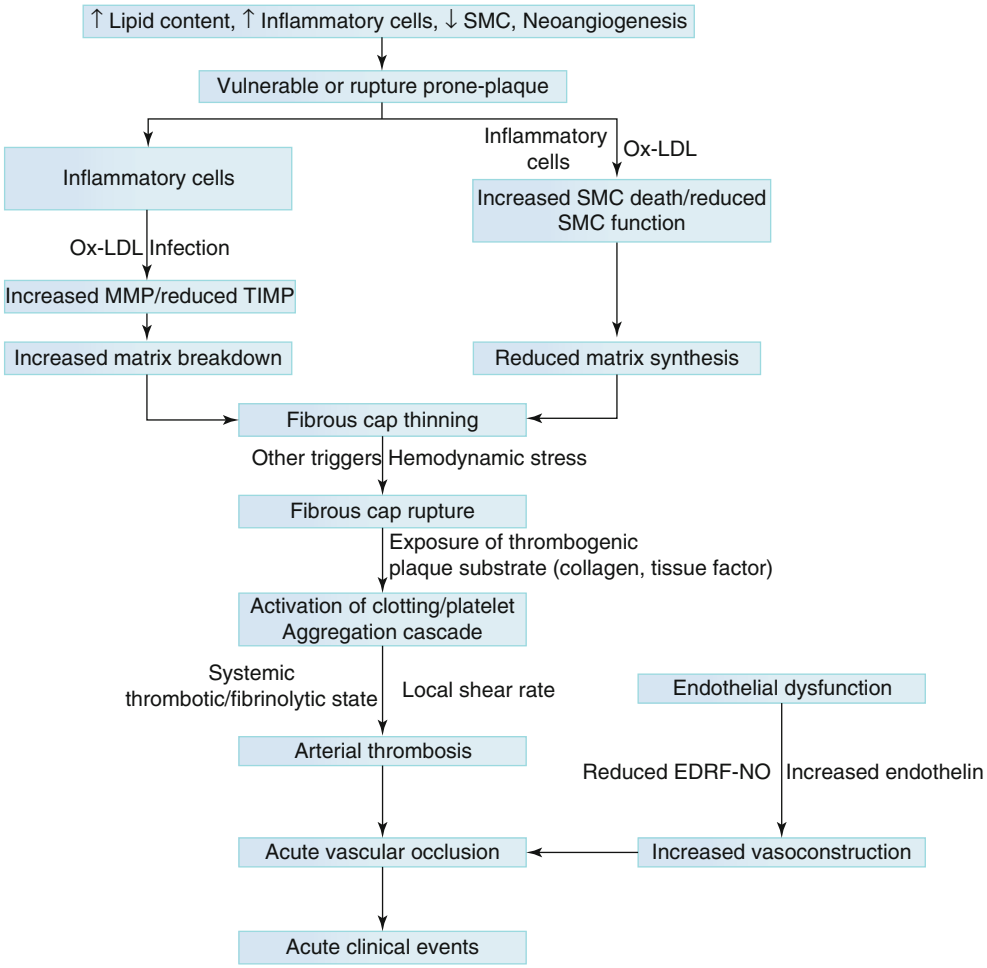

Fig. 21.1 Schematic showing pathophysiology of plaque disruption and thrombosis

Table 21.1 Key steps in atherogenesis

Endothelial injury with increased infiltration of atherogenic lipoproteins at sites of low or oscillating shear stress
Subendothelial retention and modification of atherogenic lipoproteins (LULIVLDL), LDL oxidation, glycation, and aggregation
Endothelial activation with increased mononuclear leukocyte (inflammatory cell) adhesion, chemotaxis, and subendothelial recruitment
Subendothelial inflammatory cell activation with lipid ingestion through monocyte scavenger receptor expression resulting in foam cell formation
Inflammatory cell (monocyte/macrophage) proliferation
Migration to intima and proliferation of medial/adventitial smooth muscle cells/myofibroblasts in response to growth factors released by activated monocytes with matrix production and formation of fibrous plaque and fibrous cap
Abluminal plaque growth with positive (outward) arterial adventitial remodeling preserving lumen size in early stages; later plaque growth or negative remodeling results in luminal narrowing
Neoangiogenesis due to angiogenic stimuli produced by macrophages and other arterial wall cells (VEGF, IL-8)
Plaque hemorrhage and expansion of lipid core
Death of foam cells by necrosis/apoptosis leading to necrotic lipid core formation
Rupture of fibrous cap or endothelial erosion, exposure of thrombogenic substrate, and arterial thrombosis

Activation of monocytes and T cells leads to upregulation of receptors on their surfaces, such as the mucin-like molecules that bind selectins, integrins that bind adhesion molecules of the immunoglobulin superfamily, and receptors that bind chemoattractant molecules. These ligand-receptor interactions further activate mononuclear cells, induce cell proliferation, and help define and localize the inflammatory response at the site of lesions.

In hyperlipidemic apolipoprotein E (knockout mice, intercellular adhesion molecule-1 (ICAM-1) is constitutively increased at lesion-prone sites long before the lesions develop [8]. In contrast, vascular cell adhesion molecule-1 (VCAM-1) is absent in normal mice but is present at the same sites as ICAM-1 in mice with apolipoprotein E deficiency [8]. Mice that are completely deficient in ICAM-1, P-selectin, CD18, or combinations of these molecules, have reduced atherosclerosis in response to high-fat diet. Proteolytic enzymes may cleave adhesion molecules such that in situations of chronic inflammation, it may be possible to measure the "shed" molecules in plasma as markers of a sustained inflammatory response to help identify patients at risk for atherosclerosis or other inflammatory diseases [16, 17].

Table 21.2 Endothelial dysfunction in atherosclerosis: key phenotype

Reduced vasodilator and increased vasoconstrictor capacity
Enhanced oxidant stress with increased inactivation of nitric oxide
Increased expression of endothelin
Enhanced leukocyte (inflammatory cell) adhesion and recruitment
Increased adhesion molecule expression (ICAM, VCAM-1)
Increased chemotactic molecule expression (MCP-1, IL-g, osteopontin)
Increased prothrombotic and reduced fibrinolytic phenotype
Increased tissue factor expression and reduced nitric oxide bioavailability
Increased plasminogen activator inhibitor (PAI-1) expression
Increased growth-promoting phenotype
Reduced nitric oxide bioavailability
Increased endothelin expression

Table 21.3 Factors contributing to endothelial dysfunction

Dyslipidemia and atherogenic lipoprotein modification
Increased LDL, VLDL, LP(a)
LDL modification (oxidation, glycation)
Reduced HDL or dysfunctional HDL
Increased oxidant stress
Hypertension, excess angiotensin II, diabetes, smoking
Obesity and insulin resistance
Estrogen deficiency
Elevated homocysteine levels
Advancing age
Genetic factors
Infections

Endothelial Activation/Dysfunction and Inflammation in Atherogenesis

Several studies have suggested that one of the earliest steps in atherogenesis is endothelial activation or injury/dysfunction with infiltration and retention and modification of atherogenic lipoproteins (predominantly the apo B-100-containing lipoproteins) in the subendothelial space [18–22] (Tables 21.2 and 21.3).

Endothelial activation and endothelial injury/dysfunction predisposing to atherosclerosis is caused by risk factors such as elevated and modified atherogenic lipoproteins (apo B-100-containing lipoproteins such as LDL/VLDL/IDL cholesterol); reduced HDL cholesterol; oxidant stress caused by cigarette smoking, hypertension, and diabetic mellitus; genetic alterations; elevated plasma homocysteine concentrations; infectious microorganisms such as herpes viruses or *Chlamydia pneumoniae*; estrogen deficiency; angiotensin II signaling; and advancing age [20]. Endothelial activation and injury/dysfunction may manifest in (a) increased adhesiveness of the endothelium to inflammatory cells (leukocytes) or platelets, (b) increased vascular permeability, (c) change from an anticoagulant to a procoagulant phenotype, (d) change from a vasodilator to a vasoconstrictor phenotype, or (e) change from a growth-inhibiting to a growth-promoting phenotype through elaboration of cytokines. Abnormal vasomotor function has been one of the most well-studied manifestations of endothelial dysfunction in subjects with either established atherosclerosis or in those with risk factors for atherosclerosis. Normal healthy endothelium produces nitric oxide from arginine through the action of a family of enzymes known as nitric oxide synthases [20]. Nitric oxide acts as a local vasodilator by increasing smooth muscle cell cyclic guanosine monophosphate (GMP) levels while at the same time inhibiting platelet aggregation and smooth muscle cell proliferation [20]. In the presence of risk factors, a reduced vasodilator response to endothelium-dependent vasodilator stimuli or even paradoxical vasoconstrictor response to such stimuli have been observed in large vessels as well as in the microcirculation, even in absence of structural abnormalities in the vessel wall [20]. These abnormal vasomotor responses have been attributed to reduced bioavailability of endothelium-derived relaxing factor(s), specifically nitric oxide, due to rapid inactivation of nitric oxide by oxidant stress or excess generation of asymmetric dimethylarginine and/or increased production of vasoconstrictors such as endothelin [20].

One of the major contributors to endothelial injury is LDL cholesterol modified by processes such as oxidation, glycation (in diabetes), aggregation, association with proteoglycans, or incorporation into immune complexes [20, 23]. Oxidized LDL has been shown to be present in the atherosclerotic lesions of both experimental animals and humans [24]. Subendothelial retention of LDL particles results in progressive oxidation and its subsequent internalization by macrophages through the scavenger receptors. The internalization leads to the formation of lipid peroxides and facilitates the accumulation of cholesterol esters, eventually resulting in the formation of foam cells. Once modified and taken up by macrophages, LDL activates the foam cells. In addition to its ability to injure these cells, modified LDL is chemotactic for other monocytes and can upregulate the expression of genes for macrophage colony-stimulating factor (M-CSF) and monocyte chemotactic protein derived from endothelial cells [25, 26]. Thus, it may help expand the inflammatory response by stimulating the replication of monocyte-derived macrophages and the entry of new monocytes into lesions. Continued inflammatory response stimulates migration and proliferation of smooth muscle cells that accumulate within the areas of inflammation to form an intermediate fibroproliferative lesion resulting in thickening of the artery wall.

The inflammatory and immune response in atherosclerosis consists of accumulation of monocyte-derived macrophages and specific subtypes of T lymphocytes at every

stage of the disease [27–30]. The fatty streak, the earliest type of lesion, common in infants and young children, consists of monocyte-derived macrophages, macrophage-derived foam cells, and T lymphocytes. The critical role of the macrophage in atherogenesis is supported by the drastic reduction of atherosclerosis when M-CSF null genotype is introduced in murine models of severe dyslipidemia induced by diet or genetic manipulation [31].

Continued inflammation results in increased numbers of macrophages and lymphocytes, which both emigrate from the blood and multiply within the lesion. Activation of these cells leads to the release of proteolytic enzymes, cytokines, chemokines, and growth factors, which can induce further damage and eventually lead to focal necrosis. Necrosis and/or apoptosis of foam cells results in the formation of the necrotic lipid core in the plaque. Thus, cycles of accumulation of mononuclear cells, migration and proliferation of smooth muscle cells, and formation of fibrous tissue lead to further enlargement and restructuring of the lesion, so that it becomes covered by a fibrous cap that overlies a core of lipid and necrotic tissue resulting in the formation of an advanced and complicated atherosclerotic plaque.

The inflammatory response itself can influence lipoprotein transfer within the vessel wall. Proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and M-CSF, increase binding of LDL to endothelium and smooth muscle and increase the transcription of the LDL receptor gene [1]. After binding to scavenger receptors in vitro, modified LDL initiates a series of intracellular events that include the induction of proteases and inflammatory cytokines [1]. Thus, a vicious circle of inflammation, modification of lipoproteins, and further inflammation can be maintained in the artery by the presence of these modified lipoproteins.

Monocyte-derived macrophages are present in various stages of atherosclerosis and act as scavenging and antigen-presenting cells. They produce cytokines, chemokines, growth-regulating molecules, tissue factor, metalloproteinases, and other hydrolytic enzymes. The continuing entry, survival, and replication of monocytes/macrophages in lesions depend in part on growth factors, such as M-CSF and granulocyte-macrophage colony-stimulating factor (GM-CSF), whereas IL-2 is involved in a similar manner for T lymphocytes. Recent experimental observations suggest that in and out trafficking of macrophages within the atherosclerotic vascular wall may be regulated by the microenvironment within the lesion with ingress and retention being promoted by a proinflammatory milieu related to oxidized lipids, whereas egress via the lumen or via transformation into migratory dendritic cells and subsequent immigration to regional lymph nodes is associated with reduced proinflammatory lipids in the lesion, an environment promoted by high HDL levels favoring lesion regression [32]. Dendritic cells have been identified within the subendothelium and the adventitia of normal blood vessels. An increase in the number and activity of subendothelial dendritic cells has been observed in the atherosclerotic lesion raising the possibility that dendritic cells may be involved in the pathophysiology of atherosclerosis [33].

Activated macrophages as well as lesional smooth muscle cells express class II histocompatibility antigens such as HLA-DR that allow them to present antigens to T lymphocytes [1, 27–30]. Atherosclerotic lesions contain both CD4 and CD8 T cells implicating the immune system in atherogenesis [27–30]. T cell activation, following antigen processing, results in production of various cytokines, such as interferon-γ (INF-γ) and TNF-α and TNF-β, which can further enhance the inflammatory response [1]. Antigens presented include oxidized LDL and heat shock protein 60 which may participate in the immune response in atherosclerosis [5, 27–30].

Macrophages, T cells, and endothelial and smooth muscle cells in the atherosclerotic lesions express CD40 ligand and its receptor, which may play a role in atherogenesis by regulating the function of inflammatory cells [34, 35]. The antiatherogenic effects of CD40-blocking antibodies in the murine model of atherosclerosis suggest that CD40-mediated signaling may play an important role in atherogenesis [36].

Phenotypic Heterogeneity of Monocytes/Macrophage

Recently, it has been shown that a considerable degree of monocyte/macrophage heterogeneity exists when various macrophage markers are used to identify macrophage subsets [37, 38]. Broadly, this concept recognizes M1 macrophages (classically activated) that have largely proinflammatory effects with a unique gene expression profile as compared to M2 macrophages (alternatively activated) that are more likely to be involved in healing and possibly inflammation resolution with their own unique gene expression profile [37, 38]. The precise basis and mechanisms for macrophage polarization into various subsets and the pathophysiologic significance of the monocyte/macrophage heterogeneity remains to be determined although recent experimental studies have suggested that atheroprotective lipoproteins (HDL) modulate the circulating or lesional monocyte macrophages into a dominantly M2 phenotype [39, 40].

Epherocytosis by Macrophages

Macrophages in atherosclerosis undergo apoptosis at various stages of evolution of the atherosclerotic lesion, and the apoptotic macrophages are rapidly cleared by another subset of macrophages using various receptors such as MERTEK in

a process called epherocytosis, thereby preventing post-apoptotic necrosis and consequent activation of inflammatory pathways [41–43]. Early in the course of plaque formation, epherocytosis is efficient and prevents necrotic debris accumulation; however, in advanced lesions, epherocytosis is impaired, contributing to necrotic debris accumulation and further activation of the inflammatory cascade; in fact deletion of MERTEK receptor gene has been shown to expand the necrotic lipid-rich core in animal models of atherosclerosis [41–43]. Similarly, partial deletion of NPC1 gene involved in free cholesterol-induced macrophage apoptosis is associated with more lesion cellularity and less necrotic core formation in animal models [44]. These data suggest that certain macrophage subsets may actually play a favorable role in atherosclerosis by participating in epherocytosis [41].

Cholesterol Crystals and NLRP Inflammasome Activation

Cholesterol crystals, commonly observed in experimental as well as human atherosclerotic lesions, may play an important role in plaque inflammation [45–47]. Using experimental models, it has recently been shown that following macrophage activation by a first signal such as might be delivered by oxidized LDL and toll-like receptor-mediated signaling, cholesterol crystal uptake induces a proinflammatory cytokine activation leading to secretion of active interleukin-1 beta which plays a pro-atherogenic role [45–47]. The activation of the inflammatory cytokine secretion by ingested cholesterol crystals has been shown to involve the NLRP3 inflammasome complex analogous to urate crystal-induced inflammatory response [45–47]. Abela and colleagues have also argued that the sharp and pointed needlelike tips of cholesterol crystals in human plaques may penetrate the overlying fibrous cap, leading to its rupture or disruption with subsequent development of thrombosis [47].

Platelet adhesion and mural thrombosis are ubiquitous in the initiation and generation of the lesions of atherosclerosis in animals and humans [1]. Platelets can adhere to dysfunctional endothelium, exposed collagen, and macrophages. When activated, platelets release their granules, which contain cytokines and growth factors that, together with thrombin, may contribute to the migration and proliferation of smooth muscle cells and monocytes. Activation of platelets leads to the formation of free arachidonic acid, which can be transformed into prostaglandins such as thromboxane A2, one of the most potent vasoconstricting and platelet-aggregating substances known, or into leukotrienes, which can amplify the inflammatory response.

Angiotensin II, a potent vasoconstrictor, may also contribute to atherogenesis by stimulating the growth of smooth muscle, increasing oxidant stress, inducing LDL oxidation, and promoting an inflammatory response [1, 36, 48, 49].

Elevated plasma homocysteine concentrations, resulting from enzymatic defects or vitamin deficiency, may facilitate atherothrombosis by inducing endothelial dysfunction with reduction in vasodilator capacity and enhanced prothrombotic phenotype and smooth muscle replication [50–52]. Hyperhomocysteinemia is associated with an increased risk of atherosclerosis of the coronary, peripheral, and cerebral arteries [50–52]. However, several clinical trials testing the effects of reduction of plasma homocysteine levels by vitamins such as folic acid, B6, and B12 have been negative [53].

Infection: Oral and Gut Microflora in Atherosclerosis

A number of stimuli maybe responsible for provoking and sustaining a chronic inflammatory response in the vessel wall in atherosclerosis. Among the key potential culprits are the modified lipoproteins, cholesterol crystals, and possibly infectious agents. Oxidatively modified lipoproteins can induce a variety of proinflammatory genes in the vessel wall that are responsible for recruiting and activating inflammatory cells such as ICAM- and VCAM-type adhesion molecules, chemotactic cytokines such as MCP-1 and IL-8, and colony-stimulating factors such as M-CSF. In addition to modified lipoproteins, it has been suggested that arterial wall infections with organisms such as *Chlamydia pneumoniae* and CMV/herpes virus as well as remote infections such as chronic bronchitis, gingivitis, and *Helicobacter pylori* infection may affect inflammation, thereby contributing to atherogenesis and/or plaque disruption and thrombosis in the presence of preexisting atherosclerosis [54–61]. However, recent large-scale clinical trials have failed to demonstrate any clinical benefit of using antibiotics targeting *Chlamydia pneumoniae*, raising questions and serious doubts about a causal link between infection and atherothrombosis [62–65].

More recently, oral and gut microflora have also been implicated in the pathogenesis of human and experimental atherosclerosis [66, 67]. Using 454 pyrosequencing of 16S rRNA genes to determine the microbial composition of atherosclerotic plaques, Omry et al. identified Chryseomonas in all atherosclerotic plaque samples and Veillonella and Streptococcus in the majority [66]. Interestingly, the combined abundances of Veillonella and Streptococcus in atherosclerotic plaques correlated with their abundance in the oral cavity [66]. Moreover, several bacterial taxa in the oral cavity and the gut correlated with plasma cholesterol levels, and the overall results of the study suggest that bacteria from the oral cavity, and perhaps even the gut, may correlate with disease markers of atherosclerosis [66]. Although the precise mechanisms by which specific patterns of gut microflora contribute

to pathogenesis of atherosclerosis, it has been suggested that by-products of phosphatidylcholine metabolism generated by gut microflora (such as choline) and subsequent hepatic metabolism of absorbed products (such as trimethylamine N-oxide) may lead to enhanced foam cell formation by increasing scavenger receptors on monocytes [67].

Innate Immunity in Atherosclerosis

Toll-like receptors (TLRs) are a family of transmembrane receptors that serve as signaling receptors in the innate immune system; their ligation by exogenous and possibly endogenous ligands triggers a proinflammatory signaling cascade in various cells linking innate immunity to inflammation [68, 69]. Recent studies have shown that TLRs are expressed in murine and human atherosclerotic lesions and that hyperlipidemia induces proinflammatory signaling, in part through these receptors and their downstream adaptor molecules such as MyD88 (myeloid differentiation factor) contributing to vascular inflammation, neointimal hyperplasia, and atherosclerosis in murine models [69–71].

Neoangiogenesis in Atherosclerosis

Neovascularization supports chronic inflammation and fibroproliferation, processes that are involved in atherogenesis. Several studies have demonstrated increased neoangiogenesis in atherosclerotic lesions, and hypercholesterolemia has been shown to increase adventitial neovascularity in porcine arteries before the development of an atherosclerotic lesion [72, 73]. Proinflammatory chemokines such as IL-8 and other angiogenic growth factors such as vascular endothelial growth factor (VEGF) have been demonstrated in atherosclerotic lesions where they could contribute to angiogenesis. Angiogenesis may contribute to plaque progression by providing a source of intraplaque hemorrhage which in turn may provide red cell membrane-derived cholesterol contributing to the expansion of the necrotic lipid core. In addition, neovascular channels may also provide a source of inflammatory cells into the vessel wall; thus, angiogenesis and inflammation appear to be linked pathophysiologic processes [74]. Perivascular accumulation of mast cells has been identified as a potential contributor to adventitial neovascularity, capillary leaks, and intraplaque hemorrhage; furthermore, substance P derived from local nerve endings in the perivascular space has been suggested as a potential trigger for mast cell activation and degranulation [75, 76].

Recently, the ability of macrophages to undergo transdifferentiation into functional endothelial cells has been demonstrated, suggesting a more direct link between inflammation and angiogenesis [77]. Recent preliminary data demonstrating an inhibitory effect of angiostatin in murine models of atherosclerosis suggests the potential pro-atherogenic role for angiogenesis [78].

Table 21.4 Determinants of plaque vulnerability

Large lipid core
Thin fibrous cap
Increased number and activity of inflammatory cells (macrophages, T cells, mast cells)
Reduced collagen and smooth muscle cell content
Increased neovascularity and intraplaque hemorrhage
Outward adventitial remodeling

Plaque Rupture, Plaque Erosion, and Thrombosis

Thrombosis complicating atherosclerosis is the mechanism by which atherosclerosis leads to acute ischemic syndromes of unstable angina, non-Q-wave and Q-wave myocardial infarction, and many cases of sudden ischemic cardiac death [79–83] (Table 21.4). In most cases, coronary thrombosis occurs as a result of uneven thinning and rupture of the fibrous cap, often at the shoulders of a lipid-rich lesion where macrophages and T cells enter, accumulate, and are activated and where apoptosis may occur [79–83]. Thinning of the fibrous cap may result from elaboration of matrix-degrading metalloproteinases (MMPs) such as collagenases (MMP-1, MMP-13), gelatinases (MMP-2, MMP-9), elastases (MMP-12), and stromelysins (MMP-3) and/or other proteases such as cathepsins, by inflammatory cells, chiefly macrophages [79–83]. These proteases may be induced or activated by oxidized LDL, cell-to-cell interaction between macrophages and activated T cells, CD40 ligation, mast cell-derived proteases, oxidant radicals, matrix proteins such as tenascin-C, and infectious agents [79–83]. Thinning may also result from increased smooth muscle cell death by apoptosis/necrosis and consequent reduced matrix production; increased smooth muscle cell death may result from oxidized LDL, cleavage products of tenascin-C, or direct contact with plaque-infiltrating CD4+ T cells expressing TRAIL (TNF-related apoptosis-inducing ligand) [84–87].

Inflammatory cells, specifically the macrophages, are also the main source of tissue factor in the atherosclerotic plaque [88]. Tissue factor, when exposed to circulating blood, interacts with activated factor VII to generate activated factor X; activated factor X in turn cleaves thrombin from prothrombin. Thrombin is involved in recruiting and activating platelets as well as the clotting cascade, thereby initiating thrombus formation. Tissue factor expression is increased in atherosclerotic plaques, particularly in unstable coronary syndromes [88]. The lipid core of the atheromatous

lesion is heavily impregnated with tissue factor derived from dead (possibly apoptotic) macrophages and foam cells, accounting for its high thrombogenicity. Macrophage tissue factor expression may be induced by a variety of signals in the atherosclerotic plaque, including various cytokines, infectious agents, and oxidized lipoproteins. Thrombosis may also occur on a proteoglycan-rich matrix without a large lipid core, and in such cases, evidence of superficial endothelial erosion is found [89]. This plaque erosion may account for thrombosis in a relatively higher proportion of young victims of sudden death, particularly in women and smokers [90]. The precise molecular basis for these plaque erosions is not clear although endothelial desquamation through activation of basement membrane-degrading MMP may be involved [83].

Plaques with a large core, activated inflammatory infiltration, and a thinned fibrous cap are therefore considered vulnerable or unstable plaques. Their identification may be particularly difficult because they may not produce symptoms because of lack of flow-limiting stenoses and may thus escape detection by stress testing and even angiography. Inflammation in atherosclerosis may be accompanied by elevation of circulating proinflammatory markers such as C-reactive protein (CRP), interleukin-6, serum amyloid A, and a variety of soluble leukocyte adhesion molecules [90–93]. Elevated CRP levels have been shown to predict an increased risk of adverse cardiac events in patients with symptomatic vascular disease as well as in asymptomatic subjects at risk for vascular disease [90].

Conclusions

Atherosclerosis is a complex disease process that involves lipoprotein influx and retention, lipoprotein modification, increased prooxidant stress, and inflammatory, angiogenic, and fibroproliferative responses intermingled with extracellular matrix and lipid accumulation, resulting in the formation of an atherosclerotic plaque. Endothelial activation/dysfunction is common in atherosclerosis and often manifests as a reduced vasodilator or enhanced vasoconstrictor phenotype that contributes to luminal compromise. Thrombosis resulting from plaque rupture or superficial erosion complicates atherosclerosis, often resulting in abrupt luminal occlusion with resultant acute ischemic syndromes (Fig. 21.1). An improved understanding of the pathophysiology of atherosclerosis is providing novel directions for its prevention and treatment. In particular, the recognition of the important role of inflammation could lead to novel therapeutic interventions directed at selective inhibition of inflammatory cascade in the vessel wall. Targeting inflammatory triggers such as lipoproteins, angiotensin II, and possible infectious agents is likely to lead to improved outcomes in patients with atherosclerosis.

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Coronary Blood Flow and Myocardial Ischemia

22

Brian R. Weil and John M. Canty Jr.

Introduction

Because of the limited anaerobic capacity of the myocardium, the heart relies on a continuous supply of oxygen from the coronary circulation to maintain contractile activity. As a result, cardiac function is dependent on the maintenance of an adequate balance between oxygen supply and demand. Although several mechanisms exist to match coronary blood flow to the metabolic demands of the heart, disruption of this balance by diseases affecting coronary flow can immediately precipitate ischemia-induced contractile dysfunction, resulting in hypotension and further myocardial ischemia. The aim of this chapter is to summarize the mechanisms underlying coronary blood flow regulation and discuss the metabolic and functional consequences of acute and chronic myocardial ischemia.

Control of Coronary Blood Flow

A unique characteristic of the coronary circulation is the marked variation in perfusion throughout the phases of the cardiac cycle, such that arterial inflow is out of phase with venous outflow (Fig. 22.1; [1]). In contrast to the pattern of blood flow through arteries in other tissues, coronary arterial inflow is highest during diastole. This flow pattern is the result of compressive forces exerted by the contracting myocardium during systole, which lead to an increase in tissue pressure, redistribution of blood flow from the subendocardium to the subepicardium, and the obstruction of arterial inflow. These contraction-mediated compressive forces also reduce the diameter of the intramyocardial microcirculation (arterioles, capillaries, and venules) and increase coronary venous outflow, which peaks during this phase of the cardiac cycle. Upon relaxation of the heart during diastole, decompression of the coronary vasculature results in a decline in coronary venous outflow and an increase in arterial inflow with a transmural gradient favoring perfusion of the subendocardium.

Determinants of Myocardial Oxygen Demand

As an adaptation to the high oxygen demands of the heart, myocardial oxygen extraction from the coronary circulation is near-maximal at rest, approximating 75 % of arterial oxygen content [2]. As a result, elevations in myocardial oxygen consumption must be met by proportional increases in coronary flow to maintain sufficient oxygen delivery [3]. Because the myocardial oxygen requirements for maintaining basal

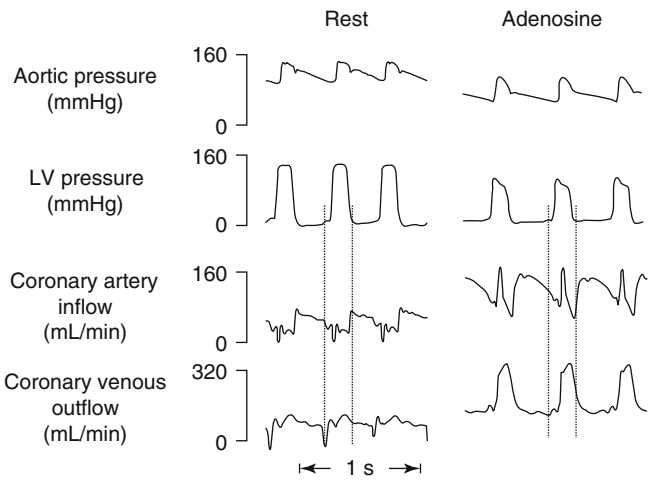

Fig. 22.1 Coronary arterial inflow and venous outflow vary throughout the cardiac cycle. Systolic contraction (*dotted vertical lines*) compresses the coronary microcirculation, thereby impeding coronary arterial inflow and increasing coronary venous outflow. During diastole, decompression of the coronary vasculature allows arterial inflow to increase. Administration of the vasodilator adenosine amplifies the phasic variations in venous outflow (Modified from Canty and Brooks [1]. With permission from The American Physiological Society)

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_22,

metabolism are low (~15 % of resting oxygen consumption), the majority of oxygen consumed by the heart is used to support contraction. Consequently, the major determinants of myocardial oxygen consumption are heart rate, systolic pressure (myocardial wall stress), and left ventricular contractility. A twofold increase in any of these individual factors requires an ~50 % increase in coronary blood flow; thus, the ability to increase coronary flow to meet the oxygen demands of the heart is critical to maintaining cardiac contractile function.

Coronary Autoregulation

Under normal hemodynamic conditions, resting coronary blood flow averages 0.7–1.0 mL/min/g and can increase between four and fivefold during vasodilation [4]. Through a process termed *autoregulation*, coronary blood flow is maintained over a wide range of coronary artery pressures when the determinants of myocardial oxygen consumption are kept constant, thereby matching myocardial oxygen supply with oxygen demand (Fig. 22.2; [6]). This phenomenon occurs via alterations in coronary vascular resistance that are mediated by a number of factors, including the accumulation of local metabolites, endothelium-derived substances, autonomic nervous system innervation, and circulating paracrine influences (discussed below). However, the dilatory capacity of coronary resistance arteries is exhausted as coronary pressure drops below the lower autoregulatory limit. At this point, coronary blood flow becomes pressure-dependent and further reductions in pressure will likely lead to the onset of ischemia.

The lower autoregulatory limit has been estimated from preclinical and clinical studies showing that coronary

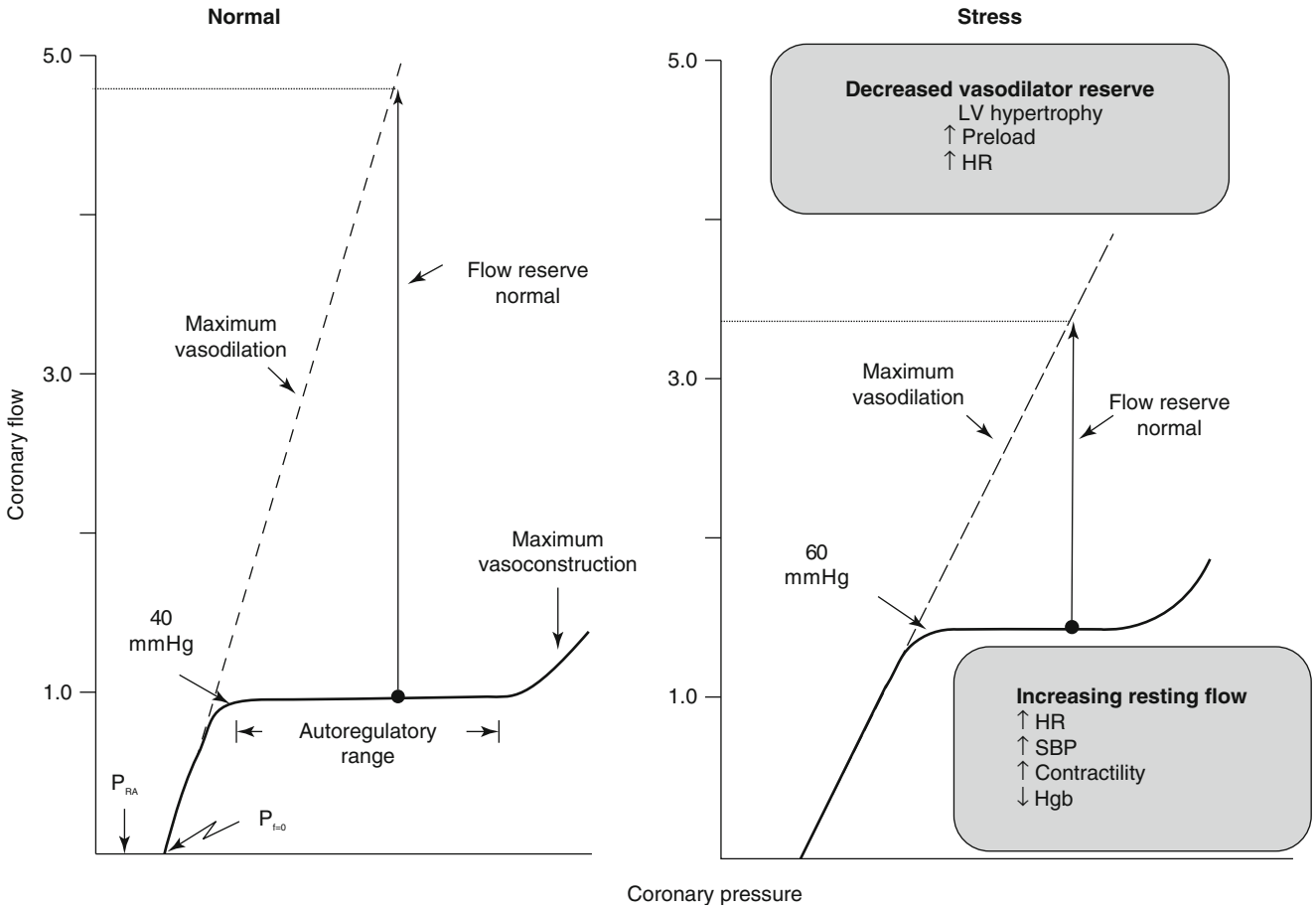

Fig. 22.2 Coronary autoregulation at rest and during metabolic stress. In the normal heart (*left panel*), myocardial oxygen supply and demand remain matched over a wide range of coronary pressures through autoregulatory changes in coronary blood flow (*heavy lines*). Subendocardial vasodilator reserve is exhausted at a coronary pressure of ~40 mmHg; as pressure falls below this lower autoregulatory limit, coronary flow can no longer be maintained, resulting in the onset of myocardial ischemia. If pressure continues to drop, the cessation of coronary flow occurs at a pressure slightly higher than right atrial pressure (P_{RA}) known as zero flow pressure ($P_{f=0}$). During maximum vasodilation, coronary blood flow can increase to values approximately five times above resting flow (*vertical black lines*), although this response is reduced in the presence of factors that increase coronary resistance or reduce the time available for perfusion. In addition, the elevation in resting flow to meet the increased myocardial oxygen demands associated with metabolic stress (i.e., tachycardia) reduces coronary flow reserve and promotes the development of ischemia at higher coronary pressures (*right panel*) (Modified from Canty [5]. With permission from Elsevier)

blood flow cannot be maintained at coronary pressures below 40 mmHg [6]. This lower autoregulatory pressure limit increases during tachycardia because of increased flow requirements and a reduction in the duration of diastole (i.e., time available for perfusion) [7]. Furthermore, transmural variations in the lower autoregulatory pressure limit exist such that autoregulation is exhausted at a higher coronary pressure in the subendocardium (40 mmHg) compared with the subepicardium (25 mmHg) [6]. This is the result of the elevated resting flow and oxygen consumption in the subendocardium, as well as this region's heightened sensitivity to systolic compressive effects on vasodilator reserve (see next section). This transmural difference in the lower autoregulatory pressure limit contributes to the enhanced vulnerability of the subendocardium to ischemia distal to a coronary stenosis [8].

Determinants of Coronary Vascular Resistance

The three major components of resistance to coronary blood flow are summarized in Fig. 22.3 [4]. The first component (R1) is the resistance offered by the large epicardial conduit arteries. Under normal circumstances, these conduit vessels offer negligible resistance to flow, as evidenced by the lack of a measurable drop in pressure in this segment of the coronary circulation. However, the contribution of this component to total coronary resistance increases in the presence of hemodynamically significant epicardial artery stenoses (more than 50 % reduction in diameter) and may even reduce resting flow when the artery becomes severely narrowed (more than 90 %).

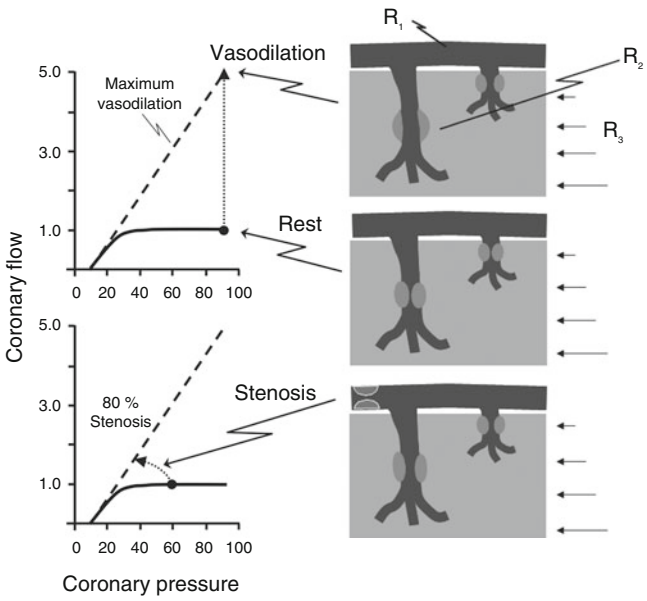

Fig. 22.3 Components of resistance to coronary blood flow. Under normal conditions, the resistance to flow offered by the epicardial conduit arteries (R_1) is minimal, while the majority of resistance resides in the arterioles and resistance arteries (R_2) and the time-varying extravascular compressive forces induced by cardiac contraction (R_3), which are highest in the subendocardium. The development of a severe epicardial stenosis results in a reduction in R_2 and an increasing contribution of R_1 to coronary flow resistance (Modified from Canty [5]. With permission from Elsevier)

The coronary resistance arteries and arterioles (20–200 um in diameter) are the source of the second component of coronary resistance (R2). This component of resistance results from variations in smooth muscle tone in response to a myriad of vasodilator and vasoconstrictor signals that arise in response to physical forces (intraluminal pressure and shear stress), neurohumoral and endothelium-derived factors, and changes in the metabolic demands of the tissue (discussed below). The smaller coronary capillaries and venules contribute little resistance to flow: in the maximally vasodilated heart, capillary resistance accounts for no more than 20 % of microvascular resistance [9]. As a result, minimal coronary vascular resistance of the microcirculation is primarily determined by the density and lumen diameter of arterial resistance vessels, the latter of which is highly dynamic and endows the normal heart with substantial coronary flow reserve.

Extravascular compressive resistance, the third component of coronary resistance (R3), varies throughout the cardiac cycle and arises from cardiac contraction-mediated elevations in left ventricular pressure. Following ventricular contraction during systole, the ensuing increase in coronary backpressure limits the driving pressure for coronary flow and impedes subendocardial perfusion. The systolic compression of microcirculatory vessels accelerates flow from the arterial microcirculation to the coronary venous system while also forcing blood within the subendocardial arterial vessels back towards the superficial subepicardial arterial vessels, producing an arterial backflow that reduces systolic epicardial inflow [10].

Regulation of Vascular Resistance by the Coronary Microcirculation

During basal conditions in the normal heart, ~90 % of coronary resistance occurs in the small arteries and arterioles that make up the coronary microcirculation (R2) [9, 11]. The resistance offered by this segment of the coronary circulation is ultimately dictated by the integration of vascular responses to local physical factors, vasodilator metabolites, autacoids, and neural modulation. Interestingly, considerable spatial heterogeneity of specific resistance vessel control mechanisms exists throughout the longitudinal distribution of the coronary microcirculation. For example, resistance arteries (100–400 um diameter) primarily regulate their tone in response to local shear stress and luminal pressure changes (myogenic response), while arterioles (<100 um diameter)

are more sensitive to changes in local tissue metabolism and directly control perfusion of the low-resistance coronary capillary bed.

Intraluminal Physical Forces

It has been suggested that one of the most important mechanisms of coronary autoregulation is the myogenic response of the coronary microcirculation, which refers to the ability of vascular smooth muscle to counter changes in distending pressure by altering coronary arteriolar diameter [12]. As a result, reductions in distending pressure result in vasodilation of resistance vessels, while elevations in distending pressure elicit vasoconstriction (Fig. 22.4a). Although the exact cellular mechanisms underlying myogenic tone are unclear, the process is dependent on calcium entry to smooth muscle cells, likely via stretch-activated L-type Ca^{2+} channels, resulting in crossbridge activation. Myogenic regulation of resistance vessel tone occurs in the absence of endothelial cells and functional innervation, suggesting that it is an inherent property of vascular smooth muscle cells and, in vivo, appears to occur primarily in arterioles smaller than 100 μm [14].

The vasomotor tone of coronary resistance arteries and arterioles is also influenced by local changes in shear stress (Fig. 22.4b). For example, elevations in shear stress exerted on the vessel wall as a result of increased blood flow stimulate vasodilation through a process termed flow-mediated vasodilation. This phenomenon was first described in isolated coronary arterioles by Kuo and colleagues [15, 16], who showed that flow-mediated vasodilation was endothelium-dependent and mediated by nitric oxide (NO), since it could be abolished by mechanical removal of the endothelium or the presence of an L-arginine analogue. Mechanisms underlying this response appear to vary by vessel size, with large animal studies showing that a hyperpolarizing factor regulates flow-induced dilation of epicardial conduit arteries [17], while NO predominates in the resistance vasculature [15]. It has also been suggested that vasodilation by EDHF represents a compensatory pathway that is upregulated in acquired disease states in which NO-mediated vasodilation is impaired [13, 18].

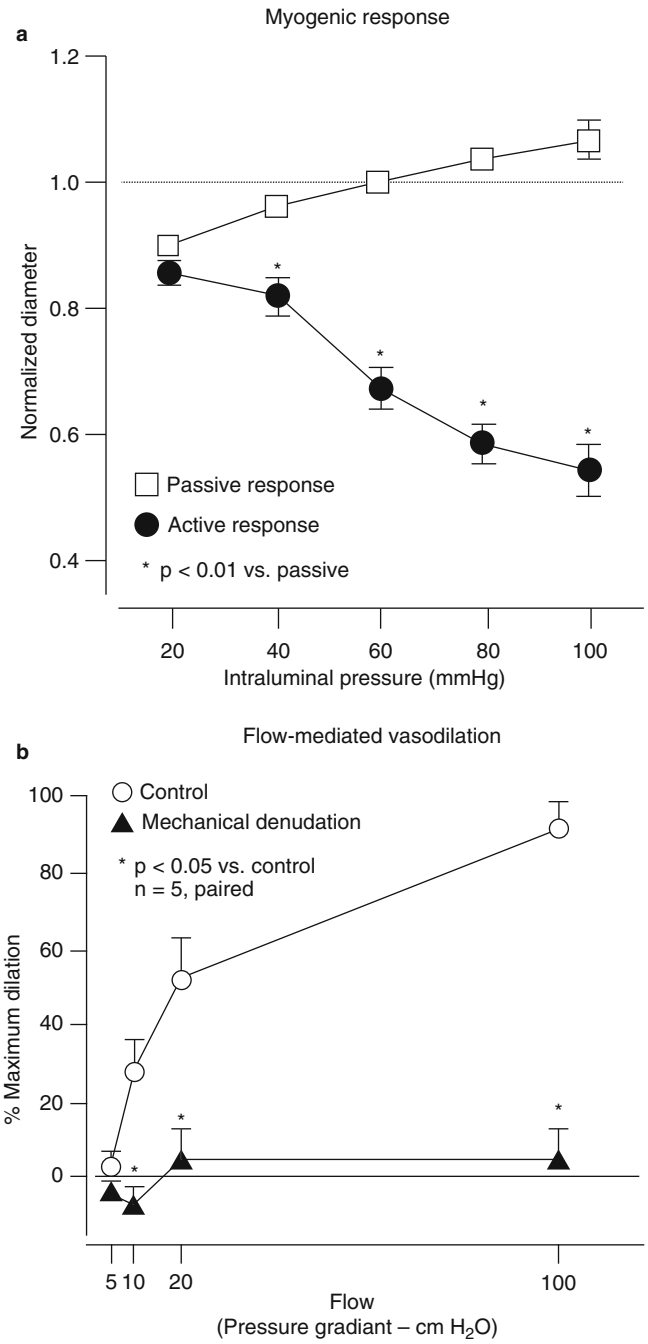

Fig. 22.4 Intraluminal physical forces elicit changes in coronary arterial resistance vessels. (**a**) Elevations in distending pressure from 20 to 100 mmHg result in vasoconstriction of isolated human coronary arterioles, consistent with myogenic regulation of vasomotor tone (Modified from Miller et al. [12]. With permission from the American Physiological Society). (**b**) The development of a pressure gradient across an isolated coronary artery causes an increase in intraluminal flow and progressive flow-mediated vasodilation that is dependent on the presence of a functional endothelium (Modified from Miura et al. [13]. With permission from Wolter Kluwers Health)

Metabolic Mediators

The search for the specific mediators of metabolic vasodilation has been complicated by the considerable redundancy of mechanisms involved in the local control of metabolic coronary flow regulation [19]. Because of this, coronary autoregulation and metabolic coronary flow regulation are unaffected by blockade of single mechanisms at normal coronary pressures. Nevertheless, during elevations in myocardial metabolic activity, there is accumulation of several factors that have been proposed to contribute to coronary

vasodilation. While a brief discussion of these potential factors mediating metabolic flow regulation is included below, interested readers are directed to more comprehensive reviews of this topic for further information [20, 21].

Adenosine has received considerable attention as a metabolic mediator of resistance artery control. While the exact mechanism of adenosine-mediated vasodilation is unclear, it likely occurs via binding of A2 receptors on the vascular smooth muscle, resulting in subsequent increases in cyclic adenosine monophosphate (cAMP) and the opening of intermediate calcium-activated potassium channels [22]. Although adenosine does not directly dilate larger resistance arteries or conduit arteries, these vessels experience flow-mediated dilation from the concomitant increase in local shear stress as arteriolar resistance falls [23]. Adenosine predominantly dilates coronary arterioles smaller than 100 μm in diameter [24], which corresponds to the segment of the coronary circulation in which coronary autoregulation and metabolic flow regulation occur. Also, since adenosine production is directly related to the metabolic state of the cell, it seems likely that it could serve as a local vasodilator factor to couple elevations in myocardial metabolic activity with coronary arteriolar vasodilation. However, despite its appeal as a local metabolic regulator of coronary resistance, substantial in vivo experimental data convincingly demonstrate that adenosine is not required for metabolic or autoregulatory adjustments in coronary flow in the normal heart of dogs, swine, or humans [25]. Nevertheless, it may promote vasodilation in particular circumstances, such as hypoxia and acute, exercise-induced myocardial ischemia occurring distal to a coronary stenosis [19].

Coronary vascular smooth muscle express ATP-sensitive potassium channels that are tonically active under conditions of normal arterial inflow and regulate vasomotor tone by altering the cell membrane potential, thereby influencing intracellular calcium concentrations and smooth muscle contractile state. The notion that these channels can modulate coronary metabolic and autoregulatory responses is supported by data demonstrating that inhibition of K^+-ATP channel activity with glibenclamide causes constriction of small arterioles (<100 μm), reduces coronary flow, and exacerbates myocardial ischemia distal to a coronary stenosis [21]. However, it is likely that K^+-ATP channels are a common effector of metabolism-mediated changes in coronary flow and not a sensor of metabolic activity, as many of the other candidates for metabolic flow regulation ultimately exert their actions by influencing K^+-ATP channel activity [26].

Hypoxia and acidosis have also been suggested as potential mediators of coronary flow regulation. Local O_2 is a potent coronary vasodilatory stimulus and coronary flow increases in proportion to reductions in arterial oxygen content (reduced O_2 or anemia) [2]. However, there is a paucity of data demonstrating a direct effect of oxygen on metabolic or autoregulatory adjustments to flow. Similarly, the precise role of arterial hypercapnia and acidosis (CO_2) in coronary flow regulation remains unclear. Although it has been suggested that CO_2 produced during acute ischemia may dilate coronary arterioles, it is unlikely that CO_2 is a mediator of exercise-induced coronary vasodilation in light of the fact that coronary venous CO_2 tension and pH remain unchanged during exercise [21].

Endothelium-Derived Factors

The net effect of the various factors regulating coronary blood flow is dependent on the presence of a functional endothelium. Building on Furchgott and Zawadski's [27] original demonstration that acetylcholine-mediated vasodilation is converted to vasoconstriction in the absence of the endothelium, more recent studies have shown that coronary artery resistance arteries exhibit endothelial modulation of diameter and that the endothelium-dependent response to physical forces and paracrine mediators varies with resistance vessel size [16, 21]. The major endothelium-derived factors involved in the regulation of coronary vascular resistance are summarized below and in Fig. 22.5.

Nitric oxide (NO) is a labile, lipid-soluble gas synthesized in endothelial cells from the amino acid L-arginine via the action of endothelial NO synthase (eNOS) [28]. Following its production, NO diffuses abluminally to vascular smooth muscle cells where it binds guanylate cyclase, increasing cyclic guanosine monophosphate production and producing relaxation through mechanisms that involve a reduction in cytosolic Ca^{2+} concentrations. NO-mediated vasodilation is enhanced by cyclical or pulsatile changes in coronary shear stress, and chronic upregulation of eNOS occurs in response to sporadic elevations in coronary flow, such as during exercise training. Although NO-mediated vasodilation of both epicardial arteries and coronary resistance vessels occurs in response to increased blood flow in vitro and in vivo [29–32], the administration of L-arginine analogues that competitively inhibit NO synthesis has revealed that this response is not mandatory for exercise-induced increases in coronary blood flow to occur [29, 33, 34].

In addition to NO, endothelial cells also produce prostacyclin and other vasodilator prostanoids through cyclooxygenase-mediated metabolism of arachidonic acid. These substances elicit vasodilation via an increase in intracellular cyclic AMP and subsequent opening of K^+-ATP channels in coronary vascular smooth muscle [35]. Although prostacyclin contributes to tonic coronary vasodilation in humans, cyclooxygenase inhibitors do not affect flow distal to a stenosis or limit oxygen consumption with increases in metabolism, suggesting that other compensatory pathways can overcome prostacyclin inhibition to mediate vasodilation in these circumstances. Interestingly, cyclooxygenase inhibition reduces collateral perfusion in dogs, indicating that vasodilator prostaglandins are important determinants of coronary collateral resistance [36].

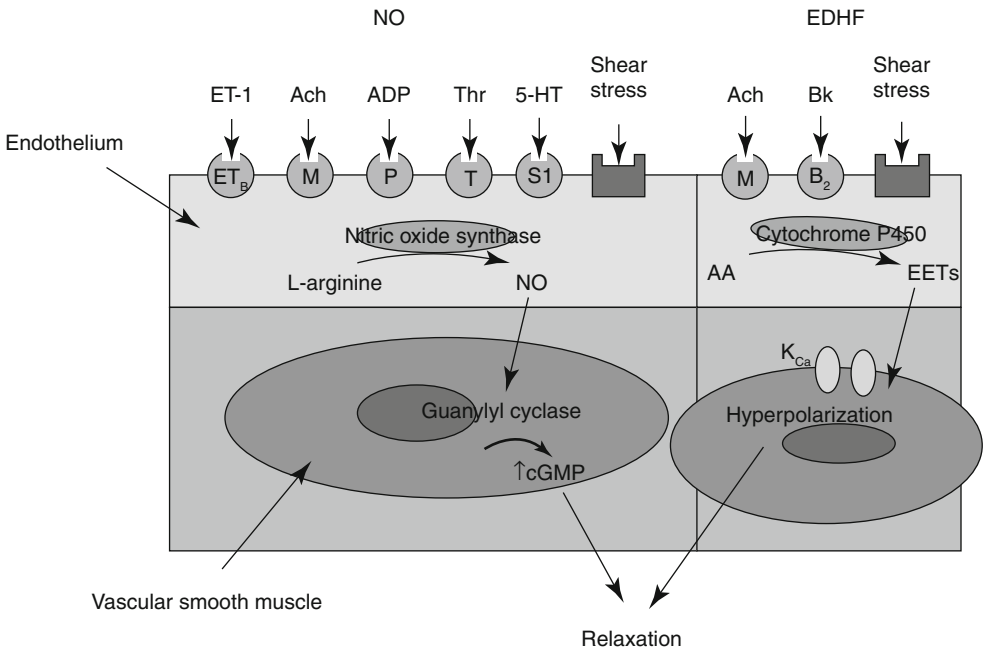

Fig. 22.5 Endothelium-dependent coronary vasodilation. In the normal coronary circulation, endothelium-dependent vasodilation occurs following elevations in luminal flow or shear stress, as well as in response to various agonists that bind to receptors on the endothelial cell surface. These stimulate the production of nitric oxide (*NO*), endothelium-dependent hyperpolarizing factor (*EDHF*), or *EETs* (epoxyeicosatrienoic acid products), which diffuse into vascular smooth muscle and cause relaxation. *Thr* thrombin, *Ach* acetylcholine, *ADP* adenosine diphosphate, *5-HT* serotonin, *Bk* bradykinin, *AA* arachidonic acid, K_{Ca} calcium-activated potassium channel, *cGMP* cyclic GMP (Modified from Canty [5]. With permission from Elsevier)

Endothelium-derived vasodilating factors other than NO and prostaglandins have also been identified as mediators of flow-mediated dilation and vasodilation to selected agonists (e.g., bradykinin) in the human coronary microcirculation. Because these substances promote vasodilation by opening K^+-ATP channels and hyperpolarizing the vascular smooth muscle, they are referred to as endothelium-derived hyperpolarizing factors (EDHFs). Although attempts to uncover the exact biochemical composition of EDHF continue, it appears that several factors mediate endothelium-derived hyperpolarization, including cytochrome P-450-dependent metabolites of arachidonic acid and hydrogen peroxide [37, 38]. Although there are data to suggest that EDHF-mediated vasodilation is not a critical component of metabolic coronary flow regulation [39], the exact role of EDHF in coronary vasodilation remains unclear.

Besides the vasodilating substances discussed above, the endothelium also produces the potent vasoconstrictor peptide, endothelin (ET)-1. In contrast to the relatively transient vasodilation elicited by endothelium-derived relaxing factors, ET-1 elicits prolonged contraction of vascular smooth muscle cells. ET-1 vasoconstrictor activity is mediated by two distinct receptor subtypes, ET_A and ET_B. ET_A receptors are located exclusively on vascular smooth muscle cells, where ET-1 binding activates the phospholipase C-inositol triphosphate pathway resulting in an increase in intracellular calcium, subsequent phosphorylation of myosin kinase and, in turn, long-lasting smooth muscle cell contraction [40, 41]. In contrast to ET_A receptors, ET_B receptors are expressed by both the endothelium and vascular smooth muscle and can mediate dual vasoregulatory actions of ET-1 [42]. Activation of ET_B receptors expressed by the vascular smooth muscle elicits vasoconstriction, while ET-1 binding to ET_B receptors on endothelial cells results in NO-mediated vasodilation [40, 41]. Although ET-1 has a minimal influence on the regulation of coronary blood flow in the normal heart, its contribution to coronary vascular tone can increase with advancing age and in pathophysiologic states characterized by elevated ET-1 activity, such as hypertension, metabolic syndrome, and heart failure [43–45].

Neural Control

Signaling from sympathetic and vagal nerves that innervate the coronary circulation can alter coronary resistance by directly affecting vascular smooth muscle tone, as well as by stimulating the release of vasoactive factors from endothelial cells. As a result, the net effect of autonomic nervous system activity on coronary flow is often dependent on the functional state of the endothelium. For example, in normal coronary arteries, acetylcholine elicits vasodilation of conduit and resistance arteries, reflecting the net action of a direct muscarinic constriction of vascular smooth muscle counterbalanced by endothelium-dependent vasodilation caused by acetylcholine-stimulated

and flow-mediated release of NO. However, in patients with atherosclerosis or other cardiovascular risk factors that impair endothelial function, the reduction in NO bioavailability leads to net vasoconstriction, particularly in stenotic segments of the coronary circulation [46].

Although there is no resting sympathetic tone in the heart under normal conditions, sympathetic activation yields changes in coronary tone that are mediated by norepinephrine released from myocardial sympathetic nerves, as well as circulating norepinephrine and epinephrine [47]. The effect of sympathetic stimulation on coronary resistance vessel tone is dependent on the net actions of beta-adrenergic type 1 receptor-mediated increases in myocardial oxygen consumption (and associated metabolic vasodilation), direct beta-adrenergic type 2 receptor-mediated coronary vasodilation, and alpha-adrenergic type 1 receptor-mediated coronary vasoconstriction. With exercise-induced sympathetic activation, beta-adrenergic receptor-mediated feed-forward vasodilation outweighs alpha-adrenergic-mediated vasoconstriction and is thought to account for a significant portion (~25 %) of the increase in coronary flow in these conditions [48]. However, cardiac denervation or pharmacological blockade of the autonomic nervous system is not associated with the development of myocardial ischemia during exercise, suggesting that other vasodilator mechanisms compensate under these circumstances. Thus, autonomic nervous system control seems to be involved in coupling coronary blood flow to myocardial metabolic demands but is not vital for exercise-induced hyperemia [21].

Physiological Assessment of Coronary Artery Stenoses

Although the epicardial coronary arteries normally serve as conduits to the coronary resistance vasculature, this relationship is dramatically altered in the presence of an epicardial stenosis where the epicardial component of resistance increases with stenosis severity and limits myocardial perfusion. Clinically, this typically occurs in patients with obstructive epicardial coronary artery disease, where epicardial stenoses arising from atherosclerotic plaque increase coronary resistance and reduce maximal myocardial blood flow [49]. The accurate physiologic assessment of stenosis severity is therefore an important component of the management and treatment of these patients.

Stenosis Pressure-Flow Relationship

The influence of epicardial coronary stenoses on coronary blood flow can be predicted by the Bernoulli principle, which describes the relationship between the velocity and pressure exerted by a moving liquid [50] (Fig. 22.6). Three hemodynamic factors influence the pressure drop across a stenosis: viscous losses, separation losses, and turbulence, although the contribution of turbulence is usually relatively minor. The most important geometric determinant of stenosis resistance for a given level of flow is the minimum lesional cross-sectional area within the stenosis [51]. This component of resistance is often dynamic due to small changes in luminal area that arise from thrombi or vasomotion of the affected vessel, resulting in major changes to the stenosis pressure-flow relationship because resistance is inversely proportional to the square of the lumen cross-sectional area. Consequently, increases in stenosis severity cause small reductions in luminal area that lead to large reductions in post-stenotic coronary pressure and maximal coronary perfusion.

With coronary autoregulation intact, resting flow can be maintained at a constant level by compensatory vasodilation of resistance vessels as stenosis severity increases. However, the pressure-flow relationship in the vasodilated heart is more sensitive to changes in stenosis severity, making physiological or pharmacological stress essential for the identification of hemodynamically severe stenoses. The substantial physiological coronary flow reserve (up to 5× resting values following vasodilation) is generally not affected until stenosis severity exceeds a 50 % diameter reduction (75 % reduction in cross-sectional area) and epicardial conduit artery resistance begins to contribute to total coronary vascular resistance. With further increases in stenosis severity, the curvilinear coronary pressure-flow relationship steepens, leading to an increase in stenosis resistance and reduction in coronary pressure distal to the stenosis that ultimately result in a progressive decline in maximal vasodilated blood flow. A stenosis exceeding 90 % diameter reduction is considered a critical stenosis, a situation in which subendocardial flow reserve is completely exhausted at rest [5].

Concept of Maximal Perfusion and Coronary Reserve

The concept of coronary reserve was originally proposed in the early 1990s by Gould to describe the ability to increase coronary flow above resting values in response to pharmacologic vasodilation [52]. The development of invasive catheter-based approaches to assess intracoronary pressure and flow has facilitated the assessment of coronary reserve in humans and advanced our understanding of factors contributing to alterations in myocardial perfusion in patients with epicardial artery stenoses (Fig. 22.7). Three primary indices are currently used to quantify coronary flow reserve: absolute flow reserve, relative flow reserve, and fractional flow reserve (Fig. 22.8).

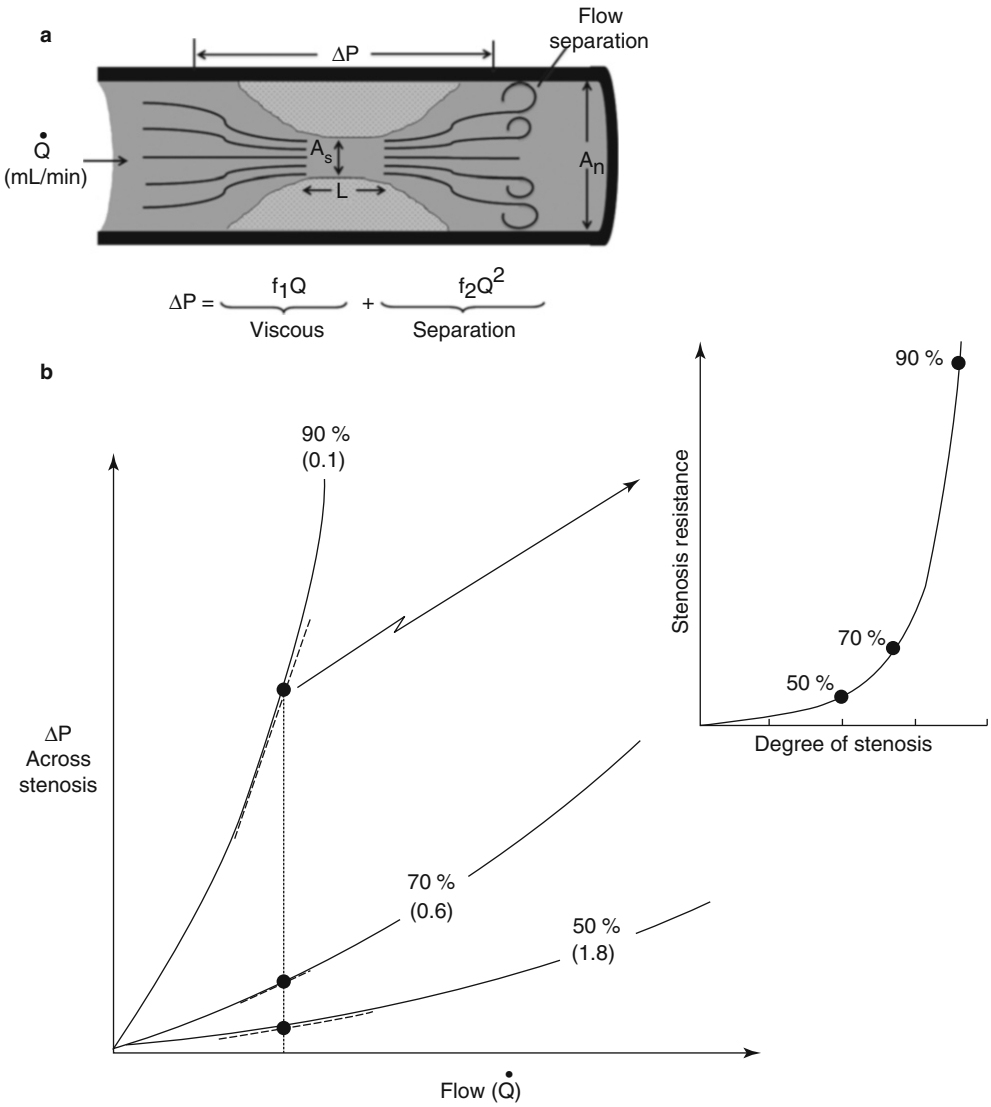

Fig. 22.6 Stenosis pressure-flow relations. (**a**) The relationship between pressure drop across a stenosis and coronary flow can be described by the Bernoulli equation, such that the pressure drop is inversely related to the minimum stenosis cross-sectional area and varies with the square of the flow rate as stenosis severity increases. ΔP pressure drop, Q flow, f_1 viscous coefficient (calculated as $f_1 = (8\pi\mu L)/A_s^2$), f_2 separation coefficient (calculated as $f_2 = (\rho/2)((1/A_S) - (1/A_n))^2$), where A_s area of the stenosis, A_n area of the normal segment, L stenosis length, μ viscosity of blood, ρ density of blood (Modified from Canty [5]. With permission from Elsevier). (**b**) As stenosis severity increases, the pressure-flow relationship exhibits a *curvilinear* shape, such that small elevations in the pressure drop across a stenosis result in large reductions in flow. This is due to the fact that, at resting flow levels (*dashed vertical line*), stenosis resistance rises exponentially with increases in the degree of stenosis severity (*solid line* in inset). Percentage values represent the percent diameter narrowing, with measurements in parentheses indicating minimal cross-sectional area for a given lesion. The pressure-flow relationship is calculated using a proximal vessel internal diameter of 3 mm (lumen area 7.1 mm^2) (Modified from Klocke [51]. With permission from Elsevier)

Absolute flow reserve is expressed as the ratio of maximally vasodilated flow to the corresponding resting flow value in a specific region of the heart and quantifies the ability of flow to increase above resting values in response to stress (Fig. 22.8a). In the normal heart, vasodilated flow is generally four to five times higher than resting flow. Patients with stress-induced ischemia most frequently have absolute flow reserve values below 2. It is important to note that reductions in this index of flow reserve can arise from inappropriate elevations in resting coronary flow (e.g., due to altered hemoglobin content, baseline hemodynamics, or resting oxygen extraction), as well as physiological factors affecting minimum coronary resistance. A significant limitation of absolute flow reserve measurements is the inability to separate the contribution of epicardial stenoses to reductions in flow reserve from impairments in flow that arise from functional abnormalities in the coronary microcirculation which commonly occur in patients with atherosclerotic vascular disease.

Relative flow reserve is an alternative approach to assess the significance of a stenosis that circumvents the influence of variations in mean arterial pressure and heart rate (Fig. 22.8b). This index is calculated by assessing relative differences in regional perfusion between a stenotic area and an assumed normal region of the same heart during maximal pharmacologic vasodilation or exercise stress [53]. Because this approach requires a normal reference segment within the left ventricle for comparison, it is difficult for relative flow reserve measurements to accurately quantify stenosis severity in patients with balanced multi-vessel disease or diffuse impairments in the vasodilatory capacity of the microcirculation.

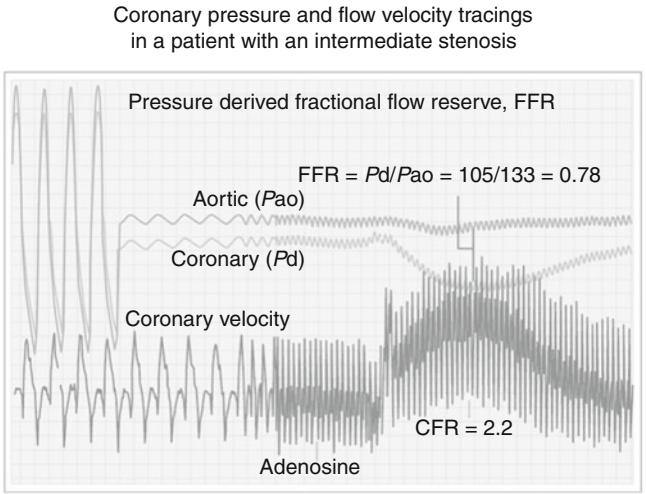

Fig. 22.7 Example coronary pressure and flow velocity tracings in a patient with an epicardial coronary stenosis. Intracoronary administration of adenosine elicits a transient increase in flow velocity and reduction in mean distal coronary pressure (*Pd*). These recordings enable the assessment of absolute coronary flow reserve (*CFR* ratio of peak flow to resting flow) and fractional flow reserve (*FFR* ratio of coronary pressure to mean aortic pressure) (Modified from Canty [5]. With permission from Elsevier)

Fractional flow reserve is an indirect index of stenosis severity (Fig. 22.8c). It is calculated by measuring the pressure for microcirculatory flow distal to a stenosis (distal coronary pressure minus coronary venous pressure) relative to the coronary driving pressure available in the absence of a stenosis (mean aortic pressure minus coronary venous pressure). Clinically, this is often simplified by assuming linearity of the vasodilated pressure-flow relationship (despite its curvilinear shape at reduced coronary pressures) and a coronary venous pressure of zero, resulting in an index of fractional flow reserve equaling mean distal coronary pressure/mean aortic pressure (*P*d/*P*ao). Critical values corresponding to hemodynamically significant stenoses are below 0.7. Advantages of this approach include the ability to assess the physiologic significance of intermediate stenoses in a manner that is not influenced by changes in resting flow, as well as the prognostic information offered by routine measurement of fractional flow reserve in patients with multi-vessel disease undergoing percutaneous coronary intervention [54]. Although there are limitations to this approach, such as the inability to assess abnormalities in microcirculatory flow reserve and failure to account for alterations in coronary venous pressure, fractional flow reserve remains the most direct method for assessing the

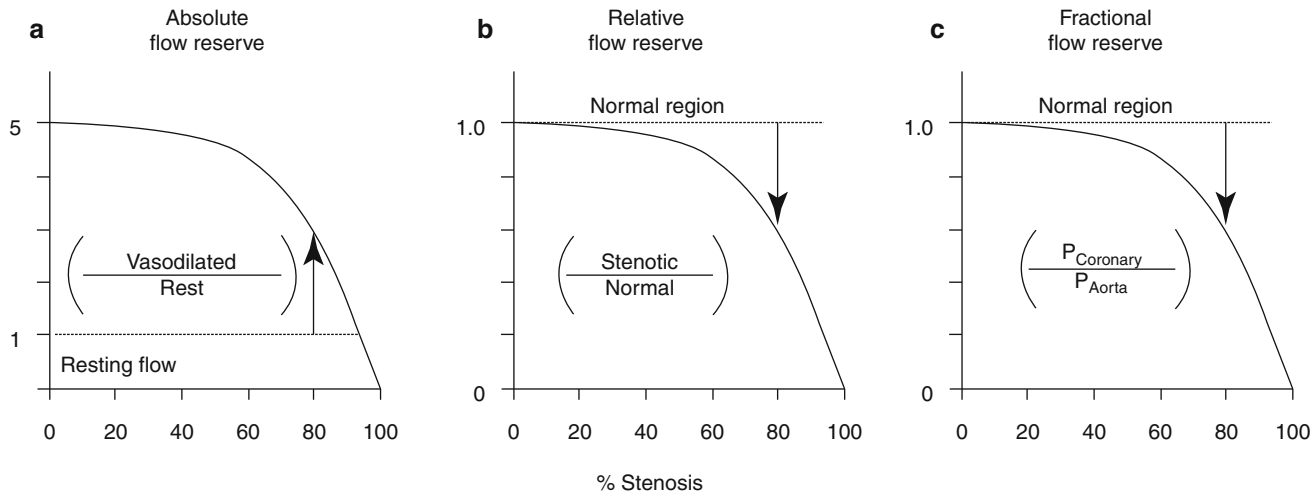

Fig. 22.8 Indices of coronary flow reserve. (**a**) Absolute flow reserve is calculated as the ratio of coronary flow during vasodilation to coronary flow at rest. (**b**) Relative flow reserve compares coronary flow during vasodilation in a region of the heart perfused by a stenotic artery to that in a remote area of the same heart that is assumed to be normal. (**c**) Fractional flow reserve is an indirect measure of maximal flow calculated by measuring the driving pressure for microcirculatory flow distal to a stenosis (distal coronary pressure – coronary venous pressure) relative to the coronary driving pressure in the absence of a stenosis (mean aortic pressure – coronary venous pressure) (Modified from Canty [5]. With permission from Elsevier)

physiological significance of stenoses in relation to coronary anatomy [55].

Regardless of the approach used, coronary flow reserve measurements are each based on the assumption that the selected pharmacologic vasodilating agent consistently achieves maximal vasodilation of the resistance vasculature in healthy subjects as well as patients with atherosclerotic disease and impaired endothelial function. However, this is not always the case, since structural and/or functional abnormalities in the microcirculation often influence perfusion of ischemic and remote areas of the heart in patients with coronary risk factors. Additionally, currently available approaches are limited by the fact that coronary flow measurements are averaged across the entire wall of the heart, thereby prohibiting the assessment of transmural variations in flow reserve.

Coronary Collateral Circulation

When a coronary stenosis proceeds to a total coronary occlusion, proliferation of native coronary collateral vessels is initiated by changes in blood flow caused by the development of an intracoronary pressure gradient between the source and recipient vessels. This collateral circulation offers a potential alternative conduit to facilitate blood flow to areas of the heart normally perfused by the stenotic or occluded artery. The extent of coronary collateral-mediated perfusion varies significantly among patients with chronic epicardial stenoses, such that some patients do not exhibit meaningful collateral flow during balloon angioplasty occlusion, while others experience proliferation of collateral vessels to the extent that resting perfusion is maintained and stress-induced ischemia is avoided at submaximal cardiac workloads. The ability to recruit collaterals is clinically relevant: patients with well-functioning collaterals (i.e., fractional flow reserve >0.25 during a brief coronary occlusion) have a significantly lower long-term cardiovascular event rate and improved survival compared with patients exhibiting a poorly developed collateral circulation [56].

Arteriogenesis and Angiogenesis

As stenosis severity exceeds 70 %, there is a fall in resting distal coronary pressure that results in the development of an interarterial pressure gradient between the vessels in the region of the heart fed by the stenotic vessel and nearby preexisting coronary collateral vessels. This stimulates the proliferation of coronary collaterals through a process termed arteriogenesis, in which preexistent arterial-arterial anastomoses enlarge via the proliferation of vascular smooth muscle and endothelial cells [57]. Although the precise factors regulating this process remain incompletely understood [58], it appears that physical forces (i.e., shear stress) and the release of growth factors in response to ischemia play important roles. Moreover, the development of collaterals through arteriogenesis likely relies on NO production from the endothelium; thus, patients with risk factor-induced impairments in endothelial function may have a limited ability to form a functional coronary collateral circulation [59, 60].

Although most functional collateral flow develops as a result of arteriogenesis, collateral perfusion can also arise from angiogenesis, which refers to the sprouting of small capillary-like structures from existing blood vessels. The formation of these vessels may provide collateral flow when they are present in the border zone between ischemic and non-ischemic regions, as well as facilitate oxygen extraction by reducing the intercapillary distance in ischemic tissue. However, alterations in capillary density without concomitant changes in arteriolar resistance will have a minimal effect on myocardial perfusion, since capillary resistance represents a very small component of total microcirculatory resistance.

Regulation of Collateral Resistance

The resistance offered by the network of collateral vessels is dynamic and able to undergo both long- and short-term adjustments that modify perfusion of collateral-dependent myocardium. Long-term adaptations involve vessel growth and remodeling, while short-term changes primarily involve alterations in the vasomotor tone of the collateral circulation. Similar to native resistance vessels, collaterals constrict during blockade of endothelial nitric oxide synthase, indicating that nitric oxide contributes to their basal tone [19]. In contrast, however, experimental studies have demonstrated that coronary collaterals exhibit tonic prostaglandin-mediated vasodilation, with cyclooxygenase inhibition exacerbating myocardial ischemia in dogs [61]. Collateral perfusion is also controlled by the microcirculatory vessels distal to a stenosis in collateral-dependent myocardium, which initially appear to function similarly to those in the normal resistance vasculature. However, in chronic conditions these vessels undergo structural and functional alterations that affect blood flow distal to a stenosis. Some of the chronic vascular adaptations include arteriolar wall thickening and lumen narrowing, an attenuated myogenic response, endothelial vasodilator dysfunction, and a heightened sensitivity to endothelin-1-mediated vasoconstriction [62–65]. These chronic alterations in microvessel structure and function may adversely influence the metabolic and autoregulatory responses of collateral-dependent myocardium as well, thereby precipitating ischemia in this area of the heart.

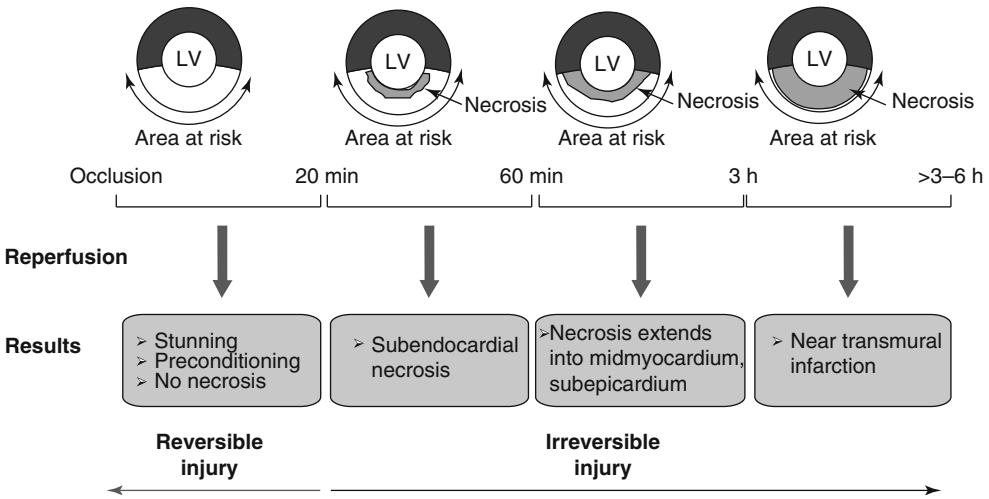

Fig. 22.9 Time course of necrosis in acute ischemia. In the absence of a functional collateral circulation, irreversible injury begins after 20 min of coronary occlusion and progresses from the subendocardium to the subepicardium. Necrosis can be avoided with earlier restoration of blood flow, although post-ischemic dysfunction can persist (myocardial stunning). The extent of irreversible injury increases as the duration of ischemia is extended, with necrosis of the inner third of the left ventricular wall apparent after 60 min. Between 3 and 6 h after the onset of occlusion, complete transmural infarction occurs (Modified from Kloner and Jennings [66]. With permission from Wolters Kluwer Health)

Metabolic and Functional Consequences of Ischemia

The sudden interruption of regional myocardial blood flow following an acute coronary occlusion may dramatically affect cardiac contractile performance, depending on the duration of ischemia, the transmural location of the occlusion, the amount of residual coronary flow, and the hemodynamic determinants of oxygen consumption (Fig. 22.9). Metabolically, cessation of myocardial perfusion prohibits continuation of aerobic metabolism, leading to the depletion of creatine phosphate and enhanced reliance on anaerobic glycolysis. Shortly thereafter, a progressive reduction in tissue adenosine triphosphate (ATP) levels occurs, along with an accumulation of lactate and other catabolites. The continued diminution of ATP leads to decreased activity of ATP-dependent ion transport pumps, including the Na^+/K^+-ATPase pump, ultimately resulting in extracellular K^+ accumulation and electrophysiological abnormalities. Eventually ATP levels decrease below levels necessary to maintain cell membrane function, triggering the onset of cardiomyocyte death.

Irreversible Injury and Myocyte Death

In the absence of a functional collateral circulation, a total coronary occlusion will generally begin to elicit irreversible myocardial injury after approximately 20 min [66]. Because of the higher resting oxygen consumption of the subendocardium and the compression-mediated redistribution of collateral flow to the outer layers of the heart at reduced coronary pressures, injury begins in the subendocardium and progresses towards the subepicardium. Studies of experimental myocardial infarction demonstrate that the entire subendocardium is irreversibly injured within 1 h of occlusion, with transmural infarction completed within 4–6 h. This time course of events is accelerated by the presence of factors that either increase myocardial oxygen consumption or reduce oxygen delivery. In contrast, residual coronary flow through collateral vessels or through an incompletely occluded coronary artery can delay the progression of irreversible injury. For example, subendocardial collateral blood flow of ~30 % of resting coronary flow can prevent infarction after ischemic periods of more than 1 h, while the maintenance of flow at ~50 % of resting values can prevent the development of significant injury for at least 5 h [67].

Brief periods of reversible ischemia prior to prolonged occlusion can actually reduce irreversible injury through a protective mechanism termed acute preconditioning [66, 68]. Originally described by Murry et al. [69] in 1986, this phenomenon was shown to delay ATP depletion, decrease oxygen consumption, and diminish the development of cellular necrosis following sustained ischemia, ultimately reducing infarct size [70]. Although these protective benefits are lost when the time period between preconditioning episodes and prolonged occlusion is extended to several hours, the protective effect returns 24 h later and may persist for up to 96 h, during a window referred to as late or delayed preconditioning [71]. More recently, it has been shown that the myocardium can be protected against ischemia-induced injury by intermittent ischemia or administration of cardioprotective agents at the time of reperfusion (postconditioning) [72]. Since it does not require

treatment prior to occlusion and can be induced after the onset of myocardial ischemia, this mechanism of cardioprotection offers exciting potential for clinical applicability [68].

In the absence of protective pre- or postconditioning, prolonged ischemia will ultimately elicit cardiomyocyte death through several mechanisms [73]. Upon reperfusion, myocyte necrosis and sarcolemmal disruption occur, followed by the leakage of cell contents into the extracellular space and further injury that is amplified by secondary leukocyte infiltration of the damaged area. Approximately 24 h later and continuing for up to 2 weeks, myocytes in the peri-infarct zone and remote myocardium that were initially preserved undergo programmed cell death or apoptosis, leading to further myocardial injury. At later time points (i.e., months after the ischemic insult), there is continued loss of myocytes that is attributed in part to pathological autophagy, which involves the lysosomal degradation of cellular components and eventual induction of cell death. Although the precise timing of each mechanism's involvement in myocardial infarction is incompletely understood, approaches aimed at preventing cardiomyocyte death have the potential to limit adverse ventricular remodeling and avert the progression to chronic heart failure [74].

Functional Consequences of Reversible Ischemia

Clinically, reversible ischemia occurs more frequently than irreversible injury and can arise in a supply- or demand-induced fashion. Immediately upon coronary occlusion, there is a drop in coronary venous oxygen saturation and concomitant reduction in ATP production, ultimately leading to a decline in regional contractile function that reaches dyskinesis within 1 min. This deterioration of regional contractility precipitates a reduction in global left ventricular contractility (dP/dt), a gradual rise in left ventricular end-diastolic pressure, and a drop in systolic pressure, the magnitude of which each depend on the size of the ischemic area and severity of the ischemic insult. Upon restoration of normal myocardial perfusion, acute and delayed effects on regional function persist and range from myocardial stunning to the development of hibernating myocardium, a state characterized by chronic contractile dysfunction and regional cellular alterations that downregulate contractile and metabolic function to protect the heart from irreversible injury [5] (Fig. 22.10).

Stunned Myocardium

Following single, brief (<2-min) episodes of ischemia, contractile function normalizes rapidly upon reperfusion. However, as the duration and/or severity of ischemia increases, there is a temporal delay in the recovery of myocardial function following restoration of blood flow. This phenomenon is termed myocardial stunning and was first described by Heyndrickx and colleagues after single 15-min total coronary occlusions [75], with subsequent studies showing that post-ischemic dysfunction can persist despite normalization of perfusion after stress-induced ischemia distal to a stenosis [76, 77]. An important defining characteristic of stunned myocardium is the dissociation of the typically close relation between myocardial flow and function, such that depression of function occurs in the presence of normal resting perfusion. Mechanistically, this process likely involves oxygen-derived free radical-mediated injury to the heart and diminished myofilament sensitivity to calcium [78].

Besides occurring with reversible ischemia, stunned myocardium often coexists with infarcted myocardium in patients undergoing restoration of blood flow following myocardial infarction and may contribute to delayed improvements in contractility following reperfusion therapy. In clinical scenarios, acutely stunned myocardium is important to identify because contractile function can be normalized by the administration of various inotropic agents. Moreover, in contrast to other states of contractile dysfunction, stunned myocardium typically resolves within days following reperfusion, given that there are not subsequent limitations in myocardial blood flow. However, repetitive ischemic episodes prior to recovery of function may cause a state of persistent dysfunction or chronic stunning. Alternatively, exposure to repetitive ischemia may lead to the chronic development of viable dysfunctional myocardium, as described below.

Short-Term Myocardial Hibernation

During steady-state ischemia, it is possible for reductions in myocardial contractile function to occur in concert with diminished blood flow through a phenomenon termed short-term hibernation [67]. In this situation, the concomitant reductions in perfusion and contractile activity result in the development of a reduced steady-state level of oxygen consumption and energy utilization. This prolonged perfusion-contraction matching allows the heart to maintain viability for an extended period of time without progressing to irreversible injury despite persistent hypoperfusion. Although the duration over which short-term hibernation can maintain viability depends on the severity of ischemia, infarction generally develops when the ischemic period exceeds 12 h [79, 80]. In light of the brief time period over which this phenomenon occurs, it is likely that the responses that characterize short-term hibernation are physiological adaptations in myocardial substrate and energy metabolism [67]. These adaptations are reflected by an initial fall in creatine phosphate and ATP levels, followed by a stabilization period during which restoration of creatine phosphate concentrations prevents further depletion of ATP [81]. This pattern of events is accompanied by a transient elevation in tissue lactate concentrations that normalizes with persistent ischemia. Once perfusion is reestablished, myocardial stunning occurs with contractile function slowly improving over

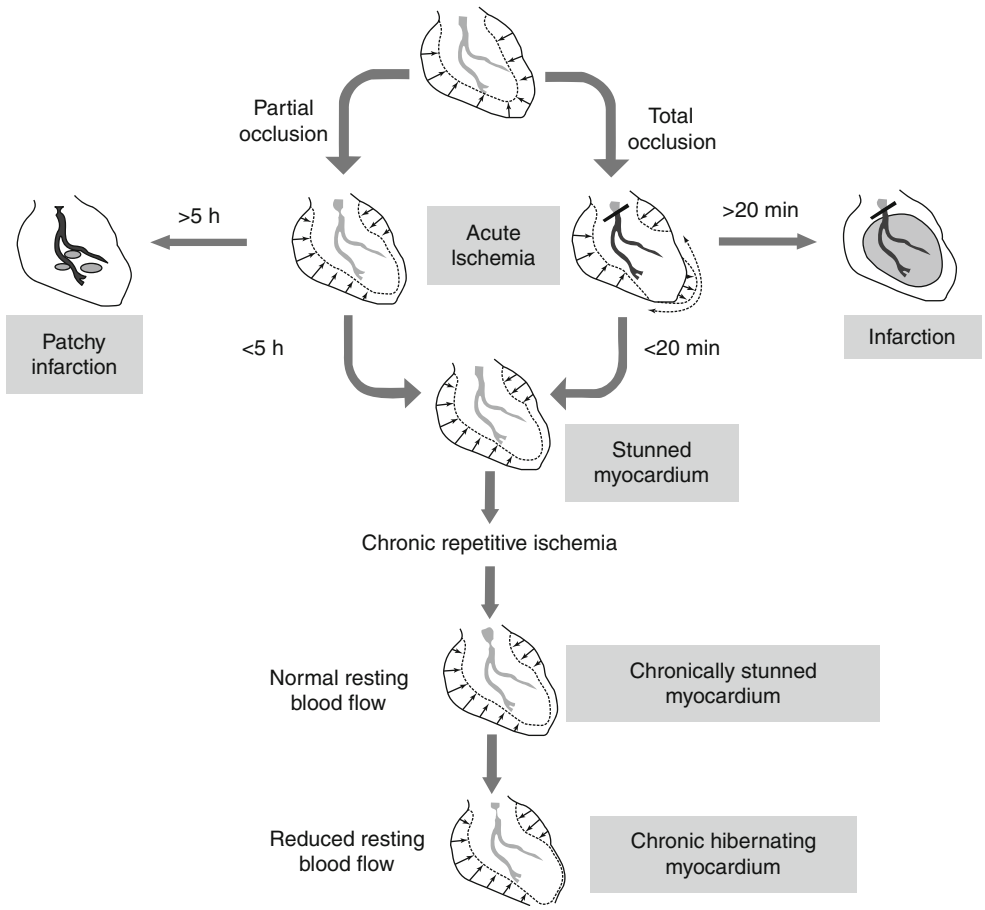

Fig. 22.10 Consequences of acute and chronic myocardial ischemia. Acute ischemia induced by a partial (*left*) or total (*right*) occlusion elicits contractile dysfunction proportional to the reduction in blood flow. The time course of irreversible injury depends on the severity of the occlusion such that moderate ischemia provoked by a partial occlusion may persist for up to 5 h without evidence of infarction. If blood flow is reestablished before the onset of irreversible injury, myocardial contractile function remains depressed despite normal perfusion (stunned myocardium). Over time, the frequency of ischemia may increase to the extent that there is insufficient time for recovery between ischemic episodes. Initially, contractile dysfunction with normal resting flow (chronically stunned myocardium) is apparent, but continued exposure to repetitive ischemia ultimately results in a transition to chronic hibernating myocardium characterized by a reduction in resting blood flow. Contractile dysfunction at each stage is illustrated by ventriculograms (*dotted lines* and *arrows*) (Modified from Canty [5]. With permission from Elsevier)

the course of several days [82]. Over time, repetitive episodes of short-term hibernation can prompt molecular remodeling of myocytes and the development of viable, chronically dysfunctional myocardium.

Chronic Hibernating Myocardium

Hibernating myocardium is characterized by contractile dysfunction with reduced resting blood flow in the absence of acute ischemia or significant necrosis [5, 83]. Clinically, this pathophysiologic entity is common in patients with ischemic cardiomyopathy and often coexists with non-transmural infarction, although it can also occur in the absence of heart failure or global left ventricular dysfunction. While chronic segmental contractile dysfunction is present in both stunned and hibernating myocardium, the critical difference between these conditions relates to relative resting blood flow. When resting flow relative to a remote region is normal, the myocardium is chronically stunned. In contrast, hibernating myocardium is distinguished by a reduction in relative resting flow. It was originally postulated that hibernating myocardium arose from a primary reduction in flow, similar to the development of short-term hibernation after prolonged moderate ischemia. Although this may be the mechanism underlying the development of hibernating myocardium in patients with acute coronary syndrome, experimental studies of large animals with a slowly progressing coronary stenosis have revealed that the physiologic severity of stenosis and repetitive ischemia are the major determinants of the progression from stunned to hibernating myocardium [5]. In these models, regional dysfunction with normal resting flow (chronically stunned myocardium) precedes the development of hibernating myocardium, demonstrating that reductions in relative resting flow are a consequence rather than a cause of contractile dysfunction [84, 85].

The downregulation of resting flow in hibernating myocardium appears to reflect several metabolic and energetic

adaptations of the heart to repetitive episodes of ischemia. These include enhanced basal glucose utilization [86], diminished fatty acid utilization [87], and regional reductions in oxygen consumption. Nevertheless, experimental studies have shown that an energetic balance persists despite hypoperfusion, with some ability to increase metabolism during submaximal stress. These alterations in metabolic activity are likely due to changes at the mitochondrial level, including decreased expression of proteins involved in oxidative metabolism and electron transport [88]. These adaptations contribute to a downregulation of energy uptake and oxygen consumption, thereby slowing ATP uptake and maintaining myocyte viability during subsequent periods of acute ischemia [89].

In addition to adaptive changes in metabolic activity, hibernating myocytes also exhibit an array of structural alterations that become apparent upon pathologic analysis. However, there is considerable divergence among studies in this area, with some investigations showing an adaptive reversion to a fetal cellular phenotype [90, 91], and others demonstrating a degenerative phenotype characterized by progressive cell death and marked fibrosis [92, 93]. Although the factors that determine whether adaptation or degeneration occurs are unknown, structural degeneration appears to be more common when global impairments in left ventricular function and heart failure are present, suggesting that neurohormonal activation or circulating cytokines may modulate the phenotype of hibernating myocytes. However, even when hibernating myocardium occurs regionally in the absence of heart failure, chronic apoptosis promotes the gradual loss of local myocytes (~30 %), particularly during the transition from stunned to hibernating myocardium [94]. To compensate, remaining myocytes undergo cellular hypertrophy to maintain normal wall thickness. In the chronic setting, the cardioprotective upregulation of cell survival pathways appears to arrest myocyte apoptosis and maintain stability in function and viability. Ultimately, however, myocyte loss and/or remodeling, even without significant fibrosis, may limit the functional recovery of hibernating myocardium after revascularization [95]. Accordingly, therapeutic approaches that promote myocyte regeneration have emerged as potential strategies to restore contractile function in chronic hibernating myocardium, including the administration of growth factors, HMG-CoA reductase inhibitors (statins), and stem/progenitor cells [96–98].

Future Perspectives

Experimental and clinical investigation over the past 40 years has substantially deepened our understanding of the mechanisms involved in the regulation of coronary blood flow and the pathophysiology of myocardial ischemia. More recently, advances in imaging techniques have facilitated the translation of these discoveries to the clinical arena, where assessment of coronary perfusion is routinely used to assess the prognosis of patients with heart disease. Although a great deal of progress has been made, several gaps in our knowledge remain. For example, the specific mechanisms linking changes in metabolic activity to coronary perfusion remain incompletely understood, along with the precise role that changes in microcirculatory function and structure play in promoting the progression of ischemic heart disease. In addition, the advancement of coronary intervention techniques to successfully reopen stenotic and occluded vessels has opened several new avenues of questioning related to the likelihood of complications such as restenosis or microembolization, as well as the reversibility of myocyte and vascular adaptations to ischemia. Finally, attempts to translate therapeutic approaches that successfully promote myocyte regeneration and neovascularization in experimental animal studies to patients with ischemic heart disease persist. Gaining a greater understanding of why some patients undergo protective intrinsic adaptations to repetitive ischemia while others experience structural degeneration may help guide these efforts, along with continued investigation of novel pharmacologic interventions and the exciting possibility of tissue repair and renewal with the administration of various stem cell populations. Ultimately, sustained translational research in these and other areas will expand our knowledge and facilitate improvements in our ability to prevent, diagnose, and manage ischemic heart disease.

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Risk Factors and Prevention, Including Hyperlipidemia

23

Antonio M. Gotto Jr. and John A. Farmer

Introduction

The age-adjusted morbidity and mortality attributed to cardiovascular disease has declined significantly, although the burden of atherosclerosis remains high. In the time period from 1988 to 2008, the age-adjusted cardiovascular disease death rate has decreased by 30.6 % [1]. However, despite this encouraging decline, coronary heart disease is the cause of approximately one in every six deaths in the USA, with total cardiovascular mortality accounting for 32.8 % of all deaths. Although cardiovascular disease still presents considerable challenges, major progress has been made in the identification of individuals at risk. Additionally, significant improvements in the pharmacologic and surgical management of patients with vascular disease have occurred.

Atherosclerosis is best regarded as a syndrome that lacks a unifying hypothesis to explain all aspects of the initiation and progression of coronary, cerebrovascular, and peripheral vascular disease. Multiple risk factors have been identified that correlate with an increased statistical risk for the development of obstructive vascular disease. Prospective clinical trials have demonstrated that modification of certain risk factors reduces the progression of atherosclerosis and also reduces cardiovascular morbidity and mortality. Hypertension, smoking, and dyslipidemia remain the major modifiable risk factors, and an overwhelming body of clinical evidence has accumulated demonstrating that optimization of these factors reduces the risk for cardiovascular disease. The purpose of this chapter is to review cardiovascular risk factors with a special emphasis on dyslipidemia.

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Table 23.1 Other risk factors besides LDL cholesterol in evaluating coronary heart disease risk

Positive risk factors
Age
Family history of coronary heart disease
Hypertension
Current tobacco use
Low HDL cholesterol (<40 mg/dL)
Negative risk factor
HDL cholesterol ≥60 mg/dL[a]
Coronary heart disease risk equivalents
Multiple risk factors with >20 % risk for coronary heart disease in 10 years
Other atherosclerotic disease (stroke, peripheral vascular disease, aortic aneurysm)
Diabetes mellitus

Based on data from Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [2]
HDL high-density lipoprotein
[a]If the HDL cholesterol level is ≥60 mg/dL, subtract one risk factor (because high HDL cholesterol levels decrease coronary heart disease risk)

Non-modifiable Risk Factors

Cardiovascular risk factors may be divided into modifiable and non-modifiable entities (Table 23.1). Genetic disorders should be identified but are currently non-modifiable. Chronologic age has been linked to increased risk for coronary disease. The prevalence and incidence of atherosclerosis increases with age and represents a significant non-modifiable risk factor for coronary artery disease [3]. Gender and family history may also be linked to an increased statistical risk for atherosclerosis. The history of a heart attack in both parents increases the risk for heart attack with an odds ratio of 2.9 [4]. The presence of non-modifiable risk factors such as genetic tendencies may also coexist with non-genetic factors that are present due to lifestyle and cultural issues. A complete family history should be obtained in all individuals with a special emphasis on potentially modifiable risk factors such as obesity, hypertension, and dyslipidemia.

C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_23, © Springer Science+Business Media New York 2013

Hypertension and dyslipidemia should especially be evaluated since lifestyle interventions, including decreased consumption of saturated fat and sodium, increased exercise, and smoking cessation, may reduce the impact of nonmodifiable genetic factors.

Modifiable Risk Factors

The major modifiable risk factors for the initiation and progression of atherosclerosis are hypertension, dyslipidemia, and the use of tobacco products.

Hypertension

Elevations of both systolic and diastolic blood pressure have been correlated with increased risk for coronary artery disease, stroke, and congestive heart failure. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) incorporated evidence from recent clinical trials in hypertension in order to improve the management of individuals with elevated blood pressure [5]. The JNC VII report streamlined the classification of blood pressure and also introduced the term prehypertension, which replaces the older categories of normal and high-normal blood pressure that may have suggested an attitude of complacency with the implication that little action would be required. The term prehypertension was introduced to encourage clinicians to utilize more aggressive clinical interventions to optimize blood pressure as a means of reducing vascular risk. Normal blood pressure is defined as a systolic blood pressure of less than 120 mmHg and a diastolic blood pressure of less than 80 mmHg. Prehypertension is defined as a systolic blood pressure between 120 and 139 mmHg or a diastolic blood pressure of 80–89 mmHg. The diagnosis of established hypertension is divided into two stages. Stage I is defined as a systolic blood pressure of 140–159 mmHg or a diastolic blood pressure of 90–99 mmHg. Stage II hypertension is classified as a systolic blood pressure greater than or equal to 160 mmHg or a diastolic blood pressure greater than or equal to 100 mmHg. The intent of the JNC VII report was also to emphasize the increasing prevalence of hypertension and poor rates of blood pressure control [6]. The National Health and Nutrition Examination Survey (NHANES) documented that at least 50 million Americans have hypertension warranting treatment and that there is relatively poor achievement of clinical goals (<35 %). The JNC VII report emphasized that cardiovascular risk begins at a blood pressure of 115/75 mmHg and doubles with each increment of 20/10 mmHg. Individuals who are normotensive at age 55 have a 90 % lifetime risk for the development of hypertension.

Clinical trials had previously shown a reduction in cardiovascular events with blood pressure control, although the impact on total mortality was controversial. However, long-term follow-up from the Systolic Hypertension in the Elderly Program (SHEP) trial has clearly demonstrated a reduction in total mortality with long-term blood pressure control [7]. Controversy has also arisen as to the choice of initial antihypertensive agent. The JNC VII states that the primary objective is to optimize the blood pressure, which appears to be more important than the choice of initial antihypertensive agent. At least five classes of antihypertensive agents have been demonstrated to reduce cardiovascular events, including thiazide and thiazide-type diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, and calcium antagonists. Absent from this group are the alpha-blockers. Clinical trials designed to test the superiority of individual agents have produced mixed clinical results. In general, reduction of cardiovascular morbidity and mortality is dependent on the degree of blood pressure reduction, although secondary end points (glucose tolerance, dyslipidemia, etc.) may be differentially altered by various agents. Combination therapy is required in a significant number of patients with hypertension. In several of the more recent trials, two or three drugs were necessary to optimize blood pressure reduction.

Tobacco Use

The use of tobacco products has long been recognized as a major contributor to the risk for cardiovascular disease [8]. Smoking is an independent risk factor for the development of cardiovascular disease and also increases risk for sudden cardiac death [9]. Fortunately, the consumption of tobacco products has decreased in the USA. Recent epidemiologic studies have demonstrated that the percentage of American adults greater than 18 years of age who are current cigarette smokers has declined from 24.1 to 19.3 % between 1998 and 2008 [10]. However, the burden of cardiovascular morbidity and mortality associated with smoking remains significant. The use of tobacco products results in approximately 443,000 premature deaths per year secondary to smoking-related illness. About 49,000 of these deaths are attributable to secondhand smoke. In adult smokers older than 35 years of age, 32.7 % of the deaths were related to cardiovascular disease [11]. Studies have estimated that the average male smoker dies 13.2 years earlier when compared to male nonsmokers, and female smokers die 14.5 years earlier than female nonsmokers. The risk for the development of cardiovascular disease linked to the consumption of tobacco products varies with the intensity and duration of smoking. Clinical studies have demonstrated that there is a strong association between the duration of time since

discontinuation of tobacco products and the onset of cardiovascular disease. For example, epidemiologic observations from the Framingham Heart Study indicate that the risk for the development of cardiovascular disease correlates with the number of pack-years consumed when compared to nonsmokers [8]. However, the risk for development of cardiovascular disease among individuals quitting more than 5 years prior to the baseline exam and within 5 years prior to the baseline exam was similar and twice as high as that of nonsmokers. Recommendations have been made to incorporate the effect of pack-years and time since the discontinuation of tobacco products in the Framingham risk projection algorithm.

The mechanism by which the use of tobacco products results in increased risk for cardiovascular disease is multifactorial and is manifested by a number of pro-atherogenic abnormalities. The use of tobacco products has significant effects on the lipid profile. Smokers frequently exhibit the components of the atherogenic lipid profile or lipid triad, which is characterized by elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, and small dense low-density lipoprotein (LDL) particles. The adverse effect of tobacco smoke on the activity of lipoprotein lipase has been proposed as a potential mechanism for this lipid phenotype [12]. However, the consumption of tobacco products may also produce adverse effects in lipid metabolism in subjects without overt dyslipidemia. Reverse cholesterol transport is thought to be a major mechanism by which HDL cholesterol exerts a protective effect against the development of atherosclerosis. Smoking has been shown to adversely affect lipid transfer proteins and enzymes involved in reverse cholesterol transport compared to nonsmokers [13]. The cessation of the consumption of tobacco products has been clearly demonstrated to reduce cardiovascular mortality and should be a cornerstone in the implementation of lifestyle modifications.

Dyslipidemia

Dyslipidemia is a major modifiable risk factor for the development of coronary artery disease. Early controversy regarding the validity of the lipid hypothesis occurred since the utility of total cholesterol levels to predict cardiac risk is relatively modest due to a significant overlap of values in subjects with and without coronary artery disease. Subsequent investigations demonstrated that cholesterol is distributed in several lipoproteins that have a variable impact on the risk for development of coronary artery disease. The major circulating lipoproteins are the triglyceride-rich particles (chylomicrons, very-low-density lipoprotein [VLDL], and intermediate-density lipoprotein [IDL]), low-density lipoprotein, high-density lipoprotein, and lipoprotein(a).

Triglyceride-Rich Lipoproteins

The major triglyceride-rich lipoproteins are chylomicrons, VLDL, and IDL. VLDL is the major endogenously produced lipoprotein and is predominantly hepatic in origin. Chylomicrons are derived from the diet and are large particles with a density of less than 0.95 g/mL, while chylomicron remnants are partially metabolized particles and have a density of less than 1.006 g/mL [14]. Pure hyperchylomicronemia is rare and is predominantly a pediatric condition determined by genetic abnormalities. The persistence of chylomicrons in the circulation may occur due to the absence of the major catabolic enzyme in triglyceride metabolism (lipoprotein lipase) or of apolipoprotein C-II, which is the normal activator of lipoprotein lipase. Chylomicrons may also be seen in adults with uncontrolled diabetes mellitus, multiple myeloma, systemic lupus erythematosus, or acute intermittent porphyria. Hyperchylomicronemia is considered to not play a major role in the initiation and propagation of atherosclerosis, although the risk of pancreatitis is significantly increased. Chylomicron remnants possess apolipoprotein B, are relatively cholesterol-rich, and do have the potential for vascular endothelial cytotoxicity, however. Chylomicron remnants have been correlated with increased risk for the development of coronary and peripheral vascular disease [15].

The primary and independent role of hypertriglyceridemia in the pathogenesis of coronary heart disease has been controversial for many years [16]. Hypertriglyceridemia is present in many conditions that are associated with increased risk for coronary artery disease, such as obesity, diabetes mellitus, physical inactivity, tobacco consumption, and the metabolic syndrome, which makes it difficult to determine the primary role of hypertriglyceridemia in the pathogenesis of atherosclerosis. VLDL is produced by the liver and transports endogenously produced triglycerides to the periphery. VLDL may be metabolized by lipoprotein lipase, which is ubiquitous and localized on the vascular endothelium. Overproduction of triglycerides may occur in a variety of genetic conditions including familial hypertriglyceridemia and familial combined hyperlipidemia. IDL is generated following partial catabolism of VLDL and is also a triglyceride-rich particle. It migrates in the broad beta region on lipoprotein electrophoresis and is present in conditions such as diabetes mellitus. Type III hyperlipoproteinemia (HLP), also known as dysbetalipoproteinemia or broad beta disease, is characterized by elevated cholesterol and triglyceride levels, due to a decreased ability to convert VLDL and IDL to LDL combined with reduced clearance of chylomicron remnants. The level of IDL has been positively correlated with increased risk for atherosclerosis [17].

Low-Density Lipoprotein (LDL)

LDL is the major lipoprotein involved in the pathogenesis of atherosclerosis. It is a metabolic end product and if not

Table 23.2 Fredrickson classification of the hyperlipidemias

Phenotype	Elevated lipoprotein(s)	Elevated lipid levels	Plasma TC	Plasma TG
I	Chylomicrons	TG	N to ↑	–
IIa	LDL cholesterol	TC	↑↑	N
IIb	LDL cholesterol and VLDL cholesterol	TG, TC	↑↑	↑↑
III	IDL	TG, TC	↑↑	↑↑↑
IV	VLDL cholesterol	TG, TC	N to ↑	↑↑
V	VLDL cholesterol and chylomicrons	TG, TC	↑ to ↑↑	↑↑↑↑

Based on data from Gotto and Pownall [21]
IDL intermediate-density lipoprotein, *LDL* low-density lipoprotein, *N* normal, *TC* total cholesterol, *TG* triglyceride, *VLDL* very-low-density lipoprotein

cleared from the circulation, can become oxidized or chemically modified. LDL particles may then accumulate within the monocyte–macrophage system with subsequent generation of a cholesterol-rich foam cell, which is the initial feature of atherosclerosis. The LDL particle may be divided into seven subforms, with a density ranging from 1.019 to 1.063 g/mL and a diameter of 180–280 Å. The lowering of LDL by multiple interventions including pharmacologic therapy has been clearly demonstrated to reduce the risk for coronary heart disease, and LDL cholesterol is recommended as the primary target of therapy by the National Cholesterol Education Program [18].

High-Density Lipoprotein (HDL)

HDL is a small cholesterol-rich particle that migrates in the alpha region on lipoprotein electrophoresis. HDL cholesterol has been designated as a negative risk factor due to multiple epidemiologic studies and experimental interventions that have correlated elevated levels with a reduced risk for cardiovascular events. The mechanism by which HDL exhibits anti-atherogenic activity is multifactorial [19]. HDL plays a major role in reverse cholesterol transport, the process by which cholesterol is removed from lipid depots in the periphery and transported to the liver for excretion. In addition, LDL requires oxidation prior to the recognition and unregulated uptake by the foam cell, and HDL cholesterol is a natural antioxidant that protects LDL from oxidative stress. HDL may also have effects on platelet function and thrombosis.

HDL metabolism is intimately interrelated with triglyceride catabolism, and elevated levels of HDL cholesterol may be a marker of the efficiency of VLDL cholesterol metabolism. Low HDL cholesterol is associated with increased cardiovascular risk and has been correlated with physical inactivity, obesity, diabetes mellitus, hypertriglyceridemia, genetic conditions, and the use of tobacco products. However, measurements of circulating HDL cholesterol do not necessarily indicate the functional capacity of the HDL particles. Genetic conditions, such as possession of the apolipoprotein A-I variant known as Apo A-I_{Milano}, may be associated with low HDL cholesterol levels but not with an increased incidence of coronary artery disease. Human studies involving infusions of a recombinant form of Apo A-I_{Milano} have demonstrated significant regression of atherosclerosis and may have therapeutic implications [20].

Clinical Dyslipidemia

Major advances have been made in the measurement of circulating lipoproteins. The capacity to quantify apolipoproteins, particle size and density, and genetic abnormalities has significantly advanced. However, the determination of the lipid phenotype utilizing the Fredrickson classification still has substantial clinical utility, although it does not differentiate between primary and secondary dyslipidemias and includes no consideration of HDL cholesterol, lipoprotein(a), lipoprotein subforms, or particle number and density (Table 23.2).

Primary and Secondary Dyslipidemias

The lipid profile in a primary dyslipidemia is generally the result of an interaction between genetic tendencies and lifestyle influences. The diagnosis of a primary genetic dyslipidemia requires a systematic exclusion of all secondary causes of dyslipidemia (Table 23.3). A variety of clinical disorders express dyslipidemia as a secondary feature (Table 23.4).

National Cholesterol Education Program (NCEP) Guidelines

The NCEP has established guidelines for the screening, diagnosis, and treatment of dyslipidemia. The guidelines specify desirable ranges for the various lipid fractions [2]. A total cholesterol level of less than 200 mg/dL is considered desirable, while levels between 200 and 239 mg/dL are classified as borderline high and levels of 240 mg/dL or higher are considered to be elevated. For LDL cholesterol,

Table 23.3 Selected causes of primary dyslipidemia

Hypercholesterolemia
Heterozygous familial hypercholesterolemia
Homozygous familial hypercholesterolemia
Familial defective apolipoprotein B-100
Polygenic hypercholesterolemia
Disorders of HDL metabolism
Familial hypoalphalipoproteinemia
Lecithin: cholesterol acyltransferase deficiency
Familial apolipoprotein A-I/C-III deficiency
Tangier disease, fish-eye disease
Apolipoprotein A-I_{Milano} (A-I variant)
Primary combined hyperlipidemias
Familial combined hyperlipidemia
Type III hyperlipidemia
Primary hypertriglyceridemia
Familial hypertriglyceridemia (type IV or V hyperlipidemia)
Familial chylomicronemia
Lipoprotein lipase deficiency
Apolipoprotein C-III deficiency

Based on data from Gotto and Pownall [21]
HDL high-density lipoprotein

Table 23.4 Selected causes of secondary dyslipidemia

	Secondary	
↑ LDL cholesterol	Hypothyroidism	Cholestasis
	Nephrotic syndrome	Dysglobulinemia
	Chronic liver disease	Anorexia nervosa
↑ TG	Excessive alcohol consumption	Diuretics
	Obesity	Exogenous estrogens (oral administration)
	Pregnancy	Isotretinoin
	Diabetes mellitus	Cushing's syndrome
	Hypothyroidism	Oral contraceptives
	Chronic renal failure	
	Beta-blockers	
↓ HDL cholesterol	Physical inactivity	Obesity
	Smoking	Hypertriglyceridemia
	Diabetes mellitus	

Based on data from Gotto and Pownall [21]
HDL high-density lipoprotein, *LDL* low-density lipoprotein, *TG* triglycerides

levels below 100 mg/dL are considered optimal, between 100 and 129 mg/dL are near or above optimal, between 130 and 159 mg/dL are borderline high, between 160 and 189 mg/dL are high, and at 190 mg/dL or above are very high. Levels of HDL cholesterol below 40 mg/dL are classified as low, while levels at 60 mg/dL or above are high. Finally, normal triglyceride levels are considered to be less than 150 mg/dL; borderline-high levels are between 150 and 199 mg/dL; high levels are between 200 and 499 mg/dL; and very high levels of triglycerides are 500 mg/dL or greater.

Because the process of atherogenesis begins relatively early in life, the NCEP recommends that all adults above the age of 20 have a lipid profile performed at least once every 5 years. The rationale for early screening stems from recent epidemiologic data documenting the prevalence of abnormal lipid values as 20.3 % in youths between the ages of 12 and 19 years [22]. In addition, the prevalence of obesity is increasing in young Americans, and 43 % of obese youths have at least one abnormal lipid value. The Adult Treatment Panel emphasizes the determination of short-term (<10 years) risk for the development of coronary artery disease as a means of assessing the aggressiveness of treatment. Subjects with documented coronary artery disease or a coronary risk equivalent are felt to be at high risk and are candidates for aggressive therapy. Coronary risk equivalents include non-coronary forms of atherosclerotic disease, diabetes mellitus, and at least two risk factors with a calculated 10-year coronary heart disease risk over 20 %.

Global Risk Assessment

The National Cholesterol Education Program and the Adult Treatment Panel published guidelines in 2001, referred to as ATP III [2]. However, multiple clinical trials utilizing statin therapy were subsequently completed, and an update was published in 2004 recommending more aggressive therapy [23]. The trials that were analyzed in the 2004 update included the Heart Protection Study [24], Prospective Study of Pravastatin in the Elderly at Risk [25], Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial—Lipid-Lowering Trial [26], Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm [27], and the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 trial [28]. The next version of guidelines from the NCEP, called ATP IV, is expected to be released in 2013.

Global cardiovascular risk is calculated utilizing a modified version of the Framingham algorithm (Fig. 23.1). Subjects who are free of documented coronary artery disease but who demonstrate two or more risk factors in combination with a high LDL cholesterol should have their global risk calculated as a means of identifying target goals for LDL cholesterol and the initiation of pharmacologic therapy. The Framingham risk score is determined by evaluating the major risk factors (smoking, total cholesterol, HDL cholesterol, age, blood pressure, and gender). The emerging risk factors, such as lipoprotein(a), high-sensitivity C-reactive protein, or other markers of inflammation, are not generally included as part of routine screening. However, ATP III acknowledges that the presence of such factors may influence clinical judgment regarding the need for more intensive therapy. Recommendations from the Centers for Disease Control and Prevention and the American Heart Association validate the use of C-reactive protein in this way [29].

1. Add Up Points by Risk Factor

Age (years)	Points	
	Men	Women
20–34	–9	–7
35–39	–4	–3
40–44	0	0
45–49	3	3
50–54	6	6
55–59	8	8
60–64	10	10
65–69	11	12
70–74	12	14
75–79	13	16

TC (mg/dL)	Points by Age (years)									
	20-39		40-49		50-59		60-69		70-79	
	M	W	M	W	M	W	M	W	M	W
<160	0	0	0	0	0	0	0	0	0	0
160–199	4	4	3	3	2	2	1	1	0	1
200–239	7	8	5	6	3	4	1	2	0	1
200–279	9	11	6	8	4	5	2	3	1	2
≥280	11	13	8	10	5	7	3	4	1	2

	Points by Age (years)									
	20–39		40–49		50–59		60–69		70–79	
	M	W	M	W	M	W	M	W	M	W
Nonsmoker	0	0	0	0	0	0	0	0	0	0
smoker	8	9	5	7	3	4	1	2	1	1

Systolic BP (mmHg)	If untreated		If treated	
	M	W	M	W
<120	0	0	0	0
120–129	0	1	1	3
130–139	1	2	2	4
140–159	1	3	2	5
≥160	2	4	3	6

HDL-C (mg/dl)	Points	
	Men	Women
≥60	–1	–1
50–59	0	0
40–49	1	1
<40	2	2

2. Estimate Risk

MEN		WOMEN	
Points Total	10-year Risk %	Points Total	10-year Risk %
<0	<1	<9	<1
0	1	9	1
1	1	10	1
2	1	11	1
3	1	12	1
4	1	13	2
5	2	14	2
6	2	15	3
7	3	16	4
8	4	17	5
9	5	18	6
10	6	19	8
11	8	20	11
12	10	21	14
13	12	22	17
14	16	23	22
15	20	24	27
16	25	≥25	≥30
≥17	≥30		

Fig. 23.1 Framingham risk algorithm to estimate 10-year risk for coronary heart disease. *BP* blood pressure, *HDL-C* high-density lipoprotein cholesterol, *M* men, *TC* total cholesterol, *W* women (Based on data from Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [2])

In the initial patient assessment, physicians should establish a risk factor profile that consists of the level of LDL cholesterol combined with six other positive risk factors and one negative risk factor (Table 23.1). The presence of an HDL cholesterol level greater than 60 mg/dL allows one risk factor to be subtracted from the total score. Subjects are considered to be at significant risk if two or more coronary heart disease risk factors are present and should be treated with more aggressive interventions even if atherosclerotic disease has not been documented. Age is defined differently for men and women in risk factor tabulation due to gender-mediated differences in cardiovascular event rates.

Primary Prevention

The lipid goals for primary prevention define a total cholesterol of less than 200 mg/dL as a desirable level. Cholesterol levels between 200 and 239 mg/dL are classified as borderline high, while levels of 240 mg/dL or higher are considered to be elevated. The relationship between total cholesterol and cardiovascular risk is not linear, and definite thresholds below which lipid lowering is either ineffective or detrimental have not been established.

The total risk factor score should be determined as a means of gauging the necessity and intensity of therapy (Fig. 23.1). Individuals with both an acceptable risk factor score and lipid levels that are within the normal range do not require therapy, although instruction in hygienic measures such as increased physical activity and dietary interventions should be provided to reduce long-term risk for the development of cardiovascular disease. Low-risk patients should have a risk factor score determined every 5 years. Individuals with total cholesterol levels in the borderline range but with normal HDL cholesterol and less than two risk factors should also be instructed on hygienic measures. However, these individuals require more frequent follow-up evaluations, with risk factors reassessed biannually.

A complete lipid profile is recommended in subjects with low HDL cholesterol who also have two or more risk factors.

If the total cholesterol level falls in the high or borderline-high categories, LDL cholesterol is considered to be desirable if it is below 130 mg/dL. LDL cholesterol above 160 mg/dL is considered to be elevated even in the absence of documented coronary artery disease. Borderline-high LDL cholesterol is considered to be between 130 and 159 mg/dL. Subjects with desirable LDL cholesterol levels should be managed with dietary measures and increased physical activity.

Secondary Prevention

Patients following an acute coronary event are at high risk, and intensive therapy should be instituted prior to hospital discharge. The rationale for aggressive intervention is the significant risk of a recurrent event. Patients are frequently discharged following an acute coronary event on less than optimal therapy. The institution of discharge guidelines from the American Heart Association has demonstrated improvement in quality outcomes following the implementation of recommended therapies [30]. Cholesterol levels fall following an acute event, but lipid values obtained within the first 24 h are generally reliable. In the presence of documented coronary artery disease, the therapeutic goal for LDL cholesterol is less than 100 mg/dL and may be less than 70 mg/dL in selected high-risk individuals such as diabetics, who are classified as having a coronary risk equivalent [31]. Pharmacologic therapy may be instituted in conjunction with a diet and exercise program in individuals who would not be expected to meet NCEP goals with hygienic measures as the sole intervention. Following achievement of LDL cholesterol goals, other lipid abnormalities, such as elevated triglycerides, should be addressed. The utilization of non-HDL cholesterol, which includes all apolipoprotein B-containing particles, as a secondary target has been advocated as a means of circumventing the controversy regarding the relative contribution of hypertriglyceridemia to coronary risk [32]. The goals for non-HDL cholesterol may be determined by adding 30 mg/dL to the goals for LDL cholesterol.

Treatment of Lipid Disorders

Lifestyle Intervention

The NCEP has advocated that changes in lifestyle should be the first line of preventive treatment and continued even if pharmacologic therapy is employed. The key intervention is restriction of saturated fat consumption (<7 % of total calories) and cholesterol (<200 mg/day) in order to optimize the lipid profile and maintain ideal body weight [2]. Additionally, the restriction of sodium in hypertensive individuals should be implemented. The percentage of subjects with hypertension in the USA who followed a DASH (Dietary Approaches to Stop Hypertension) diet was 19.4 % in 1994–2004, which was a decline from previous surveys, indicating a relatively poor institution of lifestyle interventions [33]. Dietary modifications should also be coupled with attempts to increase the level of aerobic physical activity. Although the NCEP does not list physical inactivity as a major risk factor, reduced physical activity has an adverse effect on other cardiac risk factors including body mass index, lipid parameters, inflammatory markers, and glucose tolerance. Recent epidemiologic studies demonstrate that only 43.5 % of American adults are aerobically active, which represents a minimal change over the past decade despite widespread public health attempts to increase the level of physical activity in the USA [34]. Physical inactivity is a major public health problem in the USA, and a significant number of youths between the ages of 12 and 19 years are physically inactive [35]. The American Heart Association has advocated interventions to increase physical activity, based on recommendations from the United States Department of Health and Human Services' physical activity guidelines [36]. The American Heart Association recommends at least 150 min/week of moderate-intensity physical activities such as brisk walking or 75 min/week of vigorous-intensity aerobic physical activity, or any equivalent combination. The health benefits of physical activity occur across the age spectrum, in both sexes, and in every studied racial and ethnic group. The recommendations for physical activity among children should be at least 60 min/day every day or higher.

Drug Therapy

Failure to achieve lipid goals by diet and exercise alone may necessitate the institution of pharmacologic therapy. The decision to initiate a lipid-modifying agent should take into account the cost and potential long-term adverse effects of pharmacologic therapy. Additionally, the possibility of drug–drug interactions is a consideration. In relatively low-risk primary prevention subjects, dietary therapy should be attempted for at least 3 months before considering the addition of a pharmacologic agent. However, in individuals with genetic abnormities such as familial hypercholesterolemia who fit the criteria for primary prevention, pharmacologic therapy may be warranted earlier due to the high incidence of premature atherosclerosis. Additionally, in secondary prevention, earlier and more aggressive initiation of pharmacologic therapy may be considered.

ATP III established guidelines for the use of pharmacologic therapy based on the level of LDL cholesterol in association with other risk factors (Table 23.5). Pharmacologic therapy should be targeted at the lipid phenotype (e.g., elevated total cholesterol and LDL cholesterol or abnormalities predominantly involving triglycerides and HDL cholesterol).

Table 23.5 Treatment decisions based on LDL cholesterol

		Lifestyle modifications	Drug treatment
Risk category	LDL-C goal	Initiation level	Initiation level
0–1 other risk factors[a]	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160–189, LDL-C-lowering drug optional)
2+ other risk factors (10-year risk ≤20 %)	<130 mg/dL	≥130 mg/dL	10-year risk 10–20 %: ≥130 mg/dL
			10-year risk <10 %: ≥160 mg/dL
CHD or CHD risk equivalents (10-year risk >20 %)	<100 mg/dL (optional: <70 mg/dL)	≥100 mg/dL	≥100 mg/dL (<100 mg/dL: drug optional)

Adapted from Grundy et al. [23]. With permission from Lippincott Williams & Wilkins
CHD coronary heart disease, *LDL-C* low-density lipoprotein cholesterol
[a]Almost all people with 0–1 other risk factors have a 10-year risk <10 %: thus, 10-year risk assessment in people with 0–1 risk factor is not necessary

Pharmacologic Agents with a Predominant Effect on LDL Cholesterol

Bile Acid Sequestrants

The bile acid sequestrants, or resins, are quaternary ammonium salts. Cholestyramine, colestipol, and colesevelam are the currently available agents. The efficacy, mechanism of action, and side effect profile of the three available resins are basically similar, although colesevelam has a unique polymeric property that reduces gastrointestinal side effects and drug–drug interactions. Colesevelam may bind an equivalent amount of bile acids at a lower dose due to the structural modification of the molecule. Additionally, recent studies have indicated that colesevelam improves glycemic control, although the clinical implications of this remain to be determined [37]. The increased fecal loss of bile acids results in a reduction in intrahepatic cholesterol and a subsequent up-regulation of the LDL receptor. The bile acid sequestrants produce an increase in plasma clearance of LDL cholesterol due to receptor up-regulation combined with increased gastrointestinal loss. The gastrointestinal loss generally exceeds the clearance of LDL cholesterol by the LDL receptor, and the resulting decrease in intrahepatic cholesterol stimulates the rate-limiting enzyme in cholesterol synthesis (3-hydroxy-3-methylglutaryl coenzyme A, or HMG-CoA reductase) with increased cholesterol production and a blunting of the long-term efficacy of bile acid resin monotherapy.

The bile acid resins are associated with a variety of gastrointestinal side effects, although palatability may be improved by mixing with food. Cholestyramine is dosed at a maximum of 24 g/day, and colestipol is dosed at a maximum of 30 g/day. Colesevelam is administered in caplet form at a dose of six pills per day (625 mg of colesevelam per caplet) and has been demonstrated to have increased compliance. The administration of bile acid resins does not generally have a major effect on HDL cholesterol, although modest increases may be seen. Patients who can tolerate the maximum dose of bile acid resins may achieve an LDL cholesterol reduction of approximately 15–30 %. Additionally, colesevelam has been demonstrated to reduce LDL particle number and increase LDL particle size independent of baseline lipid levels, although the clinical implications remain to be determined [38]. The bile acid resins may result in an increase in circulating plasma triglycerides. The clinical usage of bile acid resins has declined in the past decades due to their side effects and the availability of more efficacious and palatable agents such as the statins. However, colesevelam represents an effective alternative agent to be utilized in patients with statin intolerance, since it is associated with reduced drug–drug interactions and fewer gastrointestinal side effects compared to other resins.

HMG-CoA Reductase Inhibitors

The development of the statins markedly improved the management of complex lipid disorders. Their mechanism of action involves partial inhibition of the rate-limiting enzyme in cholesterol synthesis with a subsequent decrease in cholesterol production. The reduced intrahepatic cholesterol levels result in an up-regulation of the apolipoprotein B/E receptor and increased plasma clearance of LDL cholesterol. Additionally, statins may exhibit a number of pleiotropic, or non-lipid, effects on endothelial function, clotting, inflammation, and plaque stability. Multiple clinical trials have demonstrated the efficacy of statins across the spectrum of atherosclerosis risk [39]. The currently available agents in order of their commercial release are lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin, and pitavastatin. They differ in structure and may also be classified on the basis of lipophilicity and metabolic handling. Despite these differences, the statins seem to share a common mechanism. Lipophilic agents such as atorvastatin may have a direct intrahepatic effect on the synthesis of apolipoprotein B-containing particles and may have an added effect on VLDL synthesis. Depending on the agent and dose utilized, decreases in LDL cholesterol ranging from 20 to 60 % may be expected.

The major impact on LDL cholesterol occurs with the initial dose, and an additional lowering of approximately 6–7 % occurs with each doubling of the statin dose [40].

The side effect profile of statins is well documented, and the potential risks of therapy are considerably outweighed by the clinical benefits of statins as demonstrated in prospective clinical trials [39]. The major side effect attributed to the statins is liver and muscle toxicity. Hepatic toxicity is defined as elevations in transaminase enzymes that exceed three times the upper limit of normal. Statin-induced elevations in transaminases are generally reversible following discontinuation of the drug, and the incidence of fatal hepatic necrosis with statin monotherapy is extremely low. Clinical studies have demonstrated that the incidence of significant elevations of transaminases is less than 1–3 % [41]. It is recommended that liver enzymes be monitored early in the course following the initiation of statin therapy, as well as in patients felt to be at increased risk due to the concomitant administration of other potentially hepatotoxic drugs or with preexisting liver disease.

Statin myotoxicity can be troublesome. A clinical spectrum exists that includes myalgia, myopathy, and rhabdomyolysis. Statin toxicity (myopathy) is defined as myalgia or muscle weakness with a level of creatine kinase greater than ten times the upper limit of normal. However, statin-associated elevations in creatine kinase are not always accompanied by muscle symptoms [42]. The prevalence of myotoxicity with statin monotherapy is 0.1–0.5 % and up to 2.5 % with combination therapy [43]. However, the presence of statin-associated myalgia in the absence of physical or biochemical findings is relatively common and is a clinical diagnosis that is verified by the resolution of symptoms with statin cessation. Rhabdomyolysis is the most feared statin side effect and is characterized by diffuse destruction of myocytes with a resulting release of myoglobin into the bloodstream and the potential for renal failure. Fortunately, the occurrence is low (1/100,000), but risk is increased when statins are combined with agents such as fibric acid derivatives. The mechanism of myotoxicity is complex and may be secondary to modulation of membrane fluidity, alteration of the membrane cholesterol/phospholipid ratio, impaired mitochondrial function, and abnormal calcium signaling [44]. Additionally, induction of apoptosis or increased lipid peroxidation may also occur. Statin therapy results in the depletion of metabolic intermediates such as ubiquinone (coenzyme Q10), although current clinical data do not support the utilization of coenzyme Q10 supplementation as a means of treating statin myotoxicity [45].

Ezetimibe

Ezetimibe was developed as a novel agent that selectively inhibits cholesterol absorption. Niemann–Pick C1-like 1 (NPC1L1) is a polytopic transmembrane protein that mediates cholesterol absorption and is localized at the apical membrane of enterocytes and in the canalicular membrane of hepatocytes [46]. Ezetimibe blocks NPC1L1-mediated cholesterol absorption and reduces the level of circulating cholesterol. The reduction in cholesterol absorption decreases intrahepatic cholesterol with a subsequent up-regulation of the apolipoprotein B/E receptor and increased plasma clearance of LDL cholesterol. Ezetimibe may have a dual mechanism of action, and experimental studies have demonstrated that ezetimibe increases cholesterol excretion from hepatic cells utilizing the ABCG5/G8 transport mechanism [47]. Ezetimibe has a long half-life and undergoes extensive glucuronidation within the intestinal wall and hepatic tissue. Systemic absorption is minimal, and systemic side effects with ezetimibe are extremely uncommon. Ezetimibe has minimal drug–drug interactions, although it is bound by the bile acid sequestrants. Gastrointestinal absorption in humans is characterized by a Gaussian distribution. The average individual absorbs approximately 55 % of gastrointestinal cholesterol, and in these individuals ezetimibe may be expected to reduce LDL cholesterol by approximately 20 %. Hyperabsorbers of cholesterol may experience much more dramatic LDL cholesterol lowering with ezetimibe. A recent clinical trial found that the combination of ezetimibe and simvastatin reduced the risk of major atherosclerotic events in patients with advanced chronic kidney disease, a population subgroup that had not previously been shown to benefit with LDL cholesterol reduction [48].

Pharmacologic Agents Predominantly Affecting Triglycerides and HDL

Nicotinic Acid

Nicotinic acid is an essential B vitamin that acts as a cofactor in the intermediate metabolism of carbohydrates. Deficiency of nicotinic acid results in pellagra, which may be prevented by 1–5 mg/day of nicotinic acid. Pharmacologic doses of nicotinic acid demonstrate beneficial effects on all circulating lipoproteins with the exception of chylomicrons. Nicotinic acid is the only approved lipid-lowering pharmacologic agent that has been shown to lower lipoprotein(a). It is generally employed at a dosing range between 1.5 and 5 g/day and may be expected to reduce LDL cholesterol by up to 25 %. Triglyceride levels fall between 20 and 50 %, with an accompanying rise in HDL cholesterol of up to 35 %. The use of nicotinic acid is hampered by its side effect profile, which ranges from mild flushing, which is common, to life-threatening fulminant hepatic necrosis, which is rare [49]. The mechanism of flushing is vasodilation and is prostaglandin-mediated. Nicotinic acid induces flushing through interaction with dermal Langerhans cells, resulting in increases in prostaglandins D2 and E2, which subsequently interact with the prostaglandin D2 receptor DP1 [50]. The extended-release forms of nicotinic acid are associated with a reduced

incidence of vasodilation, which may also be diminished by aspirin administered approximately 30 min before dosing. Additionally, an antagonist to the DP1 receptor, laropiprant, has been developed. Nicotinic acid is associated with a variety of gastrointestinal issues including activation of peptic ulcer disease. Metabolic abnormalities, including hyperuricemia and glucose intolerance, may also be induced. A recent clinical trial did not show benefit with extended-release nicotinic acid in patients optimally treated to low LDL cholesterol levels; however, the study may have been underpowered, and nicotinic acid remains the most effective available agent for raising HDL cholesterol [51].

Fibric Acid Derivatives

The currently available fibric acid derivatives in the USA are clofibrate, gemfibrozil, and fenofibrate. The fibric acid derivatives have a complex mechanism of action that is mediated by activation of the peroxisome proliferator-activated receptor α (PPAR-α) system. The resultant activation of lipoprotein lipase causes increased catabolism of triglyceride-rich lipoproteins. Gemfibrozil and fenofibrate have a large clinical experience in the USA. Gemfibrozil is dosed at 1,200 mg/day in divided doses. Fenofibrate has several dosing ranges depending on the brand but may be utilized once per day. Fibric acid derivatives generally result in a reduction in triglycerides of 20–50 %, which is associated with an increase in HDL cholesterol of 10–15 %. The magnitude of tri-glyceride reduction is partially related to pretreatment levels and the functional activity of the apolipoprotein B/E receptor, as well as to increased oxidation of fatty acids. The fibric acid derivatives may also favorably alter the composition of LDL particles to a larger, more buoyant form that may exhibit decreased atherogenicity, although LDL cholesterol levels may rise [52]. The fibric acid derivatives have additionally been demonstrated to exhibit a number of potentially beneficial effects on hemostatic parameters. The adverse effects of fibric acid derivatives are generally mild and do not require cessation of therapy. The most common side effects of the fibric acid derivatives are dyspepsia and nausea. The fibric acid derivatives have been associated with an increased incidence of gallstones. Hepatic and muscle toxicity have been reported but are not common with fibric acid monotherapy. Gemfibrozil (as opposed to fenofibrate) inhibits the glucuronidation of statins and may increase the blood levels of active statins and the risk for myotoxicity.

Special Issues

Age

Therapeutic advances in primary and secondary prevention, coupled with improved interventions in patients with acute coronary syndromes, have significantly altered age-adjusted cardiovascular mortality. This decline in mortality has resulted in an increased prevalence of individuals with cardiovascular disease above the age of 60 years. The American Heart Association has estimated that approximately 82.6 million American adults have one or more types of cardiovascular disease, and 40.4 million are estimated to be above the age of 60 [53]. The average age of the first myocardial infarction is currently 64.5 years for men and 70.3 years for women. In individuals above 80 years of age, 14.5 % of men and 14.8 % of women have had a prior stroke. Risk factors are also prevalent in individuals above the age of 65. The American Heart Association has determined that 64 % of men and 69.3 % of women in the age group from 65 to 74 years are hypertensive. Diabetes mellitus and dyslipidemia are also common in older individuals. The total prevalence of diabetes mellitus in the USA is expected to double in the time period from 2005 to 2050 [54]. The increase in diabetes is projected to be the largest for the elderly population and has been predicted to increase by 220 % in individuals between the ages of 65 and 74 years and by 449 % among individuals greater than 75 years of age. Data from the Minnesota Heart Study indicates that middle-aged and older people have experienced substantial decreases in mean cholesterol levels, which is at least partially due to increased recognition and utilization of pharmacologic therapy [55]. In the elderly population, pharmacologic therapy with statins has been shown to be effective in reducing LDL cholesterol levels and risk for recurrent cardiovascular events [56]. Clinical concerns had been previously raised as to the possibility that the lowering of cholesterol levels may negatively impact upon cognitive function. However, subgroup analysis of the PROSPER trial, which utilized pravastatin in the elderly, did not demonstrate either harm or benefit relative to cognitive function as assessed by neuropsychological performance testing [57].

Evidence indicates that atherosclerotic lesions begin to develop during childhood, decades before the clinical signs of atherosclerotic disease appear. In addition, rates of overweight and obesity are rapidly increasing among children and adolescents and are likely to predispose to the long-term development of risk factors for cardiovascular disease [58]. In order to prevent the development of risk factors and of future cardiovascular disease in children, an Expert Panel of the National Heart, Lung, and Blood Institute recently issued guidelines for pediatric care [59]. A new and controversial recommendation is to perform lipid screening on all children at 9–11 years of age, followed by another lipid profile between 18 and 21 years of age. Previous guidelines from the American Heart Association and the American Academy of Pediatrics (AAP) have recommended lipid screening only in high-risk children, such as those with underlying disease states or positive family history for cardiovascular risk factors. Guidelines from the AAP issued in 2008 state that

pharmacotherapy may be considered in children at least 8 years of age if they have elevated LDL cholesterol levels despite lifestyle modifications [60]. Drug therapy may be initiated if LDL cholesterol levels are at least 190 mg/dL in children with no other risk factors, at least 160 mg/dL in children with a family history of premature cardiovascular disease or with at least two risk factors, or at least 130 mg/dL in children with type 2 diabetes. Pharmacotherapy is only an option in patients under the age of 8 years if they are homozygous for familial hypercholesterolemia.

Women

Cardiovascular disease is the leading cause of death for women in the USA. Premenopausal women have a lower incidence of acute coronary events when compared with age-matched male subjects. In the postmenopausal years, LDL cholesterol begins to rise, with an accompanying increase in cardiac event rates. Women tend to have the same modifiable risk factors as men, although the presence of diabetes mellitus seems to exert a greater negative effect in women. Considerable advances have been made in the recognition of gender-mediated differences related to cardiovascular disease [61]. The absolute numbers of women living and dying with cardiovascular disease and stroke exceed the levels in men, and the absolute number of annual cardiovascular deaths in women has exceeded that of men since 1984. Additionally, women account for 60 % of the cases of fatal cerebrovascular disease in the USA.

The benefits of risk factor modification for secondary prevention in women are robust. However, the impact of pharmacologic therapy in women for primary prevention has been controversial due to a relative paucity of prospective data. Favorable evidence was provided by the recent JUPITER trial, which randomized 6,801 women greater than 60 years of age with an LDL cholesterol less than 130 mg/dL coupled with an increased level of high-sensitivity C-reactive protein (greater than 2 mg/L) to receive either rosuvastatin or placebo [62]. The trial was stopped prematurely after a medium duration of 1.9 years because of a 44 % reduction in the primary endpoint of major cardiovascular events. The hazard reduction was similar for women and men, although the absolute benefit in women appeared to be lower due to a lower baseline risk.

Obesity and the Metabolic Syndrome

The prevalence of obesity in the USA has reached epidemic proportions in children, adolescents, and adults and will have long-term implications for cardiovascular morbidity and mortality. Epidemiologic data has determined that 68 % of American adults are overweight or obese [63]. Overweight children and adolescents have been shown to have a significantly increased risk for the long-term development of the traditional risk factors such as hypertension, hyperlipidemia, and diabetes mellitus [58]. The localization of fat may be a major determinant of subsequent risk for the development of atherosclerosis. Central obesity can be measured by the waist–hip circumference ratio or quantified by computed tomography. The waist–hip ratio is associated with increased cardiovascular risk when in excess of 0.95 in men and 0.8 in women.

The term metabolic syndrome was proposed to describe a cluster of risk factors for cardiovascular disease and type 2 diabetes. Several definitions have been utilized for diagnosis of the metabolic syndrome. However, the American Heart Association, in conjunction with other organizations, has recently established a definition including five risk factors [64]. The diagnosis of the metabolic syndrome requires that three or more of the following risk factors are documented:

1. Fasting plasma glucose greater than or equal to 100 mg/dL, or therapy for hyperglycemia
2. HDL cholesterol less than 40 mg/dL in men or less than 50 mg/dL in women, or drug therapy for reduced HDL cholesterol
3. Triglycerides greater than or equal to 150 mg/dL, or drug treatment for elevated triglycerides
4. Waist circumference greater than or equal to 102 cm in men or greater than or equal to 88 cm in women in the USA
5. Systolic blood pressure greater than or equal to 130 mmHg and/or diastolic blood pressure greater than or equal to 85 mmHg, or drug treatment for hypertension

The prevalence of the metabolic syndrome varies according to the definition used, but data from the NHANES survey (2003–2006) documented that the prevalence of the metabolic syndrome was 34 % in adults greater than 20 years of age [65]. The prevalence of the metabolic syndrome considerably increases the risk for the development of cardiovascular disease. A recent meta-analysis of prospective studies demonstrated that individuals who fit diagnostic criteria for the metabolic syndrome had a relative risk of 1.78 for the development of cardiovascular disease [66]. Additionally, women tended to have a higher cardiac risk relative to male subjects. The cardiovascular risk associated with the metabolic syndrome varies according to the number and severity of the component risk factors present. The metabolic syndrome is treated with lifestyle modifications and with pharmacologic therapy in individuals who do not normalize their risk factor profile with lifestyle changes alone.

Diabetes Mellitus

Type I and type II diabetes mellitus are associated with increased cardiovascular risk. The current increase in incidence and prevalence of obesity in both adolescents and adults is temporally accompanied by an increase in the risk for the development of diabetes mellitus. Long-term studies initiated in youths who were followed into adulthood have

shown that individuals who are prediabetic are more likely to develop a constellation of metabolic disorders in young adulthood, including obesity, hypertension, dyslipidemia, and the metabolic syndrome, which all predispose to the development of cardiovascular disease [67]. The cardiovascular mortality associated with diabetes increases significantly with age, and it has been estimated that 68 % of individuals with diabetes greater than 65 years of age die of cardiovascular disease. Heart disease rates among adults with diabetes are two to four times higher than in nondiabetic individuals. Women with diabetes lose gender-mediated protection from cardiovascular disease and also demonstrate a higher post-myocardial infarction rate when compared to men.

Diabetes is classified as a coronary risk equivalent and should prompt aggressive risk factor management. The carbohydrate abnormality in diabetes is linked to increased risk for microvascular complications (peripheral neuropathy and retinopathy). In addition, diabetes mellitus is frequently associated with obesity, dyslipidemia, and hypertension, which predispose to macrovascular complications such as heart attack, peripheral vascular disease, and stroke. The dyslipidemia often found in patients with type II diabetes is characterized by borderline elevations of triglycerides, low levels of HDL cholesterol, and increased numbers of small dense LDL particles. Clinical trials performed with statin therapy have clearly demonstrated reductions in cardiovascular morbidity and mortality in patients with diabetes [68]. The lipid triad would appear to be an ideal target for fibric acid derivatives therapy. However, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) was a large-scale study in 9,795 subjects with type 2 diabetes who were randomized to study the effect of fibric acid derivatives on coronary events [69]. The administration of fenofibrate did not decrease coronary events, although a significant number of individuals in the group randomized to placebo received statin therapy, which may have confounded the results.

Weight loss and control of the carbohydrate abnormality may improve diabetic dyslipidemia. Optimization of hemoglobin A_{1c}, which is a marker of long-term carbohydrate control, has been demonstrated to reduce the risk for retinopathy and peripheral neuropathy. However, appropriate target values of hemoglobin A_{1c} as a means of reducing macrovascular complications are controversial. Guidelines have generally recommended a target goal for hemoglobin A_{1c} of 7 %. Recent large-scale trials have evaluated the potential benefits of lower targets, but they have not demonstrated macrovascular benefits and have shown only limited improvements in microvascular complications, in addition to an increased rate of hypoglycemia [70, 71].

The therapeutic approach to individuals with diabetes mellitus would be aggressive lipid lowering (to LDL cholesterol levels less than 100 mg/dL or in high-risk individuals to less than 70 mg/dL), optimization of the carbohydrate abnormality, blood pressure control, weight loss, and exercise.

Summary

Significant progress has been made in the early identification of individuals at risk for coronary artery disease. Additionally, major advances in the management of patients with established cardiovascular disease have occurred. However, the burden of atherosclerosis remains large, and a significant number of individuals at risk have not received optimal medical therapy in spite of overwhelming clinical trial evidence demonstrating improvements in cardiovascular morbidity and mortality with lipid modification. Challenges for the future include improved identification of individuals at risk for cardiovascular disease and thorough institution of the proven therapeutic interventions that decrease cardiovascular morbidity and mortality.

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Stable Angina

24

Sachin Mehta and Neal Kleiman

Introduction

As the twenty-first century progresses, the prevalence of coronary artery disease (CAD) will reach epidemic proportions in both the western and the developing world. In the USA, it is estimated that more than 13 million people have CAD [1]. As the population ages, and as the frequency of diabetes increases, these numbers will be expected to increase exponentially. The associated morbidity and costs exceed those of any other chronic disease in modern industrialized society. While tremendous progress in diagnostic techniques as well as in medical and interventional management has occurred over recent decades, the impetus for more novel strategies remains.

This chapter will review the current approach to stable angina. Although a variety of etiologies of angina pectoris exists (Table 24.1), this discussion will assume that the most common pathology manifesting this entity is coronary artery atherosclerosis.

Clinical History

As with other diseases, a careful history is essential in diagnosing angina pectoris accurately. Attention to specific details often allows clinicians to discern between other potential causes of chest discomfort and thus offset the expense and risk of unnecessary testing. Exploring the quality, location, duration, and relieving and exacerbating features of the symptoms often permits a correct diagnosis. Angina pectoris typically manifests as a "heavy," "squeezing" chest discomfort brought on by exertional stress. The discomfort generally has a retrosternal component, often described as "bandlike" in nature. Radiation to the throat, jaw, and left shoulder is common. Relief usually occurs within minutes of cessation of the precipitating stress. Under most circumstances, sublingual nitroglycerin also succeeds in providing rapid relief. Anginal symptoms are considered stable if there has been no change in the pattern of intensity, frequency, or duration over several weeks. Grading of the severity of angina pectoris is useful in monitoring progression of symptoms, conveying information to other clinicians, and assessing treatment strategies (Table 24.2). Symptoms that are described as fleeting, sharp, or pinpoint in location are not suggestive of angina pectoris. Similarly, the absence of characteristic precipitating and relieving features should lead the clinician to suspect other diagnoses.

Classical symptoms of myocardial ischemia may not always be present in patients with angina pectoris. Particularly in the elderly, and in patients with diabetes, symptoms of recurrent nausea or unexplained vomiting may

Table 24.1 Etiologies of angina pectoris

Pathology	Disease
Coronary artery obstruction	Atherosclerosis
	Vasospasm
	Vasculitis
	Dissection
	Myocardial bridge
	Anomalous coronary origin
	Kawasaki's disease
Left ventricular hypertrophy	Hypertension
	Aortic valvular/subvalvular stenosis
	Idiopathic/familial hypertrophic cardiomyopathy
Right ventricular hypertrophy	Pulmonary hypertension
	Pulmonary stenosis

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DOI 10.1007/978-1-4614-6705-2_24,

Table 24.2 Canadian cardiovascular society classification of angina pectoris

Class I	"Ordinary physical activity does not cause angina" such as walking or climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation
Class II	"Slight limitation of ordinary activity" walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, or in wind, or when under emotional stress, or only during the few hours after awakening
	Walking more than two blocks (100–200 m) on the level and climbing more than one flight of stairs at a normal pace and in normal conditions
Class III	"Marked limitation of ordinary physical activity" walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace
Class IV	"Inability to carry on any physical activity without discomfort" anginal syndrome may be present at rest

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be the first clinical clues. Dyspnea on minimal exertion may be due to ischemia-induced left ventricular dysfunction (systolic, diastolic, or both) or mitral regurgitation. Finally, syncope due to an ischemia-mediated mechanism may be a presenting symptom. For example, in one review of individuals presenting to a hospital for syncope without chest pain, approximately 7 % of the patients were found to have acute ischemia [2].

Independent "classical" risk factors for CAD must also be kept in mind when obtaining a clinical history. These risk factors include hypertension, diabetes mellitus, hyperlipidemia, smoking, and a family history of ischemic heart disease (in first-degree relatives with cardiovascular events when younger than 60 years of age). In women over age 50, early menopause or a prolonged estrogen-deficient state should also be considered possible risk factors. Newer risk factors have been identified as well and are gradually assuming roles similar to those identified during previous decades. These include markers of inflammation including C-reactive protein [3–6] as well as certain newly identified genetic mutations [7–16].

Physical Examination

There are no clinical findings specific to CAD. However, since CAD is the most common heart disease of western society, any abnormal cardiac findings should be viewed as possibly related to chronic ischemic disease. The physical examination should focus on the detection of general findings that may be relevant to diagnosis and management. For example, hyperlipidemic syndromes may first be discovered by observing the skin lesions of xanthelasma or tendinous xanthomata. Patients with diabetes may show signs of microvascular disease, such as retinopathy, prior to manifesting large-vessel atherosclerosis. Evidence of peripheral vascular disease may be detected by the presence of carotid or femoral bruits and diminished peripheral pulses. Palpation of the precordium may provide evidence of left ventricular dysfunction by revealing a laterally displaced and sustained apical impulse. Auscultation of the chest may reveal a fourth heart sound (S4), indicating chronic hypertension with left ventricular hypertrophy.

During an acute anginal attack, the presence of a fourth heart sound may be secondary to ischemic, noncompliant myocardium. Careful examination of the venous system will give an indication of the volume status of a patient as well as of ventricular compliance. Elevated jugular venous pressure and/or peripheral edema may be findings of right heart failure, with or without concomitant left ventricular dysfunction. Certain physical findings may lead to a diagnosis other than angina. Palpation of a right ventricular heave at the left sternal border with a prominent pulmonic component of the second heart sound suggests right ventricular hypertrophy secondary to pulmonary hypertension. Characteristic murmurs of hypertrophic obstructive cardiomyopathy or aortic stenosis would implicate these etiologies as causes of angina, but do not exclude concomitant CAD.

Diagnostic Testing

Rest Electrocardiography and Ambulatory Monitoring

A resting 12-lead electrocardiogram (ECG) should be obtained in all patients undergoing evaluation for symptoms of stable angina pectoris. However, with the exception of abnormal Q waves in contiguous leads suggesting prior myocardial infarction, there are no findings on the resting 12-lead ECG that are absolutely diagnostic of CAD. In fact, many patients with a normal ECG at rest may subsequently be found to have severe coronary atherosclerosis. Conversely, repolarization anomalies such as T-wave inversions or ST-segment abnormalities are not uncommon in the general population free of CAD. Certain ECG abnormalities, namely, left anterior fascicular block or left bundle branch block occurring in patients with classic angina pectoris, may identify a subset of patients at a higher risk of death or myocardial infarction. However, it is important to remember that the variety of abnormal ECG findings has a low sensitivity and specificity to reach diagnostic conclusions.

The principle of ambulatory electrocardiographic (Holter) monitoring is to detect symptomatic or asymptomatic evidence of myocardial ischemia by evaluation of ST-segment changes during routine daily activities. While this test may be useful in some individuals, and has been the subject of a good deal of research concerning asymptomatic or "silent" ischemia, ambulatory monitoring as a clinical tool rarely provides additional useful information in the diagnosis of angina pectoris beyond that revealed by standard exercise stress testing.

Exercise Treadmill Electrocardiography

Exercise treadmill electrocardiography is a frequently used test in the diagnostic workup for symptoms of stable angina. This is also discussed fully in Chap. 9. The test is readily available, easily performed, safe, and low in cost. The goal is to correlate symptoms of angina with ST-segment changes consistent with myocardial ischemia. Objective parameters assessed during testing include maximal heart rate achieved, blood pressure response, ST-segment shifts, and workload capacity attained. Adequate sensitivity of the test is accomplished with target heart rates approximately 85 % of the age-predicted maximum (220 – age). Inability to reach this target while remaining symptom-free is considered submaximal exercise and has a very low negative predictive value for coronary artery disease, as the stress conditions met may not have been adequate to produce myocardial ischemia. Blood pressure measurements at increasing workloads are expected to show incremental increases in systolic blood pressure. Failure to do so suggests left ventricular dysfunction secondary to ischemia. ST-segment depression ≥1 mm with a horizontal or downsloping appearance is interpreted as indicative of myocardial ischemia, although other conditions, particularly increased left ventricular mass, may also produce this abnormality even in the absence of obstructive epicardial coronary artery disease. Workload capacity (usually measured in metabolic equivalents [METs]) achieved is best viewed as a prognostic marker. Treating patients empirically with antianginal medications prior to testing may be necessary, but will lower the sensitivity of the procedure. Therefore, clinicians should use their discretion in opting to discontinue medical therapy a few days before evaluation.

Exercise electrocardiography has an overall sensitivity and specificity of 68 and 77 %, respectively. Sensitivity is greatest in patients with multivessel disease, noted to be 81 % in an overview of 24,000 patients who eventually underwent coronary angiography [17]. Indicators of severity of disease include onset of symptoms or positive ST-segment changes at a low workload capacity (≤5 METs), sustained drop of ≥10 mmHg in systolic blood pressure, or delayed recovery of ST-segments after stopping exercise. In contrast, patients capable of achieving a workload capacity of 10 METs or more have an excellent prognosis, regardless of the extent of CAD [18, 19]. Clearly, such information derived from the exercise study will guide further diagnostic and management decisions, as will be discussed in a later section.

Myocardial Perfusion Imaging

Myocardial perfusion or single-photon emission computed tomography (SPECT) imaging by use of low-dose radioactive-labeled perfusion agents is a valuable test in the evaluation of CAD (see also Chap. XXX). This technique is most often used in conjunction with exercise electrocardiography. At peak exercise, where myocardial oxygen consumption and coronary blood flow are at their maximum, the perfusion tracer (thallium-201 or technetium-99m) is injected. If no obstructive coronary lesions are present, the tracer will be taken up equally in all territories of the myocardium. In any area of myocardium that is underperfused due to significant obstructive coronary lesions, impaired extraction of the tracer will produce a less-intense radioactive signal or "defect" on imaging. These stress images may then be compared to images at rest, where the defect may either "fill in" with signal, reflecting reversible ischemia in the territory, or remain unchanged, indicating a myocardial scar.

The sensitivity and specificity of SPECT imaging are in the range of 80 and 90 %, respectively. Sensitivity is highest for single-vessel disease and falls to approx 70 % for multivessel disease [20]. Additional information obtained from SPECT imaging includes identifying involved coronary arteries and the ischemic burden. Also, using the newer ECG-gated SPECT technology, assessment of stress and rest left ventricular ejection fraction may be acquired.

In patients unable to exercise, pharmacologic stress tests are available. Dipyridamole, adenosine, and its analogues are vasodilators that enhance blood flow to normally perfused myocardium, with a lower tracer uptake in underperfused areas. These agents are safe and also provide results with high sensitivity and specificity. Either agent may also precipitate angina in the absence of epicardial disease, but here scintigraphic findings are normal. Both drugs are contraindicated in patients with reactive airway disease, as they may precipitate acute bronchospasm. Regadenoson, an A2A adenosine receptor agonist, is safe to use in this setting [21–23]. Similarly, a dobutamine stress test is a reasonable alternative to use for assessing coronary artery disease in patients with underlying pulmonary disease.

Exercise Radionuclide Ventriculography

The value of radionuclide ventriculography in the detection of CAD is much diminished in light of more advanced techniques now utilized. It had been proposed that failure to increase ejection fraction more than 5 % during peak exercise was diagnostic of CAD. However, this finding has poor specificity [24]. Perhaps the best use of this test is in deciding which patients may benefit from revascularization. The observation at high stress levels of wall motion abnormalities that recover at rest indicates myocardium that may be protected by a revascularization procedure.

Rest and Stress Echocardiography

Rest echocardiography alone is not sensitive for the detection of CAD, as many patients with disease have both a normal left ventricular ejection fraction and wall motion at rest. In rare cases, abnormal Doppler velocities in the aortic root may signal narrowing of the left main coronary artery. However, other pathologies responsible for nonspecific symptoms may be recognized—for example, hypertrophic cardiomyopathy or valvular disease.

Stress echocardiography used in combination with rest imaging offers a good opportunity to observe signs of myocardial ischemia. Stress may be performed with exercise or more commonly with dobutamine, adenosine, or dipyridamole. The preferred agent is dobutamine. At high infusion rates (10–40 μg/kg/min), localized hypokinesis or impaired systolic wall thickening relative to rest images signals the presence of compromised myocardium. Transient LV dilation and impaired diastolic function as assessed by transmitral Doppler inflows may be other clues to ischemia. Additional benefits of this technique include accurate assessment of left ventricular mass and ejection fraction, assessment of concomitant valvular heart disease, and estimates of right and left heart filling pressures using Doppler techniques. Limitations include the inability to achieve adequate two-dimensional views in 5–15 % of studies. Overall, relative to myocardial perfusion imaging, dobutamine stress echocardiography has been found to detect CAD with a comparable sensitivity and specificity in the hands of experienced operators [25]. It also has the additional advantage that technically difficult studies in which the presence or absence of an abnormal response cannot be discerned are easier to identify than they are with scintigraphic testing.

Invasive Testing

Although coronary angiography is the best test to define the anatomical severity of CAD, it is often not required as the first choice to establish the diagnosis of angina pectoris in patients with stable symptoms. Exceptions include patients presenting with a history of angina associated with malignant ventricular arrhythmias and those who are found to have significant regional wall motion abnormalities or reduced ejection fraction seen on echocardiogram. Furthermore, there may be a lower threshold to perform invasive studies in patients with specific occupations, such as in airline pilots [26].

The optimal use of coronary angiography is for patients who are moderately or severely symptomatic or who have strongly positive noninvasive tests, and in whom knowledge of the degree of coronary disease may lead to decisions of appropriate revascularization procedures. Such scenarios include patients with myocardial ischemia at low exercise thresholds (<5 METs) or a myocardial perfusion scan indicating a moderate to severe (>15 %) defect size. Angiographic lesions reducing the lumen by 70 % are thought to be consistent with symptoms and signs of myocardial ischemia. Following evaluation of the coronary arteries, left ventriculography is usually performed for assessment of ejection fraction and wall motion abnormalities. The benefit of revascularization in asymptomatic patients with subsequent ischemia found on noninvasive testing has not been established. The National Heart, Lung, and Blood Institute (NHLBI)-sponsored International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial is currently undergoing evaluation to compare optimal medical therapy (OMT) versus OMT and revascularization in patients with stable coronary artery disease with at least moderate ischemia on stress imaging [27, 28].

Although coronary angiography remains the "gold standard" in defining the anatomic appearance of CAD, visual interpretation of the severity of lesions varies between observers [29]. In addition, major discrepancies between angiographic and postmortem findings have been found to exist, usually yielding underestimation of lesion severity by angiography [30]. These difficulties arise due to the limitations of angiographic imaging. A contrast-filled vessel lumen provides only a planar two-dimensional longitudinal view of a lesion, the severity of which may be misrepresented by the angiographic viewing angle. Obtaining multiple views may help resolve this issue; however, optimal imaging is often limited by radiographic foreshortening or overlapping vessels that obscure the arterial segment in question, particularly in tortuous vessels. These limitations may be overcome by the use of intravascular ultrasound (IVUS) or optimal coherence tomography (OCT) [31]. Such technology allows visualization of the entire circumference of the vessel wall. IVUS and OCT also allow characterization of deeper intramural structures or characterization of the physiologic significance of observed narrowed vessels. Tomographic views may demonstrate eccentricity of lesions, diffusely diseased segments, and ostial disease, all of which may be underestimated by conventional angiography. Finally, by virtue of the ability of

IVUS and OCT to characterize intramural anatomy, insight into the pathophysiology of coronary lesions is often gained.

While angiography, IVUS, and OCT assess coronary anatomy, fractional flow reserve (FFR) can be used to assess the functional significance of a coronary lesion. FFR (the mean ratio of aortic to distal coronary pressure) values across a lesion of less than 0.80 after intravenous adenosine indicate a functional limitation to coronary flow by the lesion [32–34]. Conversely, lesions that yield an FFR of greater than .80 signify lesions that do not benefit *from revascularization* [34, 35].

It is essential to keep in mind the imperfect sensitivity of noninvasive testing in diagnosing CAD. Therefore, in any patient where clinical suspicion is high despite a negative noninvasive test, coronary angiography should be performed.

Diagnostic Strategy

A thoughtful and systematic diagnostic approach is necessary to ensure cost-effective and accurate diagnoses. The value of a diagnostic test is related to the difference between the pretest probability of the diagnosis in question and the posttest probability using information derived from the diagnostic procedure. This concept is the foundation of Bayesian theory, which utilizes the patient's clinical information to arrive at pre- and posttest probabilities for CAD. For example, the use of exercise electrocardiography alone as a diagnostic tool has varying diagnostic power depending on the prevalence of CAD in selected patient populations (Fig. 24.1). Thus, in patients with a low pretest probability of CAD, positive results of the test minimally increase the posttest probability, primarily due to high false-positive rates. Conversely, in patients with a high pretest probability, minimal additional information is obtained about the likelihood of CAD. It is clear from Fig. 24.1 that the exercise treadmill is most powerful for predicting CAD in patients with an intermediate pretest probability (30–70 %) for CAD (Table 24.3). It is also important to realize that the aim of exercise testing is not solely the detection of CAD but also the integration of a larger picture including an objective measure of overall exercise performance, the ease of provocation of symptoms, and obtaining prognostic information. Figure 24.2 illustrates an algorithmic approach to diagnostic testing. Patients with a higher likelihood of CAD should receive adjunctive imaging that can provide further prognostic information and guide management decisions more precisely. While myocardial perfusion imaging and

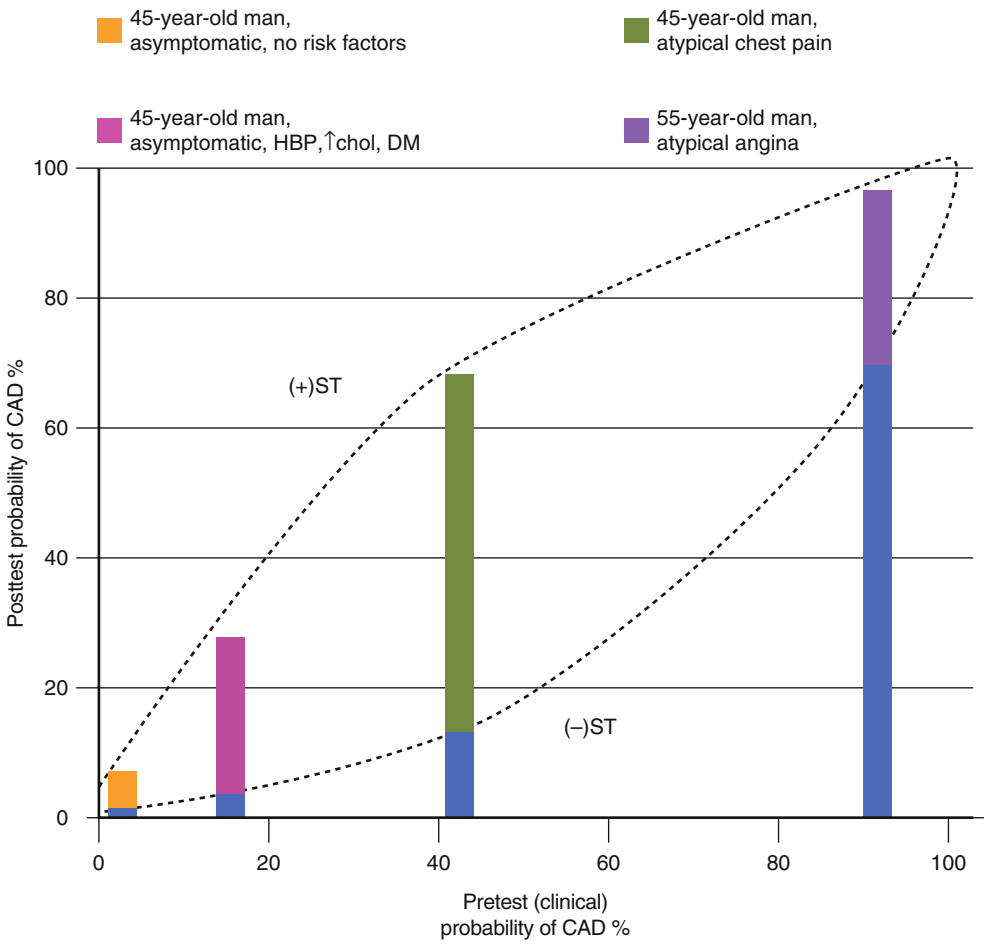

Fig. 24.1 Illustration of Bayes' theorem in ascertaining the probability of coronary artery disease by exercise electrocardiography. Four specific patient examples are shown along with pre- and posttest probabilities based on negative ("–" ST) or positive ("+" ST) test results. The value of the test is most useful for patients with intermediate pretest probability for coronary disease

Table 24.3 Profiles of low, intermediate, and high probability CAD

	Low probability (<30 %)			Intermediate probability (30–70 %)			High probability (>70 %)		
Age	Any age[a]	<40	>45	A. <40	>40	B. >40[b]	>40	>40	>55
Symptoms	Asymptomatic	Atypical	Asymptomatic	Typical	Atypical	Asymptomatic	Typical	Typical	Typical
Risks	0	≤2	≤2	0	≥2	≥2	≥2	≥2	0–5
ECG	Normal	Normal	Normal	Abnormal[c]	Abnormal	Normal or abnormal	Normal	Abnormal	Normal

[a]Diagnostic testing not indicated
[b]Patients considering onset of new vigorous exercise regimen or those with high-risk occupation (aviators, firefighters)
[c]"Abnormal ECG" refers to nonspecific abnormalities

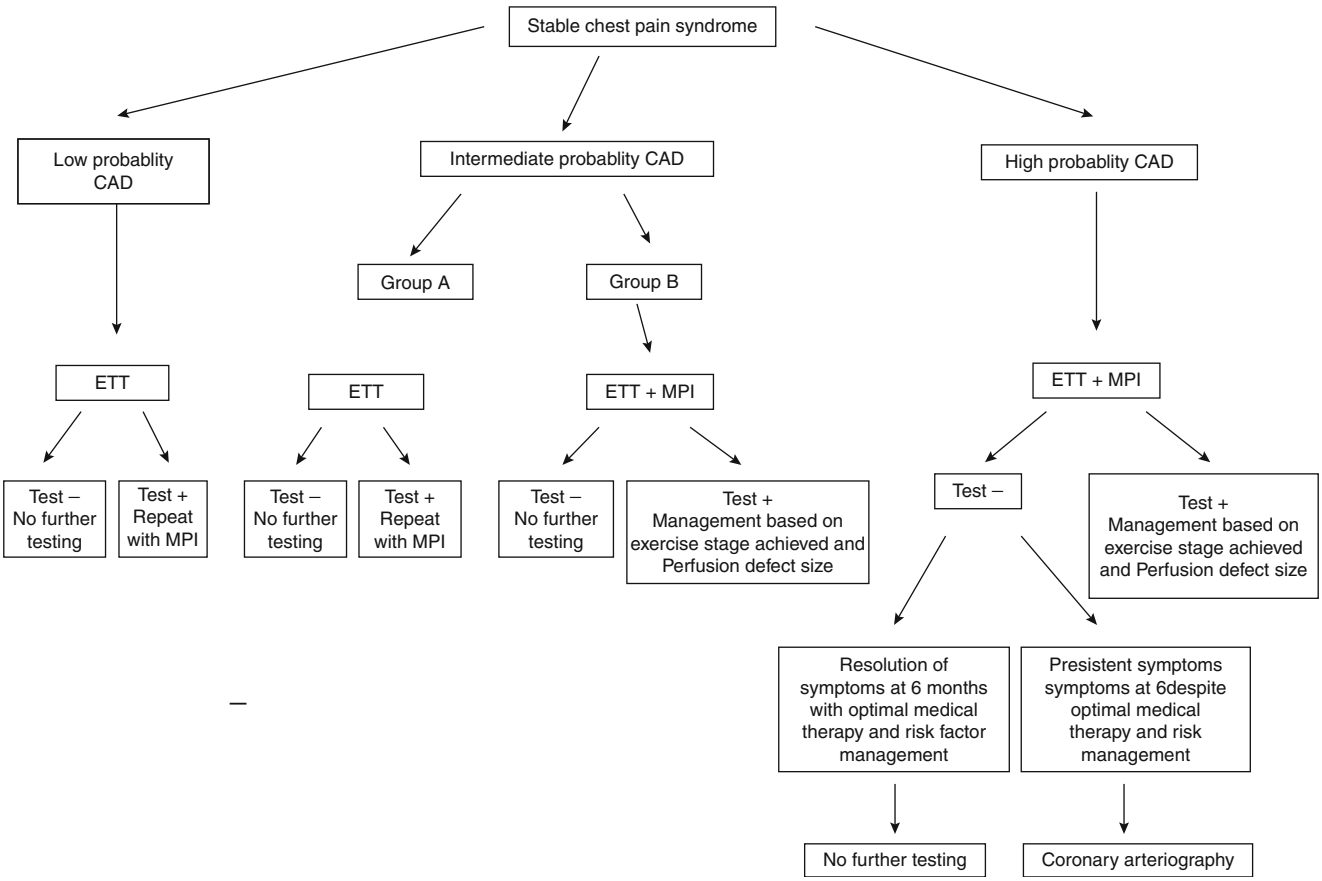

Fig. 24.2 Choice of diagnostic test

stress echocardiography may have comparable sensitivity for detecting CAD, there is a larger body of data based on quantitative perfusion defect size [36, 37]. Patients who are unable to exercise, who have left bundle branch block, or who have underlying hypertrophic or infiltrative cardiomyopathies should undergo pharmacologic stress due to the poor specificity of stress ECG in these conditions.

Medical Therapy

Antiplatelet Agents

Aspirin, available since the nineteenth century for its pain-relieving effects, was not recognized as an antiplatelet drug until the 1970s. It has now become the mainstay of treatment for both chronic and acute coronary syndromes. The antiplatelet effect of aspirin is believed to arise predominantly from its ability to diminish platelet production of thromboxane A2 (TXA2), a vasoconstrictor and proaggregant. In an overview by the Antiplatelet Trialists of more than 300 studies involving 140,000 patients with stable angina pectoris, previous myocardial infarction, prior stroke, and coronary bypass, aspirin was shown to significantly reduce the risk events of myocardial infarction and vascular death [38]. Doses ranging from 81 to 325 mg/day have been proven effective in smaller studies. There does not appear to be any additional benefit of higher doses. In fact, observational data indicate that the risk of bleeding is higher with 325 mg than with 81 mg [39]. Recent data also indicate that as many as

5–15 % of patients may be resistant to the actions of aspirin. It is difficult to define aspirin resistance precisely. However, when patients are categorized as aspirin-resistant on the basis of adenosine diphosphate (ADP)-induced platelet aggregation [40] or by chronic urinary excretion of TXA2 metabolites [41], they have higher rates of myocardial infarction.

Aspirin is relatively ineffective in preventing platelet aggregation by physiologic agonists such as ADP or collagen. Clopidogrel, ticlopidine, prasugrel, and ticagrelor belong to a unique class of antiplatelet agents that interfere with ADP-mediated platelet activation. These drugs inhibit the action of ADP on one of the three purinergic receptors on the human platelet, P2Y12 [42]. Ligation of this receptor by ADP stimulates the platelet shape change reaction as well as conversion of GP IIb-IIIa to the active conformation, thus permitting platelet aggregation to occur [43]. Although this class of agents has not been studied specifically in patients with stable angina, evidence from a large trial in patients with atherosclerotic vascular disease has demonstrated a decreased incidence of myocardial infarction and vascular death, particularly in patients who also have peripheral vascular disease [44]. Clopidogrel lacks the risk of transient neutropenia present with ticlopidine and may also be an effective secondary prevention *agent* [44]. For these reasons, ticlopidine or clopidogrel may be acceptable substitutes for aspirin in the rare instances of documented aspirin intolerance. In fact, the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial suggested that clopidogrel was more effective than aspirin in preventing future myocardial *infarctions* [44]. The superiority of aspirin in combination with a thienopyridine on secondary prevention in the setting of CAD is established following PCI or in patients with acute coronary syndromes for up to 1 year [45, 46].

The utility of clopidogrel in preventing primary or secondary events when added to patients with stable coronary artery disease was evaluated in the CHARISMA trial [47]. In this trial, more than 15,000 patients with either clinically evident cardiovascular disease or multiple risk factors received clopidogrel (75 mg/day) plus low-dose aspirin (75–162 mg/day) or placebo plus low-dose aspirin and followed them for a median of 28 months. The primary efficacy endpoint was a composite of myocardial infarction, stroke, or death from cardiovascular causes. Overall, clopidogrel combined with aspirin was not more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular *causes* [47].

Table 24.4 Commonly used drugs in stable coronary artery disease

Drug	Dose range
Antiplatelets	
Aspirin	75–325 mg qd
Nitrates	
Sublingual NTG tablets	0.3–0.6 mg prn, maximum three doses in 15 min
Sublingual NTG spray	0.4 mg prn, maximum three doses in 15 min
NTG paste/ointment	0.5–2″ 2 % NTG q 8 h/off 8–10 h daily
NTG patch	0.1–0.8 mg/h, on 12 h/off 12 h
Isosorbide dinitrate	10–60 mg (7 a.m., noon, 5 p.m.)
Isosorbide mononitrate	20 mg (8 a.m. and 3 p.m.)
Beta-blockers	
Cardioselective	
Metoprolol	25–150 mg bid
Atenolol	25–100 mg qd
Bisoprolol	5–10 mg bid
Noncardioselective	
Propranolol	20–80 mg qid
Nadolol	40–80 qd
Carvedilol	3.125–25 mg bid
Calcium-channel blockers	
Nondihydropyridines	
Diltiazem	30–90 mg qid
Verapamil	80–120 mg tid
Dihydropyridines	
Nifedipine	30–60 mg qd
Amlodipine	5–10 mg qd
Felodipine	5–20 mg qd
HMG CoA reductase inhibitors	
Rosuvastatin	5–40 mg q hs
Atorvastatin	10–80 mg q hs
Simvastatin	5–40 mg q hs
Pravastatin	10–40 mg q hs
Lovastatin	20–80 mg q hs
Fluvastatin	20–40 mg q hs

Nitrates

Sublingual nitroglycerin administered during an anginal attack is an effective means of aborting the episode within minutes. Smooth muscle relaxation in vascular tissue mediated by nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) results in venodilation and peripheral artery and coronary artery dilation [48]. The resulting decrease in preload and afterload reduces myocardial oxygen demand, while myocardial oxygen supply is improved. These effects may persist for up to 30 min.

A variety of nitrate formulations exist, ranging from short-acting to long-acting preparations (Table 24.4). Because of nitrate tolerance, longer-acting derivatives are best suited for patients with more frequent and severe symptoms. To avoid the development of tolerance, an 8–10-h nitrate-free interval is needed. Hence, patients should take nitrates only during periods when episodes most commonly occur.

Although nitrates clearly relieve anginal symptoms, no trials exist to demonstrate their effect on cardiovascular morbidity or mortality in stable angina pectoris. Nitrates are contraindicated in patients treated with phosphodiesterase-5 antagonists commonly prescribed for erectile dysfunction (sildenafil, vardenafil, tadalafil) [49, 50].

β-Adrenergic Blockers

β-Adrenergic blocking agents are essential components of the successful management of stable angina pectoris. Well recognized for their antihypertensive and antiarrhythmic properties, beta-blockers exert a powerful anti-ischemic effect in patients with CAD. β1-Receptor blockade in the heart reduces myocardial oxygen demand by reducing heart rate and myocardial contractility. Additionally, increased diastolic perfusion time and reduced wall stress improve myocardial oxygen supply. Therapy is usually titrated to achieve a heart rate in the 50–60 beats/min range.

Beta-blockers are generally well tolerated. Serious side effects include excessive bradycardia, heart block, hypotension, and bronchospasm. More common side effects are fatigue and impotence. Even with cardioselective β1-blocking agents, some β2-blockade occurs, making beta-blockers contraindicated in patients with severe asthma or chronic obstructive pulmonary disease. Patients with mild reactive airway disease generally tolerate cardioselective β1 blockers well, although dose titration should be tailored cautiously.

Because abundant data exist indicating prolonged survival in patients following acute myocardial infarction, as well as in patients with hypertension [51–53], beta-blockade therapy was practically a mandated requirement for individuals with underlying coronary artery disease and stable angina pectoris. However, while it is still a first-line agent in the treatment of chronic stable angina, contraindications must be considered including acute decompensated heart failure, conduction disturbances, airway reactive disease, and side effects that may be life altering (sexual dysfunction, depression, and lethargy) from beta-blockade therapy.

Calcium-Channel Antagonists

The calcium-channel antagonists are a heterogeneous group of compounds, which act through the common mechanism of decreasing calcium entry into smooth muscle cells and myocytes. The net effect is both coronary and peripheral vasodilation, an improvement in myocardial oxygen supply, and a reduction in oxygen consumption through afterload reduction. The nondihydropyridine drugs, verapamil (a phenylalkylamine) and diltiazem (a benzothiazepine), have the additional effect of decreasing the heart rate. Conversely, abrupt lowering of the blood pressure with dihydropyridines such as nifedipine may produce a reflex tachycardia, though this unwanted effect is less of an issue with longer-acting formulations. Other side effects of these agents include ankle edema, headache, flushing, and hypotension. Profound bradycardia may occur with high doses of verapamil as a result of its AV node blocking ability. In addition, due to the potent negative inotropic effect of verapamil and, to a lesser degree, diltiazem, these drugs are relatively contraindicated in patients with depressed left ventricular function. However, amlodipine has been well tolerated in patients with congestive heart failure [54].

All classes of calcium-channel antagonists have been shown to reduce exercise-induced angina. However, unlike beta-blockers, these agents have not been shown to improve survival in patients with known CAD. Meta-analyses suggest that they may actually increase long-term mortality [55, 56] but these were based mainly on studies using the short-acting dihydropyridines, which are rarely used now. There is now good evidence that verapamil and diltiazem can reduce reinfarction rates when used for secondary prevention after myocardial infarction, provided that there is no evidence of left ventricular dysfunction [57, 58]. Therefore, they may be considered a reasonable alternative when beta-blocker therapy is contraindicated, as in cases of severe reactive airway disease. Beta-blockers and calcium-channel antagonists may be used in combination for patients requiring a more intensified medical regimen.

Ranolazine

Ranolazine is a recently approved agent in treating stable angina. In addition to partial inhibition of fatty acid oxidation, there is suggestion that this agent prevents calcium overload in the myocardial cell thereby decreasing diastolic tension [59]. The efficacy of ranolazine has been demonstrated in several trials [60–62]. Based on the ERICA and CARISA trials, the FDA approved ranolazine for the treatment of chronic stable angina in patients who continue to have ischemic symptoms despite nitrate, calcium-channel blocker, and beta-blocker *therapy* [61, 62].

Lipid-Lowering Therapy

Numerous randomized studies of HMG CoA reductase inhibitors (statins) support their routine use in patients with CAD. Lowering total cholesterol and low-density cholesterol (LDL) levels in patients with hypercholesterolemia reduced the incidence of death and myocardial infarction in the primary prevention West of Scotland Trial (WOSCOPS) [63]. The Air Force/Texas Coronary Atherosclerosis Prevention Trial (AFCAPS/TEXCAPS) evaluated men and women with average cholesterol levels and without CAD. This study was terminated prematurely due to the superior benefit shown with lovastatin in preventing acute coronary syndromes [64]. The Scandinavian Simvastatin Survival Study (4S trial) of hypercholesterolemic patients with stable angina or previous myocardial infarction clearly established the secondary prevention benefit of cholesterol lowering in patients with known CAD [65]. The Cholesterol and Recurrent Events (CARE) trial provided strong evidence that treatment with

40 mg of simvastatin daily in postmyocardial infarction patients with average cholesterol levels prolonged survival and reduced recurrent cardiac events [66]. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) [67] studied primary prevention of CAD in hypertensive patients with low-dose atorvastatin and demonstrated a significant reduction in cardiovascular events in the study group that resulted in premature termination of the trial.

The Heart Protection Study (HPS) [68] revealed that patients with a total cholesterol greater than 135 mg/dL who were at high risk for coronary artery disease derived benefit from simvastatin (40 mg) even when the enrollment LDL was less than 100. Within this study, the composite endpoint of death, stroke, or myocardial infarction was reduced by 35 % at 3-year follow-up. Finally, the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) [69] study demonstrated that intensive LDL-lowering therapy with atorvastatin 80 mg daily (median LDL achieved was 62 mg/dL) compared with moderate LDL reduction achieved (median LDL 95 mg/dL) by using pravastatin 40 mg daily reduced cardiovascular endpoints significantly in patients presenting with acute coronary syndromes. On the basis of these overwhelming data, the National Cholesterol Education Program (NCEP) has recommended cholesterol lowering in all patients at high risk for CAD or extracardiac atherosclerosis to LDL levels to a goal of less than 100 mg/dL with an option of decreasing LDL to less than 70 at the discretion of the provider via increased statin dose or additional hyperlipidemic medications [70].

An often-forgotten risk factor in CAD is serum triglyceride level. Although most epidemiological studies have demonstrated an association between triglyceride level and heart disease, the strength of the association often weakens when controlled for HDL levels. However, a recently completed 8-year follow-up study in asymptomatic men with elevated triglyceride levels found an increased rate of cardiac events and all-cause mortality, independent of HDL levels [71]. Thus, patients with CAD should be aggressively treated to reduce their triglyceride levels as well as LDL cholesterol. Effective treatments include the use of fibric acid derivatives, such as gemfibrozil or clofibrate. Niacin is also an effective triglyceride-lowering agent. In a small study of 164 patients, the addition of niacin (mean dose of 2.4 g/day) to low doses of simvastatin (mean dose 13 mg/day) led to regression of atherosclerosis and reduced clinical events by 60 % when compared to placebo [72]. The use of combined therapies for mixed hyperlipidemia disorders raises concerns over increased risk of hepatic toxicity and skeletal myopathy. Combination therapy is not absolutely contraindicated; however, individual dose adjustment must be considered when combining therapies. Patients should be monitored closely for laboratory indicators of these complications. Newer-generation HMG CoA reductase inhibitors have been shown to be useful in reducing borderline increases in triglyceride level and may obviate the need for combined therapies in some circumstances [73].

Hormone Replacement Therapy

The controversy of hormone replacement therapy for the primary and secondary prevention in CAD has been resolved by the Women's Health Initiative (WHI) [74] and the Heart and Estrogen/Progestin Replacement Study (HERS) [75].

Although lack of estrogen has been implicated as a risk factor for CAD for more than three decades, only in recent years have well-designed trials been initiated to assess the efficacy of estrogen replacement. The beneficial effect of hormone replacement therapy on the lipid profile is less of an issue. Many studies have demonstrated the lowering of LDL and lipoprotein(a) levels, while elevating HDL [76]. The proposed efficacy of hormone replacement therapy was believed to arise from this enhanced lipid profile and to positive effects of estrogen-mediated endothelial vasomotor function.

The data suggesting the benefit of hormone replacement therapy in CAD have come from observational studies [77, 78]. The Nurses' Health Study found that a large cohort of women currently using hormone replacement therapy had a 50 % reduction for myocardial infarction or all-cause mortality as compared to nonusers [79]. Observational studies such as these may be criticized for inherent selection biases. For example, individuals choosing to use hormone replacement therapy typically lead a more healthful lifestyle, seek regular medical care, and follow exercise regimens. The Heart and Estrogen/Progestin Replacement Study (HERS) was a double-blinded, randomized secondary prevention trial that evaluated the efficacy of hormone replacement therapy in ischemic heart disease. Despite improved lipid profiles in the treatment arm, there was no significant benefit in preventing recurrent myocardial infarction or cardiac death during an average 4-year follow-up. Thromboembolic events, including pulmonary embolism, occurred more frequently in the treated arm, particularly in the first year after beginning *therapy* [75]. The results of the Women's Health In*itiative* [74] showed an increased risk of adverse coronary events when estrogen and progesterone combination therapy was used for primary prevention. Based on these trials, hormonal therapy is not indicated for either primary or secondary prevention of coronary heart disease, although in patients at low risk for cardiac complications, hormone replacement therapy may still be indicated for treatment of symptoms resulting from estrogen deficiency.

Antioxidant Therapy

It is hypothesized that the oxidation of LDL cholesterol particles may play a pivotal role in the initiation and progression of atherosclerosis. There are observational study data to

suggest that naturally occurring antioxidants may slow this process. However, as previously mentioned, selection biases of epidemiological studies render these data inconclusive.

To date, three randomized, double-blind, placebo-controlled trials have examined the effects of antioxidants on cardiovascular events. The Physicians Health Study was a primary prevention trial of 22,000 physicians over a 12-year period. Supplementing a diet with the antioxidant β-carotene produced no reduction in cardiovascular morbidity or mortality [80]. Conflicting evidence exists in secondary prevention. A Finnish study failed to detect any benefit of vitamin E or β-carotene in limiting progression to severe symptomatic angina or myocardial infarction in men with established CAD [81]. In contrast, the Cambridge Heart Anti-Oxidant Study (CHAOS), using a higher dose of vitamin E (400–800 IU), demonstrated a 47 % risk reduction in cardiovascular death and nonfatal myocardial infarction [82]. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI) Prevention study [83] and Heart Outcome Prevention Evaluation study [84] did not show any benefit from antioxidant therapy.

Based on the current data, the empiric use of antioxidant therapy for primary or secondary prevention of coronary atherosclerotic heart disease is not recommended.

Exercise

One of the most beneficial and cost-effective treatments in treating chronic stable angina is exercise. Exercise conditioning increases work capacity, reduces myocardial O2 demands, increases potential O2 supply, improves the supply/demand balance at any given submaximal workload thereby reducing the risk of ischemia, and raises the exercise threshold for cardiac ischemia in coronary artery disease [85, 86]. In one study, exercise was compared to revascularization in the treatment of stable angina [87]. One hundred and one male patients with stable angina were randomized to an exercise-based regimen and medical therapy or PCI with medical therapy. The aim of the study was to compare the effects of each therapeutic strategy on clinical symptoms, angina-free exercise capacity, myocardial perfusion, cost-effectiveness, and frequency of a combined clinical endpoint (death of cardiac cause, stroke, CABG, angioplasty, acute myocardial infarction, and worsening angina with objective evidence resulting in hospitalization). The exercise program consisted of six 10-min observed sessions on a bicycle ergometer at 70 % of the symptom-limited maximal heart rate for 2 weeks. After this 2-week program, a maximal symptom-limited ergospirometry was performed to calculate the target heart rate for independent training, which was defined as 70 % of the maximal heart rate during symptom-limited exercise. Patients were asked to exercise on a bicycle ergometer close to the target heart rate for 20 min/day and to participate in one 60-min group training session of aerobic exercise per week.

At 12 months, survival free of cardiac events (cardiac death, cardiac arrest, MI, stroke, revascularization, or hospitalization for worsening angina) was significantly higher with exercise training than with PCI (88 % vs. 70 % for exercise and PCI, respectively; $p = .023$). Furthermore, there was a reduction in inflammatory markers in the group randomized to exercise, while the patients who underwent PCI had no significant change [88]. Finally, on average, the expenses for 1 year of exercise training amounted to $3708 ± 156 compared with $6086 ± 370 per PCI *patient* [87].

A recent study assessed the efficacy of cardiac rehabilitation in elderly patients with stable coronary artery disease. One hundred and eleven males comprised the cardiac rehabilitation study group and were compared to 74 age-matched controls [89]. The patients were followed for up to 3,500 days, with an endpoint of death or one of the following major adverse cardiovascular events (MACE): cardiovascular death, acute coronary syndrome, refractory angina requiring revascularization, admission for congestive heart failure, or stroke. The MACE incidence was significantly lower in the cardiac rehabilitation group than in the control group (30 % vs. 62 % for exercise and control, respectively; $P = 0.001$).

A meta-analysis including more than 8,900 patients examined the effect of exercise in reducing cardiovascular events in patients with underlying coronary artery disease [90]. Compared with usual care, cardiac rehabilitation was associated with reduced all-cause mortality, cardiac mortality, total cholesterol level, triglyceride level, systolic blood pressure, and rates of self-reported smoking.

To assess the efficacy of exercise training in patients with stable angina who underwent PCI, Soga and colleagues compared PCI alone to exercise training and PCI in patients who underwent percutaneous revascularization [91]. After receiving PCI, patients were randomized to an exercise regimen and a control group. Unscheduled hospital visits for angina were significantly less common in the group randomized to exercise (20.2 % vs. 27.2 % for exercise and control, respectively; $P < 0.0001$).

In an attempt to examine the effect of exercise capacity on coronary lesion characteristics, physiology, and anatomy, investigators compared the plaque composition of coronary lesions in patients with preserved cardiorespiratory fitness (CRF) against patients with decreased CRF [92]. The investigators prospectively performed both IVUS and OCT for 77 non-culprit coronary lesions in 77 consecutive patients with stable angina who underwent PCI. Percentage of achieved predicted peak oxygen consumption (% predicted peak Vo(2)) calculated based on measured peak Vo(2) using a cardiopulmonary exercise test performed post-PCI was adapted as an indicator of patient CRF.

When individuals with preserved CRF were compared to those with decreased CRF, preserved CRF patients had significantly smaller lipid volume (32 ± 14 % vs. 45 ± 13 %, $p < 0.001$ for preserved vs. non-preserved, respectively), greater fibrous volume (57 ± 11 % vs. 49 ± 11 %, $p < 0.001$ for preserved vs. non-preserved, respectively), and thicker fibrous cap thickness (177.7 ± 20.9 μm vs. 143.7 ± 36.9 μm, $p < 0.001$ for preserved vs. non-preserved, respectively). In multivariate linear regression analysis, % predicted peak Vo(2) showed a significantly negative correlation with lipid volume ($\beta = -0.418$, $p = 0.001$) and a positive correlation with fibrous volume ($\beta = 0.361$, $p = 0.006$) and fibrous cap thickness ($\beta = 0.339$, $p = 0.008$). Previous observations have hypothesized that a high percentage of lipid volume, a low percentage of fibrous volume, and a thin fibrous cap are associated with plaque vulnerability and hence an increased risk of plaque rupture [93, 94]. These findings suggest that in patients with a preserved CRF, presumably from a good underlying exercise capacity in part due to exercise training, coronary lesion composition may be less prone to future cardiovascular events than in patients with a decreased CRF.

Clearly, exercise is a key component in treating stable angina and must be recommended to all patients with coronary artery disease. Aside from improving cardiac status, exercise is inexpensive and available to every patient.

Revascularization: Catheter-Based Methods

Percutaneous Transluminal Coronary Angioplasty

The concept of therapeutic percutaneous angioplasty was first introduced in 1964 by Dotter and Judkins [95]. However, their technique for the treatment of peripheral vascular stenosis was not widely accepted because of the frequent occurrence of local trauma and hemorrhage. The subsequent development by Andreas Gruentzig of a double-lumen balloon catheter pioneered the modern era of interventional cardiology. In September 1977 in Zurich, Gruentzig performed the first percutaneous transluminal coronary angioplasty (PTCA) procedure in humans, successfully dilating the proximal left anterior descending coronary artery of a 37-year-old man with angina pectoris [96]. Repeat coronary angiography on the 10th and 20th anniversaries of the procedure revealed continued vessel patency.

Since this initial introduction in 1977, operator experience has expanded the selection of patients for whom PTCA may be appropriate, including those with stable multivessel disease and acute coronary syndromes. The ideal candidates for PTCA were originally described as patients with stable angina pectoris as a result of single-vessel CAD without complex angiographic characteristics. In such patients, procedural success rates exceeded 97 % even before the widespread use of intracoronary stents and were associated with a low risk of early complications such as myocardial infarction or death. Clinical variables such as advanced age, history of congestive heart failure, or left ventricular dysfunction, as well as complex lesion features including calcification, presence of thrombus, eccentric morphology, and ostial location, increased the periprocedural risk of PTCA. Experienced operators in high-volume catheterization laboratories have lower complication rates compared with low-volume medical centers.

Early complications of PTCA are most often the result of abrupt vessel closure, defined as the sudden occlusion of the target vessel during or shortly after the revascularization procedure. The incidence of this complication is in the range of 1–2 %. Before the availability of intracoronary stents, the pathophysiology typically involved local vessel dissection with obstructive dissection flaps, accompanied by the development of thrombus secondary to platelet activation from exposed subendothelial vascular wall components. Currently, stenting has allowed the achievement of widely patent coronary lumina with "sealing" of dissection flaps. Subacute stent thrombosis has replaced abrupt vessel closure as the bugbear of intracoronary intervention. With increasing technological advances and improved pharmacology, stent thrombosis is now quite rare. For example, as observed in the SPIRIT IV trial, the rate of stent thrombosis at 2-year follow-up in patients who were randomized to revascularization with everolimus-eluting stents was 0.4 % [97]. Risk factors for stent thrombosis include multiple stent placement, incomplete stent apposition to the arterial wall, incomplete expansion of the stent struts, increased stent length, side-branch stenting, and residual stenosis within the stent. Resistance to the antiplatelet effects of clopidogrel and/or aspirin has also been suggested as etiologies. The clinical consequences of such an event may lead to acute myocardial infarction, the need for urgent surgical revascularization, or even death. The use of thienopyridine platelet glycoprotein IIb/IIIa antagonists and intracoronary stents have successfully reduced the incidence and adverse outcomes of acute vessel closure [98, 99], and have augmented the ability to approach patients with more complex lesions and multivessel disease. Placement of a bare-metal stent (BMS) mandates a minimal 4-week course of clopidogrel and continued aspirin to prevent subacute stent thrombosis. Clinical trials of drug-eluting stents (DES) have mandated prolonged (greater than 1 month and up to 12 months) of therapy [100–103] with clopidogrel. The CREDO trial indicated that benefits continue to accrue when clopidogrel is continued through at least the first year after stenting [45]. Finally, although rare, case reports of late stent thrombosis after 1 year in drug-eluting stents have emerged. These events appear related to the cessation of antiplatelet therapy [104, 105].

The principal limitation of PTCA is restenosis, which has been reported in 30–40 % of patients within 6 months of the procedure [106]. The most common clinical presentation of restenosis is recurrence of stable anginal symptoms. Myocardial infarction as the initial presentation of restenosis is a rare occurrence. The pathogenesis of restenosis in response to mechanical injury induced by angioplasty is incompletely understood and is probably multifactorial. A number of pharmacological agents of various classes have been evaluated for the prevention of restenosis, including antiplatelet drugs, anticoagulants, calcium-channel blockers, and antiproliferative agents. The introduction of DES with sirolimus and paclitaxel has decreased the incidence of in-stent restenosis in discrete lesions to less than 8 % and the incidence of target-vessel revascularization to less than 5 % in patients who undergo PCI of a lesion within a single vessel. Although reduced by drug-eluting stents, restenosis still occurs more commonly in patients with diabetes and small vessels [107–109]. Future improvements in stent design and newer pharmacotherapy will reduce restenosis rates.

Over the years, methods adjunctive to angioplasty have been developed to assist in managing lesions with complex characteristics. Directional coronary atherectomy employs a blade housed within a balloon catheter. Inflation of the balloon forces the blade's housing against the protruding portion of the plaque; the blade trims away the plaque and forces the debris into the housing, opening the lumen of the artery more widely. Evaluation of this technique versus balloon angioplasty has not shown conclusive improvement in 6-month restenosis rates. Moreover, the use of directional atherectomy is associated with an increased rate of periprocedural non-Q-wave infarction [110, 111]. Rotational atherectomy (Rotablator®) employs a rotary cone containing diamond chips at the end of a catheter that is capable of abrading rigid or calcified lesions. Observational data suggest that rotational atherectomy is useful in managing complex lesion subsets not suitable for balloon angioplasty alone. Direct comparison in a randomized trial against standard balloon angioplasty has shown superior procedural success rates for rotational atherectomy in complex lesions without an excess of periprocedural complications. However, restenosis rates at 6 months were significantly higher in the rotational atherectomy group than in those patients who underwent balloon angioplasty [112].

Angiogenesis

Gene-Related Therapy and Stem Cells

With the recent advances in molecular biology, the concept of gene therapy and stem cell infusion in treating medical diseases offers an attractive therapeutic avenue. Indeed, several investigations have been performed in an attempt to utilize specific genes in treating ischemic disease [113–120]. While early investigations demonstrated encouraging results, two large trials of this therapy in patients with exercise-induced ischemia were terminated prematurely due to futility.

To examine the role of stem cell therapy in ischemic CAD refractory to medical therapy, investigators randomized patients to intramyocardial injection of autologous bone marrow-derived mononuclear cells versus injection of placebo solution [121]. The primary outcome was the change in the summed stress score (SSS), a 17-segment score for stress myocardial perfusion assessed by Tc-99m tetrofosmin single-photon emission computed tomography (SPECT). Secondary endpoints included changes in LVEF, CCS class, and Seattle Angina Questionnaire quality-of-life score. After 3-month follow-up, both groups showed a significant improvement in SSS (23.5–20.1 $\{P<.001\}$ in the study group, compared with a decrease from 24.8 to 23.7 $\{P=.004\}$ in the placebo group). Patients randomized to stem cell therapy demonstrated a 3 % increase in LVEF as assessed by magnetic resonance imaging compared to no change in patients who received placebo. Finally, the improvements in CCS class and quality-of-life score were significantly greater in bone marrow cell-treated patients than in placebo-treated individuals. Other studies have reported similar findings [122–125]. However, since these studies are underpowered and have not translated to hard clinical endpoints, definitive statements regarding the treatment of ischemic heart disease with stem cells cannot be entertained at this time.

Clearly, more data must be completed before making conclusive statements and recommendations regarding gene therapy and stem cell treatment with respect to the management of chronic stable angina.

Coronary Artery Bypass Surgery

Coronary artery bypass grafting (CABG) has remained a very effective procedure for relief of angina pectoris since first used in 1964 as a "bailout" technique by Dr. Michael DeBakey [126] and further refinement by Dr. Rene Favoloro [127, 128]. Symptoms of ischemia can be alleviated in more than 85 % of patients [129]. Though initial costs are high compared to other strategies, particularly PCI, in selected patients, the expenditure is comparable when repeat PCI and long-term intensive post-PCI medical therapy may be necessary.

Over the last 30 years, modifications of the procedure have continued to lead to high success rates in more complicated patients. The use of the internal thoracic artery (left internal mammary artery) to bypass the left anterior descending coronary artery (LAD) is superior to the use of

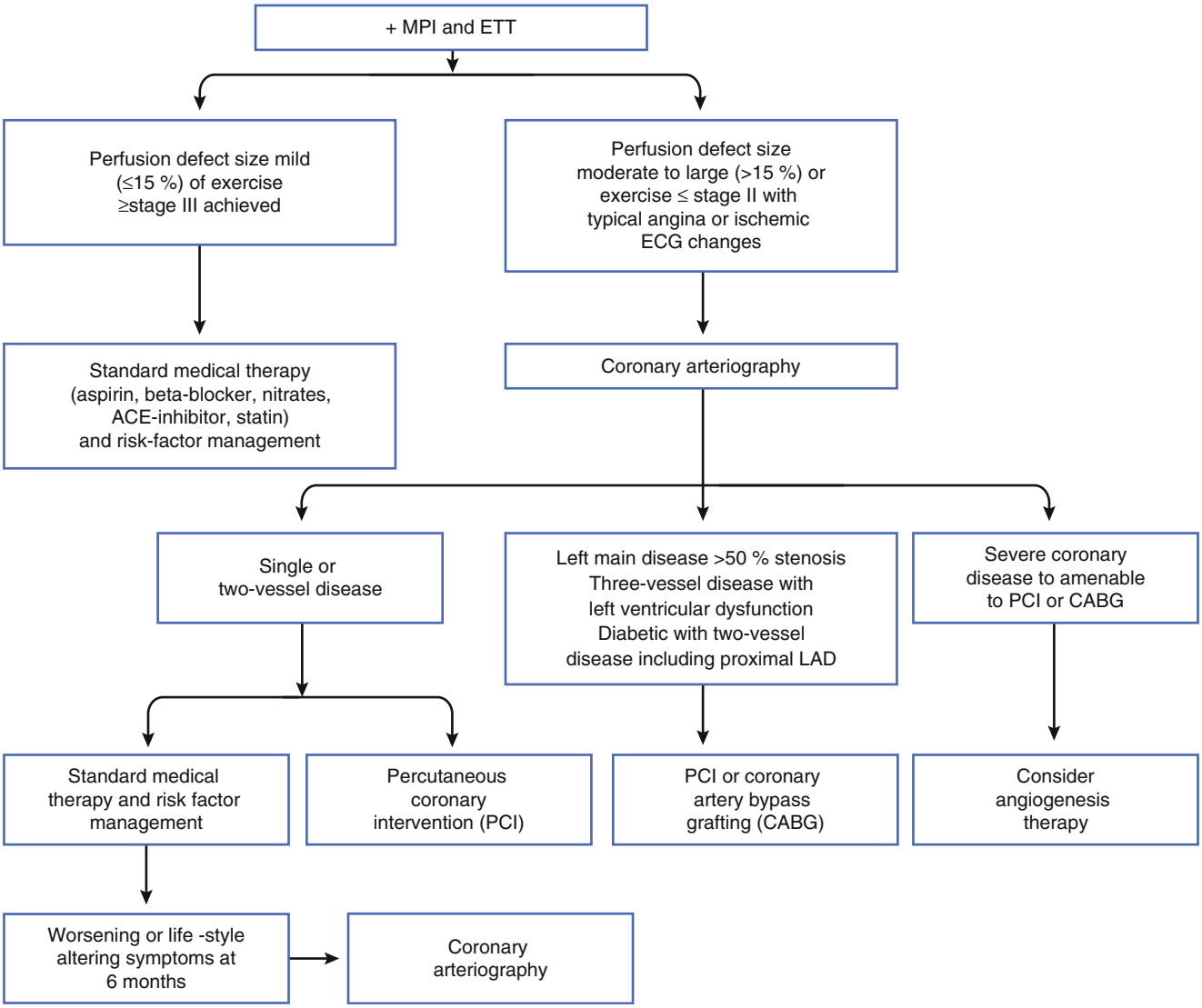

Fig. 24.3 Management strategy based on diagnostic test results

saphenous venous grafts. Patency rates for this graft are approx 90 % at 10 years compared with 30 % for saphenous vein grafts [129]. Evidence suggests that the use of two arterial grafts rather than one may lead to improved long-term symptomatic relief in selected patients [130]. A beneficial effect on mortality rates of using two rather than one arterial conduit on reoperation remains unclear. The present-day practice of chronic aspirin and aggressive lipid-lowering therapy in patients beginning immediately after CABG may make the choice of a second conduit (in addition to an internal thoracic artery) less of an issue, particularly in elderly patients.

Complication rates are related to the extent of CAD, left ventricular dysfunction, and comorbid illnesses. Overall, the perioperative composite rates of mortality and myocardial infarction approximate 5 %. Repeat operations are always associated with higher complication rates.

Management Decision Making

The goals of the effective management of stable angina pectoris are to achieve symptom relief and improve long-term survival. Management decisions should be based on prognostic information derived from an appropriately chosen diagnostic test. The choice of medical therapy and/or revascularization should be made after consideration of the known comparative efficacies of the strategy options. However, it must be emphasized that all patients should be encouraged to adopt lifestyle changes known to improve prognosis, such as smoking cessation and adoption of a low-cholesterol diet.

A management algorithm based on current available data is presented in Fig. 24.3. As mentioned previously, the diagnostic test shown to provide the most robust and objective prognostic value for risk of cardiac death or myocardial infarction is myocardial perfusion *imaging* (*MPI*) [36, 37].

The predictive value is enhanced by computer-generated quantitation of ischemic defect size. Patients with stable angina who have mild perfusion defects (<15 %) have been shown to be at low risk (<1 % per year) for cardiac death or myocardial *infarction* [36, 37]. Patients capable of achieving >10 METs (Stage III, Bruce Protocol) on exercise treadmill have a prognosis with medical therapy as good as revascularization and are considered to be at low risk for cardiac events [131]. In such patients, an initial approach of "standard medical therapy" is reasonable. Standard medical therapy consists of aspirin, beta-blockers, short-acting nitrates, and aggressive lipid-lowering therapy. Randomized trial data support such an approach. The Angioplasty Compared to Medicine trial (ACME) for stable angina pectoris demonstrated that 48 % of medically treated patients with stable angina may be rendered symptom-free by 6 months [132]. The Second Randomized Intervention Treatment of Angina (RITA-II) trial randomized more than 1,000 patients with stable angina pectoris to medical therapy or coronary angioplasty. After a median 2.7-year follow-up, interventional management (largely balloon angioplasty without intracoronary stenting) conferred no benefit in terms of death or myocardial infarction [133]. Similarly, data from the Coronary Artery Surgery Study (CASS) registry showed no mortality difference over 10 years between medical therapy and bypass grafting for single-vessel or two-vessel disease (excluding the proximal left anterior descending artery or significant left main disease), in patients with normal left ventricular function [134].

Recent trials have compared a modern aggressive medical approach against contemporary revascularization strategies. In the BARI 2D trial, more than 2,000 patients with both type 2 diabetes mellitus and ischemic heart disease were randomized to undergo either prompt revascularization with intensive medical therapy or intensive medical therapy alone and to undergo either insulin-sensitization or insulin-provision therapy [135]. Primary endpoints were the rate of death and a composite of death, myocardial infarction, or stroke (major cardiovascular events). Randomization was stratified according to the choice of percutaneous coronary intervention or coronary artery bypass grafting as the more appropriate intervention. Overall, there were no significant differences in the rates of death or major cardiovascular events between patients undergoing prompt revascularization and those undergoing medical therapy, or between strategies of insulin sensitization and insulin provision.

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial enrolled 2,287 patients (mean age 62) with stable angina who were randomly assigned to either aggressive medical therapy alone or aggressive medical therapy plus PCI with bare-metal stenting [136]. Patients were required to have both objective evidence of ischemia and significant disease in at least one coronary artery; 87 % were symptomatic and 58 % had CCS class II or III angina. Of note, the highest risk patients were excluded from this trial including those with significant left main disease, LVEF <30 %, or a hypotensive response to treadmill testing.

The primary outcome was death from any cause and nonfatal myocardial infarction during a follow-up period of 2.5–7.0 years. At the median of 4.6 years, the primary event rates were 19.0 % in the PCI group and 18.5 % in the medical therapy group ($P=0.62$). For the prespecified composite outcome of death, nonfatal myocardial infarction, and stroke, the event rate was 20.0 % in the PCI group and 19.5 % in the medical therapy group ($P=0.62$). The rates of hospitalization for acute coronary syndromes were 12.4 % in the PCI group and 11.8 % in the medical therapy group ($P=0.56$). However, patients randomized to the PCI strategy required fewer subsequent revascularization procedures (21 % vs. 33 % for PCI vs. conservative therapy respectively; $P<0.001$). At years one and two, patients assigned to PCI reported significantly fewer anginal episodes than individuals who received conservative therapy; yet, this difference was not significant at year 5.

A sub-study from the COURAGE trial examined the effect of PCI versus medical therapy on reducing the ischemic burden as measured by myocardial perfusion single-photon emission computed tomography (MPS) [137]. The authors found that adding PCI to medical therapy resulted in a greater reduction of inducible ischemia compared with medical treatment alone and that the benefit was greatest among patients with more severe baseline ischemia. They also found that the magnitude of residual ischemia on follow-up MPS was proportional to the risk of subsequent death or MI; that is, a greater residual ischemic burden after therapy with medical therapy or PCI and medical therapy portended a greater increased risk of death or MI. As an aggregate, the data suggest that in patients with stable angina and a moderate to large amount of ischemic burden at baseline, PCI may be preferable to medical therapy alone since revascularization is more likely to produce a lower residual ischemic burden. Finally, an important caveat concerning the COURAGE study includes the use of bare-metal stents, which have been supplanted increasing by drug-eluting stents in contemporary practice. It is plausible to assume that newer-generation DES and more effective pharmacotherapy will decrease revascularization rates thus yielding less frequent episodes of angina in patients who receive PCI.

Although data suggests that in patients with a low ischemic burden, an initial strategy of aggressive medical therapy is reasonable, there is no dispute that revascularization is effective in relieving symptoms of angina that persist despite adequate medical regimens. Therefore, patients with a low ischemic burden or substrate who have lifestyle-altering stable angina persisting after 6 months of aggressive medical

therapy should proceed to coronary angiography with the intent of revascularization.

As mentioned above, in patients with a moderate to severe perfusion defect size (>15 %) or poor treadmill exercise tolerance (<5 METs) [37], revascularization along with aggressive medical therapy should be considered as an initial treatment strategy rather than solely medical management. For example, the Coronary Artery Surgery Study (CASS) registry has clearly shown a survival benefit of revascularization in patients with three-vessel disease, left main obstruction in excess of 50 % stenosis, or two-vessel disease involving the proximal left anterior descending artery when compared to medical therapy alone [134]. Furthermore, as described above, results from the nuclear sub-study of COURAGE suggest revascularization when the ischemic burden at baseline is large [137].

Following determination of the extent of CAD and the need for revascularization, the decision of percutaneous coronary intervention versus coronary artery bypass grafting arises. In the past, there was little dispute that the symptomatic patient with significant disease in the left main coronary artery should proceed directly to bypass grafting. Furthermore, in patients with multivessel obstructive CAD, surgery was the preferred revascularization option along with aggressive medical therapy. On the other hand, percutaneous intervention was chosen for single-vessel disease not involving the left main artery.

Over the past several years, many trials have demonstrated that a percutaneous approach in patients with left main artery or multivessel disease may be considered rather than coronary artery bypass surgery. The results of these trials are uniform and consistent in showing similar risks of death and nonfatal myocardial infarction in long-term follow-up for as long as 10 years. However, an increase in the need for repeated revascularization procedures has been observed in percutaneous-treatment arms. In the Bypass Angioplasty Revascularization Investigation (BARI) trial, an 8 % repeat revascularization rate for coronary artery bypass versus 54 % for coronary angioplasty was reported [138]. It was also clear from this trial that the subgroup of patients with diabetes mellitus requiring glucose-lowering treatment benefited significantly more from bypass grafting than from angioplasty. There was no difference in mortality or the combined endpoint of death, MI, or stroke at 5 years between patients treated with PCI (bare-metal stents) or coronary artery bypass surgery for patients with stable angina and multivessel disease in the Arterial Revascularization Therapy Study (ARTS) [139]. However, event-free survival was lower with stenting due to a significant increase in the need for repeat revascularization.

The percutaneous approach used in BARI and ARTS was balloon angioplasty and PCI with bare-metal stents, respectively. In SYNTAX [140], a more contemporary strategy was utilized with drug-eluting stents. This trial randomly assigned 1,800 patients with three-vessel or left main coronary artery disease to either CABG or PCI with the paclitaxel-eluting stent. All patients were eligible for either procedure and were treated with the intention of complete revascularization. The SYNTAX score, an angiographic tool used to grade the extent of disease and lesion complexity, was assigned to each patient [141]. The composite primary endpoint (death from any cause, stroke, MI, or repeat revascularization) was significantly higher in the PCI group (17.8 % vs. 12.4 % for PCI and CABG, respectively; $p = .002$). This result was driven primarily by more frequent revascularization with PCI (13.5 % vs. 5.9 % for PCI and CABG, respectively, $p < .001$). When stratified by SYNTAX grade, results suggested that among patients with low SYNTAX scores, the clinical outcomes were comparable with PCI and CABG, whereas in patients with higher SYNTAX scores, outcomes were better with CABG. In a prespecified powered subgroup of 705 randomized patients who had left main disease from the SYNTAX trial, DES was compared against CABG for unprotected left main revascularization. Major adverse cardiac and cerebrovascular event rates at 1 year in left main patients were similar for CABG and PCI. While the stroke rate was higher at 1 year in the patients randomized to CABG, repeat revascularization was higher in the patients assigned to PCI [142].

The recent PRECOMBAT trial compared PCI with DES against CABG for patients with unprotected left main disease. Six hundred patients were randomized to either CABG or PCI with a sirolimus-eluting stent [143]. The primary endpoint was a composite of major adverse cardiac or cerebrovascular events (death from any cause, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization) at 1 year. Event rates at 2 years were also compared between the two groups. PCI was demonstrated to be noninferior at 1 year. Furthermore, event rates were not significant between the two groups at 2 years. Finally, at 2 years, ischemia-driven target-vessel revascularization occurred more frequently in the patients assigned to PCI versus CABG (9.0 % vs. 4.2 % for PCI and CABG, respectively; $P = 0.02$). The observations from the SYNTAX sub-study and PRECOMBAT must be interpreted in the setting of first generation drug-eluting stents. To reiterate, newer technology certainly will decrease subsequent cardiovascular events in patients treated with PCI.

Importantly, when interpreting data from clinical trials, physicians must acknowledge that the outcomes are determined by the composite endpoints chosen for each study. Each endpoint, though weighted the same in the final composite, is not inherently equal. For example, a devastating stroke is not equivalent to a revascularization procedure for angina without evidence of myocardial damage. These nuances must be kept in mind when interpreting the studies and in discussing treatment options with patients.

Impressions

In all patients with underlying coronary artery disease, the clinician must perform an accurate history and physical to identify and classify anginal status [18]. A baseline medical regimen of antiplatelet, anti-ischemic, and lipid-lowering therapy is a prerequisite for adequate treatment. For patients with anatomy that confers a low ischemic burden and stable symptoms, an initial plan of intense medical therapy without intervention is appropriate. However, if symptoms persist or worsen despite medical therapy, revascularization should be pursued.

Alternatively, in patients with a high degree of ischemic burden, an initial strategy of aggressive medical therapy and revascularization should be considered. Choosing a revascularization route is based on the area of ischemic defect, patient comorbidities, and clinical scenario. Initially, left main and multivessel disease was designated toward coronary artery bypass surgery. Furthermore, data from several trials had suggested that certain subgroups of patients may benefit more from bypass surgery including patients with diabetes mellitus. However, as antiplatelet, antithrombotic, and stent design have improved, the gap between bypass surgery and PCI is decreasing such that PCI increasingly is being utilized for advanced coronary disease. Finally, irrespective of the revascularization route pursued, exercise training and diet modification must be incorporated into every patient's management. Indeed, an exercise regimen not only stabilizes advanced coronary disease, exercise can also prevent it from developing in the first place.

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Unstable Angina and Non-ST Segment Elevation Myocardial Infarction (Acute Coronary Syndromes)

25

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Introduction

Every 25 s, an American will have a coronary event (unstable angina or a myocardial infarction). Approximately every minute, someone will die of a cardiovascular catastrophe [1]. The proportion of patients who present to the emergency department with a diagnosis of ST segment elevation on the standard 12-lead electrocardiogram (ECG) varies by different registries with estimates from 32 to 47 % [2, 3]. Since the diagnostic sensitivity and specificity of the ECG are poor in this setting, there is a strong impetus for effective emergency room stratification. The spectrum of "acute coronary syndrome" includes unstable angina and non-ST segment elevation myocardial infarction as the clinical presentations. The distinction between these syndromes is usually made retrospectively based on biochemical markers and angiographic results. Therefore, initial treatment algorithms are identical. Four clinical scenarios are consistent with a diagnosis of unstable angina (Table 25.1). From a pragmatic standpoint, this diagnosis excludes external factors that may exacerbate the symptoms of coronary ischemia including thyrotoxicosis, tachyarrhythmias, or cardiomyopathies that increase the mismatch between myocardial supply and demand since appropriate treatment of unstable angina due to these entities is specific to the underlying disease process.

Patients with acute chest pain represent a heterogeneous population. An approach to management must take into account the severity of symptoms, the circumstances in which they occur, and the indicators of risk that lead to death or myocardial infarction. The Braunwald Classification of Unstable Angina [4] summarizes these important items and assists in early stratification of patients at higher risk for adverse clinical outcomes (Table 25.2). Clinical features to consider when first evaluating the patient include a history of coronary artery disease (CAD), the presence or absence of ST segment elevation or depression, hemodynamic status, signs of congestive heart failure, or deleterious electrical activity. A number of scoring systems to determine risk have been developed [5–7]. These scores were based on the clinical characteristics of patients enrolled in large trials of acute coronary syndromes and are intended to allow rapid prognostication and triage to a variety of treatments based on individualized risk–benefit ratio (Tables 25.3 and 25.4, Fig. 25.1) [5].

Contemporary use of the term "unstable angina" is being replaced with the term "acute coronary syndrome." This new vernacular has developed for three reasons. First, the syndromes that do and do not cause ST segment elevation share a common fundamental pathology, namely, vascular inflammatory changes leading to disruption of a previously stable atherosclerotic plaque and subsequent intravascular thrombosis. Second, the term acute coronary syndrome reflects the development of increasingly "sensitive" markers of myocardial necrosis. Patients with small amounts of myonecrosis as well as those with recent, rather than acute, episodes of necrosis who were previously classified as having "unstable angina" are now recognized as having myocardial infarction using the modern classification scheme espoused by the joint European Society of Cardiology/American College of Cardiology guidelines [8]. Third, effective forms

Table 25.1 Clinical presentations of unstable angina

1. Rest angina
2. New onset angina of CCSC class III or IV within 4 week of presentation
3. Increasing frequency and intensity of previously stable angina to CCSC class III or IV
4. Angina within 6 week of myocardial infarction

CCSC Canadian Cardiovascular Society Classification

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DOI 10.1007/978-1-4614-6705-2_25,

Table 25.2 Braunwald classification of unstable angina

Severity	
Class I	New onset, severe, or accelerated angina
	Patients with angina of less than 2 months duration, severe or occurring three or more times per day, or angina that is distinctly more frequent and precipitated by distinctly less exertion; no rest pain in the last 2 months
Class II	Angina at rest; subacute
	Patients with one or more episodes of angina at rest during 3 preceding months but not within the preceding 48 h
Class III	Angina at rest; acute
	Patients with one or more episodes at rest within the preceding 48 h
Clinical circumstances	
Class A	Secondary unstable angina
	A clearly identified condition extrinsic to the coronary vascular bed that has intensified myocardial ischemia, e.g., anemia, infection, fever, hypotension, tachyarrhythmia, thyrotoxicosis, hypoxemia secondary to respiratory failure
Class B	Primary unstable angina
Class C	Postinfarction unstable angina (within 2 week of documented myocardial infarction)

Intensity of treatment

1. Absence of treatment or minimal treatment
2. Occurring in presence of standard therapy for chronic stable angina (conventional doses of oral beta-blockers, nitrates, and calcium antagonists)
3. Occurring despite maximally tolerated doses of all three categories of oral therapy, including nitroglycerin

Adapted from Braunwald [4]. With permission from Lippincott Williams & Wilkins
CCSC Canadian Cardiovascular Society Classification

Table 25.3 TIMI risk scores

TIMI risk score factors	Score
Age ≥65	1
Aspirin use in the previous 7 days	1
Known CAD (>50 % stenosis)	1
Angina (≥2 episodes in previous 24 h)	1
≥Risk factors for CAD[a]	1
Elevated cardiac enzymes	1
ST changes ≥0.5 mm	1

[a]Current smoker, family history of CAD, hypertension, hypercholesterolemia, or diabetes

Table 25.4 PURSUIT risk scores

PURSUIT risk variables		Mortality at 30 day (USA/NSTEMI)	Mortality/MI at 30 day (USA/NSTEMI)
Age	50	0	8/11
	60	2/3	9/12
	70	4/6	11/13
	80	6/9	12/14
Gender	Male	1	1
	Female	0	0
Worst CCS in last 6 week	Class I–II		
	0	0	
	Class III–IV	2	2
Heart rate	80	0	0
	100	1/2	0
	120	2/5	0
Systolic BP	120	0	0
	100	1	0
	80	2	0
Heart failure	Yes	3	2
	No	0	0
ST depression	Yes	3	1
	No	0	0

Adapted from Boersma et al. [6]. With permission from Lippincott Williams & Wilkins

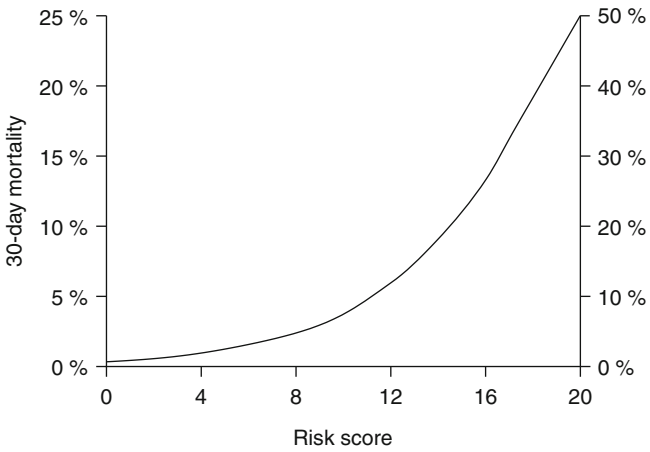

Fig. 25.1 Conversion of PURSUIT risk score to probability of clinical events in the PURSUIT trial (Adapted from Boersma et al. [6]. With permission from Lippincott Williams & Wilkins)

of therapy do not differ between patients with or without biochemical indications of necrosis but rather are distinguished according to their risk assessment and to the presence and direction of ST segment changes on the surface ECG.

The majority of patients presenting with non-ST segment elevation acute coronary syndromes have multiple plaques in the coronary arteries [9]. However, in most studies, approximately 20 % of patients with suspected acute coronary syndrome are found to have minimally obstructed or normal coronary arteries. This proportion is somewhat lower in studies that use more stringent entry criteria and may reflect the persistently vexing clinical nature of the diagnosis that persists despite the availability of sensitive markers of myonecrosis.

The precipitating event leading to myocardial ischemia is most commonly coronary plaque disruption or erosion [10]. Plaques vulnerable to this process tend to be relatively soft and lipid-rich and have abundant extracellular matrix and

smooth muscle cells. Following disruption of the fibrous cap, platelets are activated by local thrombogenic and inflammatory factors [11, 12]. The final local component of arterial damage involves local vasoconstriction, most likely in response to secretion of platelet-derived serotonin and thromboxane A2 (TXA2), while the final distal event usually consists of embolization of platelet-fibrin microthrombi [13]. Unlike what is usually seen in patients with ST segment elevation myocardial infarction, patients with non-ST segment elevation unstable angina most frequently present with subtotally occluded coronary arteries [14].

Use of fibrinolytic drugs in the setting of non-ST segment elevation acute coronary syndromes has been shown to be detrimental probably as a result of the way these drugs activate the thrombotic system. While this phenomenon may be of minor importance compared to restoring antegrade flow in a totally occluded vessel, it may cause increased necrosis in the myocardium fed by partially obstructed vessels [15, 16]. Medical treatment is based primarily on antithrombotic and antiplatelet agents. The utility of most of these therapies has been codified and promulgated as sets of guidelines by a joint American College of Cardiology/American Heart Association committee [17] and by a committee of the European Society of Cardiology [18].

This chapter will review the diagnostic utility of biochemical markers in non-ST segment elevation acute coronary syndromes. The role of traditional agents in the initial management of acute coronary syndrome will be reviewed. The efficacy and safety of conventional and more novel antiplatelet and antithrombotic therapies will be examined. Finally, the decision to pursue a conservative versus an invasive strategy will be explored.

Biochemical Markers and Unstable Angina

The identification of patients presenting to the emergency room with acute chest pain at high risk for subsequent cardiac events remains a challenge. In the setting of non-ST segment elevation acute coronary syndrome, further risk stratification is utilized to assist in treatment. Sensitive biochemical markers of myocardial injury were developed to provide early risk stratification.

Cardiac troponin T and cardiac troponin I are structural sarcomeric proteins that regulate the calcium-mediated contractile process in cardiac muscle. A small quantity of cardiac troponin remains free in the cytosol of cardiac myocytes. Troponin T and I are absent from the circulation under normal circumstances, so their detection in the serum may represent early signs of myocardial damage. This is in contrast to the MB fraction of creatine kinase (CK-MB) in which basal levels can be detected in the plasma of normal individuals. Therefore, serum troponins are useful markers for detection of myocardial damage. The timing of cell necrosis and biomarker release has been established for creatine kinase and its isoenzymes but still remains controversial for the troponins. Blood levels may rise as early as 3 h after the onset of symptoms, although a time frame of 6–12 h generally is more accepted. This approach is logical given that a patient may seek medical attention during ACS within a time frame that prohibits detection of troponin elevation in the blood. In this fashion, utilizing the change in troponin value over several hours can assist the clinician in identifying a myocardial infarction. Indeed, a recent study suggests that the difference/change in early serial troponin values in addition to an initial troponin level at baseline adds important prognostic information in diagnosing myocardial infarction. The authors found that in combination with a baseline troponin value at admission, the serial change in troponin concentration within 3 h increased the positive predictive value for ruling in myocardial infarction from 75.1 % at admission to 95.8 % after 3 h [19].

Normal or undetectable levels of troponin should not be viewed as excluding the presence of an acute coronary syndrome when the measurements are performed within the first 12 h of the onset of angina. Elevated levels of troponin T and troponin I may persist beyond 10 days, particularly in patients with renal disease or congestive heart failure [20]. The goal of measuring cardiac troponin in the emergency room is to assist in the early identification of patients presenting with acute chest pain without ST segment elevation who may have severe coronary ischemia and therefore be at an increased risk of adverse clinical outcomes. Serial cardiac troponin determination has in many cases replaced creatine kinase in the diagnosis of myocardial infarction; both markers are used in most medical centers. Numerous studies have demonstrated that "early" elevation of troponin in the emergency room provides independent prognostic value for adverse outcomes including death, recurrent myocardial infarction, and need for revascularization in patients presenting with and without ST segment elevation ischemic chest pain [21–25]. However, these studies were performed in high-risk patients in whom the majority had documented CAD and abnormal ECGs on admission. Also, elevation of CK-MB subsequently occurred in more than 95 % of patients developing myocardial infarction [22]. Therefore, although "early" positive troponin may be a marker for adverse cardiac events, the negative predictive value of elevated troponin within the first 6 h after the onset of symptoms remains in question. Indeed, in a study assessing more than 10,000 patients admitted for acute chest pain, patients with a <1 % likelihood of cardiac complications could be selected using the clinical features of admission ECG, description of chest discomfort, and hemodynamic status [26]. The Diagnostic Marker Cooperative study evaluated the sensitivity of biochemical markers for 955 consecutive patients presenting to

the emergency room with chest pain. The authors of this study concluded that the most sensitive and specific markers were CK-MB isoforms at 6 h (91 and 89 %), CK-MB at 10 h (96 and 98 %), and troponin at 18 h (96 and 93 %) [27].

An informative prospective trial to assess the value of cardiac troponin I included more than 1,200 patients presenting to an emergency department with acute chest pain. Initial cardiac troponin I and CK-MB were collected [26, 28]. This patient population represented the "real-world" situation of a heterogeneous group of patients, *without* regard to admission ECGs or CAD history. The positive predictive value for cardiac events up to 72 h for "early" positive cardiac myocardial troponin I (>.4 ng/mL) in all patients was 19 % versus 22 % for CK-MB. Among patients ruling out for acute myocardial infarction, cardiac troponin I had a positive predictive value for cardiac events of ventricular arrhythmias, hemodynamic collapse, or the need for semiurgent revascularization of only 8 %. A similar study assessing initial emergency room troponin, CK-MB, and admission ECG has shown that only ST segment depression in the baseline ECG carried independent prognostic value to predict cardiac events at 30 days in acute chest pain patients without ST segment elevation [28].

The negative predictive value of serial troponin determination appears powerful. In patients with negative test results, the risk of major cardiac events appears very low. In a study by Hamm et al., negative troponin T or I within 12 h of chest pain and without ST segment elevation was associated with a 1.1 and 0.03 % risk of myocardial infarction or death over 30 days, respectively [28].

The predictive value of troponin determination suggests that when the measurements are used injudiciously, their routine use may confuse the scenario when a valid clinical history and benign ECG suggest a presentation not consistent with an acute coronary syndrome. Abnormal levels of troponin may occur in renal insufficiency, cancer, rhabdomyolysis, pulmonary embolism, and accelerated hypertension [29–33]. Analysis of data from the Global Use of Strategies to Open Occluded Coronary Arteries IV trial reveals that serial troponin measurements provide good cardiac prognostic information across the spectrum of renal failure [34]. Furthermore, several studies have reported a negative prognostic implication in patients with elevated troponin irrespective of underlying mechanism [35–38]. Although the presence of circulating troponin may be associated with adverse outcomes in such patients, it does not necessarily indicate the presence of an acute coronary syndrome. In an attempt to aid in both sensitivity and specificity, new troponin serum biomarkers have been developed and are indeed more accurate in establishing or ruling out acute coronary syndrome [39, 40].

Perhaps the best use of troponin is in patients with a moderate probability of having an acute coronary syndrome and minimal ECG abnormalities. In patients with negative cardiac troponin measurements, triage may be handled in a more cost-effective manner given the low likelihood of a cardiac event. Consideration of discharge home, admission to a ward other than the intensive care unit, or early stress testing may be warranted.

In addition to serum troponin, other blood serum markers are being developed to assist with risk stratification in patients who presents with non-ST segment acute coronary syndrome. Since myoglobin is released and cleared quickly after cell injury, myoglobin levels rise and fall rapidly after cell necrosis. However, myoglobin is also released after skeletal muscle injury, and therefore its specificity is limited. C-reactive protein (CRP) is an acute phase reactant associated with the presence of ongoing inflammation. Elevated levels of C-reactive protein have been correlated with adverse clinical outcomes at 14 days in patients presenting with acute coronary syndromes [41] A mechanism of CRP induced endothelial dysfunction in patients undergoing acute coronary syndrome has been suggested [42]. A rapid decline of CRP levels parallels resolution of clinical symptoms, but persistent elevation for up to 15 days is associated with an unfavorable outcome [43]. These studies strongly implicate inflammation as a key factor in the pathophysiology of acute coronary syndrome.

Heart fatty acid-binding protein (H-FABP) is a member of a larger family of proteins found in a diverse array of tissues and is involved in intracellular lipid transport. As with myoglobin, this protein is found in cardiac and skeletal muscle, yet the relative amount of this protein is much greater in cardiac muscle. Therefore, serum measurement allows discrimination between cardiac and skeletal muscle injury [44]. H-FABP is released within 90 min of myocardial sarcolemmal damage, and is under investigation as an early marker of myonecrosis [45]. The sensitivity and specificity of this protein is similar to that of troponin in the detection of acute coronary syndrome [46–50].

Several studies have evaluated the utility of measuring myeloperoxidase (a leukocyte enzyme) in patients presenting with chest pain [51] and acute coronary syndromes [52–55]. Myeloperoxidase was an independent prognostic marker for cardiovascular morbidity and mortality at 30 days and 6 months. Ongoing studies are evaluating its utility in the risk stratification of acute coronary syndrome.

Brain natriuretic peptide (BNP) can be routinely measured in an emergency room setting and has been shown to predict mortality and the risk of congestive heart failure in patients presenting with acute coronary syndromes [56, 57]. Studies have shown that measurement of both BNP and N-terminal BNP in patients with myocardial ischemia predict short-term and long-term cardiovascular morbidity and mortality [58–60].

Soluble CD40 ligand is a transmembrane protein of the tumor necrosis factor family that is shed from the surface of

activated platelets. This protein is elevated in patients with acute coronary syndromes and in patients who have had coronary revascularization [61, 62]. Soluble CD40 ligand has been shown to have both independent and synergistic (combined with other markers such as troponin) prognostic value in patients with acute coronary syndromes [63–65].

Copeptin, the C-terminal part of the vasopressin prohormone, is currently being investigated for its role in detecting ACS in patients with chest pain. It has been demonstrated to assist in the early diagnosis of myocardial infarction when combined with troponin values [66].

To summarize, troponin, creatine kinase, and creatine kinase-MB are currently the biomarkers of choice in an attempt to risk stratify patients early in the evaluation of unstable angina. The other biochemical markers described above lack either the sensitivity or specificity of these benchmark biomarkers, or they have not been validated in large clinical trials. Current studies will determine if the newer biomarkers will assist in the management of acute coronary syndrome.

Medical Therapy

Anti-ischemic Therapy

Angina is often associated with inappropriate vasoconstriction and heart rate elevation due to excessive catecholamine secretion. The aim of anti-ischemic therapy is to alter hemodynamics and improve the balance between myocardial oxygen supply and demand. Nitrates, B-blockers, and calcium-channel blockers are all known to improve this ratio.

The recommendation for nitrate therapy is based more on observational evidence and knowledge of its physiologic effect than on clinical trial data. While useful for symptom relief, nitrates should be viewed as disease-modifying therapies. Following administration of nitroglycerin, vascular smooth muscle cells convert nitrates to the nitric oxide radical. Nitric oxide, in turn, activates intracellular guanylate cyclase to produce cyclic guanosine monophosphate (cGMP), triggers smooth muscle relaxation, and inhibits platelet aggregation. Nitroglycerin decreases preload and afterload. Finally, nitroglycerin induces coronary vasodilation [67]. Nitrate therapy should be used with caution in certain cases including right ventricular infarction or in a patient who has recently consumed a phosphodiesterase inhibitor for erectile dysfunction.

The routine use of β-blocker therapy is based on data obtained in patients with myocardial infarction, where a beneficial effect on long-term mortality is established [68–70]. Ideally, the target heart rate should be less than 60 beats/min. β-blockers should be reconsidered/held in the setting of newly decompensated heart failure, evidence of low-output state, or increased risk for cardiogenic shock. Other relative contraindications to beta blockade include a PR interval >0.24 s, second- or third-degree heart block, or reactive airways disease [17]. If β-blockers cannot be used, non-dihydropyridine calcium channel blockers are also effective in relieving chest pain, provided there is no evidence of left ventricular dysfunction. The combination of β-blockers and calcium channel blockers is usually reserved for patients with refractory symptoms, or in whom effective control of the heart rate proves elusive.

Antiplatelet Agents

Aspirin

Aspirin is standard therapy in patients with acute coronary syndromes. The efficacy of aspirin in reducing early and long-term cardiac events has been established in several randomized trials [71–74]. Early event rates have been reduced up to 50 % with a dose of 81 or 325 mg [72]. Long-term benefits extending to 2 years are seen when daily administration is continued [75]. Side effects of aspirin are relatively rare, dose-dependent, and usually present after long-term use. The only contraindication to immediate aspirin administration in the emergency room is prior aspirin allergy causing angioedema or anaphylaxis. It is recommended that a bolus of 160–325 mg in chewable form be given to rapidly achieve full inhibition of platelet aggregation and TXA2 release.

As an inhibitor of platelet aggregation, aspirin is associated with bleeding risk. Several investigators have examined the relation of aspirin use and dosage to gastrointestinal bleeding [76–80]. For example, Kelly et al. demonstrated that aspirin use can increase the risk of GI bleeding threefold even in low-dose buffered *formulations* [80]. While the relative increased risk of aspirin use with respect to gastrointestinal bleeding rate varies among each study, the general finding is that aspirin therapy is associated with an increased rate of bleed events and that higher doses confer a greater risk of hemorrhage.

The optimal aspirin maintenance dose is controversial. In the CURRENT-OASIS 7 trial, the primary composite endpoint at 30 days of death, myocardial infarction, or ischemia did not differ between patients who were randomized to a daily dose of 75–100 mg of aspirin versus patients assigned to 300–325 mg (4.2 % for the higher dose and 4.4 % for the lower dose, respectively; $p = 0.61$) [81]. Patients who received the lower dose had more episodes of recurrent ischemia (0.3 % vs. 0.5 % for the higher dose and lower dose, respectively; $p = 0.02$). Finally, patients assigned 300–325 mg had more episodes of minor bleeding (5.0 % vs. 4.4 % for the higher and the lower regimen, respectively; $p = 0.04$).

Thienopyridines

Ticlodipine and clopidogrel are acceptable alternatives when aspirin cannot be tolerated. These agents are prodrugs whose

active metabolites interfere with ADP-mediated activation of platelet P2Y12 (the "ADP receptor") [82]. In a randomized trial of patients with unstable angina, ticlodipine as monotherapy was superior to aspirin in preventing death and myocardial infarction at 6 months [83]. The rate of fatal and nonfatal myocardial infarction was 5.1 % in the ticlodipine group and 10.9 % in the control group, a risk reduction of 53.2 %. However, ticlodipine has several side effects.

Clopidogrel is a thienopyridine that has a longer half-life and is considerably better tolerated than ticlodipine. Because it is better tolerated, clopidogrel can be administered as a loading dose of 300–900 mg. The superiority of clopidogrel to aspirin for the secondary prevention of recurrent ischemic events in patients with previous stroke, myocardial infarction more than 1 month previously, or peripheral vascular disease has been shown in the CAPRIE study [84].

The efficacy of clopidogrel in acute coronary syndromes was established in the CURE trial. Over 12,000 patients with acute coronary syndrome were randomized to either aspirin alone or aspirin and clopidogrel (given with a 300 mg "loading dose" with 75 mg daily maintenance) [85]. The use of clopidogrel on a background of aspirin led to a 20 % relative reduction (CI = 0.72–0.90) in the combination of cardiovascular death, myocardial infarction, or stroke after 9 months of therapy compared with aspirin alone. Interestingly, the beneficial effect of clopidogrel became apparent within the first day after initiating treatment. Subgroup analysis revealed that this benefit was present regardless of the concomitant use of GP IIb-IIIa antagonists and of coronary revascularization strategies. Major bleeding in patients treated with clopidogrel was more common (3.7 % vs. 2.7 % for clopidogrel combined with aspirin, respectively; $p = 0.01$). Of note, clopidogrel therapy produced a similar relative risk reduction in patients who were treated medically or underwent revascularization. Furthermore, the observed benefit was similar irrespective of the patient's clinical risk profile as defined by the TIMI risk score [86]. Finally, two subsequent studies demonstrated that the administration of clopidogrel derived a greater benefit when given upfront (prior to angiography) [87, 88].

While it seems advantageous to load patients who present with acute coronary syndrome with clopidogrel, routine use in patients presenting with acute coronary syndromes has remained controversial because of the perceived bleeding risk, particularly in patients who under coronary artery bypass surgery. Within the CURE study, patients who were to undergo coronary bypass by protocol had clopidogrel withheld for 5 days. The trends, particularly within North America and Western Europe, toward earlier revascularization in patients with non-ST segment elevation acute coronary syndromes have created concern about the safety of clopidogrel administration before the coronary anatomy is determined. While observational data indicate that clopidogrel use is associated with increased bleeding at the time of coronary artery bypass surgery [89], it appears that the referral of patients to coronary artery bypass within the first 48 h after presentation is relatively uncommon. Protocols for the use of clopidogrel in patients with non-ST segment elevation acute coronary syndromes vary considerably between institutions.

Strategies during acute coronary syndrome regarding the loading dose of clopidogrel have been investigated. One study of 292 consecutive non-ST segment acute coronary syndrome patients undergoing percutaneous coronary intervention (PCI) demonstrated that patients who received a 600 mg loading dose had fewer cardiovascular events at 1 month that those who were randomized to a 300 mg loading dose (12 % vs. 5 % for 600 mg clopidogrel and 300 mg clopidogrel, respectively; $p = 0.02$) [90]. In the ARMYDA-2 trial, 255 patients were randomized to a 300 or 600 mg loading dose [91]. There was a benefit in the primary composite endpoint of death, myocardial infarction (MI), or target vessel revascularization at 30 days in the patients who received high-dose clopidogrel (4 % vs. 12 % for 600 and 300 mg of clopidogrel, respectively; $p = 0.041$). However, results from the considerably larger CURRENT-OASIS 7 trial suggest that in patients with an acute coronary syndrome who are referred for an invasive strategy, there is no difference between a higher loading and maintenance dose (600 mg load with 75 mg twice daily for 6 days followed by 75 mg a day) and lower loading and maintenance dose (300 mg load and 75 mg/day), with respect to the primary outcome of cardiovascular death, myocardial infarction, or stroke at 30 days [81]. However, in an analysis of a post-randomization subgroup, patients who received the higher dose of clopidogrel and underwent PCI derived a significant benefit with respect to the primary composite endpoint and the secondary endpoint of stent thrombosis [92]. Of note, while no interaction between clopidogrel and aspirin has been demonstrated in previous studies, in CURRENT-OASIS 7 there was evidence of an interaction for the primary outcome ($p = 0.04$). Among patients assigned to higher-dose aspirin therapy, the primary outcome occurred in 3.8 % of patients in the high-dose clopidogrel group, as compared with 4.6 % of patients in the low-dose clopidogrel arm (hazard ratio, 0.82; 95 % CI, 0.69–0.98; $P = 0.03$). While the beneficial effects of these medications are known to be additive, pharmacologic synergy between them has not been described.

Prasugrel, like clopidogrel and ticlodipine, reduces the activation and aggregation of platelets by irreversibly binding to P2Y12 receptors. Prasugrel has a more rapid onset of action and is able to achieve higher degrees of platelet inhibition than clopidogrel with much less evidence of drug-hyporesponsiveness. In TRITON-TIMI 38, patients with acute coronary syndrome who were slated to undergo PCI were randomized to treatment prasugrel or clopidogrel after a diagnostic angiogram had been performed. (Patients

Table 25.5 Currently available platelet GPIIb/IIIa receptor antagonists

Drug	Indication	Dose
Abciximab (antibody)	Elective PCI	Bolus: 0.25 mg/kg
	Urgent PCI	Maintenance: 0.125 μg/kg/min
	Refractory unstable angina pending PCI	
Tirofiban (nonpeptide)	Acute coronary syndromes	Bolus: 0.4 μg/kg/min × 30 min
		Maintenance: 0.1 μg/kg/min × 48–96 h
Eptifibatide (cyclic peptide)	Elective PCI	Bolus: 135 μg/kg
		Maintenance: 0.50 μg/kg/min × 24 h
	Acute coronary syndromes	Bolus: 180 μg/kg
		Maintenance: 2 μg/kg/min
	Urgent PCI	Bolus: 180 μg/kg, repeat in 10 min
		Maintenance: 2 μg/kg/min

presenting with ST elevation myocardial infarction received their treatment before the diagnostic angiogram was performed.) Patients assigned to prasugrel had a reduced combined rate of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke at 15 months (12.1 % for clopidogrel vs. 9.9 % for prasugrel; $p<0.001$) [93]. This difference in the primary endpoint was driven by a reduction of nonfatal myocardial infarctions. However, an increased rate of serious bleeding (1.4 % vs. 0.9 % for prasugrel and clopidogrel, respectively; $p=0.01$) and fatal bleeding events (0.4 % vs. 0.1 % for prasugrel and clopidogrel, respectively; $p=0.002$) was observed for prasugrel. In particular, patients who were ≥75 years of age, weighed ≤60 kg, and had a history of stroke or transient ischemic attack were at the greatest risk. Indeed, it seems that a more effective anti-ischemic effect is balanced by a greater risk of bleeding.

Unlike prasugrel, ticlodipine, and clopidogrel, the cyclopentyl-triazolo-pyrimidine ticagrelor does not need hepatic activation in order to ligate P2Y12. It has more rapid onset of action than clopidogrel and has greater platelet inhibition. Additionally, its binding to the receptor is less avid, resulting in a more rapid off-rate and a shorter pharmacodynamic half-life. In the PLATO study, patients with acute coronary syndromes were randomized to treatment with clopidogrel or ticagrelor. At 12 months, there was a significant reduction in the primary composite endpoint of death from vascular causes, myocardial infarction, or stroke (9.8 % vs. 11.7 % for ticagrelor and clopidogrel, respectively; $P<0.001$) without an increase in the rate of overall major bleeding. However, ticagrelor was associated with an increase in fatal intracranial bleeding (0.1 % vs. 0.01 % for ticagrelor and clopidogrel, respectively; $P=0.02$). Dyspnea occurred more frequently in the ticagrelor group (13.8 % of patients vs. 7.8 % for ticagrelor and clopidogrel, respectively; $p<.001$) [94]. Additionally, patients randomized to the ticagrelor arm had more episodes of ventricular pauses >3 s on Holter monitoring at 1 week when compared to patients who were randomized to clopidogrel (5.8 % vs. 3.6 % for ticagrelor and clopidogrel, respectively; $p=0.01$). Finally, ticagrelor is a reversible inhibitor and, therefore, has a shorter half-life when compared to clopidogrel. This may be an advantage if the patient has anatomy that requires urgent coronary artery bypass surgery. However, twice a day dosing is more difficult to maintain because of patient compliance issues.

Glycoprotein IIb-IIIa Antagonists

Awareness of the role of platelet glycoprotein IIb-IIIa (GP IIb-IIIa) in platelet aggregation resulted in a major pharmacologic breakthrough in antiplatelet therapy. The value of GP IIb-IIIa blocker drugs is that blockade of the GPIIb-IIIα2Bβ3 integrin platelet aggregation in response to all agonists, since ligation of this integrin by circulating macromolecules represents the ultimate step in the formation of firm platelet-platelet bonds.

The prototype agent is c7E3 Fab or abciximab, a chimeric fragment of a monoclonal antibody, which binds avidly to GP IIb-IIIa. Since the introduction of abciximab, synthetic peptide and nonpeptide intravenous and oral formulations have been developed, each mimicking the fibrinogen binding site allowing for highly specific and reversible inhibition of the GP IIb-IIIa receptor (Table 25.5). Four trials that evaluated long-term efficacy of the oral GP IIb-IIIa inhibitors xemilofiban [95], orbofiban [96], sibrafiban [97], and lotrafiban [75] did not reveal any benefit and in fact were strongly suggestive of harm [98]. Therefore, current clinical use of GP IIb-IIIa inhibitors is limited to intravenous formulations of the monoclonal antibody abciximab, the peptide fragment eptifibatide, and the peptidomimetic tirofiban.

Abciximab is used in both elective and urgent percutaneous coronary interventions, where its protective effects have been documented. Used with aspirin and heparin, abciximab results in a significant reduction in periprocedural non-ST elevation myocardial infarction following the procedure [99, 100]. A long-term reduction in mortality has been observed in post hoc analysis, particularly in patients receiving intracoronary stents [101].

The efficacy of nonmonoclonal antibody GP IIb-IIIa inhibitors in acute coronary syndromes has been evaluated in multiple trials [102–105]. The inclusion criteria for these

trials included patients presenting with angina consistent with non-ST segment elevation acute coronary syndromes associated with ECG changes and/or the presence of cardiac enzymes. The Platelet Receptor Inhibition for Ischemic Syndrome Management (PRISM) trial investigators randomized patients to receive intravenous tirofiban or heparin for 48 h in non-ST segment elevation ischemic chest pain. The composite endpoint of death, new myocardial infarction, or refractory ischemia at 2 days statistically favored tirofiban (3.8 % vs. 5.6 % for tirofiban and heparin, respectively; $P=0.01$). This benefit was not evident at 30 days although there was significant reduction in mortality (2.3 % vs. 3.6 % for tirofiban and heparin, respectively; $p=0.02$) [102]. The PRISM-PLUS investigators evaluated tirofiban in a higher-risk population with documented ECG abnormalities or non-Q wave myocardial infarction. In contrast to PRSIM, all patients received heparin and were randomized to tirofiban or placebo. Evaluation of the primary composite endpoint at 7 days revealed a 34 % event relative risk reduction in favor of combined therapy (12.9 % vs. 17.9 % for placebo and tirofiban, respectively; CI = 0.53–0.88; $p=0.004$). A tirofiban-only arm in this study was terminated prematurely due to an observed excess mortality. The continued advantage of combination therapy persisted to 6 months, although most benefit was in the refractory ischemia component of the composite endpoint [103]. It is important to note that all patients received mandatory angiography at 48 h, and if indicated, coronary angioplasty was performed. However, in the GUSTO IV trial, a 24-h-long infusion of abciximab was not associated with a reduction in ischemic events [106].

The largest of the trials, the Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression using Integrilin (PURSUIT) study, evaluated eptifibatide or placebo with heparin in 10,948 patients. In this trial, all management decisions were left to the discretion of the physicians in an attempt to mimic "real life." A significant reduction in the rate of death or myocardial infarction was present at 96 h, 7 days, and 30 days (14.2 % vs. 15.7 % for eptifibatide vs. heparin, respectively =0.04). The effect at 30 days was attenuated to a 10 % relative reduction, although the absolute reduction in the number of events was maintained at 15 out of 1,000 patients treated. Rates of blood transfusion (including perioperative bleeding after coronary bypass) were 11.6 % versus 9.2 % for eptifibatide and placebo, respectively (relative risk, 1.3; 95 % confidence interval, 1.1–1.4) [105].

A meta-analysis of six trials with 31,402 patients to evaluate the efficacy and safety of intravenous glycoprotein IIb-IIIa inhibitors with acute coronary syndromes revealed that the combined endpoint of death and MI was reduced by 16 % at 5 days ($p=0.0003$) and 30 days ($p=0.015$) [107]. There was more benefit in men (RR = 0.81, CI = 0.75–0.89) than women; however, there was benefit in both men and women who had elevated troponin measurements. Greater benefit was obtained in patients undergoing PCI than medical treatment; however, patients on GP IIb-IIIa inhibitors had a reduced likelihood of undergoing PCI. Nevertheless, this is a post-randomization analysis, and the trials analyzed did not have a factorial design to evaluate the question of whether GP IIb-IIIa inhibitors are equally efficacious in patients managed conservatively as in those undergoing PCI. Major bleeding at 30 days was increased with an odds ratio of 1.62 (95 % CI 1.36–1.94) with no significant increase in intracranial hemorrhage [107]. Taken together, the above trials make a strong case for the use of GP IIb-IIIa antagonists in combination with heparin and aspirin, especially in patients with high-risk features.

Given that glycoprotein IIb-IIIa inhibitors are effective in acute coronary syndrome and in patients who undergo PCI, there has been debate regarding when to start treatment with this agent. The ACUITY TIMING trial assessed early initiation of glycoprotein IIb/IIIa inhibitor therapy versus delayed initiation in patients with non-ST segment acute coronary syndrome. The trial demonstrated that delayed administration was not inferior to an early strategy with respect to ischemic composite endpoints (death, myocardial infarction, or unplanned revascularization for ischemia) at 30 days. However, there were reduced rates of minor and major bleeding complications with a delayed approach (4.9 % vs. 6.1 %, for a delayed approach vs. an early strategy, respectively; $P<.001$ for non-inferiority; $P=.009$ for superiority) [108]. The EARLY ACS trial compared upstream versus delayed use of eptifibatide therapy in more than 9,000 patients with non-ST segment elevation high-risk acute coronary syndrome patients who were scheduled to undergo an invasive strategy. The primary endpoint (death, myocardial infarction, recurrent ischemia requiring urgent revascularization, or the occurrence of a thrombotic complication during percutaneous coronary intervention that required bolus therapy opposite to the initial study-group assignment at 96 h) occurred in 9.3 % of patients in the early eptifibatide group and in 10.0 % in the delayed eptifibatide group ($P=0.23$) [109]. At 30 days, the rate of death or myocardial infarction was 11.2 % in the early eptifibatide group, as compared with 12.3 % in the delayed eptifibatide group ($P=0.08$). Patients in the early eptifibatide group had higher rates of bleeding (2.6 % vs. 1.8 % for early and delayed administration, respectively; $p=0.02$) and blood transfusions (8.6 % vs. 6.7 % for early and delayed administration, respectively; $p=0.001$). There was no significant difference between the two groups in the rates of severe bleeding or nonhemorrhagic serious adverse events. Taken together, the ACUITY TIMING and EARLY ACS trials suggest that a delayed strategy of GP IIb-IIIa therapy is non-inferior to an upfront approach and is associated with less bleeding.

Antithrombotic Agents

Unfractionated Heparin

Heparin consists of an unfractionated mixture of glycosaminoglycans with molecular weights ranging from 5,000 to more than 30,000 Da. These molecules bind the serpin antithrombin. Subsequent binding of this complex to the enzyme factor Xa inhibits the soluble coagulation cascade by preventing factor Xa-induced amplification of the conversion of prothrombin (factor II) to thrombin (factor IIa). Heparin binding to antithrombin also inactivates this final enzyme in the coagulation cascade and prevents the cleavage of fibrinogen to fibrin.

Heparin therapy has a class Ia indication in the setting of unstable *angina* [17]. The efficacy of intravenous heparin in unstable angina has been suggested by many moderate-sized trials and is supported by a meta-analysis [74, 110]. The relative risk of death or MI was reduced by 33 % (CI = 0.44–1.02) [110]. A phenomenon of reactivation angina with the risk of cardiac events following cessation of heparin has been observed. This reaction is more likely to occur following prolonged administration of heparin exceeding 72 h. The use of concomitant aspirin may attenuate this effect [111]. Data that suggest prolonged unfractionated heparin infusion decreases antithrombin levels and increases thrombin generation can be observed when a heparin infusion is stopped abruptly [112]. Therefore, when using unfractionated heparin, it may be prudent to wean heparin after long durations of therapy and to continue close observation for at least 12 h after cessation.

The therapeutic effect of unfractionated heparin is not linearly related to the activated partial thromboplastin time (aPTT) value. Clinical trial observations in patients presenting with acute coronary syndrome have shown no additional benefit when aPTTs were in excess of 2.0 times the baseline aPTT. In fact, sustained anticoagulation beyond this value is associated with a tendency to increased adverse outcomes, including recurrent myocardial infarctions as well as hemorrhage [112, 113]. The mechanism of this paradoxical effect remains uncertain. In vivo and ex vivo studies have demonstrated platelet activation in the presence of unfractionated heparin in normal volunteers [114]. This effect may be more likely to occur when heparin blood levels are high [115]. Therapeutic dosing of unfractionated heparin should target an aPTT 1.5–2.0 times the baseline value. In most laboratories, this range corresponds to an aPTT in the range of 45–60 s. Dose titration is easier to achieve by the use of weight-based dosing normograms. Use of a bedside aPTT monitor also facilitates the monitoring of heparin infusions and reduces the time required to obtain a PTT level from approximately 90 min to less the 5 min. In one study, bedside aPTT monitoring was associated with reduced rates of hemorrhage compared with standard laboratory monitoring [116].

The most common complication of continuous unfractionated heparin administration is bleeding. Heparin-induced thrombocytopenia has been reported in 1.0–2.4 % of patients receiving therapeutic doses of unfractionated heparin, most commonly occurs with prolonged dosing, and is associated with a several-fold increase in hospital mortality. More rare complications include alopecia, skin necrosis, urticaria, and transient serum transaminase elevations [117, 118].

Low Molecular Weight Heparins

The low molecular weight heparins (LMWHs) are derived by fractionation of standard heparin and retrieving molecules less than 8,000 Da in size. Compared with unfractionated heparin, these products bind less avidly to plasma proteins, thereby allowing more predictable anticoagulation dosing. When administered subcutaneously, they are highly bioavailable. Compared with unfractionated heparin, these agents have a more pronounced effect on coagulation factor Xa than on thrombin. Therefore, the total antithrombotic action is not reflected by the aPTT. This anti-factor Xa effect impairs thrombin generation from prothrombin [119]. Since anti-Xa activity resides predominately in the lower molecular weight fractions, the anti-Xa activity is greater compared to unfractionated heparin and varies among the various LMWHs.

Many clinical trials have evaluated LMWHs in acute coronary syndromes without ST segment elevation. The Fragmin during Instability in Coronary Artery Disease (FRISC) trial randomized patients to receive subcutaneous dalteparin (Fragmin) or placebo [120]. Although there was a significant reduction in death and myocardial infarction at 6 days, this effect disappeared at 5 months despite continued once-daily administration of dalteparin for up to 45 days. This study did not incorporate standard heparin in the control group [121]. The related FRIC study used identical dosing and duration of dalteparin in a comparison with standard heparin. No benefit of dalteparin was observed [122].

Most data concerning LMWHs in acute coronary syndromes have been obtained using enoxaparin (Lovenox). Two early studies, the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) and the Thrombolysis in Myocardial Ischemia 11 (TIMI 11) trials, compared enoxaparin with standard heparin in patients managed with a predominately conservative revascularization strategy [123, 124]. When PCI was performed in these trials, unfractionated heparin was used as the foundation anticoagulant. ESSENCE showed a statistical benefit favoring enoxaparin. At 14 days, the composite endpoint of death, myocardial infarction, or recurrent ischemia occurred in 16.6 % of patients randomized to enoxaparin versus 19.9 % for the standard heparin group ($p = 0.019$). A statistically nonsignificant trend persisted to 30 days. Recurrent angina was responsible for approximately 75 % of all endpoints in this trial [123]. The TIMI II trial investigators evaluated an

alternative dosing regimen of enoxaparin versus unfractionated heparin in 3,910 patients presenting with non-ST segment elevation acute coronary syndromes. Enoxaparin was initially administered as an intravenous bolus of 30 mg/kg, followed by 1 mg/kg subcutaneous injections twice daily for 3 days. There was a statistically significant benefit of enoxaparin in the primary composite endpoint of death, myocardial infarction, or refractory ischemia at 8 days. The event rates were 12.4 % versus 14.5 % for enoxaparin and unfractionated heparin, respectively ($p=0.048$) [124]. A planned meta-analysis of these two trials revealed that at 1 year, the composite of death, myocardial infarction, or refractory ischemia was reduced from 25.8 to 23.3 % ($p=0.008$), while the composite of death and myocardial infarction was reduced from 13.7 to 12.7 % ($p=0.16$) [125].

Two recent trials evaluated enoxaparin in the context of a modern management strategy utilizing GP IIb-IIIa inhibitors but without early revascularization. The Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment (INTERACT) trial compared enoxaparin with unfractionated heparin in 746 patients who were also treated with eptifibatide for non-ST segment elevation acute coronary syndromes and who were managed without mandatory early revascularization. The rates of major and minor bleeding were less with enoxaparin (1.8 % vs. 4.6 %, $p=0.03$), and there was also a significant reduction in the endpoint of death or myocardial infarction (5 % vs. 9 %, $p=0.031$) [126]. In the Antithrombotic Combination Using Tirofiban and Enoxaparin (ACUTE II) study, 525 patients were randomized to receive tirofiban with either unfractionated heparin or enoxaparin. The rates of bleeding were similar and there was a trend toward decreased urgent revascularization and rehospitalization with tiroban/enoxaparin [127].

The Superior Yield of the New Strategy of Enoxaparin Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial was designed to compare the two forms of heparin in a modern context of frequent use of GP IIb-IIIa antagonists and early coronary angiography and intervention. More than 10,000 patients with high-risk features (two of the following: age >65 years, ST segment deviation, or elevated levels of cardiac biomarkers) of non-ST segment elevation acute coronary syndrome patients were randomized to enoxaparin, given as a 30 mg/kg intravenous bolus followed by 1 mg/kg subcutaneously every 12 h, or unfractionated heparin. Early angiography was encouraged. Fifty-six percent of patients in this trial received a GP IIb-IIIa antagonist and more than 90 % underwent early angiography. In patients receiving enoxaparin, a supplemental bolus of 0.3 mg/kg was given intravenously if the last dose of enoxaparin was given more than 8 h before the intervention. The composite endpoint of death or myocardial infarction at 30 days occurred in 14 % of patients assigned to enoxaparin and 14.5 % of patients assigned to unfractionated heparin [128]. Although there was no evidence that enoxaparin was a superior treatment, statistical requirements to demonstrate non-inferiority were met. The risk of severe bleeding was nonsignificantly increased in patients assigned to enoxaparin (2.9 % vs. 2.4 % for enoxaparin and heparin, respectively; $p=0.106$). However, the risk of major hemorrhage using a modified TIMI definition was significant for enoxaparin (9.1 % vs. 7.6 % for enoxaparin and heparin, respectively; $p=0.008$). This risk appeared to be increased predominately in the elderly and in patients with renal insufficiency, suggesting accumulation of the drug. The risk of abrupt closure of the revascularized coronary artery was similar between the two groups. However, an important point to consider is that about three fourths of patients in the trial had received some form of antithrombin therapy (either unfractionated or low molecular weight heparin) prior to randomization, and about one seventh of patients assigned to enoxaparin also received unfractionated heparin at some point during the hospitalization, largely during coronary intervention. Thus, contamination with nonprotocol antithrombin therapies confounds interpretation of these results.

A 2004 meta-analysis including data on 21,946 patients from six randomized trials comparing unfractionated heparin versus enoxaparin suggests that enoxaparin is associated with a significant reduction in the incidence of death or nonfatal MI at 30 days without a significant difference in major bleeding complications [129]. A similar significant reduction in the rate of death or nonfatal MI at 30 days was noted in a 2007 meta-analysis [130]. However, this more recent analysis did show a small but significant increase in major bleeding associated with enoxaparin (4.3 % vs. 3.4 % for enoxaparin and heparin, respectively; $P=0.019$). As with all meta-analysis, the utility of grouping data and results is limited by the heterogeneity of each individual study. For example, the use of GP IIb-IIIa therapy and the rate of selective coronary angiogram were not uniform among all studies.

Taken as an aggregate, it would seem safe to conclude that enoxaparin is not inferior to heparin in treating acute coronary syndrome. Use of either agent should be individualized by each patient (age, renal status, likelihood of undergoing coronary artery bypass surgery, etc.).

Fondaparinux

Fondaparinux is a synthetic heparin pentasaccharide that acts by neutralizing factor Xa. The OASIS-5 trial enrolled over 20,000 patients with non-ST segment elevation acute coronary syndrome to fondaparinux or enoxaparin. In this study, fondaparinux was not inferior to enoxaparin in the primary composite endpoint of death, myocardial infarction, or refractory ischemia at 9 days [131]. Bleeding events were significantly reduced with fondaparinux administration (2.2 % vs. 4.1 % for fondaparinux and enoxaparin,

respectively; $P<0.001$). Among patients who underwent PCI, fondaparinux was non-inferior to enoxaparin with respect to ischemic events while significantly reducing bleeding complications. This resulted in a superior net clinical benefit (death, myocardial infarction, stroke, or major bleeding: 8.2 % vs. 10.4 %, for fondaparinux vs. enoxaparin, respectively; HR 0.78; $p=0.004$) [132]. Importantly, catheter thrombus formation was observed during the early stages of the trial when PCI was performed with fondaparinux alone without the intraprocedural addition of any thrombin inhibitor, and therefore, a protocol amendment was instituted that added the use of unfractionated heparin during the procedure at the discretion of the operator during PCI. While the addition of unfractionated heparin mitigated the rate of catheter-related thrombus formation in both treatment groups, the use of fondaparinux was associated with more catheter thrombus events.

The dose of additional heparin when using fondaparinux in the setting of PCI for acute coronary syndrome to avoid catheter thrombus formation and bleeding complications was addressed in the FUTURA/OASIS-8 trial [133]. Patients received intravenously either low-dose unfractionated heparin (50 U/kg, regardless of the use of GPIIb-IIIa inhibitors) or standard-dose unfractionated heparin (85 U/kg and 60 U/kg with GPIIb-IIIa inhibitors), adjusted by activated clotting time (ACT). At 48 h after PCI, there was no significant difference between the standard and low-dose regimens in the rate of the primary composite endpoint (major bleeding, minor bleeding, or major vascular access-site complications). The composite secondary outcome of major bleeding at 48 h with death, myocardial infarction, or target vessel revascularization within 30 days occurred more in the low-dose group, nearly attaining statistical significance (5.8 % in the low heparin dose vs. 3.9 % in the high heparin dose, respectively; odds ratio 1.51; 95 % CI 1.00–2.28; $p=0.05$) [133]. Catheter thrombus rates were very low and not statistically different between the two groups.

Direct-Thrombin Inhibitors

The direct-thrombin inhibitors act independently of antithrombin and are unaffected by heparin-inactivating proteins. They are more capable than heparin in inhibiting clot-bound thrombin and can therefore theoretically prevent the perpetuation of local coagulation [134]. These drugs are administered intravenously. Prolongation of the aPTT occurs due to the direct effect on thrombin.

The prototype drug is hirudin, a naturally occurring anticoagulant found in the saliva of the medicinal leech. It is now produced through recombinant DNA technology. The clinical value of hirudin was assessed in the GUSTO-II trial. Patients with acute chest pain and without ST segment elevation were randomized to receive intravenous hirudin (0.1 mg/kg bolus and 0.1 mg/kg/h infusion) or unfractionated heparin. The primary endpoint of death, nonfatal myocardial infarction, or reinfarction at 30 days was nonsignificant (9.8 % vs. 8.9 % for heparin and hirudin, respectively; $p=0.06$) [135]. The Canadian Organization to Assess Strategies for Ischemic Syndromes (OASIS-2) study evaluated a higher hirudin dose (0.4 mg/kg bolus and 0.15 mg/kg/h infusion) in patients with acute coronary syndromes without ST segment elevation. The primary endpoint, a composite of cardiovascular death or myocardial infarction at 7 days, occurred in 3.6 % of hirudin-treated patients and 4.2 % of heparin-treated patients. Similarly, these results fell short of statistical significance. However, the composite endpoint of cardiovascular death, myocardial infarction, or refractory angina at 7 days was 6.7 and 5.6 % for heparin and hirudin, respectively; $p=0.012$. Major bleeding occurred more frequently with hirudin (1.2 % vs. 0.7 % for hirudin and heparin, respectively; $p=0.048$) [136].

Bivalirudin is a synthetic 20 amino acid analog of hirudin that inhibits clot-bound thrombin more effectively due to its smaller size. The Bivalirudin Angioplasty study compared bivalirudin with high-dose heparin during coronary angioplasty for unstable angina. There was a significant difference in the primary endpoint of death, myocardial infarction, or repeat revascularization in favor of bivalirudin at 7 and 90 days post procedure. Furthermore, there was significantly less bleeding complications with bivalirudin [137]. The Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial was a randomized, double-blind, active-controlled trial conducted among 6,010 patients undergoing urgent or elective PCI. Patients were randomly assigned to receive intravenous bivalirudin (0.75 mg/kg bolus plus 1.75 mg/kg/h for the duration of PCI), with provisional GP IIb-IIIa treatment, or heparin (65-U/kg bolus) with planned GP IIb-IIIa inhibition (abciximab or eptifibatide). The bivalirudin arm was not inferior to the heparin and planned IIb-IIIa group with respect to the primary composite endpoint of 30-day rates of death, myocardial infarction, urgent repeat revascularization, or in-hospital major bleeding [138]. Furthermore, patients in the bivalirudin arm experience significantly less bleeding complications (2.4 % vs. 4.1 % for bivalirudin with provisional IIB/IIIA and heparin with planned IIb/IIIA, respectively; $P<.001$). In the ISAR-REACT 3 trial, more than 4,500 patients who were pretreated with clopidogrel were randomized to bivalirudin or heparin therapy. There was no statistical difference in the primary composite endpoint that included death, myocardial infarction, urgent target vessel revascularization due to myocardial ischemia within 30 days after randomization, or major bleeding during the index hospitalization [139]. However, the group randomized to bivalirudin had fewer bleeding complications (3.1 % vs. 4.6 % for the bivalirudin group and the unfractionated heparin group, respectively; $p=0.008$).

Table 25.6 Early stratification for risk of adverse outcome in patients presenting with unstable angina

	Low risk	Intermediate risk	High risk
Clinical history	Effort angina with little progression	Gradual evolution of anginal symptoms to CCSC class III or IV (>4 week)	Rapid evolution of anginal symptoms to CCSC class III or II (<4 week)
	<2 cardiac risk factors	2 cardiac risk factors	Advanced age (>60)
	Negative troponin T or I		Known CAD
			Postmyocardial infarction (<6 week)
Physical exam	No abnormal cardiovascular findings	Signs of peripheral vascular disease	Hemodynamic instability
		Carotid/femoral bruits	Signs of CHF "+" S_3 gallop
		Diminished pulses	Lung rales
ECG	Normal or minimal abnormality	Minimal ST or T wave abnormalities	ST segment depression ≥1 mm

The Acute Catheterization and Urgent Intervention Triage StrategY (ACUITY) trial compared the efficacy and safety of bivalirudin in the setting of moderate to high-risk acute coronary syndrome. Over 13,000 patients were assigned to one of three treatment arms: bivalirudin alone, bivalirudin plus a GP IIb-IIIa inhibitor, or a GP IIb-IIIa inhibitor plus heparin or enoxaparin. The primary endpoint was a composite ischemic endpoint (death, myocardial infarction, or unplanned revascularization for ischemia), major bleeding, and the net clinical outcome, defined as the combination of composite ischemia or major bleeding at 30 days. The results indicate that in the patients who were treated with glycoprotein IIb-IIIa inhibitors, bivalirudin was associated with rates of ischemia and bleeding that were similar to those with heparin. Bivalirudin alone was associated with similar rates of ischemia and significantly lower rates of bleeding [140]. As an aggregate, the data indicate that bivalirudin is as effective as heparin in reducing composite ischemic endpoints and is associated with a lower rate of bleeding complications.

Statins

Multiple clinical trials have established the efficacy of HMG CoA reductase inhibitors in the primary and secondary prevention of coronary artery disease. Statins decrease C-reactive protein and hence are thought to reduce inflammation [141, 142]. This observation led to studies evaluating the role statins in acute coronary syndromes. In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, high-dose atorvastatin (80 mg/day) started within 24–96 h of admission for unstable angina or non-Q-wave myocardial infarction reduced recurrent ischemic events over a 16-week treatment period compared with placebo [143]. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial, intense LDL lowering to a mean level of 62 mg/dL with atorvastatin (80 mg/day) versus a mean level of 95 mg/dL with pravastatin (40 mg/day) in the context of acute coronary syndromes led to substantial reduction in cardiovascular morbidity and mortality (16 % reduction in hazard ratio, CI = 5–26 %) [144]. A substudy from PROVE-IT examined high-dose statin therapy versus moderate-dose statin therapy in patients who received PCI. There was a significant difference in the primary composite endpoint of major adverse cardiovascular events (MACE) in favor of the intense statin arm (21.5 % vs. 26.5 % for atorvastatin and pravastatin, respectively; $p = 0.002$) [145]. Furthermore, there was significant benefit in favor of the intense statin arm with regards to the incidence of both target vessel revascularization ($p = 0.001$) and nontarget vessel revascularization ($p = 0.017$). After adjusting for serum low-density lipoprotein cholesterol and C-reactive protein concentrations, the odds of TVR with high-dose statin therapy remained significant ($p = 0.015$). This finding suggests that the effect of intense statin therapy may be due, in part, to a pleiotropic effect that provides benefit during acute coronary syndrome.

Management Approach

Since clinical presentations of acute chest pain are diverse, the intensity of the management strategy will vary as well. The clinician must assess the patient's risk for evolving further cardiac events based on individualized risk scores (Fig. 25.1 and Table 25.6).

Although it seems intuitive that revascularization procedures confer protection against recurrent infarction and ischemia, the results of early randomized trials were inconclusive. In fact, some results questioned if aggressive therapy with revascularization should be pursued versus a more conservative approach. TIMI IIIB [16] and the Veterans Affairs Non-Q-Wave Infarction Strategy in Hospital (VANQWISH) [146] studies suggest that there is no benefit of an early invasive strategy for patients with non-ST segment elevation acute coronary syndrome. The OASIS registry of more than 7,900 consecutive patients with non-ST segment elevation acute coronary syndromes observed no difference in the rate of

cardiovascular death or myocardial infarction in countries with the highest rate of invasive procedures (59 %) versus the lowest (21 %) rate [147]. However, these studies were prior to the arrival of more effective antiplatelet and antithrombotic strategies. Thus, these data and their derived assumptions may not be applicable today.

Recent trials utilizing a modern strategy of contemporary pharmacotherapy demonstrate significant benefit in the reduction of cardiovascular endpoints when pursuing an early invasive approach. The Fragmin and Fast Revascularization during Instability in CAD (FRISC II) study evaluated 2,457 patients presenting with non-ST segment elevation acute coronary syndromes who underwent coronary angiography within 7 days. These patients were treated with dalteparin or placebo [121]. After 6 months there was a significant decrease in the composite endpoint of death or myocardial infarction in the invasive group (9.4 % vs. 12.1 % for the invasive and conservative groups, respectively; $p=0.031$). There was a significant decrease in myocardial infarction alone (7.8 % vs. 10.1 % for invasive vs. conservative management, respectively; $p=0.045$) and a nonsignificant trend toward lower mortality. Results were independent of the randomized dalteparin treatment. The greatest advantages were seen in high-risk patients.

The Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS-TIMI 18) study evaluated an early invasive strategy versus conservative treatment in 2,220 patients with ACS [148]. All patients received tirofiban at the time of study enrollment. In this trial, patients underwent coronary angiography within 4–48 h in the invasive group (median 9 h to angiography, 23 h to PCI). In the conservative arm, patients had cardiac catheterization only if they developed objective evidence of recurrent ischemia. The patients in the invasive group had a significantly lower incidence of the combined endpoint of death, MI, or rehospitalization for ACS (15.9 % vs. 19.4 %, for early invasive treatment versus conservative management, respectively; $p=0.025$) at 6 months. The absolute and relative benefits of the invasive strategy increased as the TIMI risk score increased.

The Randomized Intervention Trial of Unstable Angina (RITA-3) study evaluated the use of early angiography and revascularization in 1,810 patients with non-ST elevation ACS [149]. Compared with patients assigned to the conservative arm, patients randomized to the invasive strategy had a 34 % reduction in the combined endpoint of death, MI, or refractory angina (9.6 % vs. 14.5 % for the invasive arm and the conservative management, respectively; $p=0.001$).

As several trials have compared an invasive versus a conservative strategy in non-ST segment acute coronary syndrome, a meta-analysis was conducted using contemporary trials that incorporated advanced pharmacotherapy with antithrombin and antiplatelet agents. Bavry et al. evaluated seven trials including 8,375 patients [150]. At a mean follow-up of 2 years, the incidence of all-cause mortality was 4.9 % in the early invasive group, compared with 6.5 % in the conservative group (95 % CI 0.63–0.90, $p=0.001$). At 2 years, the incidence of nonfatal myocardial infarction was 7.6 % in the invasive group versus 9.1 % in the conservative group (95 % CI 0.72–0.96, $p=0.012$). At 13 months of follow-up, there was a reduction in rehospitalization for unstable angina (95 % CI 0.65–0.74, $p<0.0001$). These results suggest that an early invasive strategy may be beneficial.

Another meta-analysis across eight trials including over 8,000 men and over 3,000 women compared an invasive versus conservative approach in the treatment of non-ST segment elevation acute coronary syndrome [151]. In this analysis, each group was stratified to positive or negative biomarkers. Among men, an invasive strategy was associated with an odds ratio (OR) for a composite of death, MI, or ACS at 12 months of 0.56 (95 % CI, 0.46–0.67) if biomarker-positive and 0.72 (95 % CI, 0.51–1.01) if biomarker-negative (P for interaction = 0.09). Among biomarker-positive women, an invasive strategy was associated with a 33 % lower odds of death, MI, or acute coronary syndrome (OR, 0.67; 95 % CI, 0.50–0.88) and a nonsignificant 23 % lower odds of death or MI (OR, 0.77; 95 % CI, 0.47–1.25). In contrast, an invasive strategy was not associated with a significant reduction in the triple composite endpoint in biomarker-negative women (OR, 0.94; 95 % CI, 0.61–1.44; P for interaction = .36) and was associated with a nonsignificant 35 % higher odds of death or MI (OR, 1.35; 95 % CI, 0.78–2.35; P for interaction = .08). This analysis suggests that in low risk patients, particularly women, it may be preferable to pursue a conservative approach.

As several trials suggest that an early invasive approach may be beneficial when compared to a conservative route in intermediate to high-risk patients per TIMI risk score, the question of when to proceed with angiography has been evaluated. The Intracoronary Stenting With Antithrombotic Regimen Cooling-Off (ISAR-Cool) trial evaluated prolonged treatment with antithrombotic medications prior to coronary intervention [152]. In the study, 410 patients with non-ST elevation ACS were randomized to an early invasive strategy (within 6 h) or coronary intervention after 3–5 days of contemporary therapy that included aspirin, clopidogrel, heparin, and tirofiban. The combined endpoint of death or MI at 30 days was significantly reduced in the early invasive group (5.9 % vs. 11.6 % for early invasive treatment and delayed management, respectively; $p=0.04$). The Timing of Intervention in Acute Coronary Syndromes (TIMACS) trial compared early versus delayed angiography and intervention in patients with non-ST segment elevation ACS. Patients included in the study had high-risk features including advanced age (>60 years), elevated biomarkers, or ischemic ECG changes. They were randomized to early

invasive (median 14 h) or a delayed invasive strategy of at least 36 h (median 50 h) [153]. Treatment included aspirin, clopidogrel (>80 %), heparin or fondaparinux, and GP IIb-IIIa inhibitors (23 %). The primary outcome was a composite of death, myocardial infarction, or stroke at 6 months. A prespecified secondary outcome was death, myocardial infarction, or refractory ischemia at 6 months. Among all comers, there was no significant difference in the primary endpoint. However, there was a significant difference in the composite secondary endpoint ($p=0.003$), which was driven by refractory ischemia.

When patients were stratified by risk assessment, those in the highest tertile of the Global Registry of Acute Coronary Events (GRACE) score experienced a significant benefit in the primary endpoint. Specifically, in patients with a GRACE risk score of more than 140, the primary outcome occurred in 13.9 % of patients in the early intervention group versus 21.0 % in the delayed intervention group ($P=0.006$). Additionally, among these high-risk patients, the secondary composite outcome of death, myocardial infarction, or refractory ischemia occurred in 13.7 % of patients in the early intervention group versus 21.6 % in the delayed intervention group ($P=0.002$). Among patients with a GRACE score of 140 or less, there was no significant difference between the groups in either the primary composite endpoint or the secondary composite endpoint.

To assess if non-ST segment elevation acute coronary syndrome should be treated as ST elevation acute coronary syndrome, the Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes (ABOARD) study compared an immediate invasive approach (on presentation, median time 70 min) to a delayed approach (carried out the next working day, median time 21 h) [154]. Again, antithrombotic and antiplatelet management was contemporary and included a loading dose of clopidogrel, aspirin, GP IIb-IIIA administration during PCI, and antithrombotic therapy according to the operator's discretion. The primary endpoint was peak troponin during the hospitalization. The secondary endpoint was a composite of death, MI, or urgent revascularization at 1 month. There was no significant difference in either the primary or secondary outcomes between the two groups.

Impression and Conclusions

When evaluating the patient with non-ST segment elevation acute coronary syndrome, the clinician must risk stratify the patient. In addition to a thorough history and physical examination, diagnostic modalities assist in this endeavor. ECG and biomarkers provide important diagnostic and prognostic information. After risk stratifying the patient, the clinician should decide between an invasive or conservative approach. Paramount to both of these strategies is the combined pharmacotherapy of anti-ischemic, antiplatelet, and antithrombotic agents. Within each class of drugs, there are several choices. The final medley of medications and appropriate doses should be tailored to each patient's clinical scenario including their age, comorbidities, and planned treatment strategies. If an invasive approach is chosen, the decision of when to act also depends on each patient's clinical situation. In the background of these management decisions is the fact that each institution practices medicine in a distinct fashion based on the availability of backup services, personnel, and local style and that unilateral changes in practice without appropriate support may not necessarily be beneficial.

It is very important to know the data that drive and dictate treatment decisions. While guidelines are constructed by the data generated from trials, it is important to note that less than 25 % of class I recommendations are based on "adequate" evidence and that the majority of recommendations are based on expert consensus. For example, only 245 of 1,305 class I recommendations from the ACC/AHA clinical practice guidelines have level of evidence A [155]. Additionally, physicians deal with real-life situations on a daily basis. Each patient has unique disease processes and comorbidities that require clinicians to incorporate individuality in the framework of proven/recommended therapies. We are neither at the stage of truly "personalized medicine" nor at the stage of true "cookbook" medicine. Rather, each patient should be evaluated individually when applying established and recommended algorithms.

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ST-Segment Elevation Myocardial Infarction

26

Jonathan R. Enriquez and James A. de Lemos

Management of acute ST-elevation myocardial infarction (STEMI) has been transformed in the last 20 years by the results of large, prospective, randomized trials. Advances have been made in all components of acute myocardial infarction (AMI) management, from primary and secondary prevention to prehospital care, acute reperfusion therapy, adjunctive medical therapy, and management of complications. Despite this progress, however, acute MI remains the most common cause of death in industrialized nations; in addition, while mortality rates have been falling, the incidence of new infarction has not fallen in concert. Increasingly, attention is now being placed on the *quality* of AMI care, with recognition that improvement in processes of STEMI care can directly lead to better patient outcomes.

Overview of Pathophysiologic Mechanisms

The different acute coronary syndromes exist on a continuum of plaque rupture and thrombus formation (Fig. 26.1): the continuum ranges from a ruptured plaque with little or no thrombus (often asymptomatic), to a ruptured plaque with moderate thrombus leading to partial coronary occlusion (unstable angina and non-ST elevation MI), to a ruptured plaque with extensive thrombus and complete occlusion of the artery (ST-segment elevation MI). In a minority of patients, superficial plaque erosion, rather than plaque rupture, may be the precipitating event.

Angiographic studies have consistently shown that MI more commonly develops from lesions associated with minor (<70 %) rather than severe (≥70 %) luminal narrowing. Those atherosclerotic lesions which lead to acute MI tend to be associated with positive (eccentric) vessel remodeling, in which the entire vessel, including the external elastic lamina, is enlarged to accommodate the growing, lipid-rich plaque. The "vulnerable" atherosclerotic plaque has been characterized as having a dense lipid-rich core and a thin protective fibrous cap. The molecular factors that govern formation and breakdown of the extracellular matrix appear to regulate integrity of this protective fibrous cap. In vulnerable atherosclerotic lesions, inflammatory cells predominate at the shoulder region of the plaque, and local release of cytokines from these inflammatory cells contributes to weakening of the fibrous cap at this critical site.

In acute MI, thrombus forms at the site of plaque rupture and is composed of platelets, fibrin, erythrocytes, and leukocytes. Platelet activation leads to the release of specific mediators including thromboxane A2, serotonin (5HT), adenosine diphosphate (ADP), platelet-activating factor (PAF), thrombin, tissue factor, and oxygen-derived free radicals. The presence of these mediators in conjunction with the relative absence of prostacyclin (PGI2), tissue plasminogen activator (t-PA), and endothelial nitric oxide at sites of vascular injury promotes platelet aggregation and obstruction of the narrowed coronary lumen. On the surface of the activated platelet, the coagulation cascade is propagated, leading to the deposition of thrombin and fibrin, obstructing arterial blood flow and leading to myocardial necrosis.

The process of thrombotic occlusion of an epicardial coronary artery is not a static one. Variation in vasomotor tone and in the balance of endogenous fibrinolytic and procoagulant factors can lead to cyclic occlusion and reperfusion of the occluded artery. Moreover, it has been appreciated that the coronary microcirculation plays a critical role in STEMI. Microvascular obstruction can occur due to embolization of platelet and platelet-thrombin aggregates, microvascular spasm, and in situ leukocyte plugging. Even among patients with successful reperfusion of the occluded epicardial coronary artery, microvascular obstruction is associated with adverse clinical outcomes. Thus, the coronary microcirculation has emerged as an additional target for therapies in STEMI.

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_26, © Springer Science+Business Media New York 2013

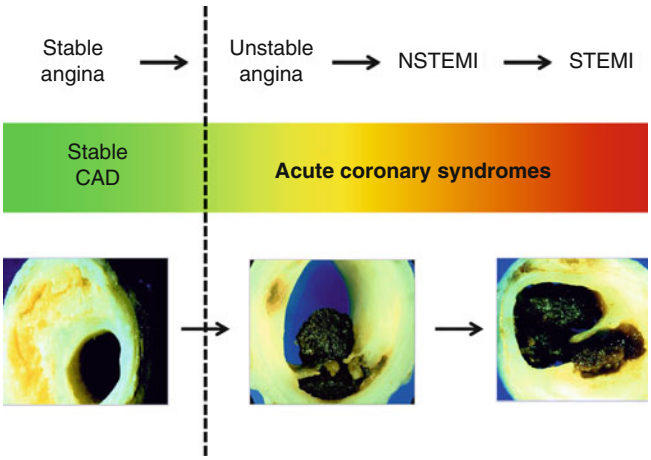

Fig. 26.1 The spectrum of coronary artery disease. The various clinical syndromes of coronary artery disease can be viewed as a spectrum, ranging from patients with stable angina to those with acute ST-elevation MI. Across the spectrum of the acute coronary syndromes, atherosclerotic plaque rupture leads to coronary artery thrombosis: in acute STEMI, complete coronary occlusion is present. In those with unstable angina or NSTEMI, a flow-limiting thrombus is usually present (Adapted from Davies [1]. With permission from BMJ Publishing Group Ltd.)

MI Classification

Patients with acute MI and ST-segment elevation experience a substantial benefit from fibrinolytic therapy, while those without ST elevation do not. Angiographic studies have shown that this difference is due to the initial status of the infarct-related artery: patients with ST-segment elevation exhibit 100 % occlusion of the artery, while patients without ST-segment elevation exhibit a severely stenotic, but nevertheless patent, coronary artery (Fig. 26.1).

As opposed to the distinction of ST-elevation MI vs. non-ST-elevation MI, the determination of Q wave vs. non-Q wave MI can only be made retrospectively and is a less useful classification in the early hours of patient management; therefore, clinical nomenclature has largely abandoned the use of Q wave vs. non-Q wave MI for the terms ST-elevation MI (STEMI) vs. non-ST-elevation MI (NSTEMI). Untreated, most patients with STEMI usually evolve a transmural infarction and develop Q waves on the surface electrocardiogram. With successful reperfusion therapy, however, 25–30 % of patients with STEMI have necrosis limited to the subendocardial regions and do not develop Q waves. Patients without ST elevation at baseline generally do not develop Q waves, since infarction is limited to subendocardial regions.

Over the last decade, the incidence of STEMI has dramatically decreased, while the relative proportion of NSTEMIs has significantly increased. In an analysis of Kaiser Health System data from 1999 to 2008, STEMIs represented approximately 50 % of all MIs in 1999, while in 2008 STEMIs comprised less than 25 % of MIs [2]. Substantial improvements in risk factor modification through lipid reduction, blood pressure control, and smoking cessation initiatives likely contributed to the reduction in STEMIs; however, the relative increase in incidence of NSTEMIs likely reflects not only the decreased incidence of STEMI but also the wider utilization of sensitive troponin testing, which facilitates detection of smaller NSTEMIs.

Diagnosis of Acute Myocardial Infarction

History

A careful history is the most important initial diagnostic step in a patient with suspected acute MI. Most patients complain of chest pain, which resembles classic angina pectoris, and describe a severe, pressure-type pain in the mid-sternum, often radiating to the left arm, neck, or jaw. The pain may be distinguished from angina by its intensity, duration (>30 min), and failure to resolve with nitroglycerin administration. The pain may be accompanied by dyspnea, diaphoresis, nausea, vomiting, and profound weakness. Several factors have been identified as potentially inciting acute MI; specifically, a higher proportion of events have been associated with morning awakening, heavy exertion, emotional stress, and sexual activity. Particular attention should be given to the quality of pain, its variation with respiration and position, and whether it is similar to prior anginal episodes in quality. Characterization of the pain may help to distinguish it from other conditions which also cause chest discomfort. Aortic dissection, for example, typically causes a "tearing" pain, radiating through to the back. Pulmonary embolism is usually accompanied by pleuritic pain, shortness of breath, and occasionally hemoptysis. Pericardial pain is also usually pleuritic and frequently changes with position, such that the patient may feel better sitting forward. The pain of pericarditis may radiate to the left shoulder or trapezius ridge. Not infrequently, inferior wall myocardial infarction (IMI) masquerades as indigestion or nausea, rather than chest pain. Differentiating this from cholecystitis, peptic ulcer, and mesenteric ischemia by history alone may be very difficult, and a high index of suspicion for myocardial infarction is necessary.

Many patients, particularly the elderly and women, present with "atypical" symptoms, which include dyspnea, indigestion, unusual locations of pain, agitation, altered mental status, profound weakness, and syncope. Furthermore, infarction may frequently be silent in diabetic patients, as a result of the neuropathy that accompanies long-standing diabetes mellitus.

Physical Exam

The physical examination should be performed efficiently, focusing on narrowing the differential diagnosis and assessing

the stability of the patient. A focused examination can help to differentiate diagnoses such as pericarditis, pneumothorax, pulmonary embolus, and aortic dissection, which may mimic acute MI. It can also identify valvular abnormalities which may complicate patient management. In addition, hemodynamic and mechanical complications of acute MI can often be detected by careful attention to physical findings.

Patients with acute MI often appear pale, cool, and clammy; in many cases, they are in obvious distress. Elderly patients, in particular, may be agitated and incoherent. Patients with cardiogenic shock may be confused and listless. Blood pressure and pulses should be checked in both arms, since a pulse deficit or decreased blood pressure in the left arm would shift the focus of the diagnostic work-up towards aortic dissection. Cardiac examination should focus on eliciting murmurs and rubs. A pericardial rub, although often difficult to appreciate, suggests that pericarditis may be the cause of a patient's chest discomfort.

A brief survey for signs of congestive heart failure should be performed. Cool extremities or impaired mental status suggests decreased tissue perfusion, while elevated jugular venous pressure, rales, and peripheral edema suggest elevated cardiac filling pressures. Examination of the peripheral arterial pulses can detect peripheral vascular disease, which in itself increases the likelihood of coronary disease.

ECG Findings (See Chap. 7)

Current guidelines recommend the implementation of systems of care to promptly identify the diagnosis of ST-segment elevation MI so that early reperfusion therapy may be administered without delay. The 12-lead ECG remains the most important initial diagnostic step in patients with suspected MI. Many emergency medical systems routinely perform 12-lead ECGs in the field, with some health-care systems allowing direct activation of reperfusion teams by EMS personnel. These enhancements to regional systems of care have been shown to improve reperfusion times [3], which are a major contributor to outcomes in patients with STEMI.

Patients reporting to the emergency room with chest pain should have a 12-lead ECG performed immediately. Attempt should be made to distinguish ST-segment elevation suggestive of MI from that of pericarditis and the normal early repolarization variant. In pericarditis, ST elevation is usually diffuse and may be associated with depression of the PR segment. In the early repolarization variant, the contour of the elevated ST segment is concave rather than convex. As soon as the diagnosis of ST-elevation MI is made, prompt activation of cardiac catheterization or fibrinolytic protocols is paramount to achieving recommended benchmarks for timely reperfusion. The presence of new left bundle branch block (LBBB) in the setting of chest pain can be suggestive of a large anterior infarction, and in the appropriate clinical context, these patients should be considered "STEMI equivalents" and considered for reperfusion therapy as well. Patients with LBBB of undetermined age present a diagnostic dilemma, and either emergency echocardiography (to look for an anterior wall motion abnormality), rapid point-of-care cardiac biomarker measurement, or cardiac catheterization should be considered. In patients with a preexisting LBBB, ECG criteria have been proposed to facilitate MI diagnosis. The most widely studied criteria, proposed by Sgarbossa et al., are specific but have very poor sensitivity [4]. Although current guidelines recommend an aggressive approach to reperfusion therapy in patients with LBBB and possible MI, these recommendations do not reflect the changing epidemiology of STEMI and also of LBBB. We recommend an individualized approach to such patients that factors in the probability of transmural infarction and the risk of the patient [5].

Cardiac Biomarkers

Measurements of cardiac troponin T and I (cTnT and cTnI) have become routine, and rapid point-of-care assays for myoglobin, CKMB, and cTn are now available. The advent of more sensitive cardiac biomarkers has facilitated the diagnosis NSTEMI; however, patients with STEMI are identified primarily on their clinical syndrome and presenting ECG. As a result, reperfusion pathways are implemented before the measurement of cardiac biomarkers has been completed. For patients with STEMI, cardiac marker measurements are used to confirm the diagnosis in patients with equivocal ECG changes, to help gauge prognosis, and sometimes to estimate the likelihood of successful reperfusion therapy. The time course of rise and fall of commonly measured biomarkers is shown in Fig. 26.2. While cardiac biomarkers have little role in the emergent *diagnosis* of STEMI, they remain valuable for prognostic assessment. For example, patients with evidence of biomarker elevation prior to the administration of reperfusion therapy are at increased risk for failure of fibrinolytic therapy or primary PCI and are at increased risk for death, independent of the success or failure of reperfusion therapy. Interestingly, this association with outcomes is also independent of infarct location and time to treatment, suggesting that measuring cardiac markers at the time of emergency room presentation provides an objective assessment of the amount of irreversible myocyte injury that has occurred prior to the initiation of therapy. In addition, the rate of rise of cardiac biomarkers can be used to help determine which patients have had successful or unsuccessful reperfusion and may help to select appropriate patients for coronary angiography after fibrinolysis. Myoglobin appears to be the most useful for this purpose, due to its smaller size, cytosolic location, and rapid renal clearance. B-type natriuretic peptide (BNP) is a cardiac hormone that is released in response to increases in wall stress. Levels of circulating

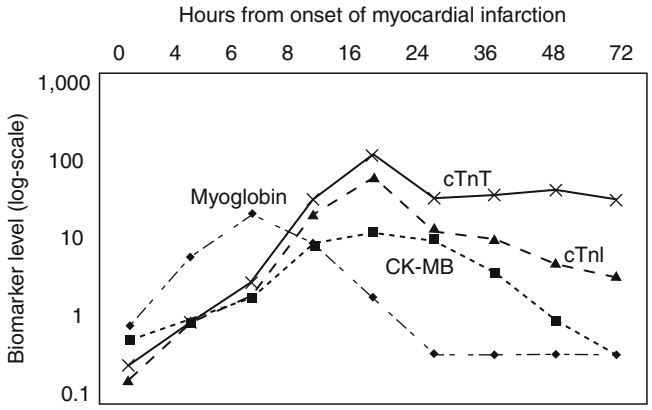

Fig. 26.2 Time course of biomarker release after acute myocardial infarction (Adapted from Christenson and Azzazy [6]. With permission from Springer Science+Business Media)

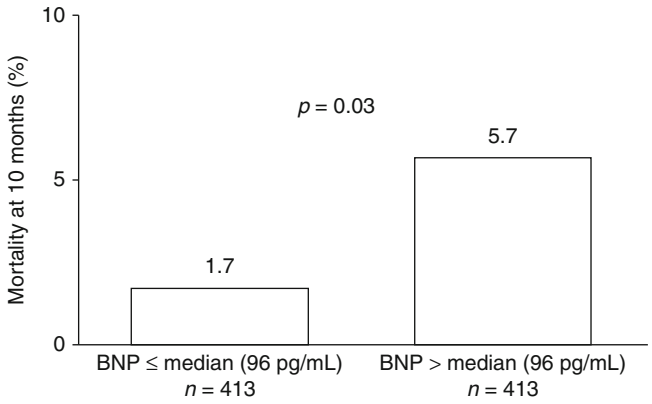

Fig. 26.3 BNP levels greater than the median were associated with a higher 10-month mortality among patients with STEMI (Based on data from de Lemos et al. [7])

BNP and the N-terminal fragment of its prohormone (NT-proBNP) are in wide clinical use for diagnosis and prognostic assessment in patients with suspected heart failure. BNP and NT-proBNP levels are also useful in STEMI. Following STEMI, BNP levels rise and peak at approximately day 2. A second peak may occur several days later as the ventricular remodeling process begins. Higher levels of BNP or NT-proBNP, measured several days after MI, have been associated with a greater likelihood of death, CHF, and ventricular remodeling after STEMI [7] and have a role for assessing prognosis (Fig. 26.3).

Echocardiography

The routine use of echocardiography in cases of strong suspicion of STEMI is likely to be of detriment rather than benefit as this will significantly delay timely reperfusion; however, in some situations such as left bundle branch of undetermined duration, paced rhythms, suspected pericarditis, or early repolarization, portable transthoracic echocardiography may be very useful. Transmural ischemia is almost always associated with hypokinesis or akinesis of the ischemic myocardial segments. Therefore, absence of regional or wall motion abnormalities argues strongly against transmural MI. Transesophageal echo (TEE) should be considered when suspicion arises for aortic dissection and CT angiography is unable to be performed.

Therapy for Acute MI

Systems of Care

While many incremental improvements have been made in recent years with medications and technologies in STEMI care, some of the most significant recent innovations have been the development of systems of care to integrate the different elements of STEMI care into a streamlined and goal-directed systematic process. The traditional approach to achieving quality of care has often relied on the individual provider at the point of care to make a correct and timely diagnosis, then to implement numerous evidence-based therapies, and to do so efficiently and accurately with every patient and at every encounter; however, this traditional "individual-based" approach has proved to be exceedingly challenging and inherently imperfect. Since timely reperfusion directly improves outcomes, better strategies were needed to provide optimal care to patients; hence, systems-level interventions were developed rather than relying on individual practice variation. In a seminal study of STEMI processes of care, several key systems-level elements were described to improve timely percutaneous revascularization [8] (Table 26.1). Hospitals utilizing such strategies have been shown to have significantly shorter door-to-balloon times, although these strategies have been largely underutilized, with only 2 % of participating hospitals integrating at least four of the five elements.

The implementation of such systems-level interventions is key to successful quality improvement (QI); however, these types of interventions represent only one piece of the puzzle of achieving optimal quality of care. The concept of continual quality improvement has been described for decades outside of the health-care industry, but is only recently emerging in the medical field as an integral piece of any institutional or public health QI initiative (Fig. 26.4). QI initiatives should start with the selection of a committed champion/team and adequate planning prior to implementation of a plan, then studying data and results, and enacting additional efforts to achieve one's goals. These features are essential components of national reporting/quality improvement programs for acute MI care, such as the ACTION Registry®-GWTG™, a component of National Cardiovascular Data Registry. We recommend participation in such initiatives to develop

Table 26.1 Reduction in door-to-balloon time with implementation of key strategies

Description of strategies to reduce door-to-balloon time	Mean reduction in DTBT Minutes	Number of strategies used	Hospitals with the no. of strategies (N = 362) No. (%)	Average of median DTBT Minutes
1. ER physicians activate the catheterization laboratory	8.2	0	137 (37.8)	110
2. Single call to a central page operator activate the cath lab	13.8	1	130 (35.9)	100
3. ER activation while the patient is en route to the hospital	15.4	2	56 (15.5)	88
4. Expecting staff to arrive in the cath lab within 20 min (vs. >30 min)	19.3	3	31 (8.6)	88
5. Having an attending cardiologist always on site	14.6	4	8 (2.2)	79
6. Providing real-time data feedback for ED and cath lab staff	8.6			

Based on data from Bradley et al. [8]

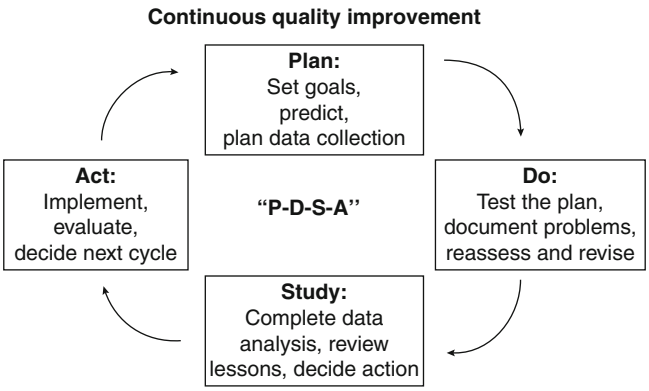

Fig. 26.4 The quality improvement cycle (Adapted from Langley et al. [9])

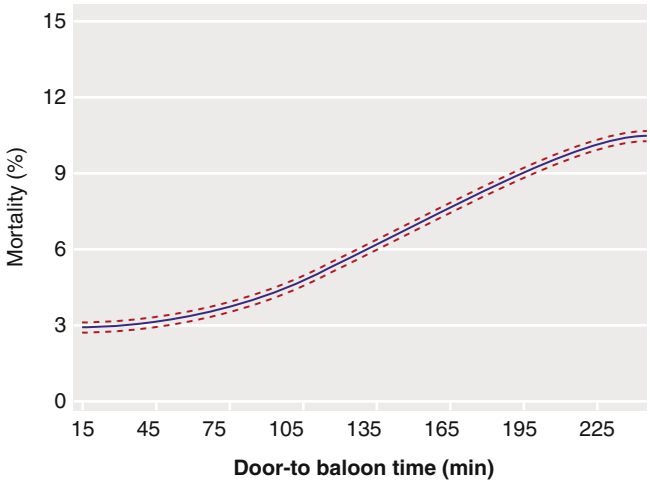

Fig. 26.5 Adjusted in-hospital mortality as function of door-to-balloon time with 95 % confidence intervals (Adapted from Rathore et al. [10]. With permission from BMJ Publishing Group Ltd.)

institutional systems of care and continual quality improvement processes to optimize treatments and outcomes of patients with STEMI.

Reperfusion Therapy

What Defines "Optimal" Reperfusion?

Early, successful coronary reperfusion limits infarct size and improves left ventricular dysfunction and survival. These benefits are due at least in part to the early restoration of antegrade flow in the infarct-related artery (IRA). In multiple analyses of the relationship between ischemic time and mortality in STEMI patients, incremental delay has been consistently associated with increased risk for mortality; subsequently, current guidelines recommend goal door-to-balloon time within 90 min and door-to-needle time within 30 min [10, 11] (Fig. 26.5).

Even among patients who achieve normal (TIMI grade 3) epicardial blood flow in the IRA after reperfusion therapy, however, tissue-level perfusion may be inadequate. Using a number of different diagnostic tools (Table 26.2), investigators have demonstrated that measures of tissue and microvascular perfusion provide prognostic information that is independent of TIMI flow grade [12]. For example, Ito and colleagues, using myocardial contrast echocardiography, found impaired tissue and microvascular perfusion in approximately 1/3 of patients with TIMI grade 3 flow after primary PCI [13]. These patients were at increased risk for the development of CHF and death. Microvascular dysfunction is thought to occur in the setting of myocardial infarction as a result of distal embolization of microthrombi, tissue inflammation from myocyte necrosis, and arteriolar spasm caused by tissue injury.

The most clinically relevant measure of tissue perfusion is a simple bedside assessment of the degree of resolution of

Table 26.2 Diagnostic tools used to evaluate tissue and microvascular perfusion in patients with ST-elevation MI[a]

Technique	Finding suggestive of microvascular injury
Myocardial contrast echocardiography	Absence of microbubble contrast uptake in the infarct zone
Doppler flow wire	Abnormal coronary flow reserve; systolic reversal of coronary flow
Nuclear SPECT imaging	Absence of tracer uptake into infarct zone
Contrast angiography	Abnormal myocardial "blush," with failure to opacify myocardium or prolonged dye washout from myocardium
MRI	Hypoenhancement of infarct zone following gadolinium contrast injection
ECG	Failure to resolve ST elevation

[a]Assumes that the epicardial infarct artery is patent. These techniques can only be presumed to reflect microvascular and tissue perfusion when the infarct artery has been successfully recanalized

Table 26.3 Summary of the 23 randomized trials of primary angioplasty vs. thrombolytic therapy

Study group	PTCA (%)	Thrombolytic therapy (%)	*p* value
Mortality			
Short term	7	9	0.0002
Long term	9.6	12.8	0.0019
Nonfatal MI			
Short term	3	7	<0.0001
Long term	4.8	10	<0.0001
Total stroke			
Short term	1	2	0.0004
Long term	[a]	[a]	
Death, nonfatal MI, or stroke			
Short term	8	14	<0.0001
Long term	12	19	<0.0001

Adapted from Keeley et al. [14]. With permission from Elsevier
[a]Data not available

ST-segment elevation on the 12-lead electrocardiogram. Greater degrees of ST resolution are associated with a higher probability of achieving a patent infarct artery and normal (TIMI grade 3) epicardial blood flow [12]. Furthermore, patients who have normal epicardial blood flow, but persistence of ST elevation on the 12-lead ECG, have been shown to have abnormal tissue and microvascular perfusion using a variety of techniques. In addition, persistent ST elevation has been shown to predict poor recovery of infarct zone wall motion and the clinical endpoints of death and heart failure [12]. In summary, ST resolution appears to integrate epicardial and myocardial (microvascular) reperfusion and thus may actually provide a more clinically useful assessment of reperfusion than coronary angiography.

Selection of Reperfusion Strategy

Primary PCI has been compared to fibrinolytic therapy in more than 20 randomized controlled trials in STEMI, which together have demonstrated clear superiority of primary PCI regarding rates of death (7 % vs. 9 %, $p<0.001$), reinfarction (3 % vs. 7 %, $p<0.001$), and stroke (1 % vs. 2 %, $p<0.001$) (Table 26.3). Data from the National Cardiovascular Data Registry report that 83 % of patients in the USA presenting with STEMI in 2009 were treated with primary PCI, compared to approximately 13 % being treated with fibrinolytic therapy [15]. For centers with primary PCI capability, current ACC/AHA guidelines [16–18] recommend that patients should proceed without delay to cardiac catheterization and revascularization if suitable anatomy is seen. However, selection of a reperfusion strategy remains challenging in many institutions since primary PCI is not readily available across all centers in the United States on a 24-h basis, 7 days a week. In many other countries, the availability of primary PCI is even more limited. Among centers without the ability to perform primary PCI, a decision must be made whether to transfer for primary PCI or administer fibrinolytic therapy on site. Generally, immediate transfer to a primary PCI center is preferred if a door-to-balloon time <120 min can be achieved. These time windows are not static, however, as longer delays may be accepted if symptom onset is late (>3 h prior to presentation), presentation is high risk (e.g., heart failure, hemodynamic or electrical instability), or patients are at high risk for intracranial hemorrhage with fibrinolytic therapy [16–18]. Unfortunately, current data demonstrate that few patients transferred for primary PCI achieve an acceptable door-to-balloon time [19]. Indeed, in many transferred patients, delays are so extensive that on-site fibrinolytic therapy should have been administered. Increasing attention to improving systems of care *across institutions* is critical in order to streamline transfer protocols for STEMI and to achieve optimal reperfusion results. The American Heart Association's Mission Lifeline program is an example of a quality improvement initiative designed to improve systems of care between transferring and receiving hospitals (see Fig. 26.6).

Pharmacologic Reperfusion

Comparison of Fibrinolytic Agents

Time is a critical determinant in the success of any fibrinolytic regimen. Patients who are treated within 1 h from the onset of chest pain have a 50 % reduction in mortality, while those than 12 h after onset of symptoms derive little, if any, benefit from presenting more fibrinolysis (Fig. 26.7). For each hour earlier that a patient is treated, there is an approximately 1 % absolute reduction in mortality [20].

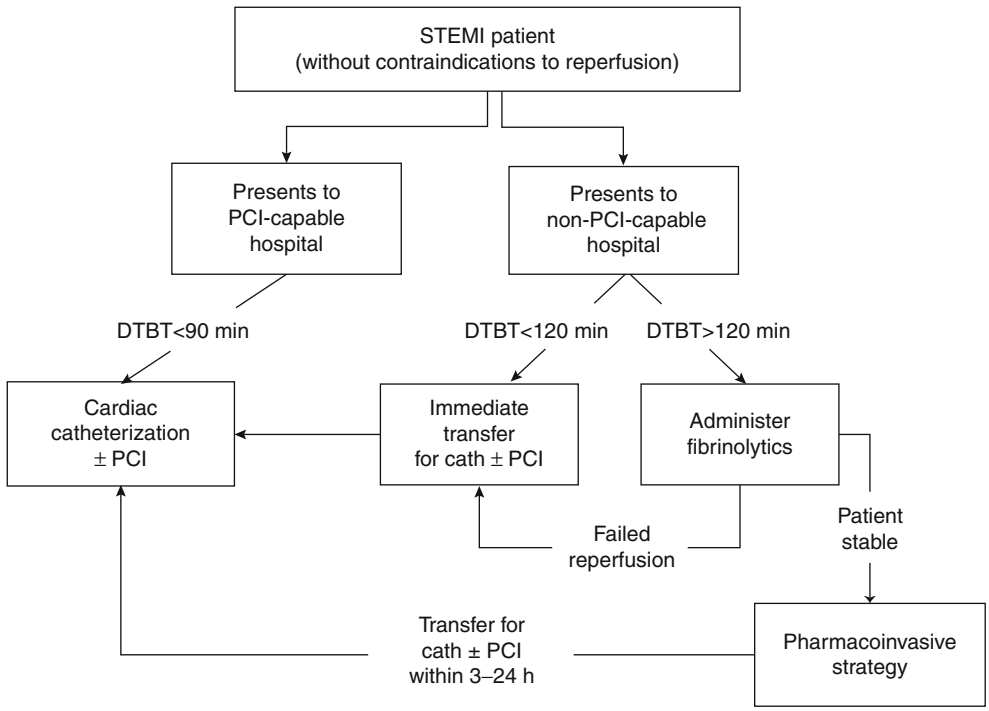

Fig. 26.6 Algorithm for management and triage of STEMI patients. *DTBT* door-to-balloon time, *PCI* percutaneous coronary intervention

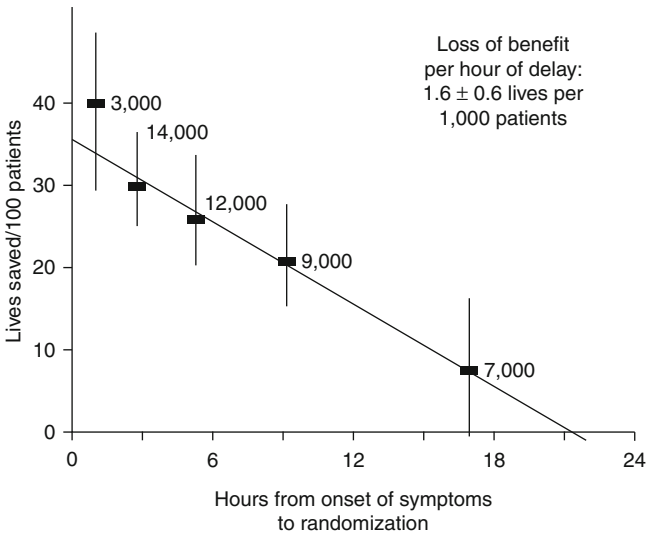

Fig. 26.7 Absolute reduction in 35-day mortality vs. delay from symptom onset to randomization and treatment among 45,000 patients with ST-segment elevation or LBBB (Reprinted from Fibrinolytic Therapy Trialists' (FTT) Collaborative Group [20]. With permission from Elsevier)

All of the fibrinolytic agents currently available are plasminogen activators, working enzymatically, directly or indirectly, to convert the single-chain plasminogen molecule to the double-chain plasmin, which has potent intrinsic fibrinolytic activity. Streptokinase (SK) was the first described fibrinolytic agent used for the treatment of STEMI, and worldwide it remains one of the most widely utilized fibrinolytics due to its relatively low cost; however, more specific fibrinolytic agents such as alteplase (t-PA) have demonstrated potential for improved survival compared to SK, as suggested by the first Thrombolysis in Myocardial Infarction (TIMI) trial, in which infarct-related artery patency with t-PA was nearly twice that achieved with SK [21]. Molecular modification of the t-PA structure has yielded agents such as reteplase and tenecteplase (TNK) with longer plasma half-lives that allow easier administration with a simplified single- or double-bolus administration regimen (Table 26.4), a factor that could prevent dosing errors and possibly decrease "door-to-needle" time. Despite these more favorable pharmacologic characteristics, however, improvements in 30-day mortality rates have not been observed with these newer agents. In the United States and many other countries, TNK is the fibrinolytic agent of choice due to comparable efficacy to t-PA, with a 20 % lower risk of non-intracranial bleeding compared to t-PA and greater ease of administration.

Reduced-Dose Fibrinolytic Therapy plus GP IIb/IIIa Inhibitors

The combination of a *reduced-dose* fibrinolytic agent and a glycoprotein (GP) IIb/IIIa inhibitor and its effect on mortality after STEMI was evaluated in the GUSTO-V and ASSENT-3 trials [22, 23], which showed no significant difference in mortality, although risk of bleeding complications were higher, when compared to fibrinolytic monotherapy. Of particular importance, both studies showed that risk of bleeding was substantially elevated in the elderly (>75 years old) with combination therapy. Therefore, the combination of

Table 26.4 Fibrinolytic agents in current clinical use

	Alteplase	Reteplase	Tenecteplase	Streptokinase
Fibrin selective	+++	++	++++	–
Half-life (min)	5	14	17	20
Dose	15 mg bolus; then 0.75 mg/kg over 30 min; then 0.5 mg/kg over 60 min (max 100 mg total dose)	Two 10 unit bolus doses given 30 min apart	0.53 mg/kg as a single bolus	1.5 million units over 30–60 min
Weight adjusted	Partial	No	Yes	No
Adjunctive heparin	Yes	Yes	Yes	+/–
Possible allergy	No	No	No	Yes
TIMI 2/3 flow (90 min) (%)	80	80	80	60
TIMI 3 flow (90 min) (%)	55–60	60	55–65	32
Efficacy vs. t-PA	NA	Similar	Equivalent	1 % ↑ mortality
Safety	NA	Similar	Similar ICH ↓ non-ICH bleeding	↓ ICH ↓ overall bleeding
Cost	+++	+++	+++	+

reduced-dose fibrinolytics and glycoprotein IIb/IIIa inhibitors is not recommended.

Adjunctive Therapy with Unfractionated Heparin and Low Molecular Weight Heparin

Unfractionated heparin is an important adjunctive agent to decrease reocclusion following administration of fibrinolytic therapy. Long-term coronary artery patency rates are highest in patients who are effectively anticoagulated at a target aPTT range of 50–70 s; however, high doses of intravenous heparin are a significant risk factor for the development of intracranial hemorrhage (ICH). Therefore, current ACC/AHA guidelines recommend a reduced dose of UFH to be given with t-PA, rPA, or TNK: a bolus of 60 U/kg (maximum 4,000 U) and an infusion of 12 U/kg/h (maximum 1,000 U/h) [16]. The usual duration of therapy for UFH is 48–72 h or until a PCI has been performed.

The use of low molecular weight heparins (LMWHs) vs. standard unfractionated heparin (UFH) has been compared in several randomized trials including ASSENT-3 [23], ASSENT-3 PLUS [24], ExTRACT TIMI-25 [25], and other smaller studies. In meta-analysis of these trials, enoxaparin was shown to significantly reduce the primary endpoint of death, recurrent MI, and major bleeding [11.1 vs. 12.9 %, $p = 0.018$; OR = 0.84 (0.73–0.97)], compared to UFH [26]. This composite outcome was largely driven by reductions in recurrent MI. Of note, an increased risk of bleeding was noted in the enoxaparin arm, compared to UFH. It should be noted that the optimal duration of LMWH in the largest of these trials, ExTRACT TIMI-25, was longer than previously recommended for UFH. Enoxaparin should be continued until PCI is performed, or up to 8 days or hospital discharge among patients not receiving PCI. Because it is renally cleared and not completely reversible, enoxaparin is not recommended for patients with severe renal insufficiency or those at high risk of bleeding.

Fibrinolytics and Clopidogrel

The addition of clopidogrel to pharmacologic reperfusion regimens reduces infarct-related artery reocclusion and improves outcomes, including reducing rates of mortality and recurrent MI [27, 28]. In the COMMIT/CCS-2 randomized trial of over 45,000 individuals with acute MI, treatment with clopidogrel reduced mortality by 0.7 % and MI by 0.2 %. Subsequently, current ACC/AHA guidelines recommend clopidogrel loading and maintenance doses for patients presenting with STEMI treated with fibrinolysis. Newer P_2Y12 receptor inhibitors, such as prasugrel and ticagrelor, have not been studied in combination with fibrinolytics and also are associated with higher bleeding rates and thus are not recommended for use in combination with fibrinolytics at this time.

Limitations of Fibrinolytic Therapy

Current fibrinolytic regimens achieve patency (TIMI grade 2 or 3 flow) in approximately 80 % of patients, but complete reperfusion (TIMI grade 3 flow) in only 50–60 % of cases (Fig. 26.8). As described above, incomplete reperfusion is associated with a poor prognosis. In addition, even after successful fibrinolysis, 10–30 % of patients suffer reocclusion of

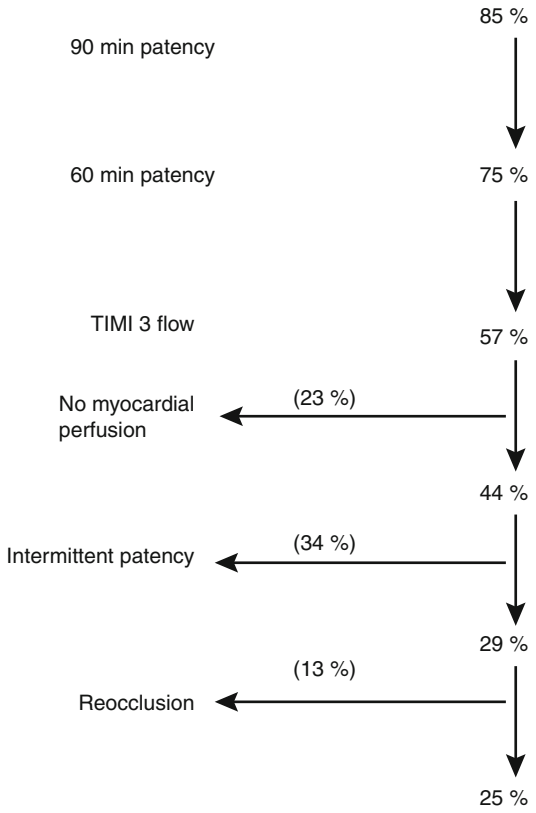

Fig. 26.8 Limitations of current fibrinolytic regimens (Reprinted from Lincoff and Topol [29]. With permission from Lippincott Williams & Wilkins)

the infarct-related artery and experience reinfarction in the following 3 months [30]. Reocclusion and reinfarction are associated with a two- to three-fold increase in mortality. Bleeding is the most common complication of fibrinolytic therapy; major hemorrhage, as defined by the TIMI criteria, occurs in 5–15 % of patients. Intracranial hemorrhage (ICH) is the most devastating of the bleeding complications, causing death in the majority of patients affected and severe disability in most survivors. In major clinical trials, ICH has occurred in 0.6–1.4 % of patients receiving fibrinolytic therapy. Risk factors for ICH include older age, female gender, low body weight, and hypertension. In particularly high-risk patients (i.e., elderly female with low body weight), the risk of ICH may be >2 %, a finding that should influence the decision as to whether to administer fibrinolytics or transfer for PCI. Contraindications to fibrinolytic therapy are shown in Table 26.5.

Table 26.5 Contraindications to fibrinolytic therapy

Absolute contraindications	Relative contraindications
Active internal bleeding	Blood pressure consistently > 180/110
History of CNS hemorrhage	History of stroke or AVM
Stoke of any kind within the last year	Known bleeding diathesis
Recent head trauma or CNS neoplasm	Active peptic ulcer
Suspected aortic dissection	Proliferative diabetic retinopathy
	Prolonged CPR
	Prior exposure to SK or APSAC (5 days to 2 years) or prior allergic reaction
	Pregnancy
	Major surgery or trauma within 2 weeks
	Anticoagulation use
	Puncture of a noncompressible vessel

Abbreviations: *CNS* central nervous system, *SK* streptokinase, *APSAC* anisoylated plasminogen streptokinase activator complex (anistreplase)

Rescue PCI

Because failure of fibrinolytic therapy is associated with increased rates of morbidity and mortality, "rescue" PCI is frequently performed in such patients. Rescue PCI is defined as coronary angiography with the intent to perform PCI due to clinical suspicion of failed fibrinolysis. A meta-analysis of eight randomized trials with 1,200 patients compared rescue PCI vs. conservative management and reported a significant reduction in recurrent MI (RR 0.58; 95 % CI 0.35–0.97) and heart failure (RR 0.73; 95 % CI 0.54–1.00), but a small absolute increase in risk of stroke and minor bleeding [31]. The ACC/AHA recommends urgent PCI after fibrinolysis in patients with hemodynamic or electrical instability, persistent ischemic symptoms, or less than 50 % resolution of ST-segment elevation (in the lead with the greatest ST elevation at presentation) 90 min following fibrinolytic therapy and a moderate or large area of myocardium at risk (anterior MI, inferior MI with RV involvement or precordial ST depression) [17]. With the emergence of data from the TRANSFER-AMI, CARESS in AMI, and other studies (discussed in greater detail below), more recent updates of ACC/AHA guidelines recommend that patients who receive fibrinolytic therapy should be transferred as soon as possible to a PCI-capable facility for consideration of PCI as needed or as part of a pharmacoinvasive strategy (discussed below). These updates also recommend considering administration of anticoagulation and antiplatelet therapy before and during patient transfer (see Fig. 26.6).

Routine Immediate PCI After Fibrinolytic Therapy: "Facilitated" PCI

The term "facilitated" PCI has been coined to signify the administration of a pharmacologic reperfusion regimen en route to the cardiac catheterization laboratory for "primary" PCI. The rationale for exploration of facilitated PCI was that

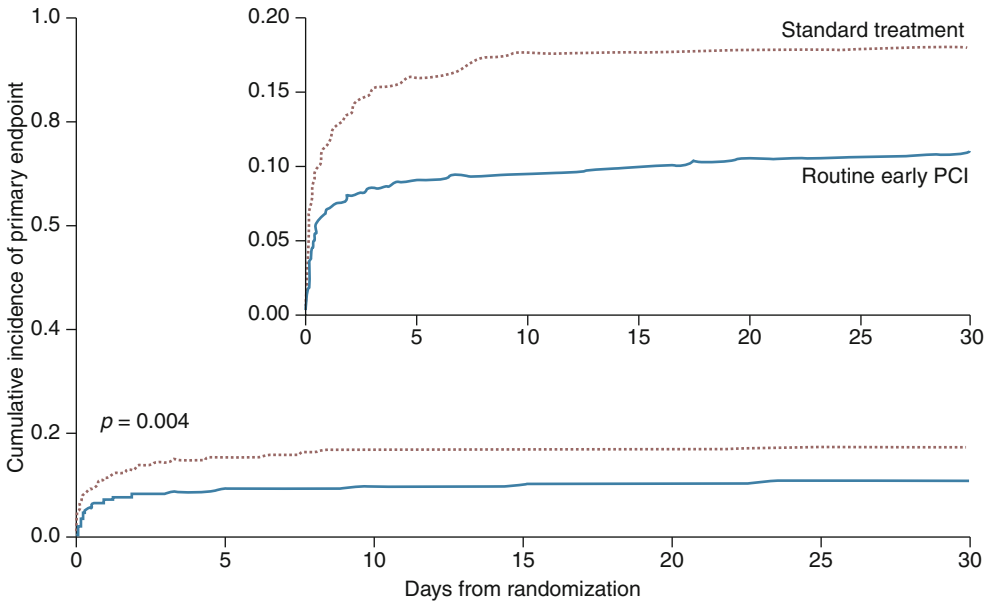

Fig. 26.9 Results of TRANSFER-AMI trial showing lower mortality, reinfarction, CHF, and shock with early routine PCI after fibrinolysis (Based on data from Cantor et al. [32])

after initial, successful fibrinolytic therapy, reocclusion and reinfarction are common, in contrast to primary PCI, which is associated with very low rates of reocclusion and reinfarction. Therefore, administration of a pharmacologic reperfusion regimen prior to primary PCI could potentially increase the probability of reperfusion prior to PCI, minimizing myocardial necrosis and "facilitating" an excellent long-term result of PCI. Facilitated PCI has been evaluated since the 1980s using various combinations and doses of fibrinolytics, GP IIb/IIIa inhibitors, anticoagulation, and clopidogrel.

Several studies have explored facilitated PCI using full-dose fibrinolytic therapy prior to PCI, the largest of which was the ASSENT-4 PCI (Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention) study, in which over 1,600 STEMI patients were randomized to receive TNK prior to PCI vs. primary PCI alone. Patients in the facilitated PCI arm suffered higher rates of the combined primary endpoint (death, shock, and heart failure) at 90 days (18.6 % vs. 13.4 %; $p=0.0045$), compared to primary PCI alone; thus, in conjunction with other data, facilitated PCI with full-dose fibrinolytic prior to PCI is not recommended. Further randomized trials have explored facilitated PCI using reduced doses of fibrinolytics with GP IIb/IIIa inhibitors prior to PCI; however, these studies also failed to show an advantage of the facilitated PCI strategy, which was confirmed in a meta-analysis of 17 randomized trials of facilitated PCI [14].

Pharmacoinvasive Strategy

In contrast to facilitated PCI, in which a fibrinolytic, GP IIb/IIIa inhibitor, anticoagulant, or a combination of these therapies is administered within 2 h prior to PCI, the concept of the pharmacoinvasive strategy refers to the administration of a fibrinolytic regimen at a facility without PCI capability, followed by transfer to a PCI-capable center for diagnostic angiography and PCI, if the coronary anatomy is suitable. In contrast to immediate PCI after administration of fibrinolytics, which has been associated with increased risk for adverse events (as described above), the pharmacoinvasive strategy anticipates transfer to a PCI-capable hospital with an associated delay to angiography (± PCI) ranging from 3 to 24 h [18]. The theoretical advantages of this strategy include: (1) rapid initial reperfusion in many patients, (2) permitting rapid "rescue" PCI if fibrinolysis fails, (3) addressing the high risk of reocclusion after fibrinolytic therapy by treating the infarct artery with PCI, and (4) by delaying the PCI procedure, the bleeding risks would be expected to be lower.

This strategy has been evaluated in six recent randomized trials, the largest of which, TRANSFER-AMI, randomized over 1,000 high-risk STEMI patients who received fibrinolytic therapy at non-PCI centers to immediate transfer and PCI vs. standard treatment. In the early PCI arm, 98.5 % patients underwent catheterization (median 2.8 h after randomization), and in the standard care arm, catheterization was performed in 88.7 % of patients (median 32.5 h). At 30-day follow-up, patients in the early PCI arm had significantly lower rates of the composite primary endpoint of death, reinfarction, recurrent ischemia, congestive heart failure, or cardiogenic shock (11.0 % vs.17.2 %; RR = 0.64; 95 % CI: 0.47–0.87), compared to standard therapy (Fig. 26.9). Additionally, no significant differences were seen between groups in rates of major bleeding. Given these data and the findings from other studies showing benefits from the pharmacoinvasive strategy, the ACC and AHA recommend this strategy (Fig. 26.6) among patients presenting to non-PCI-capable facilities who are not candidates for primary PCI [18].

Mechanical Reperfusion

Primary PCI

The preferred method of achieving coronary reperfusion in STEMI is the use of immediate or "primary" PCI for patients presenting to PCI-capable centers and for those who can be rapidly transferred. The relative benefits of primary PCI are greatest in patients at highest risk, including those with cardiogenic shock, right ventricular infarction, large anterior MI, and increased age (due partly to increased ICH rate with thrombolytic therapy). Primary PCI was initially only performed only at hospitals with surgical backup because of the potential for complications that might require immediate bypass surgery. The incidence of emergency bypass surgery with primary PCI, however, has been reported to be less than 0.5 %. Moreover, several randomized trials have demonstrated that the benefits of primary PCI can be extended to community hospitals without cardiac surgery backup, provided strict quality control procedures are in place, and STEMI volume is adequate to maintain skills [33, 34].

Intracoronary Stenting

Compared to balloon angioplasty alone, intracoronary stenting reduces the risk of early reocclusion and target-vessel revascularization (TVR) and has become the standard of care, although significant reductions in mortality have not consistently been seen [35]. Drug-eluting stents (DES), which are coated with polymers that elute antiproliferative compounds, reduce intimal smooth muscle proliferation and decrease rates of in-stent restenosis. Multiple randomized trials comparing DES to bare-metal stents (BMS) have been performed in the setting of STEMI, with the HORIZONS-AMI trial [36] providing the most definitive evidence to support the use of DES in STEMI. In this study, over 3,000 patients presenting with STEMI were randomized in a 3:1 fashion to paclitaxel-eluting stents vs. bare-metal stents. At 1-year, patients in the DES arm had significantly lower rates of target-vessel revascularization (TVR) (5.8 % vs. 8.7 %; HR = 0.65, 95 % CI: 0.48–0.89, $p = 0.006$) and restenosis (10.0 % vs. 22.9 %; HR = 0.44, 95 % CI: 0.33–0.57, $p < 0.001$) while demonstrating non-inferior rates of the composite safety endpoint of death, reinfarction, stroke, or stent thrombosis (8.1 % vs. 8.0 %; HR = 1.02; 95 % CI: 0.76–1.36). In a meta-analysis of over 30,000 patients with STEMI from both clinical trials and observational registries, DES decreased rates of TVR and resulted in similar rates of death and MI, when compared to BMS [37].

An important issue with DES is that the regrowth of the protective vascular endothelium to cover the stent struts is delayed compared with BMS, resulting in an extended window where the patient may be at increased risk for stent thrombosis. Although initial concerns about late and very late stent thrombosis with DES appear to have been exaggerated, particularly with newer, third-generation everolimus-eluting stents, patients receiving DES require longer durations of dual-antiplatelet therapy to prevent stent thrombosis compared with those receiving BMS. In the selection of DES vs. BMS, patient-related factors such as anticipated compliance with long-term dual-antiplatelet therapy, funding status, bleeding risk, and anticipated surgical procedures must also be taken into consideration, since DES adherence with dual-antiplatelet therapy is recommended for at least 1 year post-PCI to minimize risk of drug-eluting stent thrombosis. Rapid and accurate assessment of these factors can often prove challenging given the short time to assess patients in the setting of STEMI.

Of note, current guidelines recommend avoiding the temptation to routinely perform complete percutaneous revascularization patients during STEMI. Specifically, PCI to a non-infarct-related artery during PCI should be avoided in hemodynamically stable patients. These guidelines are supported by a recent analysis from the NCDR, in which patients undergoing multivessel PCI at presentation for STEMI had increased risk of in-hospital mortality (7.9 % vs. 5.1 %, $p < 0.01$) compared to patients undergoing PCI to the infarct artery alone; additionally, among patients with cardiogenic shock, those undergoing multivessel PCI also had increased risk for in-hospital mortality (36.5 % vs. 27.8 %; adjusted OR = 1.54, 95 % CI: 1.22–1.95) compared to PCI to the infarct artery alone [38].

Thrombus Aspiration

Coronary lesions in STEMI often have a large thrombus burden, which may embolize causing microvascular obstruction and diminished coronary blood flow. A strategy of thrombus aspiration prior to balloon angioplasty/stenting has been evaluated as a means of reducing complications from the large thrombus. The most straightforward technique is manual suction thrombectomy, using simple handheld syringe devices attached to a catheter (i.e., Export or Pronto devices). The first and largest study of manual thrombectomy was the TAPAS trial [39], in which over 1,000 STEMI patients were randomized to thrombus aspiration prior to conventional PCI or conventional PCI alone. Patients in the thrombus-aspiration arm had significantly lower rates of inadequate microvascular reperfusion compared to conventional PCI alone (17.1 % vs. 26.3 %, $p < 0.001$). In meta-analysis of this and other studies, manual thrombectomy has been shown to also be associated with significant reductions in death and MI during a median follow-up period of 1 year [40].

The Angiojet is an alternative device that delivers saline under high pressure, creating a vacuum that disrupts the clot and delivers it proximally into the pump component of the device. In contrast to manual aspiration, the use of mechanical thrombectomy devices has not shown consistent benefit. The most recent STEMI guidelines provide a class IIA

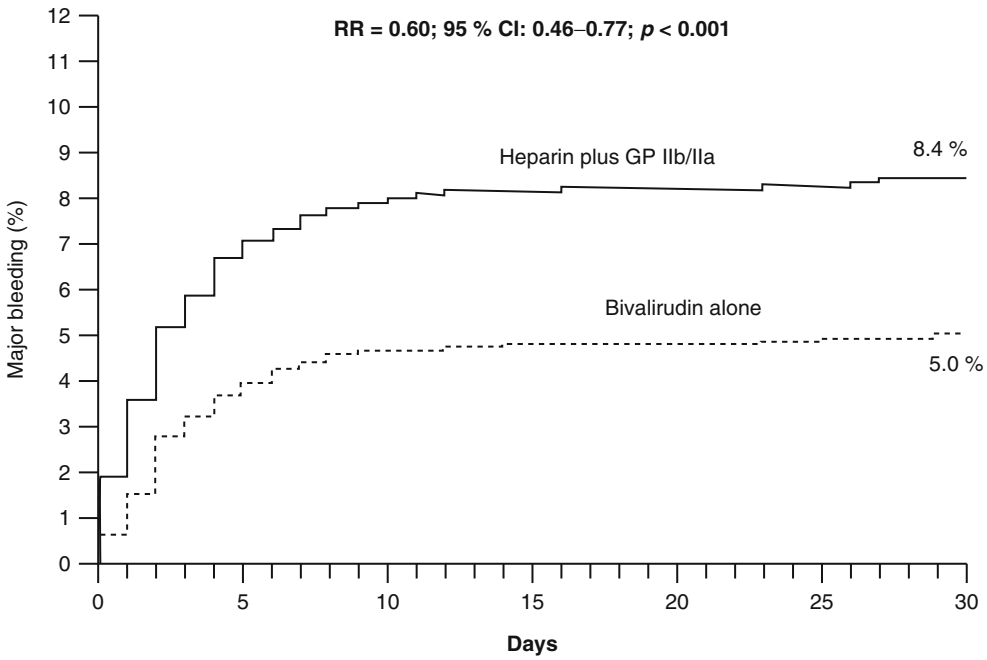

Fig. 26.10 Results from HORIZONS-AMI trial showing lower rates of major bleeding with the use of bivalirudin compared to UFH plus GP IIb/IIIa

recommendation for the use of aspiration thrombectomy in STEMI patients, but recognize that it is not yet known whether this should be performed routinely or only in patients with large clot burdens.

Adjunctive Pharmacologic Therapies During Primary PCI

Boluses of unfractionated heparin are used during primary PCI, targeting an activated clotting time (ACT) of 250–350 s, with a lower ACT of 200–250 s recommended when a GP IIb/IIIa inhibitor is also used [41]. UFH is not recommended to be continued after catheterization/PCI due to a lack of additional benefit and increased risk of bleeding complications. We do not recommend LMWH agents for use in primary PCI, due to the long half-life of these agents and the limited data in primary PCI.

Multiple studies have evaluated GP IIb/IIIa inhibitors in patients with STEMI. The CADILLAC study enrolled 2,082 patients with STEMI. These patients were randomly assigned to primary PTCA alone, primary PTCA + abciximab, stenting alone, or stenting + abciximab. Major adverse events occurred in 20 % of patients in the primary PTCA-only group, 16.5 % with primary PTCA + abciximab, 11.5 % with stenting alone, and 10.2 % with stenting plus abciximab ($p < 0.001$) [42]. In a meta-analysis of eight studies, the use abciximab during primary PCI was shown to reduce the risk of 30-day mortality, compared to placebo (2.4 % vs. 3.4 %; OR = 0.68; 95 % CI: 0.47–0.99; $p = 0.047$) [43]. Although abciximab remains the best studied agent for use in primary PCI, a meta-analysis of randomized trials comparing abciximab to eptifibatide and tirofiban found no significant differences in angiographic or clinical outcomes [44], suggesting similarity between the different members of this drug class. More recent trials (largely in non-ST-elevation ACS) have shown less benefit of GP IIb/IIIa inhibitors, particularly when patients are routinely treated with clopidogrel or other P_2Y12 inhibitors. Thus, more recently, guidelines have scaled back the recommendations for use of GP IIb/IIIa inhibitors in primary PCI. These agents now have class IIA recommendation for use in *selected cases*, such as large thrombus burden or inadequate thienopyridine loading, but are no longer recommended for routine use.

Bivalirudin is a direct thrombin inhibitor which has been evaluated as adjunctive therapy to primary PCI in the HORIZONS-AMI trial [45], in which 3,600 STEMI patients were randomized to treatment with bivalirudin alone (plus provisional GP IIb/IIIa) vs. UFH plus planned GP IIb/IIIa inhibitor use. Rates of the composite primary endpoint (death, reinfarction, target-vessel revascularization for ischemia, and stroke) were similar between groups (5.4 % vs. 5.4 %, $p = 0.94$), but rates of major bleeding were significantly lower with bivalirudin (4.9 % vs. 8.3 %; RR = 0.60; 95 % CI: 0.46–0.77; $p < 0.001$) (Fig. 26.10). Rates of stent thrombosis within 24 h were higher in the bivalirudin arm (1.3 % vs. 0.3 %, $p < 0.001$), although differences were not statistically significant when combined with overall rates of stent thrombosis within 30 days (1.9 % vs. 3.5 %, $p = 0.30$). At 1-year follow-up, rates of major adverse cardiovascular events were similar, but all-cause mortality was significantly lower among those treated with bivalirudin (3.4 % vs. 4.8 %, $p = 0.03$). The most recent ACC/AHA STEMI guidelines give a class I recommendation for the use of bivalirudin during primary PCI,

whether or not patients have already received pretreatment with UFH. Routine GP IIb/IIIa inhibitor use is not recommended in patients receiving bivalirudin. However, to prevent early stent thrombosis, consideration should be given for preferential use of ticagrelor or prasugrel over clopidogrel when bivalirudin is the anticoagulant of choice in STEMI (see below).

Late Elective PCI of an Occluded Infarct-Related Artery

For patients presenting late after the onset of STEMI (>24 h) without hemodynamic compromise or ongoing angina symptoms, it had previously not been known whether revascularization of occluded infarct-related arteries might improve clinical outcomes. The Occluded Artery Trial (OAT) randomized 2,200 patients, with an occluded infarct artery between 3 and 28 days after STEMI, to PCI of the occluded artery vs. optimal medical therapy alone. After 4 years, there was no significant difference between groups in the primary endpoint of death, MI, or severe heart failure (17.2 % vs. 15.6 %; HR = 1.16, 95 % CI: 0.92–2.00; $p = 0.20$). Current ACC/AHA guidelines recommend against PCI of an occluded infarct-related artery >24 h after STEMI patients who are asymptomatic, stable, and without evidence of severe ischemia. The optimal management of stable patients presenting >12 h but <24 h after onset of symptoms is not well defined due to the lack of sufficient data to guide therapy.

Surgical Revascularization

With the ubiquity of primary PCI and fibrinolysis for reperfusion therapy in patients presenting with STEMI, the use of emergent coronary artery bypass grafting (CABG) is relatively infrequent (3.2–10.9 %) [46]; however, emergent CABG remains an important therapy for patients with (1) left main or 3-vessel CAD, (2) ongoing ischemia after PCI, (3) lesions not amenable to PCI, (4) mechanical complications of STEMI, and (5) cardiogenic shock or malignant ventricular arrhythmias, which are listed as class I recommendations per the 2011 ACCF/AHA Guidelines for Coronary Artery Bypass Graft Surgery [46]. In general, PCI should be performed on the culprit lesion in STEMI, even if this is in a patient with left main or 3-vessel CAD, to achieve reperfusion and minimize the size of infarction. This can be performed with balloon angioplasty or bare-metal stenting, with CABG followed within days (balloon angioplasty) or after 1 month (bare-metal stent).

Optimal timing of CABG after STEMI in stable patients remains controversial. While some studies show a greater benefit of surgery within 6 h of presentation, others have reported that after adjustment for potential confounders, no significant difference is found between early vs. late surgical intervention; in accordance, the most recent guidelines advocate a broad window of acceptable delay for the performance of CABG [46]. Clinically, this can likely be translated into the use of the patient's clinical condition in determining optimal CABG timing, rather than a prespecified time interval.

Long-Term Antithrombotic Therapy

Aspirin

In the setting of acute ST-segment elevation MI, aspirin has been shown to decrease risk of reocclusion after initially successful fibrinolysis by over 50 %, reinfarction by nearly 50 %, and mortality by 25 % [47]. Aspirin should be given immediately on presentation (or preferably in the ambulance) in a dose of 160–325 mg. This first dose should be chewed to accelerate absorption. Following MI, aspirin should be continued indefinitely. Low-dose aspirin, 75–81 mg daily, is now preferred as the maintenance dose, as it is associated with similar efficacy but lower rates of bleeding and gastrointestinal effects [48].

Clopidogrel

Clopidogrel is a thienopyridine derivative which inhibits the binding of adenosine diphosphate (ADP) to the P_2Y12 platelet receptor, blocking ADP-mediated platelet activation and aggregation. As described above, clopidogrel is the only P_2Y12 inhibitor indicated in combination with fibrinolytic therapy. In contrast, for patients undergoing primary PCI, ticagrelor or prasugrel may also be used. Clopidogrel should be given as a loading dose of 600 mg to facilitate a more rapid and predictable activity profile. All subsequent doses should be 75 mg/day.

Clopidogrel is a prodrug that must be converted to its active metabolite in the liver in order to be active. This contributes to delayed onset of action and considerable interindividual heterogeneity in the response to this agent. Conversion to the active metabolite is a complex, multistep process mediated in part via cytochrome p450 2C19 enzymes in the liver. Common genetic variants at the 2C19 locus appear to influence conversion, as do routinely used drugs that block this enzyme, including several proton pump inhibitors (most notably omeprezole). We do not currently recommend that clinicians assess genetic polymorphisms in the CYP 2C19 enzyme pathway, because the genetic variants explain only a small proportion of the variance between individuals, and it has not been determined how this should influence therapy. Similarly, while bedside platelet aggregometry tests are available to measure responsiveness to clopidogrel, trials evaluating adjusted clopidogrel dosing based on results of these tests have not demonstrated substantial clinical utility [49]. Finally, although concomitant use of omeprezole appears to slightly reduce platelet inhibition to clopidogrel, and observational studies raised some initial concerns about a clinically relevant interaction, more recent studies, including a randomized

controlled trial, do not suggest that a significant risk exists. Moreover, GI bleeding risks are reduced in patients receiving PPIs with clopidogrel and aspirin [50].

Prasugrel

Prasugrel is a thienopyridine P_2Y12 inhibitor that is more rapidly acting and potent than clopidogrel and has a more predictable pharmacokinetic and pharmacodynamic profile. The TRITON-TIMI 38 study randomized over 13,000 patients with ACS (over 3,500 had STEMI) to receive prasugrel (60 mg loading dose and 10 mg daily) vs. clopidogrel (300 mg loading dose and 75 mg daily). Both study arms received concomitant aspirin. STEMI patients receiving prasugrel had a lower rate of cardiovascular death, nonfatal MI, or nonfatal stroke at 30 days (6.5 % vs. 9.5 %; HR: 0.68; 95 % CI: 0.54–0.87; $p=0.0017$) and 15 months (HR: 0.79; 95 % 13 CI: 14 0.65–0.97; $p=0.02$) [51]. Of note, clopidogrel loading dose of 600 mg was not compared in this analysis, which limits the generalizability of this study. Prasugrel did increase risk of major bleeding (2.4 % vs. 1.8 %; HR = 1.32; 95 % CI: 1.03–1.68, $p=0.03$), including an excess in life-threatening and fatal bleeds. Prasugrel is absolutely contraindicated in patients with prior stroke or TIA and relatively contraindicated in patients ≥75 years of age and those with low body weight (<60 kg), due to excess bleeding. While the role for prasugrel in non-ST-elevation ACS is somewhat controversial, STEMI is a more attractive indication for this agent, as the benefits in the STEMI subgroup were greater in magnitude than those in the overall trial.

Ticagrelor

Unlike clopidogrel and prasugrel, ticagrelor is a non-thienopyridine agent that reversibly binds to the P_2Y12 receptor. Ticagrelor has been shown to produce more intensive platelet inhibition than clopidogrel, similar to that of prasugrel, and is even more rapidly acting than prasugrel, with significant platelet inhibition seen within the first 30 min after oral dosing. In the PLATO trial, over 18,000 ACS patients (38 % with STEMI) were randomized to ticagrelor (180 mg loading dose and 90 mg twice daily) vs. clopidogrel (300 mg loading dose vs. 75 mg daily) [52]. Among STEMI patients, ticagrelor was demonstrated to be superior to clopidogrel for the primary endpoint of myocardial infarction, stroke, or cardiovascular death (10.8 % vs. 9.4 %; HR = 0.87, 95 % CI: 0.75–1.01; $p=0.07$), consistent with the overall PLATO trial findings [53]. Patients on ticagrelor had higher rates of overall non-CABG-related major bleeding (4.5 % vs. 3.8 %, $p=0.03$), although rates of fatal or life-threatening bleeding were not significantly different (5.8 % vs. 5.8 %, $p=0.70$), compared to clopidogrel. Of note, ticagrelor was noted to significantly reduce all-cause mortality after MI (4.5 % vs. 5.9 % with clopidogrel; $p<0.001$), although prasugrel did not demonstrate a similar benefit in the TRITON-TIMI 38 trial. The reasons for this mortality reduction are unclear, but it could be related to a preconditioning effect of ticagrelor due to prevention of adenosine reuptake [54]. Increasing adenosine levels contribute to several notable side effects of ticagrelor, including dyspnea and occasional heart block. This agent should be used in caution in patients with asthma and conduction abnormalities.

In the most recent STEMI guidelines, all three agents, clopidogrel, prasugrel, and ticagrelor, have class I indications for patients undergoing primary PCI. Clinicians should be aware of the higher bleeding risks with prasugrel and ticagrelor and should expect higher procedural bleeding complications than are seen with clopidogrel.

Warfarin/Oral Anticoagulation

Although warfarin monotherapy appears to be at least as effective as aspirin for secondary prevention post-MI, warfarin is not used for this purpose due to the inconvenience and adverse bleeding profile. In contemporary practice, warfarin should only be added to low-dose aspirin when an independent indication for anticoagulation exists, such as atrial fibrillation, a mechanical heart valve, deep venous thrombosis or pulmonary embolism, or *documented* left ventricular mural thrombus. Given the high risks of "triple therapy" (see below), prophylactic warfarin is no longer indicated for patients with large anterior MI if thrombus is not seen by echocardiography. Direct factor Xa inhibitors have been evaluated for the reduction of adverse events after MI in recent studies with conflicting results. In the APRAISE-2 trial, apixaban was compared to placebo in 7,000 patients, although the trial was stopped early due to increased risk of major bleeding (1.3 % vs. 0.5 %, HR = 2.59, 95 % CI: 1.50–4.46, $p=0.001$), without significant reductions in the primary efficacy endpoint [55]. The ATLAS-2 study randomized over 15,000 ACS patients to rivaroxaban (2.5 and 5 mg) vs. placebo. The authors reported a significant reduction in the primary efficacy endpoint (death from cardiovascular causes, myocardial infarction, or stroke) after combining rivaroxaban dose arms (8.9 % vs. 10.7 %; HR = 0.84, 95 % CI: 0.74–0.96; $p=0.008$), although risk of major bleeding was higher (2.1 % vs. 0.6 %; HR = 3.96, 95 % CI: 2.46–6.38; $p<0.001$) compared to placebo [56]. Of note, there was a lack of consistent and dose-dependent reduction in MI, stroke, and cardiovascular death between doses of rivaroxaban, calling into question the validity of reported benefit seen in this study. Considering in totality the results of prior studies which have evaluated long-term anticoagulation post-MI for the reduction of CV events, greater harm than benefit has been consistently observed; therefore, we feel that great caution must be employed when considering the use of novel anticoagulant therapies in such settings.

An increasingly challenging scenario is the combination of aspirin, clopidogrel, and oral anticoagulation. Evidence

Table 26.6 Randomized trial of beta-adrenergic antagonists in AMI

Study	Agent	*N*	Duration	RR death (95 % CI)	*p* value
During AMI					
ISIS-1	Atenolol	16,027	7 days	0.85 (0.73–0.99)	0.04
MIAMI	Metoprolol	5,778	15 days	0.87 (0.67–1.08)	0.29
TIMI IIb	Metoprolol	1,434	6 days	1.00	0.98
Therapy started post-AMI, LV dysfunction					
Norwegian	Timolol	1,884	33 months	0.61 (0.46–0.80)	<0.001
BHAT	Propranolol	3,837	25 months	0.72 (0.64–0.80)	<0.005
CAPRICORN	Carvedilol	1,959	1.3 years	0.77 (0.60–0.98)	0.03

suggests that "triple therapy" is associated with substantially increased risks for bleeding; in a cohort of more than 80,000 patients with atrial fibrillation, incidence of fatal and nonfatal bleeding was 3.7 % per year with aspirin alone, 7.4 % per year with aspirin plus clopidogrel, and 15.7 % per year with triple therapy [57]. Risk of bleeding is likely even higher with combinations of newer and more potent antiplatelet agents like prasugrel and ticagrelor. As such, we recommend attempting to avoid altogether or to minimize the duration of triple therapy. Consideration should be given to using BMS instead of DES, which would allow the duration of clopidogrel to be reduced to 1 month. For patients with atrial fibrillation, a reevaluation of the risks of bleeding and stroke (using a tool such as the CHADS2 score) should be performed, and the threshold to initiate or continue warfarin should be higher among patients on aspirin and clopidogrel. For patients that require triple therapy, the INR should be maintained at the lowest end of the therapeutic range [58], aspirin dose should be reduced to 81 mg, and GI prophylaxis with an H2 antagonist or PPI such as pantoprazole should be considered. Novel oral anticoagulants such as dabigatran or rivaroxaban may be considered for thromboembolic prevention in non-valvular atrial fibrillation, due to lower rates of intracranial hemorrhage and shorter half-lives, compared to warfarin, but bleeding is still notably increased when added to aspirin and clopidogrel [59, 60]. Given the higher bleeding risks of ticagrelor and prasugrel, these agents should not be used in combination with oral anticoagulants.

Anti-ischemic Therapy

Beta-Blockers

β-Blockers exert their beneficial effect in acute MI by preventing catecholamine-mediated β_1-receptor activation, leading to decreased contractility and heart rate, thereby improving the balance between oxygen supply and demand. These drugs also exert an antiarrhythmic effect, as evidenced by an increase in the threshold for ventricular fibrillation in animals and a reduction in complex ventricular arrhythmias in humans. β-Blockers may prevent plaque rupture by reducing the mechanical stresses imposed on the plaque. Finally, β-blockers appear to attenuate adverse remodeling post-MI and prevent the development of heart failure.

β-Blockers were among the first therapeutic interventions used to limit the size of an acute MI. Administration of a β-blocker very early following onset of acute MI decreases infarct size, recurrent MI, and mortality (Table 26.6). When β-blockers have been used in conjunction with fibrinolytic therapy, they provide incremental benefit, particularly if they can be administered early after the onset of infarct symptoms. Tabulation of the results from the available studies indicates a highly significant reduction of approximately 30 % in the incidence of sudden death and a nonsignificant reduction of only about 12 % in the incidence of non-sudden death. The fact that β-blockers were particularly effective in reducing sudden death again suggests that they exert much of their early beneficial effect by reducing the frequency and severity of arrhythmias. In addition, β-blockers appear to significantly decrease the risk of cardiac rupture.

In addition to the early benefits of β-blockers, when given long term, these agents significantly reduce the incidence of nonfatal reinfarction and also reduce long-term mortality (Table 26.6) [61]. The benefits from routine beta-blocker use seem to persist as long as the active agent is continued and appear to extend to most patient subgroups. The long-term mortality benefits of the β-blockers extend to most members of this class of agents. There does not seem to be a significant difference between agents with or without cardioselectivity. Considering the low cost of routine beta-blocker use, and its substantial benefit, such therapy has a very favorable cost-effectiveness ratio and represents one of the few "bargains" left in contemporary cardiology.

The Carvedilol Postinfarction Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial examined the incremental effect of beta-blockade (with carvedilol) in the post-MI setting over and above the effects of other established therapies, including ACE inhibitors. Over a 6-month treatment period post-MI, the group treated with carvedilol had smaller LV volumes and improved LV ejection fraction and wall motion score index vs. the placebo group, as well as a more favorable clinical course [62]. Thus, in the current era, beta-blockade appears to add favorable and independent

effects on the post-MI remodeling process in the presence of ACE inhibition.

Prior standard of care included the routine early administration of IV beta-blockade to the most patients presenting with MI. However, this practice of early IV beta-blocker use was evaluated in the COMMIT/CCS-2 trial, which randomized over 45,000 MI patients (93 % with STEMI) to metoprolol (up to 15 mg IV then 200 mg daily) vs. placebo. No overall benefit was seen in the IV metoprolol arm; moreover, a trade-off in risk/benefit was seen: for every 1,000 treated with metoprolol, 11 patients would develop cardiogenic shock, compared to 5 fewer reinfarction and 5 fewer ventricular fibrillation events. Subsequently, the most recent STEMI guidelines now recommend that early IV beta-blockade be used rarely, except in cases of hypertension and/or atrial arrhythmias, and only in the absence of signs of heart failure or risk factors for shock. Notably, oral beta-blocker therapy remains a class I recommendation, although greater caution is advised to avoid administration in patients with acute heart failure, low-output state, or risk factors for shock or other contraindications.

Nitrates

The clinical effects of nitrates are mediated through several distinct mechanisms, including: (1) dilation of large coronary arteries and arterioles with redistribution of blood flow from epicardial to endocardial regions. (2) Peripheral venodilation leads to an increase in venous capacitance and a substantial decrease in preload, thus reducing myocardial oxygen demand. Nitrates are consequently of particular value in treating patients with LV dysfunction and CHF. (3) Peripheral arterial dilation, typically of a modest degree, may decrease afterload. In addition, nitrates have been shown to relieve dynamic coronary constriction caused by vasospasm. Nitrates may also have an inhibitory effect on platelet aggregation, though the clinical significance of this finding is unclear.

A review of evidence from all pertinent randomized clinical trials does not support routine use of intermediate or long-term nitrate therapy in patients with uncomplicated acute MI. However, it is reasonable to use nitroglycerin for the first 24–48 h in patients with acute MI and recurrent ischemia, CHF, or hypertension. Sublingual or intravenous nitrates are particularly effective in patients with pulmonary congestion, due to their venodilating properties. However, they should be used cautiously in patients with inferior MI as they may precipitate hypotension in patients with right ventricular infarction or those with pronounced vagal symptoms.

Calcium Channel Blockers

All of the currently available calcium channel antagonists block the entry of calcium into cells via voltage-sensitive (L type) calcium channels. In vascular smooth muscle cells, this causes coronary and peripheral vasodilation. In cardiac tissue, this leads to depression of myocardial contractility, cardiac pacemaker function, and AV nodal conduction. The differences between the three classes of calcium channel blockers relate to differences in their primary sites of actions.

Dihydropyridine calcium channel antagonists can be viewed as almost pure vasodilators. They dilate resistance vessels in both the peripheral and coronary beds and improve coronary blood flow. However, this is countered by a reflex increase in heart rate, making the overall effect on oxygen demand unpredictable. Amlodipine, a third-generation dihydropyridine agent, causes less reflex tachycardia than other dihydropyridines and usually has a neutral effect on heart rate. Short-acting nifedipine is absolutely contraindicated in MI, as it causes reflex tachycardia and rapid hemodynamic fluxes which are poorly tolerated in STEMI, particularly in the elderly. Dihydropyridines have been uniformly unsuccessful in reducing either mortality or the rate of reinfarction in multiple trials. Thus, while sustained-release dihydropyridine preparations remain useful for treating hypertension, they should only be used in AMI when other evidence-based medications, such as beta-blockers, ACE inhibitors, and angiotensin-receptor blockers, have been exhausted.

Verapamil and diltiazem can be considered together because their net pharmacologic effect is that of slowing the heart rate and, to some extent, reducing myocardial contractility, thereby reducing myocardial oxygen demand. Of the two agents, verapamil has greater negative inotropic and chronotropic effects. A pooled analysis indicated that verapamil and diltiazem had no effect on mortality following acute MI [63]. In patients with CHF or LV dysfunction, these agents have been associated with an *increase* in mortality. Although diltiazem and verapamil have been shown to reduce nonfatal MI, it must be noted that these studies compared diltiazem and verapamil with placebo and not with a beta-blocker. Because β-blockers consistently reduce both mortality and reinfarction, they are recommended for all patients who can tolerate such medications. Verapamil or diltiazem may be a reasonable alternative for those patients who cannot tolerate a beta-blocker, provided they have no evidence of CHF and do not have severe LV dysfunction. It should be noted, however, that many patients who cannot tolerate a beta-blocker because of concern of excessive bradycardia or CHF may experience similar complications from diltiazem or verapamil.

Antagonists of the Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) is activated following infarction and has been implicated in healing and remodeling following MI. Angiotensin is directly involved in collagen synthesis and breakdown pathways and

Table 26.7 Randomized trials of ACE-inhibitor therapy post-AMI

Study	Agent	*N*	Duration	RR death (95 % CI)	*p* value
Therapy started during infarction					
ISIS-4	Captopril	58,050	35 days	0.93 (0.87–0.99)	0.02
GISSI-3	Lisinopril	19,394	42 days	0.88 (0.79–0.99)	0.03
CONSENSUS II	Enalaprilat	6,090	41–180 days	1.11 (0.93–1.29)	0.26
Therapy started post-AMI, LV dysfunction					
SAVE	Captopril	2,231	42 months	0.81 (0.68–0.97)	0.02
AIRE	Ramipril	2,006	15 months	0.73 (0.69–0.89)	0.002
TRACE	Trandolapril	1,749	24–50 months	0.78 (0.70–0.86)	<0.001

may mediate post-MI tissue repair. Aldosterone is a key contributor to myocardial fibrosis and arrhythmia development.

ACE inhibitors have become a mainstay in the treatment of patients with acute MI because they prevent the deleterious left ventricular chamber remodeling that may occur after MI and because they may prevent the progression of vascular pathology. LV remodeling is characterized by alterations in ventricular mass, chamber size, and shape, all of which result from myocardial injury or pressure or volume overload. These processes, which occur in the non-infarcted myocardium, contribute to progressive LV remodeling and LV dysfunction. Substantial experimental and clinical data exist that support the pivotal role of the RAAS in contributing to these cellular processes.

An observational analysis by the ACE Inhibitor Myocardial Infarction Collaborative Group, which included approximately 100,000 patients with acute MI treated within 36 h of the onset of chest pain, found a 7 % lower 30-day mortality among those given ACE inhibitors (Table 26.7) [64]. The absolute benefit was particularly large in some high-risk groups, such as those in Killip class II or III (23 lives saved per 1,000 patients) and those with an anterior MI (11 lives saved per 1,000 patients). ACE-inhibitor therapy also prevented nonfatal CHF, but was associated with an excess of persistent hypotension and renal dysfunction.

Additional studies have suggested that ACE inhibitors may improve clinical outcomes by reducing LV remodeling and specifically LV enlargement. These data provide compelling evidence that the remodeling process itself, independent of drug effect, is associated with adverse natural history outcomes in patients with LV dysfunction. Those patients with more substantial post-MI LV dilation were at higher risk of death during follow-up. The benefits of ACE inhibition appear to be class specific, with little difference between agents (Table 26.7).

ACE inhibitors only partially block production of angiotensin II in the human heart because of the existence of ACE-independent pathways that convert angiotensin I to angiotensin II. This experimental finding led to the development of angiotensin-receptor antagonists that offer more complete protection against angiotensin II by directly blocking the angiotensin type I receptor. The Valsartan in Acute Myocardial Infarction (VALIANT) trial compared the effects of the angiotensin-receptor blocker (ARB) valsartan, the ACE inhibitor captopril, and the combination of valsartan and captopril in 14,808 high-risk patients with clinical or radiologic evidence of heart failure, evidence of LV systolic dysfunction, or both after acute MI. During a median follow-up of 24.7 months, mortality was 19.9 % in the valsartan group, 19.5 % in the captopril group, and 19.3 % in the valsartan and captopril group [65]. Hypotension was notably more common in the group receiving both valsartan and captopril, suggesting that the combination of ACEI and ARB leads to an increase in the rate of adverse events without improving overall survival. On the other hand, ARB monotherapy represents a reasonable alternative to ACEI monotherapy. However, given the established benefits of ACE inhibitors post-MI, and their low cost, we recommend that angiotensin-receptor antagonists be reserved for those patients who are intolerant to ACE inhibitors.

The mineralocorticoid aldosterone is another component of the RAAS that may significantly contribute to the development of adverse ventricular remodeling in patients with LV systolic dysfunction. In addition, aldosterone may contribute to cardiac fibrosis post-MI. In the EPHESUS study, over 6,600 patients with AMI complicated by left ventricular dysfunction (left ventricular ejection fraction ≤40 %) and signs of heart failure or diabetes were randomized to the selective aldosterone inhibitor eplerenone or placebo in addition to standard therapy which could include reperfusion, aspirin, statin, ACE inhibitor/ARB, and a beta-blocker. Eplerenone, when administered at a dose of up to 50 mg daily between days 3 and 14 after infarction (mean 7.3 days), resulted in a 15 % reduction in total mortality ($p=0.008$) and a 17 % reduction in cardiovascular mortality ($p=0.005$), mainly due to a 21 % reduction in sudden cardiac death ($p=0.03$) [66]. Of the patients enrolled, 87 % were already being treated with ACE inhibitors, and 75 % received beta-blockers, indicating that the aldosterone inhibitor indeed provided incremental benefit to optimal therapy. Further studies will be required to determine whether aldosterone blockade should be restricted to patients with early evidence of LV dysfunction or whether they should be used in a manner similar to ACE inhibitors and beta-blockers in all patients with

myocardial infarction, regardless of LVEF. Although a similar benefit with a less selective (and expensive) agent such as spironolactone has not been proven, we believe it reasonable to use spironolactone for this purpose. For patients with LVEF≤40 % with heart failure or diabetes, STEMI guidelines recommend the addition of an aldosterone antagonist to patients already receiving an ACE inhibitor, provided that renal dysfunction (creatinine >2.5 mg/dL in men and >2.0 mg/dL in women) and hyperkalemia (potassium >5.0 mg/dL) are not present.

Mineralocorticoid antagonists represent one of the most underused evidence-based medications post-MI. In part, this reflects appropriate concerns about the risk for hyperkalemia with these agents. However, with careful follow-up, many patients can safely receive these highly effective and inexpensive agents.

Analgesia

Traditionally, morphine has been routinely given to patients with MI for alleviation of pain and relief of dyspnea in patients with pulmonary edema. A retrospective analysis in patients with unstable angina and NSTEMI from the CRUSADE registry reported increased risk of mortality among patients given morphine (adjusted OR 1.48, 95 % CI: 1.33–1.64), although the clinical implications of these results are limited due to the potential for residual confounders, similar to other observational analyses. The most recent STEMI guidelines continue to give a class I recommendation for the use of morphine for the management of pain.

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) is contraindicated (excluding aspirin) during hospitalization for MI (including elective COX-2 inhibitors) due to increased risk of MI, heart failure, worsening of hypertension, myocardial rupture, and mortality. Since patients are often taking these medications prior to admission, these medications should be promptly discontinued and avoided during hospitalization and after discharge.

In-Hospital Management Following AMI

Ongoing Risk Stratification Throughout the Hospital Stay

Risk stratification in acute MI actually should begin the moment a patient arrives in the emergency room and should continue through hospital discharge and beyond. When the patient is first seen, historical, physical exam, ECG, and serum marker information are rapidly integrated, both to arrive at a diagnosis and also to estimate a patient's a priori risk for adverse outcome. For example, older age, female sex, presence of diabetes, and history of prior MI or CHF are all associated with increased risk. In addition, tachycardia or bradycardia, hypotension, and evidence for CHF are markers for increased risk that are easily obtained from a focused examination. The ECG provides incremental predictive value, in addition to distinguishing ST-elevation MI from non-ST-elevation MI. An anterior location of infarction (or an inferior infarction with RV extension or anterior ST depression) and greater ST deviation are associated with larger infarcts and increased risk. Poor resolution of ST elevation identifies a suboptimal reperfusion result and an increased risk for heart failure and death. Impaired renal function at baseline and during hospitalization is also associated with increased risk. Finally, elevated serum markers at presentation, even in patients with known ST elevation, predict an increased risk for mortality. Scoring systems such as TIMI risk score [67] for STEMI can be used to quantitatively predict a patient's risk of adverse events following STEMI (Fig. 26.11). This scoring system has been validated in multiple different datasets.

After initial risk stratification is completed, subsequent risk-stratification steps should focus on identifying patients at risk for electrical, mechanical, and ischemic complications and selecting those patients who will benefit most from particular therapies, such as revascularization. It should be remembered that with many therapies, absolute risk reduction is highest in those patients at greatest risk; therefore, the higher the risk for an individual patient, the more aggressive the care should be.

Risk stratification is also crucial to determine appropriate length of stay in the ICU and the hospital. Although length of stay in the pre-reperfusion era often extended beyond 1 week for patients presenting with STEMI, several analyses have demonstrated that discharge in 3 days or less after MI in low-risk patients (those without angina or residual ischemia, bleeding, heart failure, or arrhythmia) is both safe and cost-effective [68].

Assessment of Left Ventricular Function

Left ventricular function is the single most important determinant of long-term survival after myocardial infarction; for example, patients with significant left ventricular dysfunction (LVEF≤40 %) post-MI have a 5-year mortality of >25 %. In addition, patients with LV dysfunction and multivessel coronary artery disease derive significant benefit from surgical revascularization. Due to the importance of LV function to risk assessment, all patients should have an ejection fraction measurement following an acute MI. Since reversible LV dysfunction, termed myocardial stunning, may follow an ischemic insult, initial measurements may significantly underestimate true LV function, and thus a repeat assessment of LVEF may be necessary after discharge. Although echocardiography, contrast ventriculography, and radionuclide angiography are all reliable methods for assessing LVEF, echocardiography has the advantage of providing structural information as well.

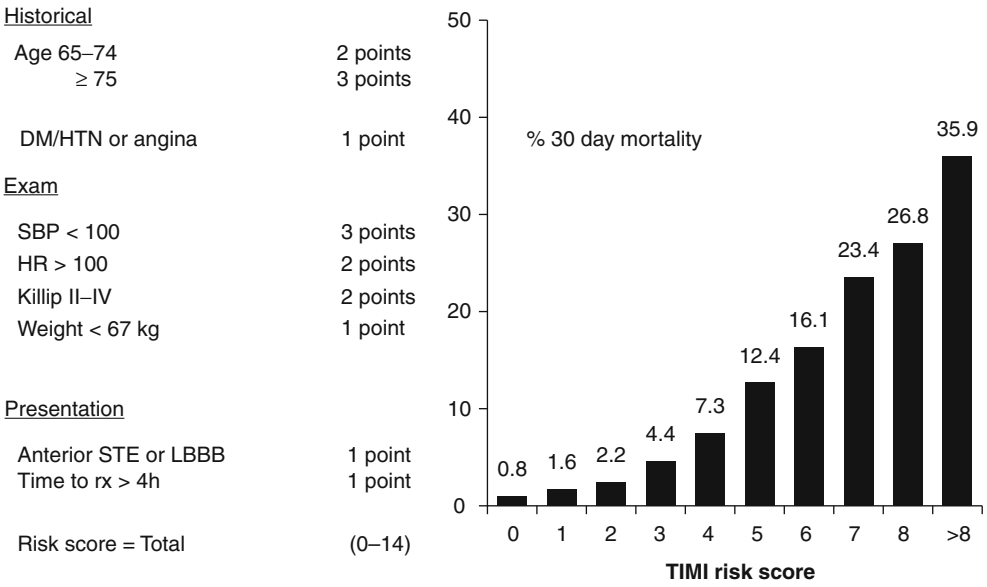

Fig. 26.11 TIMI risk score and associated 30-day mortality for STEMI (Reprinted from Morrow et al. [67]. With permission Lippincott Williams & Wilkins)

Risk Factor Modification

Correction of modifiable risk factors is essential for the treatment of patients following myocardial infarction. The benefits of aggressive risk factor modification, including lipid optimization, control of hypertension, dietary modification, and exercise implementation, are profound and can be more dramatic than many of the more expensive treatment strategies described in this chapter. Despite the potential benefits to be gained, patient risk factor modification often remains suboptimal after STEMI. In an analysis of over 2,400 patients from the Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) Registry, within 1 month after STEMI, only 51 % of patients reported adherence with dietary restrictions, and only 33 % reported participation in cardiac rehabilitation [69]. Cardiac risk factor modification, including lipid lowering therapy, is discussed in greater detail in Chap. 43.

Systematic interventions aimed at optimizing cardiac risk factors are included within many cardiac rehabilitation programs, which were traditionally based upon providing supervised exercise therapy. Meta-analysis of randomized trials including over 21,000 patients with coronary artery disease has demonstrated a significant reduction in mortality and recurrent MI among patients undergoing cardiac rehabilitation programs [70]. Improvements in quality of life and functional capacity are also often achieved.

Complications of Acute MI

Bleeding Complications

Advances in antiplatelet and antithrombotic medications and greater utilization of invasive therapies have led to substantial reductions in ischemic events after STEMI; however, these advances occur at a cost of increased risk of bleeding. In a recent analysis of predictors of ACS bleeding from the NCDR, STEMI patients in the lowest risk quintile on average have a 7.5 % risk of major bleeding during hospitalization, whereas those in the highest quintile have 43.4 % risk [71]. Bleeding is not only associated with significant morbidity due to pain, transfusion, and longer length of stay, but bleeding is also associated with increased mortality after MI. This association can be explained only in part due to bleeding itself and the hypovolemia, anemia, and impaired oxygenation that often accompany it; rather, this is largely related to differences in patient characteristics as well as treatments and processes of care that occur as a result of bleeding. For example, patients who bleed are more likely to have antiplatelet and anticoagulation therapies discontinued or reversed, which may result in higher risk of recurrent ischemic events or death. Supporting this theory is that patients with major bleeding have been described to have a risk for stent thrombosis sixfold that of patients without bleeding [72].

When determining a treatment plan for any STEMI patient, his/her individual risk for bleeding should be considered. Clinical risk prediction tools have been developed to quantitatively assess bleeding risk [71, 73, 74]; however, clinical assessment is more often used in routine practice. Regardless of the strategy used for risk prediction, once risk of bleeding is determined, several strategies can be employed to minimize bleeding risk. Using a radial rather than femoral access approach, in experienced operators, may reduce risk of bleeding. In a meta-analysis over 7,000 patients from randomized trials, radial access was associated with a significantly lower risk of major bleeding [0.05 % vs. 2.3 %, OR = 0.27 (95 % CI 0.16, 0.45), $p < 0.001$], although there was a trend towards higher rates of procedural failure [4.7 % vs. 3.4 % OR = 1.29

95 % CI (0.87, 1.94), $p=0.21$]. The Radial vs. Femoral Access for Coronary Intervention (RIVAL) trial, published after this meta-analysis, randomized over 7,000 patients to radial vs. femoral access and found no significant difference in non-CABG-related major bleeding (0.7 % vs. 0.9 %; HR = 0.73, 95 % CI 0.43–1.23; $p=0.23$) in analysis of the entire cohort; however, in subgroup analysis of almost 2,000 patients presenting with STEMI, major bleeding was lower in the radial group [3.1 % vs. 5.2 %, HR = 0.60 (0.38–0.94), $p<0.026$]. The most important pharmacologic strategy to reduce bleeding is using bivalirudin as the anticoagulant to support primary PCI. In the HORIZONS-AMI trial, bleeding rates were 4.9 % in the bivalirudin arm vs. 8.3 % in the group receiving UFH + GP IIb/IIIa inhibitors (RR = 0.60; 95 % CI 0.46–0.77; $p<0.001$) (Fig. 26.9). In addition, careful attention to avoid excessive dosing of antithrombotic therapies will reduce bleeding complications.

When bleeding occurs, treatment is based upon the location of the bleed. For access site-related bleeding, firm manual compression of the access site for 15–30 min is recommended. While compression assist devices exist as alternatives, we recommend manual compression in cases of bleeding complications. Blood transfusion may be required, but risks/benefits should be carefully weighed as observational data have suggested increased mortality with transfusion in stable patients with hematocrit above 25 %, as compared to those not receiving transfusion. Similarly, when deciding whether or not to discontinue antithrombotic therapies, careful consideration should be given to the risk of recurrent ischemic/thrombotic events. If bleeding can be controlled by local compression or other measures, then interruption of antithrombotic therapies is not recommended. However, if a severe or life-threatening bleeding occurs, such as in cases of intracranial hemorrhage or severe GI bleeding and risk of bleeding outweighs risk of recurrent ischemia, then discontinuation of antithrombotics may be required, although duration of interruption should be minimized and antithrombotic therapies should be reinitiated as soon as safely possible.

Mechanical Complications

Infarct Expansion and Remodeling

Following a large myocardial infarction, particularly if it involves the anterior wall and apex of the left ventricle, the infarct area may expand and cause thinning of the necrotic myocardium. Over weeks to months, the left ventricle (LV) may dilate and assume a more globular shape. This process, termed LV remodeling, has been associated with an increased risk for the development of LV dysfunction, heart failure, and death. Factors that have been found to favorably effect remodeling include ACE inhibitors, beta-blockers (described above), and establishment of a patent infarct-related artery. Indeed, one of the purported benefits of late reperfusion is improved tissue healing and the prevention of adverse left ventricular remodeling.

Recurrent Ischemia and Infarction

Following successful fibrinolysis, reocclusion of the infarct artery, and subsequent reinfarction, may occur in up to 10–15 % of patients by hospital discharge and 30 % of patients by 3 months, a complication which is associated with a two- to threefold increase in mortality. As described above, fibrinolytic therapy itself may create a pro-thrombotic state which promotes reocclusion. Reocclusion rates after primary PCI are much lower, particularly if stenting and adjunctive pharmacologic therapies are employed. Recurrent infarction may be difficult to diagnose, particularly if it occurs within the first 24–48 h post-MI, when cardiac enzymes remain elevated from the index event. Recurrent ST elevation, or a new "peak" in CKMB or myoglobin, is highly suggestive of MI. Recurrent ischemia, without infarction, is also a frequent complication post-MI. Since patients with postinfarction angina are at high risk for recurrent MI, in general, cardiac catheterization should be performed with a goal of target-vessel revascularization.

Cardiogenic Shock

Cardiogenic shock is characterized by tissue hypoperfusion, hypotension, low cardiac output, and elevated filling pressures. When cardiogenic shock occurs post-MI, it is most commonly due to infarction of 40 % or more of the left ventricle. In three large, international series of patients with STEMI receiving thrombolytic therapy, the incidence of shock has ranged from 4.2 to 7.2 % [75]. In the setting of an acute ischemic event, shock may occur in patients with either non-STEMI or STEMI, though it is about twice as likely in the setting of transmural myocardial infarction.

Although shock typically results from a substantial amount of damage to the left ventricular myocardium, other etiologies must be considered. In the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) registry [76], predominant left ventricular failure was seen in 74.5 % of patients. However, acute severe mitral regurgitation was seen in 8.3 %, ventricular septal rupture in 4.6 %, and right ventricular shock in 3.4 %. Delineation of the specific etiology of shock has obvious importance for selecting an optimal treatment strategy.

Revascularization in patients with cardiogenic shock has demonstrated significant reductions in mortality in both observational and randomized studies. The SHOCK trial is the only randomized trial completed to evaluate an aggressive, invasive approach in managing patients with shock due to left ventricular failure. In this trial [76], 152 patients were randomly assigned to emergency revascularization by either CABG or angioplasty, and 150 patients were assigned to medical stabilization which often included fibrinolytic therapy. Intra-aortic balloon counterpulsation was performed in 86 % of the

patients in both groups. The primary endpoint in this trial was 30-day mortality. The 30-day mortality rate in the invasive therapy arm was 46.7 % compared with 56 % in the conservative arm ($p=0.11$). At 6 months, however, mortality was significantly lower in the revascularization group: 50.3 % compared with 63.1 % in the medical therapy group ($p=0.027$). Early revascularization benefits were only seen in patients younger than 75 years (Table 26.8). The results of the SHOCK trial are relatively consistent with the other series in which revascularization is associated with improved outcome.

Despite successful revascularization, mortality in patients with cardiogenic shock remains very high, accounting for the majority of deaths related to acute MI. In addition to early revascularization, mechanical circulatory support devices such as an intra-aortic balloon pump (IABP) or more extensive mechanical support devices can be important therapies for the stabilization of patients in cardiogenic shock, although only limited data are available to support this practice. Meta-analyses and systematic reviews have found that IABP was associated with lower mortality only in patients treated with fibrinolysis, but not in those treated with PCI [77, 78]; however, further analysis did demonstrate significantly lower mortality in patients treated with IABP at experienced centers [79]. In comparison to IABP, percutaneous cardiac support using devices such as the Impella or Tandem Heart has demonstrated much greater improvements in hemodynamic parameters, although studies have not been adequately powered to evaluate for mortality benefits [80].

Table 26.8 SHOCK trial results

	Revascularization (%)	Medical therapy (%)	*p* value
30-day mortality			
<75 years	41	57	0.02
>75 years	75	53	0.16
6-month mortality			
<75 years	45	65	0.002
>75 years	79	56	0.09

Based on data from Hochman et al. [76]

Right Ventricular MI

Right ventricular (RV) infarction is a frequent complication of inferior wall MI (IMI) and is almost always caused by proximal occlusion of the right coronary artery. The diagnosis should be suspected in patients with IMI and unsuspected hypotension, particularly when it occurs after small doses of nitrates. Patients will usually have jugular venous distention, but will have clear lungs unless significant left ventricular infarction is present as well. A right-sided ECG should be standard in all patients with IMI, because ST elevation of ≥0.1 mV in V_4R (Fig. 26.12) is sensitive and specific for the diagnosis of RV infarction. The hemodynamic profile is one of elevated right-sided filling pressures with reduced cardiac output, findings similar to those of pericardial tamponade. In patients without ECG evidence of RV infarction, therefore, echocardiography (or placement of a PA catheter) is indicated to distinguish between the two diagnoses.

The hemodynamic derangements of RV infarction can be improved by expansion of intravascular volume with normal saline. In patients with severe RV infarction, many liters of fluid may be required to achieve hemodynamic stability. Short-term morbidity and mortality are increased in patients with right ventricular MI compared with those with IMI alone. Several studies have suggested that primary PCI, rather than fibrinolytic therapy, should be the preferred reperfusion method in these high-risk individuals. In patients who stabilize, the prognosis for full recovery of RV function is very good.

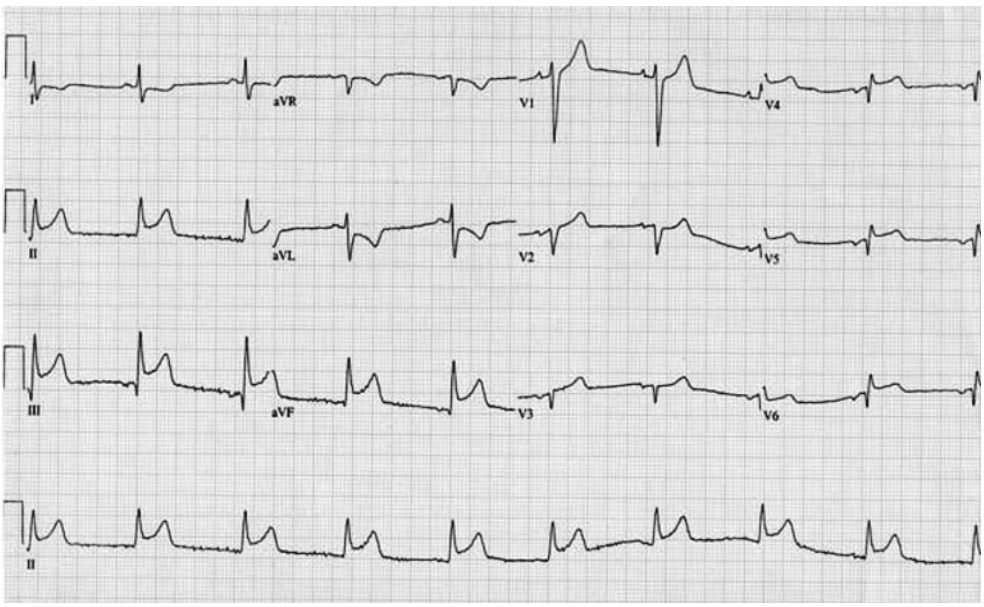

Fig. 26.12 ECG changes associated with right ventricular infarction. Note ST elevation in lead $V4_R$, a finding highly specific for RV infarction

Free Wall Rupture

Rupture of the free wall of the left ventricle is the most catastrophic mechanical complication of acute MI, with a mortality rate in excess of 90 %. The presentation is one of pericardial tamponade and hemodynamic collapse, often culminating in pulseless electrical activity. Survival is dependent on prompt recognition, emergent pericardiocentesis, and surgical repair.

The interaction of rupture and fibrinolytic therapy is complex. Although early fibrinolytic therapy lowers the risk for rupture, late fibrinolytic therapy, when given in the setting of a completed infarct with softened, necrotic tissue, may actually increase the incidence of rupture. In addition, in the fibrinolytic era, rupture appears to be occurring earlier after presentation; although the most common time frame is 1–4 days post-MI, it may occur within the first 24 h. Rupture is associated with large transmural infarctions and is more common in the elderly, women, and patients *without* prior MI. Controversy exists about an association with glucocorticoids and nonsteroidal anti-inflammatory drugs. The most common location of rupture is in the anterior and lateral distributions of the left anterior descending artery.

Incomplete free wall rupture can lead to formation of a pseudoaneurysm. In this situation, the rupture site is sealed by hematoma and the pericardium itself, and when the thrombus organizes, a pseudoaneurysm cavity is formed. The pseudoaneurysm is often quite large and typically remains filled with some degree of thrombus. In distinction to a true aneurysm, in which the wall is composed of myocardial tissue, a pseudoaneurysm communicates with the LV cavity via a narrow neck of myocardial tissue; the wall of the pseudoaneurysm is composed of thrombus and pericardium, but no myocardial tissue. Early elective repair is indicated for all suitable patients.

Septal Rupture

Rupture of the intraventricular septum typically does not present in as catastrophic a manner as does free wall rupture. Septal rupture causes an acute ventricular septal defect (VSD), with left to right flow across the lesion. The presentation is usually one of congestive heart failure which develops over hours to days (depending on the size of the defect) and is associated with a harsh holosystolic murmur, which may be difficult to distinguish from mitral regurgitation. Either Doppler echocardiography or insertion of a PA catheter can be used to confirm the diagnosis. A "step-up" in oxygen saturation seen at the level of the right ventricle is diagnostic of a VSD in this setting. Septal rupture is more common following anterior infarction, where the apical regions of the septum are involved. With inferior infarction, the basal portions of the septum are involved, and the prognosis is somewhat worse. Patients should be stabilized with pressors, usually an IABP, and vasodilators (if tolerated), followed by surgical repair and revascularization.

Left Ventricular Aneurysm

A "true" left ventricular aneurysm is a discreet "outpouching" of a thinned, dyskinetic, myocardial segment. As opposed to a pseudoaneurysm, the wall of a true aneurysm contains cardiac and fibrous tissues, and the neck is broad based. The most common site of aneurysm formation is the LV apex, due to distal occlusion of a non-collateralized left anterior descending artery. As opposed to pseudoaneurysms, the risk of rupture is small. Aneurysms are, however, associated with increased morbidity and mortality. The dyskinetic aneurysmal segment may alter overall LV geometry and impair contractile performance, thrombus frequently lines the thinned wall and may be a source for arterial embolus, and most importantly the scarred aneurysmal tissue may be a source for malignant ventricular arrhythmias. Surgical aneurysmectomy is rarely indicated, except to control malignant arrhythmias and, rarely, in an attempt to improve LV function. Anticoagulation with warfarin therapy may be indicated, if LV thrombus is present, to prevent embolization.

Acute Mitral Regurgitation

Acute mitral regurgitation following AMI is caused by ischemic dysfunction or frank rupture of a papillary muscle. This complication is more common following inferior MI, since the posteromedial papillary muscle typically has a single blood supply from the right coronary artery, while the anterolateral papillary muscle has dual supply from the left anterior descending and circumflex arteries. As opposed to rupture, this complication may occur with relatively small, but well localized, infarctions. As with septal rupture, a new holosystolic murmur is classically present in the setting of acute pulmonary edema and even cardiogenic shock. As blood pressure falls, the murmur may disappear entirely. Doppler echocardiography is particularly helpful in distinguishing acute MR from septal rupture. Treatment for this complication requires initial stabilization, usually with an IABP, pressors, and vasodilators (if tolerated), followed by prompt surgical correction.

Arrhythmia Complications

Ventricular Tachycardia and Ventricular Fibrillation (See Chaps. 15 and 16)

Ventricular tachycardia is common in patients during the first hours and days after myocardial infarction and does not appear to be associated with an increased risk for subsequent mortality if the arrhythmia is rapidly terminated. Ventricular tachycardia occurring after 24–48 h, however, is associated with a marked increase in mortality. *Monomorphic* VT is usually due to a reentrant focus around a scar, while *polymorphic* VT is more commonly a function of underlying ischemia, electrolyte abnormalities, or drug effects.

Ventricular fibrillation is felt to be the primary mechanism of arrhythmic sudden death. The incidence of primary ventricular fibrillation appears to have declined substantially in recent years. In patients with acute MI, the vast majority of the episodes of VF occur early (<4–12 h) after infarction. As with sustained VT, *late* VF occurs more frequently in patients with severe LV dysfunction or CHF and is associated with a poor prognosis. Patients with VF or sustained VT associated with symptoms or hemodynamic compromise should be cardioverted emergently. Underlying metabolic and electrolyte abnormalities must be corrected, and ongoing ischemia should be addressed. Amiodarone is a particularly effective antiarrhythmic agent in the setting of acute MI and should be used to treat VF. In patients with VF or hemodynamically significant sustained VT occurring more than 48 h after MI, the ACC/AHA STEMI guidelines give a class I recommendation to the placement of an ICD for the prevention of sudden cardiac arrest as long as the arrhythmia is not due to recurrent ischemia/reinfarction. In cases of sustained VT, VF, or cardiac arrest occurring more than 48 h after MI (secondary prevention), we recommend ICD implantation prior to discharge. For primary prevention of sudden cardiac arrest in patients with reduced ejection fraction post-MI, current ACC/AHA/HRS guidelines recommend delaying ICD implantation for ≥40 days after MI and reassessing LVEF to make sure the patient is still eligible [81].

Bradyarrhythmias (See Chaps. 15 and 16)

Bradyarrhythmias are common in the setting of acute MI and may be due to either increased vagal tone or ischemia/infarction of conduction tissue. Sinus bradycardia is usually a result of stimulation of cardiac vagal receptors, which are located most prominently on the inferoposterior surface of the left ventricle. If the heart rate is extremely low (<40–50 bpm) or if hypotension is present, intravenous atropine should be given.

Mobitz type I (Wenckebach) second-degree AV block is also very common in patients with inferior wall MI and may be a function of either ischemia or infarction of the AV node or increased vagal tone. The level of conduction block is usually within the AV node, and therefore, the QRS complex is narrow and the risk for progression to complete heart block is minimal. Again, atropine can be used for patients with significant bradycardia, hypotension, or symptoms. Temporary pacing is rarely required unless there is hemodynamic or electrical instability. Mobitz type II block is much less common than Mobitz type I block in the setting of an inferior MI. As opposed to Mobitz type I block, Mobitz type II block is more frequently associated with anterior MI, an infra-nodal lesion, and a wide QRS complex. Since Mobitz type II block can progress suddenly to complete heart block, a temporary pacemaker is indicated.

Although compete heart block may occur with either inferior or anterior MI, the implications differ considerably depending on the location of the infarct. With inferior MI, heart block often progresses from first-degree or Wenckebach to third-degree AV block. The level of block is usually within or above the level of the AV node, the escape rate is often stable, and the effect transient. Although temporary pacing is indicated for hemodynamic or electrical instability, a permanent pacemaker is rarely required. With anterior MI, complete heart block is usually a result of extensive infarction that involves the bundle branches. The escape rhythm is usually unstable and the AV block permanent. Mortality is extremely high, and permanent pacing is performed unless there are contraindications.

Supraventricular Arrhythmias (See Chaps. 15 and 16)

Atrial fibrillation occurs in up to 15 % of patients early after MI, with atrial flutter and paroxysmal supraventricular tachycardia occurring much less frequently. Ischemia itself is rarely a cause of atrial fibrillation, except in rare cases of atrial infarction. Precipitants of atrial fibrillation post-MI include right or left ventricular failure and pericarditis. Although the arrhythmia itself is usually transient, it is a marker for increased morbidity and mortality, probably because of the conditions associated with its development. Management of supraventricular arrhythmias in the setting of acute MI is similar to management in other settings (see Chap. 16); however, in the setting of acute MI, the urgency with which the ventricular response is controlled should be greater. Due to their beneficial effects in acute MI, beta-blockers should be the first agents used to control rate. If true contraindications to beta-blockers are present, diltiazem or verapamil are appropriate alternatives in patients without heart failure or significant LV dysfunction, and digoxin may be considered for patients with concomitant LV dysfunction or hypotension. Of the antiarrhythmic agents available, amiodarone is probably the safest in the peri-infarct setting. When weighing the risks and benefits of anticoagulant therapy for stroke prevention in patients with atrial fibrillation, consideration should be given to the associated increased risk of bleeding when anticoagulants are added to aspirin and clopidogrel (see warfarin section above).

Other Complications

Pericarditis

Asymptomatic pericardial effusion occurs in as many as 25 % of patients following transmural MI; these effusions are rarely associated with symptoms or hemodynamic compromise. Fibrinous pericarditis may also occur in the days to weeks following transmural infarction and may be confused with postinfarction angina or recurrent MI. The pain of pericarditis is usually pleuritic, positional, and often radiates to the trapezius ridge. A pericardial friction rub may be present. Treatment

should consist of aspirin, but nonsteroidal anti-inflammatory agents should be avoided, since they may inhibit healing of the infarct. If an effusion is seen on echocardiography in a patient with symptomatic pericarditis, anticoagulants should be held unless absolutely necessary. Dressler's syndrome is characterized by pericardial pain, generalized malaise, fever, elevated WBC, elevated ESR, and pericardial effusion. It occurs several weeks to several months post-MI and is felt to be immunologically mediated. Again, higher-dose aspirin should be used as primary therapy, avoiding steroids and nonsteroidal anti-inflammatory drugs until the patient is at least 1 month post-MI.

Left Ventricular Mural Thrombus

In the current era of reperfusion therapy, left ventricular mural thrombus occurs in approximately 10 % of patients with transmural anterior MI. The risk for subsequent arterial embolization is approximately 10 % and is higher in patients with mobile thrombus detected by echocardiography. Although early echocardiography can detect mural thrombus in many cases, patients with large anterior MI and aneurysm remain at risk for systemic embolization even if no thrombus is initially detected. Contrast-enhanced cardiac MRI appears to have greater sensitivity than echocardiography for the detection of LV thrombus [82]. When LV thrombus is detected, initial anticoagulation with UFH or LMWH followed by warfarin for 3–12 months is recommended by the AHA/ASA [83]; however, since the risk of embolization is mainly within the first 4 months after MI [84], the benefit of continuing anticoagulation beyond 4 months should be weighed against the risk of bleeding, especially in patients treated with concomitant dual-antiplatelet therapy.

Other risk factors for stroke after MI, besides the presence of LV thrombus, include increasing age, nonwhite race, diabetes, hypertension, atrial fibrillation, and prior stroke. Depressed LV systolic function and CHF are also risk factors for stroke, but likely due to increased risk for LV thrombus. In meta-analysis, the incidence of stroke within 1 year after MI is reported to be 21 per 1,000 patients. However, stroke risk is greatest early after MI, during hospitalization; therefore, patients should be closely monitored for the prevention and management of this potential adverse event [85].

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Cardiopulmonary Resuscitation

27

Joseph P. Ornato

Introduction

Out-of-hospital cardiac arrest claims the lives of approximately 382,800 adult Americans each year [1]. The median survival to hospital discharge rate with any first recorded rhythm is 11.4 %. However, since only 60 % of these cases are treated by emergency medical services (EMS) personnel (the remainder are found dead on EMS scene arrival), the overall national survival rate from out-of-hospital cardiac arrest is approximately 6.8 %.

Most episodes of out-of-hospital cardiac arrest in adults occur in the home. The most common victim is a male who is 50–75 years of age. The majority of these victims have underlying structural heart disease, usually in the form of coronary atherosclerosis. Although 75 % of out-of-hospital cardiac arrest victims have significant atherosclerotic narrowing (>75 %) in one or more major coronary artery, fewer than half of all sudden deaths occur *during* an acute myocardial infarction (AMI).

Out-of-hospital cardiac arrest occurring in public places is usually caused by a chance arrhythmic event that is triggered by an interaction between structural heart abnormalities and transient, functional electrophysiological disturbances. In the majority of cases, the initiating event is a ventricular tachyarrhythmia, either pulseless ventricular tachycardia (VT) that degenerates rapidly to ventricular fibrillation (VF) or "primary" VF [2].

The majority of neurologically intact survivors of sudden, unexpected cardiac arrest come from a subset of patients whose event is initiated by a ventricular tachyarrhythmia. In such cases, the single most important determinant of survival is the time interval from initiation of the cardiac arrest until defibrillation can be provided to terminate the ventricular tachyarrhythmia and restore a more normal rhythm accompanied by effective perfusion of vital organs.

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Principles of Resuscitation

The American Heart Association (AHA) uses a "chain of survival" metaphor to represent the sequence of events that ideally should occur to maximize the odds of successful resuscitation from cardiac arrest in adults [3]. The "chain" had four links initially: early access, early cardiopulmonary resuscitation (CPR), early defibrillation, and early advanced cardiac life support (ACLS) [3]. It now has five links: immediate recognition of cardiac arrest and activation of the emergency response system, early CPR with emphasis on chest compressions, early defibrillation, effective advanced life support, and integrated post-cardiac arrest care [4].

The outcome of resuscitation is influenced strongly by the patient's initial cardiac rhythm. The likelihood of survival is relatively high if the initial rhythm is pulseless VT (VT) or ventricular fibrillation (VF). This is particularly true if the VF is "coarse," the arrest is witnessed, and rescuers provide prompt CPR and defibrillation when indicated. The best outcomes from VT/VF in adults occur regularly in the electrophysiology laboratory, where prompt defibrillation (within 20–30 s) results in virtually 100 % survival. The next best reported outcomes are in cardiac rehabilitation programs, where defibrillation occurs in 1–2 min and survival is approximately 85–90 %. At Chicago's O'Hare and Midway airports, 61 % of cardiac arrest patients whose initial rhythm is VF survive to hospital discharge [5]. Survival from out-of-hospital VT/VF treated by police officers equipped with automated external defibrillators (AEDs) in Rochester, MN, averages 50 % with a median time from collapse to defibrillation of about 5 min [6]. Outcomes in many locations with EMS systems that cannot provide defibrillation until 10 min or more after patient collapses typically yield survival rates of <10 %. Thus, survival from cardiac arrest due to ventricular tachyarrhythmias

C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_27,

is highly dependent on the time interval from collapse to defibrillation. For every minute delay from the patient's collapse to defibrillation, the chance for survival diminishes by approximately 7–10 % [3].

If the initial rhythm is not VT or VF, survival is typically <2–3 % in most reported series. Asystolic patients whose cardiac arrest is unwitnessed rarely survive to hospital discharge neurologically intact, even when they are treated promptly. The only common exceptions are witnessed cardiac arrest patients whose initial bradycardia or asystole (bradyasystole) is due to increased vagal tone or other relatively easily correctible factors (e.g., hypoxia of brief duration).

Pulseless electrical activity (PEA) is, by definition, the presence of an organized rhythm unaccompanied by a detectable pulse in an individual who is clinically in cardiac arrest. The latter part of the definition is important for exclusion of conditions in which the rescuer is unable to detect a pulse, but there is unmistakable evidence that there is adequate blood pressure and cardiac output to maintain vital organ perfusion (e.g., a conscious patient with profound vasoconstriction due to hypothermia). The underlying physiological cause of PEA in most cases is a marked reduction in cardiac output that is due to either profound myocardial depression or mechanical factors that reduce venous return or otherwise impede the flow of blood through the cardiovascular system. Management of patients with PEA is directed at providing effective CPR while identifying and treating the underlying cause(s).

There are two fundamental goals in resuscitating an adult from cardiac arrest. First, a rhythm must be restored with a rate that is potentially capable of generating an adequate cardiac output and perfusion pressure. Once an acceptable rhythm has been restored, attention should be focused on restoring and optimizing cardiac output, perfusion pressure, and tissue oxygenation.

CPR

The technique and quality of CPR can affect critical organ perfusion pressure and blood flow dramatically. Maintenance of both the systolic and diastolic arterial pressure is even more vital for optimizing critical organ perfusion during CPR than in non-arrest conditions. Since flow to most vital organs (except the heart) occurs during the downstroke of closed-chest compression (systole), a minimal systolic arterial pressure of 50–60 mmHg is usually required to resist arteriolar collapse. Aortic diastolic pressure is particularly important during CPR because it is a critical determinant of the coronary perfusion pressure (CPP = aortic diastolic pressure – right atrial pressure). CPP is one of the best hemodynamic predictors of return of spontaneous circulation (ROSC) in both animal models and humans. A minimal threshold CPP gradient of approximately 15 mmHg (usually corresponding to an aortic diastolic pressure of 30–40 mmHg) provides enough myocardial blood flow to meet minimum metabolic needs of the arrested myocardium and to achieve ROSC. Uninterrupted, or minimally interrupted, chest compressions is critical for maintaining an optimal CPP and improving ROSC in animal models and humans [7].

Once an unresponsive adult patient is found to be pulseless, healthcare workers should initiate CPR with cycles of 30 chest compressions followed by two ventilations [8]. Chest compressions should be performed at a rate of at least 100/min in adults and with a compression depth of at least 2 in. It is important to allow full recoil of the chest on the upstroke to maximize venous filling and cardiac output [9, 10]. Two ventilations (with just enough pressure to cause chest rise) should be given at the end of each 30 chest compressions. Rescuers must avoid hyperventilation which will cause hypotension by impeding venous return [11, 12].

Understanding the mechanisms of blood flow during closed-chest CPR and real-time monitoring of hemodynamic parameters allows rescuers to modify chest compression techniques (the force of compression and the downstroke/upstroke ratio) when appropriate to optimize perfusion pressure and blood flow. There are at least two major mechanisms of blood flow during closed-chest CPR: the "cardiac pump" and the "thoracic pump."

It was initially believed that blood flow during CPR was caused by direct compression of the heart between the sternum and the spine ("cardiac pump"). In the mid-1970s, the cardiac pump theory began to be challenged by investigators who observed that increased intrathoracic pressure alone (without precordial compression) is capable of generating blood flow. A sudden increase in the intrathoracic pressure causes air trapping in the alveoli and small bronchioles during chest compression, creating a pressure gradient between the intrathoracic and extrathoracic cavities. In the thoracic pump theory, the heart functions as a passive conduit. Pressurization of the thorax collapses veins at the thoracic inlet, preventing venous backflow. Forward flow occurs because more muscular arteries remain open, particularly if a potent vasoconstrictor (e.g., epinephrine or vasopressin) is administered.

Transesophageal echocardiography studies demonstrate that both mechanisms are operative during CPR [13]. Physiological studies in experimental models and humans suggest a strong, probably dominant, role for the thoracic pump during closed-chest compression in adults. In addition, active decompression of the chest by application of negative pressure or suction to the sternum may further enhance cardiac output by improving venous inflow and/or by increasing the intrathoracic pressure difference between the upstroke and downstroke phase of chest compression (active

compression–decompression CPR, also known as ACD-CPR). Unfortunately, ACD-CPR did not improve survival compared to standard CPR in a large, well-controlled, randomized clinical trial [14]. Use of an impedance threshold valve in patients in cardiac arrest increases the efficiency of CPR and when combined with other efficient forms of chest compression, can increase the diastolic arterial pressure to >50 mmHg in animal models [15]. However, this device did not improve survival in a large, placebo-controlled, randomized clinical trial [16].

Chest compression delivers blood and oxygen to the myocardium, allowing a buildup of high-energy phosphates intracellularly and decompressing the right ventricle which is typically volume overloaded from continued venous return. Interrupting chest compressions causes the coronary perfusion pressure and flow to fall precipitously, forcing cells to expend their high-energy phosphate reserves [17]. Even brief (i.e., 10–15 s) pauses or delays in performing chest compressions can decrease the probability of successful defibrillation and return of spontaneous circulation in animal models [18] and humans [19].

Cardiovascular Assessment During Resuscitation

Echocardiography

Conventional transthoracic echocardiography is of value during CPR but is sometimes limited because it is difficult to image the heart when the chest wall is in motion. Transesophageal echocardiography provides high-resolution, real-time images during CPR. Echocardiography can be used to (1) better define the mechanism of blood flow during chest compression; (2) determine the presence of pericardial effusion, intracardiac tumor or clot, chamber enlargement or hypertrophy, severe volume depletion, pneumothorax, or thoracic aortic dissection; (3) better define the cause of PEA; (4) evaluate global and regional wall motion after ROSC; and (5) provide a visual guide for positioning intracardiac catheters and pacemaker wires.

Capnography

The percentage of carbon dioxide (CO_2) contained in the last few milliliters of gas exhaled from the lungs with each breath is termed the end-tidal carbon dioxide concentration ($P_{et}CO_2$). During normal respiration and circulation, the $P_{et}CO_2$ averages 4–5 %. Two units of measure are popularly used in reporting the $P_{et}CO_2$: percentage and mmHg (1 % equals 7.6 mmHg). The $P_{et}CO_2$ can be used to confirm endotracheal (ET) tube airway placement, particularly in the noncardiac arrest patient who has a pulse and an adequate blood pressure (where the sensitivity and specificity of the $P_{et}CO_2$ for detecting correct ET tube placement approach 100 and 90 %, respectively) [20]. Ventilation through an ET tube that has been properly inserted in the trachea yields a $P_{et}CO_2$ of 4–5 % in a patient with a normal cardiac output and no significant ventilation–perfusion gradient. Ventilation through an ET tube that has been inadvertently inserted into the esophagus results in a $P_{et}CO_2$ of <0.5 % [21].

There is a logarithmic relationship between the $P_{et}CO_2$ and the cardiac output [22]. At normal or elevated levels of cardiac output, ventilation is the rate-limiting factor responsible for eliminating the large amount of CO_2 passing through the pulmonary circuit (e.g., hyperventilation lowers, and hypoventilation raises, the $P_{et}CO_2$). In this range, the $P_{et}CO_2$ closely approximates arterial CO_2 tension (P_aCO_2) and can be used as a "real-time" guide to the adequacy of ventilation. At low levels of cardiac output (below approximately 50 % of normal in animal models), ventilation has much less effect on the $P_{et}CO_2$. If ventilation is kept relatively constant in this range, an increase or a decrease in the cardiac output will usually be reflected by a rise or fall in the $P_{et}CO_2$, respectively. During CPR, the $P_{et}CO_2$ is typically between one-quarter and one-third of the normal, paralleling the low cardiac output and pulmonary blood flow [23–25]. As CO_2 builds up in venous blood, hyperventilation cleanses the reduced quantity of venous blood traversing the lungs of CO_2, resulting in a low arterial (P_aCO_2) and a high central venous ($P_{cv}CO_2$) CO_2 concentration (a venoarterial CO_2 and pH gradient). Within seconds following ROSC, the improved cardiac output delivers large quantities of CO_2-rich venous blood to the lungs, and the $P^*_{et}CO_2$ climbs suddenly to normal or above-normal levels [23–25]. The dramatic change from a low to a high $P_{et}CO_2$ due to venous CO_2 washout is often the first clinical indicator that ROSC has occurred.

Monitoring the $P_{et}CO_2$ during CPR can be used as a guide to the patient's hemodynamic status. Inadequate chest compression is usually accompanied by a very low (i.e., <1 %) $P_{et}CO_2$ that increases linearly with increasing sternal compression depth and force [26]. Administration of sodium bicarbonate intravenously causes a transient rise in $P_{et}CO_2$ as the substance dissociates into water and CO_2. Vasoconstrictors (e.g., epinephrine, vasopressin) will cause a decrease in $P_{et}CO_2$ as systemic vascular resistance increases and total cardiac output declines [27]. Disorders that cause significant ventilation–perfusion mismatch (e.g., pulmonary embolization) or decrease in production of CO_2 (e.g., hypothermia) are accompanied by a low $P_{et}CO_2$. The initial $P_{et}CO_2$ also has prognostic value. A $P_{et}CO_2$ level ≤10 mmHg (i.e., approximately 1.5 %) measured 20 min after the initiation of ACLS accurately predicts death in patients with cardiac arrest associated with electrical activity but no pulse [28]. Common causes of a low $P_{et}CO_2$ level during resuscitation are listed in Table 27.1.

Table 27.1 Common causes of a low (i.e., <2 %) $P_{et}CO_2$ level during resuscitation

Inadequate ventilation
Unrecognized esophageal intubation
Airway obstruction
Inadequate blood flow
Inadequate chest compression
Hypovolemia
Tension pneumothorax
Pericardial tamponade
Ventilation-perfusion mismatch
Pulmonary embolism
Decreased metabolism
Hypothermia

There are two methods to measure $P_{et}CO_2$ during resuscitation: colorimetric and waveform. The former provides a relatively inexpensive way to estimate the $P_{et}CO_2$ value and is adequate for determining ET tube location in patients who have a reasonably normal cardiac output and blood pressure. However, it is inaccurate for this purpose in patients who are in shock or receiving CPR because it cannot distinguish a low value due to poor blood flow vs. esophageal ET placement [20]. Waveform capnography, which does not have this limitation, is highly accurate in confirming ET location if there is a clear capnographic waveform (regardless of the $P_{et}CO_2$ value). It also provides a good indication of blood flow during low flow states such as CPR. For example, poor-quality chest compressions will usually show a waveform, but the $P_{et}CO_2$ value will be low (i.e., 1–2 % or less). The $P_{et}CO_2$ value will increase as blood flow improves (i.e., by pushing more forcefully on the chest).

The 2010 American Heart Association Advanced Cardiac Life Support Guidelines assign a level 1 recommendation to the use of waveform capnography to confirm ET placement during resuscitation [29]. An alternative to the measurement of $P_{et}CO_2$ for confirmation of airway placement is the use of an aspiration syringe or bulb device. Such devices are attached to the ET tube immediately after it is inserted. Suction is applied to the ET tube using an aspiration syringe or bulb. If the tip of the ET tube is in the trachea, air is aspirated readily since the cartilage-containing trachea does not collapse. If the tip of the ET tube is in the esophagus, application of suction causes the esophagus to collapse. In such a case, there is resistance to the flow of air during aspiration.

Advanced Airway Management

One of the traditional goals in resuscitation has been to establish a definitive airway that will allow delivery of oxygen and protect the airway from aspiration. In addition, certain medications (i.e., epinephrine, lidocaine, vasopressin) can be administered via the ET tube if an intravenous or intraosseous line cannot be inserted. As a rule of thumb, 2 to 2 1/2 times the standard IV dose should be administered via the ET route because of erratic absorption [29].

A higher initial priority should be placed on providing high-quality chest compressions rather than early intubation, with initial ventilation provided by a bag valve mask or other alternative device [29]. Alternative airway devices such as the laryngeal mask airway (LMA), Combitube, or King airway have become highly popular alternatives to ET insertion because they are easy to use and can be inserted blindly by minimally trained rescuers (e.g., nurses, paramedics) without the need for a laryngoscope.

Use of Vasopressors and Inotropic Agents

Epinephrine

Epinephrine is the vasopressor of choice for use during CPR [29]. It improves coronary and cerebral blood flow by increasing peripheral vasoconstriction. By enhancing coronary perfusion pressure, epinephrine facilitates the resynthesis of high-energy phosphates in myocardial mitochondria and enhances cellular viability and contractile force.

The AHA currently recommends epinephrine in a dosage of 1 mg by the IV or intraosseous route every 3–5 min during CPR in adults. The use of higher doses of epinephrine is not recommended. If the dose is given by peripheral injection, it should be followed by a 20-mL flush of IV fluid to ensure drug delivery into the central compartment.

Vasopressin

Vasopressin produces significantly higher coronary perfusion pressure and myocardial blood flow than epinephrine during closed-chest CPR in animal models [30]. Both vasopressin and adrenocorticotropin concentrations are higher during CPR in patients in whom resuscitation is successful compared to those in whom it fails [31]. Survival from cardiac arrest in adults is similar with the use of epinephrine, vasopressin, or a combination/alternation of the two [32–34]. The AHA currently allows the use of vasopressin in a dose of 40 units in place of the first two doses of epinephrine at the discretion of the code team leader. The duration of action of each dose of vasopressin is approximately 10–20 min during resuscitation.

Dobutamine

Dobutamine may be the ideal agent to use after ROSC, particularly if congestive heart failure rather than hypotension is

present. In animal models, dobutamine that is initiated within 15 min of successful resuscitation can successfully overcome the global systolic and diastolic left ventricular dysfunction resulting from prolonged cardiac arrest and CPR [30]. At present, the AHA recommends giving 2.0–20 mcg/kg/min of dobutamine (500 mg mixed in 250 mL of D5W or normal saline), using the smallest effective dose needed to improve hemodynamics. The maximum dose is 40 mcg/kg/min.

Acid–Base Management

The marked fall in cardiac output during CPR reduces tissue oxygen delivery to critically low levels. Cells shift to anaerobic metabolism, causing a gradual building up of lactic acid. The PCO_2 level begins to increase inside cells, including heart muscle cells in which the concentration of CO_2 may reach very high levels (>400 mmHg), at which point PEA develops [35].

There is a dynamic equilibrium between intracellular CO_2 and the blood traversing each capillary bed in the body. As CO_2 diffuses into capillary blood in exchange for oxygen, the CO_2 is transported to the heart and lungs in venous blood. Because of this, central (mixed) venous blood during closed-chest compression is acidotic (pH approximately 7.15) and hypercarbic (P_vCO_2 approximately 74 mmHg). CO_2 is removed from the lungs during ventilation. During well-performed closed-chest compression, arterial blood pH is usually normal, slightly acidotic, or mildly alkalotic. Early in resuscitation, arterial blood can be slightly alkalotic while the venous blood is acidotic. Severe arterial acidosis early during closed-chest compression is usually due to inadequate ventilation or other forms of acidosis (e.g., lactic acidosis). The best solution is to improve the technique of closed-chest compression.

In the past, administration of sodium bicarbonate was recommended for use early during closed-chest compression because of the belief that bicarbonate would buffer the H^+ ion produced during anaerobic metabolism. However, sodium bicarbonate itself contains a large amount of CO_2 (260–280 mmHg). In plasma, the CO_2 is released and diffuses into cells more rapidly than HCO_3^-, causing a paradoxical rise in intracellular PCO_2 and a fall in intracellular pH. The increases in intracellular PCO_2 in heart muscle cells decrease cardiac contractility, cardiac output, and blood pressure. Sodium bicarbonate causes other potentially harmful effects, including paradoxical acidosis of cerebrospinal fluid, hyperosmolality, alkalemia, and sodium overload.

At present, there are no convincing data indicating that treatment with sodium bicarbonate is of benefit during closed-chest compression and it does not improve survival in experimental animals. The AHA no longer recommends routine administration of sodium bicarbonate during resuscitation because it provides minimal, if any, benefit and adds significant risk.

There are a small number of "special situations" in which sodium bicarbonate is indicated for use and, in some cases, repeatedly during resuscitation [29]. Such circumstances include severe hyperkalemia, known severe metabolic acidosis, and certain toxicological conditions (e.g., tricyclic antidepressant or barbiturate overdose). Alternate buffer agents do not improve survival during cardiac resuscitation [36].

Management of Ventricular Tachyarrhythmias

Prompt electrical countershock is the treatment for VF and pulseless VT [29]. The energy setting for biphasic defibrillation should follow the manufacturer's recommendation for that specific device (generally in the range of 120–200 J). If unsure, use the highest energy setting available (usually 200 J). Subsequent shocks, if needed, should be at the same energy level or higher (if available) at the discretion of the rescuer. A setting of 360 J should be used for monophasic defibrillation. If VF or pulseless VT persists after 1 shock and approximately 2 min of CPR, a vasopressor should be given to increase coronary and cerebral perfusion.

Amiodarone (300 mg IV or IO initially followed by subsequent 150 mg doses) is first-line therapy for patients with recurrent or refractory VF or pulseless VT because it has been shown to improve short-term survival compared to traditional ACLS treatment including lidocaine [37, 38]. Lidocaine (1–1.5 mg/kg IV or IO, followed by 0.5–75 mg/kg every 5–10 min for up to a total dose of 3 mg/kg) may be considered if amiodarone is unavailable [29]. Magnesium sulfate (1–2 g diluted in 10 mL of D5W and given slowly IV) is only indicated if torsade de pointes is present, since clinical studies have shown that it is of no benefit in treating VF or pulseless VT [39, 40].

Management of Bradyasystolic Cardiac Arrest

Survival is poor regardless of therapy for cardiac arrest patients who present with bradyasystole. It is always important to exclude disconnection of a lead or monitor electrode prior to concluding that a "flat line" is the patient's rhythm, as some patients with such a tracing may have VF (a rhythm more amenable to treatment) masquerading as asystole. Whenever there is any doubt, the monitor lead should be switched quickly to another lead to confirm the diagnosis prior to treatment.

Treatment with atropine sulfate and electrical pacing are no longer recommended for patients in bradyasystolic cardiac arrest since no clinical trials have shown a survival benefit from these approaches. Rescuers should focus on

providing minimally interrupted, high-quality CPR, administering vasopressors to maintain coronary and cerebral perfusion pressure, and correcting treatable causes of the cardiac arrest.

Management of Pulseless Electrical Activity

PEA is present when there is organized electrical activity on the electrocardiogram but no effective circulation, as manifest by a lack of a detectable pulse. There are many underlying potential causes, but the most common denominator may involve myocardial ischemia and dysfunction due to intramyocardial increases in CO_2. Prognosis is generally poor unless a discrete and treatable etiology for PEA can be discerned and corrected. Efforts should be directed toward correcting treatable causes (e.g., hypovolemia, hypoxemia, acidosis, tension pneumothorax, and pericardial tamponade) of this condition, providing high-quality, minimally interrupted CPR, and administering vasoconstrictors to maximize coronary and cerebral perfusion.

Post-resuscitation Care

The AHA has recently issued a Policy Statement [41] calling for the establishment of regional systems of post-resuscitation care to manage cardiac arrest patients with a "care bundle" (Table 27.2). The Statement defines two levels of cardiac resuscitation centers: level 1 for regionalized centers that can provide the entire continuum of care for these patients and level 2 for all other hospitals that can initiate therapeutic hypothermia (when indicated) and refer appropriate patients promptly to the level 1 regional center. The current AHA Guidelines on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care site a level 1 recommendation for treating resuscitated cardiac arrest patients with evidence of STEMI on their electrocardiogram just as any other STEMI patient, including timely cardiac catheterization and PCI when indicated, regardless of the patient's initial neurological status [29]. Thus, hospitals that serve as primary PCI centers for treating STEMI patients are ideally suited to serve as level 1 centers.

There is strong scientific evidence, including placebo-controlled randomized clinical trials, supporting the use of therapeutic hypothermia (32–32 °C for 18–24 h duration) in patients who remain comatose (i.e., unable to follow verbal commands) following out-of-hospital cardiac arrest, particularly those whose initial arrest rhythm is ventricular fibrillation [42, 43]. There is less published evidence to support its use in patients with inhospital arrest and/or those whose initial cardiac arrest rhythm is not ventricular fibrillation, although many of these patients are being treated based on clinician judgment while awaiting further data. Common indications and contraindications for use of therapeutic hypothermia in adults post-cardiac arrest are listed in Table 27.3.

Table 27.2 Post-resuscitation care bundle

Therapeutic hypothermia
Cardiac catheterization/percutaneous coronary angiography for ST-elevation MI
Goal directed management of:
Hemodynamics
Oxygenation/ventilation
Glucose
Metabolics (i.e., electrolytes, renal function)
Electroencephalographic monitoring (preferably with continuous EEGs)

Table 27.3 Common indications and relative contraindications for use of therapeutic hypothermia in adults post-cardiac arrest

Indications
Comatose (i.e., unable to follow verbal commands) post-cardiac arrest
Initial cardiac arrest rhythm of ventricular fibrillation
Initial cardiac arrest rhythm of asystole or PEA if witnessed and prompt CPR < 45 min total duration of resuscitation prior to sustained return of spontaneous circulation (ROSC)
Contraindications
Terminal illness
Do not attempt resuscitate order
Uncontrolled major bleeding
Sepsis

Frequent, preferably continuous, recordings of the patient's electroencephalogram (EEG) should be made during post-resuscitation care (level 1 AHA guideline recommendation) since almost a third of these patients will experience seizure activity which may not be recognized otherwise if the patient is receiving paralytic drugs [29]. Finally, since drug metabolism (including sedatives and paralytics which are often used to manage these patients while they are on a ventilator) is reduced markedly due to therapeutic hypothermia, the resuscitation team should wait at least 72 h after normothermia is established to make a decision whether to terminate further aggressive care to allow sufficient time for the effects of any administered drugs to wear off.

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Cardiac Rehabilitation and Secondary Prevention After Acute MI

28

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Introduction

Exercise-based cardiac rehabilitation programs were initially designed primarily to counteract the debilitating effects of prolonged bed rest therapy for patients with an acute MI. They have since progressively evolved into multifaceted secondary prevention programs and are currently part of the recommended standard of care for cardiac patients. This chapter is designed to provide health-care professionals a brief history of this evolutionary process and the supporting scientific evidence of the importance of exercise-based cardiac rehabilitation/secondary prevention programs (CRSPP) and to outline guidelines for their component and staffing requirements.

Historical Prospective

An acute MI, secondary to a coronary thrombosis, was initially recognized as a clinical entity during the second decade of the twentieth century [1]. Shortly thereafter, pathologists determined that at least 6 weeks of healing was required before the involved necrotic area of myocardium was significantly strengthened by deposition of firm scar tissue. This observation caused concern among clinicians that any physical exertion during the healing process might result in the development of a ventricular aneurism or trigger myocardial rupture or a fatal cardiac arrhythmia. Thus, for over the following four decades, such concerns resulted in the mainstay of therapy, for even an uncomplicated MI, being prolonged hospitalization with absolute bed rest for 6–8 weeks. Further, following hospitalization, patients were generally restricted from moderate-intensity activities, such as stair climbing, and from resuming occupational or vigorous recreational physical exertion for at least a year.

The necessity for absolute bed rest with restrictions on all physical activity following an acute MI was challenged beginning in the 1940s by the demonstration of the safety of chair rest even if initiated only a few days after the coronary event [2]. Further, physiological studies revealed that myocardial oxygen requirements of someone in a sitting position were actually lower than in the supine position, as was using a bedside commode as compared to a bed pan. In addition, this so-called "armchair treatment" was subsequently observed to reduce peripheral venous pooling and an associated increased risk of lower extremity thrombophlebitis [2].

However, it was not until the 1960s and early 1970s that prolonged immobilization was finally abandoned and early ambulation was generally prescribed following an acute MI. The principal convincing scientific evidence, which promoted this change, was the demonstration of the detrimental physiologic effects of prolonged bed rest even in healthy young men [3–5]. These adverse effects included a marked reduction in cardiorespiratory endurance, as assessed by maximal oxygen uptake ($\dot{V}O_2$ max) during exercise testing; a decrease in circulating blood volume, especially in its plasma component (thereby increasing blood viscosity and risk of thrombophlebitis); sinus tachycardia; orthostatic hypotension; reduced skeletal muscle mass and strength; and a small decline in pulmonary ventilation. Based on these findings, it became quite evident that many of the patients' usual symptoms, clinical findings, and comorbidities following prolonged bed rest were actually caused by the therapy, rather than the underlying cardiac disease process.

In addition, pilot nonrandomized clinical trials in the 1960s and early 1970s demonstrated the safety and favorable outcomes of early ambulation and supervised, progressive, low-intensity physical activity, such as provided by Wenger's 14-step programs for patients with uncomplicated MIs [6]. The average length of hospitalization also was reduced by this approach from 6–8 weeks to 14 days or less, during which time a core educational program and risk factor

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_28,

interventions were initiated and a low-intensity (3–5 METs[1]) exercise stress test was often performed prior to the patient's discharge. Medically directed, supervised, predominantly exercise-based, rehabilitation programs also were introduced during the early posthospital period in various settings, including hospital outpatient fitness facilities, community centers, and university recreational centers [7]. In the 1970s and 1980s, a number of randomized trials of such programs were performed in the United States and Europe. In these controlled trials, post-MI patients were randomly assigned to supervised outpatient exercise programs, generally alone or along with risk factor interventions, or to a usual care group. Meta-analysis of these studies confirmed the safety and the functional and psychosocial benefits of cardiac rehabilitation, as well as reduced cardiovascular disease (CVD) mortality [8, 9].

Contemporary Status and Objectives

Currently in order to be officially recognized and certified as a cardiac rehabilitation program, eligible for coverage by third-party health insurance providers, programs are required to provide, in addition to supervised exercise training, other long-term comprehensive services targeted at reducing risk of future CVD events. Broad objectives of such contemporary programs are as follows [10–12]:

- Limit the physiologic and psychological impact of the underlying disease process
- Help control associated clinical symptoms
- Stabilize or partially reverse the underlying atherosclerotic process
- Reduce risk of subsequent CVD clinical events and enhance survival
- Improve the patient's psychosocial and vocational status and quality of life

Potential Candidates for Services

Potential candidates for CRSPP are from among the about 1.1 million survivors per year of an acute MI, more than seven million patients with stable angina pectoris, over 700,000 patients a year following revascularization via percutaneous coronary interventions or coronary artery graft surgery, about five million patients with compensated chronic heart failure (CHF), eight to ten million patients with peripheral artery disease (PAD), and patients following corrective cardiac valvular and congenital heart disease surgical procedures and cardiac transplantation [13]. Unfortunately, despite the proven benefits and recognition as a standard of care for patients with CHD, only a small percentage of eligible patients participate in CRSPP, e.g., only 14–31 % per year of patient's post-MI [14]. Reasons for nonparticipation include the following:

- Failure of a required physician's referral, a necessary initial step for enrollment. Such a referral is currently endorsed as a measure of satisfactory performance of health-care delivery.
- Limited public awareness of such programs and their potential benefits.
- Lack of patient self-efficacy (i.e., confidence in their ability to safely exercise) or unwillingness to exercise and/or a dislike of exercising.
- Poor ecologic accessibility of programs.
- Inadequate third-party health insurer's reimbursement for such services (only a limited number of sessions are covered).

Underutilization of CRSPP is considerably higher in women, older individuals, ethnic minorities, and economically disadvantaged population subgroups, despite the evidence of beneficial effects being similar across demographic groups.

Supporting Evidence of Benefits

Scientifically documented beneficial effects of the exercise training component of cardiac rehabilitation programs include the following [15–19]:

- A reduction in cardiac mortality and in all-cause mortality.
- Improved cardiorespiratory endurance, as evidenced by an 11–36 % increase in peak $\dot{V}O_2$ during an exercise test with the greatest improvement in the most deconditioned individuals. This is clearly the best established favorable outcome of the exercise component of CRSPP, not only for CHD patients but also for those with compensated CHF and following revascularization procedures and cardiac transplantation. Enhanced physical fitness not only improves survival but enhances the quality of life and the ability of older individuals to live longer independently.
- A reduction in recurrent nonfatal clinical CVD events and requirements for cardiac interventional procedures for patients with CHD.

The most recent meta-analysis of the secondary morbidity and mortality preventive effects of rehabilitative programs by Clark et al. [19] involved 63 randomized trials in which 21,295 CHD patients were enrolled. Both structured exercise alone or in combination with risk factor modifications resulted in 26–28 % in all-cause mortality and a 24–38 % reduction in recurrent MI at the 12-month follow-ups.

Furthermore, research has demonstrated multiple plausible biologic mechanisms for these apparent cardioprotective

[1] 1 MET = the energy expenditure at rest or about 3.5 ml of 0_2 per minute.

effects of exercise training and improved physical fitness [20–22]. These mechanisms have been classified as antiatherosclerotic (reducing disease progression or resulting partial regression), anti-ischemic (via decreasing myocardial oxygen demands and increasing coronary blood flow), antithrombotic (reducing clot formation and increasing fibrinolysis), and antiarrhythmic (improving myocardial electrical stability) [22].

Phases of CRSPP

The continuum of care of the acute MI patient undergoing rehabilitation is currently divided into four phases [10] as follows:

1. The inpatient phase (previously phase I). Currently the average length of stay for an uncomplicated MI is 3–4 days. In addition to progressive ambulation and low-intensity physical activity, prior to hospital discharge, patients generally receive instruction regarding their medications and education about disease symptoms and signs.
2. Transitional care. Patients with more complicated conditions may be referred to a transitional care facility, a home recovery program with a visiting nurse for follow-up assessments and care (generally covered by Medicare and other medical coverage plans), and/or early follow-up outpatient visits with the patient's cardiologist or primary care provider for initiation or adjustment of medications and additional cardiac assessments. It should be noted that current guidelines call for aggressive lifestyle and pharmacologic risk factor interventions, as well as the routine administration, unless there are contraindications, of several drugs proven in randomized trials to be cardioprotective for CHD patients against secondary CVD events [21]. These prophylactic cardioprotective drugs include antiplatelet drugs, a beta (β)-adrenergic receptor blocker, an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARP), and a statin. Also during this phase, the patient should be stratified for relative risk of recurrent CVD events in the hospital by testing for exercise or pharmacologic-induced myocardial ischemia and dysrhythmias and for left ventricular function.
3. Early outpatient phase (previously phase II). In patients with an uncomplicated MI, this may be initiated as early as 1–2 weeks postevent, generally in a hospital outpatient fitness facility. This phase of cardiac rehabilitation usually is 6–8 weeks duration and is generally at least partially covered by third-party health insurance providers.
4. Maintenance and follow-up (formerly phase III and IV). This generally begins within 2–3 months following a cardiac event and the completion of the early outpatient phase of rehabilitation and may be continued to be provided in a hospital's outpatient facility or in a community center, a university recreational facility, a commercial health/fitness center, or at home (with or without transphone electrocardiographic monitoring of the exercises), under the direction of rehabilitation staff with regular follow-up assessments.

Core Components

The American Heart Association (AHA), the American College of Cardiology Foundation (ACCF), and the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) have published recommended multifaceted components for CRSPP along with specific evidence-based recommended outcomes [10–12].These are briefly summarized in Table 28.1. It should be noted that these services should be individualized for each patient and carried out in consultation or collaboration with the patient's cardiologist or primary care physician.

Recommendations for promotion of physical activity and for the core exercise training components are covered separately in more detail.

Physical Activity (PA) and Prescriptive Exercise

PA Counseling

Prior to discharge from the hospital, the cardiac patient needs individualized counseling regarding performance of activities of daily living and recreation at home during the convalescent period. A low-intensity (≤5 MET) ECG-monitored graded exercise test is a useful assessment tool for providing this advice. Further, if climbing a flight of stairs is required at home, the patient's capability for performing this activity should be assessed prior to hospital discharge. Other PA-related topics generally covered prior to discharge include recommendations to avoid isometric exertion and high-intensity/"burst" activities, travel restrictions, and capability for sexual activity. The latter topic should be dealt with directly and openly since patients are generally reluctant to initiate these discussions [38, 39]. Research has shown that sexual activity in middle-aged, post-MI patients results in heart rates ranging from 90 to 144 beats/min (with an average of 117 beats/min). Generally, in terms of myocardial oxygen requirements, it is equivalent to climbing one flight of stairs; thus, it should be well within the capacity of most asymptomatic convalescing post-MI patients. Similarly, personal self-care and light household activities are appropriate for those who progressed well during the inhospital and early posthospitalization physical activity (PA) program.

Table 28.1 AHA/ACCF/AACVPR Recommended "core" components and risk-reduction goals

Component/goal	Recommendation
1. Baseline assessments Goal: risk stratification and development of individualized strategies and goals	Detailed history and physical examination 12-lead ECG and assessments for left ventricular function (LVF) and to detect myocardial ischemia and arrhythmias
2. Monitor compliance with drugs to control CVD risk factors and those proven by randomized trials to protect against secondary events	1. ACE inhibitor or an ARB is recommended for all patients, especially for those with LV ejection <40 %, hypertension, chronic renal disease, or diabetes [11] 2. β-blocker. Metoprolol succinate, carvedilol, or bisoprolol preferred, in all patients with a MI, LV dysfunction, or CHF [11] 3. Antiplatelet agents. Aspirin is recommended for all patients with CHD with clopidogrel for those intolerant to aspirin or in combination with aspirin [11] 4. Statins. Intense therapy reduces risk of recurrent CVD events and mortality not only in patients with an acute MI by lowering elevated low-density lipoprotein cholesterol (LD-C) levels but even in those with low LDL-C probably related to pleiotropic additional benefits [23–26]; this includes stabilization of plaques vulnerable to disruption [26]
3. Patient (and family) education	Hospital or community health classes and video and Internet programs regarding CHD pathophysiology and clinical symptoms, the need for risk factor modification, CPR training, etc.
4. Nutritional assessment and counseling Goal: heart-healthy lifetime eating patterns reducing recurrent CVD events	Individualized assessment and lifetime eating habit modifications to help maintain or control elevated BP, improve blood lipids, reduce excess body weight, and manage diabetes and other comorbidities [27]
5. Weight management Goal: body mass index/18.5–24.9 kg/m^2, waist circumference (WC) – women < 35 in. (<89 cm), men < 40 in. (<102 cm)	Body weight and WC assessment recommended at each visit. Weight management consistently encouraged through reducing caloric intake, increasing lifestyle PA, and behavior modification. The initial goal is for a 5–10 % weight reduction from baseline level; if successful, further weight loss can be attempted if indicated [28]
6. Cessation of smoking and other tobacco products Goal: complete cessation and avoidance of exposure to environmental tobacco smoke	Tobacco use should be assessed at each visit (including chewing tobacco, a contributor to nicotine addiction). Every user should be advised to quit with a message that the risk of smoking-related deaths is high and is associated with a substantial loss of quality and length of life, while quitting substantially reduces these risks [29]. Willingness to quit should be assessed at each visit. For those smokers motivated to make a serious attempt at quitting, a quit date should be set and a plan developed for quitting. This includes pharmacotherapy and /or referral to a smoking-cessation program. Arrangements for follow-up of smoking status and maintenance of quitting are recommended at each visit
7. Blood pressure (BP) management Goal [30]: Short term – < 140/90 mm Hg Long term – < 130/85 mm Hg	Baseline BP measurements in the resting and standing position should be performed at repeated visits to establish baseline and at each follow-up visit. Lifestyle modification should be encouraged for all patients to include weight control; increased daily PA; smoking cessation; reduced sodium and alcohol; and dietary emphasis on whole grains, fruits, vegetables, and low-fat or fat-free dairy products, such as provided by the Dietary Approach to Stop Hypertension (DASH) eating plan [31]. Patients with persistent BP > 140/90 mm Hg should also receive additional antihypertensive drug therapy if BP is still elevated despite a β-blocker and ACE inhibitor or ARB therapy prescribed for secondary prevention, in concert with the patient's primary care provider

8. Lipid/dyslipidemia management Primary goal [32]:LDL-C <100 mg/dl Therapeutic option supported by clinical trial [33]:LDL-C <70 mg/dl Secondary goal (after LDL-C target achieved and triglycerides (G) are 200–500 mg/dl):non-high-density lipoprotein cholesterol (non-HDL-C) <130 mg/dl [32]	A blood lipid battery should be assessed in the fasting state at least twice at baseline and following initiation of therapy. Lifestyle modifications have been proven to favorably impact abnormal blood levels of all major lipids and their lipoprotein carriers [31–34]. Eating habits should be modified to reduce saturated fat to <7 % of total calories, trans fats to <1 % of total calories, and dietary cholesterol to ≤200 mg/dl. Statin dose should be titrated in the absence of adverse effects to upper recommended dosage level for the specific prescribed statin presented to achieve LDL-C goal. If the goal is still not achieved, the addition of a second cholesterol-lowering drug, such as ezetimibe, should be considered in consultation with the patient's primary care provider. Patients with TG levels ≥500 mg/dl should be prescribed a fibrate to reduce risk of acute pancreatitis. For those with TG levels ≥150 mg/dl, achieving the non-HDL-C target with fibrate, or niacin, has been shown by meta-analysis to reduce CHD risk [35]. HDL-C <40 mg/dl in men and <50 mg/dl in women is considered a major risk factor for CVD and can be favorably increased by lifestyle modifications [34]. A meta-analysis of 18 placebo-controlled trials involving >45,000 participants reported a significant reduction in relative risk of major CVD events associated with an increase in HDL-C [36]. However, there is as yet no randomized trial evidence that raising HDL-C after achieving the LDL-L goal is effective in secondary prevention of CHD. A recent major randomized trial (AIM-HIGH) sustained-release niacin was added to statin in patients with CHD who had reached their goal LDL-C levels but still had reduced HDL levels [37]. The study was prematurely discontinued after three years, because there was no reduction in CVD clinical events despite a significant increase in HDL-C, as well as safety issues. Thus, physicians have a dilemma pertaining to targeting reduced HDL-C despite lifestyle and statin therapy
9. Diabetes management [11] Goal: HbA1c <7 mmol/dl and ideally a fasting plasma glucose >115 mg/dl	For patients with known diabetes, dietary and medication regimes, frequency of glucose monitoring, and history of hypoglycemic events should be determined at baseline. Baseline fasting glucose and HbAIc levels and glucose levels before and after exercise should be obtained. Exercise training should be temporarily prohibited if blood glucose is <100 mg/dl or >300 mg/dl. The patient's dietary regimen and oral hypoglycemic agent and/or insulin therapy for diabetes management should be monitored in concert with the patient's primary care provider.
10. Psychosocial management [11] Goal: reduction of anxiety and depression and provide social support. Improved emotional well-being and stress management skills	Commonly present psychological problems in CHD patients, such as chronic anxiety and mental depression, should be identified by interview and/or standardized assessment instruments. Either individual and small-group counseling sessions should be provided or the patient should be referred to appropriate mental health specialists, particularly for those experiencing clinically significant psychological problems, for counseling and possible psychotropic medication

Another PA which should be encouraged, as part of patient's lifestyle promotion plan, is walking more. This activity can be progressively increased in duration and rate on an individually tolerated basis. A desirable optimal goal should be 30–60 min of walking at least 5 days per week (i.e., 150 min/week). This activity can be performed in increments as little as 10 min at a time. This volume of walking and/or other moderate-intensity recreational activities, such as working around the house and yard, has been repeatedly demonstrated in longitudinal observational studies to reduce risk of initial CVD events [40, 41]. In addition, the patient should be encouraged to progressively replace prolonged sedentary/sitting activities, such as TV watching and operating a computer, with standing, walking, and gradually more active moderate-intensity recreational pursuits. This recommendation is based on recent observational studies which report that prolonged sedentary/sitting behavior appears to be a risk factor for CVD and all-cause mortality, apparently independent of one's PA and exercise status [42, 43].

Exercise Training

The exercise training component has always been the cornerstone and most visible part of the outpatient CRSPP. As previously mentioned, in addition to its role in improving physical fitness, it significantly contributes to reduced morbidity and mortality and improved quality of life of cardiac patients. Prior to the initiation of a prescriptive, supervised exercise program, the patient should have a symptom-limited, graded exercise test and undergo risk stratification to establish an appropriate exercise prescription and the required level of supervision when initiating an exercise program. This is because the risk of recurrence of serious CHD events while exercising is greatest in patients with ECG-demonstrated symptomatic or nonsymptomatic myocardial ischemia, poor left ventricular function, and/or ventricular rhythm disturbances. Special attention should also be provided to those patients with a prior non-Q-wave/non-ST-wave elevation myocardial infarction (non-STEM I). A number of validated algorithms are available based on the above-mentioned data for stratification of post-MI patient (low, intermediate, or high) categories of related risk for future CVD events and relative risk during exercise (10, p. 61). Decisions on the need for further cardiac assessments and interventions, intensity of medical supervision, and continuous or intermittent ECG monitoring during exercise and the exercise prescription are based on the results of risk by anatomic and functional testing. The purposes of ECG monitoring during exercise training include:

- To detect myocardial ischemia and serious dysrhythmias
- To monitor compliance with the prescribed heart rate
- To increase the patient's self-confidence for exercise safely

Aerobic Exercise Training. The individualized aerobic/cardiorespiratory endurance exercise prescription includes the mode, frequency, and intensity. Both lower extremity and upper extremity dynamic exercise should be included in the program. Examples of commonly employed lower extremity exercises used in CRSPP are walking on a track or treadmill, operating a cycle ergometer, and less commonly supervised water activities. Jogging is generally not recommended in the initial phase of an early outpatient program, because its metabolic requirements are generally too high, but it may be subsequently added. Upper extremity dynamic exercise can be performed using an arm cycle ergometer, rowing machine, or commercially available cycle ergometers that combine upper and lower extremity exercise. The usual prescribed frequency of aerobic exercise sessions is 3–5 per week [44]; to achieve improvement in cardiorespiratory endurance, the intensity of exercise should be maintained between 40 and 85 % of $\dot{V}O_2$ max, which generally corresponds to about 50 and 70 % of maximal heart rate. The most commonly used method in CRSPP to determine the training heart rate (THR) is referred to as the heart rate reserve (HRR) method. The HRR is the standing heart rate at rest minus the peak HR (PHR) attained during a symptom-limited exercise test. The HRR is then multiplied by the desired percentage of functional capacity at which you desire the patient to exercise, and this value is added to the RHR. For example, if the patient's resting HR is 60 bpm and his/her PHR is 160 bpm, the HRR is 100. At an initial exercise intensity of 50 % $\dot{V}O_2$ max, the THR is $0.5 \times 100 + 60$ (RHR) or 110 bpm. The prescriptive THR for upper extremity training can be determined directly from the maximal HR achieved during an ergometer training, using a similar approach as for lower extremity exercise, or it can be estimated from the PHR obtained from the treadmill or exercise ergometer test. For cardiac patients on a recommended β-blocker, which minimizes the HR response to exercise, the Borg rating of perceived exertion (RPE) is generally used instead of THR for exercise prescription [10, p. 80, 45]. Using the original Borg 6 to 20 RPE scale, the recommended initial prescribed exercise intensity is associated with an RPE of 11 to 13 ("fairly light to somewhat hard") and gradually progressed up to 15–16 ("hard").

An AHA scientific statement on the benefits of aerobic exercise training for the patients with CHF, along with specific exercise recommendations, has been published [46]. Exercise also has been referred to as the "cornerstone of PAD treatment" for patients with claudication [47].

Resistance Training. During the past two decades, there has been a proliferation of studies demonstrating the safety and potential benefits of resistance exercise for rehabilitation of cardiac patients. As a result, there currently is general acceptance of its role in rehabilitation of the cardiac patient and the formalization of guidelines for the implementation [10, p. 118, 44, 48]. Resistance training can usually be safely

initiated as early as 7–8 weeks following an MI. Ideally the resistance training program should consist of 6–8 different upper and lower extremity exercises, using a weight machine or free weights (dumbbells), two to three times a week. One to three sets of these exercises should be performed with 8–15 repetitions maximum for each muscle group (repetitive maximal is the maximal number of times a load can be lifted). The load may be increased 5 % when the weight can be comfortably lifted 15 times.

Warm-Up and Cooldown. A 10- to 15-min warm-up session should proceed, and a similar length cooldown should follow each exercise session. This should include upper and lower body flexibility/stretching exercises and lower-intensity exercise. These exercises are postulated to reduce the risk of exercise-induced musculoskeletal injuries and cardiovascular complications.

Contraindications for Exercise Training and Safety

As mentioned, risk stratification is useful for determining the appropriate level of supervision during exercise training for individual patients. Further, there may be restrictions on exercise based on cardiac status and comorbidities (e.g., poorly controlled diabetes or severe pulmonary disease or orthopedic problems, which may be contraindicative or require closer supervision). In addition, it is generally recommended that cardiac patients with the following conditions should be excluded from exercise training:

- Unstable myocardial ischemia
- Chronic heart failure that is poorly compensated
- Uncontrolled arrhythmias
- Severe, symptomatic aortic stenosis
- Obstructive hypertropic cardiomyopathy
- Severe pulmonary hypertension
- Severe uncontrolled hypertension (≥200 mm Hg resting systolic or diastole BP > 110 mm Hg)
- Active or suspected myocarditis
- A large aortic aneurism
- Thrombophlebitis or recent pulmonary embolism

Exercise Risks. Heavy physical exertion can trigger an acute MI or sudden cardiac death in apparently healthy people of all ages in the general population generally due to silent underlying congenital cardiovascular disease or coronary atherosclerosis. However, such episodes are rare in the general population. Further, the relative safety of the exercise components of CRSPP have been documented among patients in cardiac rehabilitation programs, who have been screened and whose exercise is supervised by well-trained personnel [49, 50]. For example, Franklin et al. [50] reported the average incidence of a nonfatal MI was 1 per 220,000 person-hours of exercise and the incidence of cardiac arrest was 1 per 117,000 h of exercise and fatal coronary events 1 per 750,000 of exercise in 142 programs. Of the 21 reported episodes of cardiac arrest in this study, 17 were successfully resuscitated. Thus, the safety of supervised CRSPP exercise training, using recommended guidelines and well-trained supervisory personnel, has been clearly established.

Program Personnel Requirements

As repeatedly mentioned, outpatient CRSPP are characterized by comprehensive multicomponent services, including medical assessments and evidence-based lifestyle and pharmacologic management of risk factors for CVD in addition to supervised prescribed exercise. Detailed guidelines for facilities, equipment, administration of such programs, and personnel and their competency requirements have been published [10]. Although the number of staff members and professional specialists and consultants vary a great deal from one facility to another, the recommended collective knowledge base and competency of the staff should include a comprehensive understanding of the pathophysiology and clinical manifestations of CHD and strategies for management of its risk factors, cardiovascular emergency response procedures, healthy dietary practices, exercise physiology, pharmacology, and behavior modification strategies. The professions most frequently on the staff to deliver these services in addition to physicians include specially trained registered nurses, certified exercise specialists, mental health professionals, physical therapists, registered dieticians, health educators, pharmacists, and vocational counselors and occupational therapists. The leader of this multidisciplinary team is the medical director, who is responsible for assuring that the CRSPP is safe and medically appropriate for each individual patient and is comprehensive and cost-effective. An authoritative statement from the AACVPR and the AHA provides a detailed description of the qualifications and duties of the medical director [51]. The program administrator or director, responsible for day-to-day operations, is generally a PhD-level exercise physiologist. A case manager, an RN, or another health professional team member is generally assigned to each patient in the program. Case management in the context of a CRSPP consists of three primary responsibilities:

- Assessment of all risk factors and instructing patients on strategies to reduce them and tracking the changes
- Establishing rapport and maintaining contact with patients and their primary care provider by clinic visits, telephone, or other forms of correspondence and providing ongoing support for behavioral change and pharmacologic therapy adherence
- Providing regular follow-ups regarding progress in patients meeting their outcome goals and reducing risk of disease progression and recurrent CVD events

Summary

Cardiac rehabilitation has evolved from a program consisting of progressive ambulation and physical activity for the purpose of reversing the detrimental effects of bed rest on patients with an acute MI. It currently consists of multifaceted therapeutic approaches targeted not only at improving the patient's functional capacity but for the prevention of recurrent CVD events. Services provided by certified programs, thus, include not only supervised exercise training but also aggressive risk factor interventions, psychosocial support, and patient education. Further, the patient base for these programs now includes other types of cardiovascular medical and postsurgical conditions, including patients with CHF and PAD. The benefits of these programs have been well documented and include, in addition to improved functional capacity and associated quality of life, reduced morbidity and mortality from CVD and all causes. Guidelines for the age components, goals, and staffing recommendations, including for the medical director, are provided.

Acknowledgements Dr. Leon is supported in part by the Henry L. Taylor Professorship in Exercise Science and Health Promotion and NHLBI's supported Exercise Training to Reduce Claudication (EXERT) Study. Appreciation is expressed to Ms. Linda Estrem for preparation of this manuscript.

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Rheumatic Fever and Valvular Heart Disease

29

Blanche J. Cupido and Patrick J. Commerford

Introduction

Rheumatic fever causes most cases of acquired heart disease in children and young adults worldwide. It is generally classified as a collagen vascular disease where the inflammatory insult is directed mainly against the tissues of the heart, joints, and the central nervous system. The inflammatory response, which is characterized by fibrinoid degeneration of collagen fibrils and connective tissue ground substance, is triggered by a throat infection with Group A β(beta)-hemolytic streptococci (GAS). The destructive effects on cardiac valve tissue account for most of the morbidity and mortality seen in the disease through the serious hemodynamic disturbances produced.

Acute Rheumatic Fever

Epidemiology

During the twentieth century, the two major influences in the reduction of rheumatic fever incidence in many parts of the world were the advent of penicillin and improvements in socioeconomic conditions. At the turn of the twentieth century, the reported incidence of rheumatic fever in the United States was 100 per 100,000 population; by 1960 this had fallen to 45 per 100,000. The most recent US figures show that some regions have rates as low as 2 per 100,000. In stark contrast to these figures are those in the developing world, where rates as high as 1,500–2,100 per 100,000 have been reported in various areas of Africa, Asia, and South America. A recent study in Soweto, South Africa, reported an incidence of new cases of RHD in those over the age of 14, of 23.5 cases/100,000 per annum [1]. Furthermore, systematic echocardiographic screening, compared to clinical screening, has been shown to reveal a much higher prevalence of rheumatic heart disease – up to a tenfold increase [2].

Pathogenesis

The role of GAS in the genesis of rheumatic fever has been supported by a variety of clinical, epidemiologic, and immunologic observational studies. Pharyngeal infection with this organism is the only known cause of rheumatic fever. In situations of overcrowding, such as in schools or in military facilities, epidemics of streptococcal throat infection have resulted in approximately 3 % of those affected developing rheumatic fever [3].

Group A β(beta)-hemolytic streptococci have a variety of cell-wall antigens such as the M, T, and R proteins. It is the M-wall protein that is responsible for type-specific immunity and is widely regarded as determining streptococcal rheumatogenic potential. Patients with acute rheumatic fever are often found to have high titers of antibody to the M proteins.

The currently accepted mode of development of acute rheumatic fever is that GAS pharyngitis leads to a host response to the GAS antigens, with cross-reactivity of the GAS antibodies with antigens in human tissues such as heart and brain (molecular mimicry) [4]. This would explain the frequent observation that, following pharyngeal infection, there is a 3-week asymptomatic period and also the finding that rheumatic fever is rare in very young children. The peak incidence of rheumatic fever is between the ages of 5 and 18 years.

Host factors such as HLA subtypes have also been cited as possible explanations in the varying susceptibility to disease. Approximately 60–70 % of patients worldwide are positive for HLA-DR3, DR4, DR7, DRW53, or DQW2 [5].

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_29,

Table 29.1 Modified criteria for diagnosis of acute rheumatic fever

Major	Minor
Carditis	Fever
Chorea	Arthralgia
Polyarthritis	Elevated ESR
Erythema marginatum	Elevated C-reactive protein
Subcutaneous nodules	Prolonged PR interval

Based on data from Ref. [7]

Clinical Presentation

There is no test specific for the diagnosis of rheumatic fever; therefore, the diagnosis of a patient's first attack of rheumatic fever is usually made by fulfilling the clinical criteria first formulated by Jones [6] and subsequently modified [7]. These are divided into major and minor criteria, and if preceded by a GAS infection, two major or one major and two minor criteria are found, a diagnosis of rheumatic fever can be made (Table 29.1).

Carditis is a pancarditis involving endo-, myo-, and pericardial tissues. Valvular involvement is frequent; if no evidence of this is found clinically despite myocarditis or pericarditis, rheumatic fever is unlikely. The mitral valve is most commonly involved, followed by the aortic valve, and gives rise to the frequent finding of regurgitant murmurs. A mitral systolic murmur, and occasionally even a mid-diastolic murmur (Carey-Coombs murmur), detected during the course of an acute attack of rheumatic fever may be transient and do not necessarily indicate permanent valvular disease. An aortic early diastolic murmur rarely disappears and is evidence of established valve disease.

Arthritis is classically described as involving several joints in succession, each for a short time resulting in the typical pattern of migratory polyarthritis. The larger joints such as the wrists, elbows, knees, and ankles are usually involved. If a patient presents with joint symptoms and evidence of recent GAS pharyngitis, but has insufficient criteria for a diagnosis of rheumatic fever, poststreptococcal reactive arthritis must be considered. This form of arthritis usually affects the small joints of the hands. It is however difficult to distinguish from ARF arthritis, and it is advised that the diagnosis of poststreptococcal reactive arthritis be avoided in high-prevalence areas so as to prevent underdiagnosis [8]. This may give rise to delayed carditis, and, therefore, patients should be followed closely.

Sydenham's chorea, characterized by purposeless involuntary movements, incoordination, and emotional lability, is seen in about 20 % of patients with rheumatic fever and most often resolves within a few weeks. It often presents 3 months after the onset of the preceding GAS pharyngitis. In this situation, the diagnosis of ARF does not require the presence of other manifestations or elevated streptococcal antibody titers.

Erythema marginatum, an erythematous macular rash of the trunk and proximal extremities, occurs in approximately 5 % of rheumatic fever cases. Lesions have pale centers with rounded or serpiginous pale-pink margins and are nonpruritic. They are transient and extremely difficult to detect, particularly in dark-skinned patients.

Subcutaneous nodules are found in 3 % of rheumatic fever cases and are painless, mobile, 0.5- to 2-cm nodules on the extensor surfaces of joints, the occipital area of the scalp, and over spinous processes.

Peritoneal involvement is rare but may simulate an acute abdomen, mimicking acute appendicitis in children.

Often problematic is confirmation of the diagnosis of preceding GAS infection. Throat swab culture is positive in only approximately 11 % of patients at time of acute rheumatic fever diagnosis [9]. A rapid streptococcal antigen test has also been utilized to confirm recent GAS infection. Another confirmatory test is the finding of a rising titer of antistreptococcal antibodies, either antistreptolysin O (ASO) or antideoxyribonuclease B (anti-DNase B).

It is important to have a high level of suspicion of rheumatic fever in any patient presenting with a pyrexial illness, tachycardia, and a progressive symmetrical polyarthritis. While most patients are between the ages of 5 and 15 at first presentation, much older patients may occasionally develop acute rheumatic fever.

Recurrence of rheumatic fever can occur at any age and must be distinguished from infective endocarditis. This is often a difficult task. A high index of suspicion must be maintained especially in high-prevalence settings. Patients with a prior history of rheumatic heart disease are at increased risk of recurrence compared to the general population. Recurrences often cause only subtle clinical signs but pose the risk of dramatically worsening valve damage. Greater sensitivity, at the expense of specificity, is therefore warranted. In light of this, the 2002–2003 WHO criteria for the diagnosis of recurrent rheumatic fever have been developed [10]. In a patient with established rheumatic heart disease, two minor manifestations plus evidence of antecedent group A streptococcus infection are sufficient for the diagnosis of acute rheumatic fever recurrence. (This has however not yet been embraced by the AHA.)

Treatment

Once the diagnosis has been made, it is customary for patients to be prescribed bed rest. Although at the time of presentation for rheumatic fever throat swabs are frequently negative for GAS, a 10-day course of oral penicillin V or a single intramuscular injection of benzathine penicillin is empirically given to eradicate any GAS present.

In order to minimize inflammatory damage to the affected tissues, often joint and cardiac, high doses of oral

salicylates (100 mg/kg/day in divided doses) are cost-effective therapy. The duration of therapy is dictated by the patient's clinical response, and most will only require therapy for 2 weeks. Naproxen has been used successfully in acute rheumatic fever and may be a safer alternative to aspirin [11].

For patients with severe carditis or for those whose valve lesions may require early surgical repair, prednisone (2 mg/kg/day) is often used instead of salicylates. The evidence for any real superiority of prednisone is weak, but patients with carditis do appear to respond more rapidly to it [12]. Two meta-analyses showed no benefit of glucocorticoids or IVIG over placebo or glucocorticoids over salicylates in reducing the risk of heart disease over the long term [12, 13].

Duration of therapy is determined by clinical and laboratory evidence of resolution of inflammation. This is often achieved in milder cases after a month of salicylate therapy, although more severe cases may require 3 months of steroid treatment and up to 5 % of cases are still active at 6 months.

Heart failure, due to severe valve regurgitation, is the usual cause of death and, when it is resistant to antifailure therapy, may necessitate urgent valve replacement surgery, even in the presence of active carditis [14].

Primary Prevention

Prompt recognition and effective treatment of GAS pharyngitis can prevent the development of rheumatic fever, reducing both morbidity and mortality.

Penicillin remains the most cost-effective agent in the treatment of GAS pharyngitis. Often a single intramuscular dose of benzathine penicillin (1.2 MU if ≥27 kg body weight) is effective. When compliance is not a concern, an alternative oral regimen such as penicillin V (500 mg three times a day in adults) may be used. First-generation cephalosporins or erythromycin estolate (20–40 mg/kg/day in 2–4 daily doses) can be used in penicillin-allergic individuals.

True primary prevention of GAS pharyngitis can only be achieved through prevention of the conditions of squalor, overcrowding, and socioeconomic deprivation that promote frequent attacks of GAS pharyngitis in communities.

Secondary Prevention

Recurrent attacks of rheumatic fever are common and can be reduced through the use of prophylactic antibiotics. Duration of secondary prevention must be individualized for patients and extended for those in poor socioeconomic conditions. Current WHO guidelines for the duration of secondary prophylaxis recommend that patients without proven carditis receive prophylaxis for 5 years after the last attack or until the age of 18 (whichever is longest). Those with carditis should receive prophylaxis for 10 years after the last attack, or at least till the age of 25 (whichever is longer). For patients with more severe valvular disease or those post valve surgery, lifelong secondary prophylaxis is recommended [15].

Antibiotic regimens whose efficacy is proven include 1.2 MU intramuscular benzathine penicillin every 3 weeks [16]. Oral therapy is often used for patients on warfarin anticoagulation and 250 mg penicillin V twice daily is recommended. Penicillin-allergic individuals may use 250 mg erythromycin twice daily.

More recently, efforts have been made to develop vaccines incorporating recombinant M protein fragments in an effort to elicit a protective antibody response. Rabbits immunized with such a vaccine have been shown to be highly immunogenic and evoke protective antibodies [17]. Animal studies have thus shown the feasibility of this strategy and human studies are awaited.

Mitral Valve Disease

Mitral Stenosis

With the rare exception of congenital abnormalities, mitral stenosis (MS) due to abnormalities of the leaflets, commissures, and cusps of the valve is due to rheumatic fever [18]. Some 40 % of patients with rheumatic heart disease have combined mitral stenosis and mitral regurgitation and a quarter have pure mitral stenosis. Mitral stenosis is more common in females. The reason for this female predominance is unclear.

Pathology

The rheumatic process affects the edges of the leaflets; with resolution of the inflammatory process, there is thickening, fibrosis, and fusion of the commissures. Involvement of the chordae tendineae results in thickening, fusion, and contraction with scarring extending down onto the papillary muscles. Dense fibrosis and calcification may reduce the normal delicate structure of the valve to a rigid, immobile, and funnel-shaped orifice.

Pathophysiology

The normal adult mitral valve orifice area is 4–6 cm^2. When MS reduces the orifice area to 2 cm^2, a higher-than-normal pressure is required to propel blood from the left atrium to the left ventricle. When stenosis is more severe (1–1.5 cm^2), a considerably elevated left atrial pressure is required to maintain a normal cardiac output even at rest, resulting in a pressure gradient across the valve (Fig. 29.1). The elevated left atrial pressure raises pulmonary capillary pressures, resulting in exertional dyspnea. Dyspnea usually first occurs with exercise, emotional stress, or infections as these require an increased rate of flow across the mitral valve and hence a higher left atrial pressure. Patients with MS do not tolerate

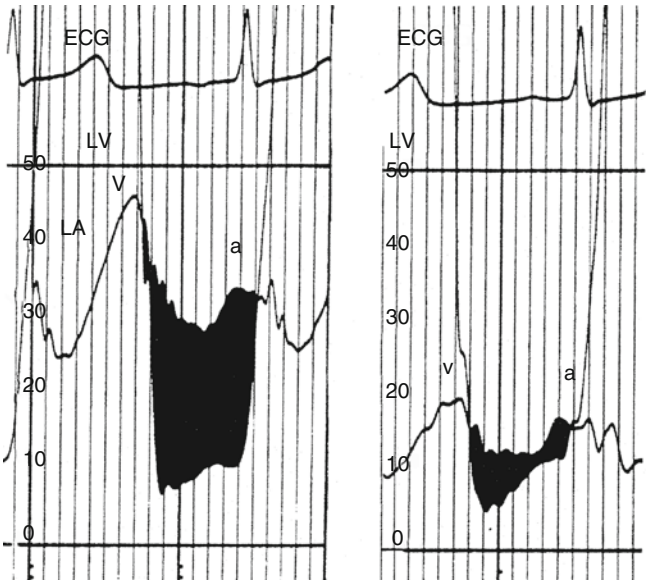

Fig. 29.1 Simultaneous recording of left atrial (*LA*) and left ventricular (*LV*) pressure in a patient with severe MS before (*left*) and immediately after (*right*) balloon valvuloplasty. *Shaded area* indicates the gradient. *a*,*v* identifying the wave in the (*LA*) tracing helps to assess the presence and severity of an end-diastolic gradient

a tachycardia. An increase in heart rate shortens diastole proportionally more than systole and hence reduces the time available for blood flow across the mitral valve [19]; the development of atrial fibrillation (AF) with a rapid ventricular rate may precipitate pulmonary edema in previously asymptomatic patients with MS.

Pulmonary hypertension in patients with MS may result from passive backward transmission of the elevated left atrial pressure or organic obliterative changes in the pulmonary vasculature. Reactive pulmonary hypertension due to pulmonary arteriolar constriction triggered by left atrial and pulmonary venous hypertension may be important in some patients. Prolonged severe pulmonary hypertension results in dilation of the right ventricle and secondary tricuspid regurgitation.

Clinical Features

History

Subclinical or unrecognized attacks of acute rheumatic fever presumably account for the fact that fewer than half of all patients with MS clearly recollect the acute event.

Dyspnea, which may be accompanied by cough and wheezing, is the major symptom of mitral stenosis. This is initially only exertional but with progression orthopnea and paroxysmal nocturnal dyspnea develop. Patients with severe mitral stenosis may tolerate modest impairment of ordinary daily activities but are at risk of developing frank pulmonary edema, which may be precipitated by exercise, chest infections, fever, emotional stress, pregnancy, intercourse, or the advent of atrial fibrillation.

Classically several different kinds of hemoptysis are described as complicating mitral stenosis.

- Sudden profuse hemorrhage (pulmonary apoplexy) results from the rupture of thin-walled dilated bronchial veins [20]. It is more common early in the disease before bronchial veins thicken and are able to withstand the raised pressure. Often profuse and terrifying, it is rarely life threatening.
- Pink frothy sputum of pulmonary edema.
- Blood-stained sputum associated with attacks of paroxysmal nocturnal dyspnea.
- Pulmonary infarction, which is a late complication of long-standing MS associated with heart failure.

Thromboembolism is an important and life-threatening complication of MS. Systemic emboli occur in approximately 20 % of patients at some time. Emboli are more common in older patients with a low cardiac output, a large left atrial appendage, and atrial fibrillation. Embolism may, however, occur in patients with mild MS and may occasionally be the presenting feature. Cerebral, renal, and coronary emboli may occur, and occasionally a large embolus may block the aorta at its bifurcation (saddle embolus). Unexpected systemic or cerebral emboli in a young patient should prompt a careful search for MS.

Uncommon manifestations include *chest pain* indistinguishable from angina pectoris, which, in the absence of coronary disease, may be due to right ventricular or left atrial hypertension. Poorly explained, it resolves with successful treatment of the stenosis. *Hoarseness* caused by compression of the left recurrent laryngeal nerve by a dilated left atrium, lymph nodes, and dilated pulmonary artery occurs in isolated cases (Ortner's syndrome). Severe untreated MS with pulmonary hypertension and right heart failure produces symptoms due to systemic venous hypertension with hepatomegaly, edema, and ascites.

Physical Examination

The typical so-called *mitral facies* with pinkish-purple patches on the cheeks is rarely appreciated in dark-skinned patients in whom the disease is common. The *pulse* is normal in character but of small volume if the cardiac output is reduced. The *venous pressure* may be normal if pulmonary hypertension has not developed. When severe pulmonary hypertension is present, a large "a" wave is found. Atrial fibrillation (AF) and tricuspid incompetence is associated with large "cv" waves and systolic hepatic pulsation. A typical feature on *palpation* is an easily palpable first heart sound (S_1). Pulmonary hypertension produces a right ventricular lift and a palpable pulmonic closure sound (P_2) in the left parasternal area.

Auscultation is best performed with the patient turned into the left lateral position. The first heart sound is typically loud. This accentuation occurs when the anterior leaflet of the mitral valve remains pliable and is due to the abrupt crossover in

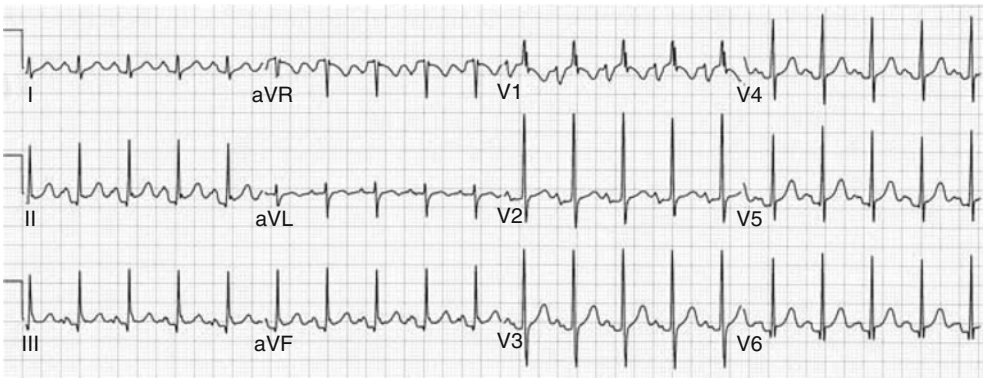

Fig. 29.2 Twelve-lead electrocardiogram in a patient with severe isolated mitral stenosis and pulmonary hypertension. It shows the combination of left atrial enlargement (P-wave broadened in lead II, biphasic in lead VI) and right ventricular hypertrophy (right axis deviation, dominant R in lead VI)

pressure between left atrium and left ventricle at the onset of systole in mitral stenosis and the rapid acceleration of the closing leaflets [21]. Normally the leaflets drift closed toward the end of diastole. In MS they are held open by the transmitral pressure gradient. Marked calcification or fibrosis of the leaflets attenuates the accentuation. In patients with pulmonary hypertension, P_2 is accentuated. The mitral valve opening snap (OS) is heard only in patients with pliable MS. Caused by sudden tensing of the anterior leaflet, it is best heard in the left parasternal area. The characteristic murmur is a low-pitched diastolic rumble best heard with the bell of the stethoscope and may be limited to the apex. Presystolic accentuation of the murmur occurs due to atrial contraction, which increases the gradient and flow across the mitral valve just prior to systole in patients in sinus rhythm. The auscultatory features of MS in obese and emphysematous patients are notoriously difficult. Simple bedside maneuvers (exercise) increase the heart rate and render the appreciation of the auscultatory features easier. Auscultation offers clues to *severity* of stenosis: The longer the murmur and the closer the OS is to the aortic component of the second sound (A2), the more severe the stenosis and *mobility* of the valve; a well-heard OS and loud, easily heard S_1 imply that the anterior leaflet is mobile.

The only important differential diagnosis to be considered is that of a *left atrial myxoma*, which may produce auscultatory features similar to those of MS. The characteristic inspiratory augmentation of the murmur of *tricuspid stenosis* should readily allow for its differentiation.

Laboratory Examination

Electrocardiography is relatively insensitive but may reveal characteristic changes in patients with moderate or severe mitral stenosis (Fig. 29.2). The *chest radiograph* usually shows an enlarged atrial appendage, and left atrial enlargement will be visible on the left lateral view. *Echocardiography* (Fig. 29.3) both confirms the diagnosis by demonstrating thickening, restricted motion and doming of the anterior leaflet and provides vital information on the mobility of the anterior leaflet, the presence and severity of calcification of the valve, and involvement of the subvalvular apparatus,

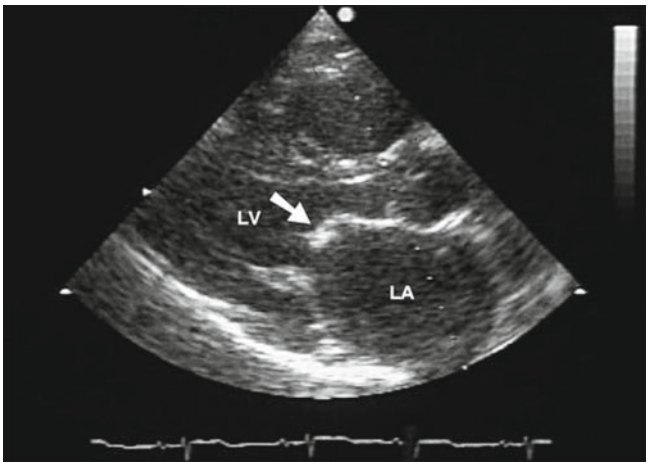

Fig. 29.3 Transthoracic echocardiographic images (parasternal long axis view) reveal left atrial (*LA*) enlargement and thickened domed anterior leaflet of the mitral valve (*arrow*)

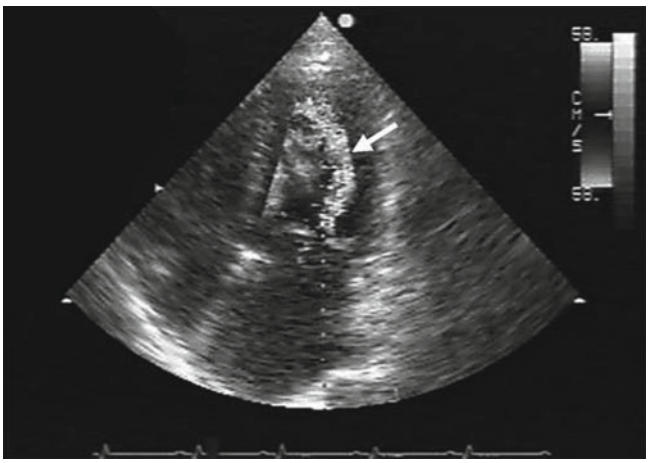

Fig. 29.4 Color-flow Doppler echocardiography demonstrates the high-velocity jet entering the left ventricle (*arrow*) (*see* Color Plate 7)

which determine selection of treatment. Color-flow Doppler *echocardiography* demonstrates the high-velocity jet entering the left ventricle (Fig. 29.4; *see* Color Plate 7) and allows quantitation of severity.

Clinical evaluation and detailed echocardiographic examination including a Doppler study usually provide sufficient information to plan management without the need for *cardiac catheterization*, which can be reserved for patients in whom doubt remains about severity of associated mitral regurgitation, other valve lesions, or left ventricular function. *Coronary angiography* may be indicated in selected patients with chest pain syndromes or in those considered to be at risk of having coronary disease before elective valve replacement surgery.

Treatment

Medical treatment includes advice regarding lifestyle and pregnancy, long-term prophylaxis against recurrences of rheumatic fever if appropriate, antibiotic prophylaxis against infective endocarditis (although the risks are low), and prophylactic anticoagulation with warfarin if AF is present (sustained or paroxysmal). There is no clear evidence that warfarin anticoagulation is of benefit in patients in sinus rhythm who have not experienced an episode of systemic embolism. Predictors of systemic embolism in patients who are in sinus rhythm include the presence of left atrial thrombus, reduced mitral valve area, and the presence of significant aortic regurgitation [22]. Current guidelines recommend long-term anticoagulation in patients with a previous embolic event, left atrial clot, and atrial fibrillation [23]. Diuretics and dietary sodium restriction reduce pulmonary congestion. β-Blockers are often prescribed. By reducing heart rate, increasing diastolic filling time, they increase exercise capacity [24]. There is no role for beta-blockers in the asymptomatic patient [25].

Surgical Treatment: Mechanical relief of obstruction may be obtained by closed mitral valvotomy, open mitral valvotomy, percutaneous balloon mitral valvuloplasty (PBMV), or mitral valve replacement. Selection and timing of the procedure require clinical judgment based on knowledge of the patient's symptoms, the severity of MS, and the risks of the procedure. PBMV has largely superseded surgical valvotomy in suitable patients with pliable leaflets and little or no significant calcification or mitral regurgitation (MR). A balloon catheter is inserted via the femoral vein and a transatrial puncture across the stenotic valve. When dilated (Fig. 29.5), it tears the fused commissures and partially relieves the obstruction. While palliative, PBMV preserves the patient's own valvular apparatus and defers mitral valve replacement with its attendant risks. Periprocedural risk is low (1–3 %), it can be performed as an emergency or in pregnant patients, and it provides excellent relief of symptoms. Severe MR may follow rupture of one of the leaflets. PBMV is usually recommended in patients with significant MS (mitral valve area <1.5 cm^2) and symptoms NYHA Class II or greater. When the valve is badly deformed, heavily calcified, or there is associated significant MR, then mitral valve replacement surgery is the only option. This is usually recommended in patients with Class III or IV symptoms [26].

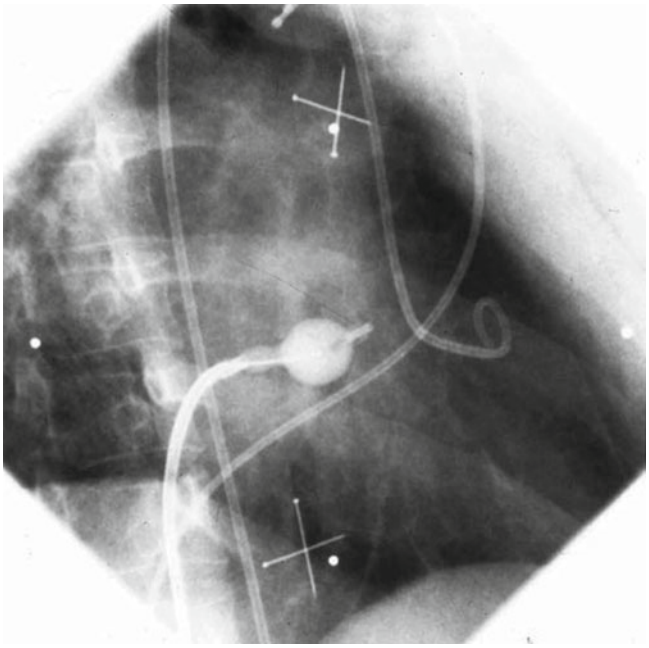

Fig. 29.5 An Inoue balloon catheter is positioned across the mitral valve. The indentation in the contrast-filled balloon as it ruptures the mitral valve commissures is evident

Clinical considerations—including the patient's age, desired level of activity, comorbid conditions, and, importantly in young women, desire for pregnancy—will influence decisions. Each patient with MS requires an individualized assessment recognizing that progression to severe stenosis is almost inevitable, medical treatment can offer only temporary relief, and valvotomy is palliative with restenosis inevitable, although the time to restenosis is unpredictable. Many patients who underwent successful closed mitral valvotomy when the procedure was introduced in the 1950s have had repeat procedures and lead successful and productive lives 40 years later after inevitable mitral valve replacement.

Mitral Regurgitation

Pathology

A number of pathological processes may affect components of the mitral valve apparatus and cause it to become incompetent (Table 29.2). The rheumatic process leads to fibrosis with resultant scarring and contracture of the valve leaflets, and a similar process affecting the chordae with scarring of the papillary muscles results in mitral regurgitation. The severe mitral regurgitation seen in acute rheumatic fever in children or adolescents is usually secondary to prolapse of the anterior leaflet, elongation of the chordae, and dilation of the annulus [27].

Table 29.2 Causes of mitral regurgitation

Chronic	Acute
Rheumatic heart disease	Infective endocarditis
Mitral valve prolapse	Chordal rupture
Mitral annular calcification	Trauma (surgery, PMBV)
Infective endocarditis	Ischemic papillary muscle dysfunction, rupture
Chordal rupture (spontaneous, infective, traumatic)	Prosthetic valve malfunction
Ischemic papillary muscle dysfunction	
Congenital clefts	
Systemic lupus erythematosus	

Pathophysiology

Isolated or pure MR is uncommon in chronic rheumatic heart disease, and there is almost always a degree of associated stenosis. In chronic MR, the mitral orifice functions in parallel with the aortic valve and considerable regurgitation into the low-pressure left atrium may occur before the aortic valve opens. This systolic unloading of the ventricle may permit the patient with chronic MR many years of relatively symptom-free survival at the risk of developing progressive left ventricular dysfunction. The loading conditions in chronic MR are favorable, the lesion favors left ventricular emptying, and if myocardial function is normal, the ejection fraction should be supernormal. An understanding of the complex hemodynamic adaptations that occur in chronic MR is important in planning patient management [28].

When left ventricular function is impaired, end-diastolic pressure rises, as does left atrial pressure, and pulmonary venous hypertension may increase the pulmonary artery pressure. Severe pulmonary hypertension is less frequent than in patients with isolated mitral stenosis.

When MR develops abruptly, the unprepared noncompliant left atrium is unable to accommodate the regurgitant load, and acute heart failure is common.

Clinical Features

History

Dyspnea is the usual presenting symptom. Most patients tolerate chronic mitral regurgitation very well unless there is a dramatic increase in the degree of MR. The great danger is that by the time that symptoms secondary to reduced cardiac output or pulmonary congestion become apparent, severe and irreversible left ventricular dysfunction may develop. *Hemoptysis* and *thromboembolism* are less common than in patients with MS. Untreated, severe chronic MR may result in pulmonary hypertension with secondary tricuspid regurgitation, hepatomegaly, and ascites with symptoms attributable to these.

Physical Examination

The *pulse* is usually normal in volume with a brisk upstroke. In the absence of pulmonary hypertension and associated tricuspid valve abnormalities, venous pressure may be normal. On precordial *palpation* the apex beat is volume loaded and displaced to the left and inferiorly. A systolic lift in the left parasternal area, due to systolic expansion of the enlarged left atrium, may be difficult to differentiate from right ventricular enlargement secondary to pulmonary hypertension.

Auscultation: The first heart sound is usually soft, and P_2 may be accentuated if pulmonary hypertension has developed. An apical pansystolic murmur commencing immediately after S_1 and continuing up to the second sound is characteristic of chronic severe mitral regurgitation. Best heard at the apex, it radiates to the axilla and back. In occasional patients in whom the regurgitant jet is directed medially, it may be heard maximally parasternally and even in the pulmonary area. The murmur, unlike that of aortic stenosis, varies little in intensity with alterations in cardiac cycle length. Severity of regurgitation does not correlate with loudness of the murmur. Failure of the murmur to accentuate with inspiration differentiates it from that of tricuspid regurgitation. An apical third heart sound frequently precedes a short mid-diastolic murmur, the result of the increased forward flow produced by the regurgitant volume and some degree of commissural fusion that is often present in rheumatic MR.

Laboratory Examination

Electrocardiography may be normal or show left atrial enlargement. A pattern of severe left ventricular hypertrophy with repolarization abnormalities is unusual and, when present, is an indication that the diagnosis may be incorrect and that the mitral regurgitation is secondary to left ventricular dilation (dilated cardiomyopathy) or that the differential diagnosis of the systolic murmur should be wider (aortic stenosis, hypertrophic cardiomyopathy). The *chest radiograph* usually reveals cardiomegaly and left atrial enlargement. *Echocardiography* confirms the diagnosis of mitral regurgitation, revealing a high-velocity jet in the left atrium during systole. In addition to its diagnostic role, echocardiography provides vital information on left ventricular dimensions and function and mitral valve morphology, which together determine management and prognosis.

Treatment

Medical treatment in the asymptomatic patient must include advice regarding prophylaxis against recurrences of acute rheumatic fever, prophylaxis against infective endocarditis, and lifestyle, pregnancy, and the need for long-term medical supervision. Careful serial evaluation with noninvasive monitoring of left ventricular function is essential. Diuretics relieve symptoms of pulmonary congestion, and digitalis is indicated in patients with severe MR and evidence of heart

failure, particularly if atrial fibrillation is present. Chronic afterload reduction with angiotensin-converting enzyme inhibitors is logical but unproven therapy.

Surgical Treatment: Mitral valve replacement results in symptomatic improvement, but long-term results are far from ideal. Mitral valve annuloplasty or repair is the preferred procedure. The timing of surgery in patients with MR is difficult. Patients with severe symptoms (NYHA Class III and IV) should be offered surgery. Asymptomatic patients or those with mild symptoms (NYHA Class II) can be observed or treated medically provided that left ventricular function is monitored meticulously; they are considered for surgery if the ejection fraction falls toward 60 % or end-systolic dimension approaches 45 mm [28]. Mitral valve repair is, for technical reasons, often not possible in patients with rheumatic MR, and when attempted, results are often unsatisfactory [29].

Mixed Mitral Stenosis and Regurgitation

Rheumatic disease of the mitral valve results in a wide spectrum of clinical presentations that range from predominant MS to predominant MR. Common and particularly difficult management problems are patients in whom the disease process results in severe deformity of the valve, which is stenotic during diastole and leaks during systole.

Clinical and laboratory features depend on which pathology is dominant; no brief description can encompass the variety of clinical signs that may be detected. *Medical treatment* in both asymptomatic and symptomatic patients is the same as that for those with pure MS and pure MR. *Surgical treatment* by means of valve replacement provides symptomatic relief, but the risks of the procedure need to be weighed against the risks of the underlying disease. It is usually recommended to patients with NYHA Class III or IV disability.

Aortic Valve Disease

Aortic Stenosis

Pathology

Congenitally abnormal valves that may be bicuspid may be only mildly obstructive in childhood, but the abnormal flow dynamics they cause damage the leaflets leading to fibrosis, rigidity, and increasing stenosis later in life. Ultimately the appearances of the congenitally abnormal valve resemble that of degenerative aortic stenosis. *Degenerative* or senile calcific disease is the most common cause of AS in older patients. Mechanical stress over many years on a valve originally normal ultimately results in deposits of calcium along the base of the cusps, rendering them immobile and obstructive. Risk factors for the development and progression of aortic stenosis are much the same as those for development and progression of atherosclerotic vascular disease.

The valvulitis of an attack of acute rheumatic fever results in adhesions along the edges of the cusps with fusion of the commissures. Fibrosis and scarring, which may be associated with calcification, result in thickening and contraction of the cusps so that the normal trileaflet structure becomes fused with a small central orifice. Varying degrees of regurgitation are common. Concentric left ventricular hypertrophy occurs, and evidence of rheumatic mitral valve involvement is common.

Pathophysiology

Minor degrees of commissural fusion produce murmurs due to turbulent blood flow, but significant hemodynamic obstruction occurs only when the cross-sectional area of the valve is reduced to about one-fourth of the normal size of 2.5–3.5 cm^2. The ventricle adapts to the gradually progressive obstruction by developing concentric left ventricular hypertrophy. Hypertrophy allows for maintenance of cardiac output in the face of a large gradient across the valve for many years without left ventricular dilation or the development of symptoms. The hypertrophied left ventricle is less distensible than normal, resulting in elevation of the left ventricular end-diastolic pressure.

Clinical Features

Isolated severe aortic stenosis (AS) without clinically evident aortic regurgitation or concomitant mitral valve involvement is usually idiopathic and degenerative rather than rheumatic in origin [30].

History

Characteristically, there is a long asymptomatic period. *Angina*, which is typical and indistinguishable from that due to atherosclerotic coronary disease, is common even though the coronary arteries are normal. It is caused by increased myocardial oxygen demand as a result of hypertrophy and reduced coronary flow reserve. *Syncope* is usually exertional and is attributed to failure of an increase in cardiac output to adapt to exercise-associated vasodilation because of the fixed obstruction at the valve. Alternatively, a vasodepressor mechanism in response to marked elevation of left ventricular systolic pressure is invoked. Premonitory symptoms, exertional dizziness, and "grayouts" may predominate and bear the same significance as syncopal episodes. *Dyspnea* on exertion early in the clinical course is due to the elevated left ventricular end-diastolic pressure. Severe manifestations such as orthopnea or paroxysmal nocturnal dyspnea are manifest late in the natural history and, if prominent, suggest that there might be associated mitral valve disease.

Physical Examination

The *pulse* in mild AS is normal. In advanced AS it is of small volume and sustained (pulsus parvus et tardus). The distinctive character is best appreciated by palpating a larger vessel such as the carotid, where the radiation of the basal *systolic thrill* may also be detected. Recognition of the classical features of the pulse is difficult, and they may not be present in older patients with an inelastic arterial bed or if there is associated aortic regurgitation. The *jugular venous pressure* may be normal unless there is heart failure or associated mitral valve disease. Prominent "a" waves occur due to reduced right ventricular compliance secondary to marked septal hypertrophy. Precordial *palpation* reveals a forceful sustained apical impulse that may not be greatly displaced in the early stage of the disease.

Auscultation typically reveals a normal or soft first heart sound. If accentuated, associated MS should be considered. In severe AS the second sound may be single due, in part, to immobility of the aortic leaflets and inaudibility of A_2. A presystolic gallop, due to a prominent fourth heart sound reflecting vigorous atrial contraction, may be heard. An aortic ejection systolic murmur is characteristic. Best heard to the right and left of the sternum and the base of the heart, it radiates to the neck and apex. Usually described as harsh and rasping in character, its intensity varies markedly. Severity of stenosis usually correlates with the duration of the murmur (long murmur, severe aortic stenosis) and the timing of the peak intensity (late peak, severe stenosis). Accentuation of the murmur after a postectopic pause is helpful in differentiating it from that of mitral regurgitation when it is well heard at the apex. An early diastolic murmur of associated aortic regurgitation is often detected. Valvar aortic stenosis must be distinguished from other causes of left ventricular outflow obstruction (Table 29.3).

Clinical evaluation of the severity of aortic stenosis is notoriously difficult. Even experienced clinicians may fail to evaluate the pulse correctly. When left ventricular failure occurs and cardiac output falls, the murmur may soften or disappear completely. Operative intervention, even at this late stage, is often successful and clinical evaluation should be supplemented by echocardiography in any patient with unexplained heart failure. Associated MS may mask manifestations of AS [32].

Laboratory Examination

Left ventricular hypertrophy with repolarization changes is manifested *electrocardiographically* in the majority of patients with severe AS. In rheumatic heart disease, the pattern may be modified by the effects of concomitant mitral valve disease and pulmonary hypertension. The cardiac silhouette on *chest radiography* may be almost normal in pure AS, with some poststenotic dilation of the ascending aorta or calcification of the aortic valve the only clue to the diagnosis. This is unusual in rheumatic AS where associated AR or mitral valve disease often results in left ventricular or left atrial enlargement. *Echocardiography* demonstrates the thickened, poorly mobile leaflets; quantitates severity utilizing the Bernoulli equation to determine valve area, velocity of the aortic jet, and gradient across the valve; and evaluates left ventricular size and function. Complete "hemodynamic" evaluation of most young patients can now be performed using this technique. *Cardiac catheterization and angiography* are indicated only in symptomatic patients being evaluated for valve replacement surgery in whom there is concern

Table 29.3 Differential diagnosis of aortic stenosis

Type of stenosis	Maximum murmur and thrill	Aortic ejection sound	Aortic component of second sound	Regurgitant diastolic murmur	Arterial pulse
Acquired	Second right sternal border to neck; may be at apex in the aged	Uncommon	Decreased or absent	Common	Delayed upstroke; anacrotic notch; ± small amplitude
Hypertrophic subaortic	Fourth left sternal border to apex (± regurgitant systolic murmur at apex)	Rare	Normal or decreased	Very rare	Brisk upstroke, sometimes bisferiens
Congenital valvular	Second right sternal border to neck (along left sternal border in some infants)	Very common in children, disappearing with age	Normal or increased in childhood; decreased with decrease in valve mobility with age	Uncommon in child; not uncommon in adult	Delayed upstroke; anacrotic notch; ± small amplitude
Congenital subvalvular	Discrete: like valvular; tunnel: left sternal border	Rare	Not helpful (normal, increased, decreased, or absent)	Almost all	Delayed upstroke; anacrotic notch; ± small amplitude
Congenital supravalvular	First right sternal border to neck and sometimes to medial aspect of right arm; occasionally greater in neck than in chest	Rare	Normal or decreased	Uncommon	Rapid upstroke in right carotid, delayed in left carotid; right arm pulse pressure greater than left

Based on data from Ref. [31]

about the presence of coronary disease (because of symptoms of angina, age, or risk factor profile) or in whom doubt remains about the severity of stenosis or the presence or severity of other valve disease after detailed clinical and echocardiographic evaluation.

Treatment

An understanding of the natural history of the condition aids management. Survival of patients with asymptomatic AS is almost normal until symptoms develop, at which time prognosis worsens dramatically [33].

Medical treatment for all patients may include prophylaxis against infective endocarditis and recurrences of rheumatic fever if rheumatic in origin. Asymptomatic patients with severe AS should be advised to avoid vigorous physical activity, particularly competitive contact sports. All patients require education about the natural history of the condition, its gradually progressive nature, the need for regular medical supervision, and the importance of promptly reporting the onset of symptoms. Exercise testing, once considered contraindicated in patients with severe aortic stenosis, now has a clear role along with regular echocardiographic and clinical review in patients with severe aortic stenosis judged to be asymptomatic [34, 35].

Aortic valve replacement surgery is the most widely used form of treatment in adults with acquired AS. Aortic valve replacement should be advised in patients with severe aortic stenosis (aortic valve area <1.0 cm^2) and symptoms considered to be due to this. Although operative mortality is higher in patients with advanced disease, frank heart failure, and apparently impaired systolic function by conventional measures, valve replacement often results in dramatic improvement in clinical state and left ventricular function. Given the poor prognosis of medical treatment, surgery is often recommended. Experience with catheter-based techniques for aortic valve implantation for aortic stenosis is accumulating rapidly in older patients judged unsuitable for, or at high risk from, open valve replacement surgery. Its role in a wider spectrum of patients remains to be determined.

Calculation of the aortic valve area both invasively and by echocardiography is flow dependent. Some patients with severe stenosis as calculated by aortic valve orifice area have milder disease by other parameters (mean gradient <30 mmHg). Such patients with low-flow/low-gradient aortic stenosis may have truly severe aortic stenosis with myocardial dysfunction secondary to the aortic stenosis; others may have moderate degrees of aortic stenosis with myocardial dysfunction due to non-valve-related factors (pseudo aortic stenosis). Distinguishing true from pseudo stenosis is most commonly done by evaluating the response to a dobutamine challenge at echocardiography or the time of catheterization [36].

Table 29.4 Causes of aortic regurgitation

Chronic	Acute
Rheumatic	Infective endocarditis
Degenerative	Dissecting aortic aneurysm
Chronic severe hypertension	Prosthetic valve malfunction
Syphilis	Trauma
Marfan's syndrome	
Infective endocarditis	
Discrete subaortic stenosis	
Ventricular septal defect with prolapse	
Rheumatoid arthritis	
Ankylosing spondylitis	
Congenital	

Aortic Regurgitation

Pathology

Diseases affecting the aortic valve leaflets, the wall of the aortic root, or both structures may result in incompetence, which develops acutely or progresses slowly over many years (Table 29.4). The inflammatory process of acute rheumatic valvulitis heals by fibrosis causing cusp retraction preventing apposition during diastole, thus allowing reflux of blood from the aorta to the left ventricle. Some commissural fusion may produce a degree of stenosis.

Pathophysiology

Adaptive processes usually account for a long latent period in chronic AR. Diastolic reflux from aorta to left ventricle results in diastolic volume overload, increased end-diastolic volume, and a large stroke volume. Increased wall stress leads to eccentric left ventricular hypertrophy, a restoration of the ratio of wall thickness to cavity dimension toward normal, and hence tends to normalize end-diastolic wall stress. Despite a very large end-diastolic volume, end-diastolic pressure remains normal or only modestly elevated because of increased diastolic compliance. Ultimately, compensatory mechanisms fail, left ventricular contractile function deteriorates, the ventricle dilates further, and interstitial fibrosis contributes to a decline in compliance. The end-diastolic pressure rises, and symptoms and signs of heart failure develop.

Clinical Features

History

There may be a long latent period in chronic AR (10–15 years) before adaptive mechanisms fail; thus, the disease may first manifest when the characteristic murmur is recognized at routine examination of an asymptomatic patient. *Dyspnea* on exertion, with orthopnea and nocturnal dyspnea if presentation is delayed, is the most common symptom.

Table 29.5 Eponymous physical signs of chronic severe aortic regurgitation

Corrigan's pulse	Bounding carotid pulse
De Musset's sign	Nodding of head with each heartbeat
Traube's sign	Pistol-shot sound heard over the femoral artery
Quincke's pulse	Capillary pulsation visible in nail bed with transillumination
Duroziez's sign	Diastolic murmur over femoral when compressed distal to stethoscope (systolic murmur if compressed proximally)
Hill's sign	Popliteal systolic pressure exceeds brachial by >60 mmHg

Angina is unusual but does occur in young patients with severe AR and normal coronary arteries. Often nocturnal, it is attributed to a slow heart rate, low diastolic blood pressure, and elevated left ventricular end-diastolic pressure resulting in reduced coronary perfusion. Symptoms of apical discomfort, awareness of the heart's activity when lying on the left side, or an awareness of pulsation in the neck and precordium are manifestations of ventricular dilation and a large stroke volume and may be manifest long before there is evidence of left ventricular dysfunction.

In *acute AR*, however, the situation is very different. The unprepared left ventricle is unable to tolerate the abrupt hemodynamic load. Acute cardiovascular collapse with hypotension and intense dyspnea may occur. The physical signs of acute AR are very different from those of the chronic state. Peripheral arterial signs are absent, the apex beat may not be prominent, and the murmur may be short, soft, and difficult to detect.

Physical Examination

The *pulse* in chronic severe aortic regurgitation is of large volume with a brisk upstroke and rapid descent (collapsing or water-hammer pulse). Systolic arterial pressure is elevated and diastolic abnormally low, with Korotkoff sounds persisting until zero. A bisferiens pulse, with both percussion and tidal waves palpable during systole, may be detected in the brachial or carotid arteries. The large pulse volume gives rise to an array of eponymous physical signs (Table 29.5). The *apex beat* is usually markedly displaced and is diffuse and volume overloaded. A systolic thrill at the base may be a manifestation of a large stroke volume in pure AR or be due to a minor degree of commissural fusion in rheumatic disease.

Auscultation in chronic severe AR reveals a normal or soft first heart sound, and a third sound may be present. The murmur of AR is an early diastolic decrescendo that commences immediately after the aortic component of the second heart sound. It is best heard with the patient sitting up, leaning forward with breath held in expiration, and the diaphragm of the stethoscope firmly applied between the apex and base. In general, the longer the murmur, the more severe the AR. A rumbling mid-diastolic murmur (Austin-Flint) is common and is attributed to antegrade flow across a normal mitral valve closing early because of the rapidly rising left ventricular end-diastolic pressure. It may be impossible to distinguish this from the murmur of mitral stenosis. The detection of a loud first heart sound and OS suggests associated MS, but absence of these does not exclude MS.

Laboratory Examination

The *electrocardiogram* in the early stages shows increased voltage in the precordial leads; with progression of the condition, repolarization abnormalities develop. *The chest radiograph* usually reveals cardiomegaly. Duration and severity of AR determines the degree of cardiac enlargement. In early, mild AR, heart size may be almost normal, while it is markedly increased in chronic severe AR with dilation of the ascending aorta. Doppler *echocardiography* and color-flow imaging readily detect even minor degrees of AR and allow quantification of severity by measuring the rate of decline in velocity of the regurgitant jet. Two-dimensional imaging of left ventricular size and function provides information on ventricular adaptation to the regurgitant load. Serial echocardiographic evaluation provides essential information on ventricular response to the regurgitant load and is vital in formulating a management plan for the asymptomatic patient. *Cardiac catheterization and angiography* are rarely necessary in young patients with rheumatic AR unless doubt remains about the severity of associated mitral valve disease after careful echocardiographic evaluation. Coronary angiography is indicated before valve replacement surgery in patients with angina and those considered to be at risk of coronary disease because of age or associated risk factors.

Treatment

Chronic aortic regurgitation may be well tolerated for years. Once symptoms develop they are usually progressive, with death occurring in 2–4 years if aortic valve replacement, the only definitive form of therapy, is not offered. *Medical treatment* for all patients includes prophylaxis against IE and recurrent ARF. Patients with severe AR, even if asymptomatic, are conventionally advised against strenuous physical exertion. All asymptomatic patients with severe chronic AR and normal LV function should be informed of the natural history of the disease and advised to have regular evaluation at 6-monthly intervals with serial measurement of left ventricular size and function.

Vasodilator therapy can logically be expected to reduce the degree of regurgitation and enhance LV performance, delaying the need for valve replacement in *asymptomatic* patients with preserved LV function. While this has been demonstrated with nifedipine [37], it has not been well tested in young patients with rheumatic AR. Digoxin, diuretics, and

vasodilators may temporarily stabilize patients with decompensated AR and heart failure awaiting valve replacement surgery. The need to prescribe any such agent, either for symptoms or evidence of LV dysfunction, should prompt consideration of aortic valve replacement.

Surgical treatment by aortic valve replacement should be offered to all patients with severe chronic AR as soon as possible after symptoms attributable to the condition have developed. Asymptomatic patients with impaired LV function require individualized assessment and evaluation, which needs to take into account the natural history of the condition and the risk of aortic valve replacement and anticoagulation. Single measures of LV function may be unreliable, and serial repeated observations may be necessary. If these reveal consistent reproducible changes and the left ventricular ejection fraction falls below 50–55 %, the left ventricular end-systolic diameter exceeds 55 mm, or the left ventricular end-diastolic diameter exceeds 70 mm, surgery is recommended [38].

Occasional patients present very late in the course of the disease with severe heart failure, markedly impaired left ventricular function, and severe AR. Aortic valve replacement in this situation carries an increased operative mortality, but the long-term outlook for survivors is unpredictable. Most will obtain at least temporary relief of symptoms, and in some, ventricular function improves markedly with removal of the abnormal loading conditions. Short duration of symptoms may be helpful in predicting those who will obtain maximum benefit.

Tricuspid Valve Disease

Rheumatic involvement of the tricuspid valve is reported in autopsy series far more frequently than it is detected clinically. This may be due to relatively minor degrees of involvement or because the physical signs are often evanescent and rapidly modified by bed rest and diuretic therapy. Severe organic tricuspid valve disease, almost always associated with significant mitral valve disease as part of a syndrome of multiple valve involvement, poses a formidable therapeutic challenge and has a grave impact on prognosis.

Tricuspid Regurgitation

Pathology

Rheumatic tricuspid regurgitation (TR) is a result of scarring and deformity of the leaflets with fibrosis of chordae impairing mobility and preventing leaflet apposition. A degree of tricuspid stenosis (TS) is common. Infective endocarditis, carcinoid syndrome, and trauma are other causes. *Functional* tricuspid regurgitation secondary to tricuspid annular dilation may occur as a consequence of right ventricular failure secondary to pulmonary hypertension of any cause.

Clinical Features

History

Symptoms due to associated involvement of left heart valves usually predominate. Peripheral edema, ascites, and painful hepatomegaly produce prominent symptoms if TR is severe.

Physical Examination

Cachexia, jaundice, ascites, and edema are prominent in untreated patients with severe TR presenting late in the course of the disease. The arterial pulse form is determined by associated valve lesions, and atrial fibrillation is common. The *venous pressure* is always elevated with prominent "cv" waves and marked "y" collapse. A degree of associated TS renders the "y" descent less prominent. *Palpation* in severe TR reveals an atrial systolic impulse at the right lower sternal edge due to right atrial expansion. *Auscultation* reveals accentuation of P_2 and a pansystolic murmur, best heard in the fourth left intercostal space, which typically increases on inspiration. When TR is very severe, this inspiratory accentuation may be very difficult to appreciate particularly if AF is present. If there is marked right ventricular dilation, the murmur may be widespread, be heard at the apex, and be easily mistaken for that of mitral regurgitation. All the clinical features of severe TR, particularly if it is functional in origin, may abate dramatically after a brief period of intense diuresis.

Laboratory Examination

Electrocardiography is unhelpful, usually showing atrial fibrillation and reflecting changes of pulmonary hypertension and the left-sided lesions responsible for its development. *Echocardiography* reveals dilation of the right atrium and ventricle with paradoxical septal motion. Color Doppler imaging readily demonstrates the regurgitant jet, and evaluation of peak velocity of regurgitant flow allows estimation of pulmonary artery systolic pressure. *Cardiac catheterization and angiography*, which may be indicated to assess other valves, left ventricular function, or coronary anatomy, seldom add any information of note to that obtained by careful clinical and echocardiographic evaluation.

Tricuspid Stenosis

Pathology

Fusion of the leaflets at their commissures consequent on rheumatic valvulitis results in a narrowed central orifice. Shortening and fibrosis of chordae limit leaflet motion. The valve is obstructive in diastole and almost invariably there is a degree of systolic regurgitation. Pathological evidence of TS may be found in 15 % of all patients with rheumatic heart disease but is the rarest clinical manifestation, occurring in only 5 %.

Clinical Features

The details on history and general physical examination are very similar to those in patients with rheumatic TR. A dominant "a" wave, which is sharp and flicking in the *jugular venous pressure* if sinus rhythm is present, is characteristic and more easily recognized than the slow "y" descent. Presystolic hepatic pulsation may be palpable.

On *auscultation* a diastolic murmur, loudest at the lower left sternal border with presystolic accentuation (if sinus rhythm is present), is heard. The murmur is accentuated on inspiration. A tricuspid opening snap is frequently recorded but clinically very difficult to distinguish from the OS of associated MS. As MS frequently coexists, only careful attention to respiratory variation will allow for differentiation of the two murmurs. A loud early diastolic murmur of AR in patients with multiple valve involvement may further confound clinical detection of the *murmur* of TS.

Laboratory Examination

Marked right atrial enlargement on *electrocardiography* in the absence of significant right ventricular hypertrophy is suggestive. Cardiomegaly on chest radiography is common with right atrial enlargement causing prominence of the right heart border. *Echocardiography* reveals thickening and doming, restricted motion, and reduced separation of the leaflets. Doppler echocardiography demonstrates increased antegrade velocity.

Treatment

Intensive *medical treatment* with bed rest, salt restriction, and diuretic therapy improves the symptoms and physical signs of systemic venous congestion, improves hepatic function, and reduces the risk of valve replacement surgery. *Surgical treatment* of rheumatic tricuspid valve disease is difficult and generally unsatisfactory but requires careful consideration at the time of correction of mitral and aortic valve abnormalities. Failure to correct significant tricuspid regurgitation may result in considerable disability in the long term.

The final decision as to what procedure is possible or necessary can often only be made by the surgeon after open inspection. Minor degrees of TS and TR, which have not caused significant venous pressure elevation, are best left alone. Although open commissurotomy may relieve TS, it may also produce severe TR, and tricuspid valve replacement with a bioprosthesis is usually necessary. Minor degrees of functional TR improve dramatically with resolution of pulmonary hypertension after mitral valve surgery. Patients with severe functional or organic TR require repair with a ring annuloplasty. If the immediate result at surgery is unsatisfactory, valve replacement is necessary. Whenever possible tricuspid valve replacement is avoided, as all prostheses are inherently stenotic in this position and, while the operation relieves symptoms, the additional procedure increases the operative morbidity and mortality of mitral and aortic valve replacement.

Multiple Valve Disease

It is conventional and convenient to describe the various clinical syndromes of valvular heart disease in isolation. Clinical reality, however, is that a wide variety of combined lesions may occur, particularly in patients with rheumatic heart disease. Only some 25 % of all patients with rheumatic heart disease have isolated MS. Others have mixed valve disease or a combination of valve lesions that may produce a wide array of clinical syndromes. Correct identification and correction of all lesions is important. Failure to identify and correct an associated severe lesion may increase operative risk. Disregard of mild or moderate associated disease at the time of surgery for the major abnormality may allow progression, necessitating reoperation with its attendant risks and thus negating benefit of the primary procedure.

When multiple valves are involved, the clinical and hemodynamic manifestations depend on the relative severity of each lesion. Generally, when lesions are of approximately equal severity, clinical manifestations produced by the more proximal (upstream) lesions predominate [39]. Careful clinical evaluation supplemented by two-dimensional and Doppler echocardiography usually serves to estimate the relative contribution of each valve to the clinical syndrome. If doubt remains, catheterization or angiography, specifically directed to answer unresolved issues, may be necessary. The final decision as to severity of individual lesions, the need for repair, and the method of repair may only be possible at the time of operation. A recent review by Unger et al. reviewed the management of multiple valve disease [40]. Table 29.6 summarizes some important considerations for various combinations of lesions.

Special Considerations

Acute rheumatic fever is a disease of poverty and overcrowding, and the majority of patients who suffer the sequelae of chronic valvular heart disease live in conditions where medical care is far from ideal. Availability of services and patients' access to and compliance with monitoring of anticoagulation, among many other factors, will influence decisions on timing and type of valve replacement surgery. Considerations of this nature, and the hemorrhagic risks attendant on poor supervision of warfarin anticoagulation, may prompt deferral of valve replacement in mildly symptomatic patients, even though measures of ventricular function suggest that under ideal circumstances it should be

Table 29.6 Diagnostic caveats in patients with multivalve lesions

		Impacts on the diagnosis of			
		AS	AR	MR	MS
The presence of	AS	NA	Prolonged PHT if left ventricular hypertrophy with impaired relaxation	High intraventricular pressure may result in higher RV whereas ERO is less affected	Low-flow, low-gradient MS, prolonged PHT if impaired ventricular relaxation
	AR	Gorlin formula using thermodilution technique invalid. Owing to high transaortic volume flow rate, maximum velocity and pressure gradients may be higher than expected for a given valve area	NA	Not significantly affected	Owing to increased antero-grade aortic flow, there is an overestimation of MVA by the continuity equation. Overestimation of PHT method. This approach is not valid
	MR	MR could favor a low-flow, low-gradient state. Aortic valve area remains accurate. High-velocity MR jet may be mistaken for the AS jet (MR is longer in duration)	Not significantly affected	NA	Owing to increased antero-grade mitral flow, there is an underestimation of MVA by the continuity equation. MVA may be underestimated by PHT method
	a. MS	Low-flow, low-gradient state. Aortic valve area remains accurate	Blunted hyperdynamic circulation	Not significantly affected	NA
	b. TR	Gorlin formula invalid	Not affected	Not affected	Gorlin formula invalid

Reprinted from Unger et al. [40]. With permission BMJ Publishing Ltd.
AR aortic regurgitation, *AS* aortic stenosis, *ERO* effective regurgitant orifice, *MR* mitral regurgitation, *MS* mitral stenosis, *MVA* mitral valve area, *PHT* pressure half-time, *RV* regurgitant volume, *NA* not applicable

performed. Alternatively, despite the known risks of premature degeneration in young patients, bioprostheses may be used in patients who wish to return to rural homes that are remote from medical supervision and where warfarin anticoagulation is impossible. Thromboembolic complications of mechanical prostheses are inevitable if warfarin anticoagulation is not possible.

Pregnancy poses particular problems to young women with valvular heart disease. It often precipitates symptoms in previously asymptomatic patients with mitral stenosis. If the valve is suitable, then prophylactic PBMV may be possible prior to pregnancy or, if necessary, it may be done during pregnancy. Asymptomatic or mildly symptomatic patients with other lesions should be advised to complete their families as soon as possible and then, ideally, an effective form of contraception instituted before valve replacement surgery becomes necessary, thus avoiding the risks of warfarin to both mother and fetus.

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Infective Endocarditis

30

Adolf W. Karchmer

Introduction

Infective endocarditis (IE) results when microbial agents infect the endothelial surface of the heart and form a vegetation, a mass of platelets and fibrin, engendered by the procoagulant activity of infecting organisms and injured local tissue, with enmeshed microorganism and scant inflammatory cells. Heart valves are the most common site for this process; however, occasionally, infection develops on the low-pressure side of a ventricular septal defect, on chordae tendineae, or on mural endocardium that has been damaged by an aberrant jet of blood or an intracardiac foreign device (transvenous pacing lead, pulmonary artery catheter). Very rarely, a similar process, infective endarteritis, arises when arteriovenous shunts, arterioarterial shunts (patent ductus arteriosus), or a coarctation of the aorta are involved.

Epidemiology

The incidence of IE generally has ranged from 1.5 to 6.2 cases per 100,000 population in developed countries over the past four decades [1–3]. The incidence increases progressively with age reaching rates of 15–30 cases per 100,000 among persons in the sixth and later decades and is higher in men than women [3, 4] While rheumatic heart disease remains an important predisposition for IE in nonindustrialized countries, in developed countries, IE is more typically associated with degenerative valve disease, injection drug abuse, and intracardiac devices [3–5]. Healthcare-associated IE, comprised of nosocomial and non-nosocomial infection (developing outside of the hospital related to extensive healthcare exposure – dialysis units, nursing homes, long-term intravenous catheters), is noted in 25–35 % of cases [3–5]. Healthcare-associated IE is notable for increased cases due to *S. aureus*, including methicillin-resistant *S. aureus* (MRSA), cases in older patients with multiple comorbidities, fewer patients treated surgically, and increased in-hospital mortality [3–6]. Infection involves cardiac implantable electrical devices (CIED) in 6–13 % of cases [4, 5, 7]. In developed countries, prosthetic valve endocarditis (PVE) accounts for 13–22 % of cases not involving injecting drug users [2, 4, 5, 8]. Based on actuarial estimates, PVE develops in 1.4–3.1 % of valve recipients within the first year after surgery and in 3.2–5.7 % after 5 years have elapsed [9]. However, with improved surgical and postoperative care, early onset cases may be less frequent. Healthcare-associated PVE (67 % nosocomial, 33 % non-nosocomial) accounts for 36 % of PVE and is associated with *S. aureus* becoming the most common cause of PVE [8]. Congenital heart disease and current injection drug use are predispositions in 11 and 10 % of cases, respectively [5].

Clinical Manifestations

Symptomatic IE likely arises within several weeks of the initiating bacteremia, although in perioperative infection of new implanted prosthetic valves, symptoms may be delayed for more than 2 months [9]. The IE syndrome may be acute with hectic fevers and chills, multiple extracardiac manifestations, and rapid development of intracardiac complications or a subacute very indolent illness with modest fevers, night sweats, anorexia, weight loss, infrequent extracardiac complications, and little or no progressive intracardiac injury. In fact, the presentations of IE are a continuum between these two extremes. The temporal evolution of IE is in large part a function of the causative microorganism. *Staphylococcus aureus* and beta-hemolytic streptococci usually result in acute presentations. In contrast, viridans streptococci, enterococci, coagulase-negative staphylococci, and the fastidious gram-negative coccobacilli, organisms often referred to by

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_30,

Table 30.1 Signs and symptoms in patients with infective endocarditis

Symptoms	Percent	Signs	Percent
Fever	80–96	Fever	80–90
Chills	40–75	Heart murmur	80–85
Sweats	25	Changing or new murmur	10–40
Anorexia	25–55	Systemic emboli	20–50
Weight loss	25–35	Splenomegaly	11–50
Malaise	25–40	Clubbing	10–20
Cough	25	Osler's nodes	7–10
Stroke	15–20	Splinter hemorrhage	5–15
Headache	15–40	Janeway lesions	2–10
Myalgia/ arthralgia	15–30	Retinal lesions (Roth spots)	2–10
Back pain	7–14	Petechiae	10–40
Confusion	10–20		

Adapted from Karchmer [10]. With permission from Elsevier

the acronym HACEK (*Haemophilus parainfluenzae, Aggregatibacter aphrophilus, Haemophilus paraphrophilus, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae*), give rise to subacute endocarditis. *Bartonella* species and *Coxiella burnetii* (the rickettsia-like agent which causes Q fever) also cause indolent IE.

Nonspecific signs and symptoms are characteristic of IE (Table 30.1); nevertheless, in the appropriate context, these clinical features should suggest the diagnosis. These settings include patients with cardiac conditions that are substrates for infection, patients with behavior patterns that predispose to endocarditis (injecting drug use), and bacteremia due to organisms that commonly cause IE. In addition, progressive cardiac valvular dysfunction or arterial emboli in the context of a nonspecific febrile illness should prompt consideration of IE.

Fever, the most common clinical feature of IE, may be absent or minimal in those who are severely debilitated or who have congestive heart failure or chronic renal failure. IE caused by coagulase-negative staphylococci or *Tropheryma whippelii* (the cause of Whipple disease) may present with little or no fever [11]. The purported increased frequency of muted presentations of IE among the elderly has not been confirmed.

In patients with IE involving native heart valves (NVE), heart murmurs commonly reflect the predisposing valve pathology rather than valve distortion due to IE itself. With acute *S. aureus* NVE, a process often engrafted on previously normal heart valves, murmurs are detected in only 30–45 % of patients on presentation but with valve damage ultimately develop in 85 %. Murmurs are often not heard in tricuspid valve endocarditis or in pacemaker-related IE. Murmurs reflecting new or progressive valve dysfunction rather than alterations in cardiac output are most commonly encountered in patients with acute IE or PVE and are less frequent in subacute NVE.

The classic, but not pathognomic, noncardiac manifestations of IE, including splenomegaly, petechiae, Osler's nodes, Janeway lesions, Roth spots, and splinter hemorrhages, are found less frequently today than several decades ago. Since many of these occur as a consequence of long-standing infection, this change likely represents the increasingly prompt diagnosis of endocarditis. Splinter hemorrhages, linear- or flame-shaped lesions beneath the nails of the fingers or toes, associated with IE are found proximally in the nails. Those seen at the distal nail margin are most likely due to trauma.

Arthralgias, myalgias, true arthritis with nonspecific inflammatory synovial fluid, and localized back pain are common symptoms that remit rapidly with antimicrobial therapy. These focal skeletal symptoms must be distinguished from metastatic infection which may require additional therapy, including drainage.

Arterial emboli, which are evident clinically in up to 50 % of patients and are also frequently subclinical discovered only at autopsy, are associated with significant morbidity and mortality in NVE and PVE. Systemic emboli are more common in patients with left-sided vegetations that exceed 10 mm in diameter (by echocardiogram) and that are located on the mitral valve, particularly on the anterior leaflet. Emboli are often a presenting symptom in patients with IE. After initiation of appropriate therapy, the frequency of emboli decreases rapidly [12–14]. Emboli that occur after 2 weeks of treatment (15–18 % of all emboli) are not in themselves evidence of failed antimicrobial therapy [12]. Renal emboli may cause gross or microscopic hematuria but rarely result in important renal dysfunction.

Neurologic symptoms and complications occur in as many as 40 % of patients and are particularly prominent when infection is due to *S. aureus*. Embolic stroke syndromes occur in 10–25 % of patients and are the most common neurologic consequences of IE; less common complications include mycotic aneurysm, intracranial hemorrhage, meningitis (either aseptic or occasionally purulent), cerebritis with microabscess formation, seizures, and encephalopathy. Clinical stroke, but not silent cerebrovascular complications or transient ischemic attacks, is associated with increased mortality, especially when there is a low Glasgow coma score [15]. Intracranial hemorrhage, which occurs in 5 % of cases, results from hemorrhagic infarction, rupture of an artery due to septic arteritis at a site of embolic occlusion, or rupture of a mycotic aneurysm. Surgically drainable brain abscesses are uncommon in IE, whereas microabscesses of brain and meninges occur in patients with IE due to *S. aureus*.

Disruptions or distortion of left heart valves or rupture of chordae tendineae with subsequent valvular insufficiency may result in congestive heart failure. Heart failure due to

aortic valve insufficiency generally progresses more rapidly than that due to mitral valve regurgitation. Similar hemodynamic consequences are seen with mechanical and bioprosthetic PVE due to valve dehiscence with paravalvular leakage or to destruction or disruption of valve parts. Bulky vegetations may obstruct the orifice of a mitral prosthesis resulting in functional stenosis [9].

Renal dysfunction in patients with IE most commonly results from reduced cardiac output or antimicrobial toxicity but may be due to hypocomplementemic glomerulonephritis with deposition of circulating immune complexes on the glomerular basement membrane. This may progress during initial therapy but then gradually improves with antimicrobial treatment.

Diagnosis

The diagnosis of IE often requires a high index of suspicion. A sensitive and specific diagnostic schema, the Duke criteria, is developed using predispositions plus the clinical, laboratory, and echocardiographic features of IE [16]. Using these clinical criteria, 74 and 26 % of more than 300 pathologically proven IE cases were classified as definite and possible IE, respectively, and none were rejected [17]. However, the Duke criteria accept as possible IE some cases considered by the experts to not have IE, i.e., made a false-positive diagnosis by comparison with expert opinion. To address the somewhat reduced specificity, Li and colleagues suggested a new widely accepted modification [18]. The modified Duke criteria (Tables 30.2 and 30.3) included evidence of infection by *C. burnetii*, as a major criterion. Additionally, the modified criteria require that 1 major plus 1 minor criterion or 3 minor criteria be present before cases are classified as possible IE and treated [18].

The Duke diagnostic schema appropriately emphasizes the role of bacteremia (blood cultures) and echocardiography in the evaluation of patients with potential IE. Endocarditis is characterized by sustained low-density (< 100 organisms/ml) bacteremia. Among patients with IE who have not had prior antimicrobial therapy and who ultimately will have positive blood cultures, at least 95 % of all blood cultures will be positive, and in 98 % of cases, one of the first two sets will yield the causative organism. The diagnostic criteria give weight to the specific organism isolated. Bacteremia with organisms rarely encountered in the absence of IE (viridans streptococci, HACEK group) is thus highly suggestive, whereas organisms associated with endocarditis as well as other infections (enterococci) must be encountered in the absence of another site of infection in order to rank as a major criterion. Organisms that commonly contaminate blood cultures, i.e., coagulase-negative staphylococci or diphtheroids, or that rarely cause IE, i.e., *Enterobacteriaceae*, must be isolated from blood repetitively as a single molecular clone (coagulase-negative staphylococci) and in the absence of an alternative infection in order to be used as a criterion [16, 17].

Incorporation of specifically defined echocardiographic findings characteristic of IE as a criterion markedly enhances the clinical utility of the schema and recognizes the high sensitivity and specificity of two-dimensional echocardiography. Echocardiography is not recommended as a screening test for febrile or bacteremic patients when endocarditis is unlikely; however, all patients suspected of having IE should be studied by echocardiogram (Fig. 30.1) [17].

Table 30.2 Criteria for diagnosis of infective endocarditis

Definitive infective endocarditis
Pathologic criteria
Microorganisms: demonstrated by culture or histology in a vegetation *or* in a vegetation that has embolized *or* in an intracardiac abscess, *or*
Pathologic lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis
Clinical criteria, using specific definitions listed in Table 30.3
2 major criteria, *or*
1 major criterion and 3 minor criteria, *or*
5 minor criteria
Possible infective endocarditis
1 major criterion and 1 minor criterion, *or*
3 minor criteria
Rejected
Firm alternative diagnosis for manifestations of endocarditis, *or*
Sustained resolution of manifestations of endocarditis, with antibiotic therapy for 4 days or less, *or*
No pathologic evidence of infective endocarditis at surgery or autopsy, after antibiotic therapy for 4 days or less

Adapted from Li et al. [19]. With permission from Oxford University Press

Diagnostic Testing

Blood Cultures

In patients with suspected endocarditis who have not received an antibiotic recently, three blood cultures, obtained from separate venipuncture sites and spaced over 24 h independent of temperature elevations, are sufficient to isolate the causative organism and to demonstrate the persistence of bacteremia that is characteristic of IE (Table 30.4 and Fig. 30.2). If blood cultures remain negative after 48–72 h and fungi or fastidious organisms are suspected, additional cultures should be obtained, possibly using special techniques such as the lysis centrifugation system or a biphasic system [17]. When initial routine blood cultures appear to be negative, the microbiology laboratory should be advised that

Table 30.3 Terminology used in criteria for the diagnosis of infective endocarditis (Table 30.2)

Major criteria
Positive blood culture
Typical microorganism for infective endocarditis from two separate blood cultures
Viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus, or*
Community-acquired enterococci in the absence of a primary focus, *or*
Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:
(i) Blood cultures drawn more than 12 h apart, *or*
(ii) All of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 h apart
Positive blood culture for *C. burnetii* or antiphase I IgG antibody titer>1:800
Evidence of endocardial involvement
Positive echocardiogram:
(i) Oscillating intracardiac mass, on valve or supporting structures, *or* in the path of regurgitant jets, *or* on implanted material, in the absence of an alternative anatomic explanation, *or*
(ii) Abscess, *or*
(iii) New partial dehiscence of prosthetic valve, *or*
New valvular regurgitation (increase or change in preexisting murmur not sufficient)
Minor criteria
Predisposition: predisposing heart condition *or* intravenous drug use
Fever≥38.0 °C (100.4 °F)
Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor
Microbiologic evidence: positive blood culture but not meeting major criterion as noted previously[a] *or* serologic evidence of active infection with organism consistent with infective endocarditis

Adapted from Li et al. [19]. With permission from Oxford University Press

Abbreviations: *HACEK Haemophilus* species, *Aggregatibacter aphrophilus, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella* species, *Kingella kingae*

[a]Excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis

IE is suspected so that it can prolong the incubation of the cultures and, where appropriate, perform special subcultures to isolate unusual organisms [1, 17]. From 5 to 15 % of patients with IE diagnosed clinically have negative blood cultures. Prior receipt of antimicrobials accounts for 35–50 % of these blood culture-negative cases. The remainder are a consequence of infection with organisms that have fastidious growth requirements [17]. In hemodynamically stable patients with subacute presentations of suspected IE who have received antibiotics within the previous 2 weeks, empiric antibiotic therapy should be delayed to allow time for additional blood cultures to be obtained without the confounding effects of further antibiotic therapy [17]. This delay, while potentially enhancing culture yields, is unlikely to allow otherwise preventable complications. In contrast, among patients with acute presentations or with deteriorating hemodynamics, empiric therapy should be initiated immediately after the initial cultures have been obtained.

If after 5 days initial blood cultures remain negative (not attributable to confounding antimicrobial therapy), serologic testing to identify infection caused by pathogens that are difficult or unlikely to be recovered from blood (*Brucella, Bartonella, Legionella, C. burnetii*, and some fungi) should be considered [17, 21] (Table 30.4 and Fig. 30.2). If valve tissue or embolized vegetations become available from these patients, the material should not only be cultured and examined by special microscopic techniques, but also the organism's identity should be sought by using the polymerase chain reaction to recover specific microbial DNA or 16S rRNA [1, 21, 22].In these persistently blood culture-negative patients, entities that mimic IE should be considered, e.g., marantic endocarditis, carcinoid syndrome, and antiphospholipid antibody syndrome.

Echocardiography

Echocardiographic evaluation with color flow and continuous as well as pulsed Doppler allows anatomic confirmation of IE, identifies intracardiac complications, and allows functional assessment of the heart. Transthoracic echocardiography (TTE), while noninvasive and 98 % specific for vegetations, detects vegetations in only about 65 % of clinical or anatomically established IE. TTE is limited by vegetation size (≤2 mm in diameter) and in adults by body habitus, chest wall configuration, or lung disease. Furthermore, TTE is not adequate for the assessment of prosthetic valves (especially in the mitral position) or the detection of perivalvular abscess, leaflet perforations, or intracardiac fistulae [23, 24]. In contrast, transesophageal echocardiography (TEE), which while invasive is extremely safe in the hands of experienced operators, detects vegetations in more than 90 % of patients with proven NVE and 82–94 % of patients with clinically diagnosed IE. In patients with PVE, the sensitivity for detecting vegetations by TEE ranged from 74 to 96 % while the sensitivity with TTE was 13–36 % [23]. TEE is clearly the optimal technique for the diagnosis of PVE and the identification of complications which impact management [23]. TEE is more sensitive than TTE (78–87 % vs. 28 %) in detecting paravalvular abscesses, intracardiac fistulae, and subaortic invasive infection, without loss of specificity [25]. Although the sensitivity of TEE for detecting abnormalities indicative of NVE and PVE is very high, false-negative studies occur in 6–18 % of patients. The rate of false-negative studies can be reduced (4–13 %) by repeat

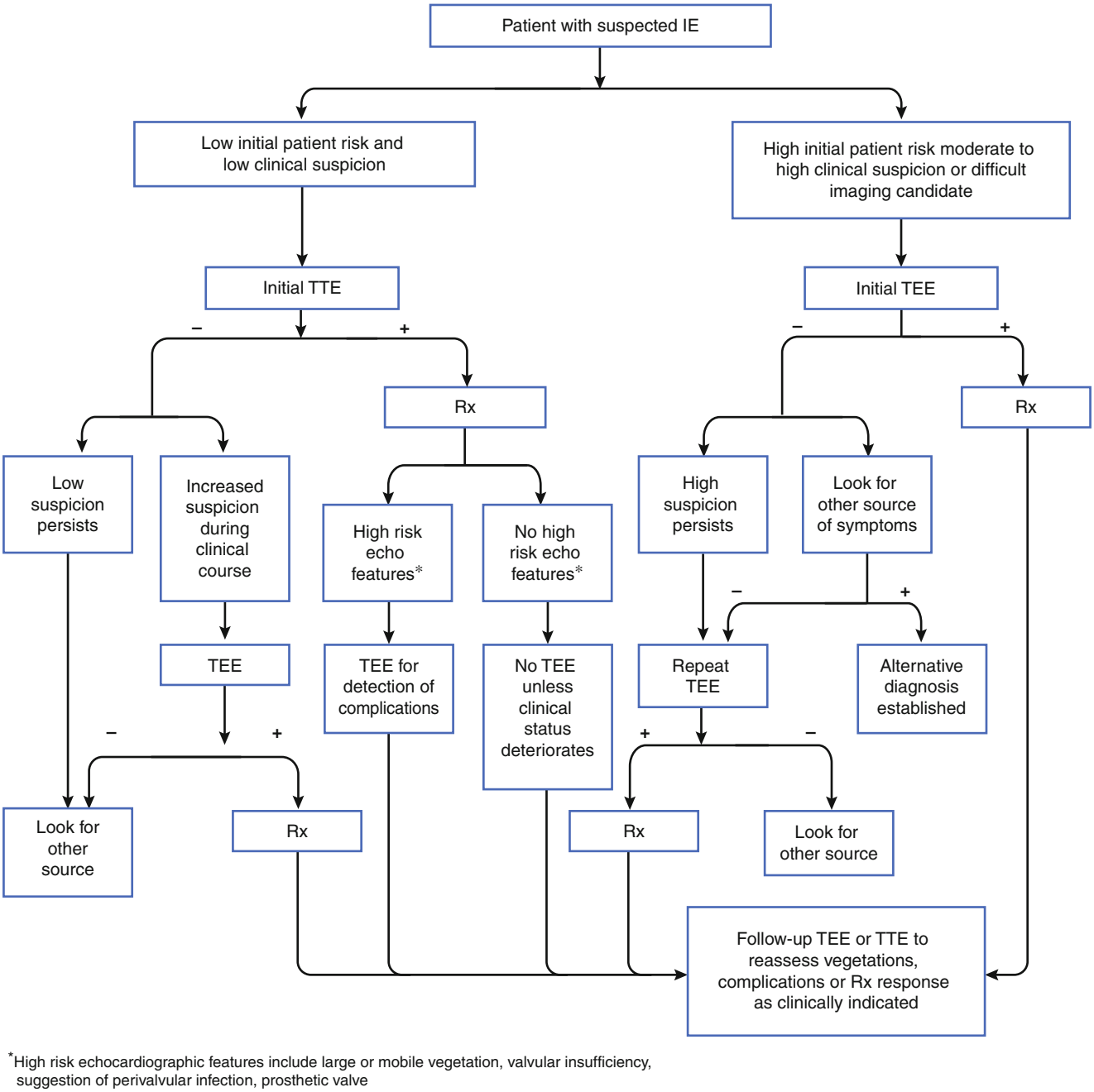


Fig. 30.1 An approach to the diagnostic use of echocardiography (Adapted from Bayer et al. [17]. With permission from WolterKluwers Health)

TEE and multiplane examinations [24]. The diagnostic yield of repeated echocardiography decreases sharply after the second study and is nil after the third [26].

Assuming that all patients with definite or possible IE by the modified Duke criteria require treatment for endocarditis, when clinical and laboratory findings are considered, the incremental information gained from a TEE beyond that from a TTE infrequently alters the decision to treat for endocarditis [27, 28]. For example, among 114 patients with suspected endocarditis studied by both TTE and TEE, 22 classified as possible IE using the TTE data were reclassified as definite IE based on TEE findings. Only 2 patients for whom the diagnosis of IE had been rejected were reclassified as possible IE based on the TEE and now required treatment. Of the 24 patients wherein the classification was changed, 12 had PVE, including both who would have been rejected in the absence of a TEE [28]. In patients at low risk of NVE, a negative high-quality TTE is generally sufficient to rule out endocarditis (Fig. 30.1) [17, 29]. In moderate-risk patients, TEE may be required to exclude IE. Echocardiography, preferably TEE, is an endorsed standard of care for patients with *S. aureus* bacteremia [30]. In a study of 768 patients with

Table 30.4 The evaluation of patients with suspected endocarditis[a]

Timing	Test or procedure	Comment
Admission: (*prior to admission if stable*)	CBC, differential, three blood cultures[b], urine analysis, electrocardiogram, creatinine, bilirubin, AST, alkaline phosphatase, prothrombin time, chest roentgenogram	Tests, other than blood cultures, do not aid with diagnosis but establish baseline for assessing the complications of IE or treatment
After admission:		
24–48 h		
Blood culture positive	TTE	TEE is the initial study of choice with suspected prosthetic valve IE
48–72 h		
Blood culture positive but TTE negative or blood culture and TTE negative	TEE	See Fig. 30.2 and text regarding initiation of therapy
72–96 h		
Blood culture negative	Two blood cultures daily for 2 days[b], ESR, rheumatoid factor, circulating immune complex titer	ESR, circulating immune complex titer, and rheumatoid factor add little value if blood cultures and echocardiogram are positive. May contribute to minor diagnostic criterion
Day 5–10		
Blood cultures remain negative (no antibiotics given)	Serologic testing and special blood cultures for fastidious organisms Retrieve material embolic to a peripheral artery for culture histologic examination, molecular testing	See text: Diagnosis of IE and Microbiology of IE. Obtain infectious disease consultation and advice of microbiology laboratory director. Consider empiric therapy (Fig. 30.2, see text)
	Repeat TEE if initially negative	Increases the yield for vegetations
Any time:		
Focal central nervous system symptoms or finding suggesting localized event	Computerized tomography (with enhancement). If evidence of hemorrhage without mass effect, consider magnetic resonance angiogram or formal angiogram. If no mass effect, consider lumbar puncture	Consider mycotic aneurysm; with acute *S. aureus* IE or new focal symptoms without infarct, consider angiography
Left upper quadrant pain (with/without left shoulder pain)	Image spleen (and kidney) for abscess or infarct	
Intracardiac complication: hemodynamic deterioration, suspected paravalvular infection	Electrocardiogram, echocardiogram	Electrocardiographic conduction changes insensitive indicator of paravalvular abscess. TEE optimal technique

Adapted from Karchmer [20]. With permission from Elsevier
CBC complete blood count, *AST* aspartate aminotransferase, *ESR* erythrocyte sedimentation rate
[a]For patients who are hemodynamically stable and have a subacute presentation
[b]Request that laboratory incubates blood cultures for 3 weeks (indicate diagnosis of infective endocarditis)

nosocomial *S. aureus* bacteremia, 52 of 53 cases of endocarditis (defined by the modified Duke criteria including a 3-month-follow-up) occurred among the 546 patients with ≥1 of the following: bacteremia for 2–4 days after the initial culture, a permanent intracardiac device (prosthetic valve or electrical lead), hemodialysis dependency, spine infection, or non-vertebral osteomyelitis. Only 1 case of endocarditis complicated the 222 bacteremic patients with none of these criteria [31]. These findings, particularly if confirmed in additional studies, suggest TTE, and TEE might be used more selectively to evaluate for possible endocarditis after nosocomial *S. aureus* bacteremia. It is not clear that this approach is appropriate for patients with community onset *S. aureus* bacteremia [31]. Furthermore, decision analysis studies suggest that in those patients at moderate IE risk, a TEE as the initial imaging study is cost-effective in contrast with a two-step approach – TTE and if negative a TEE. [29, 32]. In patients at high risk of IE, a negative TEE is not sufficient to override clinical evidence and exclude the diagnosis [17]. Cardiac catheterization, magnetic resonance imaging, and scintigraphy with various isotopes offer little beyond echocardiography in the anatomic assessment of IE.

Other Studies

Complete blood counts and differential, creatinine, selected liver function tests, prothrombin time, urine analysis, chest

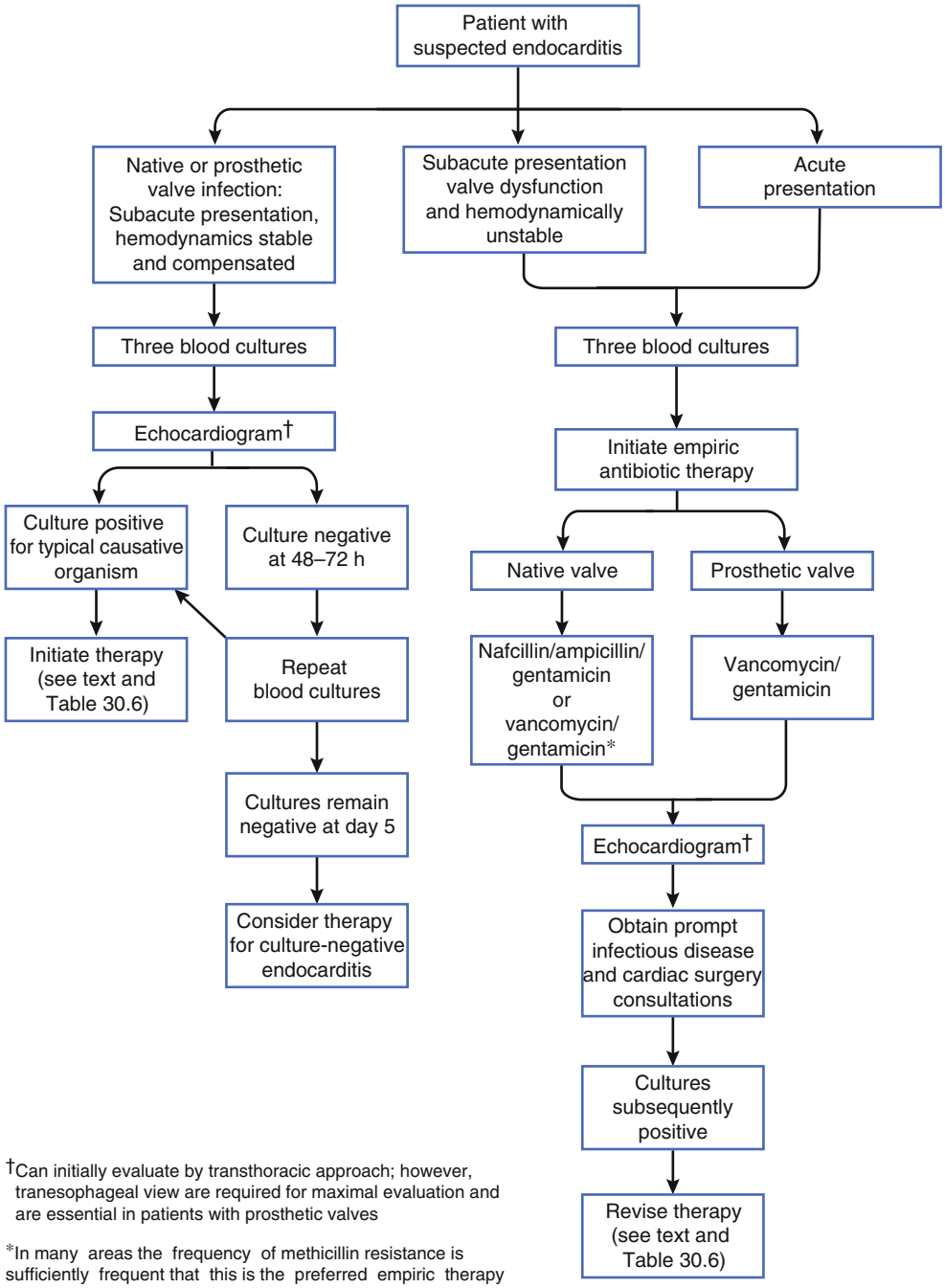


Fig. 30.2 An approach to the initiation of therapy in patients with suspected IE

radiography, and electrocardiogram are often followed serially and may be important in patient management (Table 30.4). Erythrocyte sedimentation rate, C-reactive protein, quantitative circulating immune complexes, immunoglobulin or cryoglobulin measurements, and rheumatoid factor are commonly abnormal in subacute IE and may be useful if incorporated into a minor criterion in the Duke schema. When monitoring response to therapy, a high baseline C-reactive protein and a failure of the C-reactive protein to decrease may harbinger a poor clinical outcome [33].

Causative Microorganisms

Although almost any bacteria or fungal species can cause IE, in fact, a relatively small number of bacterial species cause the majority of cases of IE (Table 30.5). *S. aureus* is the major organism causing acute NVE but also has become the single most common cause of IE in developed countries [4, 5, 35]. Non-beta-hemolytic streptococci, enterococci, coagulase-negative staphylococci, and the HACEK group are the major causes of subacute NVE. Beta-hemolytic

Table 30.5 Microbiology of infective endocarditis in specific clinical settings

	Number of cases (%)							
Organism	Native valve endocarditis		Prosthetic valve endocarditis time of onset after valve surgery			Endocarditis in drug addicts		
	Community acquired *N*=1,677	Healthcare associated N=732	<2 months *N*=199	2–12 months *N*=47	>12 months *N*=282	Right-sided *N*=346	Left-sided *N*=204	Any valves[a] *N*=912
Streptococci[b]	636 (38)	69 (9)	4 (2)	6 (13)	84 (30)	17 (5)	31 (15)	112 (12)
Pneumococci	30 (2)					–	–	–
Enterococci	149 (9)	97 (13)	16 (3)	5 (11)	31 (11)	7 (2)	49 (24)	70 (8)
Staphylococcus aureus	476 (28)	410 (56)	56 (28)	6 (13)	62 (22)	267 (77)	47 (23)	556 (61)
Coagulase-negative staphylococci	96 (6)	83 (11)	60 (30)	17 (36)	34 (12)	–	–	7/(1)
Fastidious gram-negative coccobacilli (HACEK Group)[c]	49 (3)	–	–	–	11 (4)	–	–	–
Gram-negative bacilli	22 (1)	11 (1.5)	23 (12)	2 (4)	13 (5)	17 (5)	26 (13)	45 (5)
Fungi, Candida species	5 (<1)	13 (2)	17 (8)	4 (8)	3 (1)	–	25 (12)	29 (3)
Polymicrobial/ miscellaneous	58 (3)	11 (1.5)	7 (3)	4 (8)	12 (4)	28 (8)	20 (10)	60 (7)
Diphtheroids	–	6 (1)	9 (4)	–	5 (2)	–	–	1 (0.1)
Culture negative	156 (9)	32 (4)	7 (3)	3 (6)	27 (10)	10 (3)	6 (3)	32 (3)

Based on data from Karchmer [20]; Chapter 16, Table 4, pg. 205. Additional data from: [5, 6, 8, 34]

[a]Any valves include cases not specified as right or left sided in publication as well as specified valve

[b]Includes viridans streptococci, *Streptococcus bovis*, other non-group A, groupable streptococci, *abiotrophic* species (nutritionally variant streptococci)

[c]Includes *Haemophilus* species, *Aggregatibacter aphrophilus, Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* species, and *Kingella kingae*

streptococci, *S. pneumoniae,* and *Staphylococcus lugdunensis*, a coagulase-negative staphylococcus species, are associated with valve destruction and an acute presentation. Healthcare-associated NVE often occurs as complication of bacteremia associated with intravascular devices and genitourinary tract manipulations; hence, staphylococci and enterococci are frequent causes (Table 30.5) [3, 6, 36]. Among the *S. aureus*, 20–47 % of isolates are methicillin resistant (MRSA) [3, 6, 36].

Patients with PVE can be divided into three groups: those with infection developing from perioperative events and having onset within 60 days of surgery (early PVE), those with onset a year or more after surgery and most likely resulting from community-acquired transient bacteremia (late PVE), and those developing PVE between 2 and 12 months after valve surgery. The causes of early PVE are largely coagulase-negative staphylococci, *S. aureus*, gram-negative bacilli, and fungi (primarily *Candida* species) [8]. The frequencies of organisms causing late onset PVE are similar to those noted in NVE, except that there is an increased frequency of coagulase-negative staphylococci [8]. Coagulase-negative staphylococci causing PVE within 12 months of valve surgery are predominantly *Staphylococcus epidermidis*, and 85 % are methicillin resistant, whereas 50 % of those causing PVE a year or more after surgery are non-epidermidis species, and only 30 % are methicillin resistant [9]. Like with NVE, healthcare itself is now commonly associated with PVE, and as a result, *S. aureus* is now the most common cause of PVE [8, 34].

Among injecting drug users, *S. aureus* causes more than 50 % of all IE and 70 % of tricuspid valve IE (Table 30.5). Streptococci and enterococci infect previously abnormal left heart valves in these patients. IE due to gram-negative bacilli, particularly Pseudomonas aeruginosa, and fungi occur with increased frequency among drug users. Unusual organisms, e.g., *Corynebacterium, Lactobacillus, Bacillus cereus*, and polymicrobial infections occasionally cause IE in drug users. Infective endocarditis in patients with underlying human immunodeficiency virus (HIV) infection occurs

primarily among injecting drug abusers, and its microbiology is very similar to IE in drug abusers in general.

Many unusual and fastidious organisms cause IE [21, 37]. Some cause IE in unique epidemiologic settings, e.g., *C. burnetii* in Europe and *Brucella* in the Middle East and Mediterranean Basin; others are associated with unique clinical situations, e.g., *Legionella* and *Mycobacterium chelonae* and *Mycoplasma hominis* on prosthetic valves. *Bartonella* species have been implicated increasingly as a cause of IE, often with negative blood cultures, and may account for as many as 3 % of cases of IE overall [21]. *T. whippelii* has been identified as a cause of very indolent, afebrile IE [11].

Antimicrobial Therapy

Antimicrobial therapy capable of killing (as opposed to only inhibiting growth) the organism causing IE is required for optimal treatment. The recommended therapies are based on the precise susceptibility of the etiologic agent combined with prior clinical experience with that species but must be adjusted in consideration of circumstances unique to the patient, i.e., allergies, end-organ dysfunction, interactions with other required medications, or other perceived risks of adverse events. Accordingly, it is crucial to identify the causative organism (see Diagnostic Testing, Blood Cultures). The impact of beginning empiric antimicrobial therapy immediately after blood cultures have been obtained must be carefully considered (Fig. 30.2). In patients with acute endocarditis or with severely compromised hemodynamics who will require urgent valve surgery, rapid initiation of therapy may prevent further cardiac structural damage or reduce the risk of recrudescent infection after valve surgery. However, among hemodynamically stable patients with subacute IE, especially if antibiotics have been given during the prior 2 weeks, therapy should be delayed for 2–5 days while awaiting blood culture results. If initial cultures remain negative, blood cultures should be repeated (Table 30.4 and Fig. 30.2).

Organism-Specific Regimens

Expert committees have developed regimens for the treatment of IE caused by the more commonly encountered causative microorganisms (Table 30.6) [38, 39]. Regimens for treatment of IE involving native and prosthetic valves are usually qualitatively similar (except for staphylococcal infection), but treatment for PVE is given for several weeks longer than that for NVE. In general, compromises in recommended regimens should be avoided unless supported by medical literature and required by untoward events.

Streptococcal IE

Most viridans streptococci and *Streptococcus bovis* that cause IE are susceptible to penicillin (minimum inhibitory concentration [MIC] ≤ 0.1 μg/ml). IE caused by these organisms can be treated with any of the recommended regimens (Table 30.6, 1A–E). IE caused by nutritionally deficient streptococci (now assigned to the genera *Abiotrophia* or *Granulicatella)*, PVE, or complicated streptococcal NVE should not be treated with the 2-week regimen (Table 30.6, 1C). The ceftriaxone regimen (Table 30.6, 1D) can be used in patients with a history of an allergy to penicillin that does not result in urticaria or anaphylaxis-like symptoms (immediate-type allergy). In patients who have had an immediate-type allergic reaction to penicillin or a cephalosporin, treatment with vancomycin is recommended (Table 30.6, 1E). In patients with normal renal function, uncomplicated NVE caused by penicillin-susceptible viridans streptococci has been effectively treated with a 2-week regimen using ceftriaxone 2 g IV plus an aminoglycoside (netilmicin 4 mg/kg/day or gentamicin 3 mg/kg/day) each given as a single daily dose. Combination therapy with penicillin or ceftriaxone for 6 weeks with the option to add gentamicin (1 mg/kg ideal body weight every 8 h) during the first 2 weeks is advocated for the treatment of PVE caused by penicillin-susceptible streptococci.

NVE or PVE caused by streptococci that are relatively resistant to penicillin (MIC ≥ 0.2 μg/ml but < 0.5 μg/ml) and IE caused by group B streptococci (*S. agalactiae*) are treated with combination therapy (Table 30.6, 2A). NVE or PVE caused by even more resistant streptococci (penicillin MIC > 0.5 μg/ml), nutritionally deficient streptococci (now identified as *Abiotrophia* or *Granulicatella* sp.), or *Gemella* sp. is treated with penicillin plus gentamicin or streptomycin (Table 30.6, 3A or B) or vancomycin alone for 6 weeks. If these patients report an immediate-type beta-lactam allergy, vancomycin alone is recommended (Table 30.6, 1E), whereas for those with milder penicillin allergies, ceftriaxone can be substituted for penicillin (Table 30.6, 2B).

Enterococcal IE

Enterococci are inhibited but not killed by penicillin, ampicillin, or vancomycin and are resistant to cephalosporins and antistaphylococcal penicillinase-resistant penicillins, e.g.,

Table 30.6 Recommended therapy for IE caused by specific organisms

Infecting organism	Antibiotic	Dose and route[a]	Duration (weeks)	Comments
1. Penicillin-susceptible viridans streptococci, *Streptococcus bovis*, and other streptococci Penicillin MIC ≤ 0.1 μg/ml	A. Penicillin G	12–18 million units IV daily in divided doses q 4 h	4	
	B. Penicillin G plus	12–18 million units IV daily in divided doses q 4 h	4	Avoid aminoglycoside-containing regimens when potential for nephrotoxicity or ototoxicity is increased
	gentamicin	1 mg/kg IM or IV q 8 h	2	
	C. Penicillin G plus gentamicin	Same doses as noted above	2	See text
	D. Ceftriaxone	2 g IV or IM daily as single dose	4	Can be used in patients with non-immediate penicillin allergy, intramuscular ceftriaxone is painful
	E. Vancomycin[b]	30 mg/kg IV daily in divided doses q 12 h	4	Use for patients with immediate or severe penicillin or cephalosporin allergy. Infuse doses over 1h to avoid histamine-release reaction (red man syndrome)
2. Relatively penicillin-resistant streptococci	A. Penicillin G plus	18–24 million units IV daily in divided doses q 4 h	4	
Penicillin MIC 0.2–0.5 μg/ml	gentamicin	1 mg/kg IM or IV q 8 h	2	
Penicillin MIC ≥ 0.5 μg/ml	B. Penicillin G plus gentamicin	See regimens recommended for enterococcal endocarditis (Ceftriaxone 2 g IV daily as a single dose could be used in lieu of penicillin or ampicillin in patients with non-immediate penicillin allergy)	4–6	Preferred for nutritionally variant (pyridoxal or cysteine requiring) streptococci *(Abiotrophia* or *Granulicatella* sp.) or *Gemella* sp.
3. Enterococci (in vitro evaluation for MIC to penicillin and vancomycin, beta-lactamase production, and high-level resistance to gentamicin and streptomycin required)	A. Penicillin G plus	18–30 million units IV daily in divided doses q 4 h	4–6	See text for use of streptomycin instead of gentamicin in these regimens. Four weeks of therapy recommended for patients with shorter history of illness (<3 months) who respond promptly to treatment. See text regarding duration of aminoglycoside. Gentamicin peaks are ≈ 3 μg/ml and troughs < 1 μg/ml
	gentamicin	1–1.5 mg/kg IV q 8 h	4–6	
	B. Ampicillin plus	12 q IV daily in divided doses q 4 h	4–6	
	gentamicin	Same dose as noted above	4–6	
	C. Vancomycin[b] plus	30 mg/kg IV daily in divided doses q 12 h	4–6	Use for patients with penicillin allergy. Do not use cephalosporins.
	gentamicin	Same dose as noted above	4–6	Gentamicin peaks are ≈ 3 μg/ml and troughs < 1 μg/ml
4. Staphylococci infecting native valves (assume penicillin resistance) Methicillin-susceptible	A. Nafcillin or oxacillin plus optional addition of gentamicin[c]	12 q IV daily in divided doses q 4 h	6	Penicillin – 18–24 million units daily in divided doses q 4 h – can be used instead of nafcillin, oxacillin, or cefazolin if strains do not produce beta-lactamase
		Same dose as above	3–5 days	
	B. Cefazolin plus optional addition of gentamicin[c]	2 g IV q 8 h	6	Use cefazolin for patients with non-immediate penicillin allergy
		Same dose as above	3–5 days	
	C. Vancomycin[b]	30 mg/kg IV in divided doses q 12 h	6	Use for patients with immediate penicillin allergy
5. Staphylococci infecting native valves, methicillin resistant	A. Vancomycin[b]	30 mg/kg IV in divided doses q 8–12 h	6	Daptomycin 6 mg/kg is comparable to vancomycin for infection limited to tricuspid or pulmonic valves

Table 30.6 (continued)

Infecting organism	Antibiotic	Dose and route[a]	Duration (weeks)	Comments
6. Staphylococci infecting prosthetic valves, methicillin susceptible (assume penicillin resistance)	A. Nafcillin or oxacillin plus	12 g IV daily in divided doses q 4 h	6	First-generation cephalosporin or vancomycin could be used in penicillin allergic patients.
	gentamicin plus	1 mg/kg IV or IM q 8 h	2	
	rifampin[d]	300 mg p.o. q 8 h	6	Use gentamicin during initial 2 weeks. See text for alternates for gentamicin. For patients with immediate penicillin allergy, use regimen 7
7. Staphylococci infecting prosthetic valves, methicillin resistant	A. Vancomycin[b] plus	30 mg/kg IV in divided doses q 12 h	6	Use gentamicin during the initial 2 weeks of therapy. See text for alternatives to gentamicin. Do not substitute a cephalosporin or carbapenem for vancomycin
	gentamicin plus	1 mg/kg IV or IM q 8 h	2	
	rifampin[d]	300 mg p.o. q 8 h	6	
8. HACEK organisms[e]	A. Ceftriaxone	2 g IV or IM daily as a single dose	4	Cefotaxime or other third-generation cephalosporin in comparable doses may be used
	B. Ampicillin/sulbactam	12 q IV daily in divided doses q 4 h	4	A fluoroquinolone may be considered for patients who cannot tolerate beta-lactam antibiotics

[a]Recommended doses are for adults with normal renal and hepatic function. Doses of gentamicin, streptomycin, vancomycin, and daptomycin must be adjusted in patients with renal dysfunction. Use ideal body weight to calculate doses for aminoglycosides (men = 50 kg + 2.3 kg/in. over 5 ft; women = 45.5 kg plus 2.3 kg/in. over 5 ft). Use actual body weight to calculate doses for vancomycin and daptomycin

[b]Trough levels should be 15–20 μg/ml

[c]See text regarding opinion to add gentamicin. The risk-benefit of using gentamicin is uncertain (see text)

[d]Rifampin increases the dose of warfarin or dicumarol required for effective anticoagulation

[e]HACEK organisms include *Haemophilus parainfluenzae*, *Aggregatibacter aphrophilus*, *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*

nafcillin, oxacillin, and cloxacillin. Optimal antimicrobial therapy for enterococcal IE requires a bactericidal synergistic interaction between a cell wall-active antibiotic (penicillin, ampicillin, vancomycin, or teicoplanin [not available in the United States]) that at clinically achievable concentrations inhibits the organism and an aminoglycoside (gentamicin or streptomycin) for which the organism does not have high-level resistance [40]. If high concentrations of streptomycin (2,000 μg/ml) or gentamicin (500–1,000 μg/ml) fail to inhibit the growth of an enterococcus, e.g., there is high-level resistance, and the aminoglycoside cannot exert a lethal effect or contribute to bactericidal synergism. High-level resistance to gentamicin predicts the inefficacy of kanamycin, amikacin, tobramycin, and netilmicin as well. The ability of aminoglycosides other than streptomycin or gentamicin to contribute to synergy, even against organisms not highly resistant to gentamicin, is unpredictable; thus, they should not be used to treat enterococcal IE.

Each of the standard regimens recommended for the treatment of enterococcal IE combines a cell wall-active agent and gentamicin and anticipates that a synergistic bactericidal effect will be achieved (Table 30.6, 3A–C). If the causative enterococcus does not exhibit high-level resistance to streptomycin, this aminoglycoside (9.5 mg/kg ideal body weight given intramuscularly or intravenously every 12 h to achieve peak serum concentrations of 20 μg/ml) can be used in lieu of gentamicin. When there is a history of an allergic reaction to a penicillin, the patient with enterococcal IE must be treated with vancomycin plus an aminoglycoside (Table 30.6, 3C) or undergo desensitization and subsequent treatment with a penicillin or ampicillin regimen (Table 30.6, 3A or B). Cephalosporins combined with aminoglycosides do not achieve bactericidal synergy. Aminoglycosides are not administered in single daily doses. A bacteriologic cure can be achieved in 85 % of patients with enterococcal NVE or PVE who are treated with a synergistic combination regimen.

Enterococci have become increasingly resistant, and regimens that were previously predictably effective now require careful assessment. To structure an effective regimen, the enterococcus must be tested for its susceptibility to ampicillin and vancomycin, for beta-lactamase production, and for high-level resistance to gentamicin and streptomycin. With this information, a synergistic bactericidal regimen can usually be designed; if not, an alternative can be considered (Table 30.7). If synergy cannot be effected, e.g., high-level resistance is present to both streptomycin and gentamicin or there is no effective cell wall-active antibiotic, aminoglycoside treatment offers no benefit and may result in significant toxicity. Bactericidal synergy against *E. faecalis* may be achieved by double beta-lactam combinations. Ceftriaxone (2 g q 12 h) plus ampicillin (2 g q 4 h) has been an effective treatment for enterococcal IE caused by isolates with high-level resistance to all aminoglycosides as well as more susceptible isolates [41].

Prolonged administration of aminoglycosides is often associated with nephrotoxicity or oto-vestibular toxicity. If there is

Table 30.7 Strategy for selecting therapy for enterococcal endocarditis caused by strains resistant to components of the standard regimen

I. Ideal therapy includes a cell wall-active agent plus an effective aminoglycoside (streptomycin or gentamicin) to achieve bactericidal synergy
II. Cell wall-active antimicrobial
A. Determine MIC for ampicillin and vancomycin; test for beta-lactamase production (nitrocefin test)
B. If ampicillin and vancomycin susceptible, use ampicillin
C. If ampicillin resistant (*MIC* ≥ 16 μg/ml), use vancomycin
D. If beta-lactamase produced, use vancomycin or consider ampicillin-sulbactam
E. If ampicillin resistant and vancomycin resistant (*MIC* ≥ 16 μg/ml), consider teicoplanin[a]
F. If ampicillin resistant and highly resistant to vancomycin and teicoplanin (*MIC* ≥ 256 μg/ml), see IV
III. Aminoglycoside to be used with cell wall-active antimicrobial
A. Test for high-level resistance to streptomycin (growth in media with 2,000 μg/ml) and gentamicin (growth in media with 500–2,000 μg/ml)
B. If no high-level resistance, use gentamicin. If high-level resistance to gentamicin but no high-level resistance to streptomycin, use streptomycin
C. If high-level resistance to gentamicin and streptomycin, omit aminoglycoside therapy; use prolonged therapy with cell wall-active antimicrobial (8–12 weeks) (See II, B–E)
IV. Alternative regimens and approaches
A. Treatment with chloramphenicol, tetracyclines, fluoroquinolones, rifampin, or trimethoprim-sulfamethoxazole of questionable efficacy
B. *Enterococcus faecalis* may be treated effectively with high doses of ceftriaxone plus ampicillin (see text)
C. Limited experience suggests possible efficacy of linezolid or daptomycin
D. Consider quinupristin/dalfopristin therapy for IE due to susceptible *E. faecium*
E. Consider surgery during suppressive therapy with cell wall-active antimicrobial (II) or an alternative regimen (IV, B, C)

[a]Not approved by the Food and Drug Administration for use in the United States

a high risk or if actual toxicity arises, the aminoglycoside arm of the regimen often can be truncated without loss of efficacy. Among 93 patients with enterococcal IE, 75 (81 %) were cured with combination regimens wherein the aminoglycoside component was administered a median of 15 days [42]. Of the 75 who were cured, 40 (who did not undergo surgery) were cured with less than 22 days of aminoglycoside therapy.

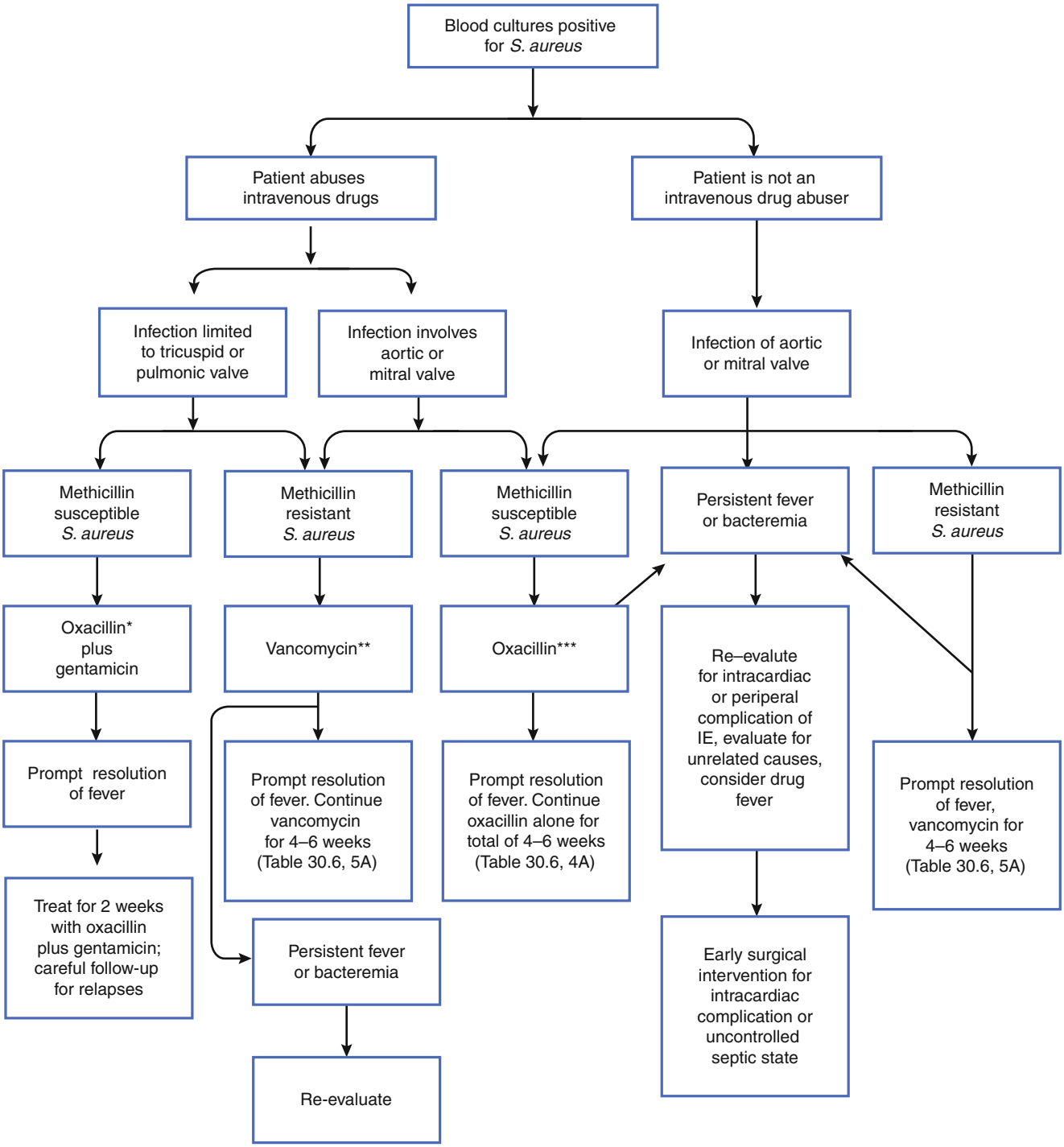
Staphylococcal IE

More than 95 % of *S. aureus* and coagulase-negative staphylococci produce a beta-lactamase and thus are resistant to penicillin. Many *S. aureus,* both those acquired nosocomially and in the community, and many coagulase-negative staphylococci are resistant to methicillin also (which implies resistance to all available beta-lactam antibiotics except ceftaroline). These organisms remain largely susceptible to vancomycin, teicoplanin, daptomycin, telavancin, and ceftaroline. The regimens recommended for the treatment of staphylococcal IE are organized around susceptibility or resistance to methicillin (the penicillinase-resistant penicillins), the valve(s) involved, and infection of a prosthetic valve (Table 30.6, 4A–C, 5, 6, 7 and Fig. 30.3). Whether strains are coagulase-positive (*S. aureus)* or negative does not impact antimicrobial selection beyond susceptibility data.

Methicillin-susceptible staphylococcal infection of a native aortic or mitral valve should be treated with a parenteral penicillinase-resistant penicillin, e.g., nafcillin or oxacillin (Table 30.6, 6A). The addition of gentamicin for the initial 3–5 days of treatment seeks to achieve more rapid control of infection through the synergistic interaction of combination therapy. Combination therapy has reduced slightly the duration of bacteremia in these patients but has not been shown to reduce the mortality rates. Recent data suggest that even 3–5 days of gentamicin, like longer courses, when combined with either vancomycin or antistaphylococcal penicillins results in a significant frequency of nephrotoxicity (≈20 %) particularly among patients aged 65 or more [43]. In the absence of improved outcome, the nephrotoxicity risk argues against routine use of optional gentamicin. Patients with a history of penicillin allergy can be treated with cefazolin or vancomycin, based on the nature of the allergic reaction (Table 30.6, 6B–C).

IE caused by methicillin-resistant staphylococci is treated with vancomycin (trough concentrations of 15–20 μg/ml (Table 30.6, 6C)). In general, rifampin is not used to treat NVE due to staphylococci. Endocarditis caused by methicillin-resistant *S. aureus* with vancomycin minimum inhibitory concentrations >1.0 μg/ml (still susceptible to vancomycin) have been associated with persistent bacteremia, emergence of resistance to vancomycin and daptomycin, and failure of vancomycin therapy [30, 44–46]. If still susceptible to daptomycin, this antibiotic given in non-FDA-approved doses of 8–10 μg/ml may be effective [47]. The complexity of effective treatment of these infections exceeds the scope of this chapter. Infectious disease consultation should be sought [45, 46]

Isolated tricuspid valve endocarditis caused by methicillin-susceptible *S. aureus* that is not complicated by paravalvular extension or metastatic extracardiac focal infection can often be treated with a penicillinase-resistant penicillin plus gentamicin (1 mg/kg ideal body weight every 8 h) administered for only 2 weeks. A significant percentage of these patients may have prolonged fevers and require longer courses of treatment. Vancomycin does not appear to be a suitable alternative to the penicillinase-resistant penicillin in this short-course regimen, which effectively excludes highly penicillin allergic patients and those infected with methicillin-resistant *S. aureus* from this short-course treatment.



*Can use nafcillin; for person with penicillin allergy that is not anaphylactic/urticarial type, may use first generation cephalosporin instead of oxacillin (Table 30.6, 4B). If patients have anaphylactic or immediate (urticarial) penicillin allergy, use vancomycin (Table 30.6, 4C). Gentamicin is used with beta lactam antibiotic here to achieve synergy and allow two week therapy. If vancomycin is used in lieu of beta lactam two week therapy is ineffective therefore do not use gentamicin.

**Daptomycin is a comparably effective alternative for treatment of right-sided endocarditis.

***Routine use of gentamicin is of questionable value (see text). Do not use vancomycin instead of oxacillin or nafcillin- for convenience only; patients with penicillin allergy are treated with cefazolin or vancomycin (Table 30.6, 4B, or 5A).

Fig. 30.3 Treatment of native valve endocarditis caused by *Staphylococcus aureus* (Adapted from Karchmer [20]. With permission from Elsevier)

Treatment with daptomycin 6 mg/kg/day as a single dose is comparable to vancomycin treatment of methicillin-resistant *S. aureus* right-sided IE [48].

A multiple drug regimen administered for 6–8 weeks is recommended for the treatment of staphylococcal PVE (Table 30.6, 6A, 7A) [9]. Rifampin, because of its unique ability to kill staphylococci that are adherent to foreign materials or that are not replicating, is an essential component of optimal therapy. However, rifampin resistance emerges frequently in this setting even when rifampin is administered in combination with a beta-lactam antibiotic or vancomycin. To prevent the emergence of rifampin resistance, a third antibiotic, preferably gentamicin if the staphylococcus is susceptible to achievable serum concentrations, is included in the initial 2 weeks of treatment. If the staphylococcus is resistant to gentamicin, another aminoglycoside or a fluoroquinolone to which the organism is susceptible should be used [9]. Treatment for staphylococcal PVE should be initiated with a penicillinase-resistant penicillin or vancomycin plus gentamicin; rifampin should be added only after the susceptibility of the staphylococcus to gentamicin has been confirmed or an effective alternative to gentamicin has been initiated.

HACEK Endocarditis

Beta-lactamase production has been confirmed in some isolates resulting in resistance to ampicillin. Third-generation cephalosporins, to which HACEK organisms are exquisitely susceptible, are recommended for treatment (Table 30.6, 8A).

Other Organisms Causing Endocarditis

Limited clinical experience with other causes of IE does not allow consensus therapeutic recommendations [37]. IE caused by *Streptococcus pneumoniae* occurs infrequently but is highly destructive and often requires surgical intervention to correct valvular dysfunction. Mortality rates often exceed 35 %. Because of the increasingly widespread resistance to penicillin among pneumococci, initial therapy with ceftriaxone plus vancomycin (Table 30.6, 1D and E) is recommended. If the pneumococcus MIC to penicillin or ceftriaxone is ≤1.0 μg/ml, either antimicrobial can be used; if the MIC is ≥2.0 μg/ml, treatment with vancomycin is advised. If pneumococcal IE is complicated by concomitant meningitis, therapy must be adjusted based on the susceptibility of the isolate to insure effective antibiotic concentrations in the cerebrospinal fluid [49]. Penicillin, or in allergic patients ceftriaxone, is recommended for initial therapy for the treatment of IE caused by *Streptococcus pyogenes* (Group A) [50].

The preferred treatment for IE caused by *P. aeruginosa* combines an antipseudomonal penicillin (ticarcillin or piperacillin) and, if the isolate is susceptible, high doses of tobramycin (8 mg/kg ideal body weight daily in divided doses every 8 h to yield peak serum concentrations of 15 μg/ml). Patients with this form of endocarditis often experience intracardiac complications, persistent infection, and require valve replacement surgery. The treatment of IE caused by *Enterobacteriaceae* should be based upon reported experience with the specific genera. Treatment often combines a third-generation cephalosporins or a carbapenem (imipenem or meropenem) and an aminoglycoside [50, 51].

Corynebacterial IE involving prosthetic or native valves may be caused by various species, including *Corynebacterium jeikeium* and non-toxigenic *Corynebacterium diphtheriae.* Usually, corynebacteria are susceptible to penicillin, aminoglycosides, and vancomycin. Aminoglycoside-susceptible strains are killed synergistically by these agents in combination with penicillin. Corynebacterial IE is generally treated with penicillin plus an aminoglycoside or with vancomycin.

Optimum antibiotic therapy for *Bartonella* IE is not known. Aminoglycosides have bactericidal activity against *Bartonella.* Regimens that have included an aminoglycoside for 2 or more weeks, often administered in combination with a beta-lactam antibiotic since therapy was initiated for apparently blood culture-negative IE, have yielded higher cure rates than non-aminoglycoside-containing regimens [52]. Many of these patients have undergoing valve replacement surgery. Some authors suggest several months of a fluoroquinolone as well. Outcomes have been inferior in patients treated with doxycycline without an aminoglycoside [52].

Treatment of IE caused by *C. burnetii* with doxycycline plus a fluoroquinolone for periods ranging from 4 years to indefinitely, with valve surgery as indicated, yields survival rates exceeding 90 % [53]. Shorter courses (18 months to 4 years) of doxycycline 100 mg orally twice daily plus hydroxychloroquine 200 mg orally three times daily (adjusted subsequently to 150–800 mg daily to maintain a serum concentration of 0.8–1.2 μg/ml) were as effective as doxycycline plus a quinolone [53]. Photosensitivity, and potential phototoxicity, is a consequence of both regimens. Patients with acute Q fever who have valve abnormalities, especially prosthetic valves, are at high risk of developing endocarditis. Endocarditis can be prevented by treating acute Q fever with doxycycline plus hydroxychloroquine for 1–15 months [54].

Amphotericin B, probably in a liposomal formulation and often combined with flucytosine, remains the antimicrobial of choice for treating fungal endocarditis, the majority of which is caused by *Candida* sp. and occurs in injecting drug users or patients with prosthetic valves. Limited experience has suggested that *Candida* IE can be treated effectively with an echinocandin (caspofungin 50–150 mg/day, micafungin 100–150 mg/day, or anidulafungin 100–200 mg/day). After

becoming stable with negative blood cultures, patients with susceptible organisms can be treated with high-dose fluconazole. Many advocate long-term, if not indefinite, suppression with fluconazole orally [55].

Culture-Negative Endocarditis

Treatment of blood culture-negative IE requires consideration of clinical presentation and epidemiologic information, the adequacy of the cultures submitted, confounding of prior antimicrobial therapy, and the valves at risk – native vs. prosthetic. The desire to cover all likely pathogens must be balanced against the complexity and toxicity of required multidrug therapy. Consideration of common bacterial pathogens causing native or prosthetic valves (early vs. late onset) directs therapy in settings where cultures are negative because they are inadequate or are confounded by prior therapy. In other settings, the rare causes of endocarditis that do not grow in routine blood cultures (*Bartonella, Coxiella, Tropheryma whippelii*, *Brucella* sp., non-candida fungi) must be sought with special tests and considered for treatment. The complexity of treatment for culture-negative IE is beyond the scope of this chapter and should be guided by an infectious disease expert [38, 39].

Monitoring Antimicrobial Therapy

Clinical and laboratory monitoring to assess the response to therapy and to allow prompt detection of complications of IE itself or of therapy is essential. Persistent fever beyond 7–10 days of presumably effective therapy can indicate treatment failure, paravalvular infection, or an extracardiac focal infection. Recrudescence of fever that had previously resolved suggests systemic emboli, processes unrelated or indirectly related to IE (catheter-related infection, deep vein thrombophlebitis, etc.) or drug fever, the latter particularly if fever recurs during the third or fourth week of beta-lactam treatment. Checking serum bactericidal titers, the highest dilution of a patient's serum that kills 99.9 % of a standard inoculum of the infecting organism, is no longer recommended when patients are treated with a consensus recommendation. Vancomycin and aminoglycoside serum concentrations should be monitored to insure appropriate dosing. Renal and hepatic function as well as complete blood counts should be monitored regularly when the treatment has the potential to adversely impact these areas. Repeat blood cultures should be obtained to assess persistent or recrudescent fever, to document cure 2–8 weeks after completing therapy, and to assess relapse if fever recurs during 2–3 months after treatment. Electrocardiograms, echocardiograms, and special radiologic imaging studies should be obtained or repeated if intracardiac or focal extracardiac complications are suspected (Table 30.4).

Outpatient Antimicrobial Therapy

Those patients who have responded to antimicrobial therapy and whose fever has resolved; who have no symptoms or signs suggesting threatening intracardiac or extracardiac complications; who are fully compliant; who have a stable, suitable home situation; and who can be followed carefully can be considered candidates for outpatient therapy. Most complications of IE arise during the initial 2 weeks of therapy. Consequently, IE patients generally, and those at increased risk for complications (e.g., acute endocarditis, *S. aureus* endocarditis, PVE) in particular, should be treated in settings that allow daily physician monitoring (usually as an inpatient) during this interval. Thereafter, they can be safely considered for outpatient therapy. Before beginning home therapy, patients must be fully appraised of the potential complications of IE and instructed to immediately seek medical care if complications or unanticipated symptoms develop. Although outpatient therapy may reduce the cost of treatment, shifting therapy to the outpatient setting must not compromise antimicrobial therapy or the required clinical and laboratory monitoring.

Surgical Treatment

Although the mortality associated with IE can be attributed in part to the increased age of patients and comorbidities, intracardiac and central nervous system complications also contribute significantly. In a study of 513 patients with complicated left-sided IE and an overall mortality rate of 26 %, 7 variables were, in a multivariate analysis, significantly associated with mortality at 6 months. These were assigned a weighted point score based on the strength of the association: Charlson comorbidity score ≥2, 3 points; moderate to severe congestive heart failure, 3 points; altered mental status, 4 points; *S. aureus* infection, 6 points; non-streptococcal infection other than *S. aureus*, 8 points; and medical therapy only, 5 points. Surgical intervention was associated with reduced mortality (odds ratio 0.35 (0.23–0.54, 95 % confidence interval)). Mortality could be predicted by the point score as follows: ≤6 points, 5–7 %; 7–11 points, 15–19 %; 12–16 points, 32 %; and >15 points, 59–69 % [56]. In other large studies, multivariable analyses have indicated that mortality is associated with advanced age, diabetes mellitus, healthcare-associated IE, NY Heart Association class III and IV heart failure, *S. aureus* or fungal infection, stroke, paravalvular complications, and septic shock; in some studies, mortality was reduced by surgical intervention [8, 57–61]. These studies suggest that some life-threatening intracardiac complications, as well as instances when antimicrobial therapy fails, can be effectively treated surgically and improve outcome.

Table 30.8 Clinical circumstances suggesting cardiac surgical intervention in patients with endocarditis

Indications[a]
Moderate to severe congestive heart failure due to valve dysfunction
Rupture into the pericardium
Partially dehisced unstable prosthetic valve
Rupture of a sinus of Valsalva aneurysm into the right heart
Persistent bacteremia in the face of optimal antimicrobial therapy
Absence of effective, bactericidal therapy
Fungal endocarditis, Brucella endocarditis, no effective antimicrobial therapy available
S. aureus prosthetic valve endocarditis with an intracardiac complication
Relapse of PVE after optimal antimicrobial therapy
Persistent unexplained fever (≥10 days) in culture-negative PVE
Relative indications[b]
Perivalvular extension of infection (myocardial, septal, or annulus abscess, intracardiac fistula)
Poorly responsive *S. aureus* endocarditis involving the aortic or mitral valve
Relapse of native valve IE after optimal antimicrobial therapy
Large (>10 mm diameter) hypermobile vegetations
Persistent unexplained fever (≥10 days) in culture-negative native valve endocarditis
Endocarditis due to highly antibiotic-resistant enterococci or gram-negative bacilli

Adapted from Karchmer [20]. With permission from Elsevier
[a]Cardiac surgery required for optimal outcome
[b]Surgery, while not always required, must be carefully considered

Recent studies using propensity analysis and multivariable analyses which adjust for prognostic factors and predictors of surgery have demonstrated a survival benefit for surgical treatment. Survival benefit is not always apparent if mortality at hospital discharge is the outcome; however, mortality is significantly reduced with follow-up 6 months after hospital discharge [57, 58, 62, 63]. Benefit accrues earliest in those with the most significant complications – the greatest propensity for surgery – aortic valve infection, congestive heart failure, and intracardiac abscess [58, 63]. Furthermore, in spite of a greater risk of postoperative valve dysfunction and relapse, surgery during the first week of treatment was associated with reduced 6-month mortality in those with the strongest indication for surgery – young patients with *S. aureus* IE, large vegetations, and heart failure [15]. Patients operated on early with lesser indications for surgery have a trend, although not significant, to increased 6-month mortality [15].

Clinical events and microbiology serve as indications for cardiac surgery (Table 30.8). Surgical indications can be divided into relative and more absolute indications; however, even the latter circumstances are to some degree relative. The treatment of each patient requires that the risk-benefit ratio and the timing of surgery be carefully evaluated and the decisions individualized. Often it is a combination of findings, rather than a single observation, that indicates the need for surgery [64].

Specific Indications

Congestive Heart Failure Due to Valve Dysfunction

Moderate to severe heart failure (New York Heart Association class III or IV) due to valve dysfunction portends a very poor prognosis; however, this can be improved by surgical intervention [9, 15, 63, 64]. In a retrospective, but rigorously controlled, analysis of patients with left-sided IE, after adjustments for clinical circumstances associated with mortality and indications for surgical intervention, mortality at 6 months for those with moderate to severe heart failure treated surgically was 12 %, similar to mortality for those with mild or no heart failure treated medically or surgically, whereas mortality for those with moderate to severe heart failure treated medically was significantly greater, 50 % [62]. In another multivariable analysis, valve surgery during the initial hospitalization was independently associated with reduced hospital and 1-year mortality among 1,359 patients with IE and any heart failure, but the absolute reduction in mortality was greater in those with NYHA class III and IV symptoms [58]. Vegetations that obstruct the valve orifice may also cause congestive heart failure and necessitate surgery. Repair of the mitral valve fenestrations and ruptured chordae tendineae allows correction of valve dysfunction in the setting of either active or healed IE without the enduring burden of a prosthetic valve.

Perivalvular Infection

In 10–15 % of patients with NVE and 45–60 % of those with PVE, perivalvular infection complicates endocarditis [9, 25]. In NVE, this complication occurs primarily with aortic valve infection. In patients with PVE or endocarditis involving native aortic valves, clinical findings may suggest perivalvular infection: persistent unexplained fever after 10 days of appropriate antibiotic therapy, pericarditis, and new-onset persistent electrocardiographic conduction disturbance [9, 25]. As an indicator of perivalvular abscess, new conduction disturbances have low sensitivity (28–53 %) [25]. The most sensitive method for detection of perivalvular infection is multiplane TEE with color Doppler [24, 25]. Among the clinical findings which suggest a need for cardiac surgery, partially dehisced unstable prosthetic valve, rupture of a periaortic abscess into the pericardial space, rupture of a sinus of Valsalva aneurysm into the right heart, and relapse of PVE after optimal therapy are often manifestations of invasive infection [64]. Occasional patients with perivalvular infection will be cured with medical treatment alone; the majority, however, require surgical intervention [64].

Uncontrolled Infection

The major manifestations of uncontrolled infection are continued positive blood cultures during therapy and persistent fever. Other causes of continued fever must be excluded before fever can be judged to be due to failure of antimicrobial therapy. Undrained perivalvular abscess may result in failure of antimicrobial therapy. For some organisms, predictable effective bactericidal therapy is not available, and surgical excision of infected valves is necessary to cure IE: fungi, *P. aeruginosa*, other highly resistant gram-negative bacilli, enterococci for which synergistic killing cannot be effected, *Brucella* species, and possibly *C. burnetii* (see Specific Therapy) [64].

S. aureus IE

S. aureus infection of native aortic or mitral valves and prosthetic valves has been associated with mortality rates of 22–46 % and independently associated with risk of hospital mortality [3–5, 65]. Retrospective studies suggest that the survival of patients with *S. aureus* left-sided NVE who appear to have perivalvular infection, remain septic during the initial week of treatment (with or without bacteremia), or who have TTE demonstrable vegetations may be improved by early aggressive surgical intervention [15]. Mortality in patients with *S. aureus* PVE is significantly increased among those with intracardiac complications and is significantly reduced by surgical intervention during active disease [65]. Endocarditis due to *S. aureus* that is restricted to the tricuspid valve can usually be cured without surgical intervention in spite of persistent fever and pulmonary emboli.

Unresponsive Culture-Negative IE

Patients with echocardiographically confirmed but blood culture-negative IE who fail to become afebrile during empiric antibiotic therapy should be considered for valve replacement. This clinical scenario suggests that empiric therapy is either not effective or that there is invasive infection. Before proceeding with surgery, especially when valve function is intact, it is important to rule out other causes of persistent fever, including drug reaction, focal undrained metastatic infection, intercurrent complications, and noninfectious endocardial involvement (atrial myxoma, marantic endocarditis, antiphospholipid antibody syndrome, lupus erythematosus with valvular disease).

Prevention of Systemic Emboli (Vegetations >10 mm in Diameter)

Vegetations on the aortic or mitral valve greater than 10 mm in diameter and those on the anterior leaflet of the mitral valve are associated with a higher frequency of systemic emboli than are smaller vegetations (37 vs. 19 %) [15, 66]. Endocarditis caused by *S. aureus* is also associated with an increased risk of systemic emboli. The risk of embolization, however, is markedly reduced after 2 weeks of effective antimicrobial therapy [13, 14, 67]. Additionally, the mortality and residual morbidity associated with embolic events is largely confined to those emboli that lodge in the central nervous system or the coronary arteries [15]. It is not possible to predict based on echocardiographic findings which patients would experience enhanced survival and reduced morbidity from surgical intervention, particularly when the hazards of surgery and the burden of a prosthetic valve are considered. Consequently, the role of surgery to prevent emboli remains controversial. Surgery is often considered after one or more embolic events during the initial 10 days of antibiotic therapy when there is a large residual vegetation [64]; however, even here, the risk, including perioperative neurologic deterioration (see below), and benefits must be weighed. Rarely is vegetation size alone an indication for surgery (perhaps only with exceptionally large hypermobile vegetations). Benefit from surgery in terms of reduced embolic events is most likely when surgery is undertaken early in therapy, the vegetation has characteristics associated with increased embolic risk, and other clinical features suggest that surgery may be beneficial, e.g., valve dysfunction with moderate congestive heart failure, an antibiotic-resistant organism, and suspected paravalvular infection. Vegectomy and repair of the mitral valve, particularly with younger patients, may reduce the risk of postoperative morbidity and thus enhance the net benefit of surgery in this circumstance [39, 50, 64].

Cardiovascular Electronic Device Infection

Cardiovascular implantable electronic devices (CIED), including pacemakers and implantable cardioverter-defibrillators, become infected with an incidence of 1.37/1,000 device-years for pocket infection alone and 1.14/1,000 device-years for device-related endocarditis. Among a cohort of 2,760 patients with definite IE, 177 (6.4 %) involved CIED [7]. These infections generally occur in conjunction with contamination at the time of implantation or generator change or when the devices erode through the skin. Occasionally, bacteremic seeding occurs, primarily with *S. aureus.* Staphylococci, divided almost equally between *S. aureus* (45 % are MRSA) and coagulase-negative staphylococci, are the major pathogens accounting for 70 % of cases with occasional cases due to enterococci, streptococci, *Corynebacterium* sp., and gram-negative bacilli. Echocardiography (TEE) identifying masses on the transvenous lead or along the intracardiac portion of the lead combined with positive blood cultures is diagnostic of CIED IE, although masses on the lead in the absence of positive blood cultures may be sterile thrombi. CIED IE is commonly complicated by septic pulmonary emboli. Infection involving the generator pocket only is often apparent clinically but can be diagnosed definitively by culture of a pocket aspirate.

Bacteremia may occur in patients with CIED in the absence of CIED IE. This is seen when other sites of infection are noted. Occasionally, left-sided IE occurs without concurrent CIED IE. *S. aureus* bacteremia in temporal proximity to device implantation or manipulation generally is considered CIED IE and managed accordingly.

Treatment of CIED infection limited to the generator pocket includes removal of the entire device and 10–14 days of antibiotic therapy and wound care. Complete device removal is also recommended for CIED IE. Antibiotic therapy in these patients follows guidelines for the analogous organism causing NVE with adjustments if extracardiac complications are present. If a replacement CIED is required, implantation at a new site is usually delayed 7 days for generator pocket infection and at least 14 days after clearing bacteremia for CIED IE [68]. Treatment of CIED IE without device removal, while attempted, is associated with a 7-fold increase in 30-day mortality. In spite of rare complications and mortality with CIED removal, when compared with delayed device removal and antibiotic therapy or no device removal, immediate device removal is associated with a 3-fold decrease in 1-year mortality [69]. Retention of infected CIED with suppressive antibiotic therapy should be restricted to patients who are not candidates for removal and have a limited life expectancy.

Timing of Cardiac Surgery

Surgery to correct valvular dysfunction that has resulted in congestive heart failure must be performed before intractable hemodynamic deterioration results. Delaying surgery under these circumstances risks additional hemodynamic deterioration and a consequent dramatic increase in perioperative mortality. Thus, the timing of surgical intervention to correct valvular dysfunction should be based upon hemodynamic status and should be independent of the duration of prior antimicrobial therapy [64, 70]. Similarly, surgery should not be delayed when the indication is uncontrolled infection [70]. Additional antibiotic therapy in this setting does not improve outcome. In fact, only 2–3.5 % of patients develop recrudescent endocarditis when a prosthetic valve is inserted in patients with active NVE [70]. Although the presence of perivalvular infection increases the risk of surgical failure and recrudescent infection, approximately 85–90 % of patients survive after surgery for perivalvular abscess and relapse of IE is rare [70]. Even with surgical treatment of PVE where the new valve is typically inserted into an infected annulus which has been debrided and reconstructed, survival approaches 85 %, and only 15–25 % of patients develop recurrent endocarditis or require additional cardiac surgery [70]. Among patients with valve dysfunction that will warrant surgery but who are hemodynamically stable and have controlled infection, surgery can often be safely delayed, but other considerations may impact timing. For example, in this circumstance, a large anterior mitral leaflet vegetation which threatens to embolize could justify early surgery.

Patients who have experienced a neurologic complication of IE and undergo cardiac surgery may experience further neurologic deterioration. Although data may vary, it appears that morbidity and mortality can be reduced by adjusting the interval between the neurologic complication and surgery or by treating the neurologic complication, e.g., clipping a ruptured mycotic aneurysm, before surgery. Among IE patients with a symptomatic embolic cerebral infarction, the frequency of neurologic deterioration postoperatively decreases as the interval between the infarct and surgery increases. The risk of deterioration is greatest during the initial 10–14 days (20–50 %), is less between day 15 and 28 (10 %), and after day 28 (1–2 %) [71, 72]. Cardiac surgery performed 4 weeks after intracerebral hemorrhage complicating IE is associated with neurologic deterioration in 15–20 % of patients [71, 72]. Patients with subclinical infarcts or TIA do not incur increased risk [15]. Depending upon the urgency of cardiac surgery, among patients who have had an embolic stroke without hemorrhage, surgery should be delayed for 2–4 weeks; among those with a hemorrhagic embolic stroke (no aneurysm), a delay of 4 weeks is advised; and with hemorrhage due to rupture of a mycotic aneurysm, the aneurysm should be clipped and cerebral edema allowed to resolve (usually 2–3 weeks after neurosurgery) before cardiac surgery [71].

Antibiotic Therapy After Cardiac Surgery

The duration of antibiotic therapy after cardiac surgery is contingent on the ease with which the causative organism is eradicated, the duration of the preoperative therapy, whether recent blood cultures or intraoperative cultures yield the organism, and the pathology encountered at surgery. Patients with endocarditis caused by a highly susceptible, easily eradicated organism, with negative cultures at surgery, and where there is no perivalvular invasive infection should complete the remainder of the standard regimen for that organism. In contrast, patients with endocarditis caused by treatment recalcitrant organisms, who are culture positive perioperatively, or who have perivalvular invasive infection (especially if it looks active or is suboptimally debrided) should receive a full course of therapy postoperatively. Most patients with PVE and perivalvular infection receive a full course of therapy after surgery [9, 70]. Although valve cultures are generally sterile, organisms remain visible on Gram stain in 50–65 % of vegetations resected from patients who have received 75–100 % of standard (per organism) antibiotic treatment and in 20–25 % of vegetations from those who have successfully completed therapy from 1 to 6 months earlier [73]. Because of the delay in clearing nonviable organisms from vegetations, valve culture and histopathologic

Table 30.9 Cardiac conditions for which periprocedure antibiotic prophylaxis is recommended

Prosthetic heart valves
Prior bacterial endocarditis
Congenital heart disease (CHD)
Unrepaired cyanotic CHD including palliative shunts/conduits
Repaired CHD with prosthetic material or device during 6 months after repair
Repaired CHD with residual defects at the repair site
Cardiac transplant recipients with valvulopathy

Adapted from Wilson et al. [75]. With permission from WolterKluwers Health

Table 30.10 Regimens for endocarditis prophylaxis in adults: dental and respiratory tract procedures

Setting	Antibiotic	Regimen
Standard	Amoxicillin	2.0 g p.o. 1 h before procedure
Unable to take oral medication	Ampicillin or	2.0 g IM or IV within 30 min of procedure
	Cefazolin or ceftriaxone	1 g IM or IV within 30 min of procedure
Penicillin allergic	Clindamycin	600 mg p.o. 1 h before procedure or IV 30 min before procedure
	Cephalexin[a]	2.0 g p.o. 1 h before procedure
	Cefazolin[a]	1.0 g IV or IM 30 min before procedure
	Cefadroxil[a]	2.0 g p.o. 1 h before procedure
	Clarithromycin	500 mg p.o. 1 h before procedure

Adapted from Wilson et al. [75]. With permission from WolterKluwers Health

[a]Do not use cephalosporins in patients with immediate hypersensitivity (urticaria, angioedema, anaphylaxis) to penicillin

evidence of acute inflammation should be used to judge adequacy of prior therapy rather than Gram stain or detection of organisms by polymerase chain reaction.

Extracardiac Complications

From 3 to 5 % of patients with IE develop a splenic abscess. Although a splenic defect is easily identified with ultrasonography or computed tomography (CT), the distinction between abscess and infarct is difficult. Progressive enlargement of a lesion suggests an abscess, which can be confirmed by guided percutaneous needle aspiration. Successful therapy of splenic abscess requires percutaneous drainage or splenectomy.

Approximately 2–12 % of patients with IE develop mycotic aneurysm, and half of the aneurysms involve cerebral arteries. In 0.5–2 % of patients with IE, cerebral mycotic aneurysms rupture. Focal neurologic symptoms and persistent headache may be premonitory symptoms. Based on serial angiograms, 50 % of mycotic aneurysms resolve with effective antimicrobial treatment of IE [74]. The risk that an asymptomatic cerebral aneurysm will rupture after completion of effective antimicrobial therapy is estimated to be low. Cerebral angiography is not recommended for all patients with IE and a neurologic deficit; however, head CT with enhancement is advised if there are neurologic symptoms. If intracerebral hemorrhage is detected, angiography is recommended. Ruptured cerebral mycotic aneurysms should be resected. Unruptured cerebral aneurysms should be followed by angiography, and those that persist or enlarge during therapy should be resected if feasible. Extracranial mycotic aneurysms are managed in an analogous fashion; persistent aneurysms involving intra-abdominal arteries should be resected.

Prevention of Endocarditis

Although the benefit of periprocedure antibiotic administration to prevent IE is debated, an expert committee of the American Heart Association has identified patients who are at high risk for IE morbidity and mortality, procedures which might increase the risk of IE among endocarditis vulnerable patients, and regimens which might be used prior to selected procedures to prevent endocarditis [75]. Reasoning that the risk for endocarditis is orders of magnitude greater related to transient bacteremia associated with activities of daily living than to that associated with a procedure and that the benefit of prophylaxis is uncertain, periprocedure prophylaxis is only advised for those patients at highest risk of IE morbidity and mortality (Table 30.9) [75].

Prophylaxis has been advised for dental procedures involving gingival tissue, periapical regions, or that perforate oral mucosa but not for administration of intraoral anesthesia and placement, adjustment, or removal of orthodontic appliances, including orthodontic brackets. Prophylaxis is not advised for shedding deciduous teeth or trauma-induced bleeding from the lips or oral mucosa [75]. Efforts to maintain good dental health reduce the risk of IE and thus should be emphasized. Similarly, patients should have dental disease treated before they undergo cardiac valve surgery. Prophylaxis is recommended for high-risk patients who undergo procedures on the respiratory tract that involve incision of respiratory tract mucosa or treatment of established infection (drainage of an abscess or empyema) but not for diagnostic bronchoscopy. Prophylaxis against staphylococci and beta-hemolytic streptococci is advised when surgical procedures involve infected skin, skin structure, or musculoskeletal tissue. Prophylaxis solely for prevention of IE is not recommended for gastrointestinal or genitourinary tract procedures. However, high IE risk patients with genitourinary infections who require cystoscopy should, if possible, have the infection treated before manipulation. Similarly, in these high-risk patients who are undergoing genitourinary or gastrointestinal procedures where antibiotics would be

used to prevent local infection, inclusion of an antibiotic effective against enterococci is suggested. The regimens recommended for use in the prophylaxis of IE have been selected because they kill or inhibit the endocarditis-causing bacteria present at the site to be manipulated (Table 30.10).

Uncertainty regarding the benefit of periprocedure antibiotic administration to prevent IE combined with risks of adverse reactions and potential wasted resources resulted in a recommendation by the United Kingdom's National Institute for Health and Clinical Excellence (NICE) for the cessation of antibiotic prophylaxis to prevent IE for all procedures in all at risk patients [76]. Limited data excluded a large increase in IE during the 2 years after the NICE guidelines were implemented widely [77]. Although efforts to prevent IE using periprocedure antibiotics may be of questionable benefit, the large increase in healthcare-associated IE, especially that related to intravascular devices, illustrates the importance of preventing healthcare-associated bacteremia.

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Hypertension: Mechanisms and Diagnosis

31

Clive Rosendorff

Introduction

Cardiovascular disease is by far the leading cause of death, in males and females, in industrialized nations. In the United States this year, about a million deaths will be due to diseases of the heart and circulation, more than twice the number for the next most frequent cause of death, cancer. The most common fatal cardiovascular diseases are coronary artery disease, congestive heart failure, and stroke; these, together with renovascular disease, all have hypertension as a major risk factor. High blood pressure (BP), affecting one in three (over 76 million) US adults, is therefore a highly lethal disease.

The relationship between BP and the relative risks of stroke and coronary heart disease is direct, continuous, and independent, and no evidence has been put forward of any "threshold" level of blood pressure below which humans are entirely safe [1].

In general, men are at greater risk for hypertension-related death than women, black persons than white, and older ones than younger ones. The age-adjusted prevalence of hypertension (both diagnosed and undiagnosed) in 2003–2006 was 75 % for older women [2]. With increasing age, the prevalence of isolated systolic hypertension with a normal diastolic blood pressure (DBP) increases considerably, and it is now generally accepted that in adults, systolic blood pressure (SBP) may be a more accurate predictor of cardiovascular risk than diastolic pressure.

An enormous amount of data—experimental, epidemiologic, and clinical—now indicates that reducing elevated BP is beneficial. The first definitive proof of this came from the Veterans Administration (VA) Cooperative Study begun in 1963, and it has been confirmed in a host of studies since, most of which utilized diuretics or β-blockers as antihypertensive agents. Since then, there have been numerous clinical trials of many different classes of antihypertensive drugs, which have shown huge reductions in cardiovascular morbidity and mortality.

In spite of the demonstrated benefits of BP reduction, physicians and other health care professionals who are responsible for identifying and treating patients with hypertension are not doing a great job. In 2006, the percentage of Americans who were aware that they had high BP was 78 and 68 % were on treatment. However, only 64 % of those treated had their hypertension controlled, equivalent to about 43 % of the total hypertensive population. So, of every 100 patients with hypertension, 78 are aware of the fact, 68 are receiving treatment, and only 43 are "controlled," with a BP < 140/90 mmHg [3]. About 13 % of those taking antihypertensive medication meet the criteria for resistant hypertension (BP > 140/90 mmHg, on three different antihypertensive drug classes or on ≥4 antihypertensive drug classes regardless of BP) [4]. Projections show that by 2030, an additional 27 million people could have hypertension, a 9.9 % increase in prevalence from 2010 [5].

Definitions and Classification

BP is a continuous variable in any population, with a distribution along a bell-shaped curve. The difference between "normotensive" and "hypertensive" BP values is, therefore, somewhat arbitrary, but since cardiovascular risk increases with BP, various operational definitions of hypertension have been developed.

The Seventh Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) defined hypertension as an SBP of 140 mmHg or greater or DBP of 90 mmHg or greater [6]. JNC 7 subdivided "hypertension" into two categories: stage 1 with a BP range of 140–159 mmHg (SBP) or 90–99 mmHg (DBP) and stage 2 with BP ≥160 mmHg (SBP) or ≥100 mmHg (DBP). The utility of

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_31, © Springer Science+Business Media New York 2013

such a classification is, first, to provide an appropriate basis for comparing patients in epidemiologic and clinical studies and, second, as an indicator of the urgency of starting therapy. For example, a patient with a BP of 142/92 mmHg (stage 1) need not be treated with antihypertensive therapy right away; repeat visits to the office or clinic should be arranged to confirm the hypertension and possibly to establish the antihypertensive efficacy of nonpharmacologic interventions (*see* Chap. 32). On the other hand, a patient with a BP of 220/118 mmHg (Stage 2) requires antihypertensive therapy without delay.

Those with a BP of 120–139 mmHg systolic and/or 80–89 mmHg diastolic are classified as "pre-hypertensive," now known to increase the risk of any cardiovascular event compared with a normal BP (<120/80 mmHg), especially if the BP is in the upper half of the pre-hypertensive range, 130–139/85–89 mmHg, and also especially if there is a high cardiovascular risk, indicated by the presence of diabetes, chronic kidney disease, coronary artery disease, coronary artery disease equivalents (stroke, carotid disease, aortic aneurysm, peripheral vascular disease), or by a Framingham Risk Score of >10 %.

Isolated systolic hypertension (ISH), the predominant form of hypertension in the elderly, is defined as an SBP of 140 mmHg or greater in the presence of a DBP of 90 mmHg or lower. The accuracy of diagnosis and staging of hypertension is markedly improved by using SBP rather than DBP as the dominant criterion.

Essential, primary, or idiopathic hypertension, defined as high BP due neither to secondary causes nor to a Mendelian (monogenetic) disorder, accounts for 90 % of all cases. The term "*primary hypertension*" is preferred since "essential hypertension" represents an archaic misunderstanding of pathophysiology, namely, that hypertension is "essential" to maintain blood flow through severely narrowed resistance vessels.

Secondary hypertension is high BP caused by an identifiable and potentially curable disorder. *Refractory or resistant hypertension* is defined as a BP of ≥140/90 mmHg despite three drugs of different classes at maximum approved doses, given at least 1 month to take effect. *Spurious hypertension (pseudohypertension)* is artifactually elevated BP obtained by indirect cuff measurement over a rigid, often calcified, brachial artery.

White coat hypertension describes patients whose BP is high (>140/90 mmHg) in an office or clinic setting, with a normal daytime ambulatory pressure (<135/85 mmHg). This is a condition with higher risk of morbid events than if the BP were normal, <120/80 mmHg. Antihypertensive medication in white coat hypertension patients may decrease clinic BP but produces little or no change in ambulatory BP; thus, drug treatment may not confer substantial benefit.

Masked hypertension is the mirror image of white coat hypertension. Here the clinic BP is normal, but ambulatory or home measurements are high and associated with high risk. Although the prevalence of masked hypertension is low, perhaps only 6 % of the normotensive population, the absolute number in the United States may approach 15–18 million.

The term *hypertensive crisis* encompasses both *hypertensive urgency and hypertensive emergency. Hypertensive urgency* is defined as DBP >120 mmHg in the absence of acute or rapidly worsening target-organ damage. *Hypertensive emergency* is defined as acute or rapidly worsening target-organ damage occurring in a hypertensive patient in association with elevated BP but irrespective of the specific BP level attained. *Malignant hypertension* is a hypertensive emergency associated with papilledema, while *accelerated hypertension* is a hypertensive emergency associated with retinal hemorrhages and exudates.

Measurement of Blood Pressure

In-office BP measurement. BP is usually measured [7] with a mercury sphygmomanometer, an aneroid manometer, or an electronic manometer, with a 12-by-26 cm cuff. The bladder of the cuff should encircle at least 80 % of the arm, so for patients with arms of greater than 30 cm circumference, pressure should be measured with a large cuff (13-by-36 cm). If an aneroid or electronic manometer is used, it should be calibrated against a mercury manometer at regular intervals. BPs should be measured with subjects both lying and standing, or sitting and standing, and repeated 5 min later when possible. The cuff should be placed over the brachial artery and the bell of the stethoscope over the artery distal to the cuff; the environment should be quiet and the patient relaxed. Serial measurements should be taken at the same time of day, preferably in the morning, before the patient has taken any antihypertensive medication (i.e., at the trough of the plasma concentration).

The cuff is pumped up to about 20 mmHg above the systolic level, which point is signaled by the disappearance of the radial pulse, and then the pressure lowered by about 2 mmHg per second. The SBP is the pressure at which the first faint, consistent, tapping sounds are heard (Korotkoff sounds, phase I). The DBP is the level at which the last regular blood pressure sound is heard and after which all sound disappears (Korotkoff sound, phase V). Below Korotkoff phase I, there is sometimes a period of silence referred to as the *auscultatory gap*; otherwise, there is a continuum of sound, including swishing beats (Korotkoff II), crisper and louder sounds (Korotkoff III), and muffling of the sound (Korotkoff IV). If the sounds continue down to zero, Korotkoff IV is recorded as the DBP.

Since BP can vary by as much as 10 mmHg between arms (and more in conditions such as coarctation of the aorta), it should be measured in both arms, at least at the initial visit. The higher pressure is recorded. All BPs should be read to the nearest 2 mmHg, not rounded off to the nearest 5 or 10 mmHg, as is done so often.

There are many sources of variability of the BP. These include poor technique, faulty equipment, a stressful setting or an anxious patient, and a patient who has been smoking or has had caffeine or alcohol. A common error is the failure to remove patients' garments with tight sleeves. The considerable interobserver variability in BP measurements can be minimized by meticulous attention to correct technique.

Home BP Measurement and Automated Ambulatory BP Monitoring. This often helps to verify the diagnosis and assess the severity of hypertension. BP values obtained outside the clinic setting are generally lower and correlate better with target-organ damage and outcomes than BP measurements obtained by health care personnel in the clinic.

Normal mean 24-h ambulatory BP is <125/75 mmHg, with a mean of <130/85 mmHg during the day and <110/70 mmHg at night. Among the biologic variations are short-term ones driven by changes in the autonomic nervous system and a slower circadian variability. BP usually falls about 15 % at night, during sleep, to rise to daytime levels an hour or two before awakening. BP usually peaks in the late afternoon and evening. Some patients (so-called *non-dippers*) have a smaller fall of BP during sleep, sometimes none; these patients are at greater risk for cardiovascular disease, a more rapid progression of hypertensive renal disease, and even cognitive dysfunction. The converse, namely, an excessive fall of nocturnal BP, also carries risk, especially for stroke and myocardial ischemia. The early-morning surge of pressure, after arising from sleep, is also associated with more cardiovascular catastrophes, compared with the remainder of the 24-h period. Obstructive sleep apnea (OSA) is associated with hypertension, and BP can be lowered in patients with OSA by the use of continuous positive airway pressure (CPAP) during sleep.

Initial Workup of the Hypertensive Patient

The initial evaluation of patients with hypertension has three objectives: (1) to find clues to secondary causes of hypertension, (2) to assess target-organ damage, and (3) to determine whether there are other risk factors for cardiovascular disease. This requires careful history taking, a complete physical examination, some basic laboratory tests, and electrocardiography (ECG).

The first step is to establish the diagnosis of sustained hypertension. BP should be measured on at least two occasions. If the hypertension is stage 1, measurements should be made within 1 month of each other; if stage 2, within a week; and if severe, immediate action is necessary to complete the workup and treat the hypertension.

Secondary Hypertension

Table 31.1 lists the common causes of secondary hypertension. If none of these causes is present, the hypertension is primary. Of the secondary causes of hypertension, some are often easy to recognize. For example, by the time Cushing's syndrome is severe enough to cause hypertension, the clinical features are usually obvious on physical examination. The same is true of acromegaly. Many cases of coarctation of the aorta are detected in infancy or childhood. However, most of the causes of secondary hypertension need to be carefully excluded in the history, the physical examination, and the laboratory workup. Tables 31.2 and 31.3 propose a simple and general approach to this process. Some of the

Table 31.1 Causes of secondary hypertension

Renal parenchymal hypertension
Renovascular disease
Coarctation of the aorta
Adrenal disorders
Adrenocortical hypertension:
Mineralocorticoid hypertension (e.g., Conn's syndrome)
Glucocorticoid hypertension (e.g., Cushing's syndrome)
Other hormonal disorders
Hypothyroidism
Hyperthyroidism
Hyperparathyroidism
Acromegaly
Neurologic disorders: increased intracranial pressure
Drugs, especially oral contraceptives, exogenous steroids, erythropoietin, cyclosporine, licorice, sympathomimetic drugs, cocaine, tricyclic antidepressants, nonsteroidal anti-inflammatory drugs, anabolic steroids

Table 31.2 Hypertension workup: history and physical examination

Symptoms and signs	Diagnosis
Secondary hypertension	
Abdominal or flank masses	Polycystic kidneys
Abdominal bruit	Renovascular hypertension
Delayed/absent femoral pulses, blood pressure gradient between arm and leg	Aortic coarctation
Truncal obesity, moon face, purple striae, buffalo hump	Cushing's syndrome
Tachycardia, tremor, pallor, sweating	Pheochromocytoma
Flank pain, frequency, dysuria, hematuria, prostatism, edema	Renal parenchymal disease
Target-organ damage	
Vision, fundoscopy	Retinopathy
Dyspnea, fatigue, signs of left ventricular failure	Left ventricular failure
Angina, previous myocardial infarction	Coronary artery disease
Focal neurologic symptoms and signs	Cerebrovascular disease
Symptoms and signs of renal failure	Hypertensive renal disease
Risk factor profiling	
Hypertension, diabetes, dyslipidemia, age, gender, body mass index, family history, smoking, artery disease, cerebrovascular disease, peripheral vascular disease, left ventricular hypertrophy	

Table 31.3 Hypertension workup: screening laboratory tests

Test	Rationale
Blood chemistry	
Blood urea nitrogen	Impaired renal function
Creatinine	Impaired renal function
Potassium	Primary aldosteronism
	Cushing's syndrome
	Renal failure
Calcium/phosphate	Hyperparathyroidism
Cholesterol (total, HDL and LDL), triglycerides, glucose, C-reactive protein, uric acid	Risk factors for cardiovascular disease
Thyroid-stimulating hormone	Hyperthyroidism
	Hypothyroidism
Urinalysis	Renal disease
Electrocardiography	LVH
Complete blood count	All new patients should have one

commonest causes of secondary hypertension are described in more detail later in this chapter.

Target-Organ Damage

Vascular Hypertrophy

Hypertrophy [8] refers to growth brought about by an increase in cell *size* rather than *number*. (An increase in cell number is hyperplasia.) In adults, the vascular smooth muscle cells (VSMC) are relatively quiescent, having an extremely low (<5 %) mitotic index. In persons with hypertension and atherosclerosis, however, VSMC undergo phenotypic modulation with hypertrophy and/or hyperplasia, altered receptor expression, altered lipid handling, and migration from the vascular media to the subintimal portion of the vessel, and the vessel shows enhanced extracellular matrix deposition. All these result in an increase in stiffness (lower compliance) of the arteries of hypertensive patients. This diffuse arteriosclerosis of hypertension increases with age. Superimposed on this may be accelerated development of atherosclerotic lesions.

Factors that stimulate vascular smooth muscle hypertrophy or hyperplasia in hypertension include endothelin, which activates the ETA subtype of the endothelin receptor to activate an intracellular transduction pathway involving phospholipase C (PLC), inositol 1,4,5-trisphosphate (IP_3), and 1,2-diacylglycerol (DAG); release of cytosolic calcium from the endoplasmic reticulum; and, possibly, the mitogen-activated protein (MAP) kinase system. Angiotensin II, acting via the AT_1 receptor subtype, has a similar intracellular transduction pathway. Other hormones or autocrine or paracrine factors that affect VSMC growth are vasopressin, catecholamines, insulin-like growth factor 1 (IGF-1), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and transforming growth factor (TGF)-β, which all stimulate growth, and nitric oxide, atrial natriuretic peptide, estrogens, and prostacyclin, which are inhibitory. This inhibition is thought to be due to an increase in apoptosis, reversing VSMC proliferation. Many studies have shown improvement in VSMC hypertrophy and hyperplasia in hypertensive patients who take drugs that inhibit the action of angiotensin II (ACE inhibitors or AT_1 receptor blockers) or calcium (calcium-channel blockers), and it could be predicted that the same effects would occur with agents that enhance inhibitory factors, such as those neutral endopeptidase inhibitors that reduce the breakdown of atrial natriuretic peptide.

SBP and pulse pressure (PP) increase with advancing age, mainly as a result of reduced elasticity (increased stiffness) of the large conduit arteries. Increased stiffness of these arteries results from collagen deposition and smooth muscle cell hypertrophy, as well as thinning, fragmenting, and fracture of elastin fibers in the media. The distending pressure of conduit vessels is a major determinant of stiffness. The two-phase (elastin and collagen) content of load-bearing elements in the media is responsible for the behavior of these vessels under stress: At low pressures, stress is borne almost entirely by the distensible elastin lamellae, while at higher pressures, less distensible collagenous fibers are recruited, and the vessel appears stiffer. Conduit vessels are relatively unaffected by neurohumoral vasodilator mechanisms.

In addition to these structural abnormalities, endothelial dysfunction, which develops over time as a consequence of both aging and hypertension, contributes functionally to increased arterial stiffness in elderly persons with ISH. Other factors that decrease central arterial compliance by damaging the endothelium include (1) diabetes, (2) tobacco use, (3) high dietary salt intake, (4) elevated homocysteine levels, and (5) estrogen deficiency. Reduced nitric oxide (NO) synthesis and/or release in this setting contributes to increased wall thickness of conduit vessels such as the aorta and common carotid artery. The functional significance of NO deficiency in ISH is supported by the ability of NO donors, such as nitrates or derivatives, to increase arterial compliance and distensibility and reduce SBP without decreasing DBP.

Increased arterial stiffness contributes to the wide pulse pressure (PP) commonly seen in elderly hypertensive patients, in part by causing the pulse wave velocity to increase. With each ejection of blood from the LV, a pressure (pulse) wave is generated and travels from the heart to the periphery at a finite speed that depends on the elastic properties of the conduit arteries. The pulse wave is reflected at any point of discontinuity in the arterial tree and returns to the aorta and LV. The timing of the wave reflection depends on both the elastic properties and the length of the conduit arteries.

In younger persons, pulse wave velocity is sufficiently slow (approximately 5 m/s) so that the reflected wave reaches the aortic valve after closure, leading to a higher DBP and

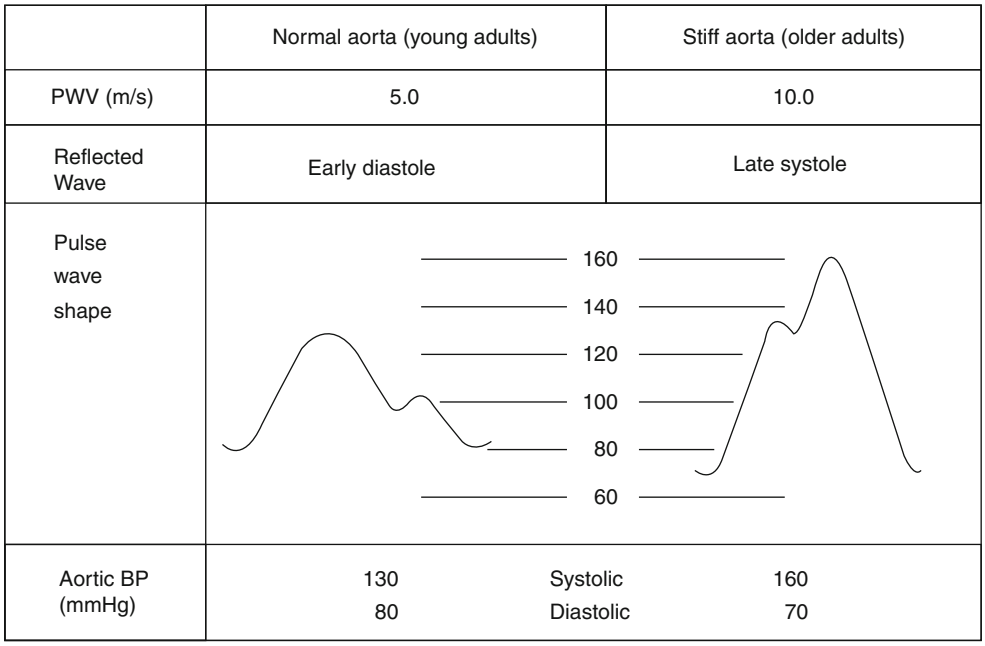

Fig. 31.1 Change in aortic pressure profile due to age-related vascular stiffening and increased pulse wave velocity (*PWV*). *Note*: Increased SBP and decreased DBP due to decreased aortic distensibility, increased PWV as a result of decreased aortic distensibility and increased distal (arteriolar) resistance, return of the reflected primary pulse to the central aorta in systole rather than in diastole due to faster wave travel, and change in aortic pulse wave profile because of early wave reflection. Note the summation of antegrade and retrograde pulse waves to produce a large SBP. This increases LV stroke work and therefore myocardial oxygen demand. There is also a reduction in the diastolic pressure–time (integrated area under the DBP curve) and therefore of the coronary perfusion pressure. This increases the vulnerability of the myocardium to hypoxia (Reprinted from Rosendorff [9]. With permission from Elsevier)

enhancing coronary perfusion by providing a "boosting" effect. In older persons, particularly if they are hypertensive, pulse wave velocity is greatly increased (approximately 10–20 m/s) due to central arterial stiffening. At this speed, the reflected wave reaches the ascending aorta before aortic valve closure, merges with the incident or antegrade wave, and produces a higher SBP (and afterload), PP, and a decreased DBP (Fig. 31.1). This phenomenon accounts for the higher SBP and PP and the lower DBP that is seen in the elderly population. The increase in SBP increases cardiac metabolic requirements and predisposes to the development of LV hypertrophy and heart failure. PP is closely related to SBP and is clearly linked to advanced atherosclerotic disease and cardiovascular events such as fatal and nonfatal MI and stroke. With aging, there is a gradual shift in the BP-risk relationships from diastolic to systolic and pulse pressure.

Most antihypertensive drugs act on peripheral muscular arteries rather than central conduit vessels. They reduce PP via indirect effects on the amplitude and timing of reflected pulse waves. Nitroglycerine causes marked reductions in wave reflection, central SBP, and LV load with smaller changes in SBP or DBP in the periphery. Vasodilator drugs lower BP by decreasing arteriolar tone, but some of them like ACEIs, ARBs, and CCBs also reduce the stiffness of conduit arteries and therefore pulse wave reflection, contributing to their antihypertensive effect.

Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) [10] is a consequence of mechanical forces such as chronic increased systolic afterloading of the cardiac myofibrils in hypertension. As they do to VSMC hypertrophy, important neurohormonal stimuli contribute to LVH, particularly the renin–angiotensin system (angiotensin II), the sympathetic nervous system, and the other growth factors listed earlier for VSMC. The clinical significance of the pro-hypertrophic actions of angiotensin II, for instance, is that ACE inhibitors or AT_1 receptor blockers could be expected to prevent, or even reverse, LVH more than antihypertensive drugs that reduce blood pressure by the same amount but have no direct action on myocardial cells. This is important because of the very adverse effect of LVH on the prognosis for patients with hypertension.

Patients with LVH (and many hypertensive patients without LVH) usually have diastolic dysfunction: their left ventricle is stiffer (i.e., less compliant) and thus requires greater distending pressure during diastole. These patients may have dyspnea (secondary to the raised pulmonary venous filling pressure), left atrial hypertrophy, a fourth heart sound, and late diastolic flow across the mitral valve (A wave) that is larger than early diastolic flow (E wave), as well as tissue Doppler features of reduced LV compliance (*see* Chap. 8). LVH may progress toward the syndrome of

systolic dysfunction and dilated cardiomyopathy with congestive heart failure.

Heart Attack and Brain Attack [11, 12]

Hypertension is a significant risk factor for both acute myocardial infarction and stroke. Both situations are marked by hypertension-induced vascular hypertrophy and/or hyperplasia, endothelial dysfunction, and accelerated atherosclerosis, caused by migration of VSMC into the subintima, subendothelial infiltration of monocytes, cholesterol deposition and oxidation, and calcification. Additional elements in acute myocardial infarction are plaque disruption, platelet adhesion and aggregation, and thrombosis. Patients with hypertension are at much greater risk of coronary events because of the malignant combination of decreased oxygen supply and the increased oxygen demand. The limitation of oxygen supply is due to either decreased coronary flow or more commonly, a decreased capacity of the arteriosclerotic coronary arteries to vasodilate (impaired coronary flow reserve) in response to the increased oxygen demand of LVH and the increased output impedance of the left ventricle.

Strokes, however, are more varied in their pathogenesis. Hypertension is the major cause of stroke. In hypertension, about 80 % of strokes are ischemic, and about 15 % are hemorrhagic. Reduction of cerebral blood flow due to arterial stenosis or thrombosis may produce any degree of tissue injury from asymptomatic and isolated neuronal dropout to huge infarction and cavitary necrosis. The extent of the ischemic injury depends on the duration and the intensity of the ischemia, and these, in turn, depend on the efficiency of the collateral circulation and the cardiac output. Hemorrhagic stroke in hypertension is probably due to rupture of microaneurysms of the small intracerebral arteries. Hypertension can also cause focal damage to small intracerebral arteries (lipohyalinosis) marked by occlusion of the vessels and the production of small ischemic cavities in the brain known as *lacunar infarcts*, frequently seen in the MRIs of patients with vascular dementia. Last, hypertension is a risk factor for berry aneurysms and subarachnoid hemorrhage.

Hypertensive Encephalopathy

Hypertensive encephalopathy [13] is an acute syndrome of severe hypertension, cerebrovascular dysfunction, and neurologic impairment that resolves rapidly with treatment. The pathophysiologic mechanism is segmental dilation along the cerebral arterioles (sausage-string appearance); when, in severe hypertension, the autoregulatory capacity of vessels is exceeded, segments of the vessel are stretched and dilated. There is then leakage of fluid into the perivascular tissue causing edema and the syndrome of hypertensive encephalopathy. Clinical features are those of encephalopathy (headache, nausea, projectile vomiting, visual blurring, drowsiness, confusion, seizures, coma) in association with severe hypertension. Papilledema, usually with retinal hemorrhages and exudates, may be present, and the sausage-string arteries may be seen in the retina. The differential diagnosis includes cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage, subdural hematoma, brain tumor, encephalitis, and epilepsy. These lesions are usually identified by their distinctive clinical features and by computed tomography (CT). Drugs, such as intravenous amphetamines and cocaine, and ingestion of tyramine by patients taking monoamine oxidase inhibitors can produce a similar clinical picture, as can lupus vasculitis, polyarteritis, or uremic encephalopathy.

Hypertension-Related Renal Damage (*See Also* Chap. 40)

Chronic kidney disease (CKD) is defined as the presence of long-standing injury to the kidney, confirmed by kidney biopsy or a glomerular filtration rate (GFR) of <60 mL/min/1.73/m^2 for longer than 3 months. The clinical associations are a serum creatinine of ≥1.2 mg/dL in women and ≥1.4 mg/dL in men and microalbuminuria (30–300 mg/day) or albuminuria (>300 mg/day). Diabetes and hypertension account for the bulk of patients with end-stage renal failure.

Hypertension is both a cause and complication of CKD, [14, 15] and lowering BP slows the progression of renal disease. In hypertension, there is inappropriately elevated sympathetic nervous system (SNS) activity or activation of the renin–angiotensin–aldosterone system (RAAS) or both. Both SNS overactivity and angiotensin II selectively constrict the efferent arterioles of the kidney, increasing glomerular filtration pressure and therefore filtration fraction. As a consequence, the colloid osmotic pressure of the fluid leaving the glomerular capillary to enter the peritubular network of capillaries is increased, resulting in greater sodium reabsorption through the tubules.

Both the SNS and the RAAS are direct vasoconstrictors of systemic resistance arterioles. Sympathetic nerves also stimulate renin release through activation of β-receptors, resulting in an increase in angiotensin II. Other mechanisms include a direct effect of angiotensin II to enhance the sodium/hydrogen antiporter of the proximal tubule cells to increase sodium reabsorption and the angiotensin II-mediated release of the mineralocorticoid hormone, aldosterone. Angiotensin II also causes morphologic changes in the kidney, mesangial cell proliferation, vascular intimal thickening and fibrosis and hyalinization of arterioles (arteriosclerosis), and the activation and release of pro-inflammatory cytokines in the renal parenchyma. There may be focal glomerulosclerosis with atrophic tubules.

Patients with CKD are at increased risk of CV events [16]. The BP goal in patients with CKD is <130/80 mmHg.

Achievement of this level of BP control in patients with CKD is often difficult, and most patients will require 2–4 antihypertensive drugs in moderate to high doses.

Hypertensive Retinopathy

The optic fundi should be examined in every new hypertensive patient; with some practice, this can often be done without having to dilate the pupils. The features of hypertensive retinopathy [17] are:

1. *Arteriolar narrowing*. The retinal artery: vein diameter ratio is about 3:4 in the normal eye. In hypertension, the artery becomes narrower, with a decrease in the A/V ratio. The arteriosclerotic arteries may have a reddish-brown ("copper-wire") appearance, and as thickening of the wall progresses, the visibility of the blood column diminishes and eventually disappears, leading to the appearance of the artery as a silver thread ("silver wire").
2. *Arteriovenous nicking*. The retinal arteries, with their thickened walls and increased intraluminal pressure, externally compress the low-pressure, thin-walled vein, causing "A/V nicking."
3. *Cotton-wool spots*. Reduced blood flow caused by sclerosis or fibrinoid necrosis of small retinal arteries may cause regions of infarction, the so-called cotton-wool spots or cytoid bodies. They are commonly referred to as exudates, but are not exudates.
4. *Aneurysms*. Although capillary microaneurysms are usually considered to be classic lesions of diabetic retinopathy, they may also occur in hypertension in the absence of diabetes.
5. *Flame hemorrhages*. In severe hypertension, there may be breakdown of the blood–retinal barrier, producing intraretinal hemorrhages that are often flame-shaped.
6. Less common ocular manifestations of hypertension are papilledema, central retinal vein occlusion, and hypertensive changes in the choroidal vessels, the last recognizable only by special techniques such as intravenous fluorescein angiography.

Hypertensive Emergency and Urgency

Hypertensive emergency is a situation in which severe hypertension is associated with acute or rapidly progressive target-organ damage, such as acute cerebrovasular (hypertensive encephalopathy, stroke, transient ischemic attack) or cardiac (acute left ventricular failure with pulmonary edema, myocardial infarction, aortic dissection) lesions or acute renal failure. The mechanism of the often extremely high blood pressure with rapid deterioration of target-organ function is not known; hypotheses include vascular endothelial damage with myointimal proliferation and pressure natriuresis producing hypovolemia with activation of vasoconstrictor hormones such as catecholamines, endothelin, and the renin–angiotensin system. Plasma renin activity is usually high. Obviously, many of these patients require urgent therapy with parenteral antihypertensive agents (*see* Chap. 32), although care should be taken not to drop mean arterial pressure too suddenly or below the lower limit of cerebrovascular autoregulation, which could induce an ischemic stroke. *Hypertensive urgencies* describe situations of very high blood pressure (>180 mmHg SBP or >110 mmHg DBP) not related to severe symptoms or acute progressive target-organ damage. For this condition, the blood pressure should be reduced by oral agents without delay.

Risk Factor Profiling

The third objective of the initial evaluation of a patient with hypertension is to get a full picture of the cardiovascular risk factors, other than hypertension, for that patient. There is a cluster of atherogenic risk factors that often accompanies hypertension, referred to as "metabolic syndrome" [18]. This is defined as hypertension, abdominal obesity (waist circumference: men >40 in [>102 cm], women >35 in [>88 cm]), dyslipidemia (triglycerides >150 mg/dL [>1.7 mmol/L], HDL-cholesterol <40 mg/dL [<1.0 mmol/L] for men and <50 mg/dL [<1.3 mmol/L] for women), insulin resistance or glucose intolerance (fasting blood glucose >110 mg/dL [>6.1 mmol/L]), a pro-inflammatory state (elevated C-reactive protein), and a prothrombotic state (elevated plasma plasminogen activator inhibitor, PAI-1) [18]. Other potent risk factors include age, gender, smoking, LDL-cholesterol, a positive history of premature cardiovascular events in first-degree relatives, left ventricular hypertrophy, and hyperuricemia. More recently, homocysteine, fibrinogen, factor VII, t-PA, and lipoprotein(a) have been shown to predict cardiovascular morbidity and mortality. These are discussed more fully in Chap. 1.

Pathogenesis of Primary Hypertension

Most of the causes of secondary hypertension (*see* section on "Common Causes of Secondary Hypertension") have been well-characterized, and their pathophysiologic mechanisms are reasonably well-understood. These causes, however, account for only 5–10 % of all hypertensive patients seen by physicians, and the remaining 90–95 % of patients with primary hypertension have a disease that is as poorly understood as it is common. Consequently, enormous research efforts have been mobilized to study the pathogenesis of primary hypertension, using animal models, human patients, and more recently, the powerful tools of cell and molecular biology. The result has been a plethora of mechanisms and theories, not all mutually exclusive, that support the concept devised by Irvine Page of a "mosaic" of

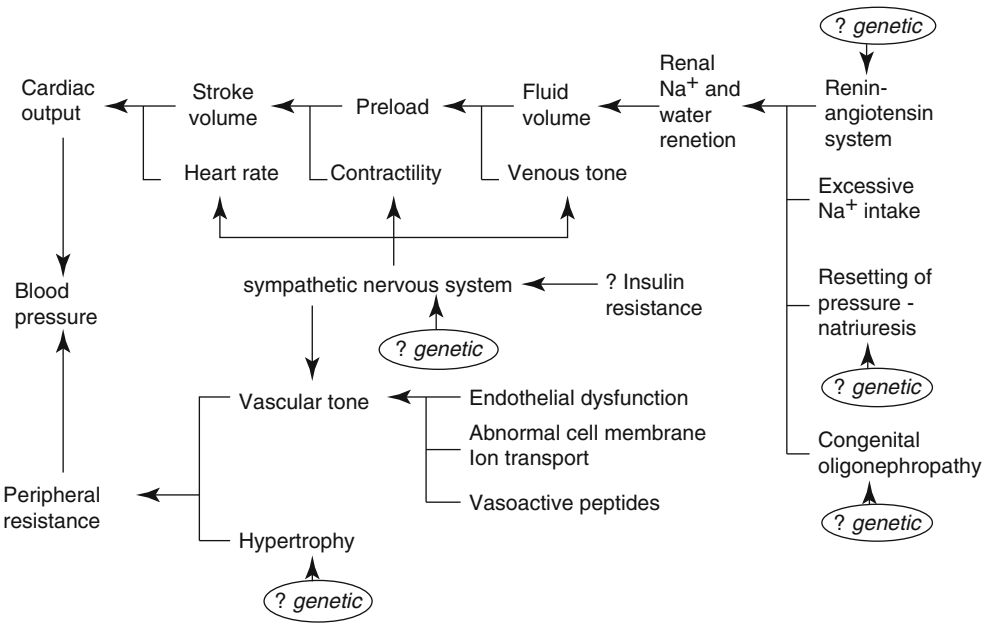

Fig. 31.2 Hemodynamic and renal control of blood pressure

mechanisms, each operating in different organs and at different levels of organization. A brief and selective survey of this topic follows.

Genetic Predisposition

Monogenic syndromes are covered in the section on "Secondary Hypertension." Primary hypertension also tends to cluster in families, but a specific genotype has not been identified. A number of associations have been suggested, but none has been confirmed. These include mutations in the genes for angiotensinogen, renin, 11β-hydroxylase, aldosterone synthase, and the α_1-adrenoreceptors; a negative association with transforming growth factor-β_1 (TGF-β_1) and the adducin protein which affects the assembly of the actin-based cytoskeleton; and polymorphisms in about 25 genes, including those for angiotensinogen, angiotensin-converting enzyme (ACE), and the angiotensin II type 1 receptor.

Increased Cardiac Output

Blood pressure is proportional to cardiac output (CO) and total peripheral resistance (TPR). Some young "borderline hypertensives" have a hyperkinetic circulation with increased heart rate and CO (Fig. 31.2). This, in turn, may be due to increased preload associated with increased blood volume or to increased myocardial contractility. Also, LVH has been described in the still normotensive children of hypertensive parents, an observation that suggests that the LVH is not only a consequence of increased arterial pressure but that it may itself reflect some mechanism, such as hyperactivity of the sympathetic nervous system or the renin–angiotensin system that causes both LVH and hypertension. In mature primary hypertension, the CO is normal and the TPR elevated. The switch from elevated CO to elevated TPR may be due to autoregulatory vasoconstriction in response to organ hyperperfusion; thereafter, the hypertension becomes self-sustaining due to the accelerated arteriosclerosis. Plasma volume is usually normal or slightly lower than normal in established primary hypertension; however, some investigators have suggested that the volumes are still higher than they should be, given the elevated blood pressure, which should produce substantial pressure natriuresis and diuresis.

Excessive Dietary Sodium

We ingest many times more sodium than we need; there is much epidemiologic and experimental evidence to show an association between salt intake and hypertension. Sodium excess activates some pressor mechanisms (such as increases of intracellular calcium and plasma catecholamines and an upregulation of angiotensin II type 1 receptors), and it increases insulin resistance. About half of hypertensive patients are particularly salt-sensitive (as defined by the blood pressure rise induced by sodium loading), as compared with about a quarter of normotensive controls. Sodium sensitivity becomes greater with age and has a strong genetic component. The mechanism of sodium sensitivity may be renal sodium retention (*see* later). Clinical trials have shown an average reduction of blood pressure of 5/2 mmHg in hypertensive patients who lower their sodium intake to approximately 100 mmol/day (roughly equivalent to a daily intake of sodium chloride of less than 0.5 g/day).

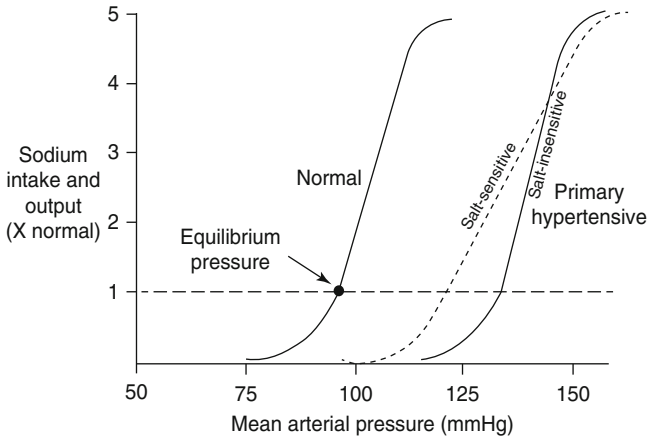

Fig. 31.3 Steady-state relations between blood pressure and sodium intake and output in normotensive subjects and in patients with salt-sensitive or salt-insensitive hypertension. Normally, an increase in sodium intake will result in a small increase in mean arterial pressure that is sufficient to increase sodium output by pressure natriuresis so that the "equilibrium pressure" is restored. In salt-insensitive hypertension, the steep curve is retained but is shifted to the right (i.e., reset at a higher mean arterial pressure). In salt-sensitive hypertension, there is a shift to the right and flattening of the curve so that sodium loading increases blood pressure by a greater amount (Modified from Hall et al. [19]. With permission from Lippincott Williams & Wilkins)

Renal Sodium Retention

Four mechanisms have been advanced to explain renal sodium retention in hypertension, resetting of the renal pressure–natriuresis curve, an endogenous sodium pump inhibitor, inappropriately high renin levels, and reduced nephron number.

Abnormal renal sodium handling may be due to a rightward shift of the pressure–natriuresis curve of the kidney (Fig. 31.3) [20]. When the arterial pressure is raised, the normal kidney excretes more salt and water; balance normally occurs at a mean perfusion pressure of around 100 mmHg, producing sodium excretion of about 150 mEq/day. Increased salt intake transiently raises blood pressure, and the pressure–natriuresis effectively restores total body sodium to normal. In patients with primary hypertension, this pressure–natriuresis curve is reset to a higher blood pressure, preventing return of the blood pressure to normal. There is some evidence in certain animal models and in humans that the rightward shift in the pressure–natriuresis curve is inherited.

A variation on this theme is a hormonal mediator of salt sensitivity, a sodium pump inhibitor, endogenous ouabain [21], which is secreted by the adrenal cortex and is natriuretic in sodium-loaded animals. Renal sodium retention stimulates ouabain release, which, by its inhibition of the sodium pump, increases intracellular sodium. In turn, sodium–calcium exchange is inhibited, and the rise in intracellular calcium causes increased vascular tone and vascular hypertrophy. This is discussed further in the section on "Abnormal Cell Membrane Ion Transport."

Some investigators believe that a more important role for the kidney is the generation of more renin from nephrons that are ischemic, owing to afferent arteriolar vasoconstriction or structural narrowing of the lumen [22]. Some patients with primary hypertension have elevated plasma renin activity, but, even in those with normal levels, it may be inappropriately high, as we would expect the hypertension to suppress renin. Others have developed the idea that hypertension may arise from a congenital reduction in the number of nephrons or in the filtration surface area per glomerulus that limits the ability of the kidney to excrete sodium, raising blood pressure, which destroys more glomeruli, thus setting up a vicious cycle of hypertension and renal glomerular dysfunction [23].

Increased Activity of the Renin–Angiotensin System

The components of the renin–angiotensin system, the biosynthesis and actions of angiotensin II, and angiotensin II signal transduction in VSMC are all described in Chap. 4. Plasma renin activity is nearly always low in association with primary aldosteronism, high with renovascular or accelerated malignant hypertension, and low, normal, or high with primary hypertension. Primary hypertension with sodium retention would be expected to depress plasma renin levels; under these circumstances, "normal" values are inappropriately high. Three explanations for this have been developed. The first, cited earlier, is that a population of ischemic nephrons contributes excess renin. The second is that the sympathetic hyperactivity associated with primary hypertension stimulates β-adrenergic receptors in the juxtaglomerular apparatus of the nephron to activate renin release. The third proposes that many of the patients with inappropriately normal or even high renin levels have defective regulation of the relationship of sodium and the renin–angiotensin system—that they are "non-modulators." This results in abnormal adrenal and renal responses to salt loads; in particular, salt loading does not reduce angiotensin II [24]. In low-renin hypertension, the hypertension is primarily due to volume overload but may in rarer cases be explained by hyperaldosteronism (*see* below), or excess 18-hydroxylated steroids, or with high levels of cortisone from inhibition of 11β-hydroxysteroid dehydrogenase. High- or normal-renin hypertensives have a higher rate of cardiovascular complications than those with low renin. Also it has been suggested that, since high- and normal-renin hypertensives are vasoconstricted, the drug of first choice in their treatment should be one that antagonizes the renin–angiotensin system, and because low-renin hypertensives are volume-overloaded, they should be treated in the first instance with a diuretic.

Increased Sympathetic Activity

There is much evidence of sympathetic hyperactivity in patients with primary hypertension. Heart rate and stroke volume are increased, at least in the early, labile, phase of blood pressure elevation and at least part of the increased vascular resistance of the established phase of hypertension may be due to the increased sympathetic tone. It is not surprising that psychogenic stress seems to predispose to high blood pressure, tension causing hypertension. Baroreceptor sensitivity is reduced in some patients with hypertension, presumably because of the arteriosclerotic stiffness of the vessels that house baroreceptors, so that a given increase in blood pressure decreases heart rate less than it normally would. In other patients, there is resetting of the baroreceptor reflex, with baroreceptor reflexes operating normally, but around a higher set point of arterial pressure.

Increased Peripheral Resistance

Small arteries and arterioles are responsible for most of the peripheral resistance, but the microvasculature is difficult to study in humans. It is much easier to study larger arteries, especially by noninvasive methods such as ultrasonography. We can make measurements of morphology such as wall thickness and wall–lumen ratio, and of physiologic processes, such as compliance or distensibility (lumen cross-sectional diameter or area change per unit pressure change). Patients with hypertension very frequently have large arteries (e.g., brachial, carotid, femoral) that are thick (owing to hypertrophy, increased wall–lumen ratio) and stiff (owing to decreased compliance). These effects are due to vascular smooth muscle cell hypertrophy in the media. Smaller arteries probably undergo either hyperplasia or remodeling, which is a rearrangement of existing cells around a smaller lumen. Increased large artery stiffness may be quantified by measuring the pulse wave velocity (PWV). PWV measurement utilizes the feature of the arterial waveform that during early systole, there is no, or minimal, interference of the incident pressure wave by the reflected pressure wave. With this assumption, PWV can be measured between two sites, a known distance apart using the pressure "foot" of the waveform to calculate the transit time. PWV is then calculated as the distance divided by the time. The augmentation index (AIx) is another noninvasive measure, this time of both large artery stiffness and small artery constriction. The AIx is the "boost" given to the peak systolic pressure waveform by a reflected wave that arrives back at the aorta more quickly than normal. The growth factors responsible for these changes are summarized in Fig. 31.4 and are discussed in more detail in Chap. 4.

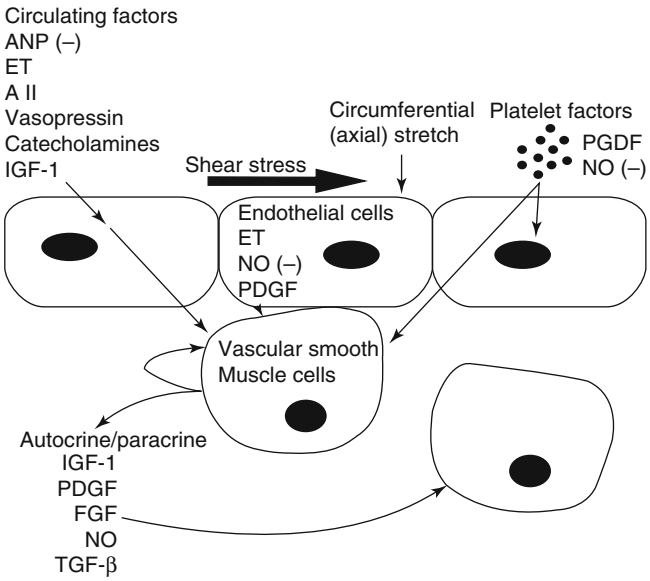

Fig. 31.4 Stimuli to vascular smooth muscle growth. *ANP* atrial natriuretic peptide, *ET* endothelin, *AII* angiotensin II, *PDGF* platelet-derived growth factor, *NO* nitric oxide, *IGF-1* insulin-like growth factor-1, *FGF* fibroblast growth factor, *TGF-β* transforming growth factor β, (–), inhibitory to hypertrophy/hyperplasia

Abnormal Cell Membrane Ion Transport

Because it is so easy to measure red cell cation concentrations and therefore the kinetics of transmembrane cation flux, the literature on abnormalities of these in primary hypertension is voluminous. There seems to be general agreement that there is decreased activity of the Na^+–K^+–ATPase pump (which pumps Na^+ *out* of the cell), possibly the result of an excess of the endogenous inhibitor ouabain (*see* earlier in the section on "Renal Sodium Retention"). There may also be increased activity of the Na^+–H^+ exchange antiporter (which pumps Na^+ *into* the cell). Both mechanisms increase intracellular sodium. This high intracellular sodium concentration (and low intracellular pH) inhibits Na^+–Ca^{2+} exchange (normally Na^+ *in* and Ca^{2+} *out*) to increase intracellular Ca^{2+}, which increases vascular tone and stimulates hypertrophy. Hyperactivity of the Na^+–H^+ exchanger in the renal proximal tubule cells may also cause increased sodium reabsorption and intravascular volume expansion [25].

Endothelial Dysfunction

Impaired biosynthesis or release of nitric oxide, the vascular endothelium-derived relaxing factor, has been described in animal models of hypertension and in human hypertension. Endothelin, a 21-amino-acid vasoconstrictor made by endothelial cells, is present in increased amounts in the

plasma of hypertensives. There may also be paracrine release of endothelin from the endothelial cells, where it is made, toward the VSMC, where it acts [26]. Hypertensives have an increased vasoconstrictor response to endothelin, as well as an enhanced expression of the endothelin gene. Prostaglandin H_2 and thromboxane A_2 are other vasoconstrictors made by endothelial cells (*see* Chap. 4).

Insulin Resistance and Hyperinsulinemia

Hypertension is more common in obese persons, possibly because of insulin resistance and the resulting hyperinsulinemia [27]. The mechanism by which insulin resistance or hyperinsulinemia increases blood pressure is obscure; possibilities include enhanced renal sodium and water reabsorption, increased renin–angiotensin or sympathetic nervous system activity, and vascular hypertrophy, all firmly established actions of insulin. While the physiologic role of insulin resistance and hyperinsulinemia has been studied most intensively in the syndrome of obesity, hypertension, and diabetes, similar abnormalities of insulin action have been described in lean hypertensives who are not diabetic. Leptin, a hormone produced by fat cells, stimulates the sympathetic nervous and renin–angiotensin systems and also promotes insulin resistance, vascular inflammation, and endothelial dysfunction.

Other Possible Mechanisms

The many other possible mechanisms that have been investigated are supported by more or less solid evidence. Notable ones are abnormal patterns of biosynthesis or secretion of adrenocortical hormones in response to various stimuli; adrenomedullin (an adrenomedullary vasodilator peptide); the kallikrein–kinin system, including bradykinin; other vasoactive peptides (natriuretic peptide, calcitonin gene-related peptide, neuropeptide Y, opioid peptides, vasopressin); dopamine; serotonin; prostaglandins; and medullipin (a renomedullary vasodepressor lipid). In addition to all the postulated mechanisms for primary hypertension, many other factors may contribute to high blood pressure in susceptible persons. Examples are increased urinary calcium with a low plasma calcium concentration, potassium and magnesium deficiency, smoking, excessive consumption of caffeine or alcohol, physical inactivity, and hyperuricemia.

Common Causes of Secondary Hypertension

"Common" is an overstatement. As a rough estimate, only about 5 % of all patients who present with hypertension have a demonstrable cause that qualify the condition as secondary. It is, however, critically important to recognize these conditions when they occur, as many are curable—by surgery or some other means.

Renovascular Hypertension

Renal hypoperfusion as a result of renovascular disease (renal artery stenosis—RAS) accounts for about 1 % of all cases of hypertension, but it is much more likely to be the cause when hypertension is rapidly progressive, accelerated, or malignant or is associated with coronary, carotid, or peripheral vascular disease [28, 29].

The mechanism of renovascular hypertension has been firmly established in animal models (based on those developed by Harry Goldblatt in the 1930s). When both renal arteries in the dog are partially occluded by clamps or when one artery is clamped and the other kidney removed, sustained hypertension develops. The two-clip–two-kidney model resembles bilateral renovascular hypertension, and the one-clip–one-kidney animal is a model for renovascular hypertension plus chronic renal parenchymal disease. A more useful model for the common form of renovascular hypertension, unilateral renal artery stenosis, is the one-clip–two-kidney model.

Mechanisms

Bilateral renovascular hypertension and *renovascular hypertension* (*unilateral or bilateral*) *with chronic renal parenchymal disease* have similar mechanisms. The decreased intrarenal vascular pressure results in increased secretion of renin from the juxtaglomerular apparatus and, consequently, increased activity of angiotensin II and aldosterone. The systemic vasoconstriction produced by angiotensin II raises the blood pressure (renin-dependent hypertension). With time, however, the renin–angiotensin dependency of the systemic hypertension wanes because of progressive retention of sodium and water, which leads to increases in extracellular fluid volume, blood volume, and blood pressure. Sodium and water retention are consequences of a reduction in the functional renal mass subjected to reduced perfusion pressure, with the associated rightward shift of the pressure–natriuresis curve (*see* Fig. 31.2), and are secondary to the effects of angiotensin II, namely, intrarenal vasoconstriction, increased net tubular sodium reabsorption, and increased aldosterone levels. At this stage, the hypertension is mainly volume-dependent. With progressive diminution in renin release and in circulating angiotensin II levels, salt and water balance is restored but at the expense of high arterial blood pressure.

This dual mechanism has important therapeutic implications. Therapy with vasodilators reduces the renal perfusion pressure even further and exacerbates volume retention. Diuretics reduce the extracellular fluid volume and enhance the activity of the renin–angiotensin system. Vasodilator

drugs in combination with volume depletion can decrease the glomerular filtration rate and can even cause acute renal failure. ACE inhibitors or angiotensin II receptor blockers may also be dangerous in renovascular hypertension because they remove the selective vasoconstrictor action of angiotensin II on efferent arterioles to maintain glomerular filtration pressure.

Unilateral renovascular hypertension is much more common than bilateral stenosis in humans. Here, the stenotic kidney releases renin, elevating circulating levels of angiotensin II to increase blood pressure. This hypertension should increase sodium excretion in the nonstenotic kidney to restore blood pressure to normal; however, this pressure–natriuresis effect (*see* Fig. 31.3) is blunted by the increased angiotensin II levels because of angiotensin II and aldosterone-mediated sodium reabsorption and because of angiotensin II renal vasoconstriction with reduction in renal plasma flow and glomerular filtration rate (GFR). Since the pressure distal to the stenosis is never completely restored to normal, even with high systemic blood pressure, the levels of renin and angiotensin II remain high, and the hypertension is "renin-dependent."

Treatment of unilateral renovascular hypertension with ACE inhibitors or angiotensin II receptor blockers reduces glomerular filtration pressure and GFR in the stenotic kidney but increases renal blood flow and GFR in the nonstenotic kidney. In some patients, the sustained hypertension of unilateral renovascular disease can cause hypertensive glomerular injury in the nonstenotic kidney, which further compromises renal function and exacerbates the hypertension. In these patients, ACE inhibitors and angiotensin II receptor blockers may further impair renal function for the reasons described earlier.

Pathology

The most common cause of renovascular hypertension is atherosclerotic stenosis of a main renal artery. Affected patients are relatively older and usually have vascular disease elsewhere. The second condition is fibromuscular dysplasia, which can be subdivided into intimal fibroplasia, medial fibromuscular dysplasia, and periadventitial fibrosis. Of these, the most common is medial fibromuscular dysplasia (or medial fibroplasia), usually a condition of young women. Other, rare, causes are renal artery aneurysms, emboli, and Takayasu's arteritis and other vasculitides.

Clinical Features

The only unique clinical finding, an abdominal bruit, is heard in about half of those who have renal artery stenosis. In general, renal artery stenosis should be suspected in severe hypertension associated with any one of the following: progressive renal insufficiency, refractoriness to aggressive treatment, and other evidence of occlusive vascular disease in young women or in patients whose serum creatinine value rises quickly after they start taking an ACE inhibitor. Laboratory findings often include proteinuria, elevated renin and aldosterone levels, and a low serum potassium value.

Diagnosis

A workup for atherosclerotic renal artery stenosis [30] should be done only if there is resistant hypertension or if there is worsening of renal function. The most cost-effective screening test is color Doppler ultrasonography. A more traditional modality of screening is the captopril renal scan. Reduced renal uptake of technetium 99 m diethylenetriamine penta acetic acid (^{99m}Tc-DTPA) and reduced renal excretion of iodine 121 (^{121}I) hippurate or ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG$_3$) are measures of renal function in stenotic kidneys. Renal function can be reduced further after a single dose of the ACE inhibitor captopril.

If the ultrasonogram or the captopril scan is positive, then magnetic resonance angiography (MRA) or CT angiography should be done. Other useful imaging tests include digital subtraction intravenous angiography and renal arteriography. Various tests detect hypersecretion of renin from the hypoperfused kidney: these are peripheral blood plasma renin activity (PRA) and the renal vein renin ratio (ratio of PRA between the two renal veins; a ratio >1.5:1 is diagnostic).

Therapy

Most patients with atherosclerotic RAS require only medical antihypertensive therapy as either primary therapy or following some revascularization procedure because revascularization alone is seldom sufficient to control the BP in middle-aged or elderly patients with RAS. The reason for this may be residual ischemic nephropathy in the affected kidney, restenosis of the affected kidney, concomitant hypertensive parenchymal damage to the contralateral kidney, or progression of atherosclerotic disease in the contralateral kidney. In contrast, percutaneous trans-renal angioplasty (PTRA), with or without stenting, is the treatment of choice in patients with fibromuscular dysplasia. Surgical revascularization of the kidney should be reserved for the rare cases of failed medical management and PTRA. ACE inhibitors or angiotensin II receptor antagonists should not be used.

Renal Parenchymal Hypertension [31, 32]

Renal parenchymal hypertension is discussed in more detail in Chap. 40. Chronic kidney disease (CKD) is the most common cause of secondary hypertension, which is present in about 80 % of patients with chronic renal failure (CRF). Primary hypertension also damages the kidneys; in the United States, hypertension ranks just below diabetes among causes of end-stage renal disease. Hypertension is, therefore, both a cause and a consequence of CKD, and often there is a

vicious circle: hypertension causes renal damage, which exacerbates hypertension.

Pathophysiologic Mechanisms

The following mechanisms have been identified.

Glomerular Hypertension

A high systemic blood pressure may be transmitted to the glomerular capillaries, particularly if the autoregulatory vasoconstrictor response of the afferent arterioles is defective. This causes an increased filtration pressure and an increased filtration rate of individual glomeruli, increased pressure within Bowman's capsule, and damage to glomerular epithelial cells. This results in a protein leak through the glomerular membrane, and the protein may then damage tubule cells. The renal damage will eventually result in a decrease of whole-kidney glomerular filtration rate, sodium and water retention, and worsening of the hypertension.

Sodium and Volume Status

A severely reduced GFR (<50 mL/min) causes sodium retention and volume expansion and, therefore, increased cardiac output. The disorder of sodium homeostasis may also be due to increased amounts of an endogenous ouabain-like natriuretic factor that inhibits the Na^+–K^+–ATPase pump.

Renin–Angiotensin–Aldosterone System

The renin–angiotensin–aldosterone system is activated in CRF because of diffuse intrarenal ischemia. The aldosterone contributes to sodium retention. Eventually, however, the expanded fluid volume inhibits renin release, and plasma renin activity may become normal. Even "normal" plasma concentrations of renin are, however, inappropriately high in relation to the state of sodium and water balance, and the hypertension remains partly due to an angiotensin-dependent increase in peripheral vascular resistance.

Autonomic Nervous System

CRF activates renal baroreceptors, which effect increases sympathetic nervous system activity and elevates plasma norepinephrine levels (as does reduced catecholamine clearance).

Other Mechanisms

In uremic patients, increased plasma levels of an endogenous compound, asymmetrical dimethylarginine (ADMA), a nitric oxide synthase inhibitor, contribute to the hypertension. Recombinant human erythropoietin (rHu-EPO), used extensively to treat the anemia of CRF, exacerbates hypertension, though how it does so is not known. The secondary hyperparathyroidism of CRF makes the hypertension worse. The mechanism, as yet undefined, is somehow related to the increase in intracellular calcium concentration.

Management

The problem in treating hypertension in patients with CRF is that diuretics and other antihypertensive agents often produce a transient drop in renal blood flow and GFR and an increase in serum creatinine; thus, management is often a delicate balancing act between achieving blood pressure control and maintaining whatever renal function is left. In general, ACE inhibitors or angiotensin receptor blockers are the antihypertensive drugs of choice (*see* Chap. 32).

Pheochromocytoma

About 0.5 % of hypertensives have pheochromocytoma as the cause of the high blood pressure. Pheochromocytomas [33, 34] can occur at any age, and they arise from neuroectodermal chromaffin cells, mostly in the adrenal medulla (85 %) but sometimes elsewhere, usually in the abdomen or pelvis (15 %). About 10 % of adrenal and about 30–40 % of extraadrenal tumors are malignant. Ten percent are familial and autosomal-dominant. The familial form seems to be due to mutations of the RET protooncogene on chromosome 10 and may be intercurrent with other tumors as a syndrome of multiple endocrine neoplasia (MEN). In MEN 2A, pheochromocytoma is associated with medullary thyroid carcinoma (MTC) and hyperparathyroidism, whereas in MEN 2B, there is no parathyroid disease but there is a characteristic phenotype (marfanoid appearance, neuromas of the lips and tongue, thickened corneal nerves, intestinal ganglioneuromatosis). Other familial syndromes with pheochromocytoma include von-Hippel–Lindau syndrome and von Recklinghausen's disease.

Pheochromocytomas secrete mainly norepinephrine (NE) and less epinephrine, plus a variety of peptide hormones, adrenocorticotropin (ACTH), erythropoietin, parathyroid hormone, calcitonin gene-related protein, atrial natriuretic peptide, vasoactive intestinal peptide, and others. Most patients have hypertension; in about half, it is sustained, with or without paroxysms, and in the other half, blood pressure is normal between paroxysms. Paroxysms of hypertension may be signaled by severe headaches, sweating, palpitations with tachycardia, pallor, anxiety, and tremor. Also described are orthostatic hypotension, nausea and vomiting, and weight loss. Any patient with this symptom complex should be screened for pheochromocytoma with measurement of the plasma or urinary concentrations of the catecholamine metabolites, metanephrine and normetanephrine. There are, however, some problems with these tests. Results can be normal in patients with paroxysmal hypertension if the test is done during a normotensive interval. Plasma or urinary metabolites of an antihypertensive drug, labetalol, may cause a false-positive result. Other medications, particularly tricyclic antidepressants, may also give false-positive results.

If plasma catecholamines are only moderately elevated (600–2,000 pg/mL), the differential diagnosis includes neurogenic hypertension and hypertension associated with increased sympathetic activity. Here, the clonidine suppression test is useful; clonidine decreases plasma catecholamine levels to normal in neurogenic hypertension, but not in pheochromocytoma. If blood or urine test findings are positive, the next step is to localize the tumor using CT or MRI. In patients with elevated metanephrines but a negative CT or MRI, scintigraphy using ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) should be done. Definitive treatment is surgery, but great care must be taken to prevent severe hypertension or hypotension during the operation or in the immediate postoperative period, utilizing α- and β-adrenergic blocking drugs and careful management of fluid balance.

Mineralocorticoid Hypertension

Aldosterone, the most abundant mineralocorticoid hormone, is synthesized by aldosterone synthase in the outer zone of the adrenal cortex (zona glomerulosa). Its synthesis and release are controlled by adrenocorticotropic hormone (ACTH), and blood levels peak in the early morning. Aldosterone blood levels are also increased by angiotensin II and lowered by an increased plasma potassium concentration. Aldosterone increases distal tubular reabsorption of sodium and chloride and secretion of potassium and hydrogen ions. Another mineralocorticoid hormone, deoxycorticosterone, produced by the inner zone of the adrenal cortex (zona fasciculata), is a much weaker mineralocorticoid than aldosterone, but it can cause hypertension when produced in large quantities.

The hypertension produced by mineralocorticoid excess is due to the increase in total exchangeable sodium, but many patients with chronic mineralocorticoid excess have normal plasma volume because the initial increase in extracellular fluid volume is restored to normal by an increased natriuresis and diuresis due to decreased sodium reabsorption in segments of the nephron other than the distal tubule (mineralocorticoid escape). The hypertension is sustained by increased vascular resistance (possibly due to augmented vascular sensitivity to catecholamines) or by central nervous system mineralocorticoid receptors, which activate the sympathetic nervous system.

Primary hyperaldosteronism (PA) [35, 36] is due either to a benign aldosterone-producing adenoma (APA) or, more rarely, to bilateral hyperplasia (BH). The classic clinical features of PA are hypertension, excessive urinary potassium excretion, hypokalemia (serum K^+ <3.5 mEq/L), hypernatremia (serum Na+ >145 mEq/L), and metabolic alkalosis. The 24-h urinary potassium excretion exceeds 30 mEq/day, and the plasma aldosterone will be high and the renin low. A hypertensive patient who is treated with diuretics or who has diarrhea may also have a low serum potassium concentration. In this situation, the serum potassium value returns to normal after recovery from the diarrhea or a few weeks after the diuretic is discontinued. Diuretics raise both PRA and aldosterone levels.

The morning ratio of plasma aldosterone concentration (PAC) to plasma renin activity (PRA), the PAC: PRA ratio, is the screening test of choice for PA. A ratio of >20 with a PAC of at least 12 ng/dL should prompt confirmatory testing. A ratio > 70 with a PAC of ≥15 ng/dL and a PRA of ≤1 ng/mL/h is virtually diagnostic. Another test sometimes done to confirm the diagnosis is based on the failure of volume expansion to suppress aldosterone (plasma aldosterone is >10 ng/dL after 2 L normal saline iv over 4 h; alternatively, urinary aldosterone >12 mcg/24 h after 3 days of 4–6 g/day of sodium chloride orally). CT or MRI of the adrenal glands completes the workup. Bilateral adrenal venous sampling is a highly specialized procedure that may reveal a unilateral source of excess aldosterone.

Glucocorticoid Hypertension [37]

The principal glucocorticoid in humans, cortisol, is synthesized in the zona fasciculata under the control of ACTH. While cortisol has only a weak mineralocorticoid effect, the circulating levels of the hormone in Cushing's syndrome are usually hundreds of times the normal value. Since most patients with Cushing's syndrome, however, do not have other findings of hypermineralocorticoidism, particularly hypokalemia, and since spironolactone, a mineralocorticoid antagonist, does not blunt the hypertensive effect of cortisol, other mechanisms must be operating. Possibilities include the glucocorticoids activating the gene transcription of angiotensinogen in the liver or increasing vascular reactivity to vasoconstrictor amines or inhibition of the extraneuronal uptake and degradation of norepinephrine or inhibition of vasodilators such as endothelial nitric oxide, kinins, and some prostaglandins, or a shift of sodium from cells to the extracellular compartment with an increase in plasma volume and, thus, in cardiac output. Also, in Cushing's syndrome, the ACTH excess may stimulate production and release of endogenous mineralocorticoids, especially 11-deoxycorticosterone (Fig. 31.5).

Other Clinical Syndromes of Adrenocortical Hypertension [38, 39]

Glucocorticoid-Remediable Hyperaldosteronism (GRA)

GRA is an autosomal-dominant disorder in which the classic features of primary hyperaldosteronism are completely relieved by glucocorticoids such as dexamethasone. Because

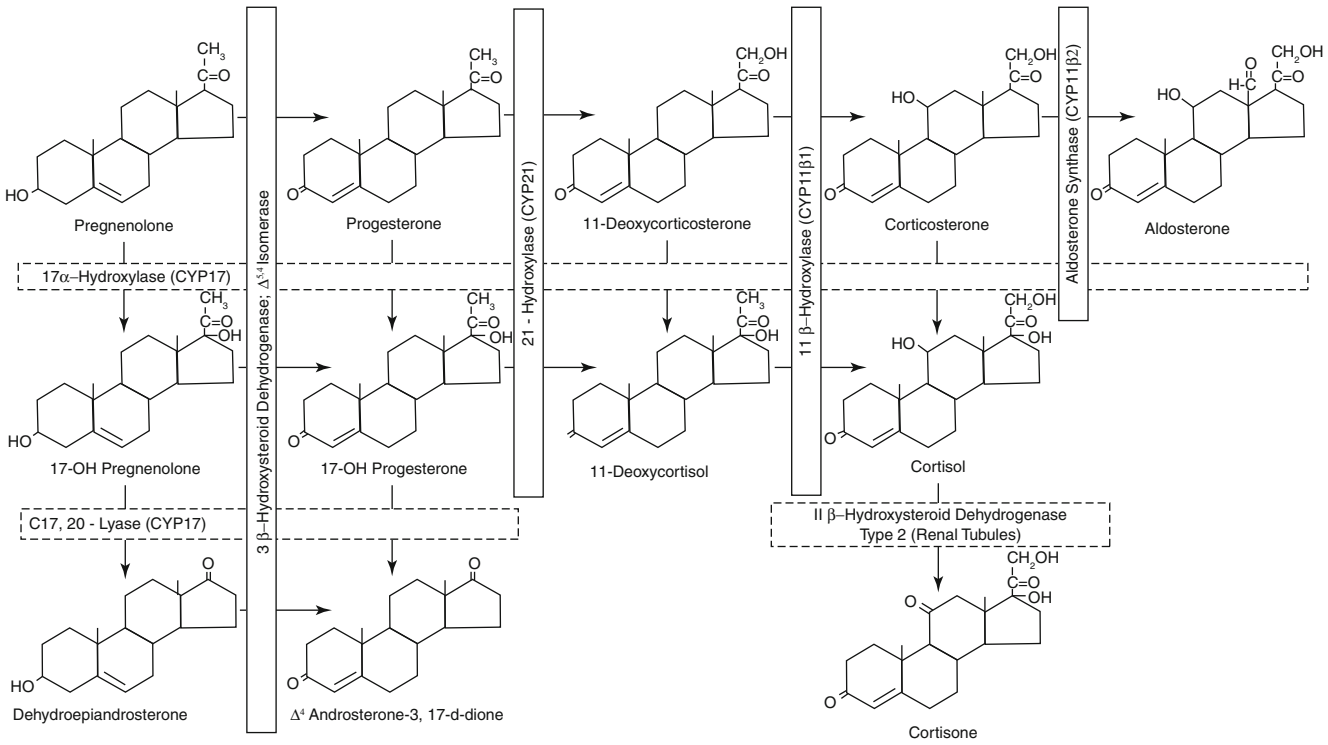

Fig. 31.5 Pathways of steroid biosynthesis in the adrenal cortex

dexamethasone suppresses ACTH, the concept was developed of increased adrenal sensitivity to the aldosterone-stimulating effects of ACTH. Recently, it has been shown that this syndrome is due to a chimeric gene produced by unequal crossing over of the 5′ regulatory region of 11β-hydroxylase (CYP11β1) and the 3′ coding sequence of aldosterone synthase (CYP11β2) (Fig. 31.5). As a result, aldosterone synthase, normally found in the zona glomerulosa, is expressed in the zona fasciculata under the control of the ACTH-sensitive 11β-hydroxylase regulatory sequence, which accounts for the aldosterone elevation and the excess formation of products of 11β-hydroxylase activity, such as cortisol. This was the first description of a gene mutation as a cause of hypertension in humans.

Pseudohyperaldosteronism (Liddle's Syndrome)

In 1963, Liddle described members of a family with hypertension and hypokalemic alkalosis who had low levels of aldosterone and no elevations of other mineralocorticoids. Treatment with the mineralocorticoid antagonist spironolactone or with other inhibitors of mineralocorticoid biosynthesis had no effect, but amiloride and triamterene, both inhibitors of distal nephron sodium reabsorption, improved hypertension and hypokalemia. Affected patients have a mutation of the β- or γ-subunits of the renal epithelial sodium channel that increases sodium reabsorption in the distal nephron.

11β-Hydroxylase (CYP11β1) Deficiency

11β-Hydroxylase converts 11-deoxycorticosterone to corticosterone and 11-deoxycortisol to cortisol (Fig. 31.5). Deficiency of this enzyme leads to reduced cortisol levels, increased ACTH secretion, and increased production of 11-deoxycorticosterone in the zona fasciculata. The 11-deoxycorticosterone induces volume expansion and hypertension. The adrenal steroid pathway is also redirected toward androgen production so that these patients also have virilization, usually recognized in infancy.

17α-Hydroxylase (CYP17) Deficiency

17α-Hydroxylase converts pregnenolone to 17-hydroxypregnenolone, progesterone to 17-hydroxyprogesterone, 11-deoxycorticosterone to 11-deoxycortisol, and corticosterone to cortisol (Fig. 31.5). Deficiency of 17α-hydroxylase reduces cortisol levels, causing increased ACTH and increased 11-deoxycorticosterone, corticosterone, and aldosterone levels. There is an absence of sex hormones.

11β-Hydroxysteroid Dehydrogenase Type 2 Deficiency

The normal renal mineralocorticoid receptor binds glucocorticoids with a similar affinity to mineralocorticoids. The 11β-hydroxysteroid dehydrogenase type 2 isoform enzyme in the renal tubules normally converts the large amounts of fully active cortisol to the inactive cortisone (Fig. 31.5),

thereby leaving the renal mineralocorticoid receptors open to the effects of aldosterone. A deficiency of this enzyme in the kidney allows for high renal levels of cortisol, producing all of the features of the hypermineralocorticoid state but with low mineralocorticoid levels (the syndrome of *apparent mineralocorticoid excess*). An acquired form of this syndrome develops in adults who eat large quantities of licorice. The active alkaloid in licorice, glycyrrhetinic acid, is an inhibitor of 11β-hydroxysteroid dehydrogenase.

Miscellaneous Causes of Secondary Hypertension

Other causes of secondary hypertension include coarctation of the aorta, hypo- and hyperthyroidism, hyperparathyroidism, sleep apnea, brain tumors and increased intracranial pressure, erythropoietin, polycythemia, inappropriate antidiuretic hormone, and a host of drugs and other chemical agents, notably exogenous steroids, cyclosporine, tacrolimus, pseudoephedrine (in nasal decongestants), monoamine oxidase inhibitors, tricyclic antidepressants, nonsteroidal anti-inflammatory drugs, herbal remedies containing ephedrine, yohimbine, or licorice, and street drugs such as amphetamines and cocaine.

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Hypertension Therapy

32

Norman M. Kaplan, Odelia Cooper, and Ronald G. Victor

Introduction

Hypertension is almost always easy to treat but often exceedingly difficult to keep under control. As documented in the latest survey of a representative sample of the US population, 71 % of hypertensives are being treated but only 48 % have their blood pressure controlled, defined as below 140/90 mmHg [1]. Although hypertension remains the most common reason for nonpregnant adults to visit a physician in the USA [2], these disappointing rates of control point to a number of problems: Many hypertensive patients have not been diagnosed or started on treatment, and many physicians have not provided adequate amounts of medication. But the most likely problem is inherent to the nature of hypertension: a lifelong condition that is usually asymptomatic for many years but that requires daily therapy that may in itself induce symptoms.

As described in the previous chapter, most hypertension is of unknown cause and therefore cannot be prevented with certainty. Nonetheless, in view of the inherent difficulty of treating the condition after it has developed, attention will first be given to the lifestyle modifications that may help delay, if not stop, the onset of the condition. All these are also of value in treating those with established hypertension; if offered to the prehypertensive, they may provide prevention as well. In particular, prevention of excess weight in children, now present in 31 % of those between ages 2–19 [1], must be an overall goal for American society, aided by constant health professional guidance.

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Lifestyle Modifications

Prevention of Hypertension

At this time, prevention of hypertension can only be achieved by healthy lifestyle, instituted early in childhood. Antihypertensive drugs can prevent hypertension in rats that are destined to become hypertensive but only if the drugs are given during an interval approximating 6–10 years of age in humans [3]. Such preventative medications will never be tested in susceptible children, so a healthy lifestyle remains the only possible preventative.

Treatment of Hypertension

Lifestyle modifications listed in Table 32.1 are often the only therapy indicated for patients with relatively mild hypertension and little overall cardiovascular risk, and they are always indicated along with drug therapy for the remainder.

The tendency for most physicians is to immediately proceed to drug therapy for any degree of hypertension. Drugs are a known quantity that are comparatively easy to prescribe and likely to be effective. Instructing, motivating, and following patients in the use of lifestyle modifications is costly in time and energy, costs that are not compensated by the insurance payers. It also can seem to be a futile exercise, because recidivism is so likely.

But the effort is still worthwhile. Even if the degrees of weight loss and sodium reduction are relatively small, marked benefits have been shown, as among the elderly hypertensives enrolled in the Nonpharmacologic Interventions in the Elderly (TONE) study [4] and the prediabetics in the Diabetes Prevention Program [5]. Moreover, other cardiovascular risk factors—dyslipidemia, glucose intolerance and

C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_32, © Springer Science+Business Media New York 2013

Table 32.1 Lifestyle modifications

Modification	Recommendation	SBP reduction
Weight reduction	Achieve goal BMI 18.5–24.9	5–20 mmHg/10-kg weight loss
DASH diet	Increased fruits, vegetables, and low-fat dairy products; decreased content of saturated and total fat	8–14 mmHg
Dietary sodium reduction	Dietary sodium intake 100 mEq/L (2.4 g sodium or 6 g sodium chloride)	2–8 mmHg
Physical activity	Regular aerobic activity (at least 30 min/day, most days of the week)	4–9 mmHg
Moderation of alcohol consumption	Alcohol intake less than two drinks per day (1 oz or 30 mL ethanol, e.g., 24 oz beer, 10 oz wine, 3 oz of 80 proof whiskey) in most men and no more than one drink per day in women and lighter-weight people	2 mmHg

diabetes, physical inactivity, cigarette smoking—may also be relieved, multiplying the benefits far beyond the reduction in blood pressure.

In a recent large national survey, 84 % of adult hypertensive individuals reported receiving some form of lifestyle modification counseling. Most were advised to reduce dietary sodium, exercise more, and lose weight, while few were advised to reduce alcohol consumption or quit smoking [6].

Prevention of Intrauterine Growth Retardation

Though not included in the list of lifestyle modifications, another effective preventive measure is the prevention of intrauterine growth retardation and rapid postnatal "catch-up" weight gain [7]. A number of epidemiological surveys have documented an increased prevalence of hypertension in adults whose birth weight was low for their gestational age. Moreover, mothers of small-for-gestational-age infants are also more susceptible to eventual cardiovascular disease [8].

The mechanism for this is uncertain. The most widely accepted hypothesis is congenital oligonephropathy—a reduced number of nephrons at birth that leads to both systemic and glomerular hypertension [9]. Regardless of how low birth weight predisposes to hypertension (as well as diabetes and coronary heart disease), the prevention of low birth weight may very well be an effective and achievable way to prevent these adult diseases.

Low birth weight is more likely in disadvantaged populations, in particular among African-Americans (who have a much higher prevalence of both hypertension and renal insufficiency). Associations with low-birth-weight babies have been noted with teenage pregnancy, short intervals between pregnancies, inadequate nutrition, familial aggregation, and other unknown factors linked to the African-American population. The opportunity for overcoming most of these contributing factors is obvious. However, recent cutbacks in support for teenage contraception, maternal nutrition, and prenatal care in the USA suggest that we will continue to pay billions for the eventual care of hypertension-related end-stage renal disease, strokes, and heart attacks instead of millions for preventive care of the disadvantaged.

Prevention and Reduction of Obesity

As difficult as it may be to overcome low birth weight, it likely will be even harder to correct the three major environmental contributions to the pathogenesis of hypertension: obesity, excess dietary sodium, and stress. Of these three, obesity is growing most rapidly, with 67.3 % of all adult Americans now overweight, defined as a body mass index (BMI) above 25, and 33.7 % obese, defined as a BMI above 30. The association of weight gain and hypertension was shown clearly among the 82,500 female nurses, 30–55 years of age, followed every 2 years from 1976 to 1992 [10]. A weight gain of only 5 kg (12 lb) from age 18 was responsible for almost a doubling of the incidence of hypertension; a 10-kg gain tripled the incidence.

When obesity is predominantly upper-body or abdominal in distribution, the dangers for hypertension, diabetes, and dyslipidemia are even greater, with a marked increase in coronary disease as a consequence of the metabolic syndrome [11]. Moreover, upper-body obesity is associated with obstructive sleep apnea, which is increasingly being recognized as a cause of hypertension [12].

The problem is obvious, the solution perhaps unattainable. As children and their parents become couch potatoes, rising only begrudgingly to change the TV channel or computer game, and eating increasingly "empty calorie" fast and junk food, the future looks even worse in regard to obesity. Nonetheless, even small amounts of weight loss can protect against a rise in blood pressure [4]. In the TONE trial, almost 1,000 elderly patients with hypertension that was well controlled on one or two drugs voluntarily discontinued their drug therapy and were randomly assigned to one of four regimes: weight loss by caloric restriction and physical activity, sodium restriction, both weight loss and sodium restriction, or nothing (usual care). After 30 months, those who lost an average of 4.7 kg (10 lb) on the weight-loss regimen had a 50 % greater likelihood of staying normotensive and free of cardiovascular complications than did those with no weight loss.

This study was done in elderly hypertensives but equally small amounts of weight loss have been shown to decrease the incidence of hypertension and diabetes in young subjects

as well [5]. Therefore, the effort is worthwhile, best directed at young people to prevent them from becoming obese but also in adults who have become overweight.

The DASH Diet

The Dietary Approaches to Stop Hypertension (DASH) diet has been shown to lower blood pressure in prehypertensives [13]. The DASH diet uses eight to nine daily portions of fruits and vegetables and more low-fat dairy products, providing more potassium, calcium, fiber, and protein and less saturated fat. Moreover, the DASH diet may be cardioprotective in ways beyond its blood pressure effect. Large blood pressure reductions have been shown in short-term feeding trials in which all meals were provided; smaller effects were seen when patients were provided comprehensive lifestyle coaching but had to cook or buy their own meals [14]. A guide to the DASH diet can be downloaded at http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/new_dash.pdf.

Bariatric Surgery

With the increase of marked obesity, bariatric surgery has become widely used, clearly with metabolic and cardiovascular benefits that extend as long as 15 years [15]. The wisdom of subjecting young people to such a procedure is debatable. Far better would be parenteral guidance to prevent their children from becoming obese.

Reduction of Sodium Intake

This goal could most easily be accomplished by lowering of the amount of sodium added to processed foods, the source of 80 % of overall sodium intake, since it is difficult to get even motivated people to individually reduce their intake by more than 40 mmol/day [16]. As amply documented, a reduction of 40 mmol/day, about one-fourth to one-third of the usual intake, will provide a 4–6-mmHg fall in systolic blood pressure among hypertensives and a 1–2-mmHg fall in blood pressure among normotensives [17]. The TONE trial provides further evidence: Those who reduced daily sodium intake an average of 40 mmol/day had a 50 % greater chance of remaining normotensive and free of cardiovascular events than did those on no sodium restriction [4].

Even the small fall in blood pressure that would occur in normotensives by such moderate sodium restriction could have a very considerable impact on the incidence of hypertension and the development of cardiovascular disease [18]. As noted by Rose [19], "All the life-saving benefits achieved by current antihypertensive treatment may be equaled by a downward shift of the whole blood pressure distributed by a mere 2–3 mmHg. The benefits from a mass approach in which everybody received a small benefit may be unexpected large."

More recent projections are that 5–15 % of all strokes and 10–20 % of all heart attacks in the USA would be prevented if the food industry could be pressured to reduce the sodium content of processed food so that daily NaCl intake fell gradually over a decade from 10 g to 7 [20].

Doubts About Universal Sodium Reduction

While few authors still question the role of sodium excess in the pathogenesis of hypertension and the wisdom of advocating a population-wide strategy of moderate sodium restriction (which could theoretically trigger neurohormonal activation), the evidence for a casual role for the high sodium content which has only recently been introduced into the food supply of industrialized societies is so extensive that most investigators are convinced that excess sodium intake is necessary, though not sufficient, for the pathogenesis of hypertension [21]. Absolute proof for the role of high sodium may never be obtained since it is not possible to monitor the sodium intake of thousands of people almost from birth through midlife and observe the effects, particularly as there is considerable variability in the pressor sensitivity of people to sodium intake. Moreover, convincing evidence for a direct and specific hypertensive effect of amounts of sodium typically consumed by humans has been obtained in chimpanzees, the species closest to man.

Potassium Deficiency

Rather than placing the blame only an excessive sodium intake, some evidence points to an imbalance between too much sodium and too little potassium in the diet. For example, surveys have noted a lower-than-recommended intake of potassium but no greater intake of sodium in poor African-Americans, particularly in the southern United States, who have a greater prevalence of hypertension. The lesser intake of potassium presumably reflects lesser consumption of meats, fresh fruits, and vegetables by the poor.

Potassium supplements will lower blood pressure slightly in those who are on a low-potassium diet, and the salutary effects of a diet rich in fruits and vegetables on blood pressure may have been provided by the increased potassium intake [22]. Potassium supplements cannot be recommended for prevention, but more fresh fruits and vegetables will likely be beneficial.

Relief from Stress

Although the evidence is not sufficient to include this lifestyle modification in Table 32.1, data support a role for stress in the pathogenesis of hypertension, likely interacting with multiple other factors to increase vascular resistance. Nonetheless, it has not been possible to show that relief of stress as provided by various relaxation methods will prevent hypertension, much less provide more than a placebo effect in lowering the pressure in those with established hypertension, with rare exception [23].

Increased Physical Activity

Physical activity whether aerobic or by resistance training [24] lowers blood pressure, and numerous surveys show a lesser incidence of hypertension in those who are physically fit. Moreover, both the duration and intensity of physical activity are directly correlated with both a reduction in cardiovascular mortality in men [25] and a prolongation of life span [26]. These benefits are largely independent of weight loss.

Some hypertensive individuals will experience an exaggerated fall in blood pressure after a session of exercise, with postexercise hypotension lasting for an hour or more [27].

Moderation of Alcohol

Excessive alcohol consumption serves as a pressor mechanism responsible for 5–10 % of the hypertension found among men [28]. The pressor effect is only seen when average daily consumption is greater than two drinks, the equivalent of 1 oz of ethanol. However, a small increase in the risk of breast cancer has been noted in women even with less than one drink per day [29]. Nonetheless, there is clearly a reduced risk of heart attack and stroke with such moderate consumption [30].

Cessation of Smoking

Although only a footnote in Table 32.1, cessation of smoking should be the first item addressed if the patient smokes. Cessation of smoking will reduce overall cardiovascular risk beyond any other maneuver, including normalization of blood pressure. Unfortunately, few patients can quit even with the aid of pharmacotherapy or when paid to do so [31]. Among those who cannot quit, each cigarette raises blood pressure acutely, and 20 or more cigarettes a day keeps the blood pressure higher throughout the time the patient is awake [32] and over time causes arterial stiffness [33]. Each cigarette activates the sympathetics, raising blood pressure by 10–15 mmHg for 30–45 min [34]. Unfortunately, the pressor effect of smoking is usually not recognized; since smoking is not allowed in clinics and physicians' offices, the pressor effect of the last cigarette will almost certainly be gone by the time the blood pressure is measured. Therefore, smoking is an important cause of masked hypertension (previous chapter), and it is essential that the smoker take his or her own blood pressure while smoking, and the physician should use that blood pressure to guide therapy.

Reduction of Dietary Saturated Fat and Cholesterol

Correction of dyslipidemia provides a small but significant lowering of elevated blood pressure, likely by a virtually immediate improvement in endothelial function that promotes vasodilation. Even without a further lowering of blood pressure, statin therapy provides a significant cardiovascular protection to hypertensive patients [35].

Maintenance of Adequate Intake of Calcium and Magnesium

Although calcium and magnesium supplements continue to be advocated by a few enthusiasts, multiple controlled trials have shown little if any lowering of blood pressure with them. An adequate intake of both can be provided by a balanced diet that includes low-fat dairy products.

Caffeine

Although the first cup of coffee will transiently raise the blood pressure by 5–20 mmHg, tolerance to this pressor effect usually develops, and most surveys do not demonstrate a relationship between hypertension and caffeine intake.

Other Modifications

A host of other lifestyle modifications, mostly dietary, have been advocated both to prevent and to control hypertension. None of these have been documented to be effective in large-scale, randomized controlled trials so we are left with the maneuvers previously described. Although the evidence that they will prevent hypertension is not conclusive, in those controlled trials which combined sodium restriction, weight loss, exercise, and moderation of alcohol in subjects with "high-normal" blood pressure, a uniform decrease in the incidence of overt hypertension has been seen (Table 32.2).

Table 32.2 Trials of lifestyle modifications and their effects on the incidence of hypertension

Trial (reference)	Number	Duration (year)	Reduction of incidence (%)
Primary prevention (Stamler et al. 1989)	201	5	54
Hypertension prevention (HPTR, 1990)	252	3	23
Trials of hypertension prevention			
I (TOHP, 1992)	564	1.5	51
II (TOHP, 1997)	495	4	21

Antihypertensive Drug Therapy

Drug therapy should begin if blood pressure remains persistently above the goal of therapy despite assiduous application of lifestyle modification or if the patient starts with a blood pressure so high (persistently above 160/100) or cardiovascular risk so great as to mandate immediate institution of treatment with antihypertensive drugs.

Goal of Therapy

It is critically important to recognize a goal for therapy at the very onset and to define that goal for the patient; otherwise, simply taking a medication may be incorrectly construed as fulfilling the need for treatment. In all expert committee guidelines, the goal of therapy is given as below 140/90 mmHg for most patients. Earlier guidelines including the JNC 7 Report recommended a more stringent blood pressure treatment goal of below 130/80 for high-risk hypertensives such as those with diabetes and/or chronic kidney disease, but this was based more on expert opinion than evidence. With the outcomes of recent trials showing that lower is not always better, guidelines committees have started to relax their recommendations about the need to achieve a lower-than-usual blood pressure goal in high-risk patients [36–38]. For hypertensive patients over age 80, new evidence suggests that the goal of treatment is to slowly lower systolic blood pressure to below 150 mmHg [39, 40].

Concerns continued to be raised over dangers of lowering blood pressure too much—to a level below which adequate perfusion of vital organs can be maintained, particularly when atherosclerotic vascular disease already impairs blood supply. This phenomenon is called a "J-curve," i.e., a falling mortality as BP is lowered down to a nadir beyond which mortality increases.

Almost all evidence for a J-curve has been seen with reductions in diastolic pressure [41]. The myocardium may be uniquely susceptible to reduced perfusion from lower diastolic levels for multiple reasons: All large coronary artery flow occurs during diastole; the myocardium usually hypertrophies and needs more blood flow, whereas the brain and kidney often shrink in size; unlike the brain and kidneys, with increased demands the heart cannot extract any more oxygen then under basal conditions; and the atherosclerotic coronary vessels may not be able to vasodilate to increase blood flow when perfusion pressure falls, i.e., poor autoregulation. Therefore, caution remains advisable in reducing diastolic blood pressure to below 60 mmHg, particularly in those with known coronary heart disease and in those in whom unrecognized CHD is very likely [42].

In the elderly with isolated systolic hypertension and "naturally" occurring low diastolic pressure, an increase in stroke has been noted in two populations when diastolic pressure were further reduced to below 65 mmHg with antihypertensive therapy [43], so caution seems appropriate in these patients as well.

Initial Choice of Therapy

A great deal of attention has been directed toward the "best" choice for initial therapy. As noted in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), most patients—even those with initial levels of blood pressure only of 155/90—require two or more drugs to reach the goal of 140/90 [44]. However, therapy begun with a low-dose thiazide-type diuretic (chlorthalidone) was equal or superior to the other three choices in ALLHAT—an ACE inhibitor (lisinopril), an α-blocker (doxazosin), or a calcium channel blocker (amlodipine). The rationale for starting with a diuretic and continuing with that diuretic, even if another agent needs to be added, has been confirmed in many trials in addition to ALLHAT [45]. When compared against all other classes, low-dose diuretics are as good in protection against heart attack and suggestively better than other classes save CCBs in protection against stroke [46] (Fig. 32.1).

The European guidelines [37] continue to include all major classes—diuretics, β-blockers, CCBs, ACEIs, and angiotensin-receptor blockers (ARBs)—as appropriate choices for initial therapy, stating, "The main benefits of antihypertensive therapy are due to lowering of blood pressure per se."

However, in May 2011, the UK National Institute for Health and Clinical Excellence (NICE) published a revision of the 2006 guideline which changed the algorithm for antihypertensive therapy, deleting from step 1 both beta-blockers for younger patients and diuretics for older and black patients (unless the patients have edema or at a high risk of heart failure) [36] (Fig. 32.2). In a defense of these changes, members of the NICE committee stated [47], "As in 2006 calcium channel blockers emerged as the most cost effective option but now more so because of their availability as generic

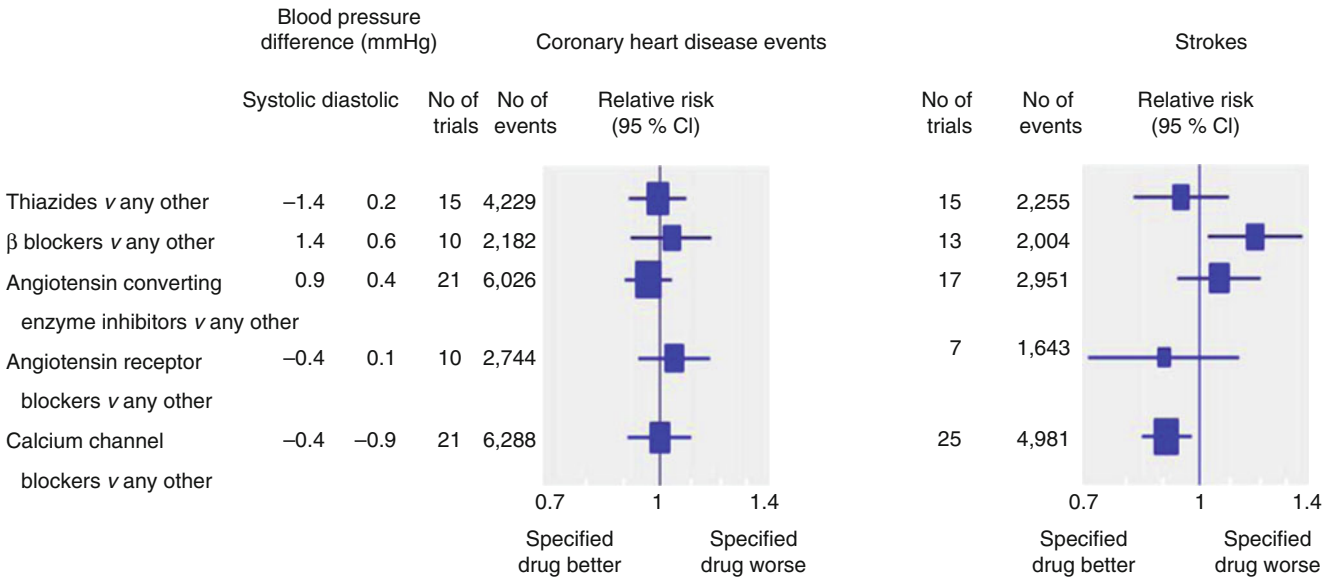

Fig. 32.1 Relative risk estimates of coronary heart disease events and stroke events in 46 drug comparison trials comparing each of the five classes of antihypertensive drugs with all of the other classes (Reprinted from Najem et al. [34]. With permission from Lippincott Williams & Wilkins)

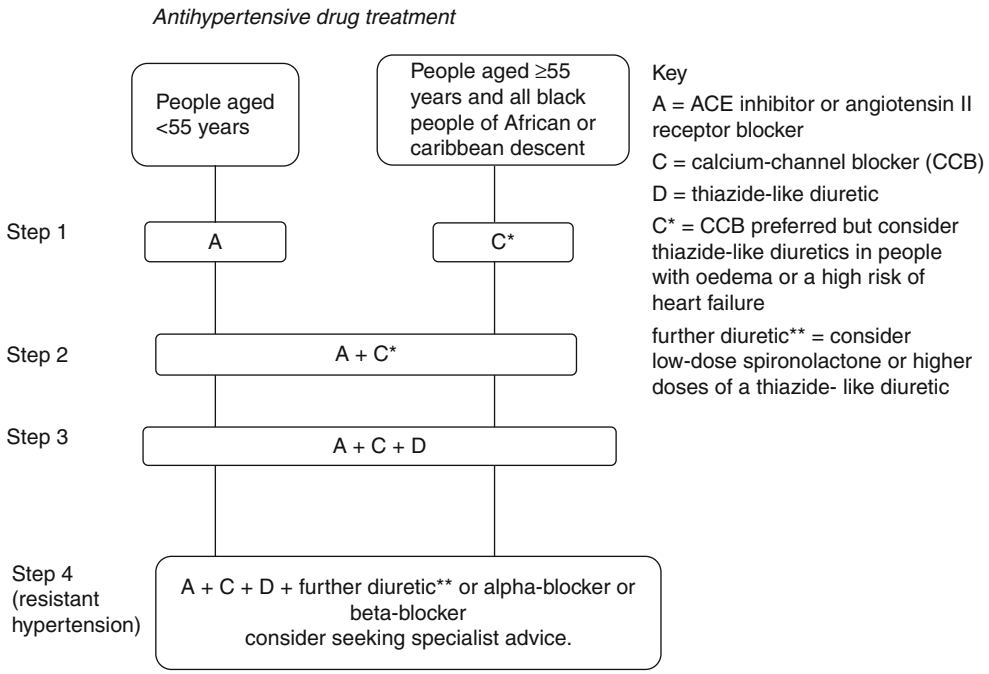

Fig. 32.2 The algorithm for choices of antihypertensive drugs in the treatment of hypertension, as recommended by the 2011 NICE guideline (Reprinted from Krause et al. [36]. With permission from BMJ Publishing Group Ltd.)

formulations. This was the principal driver for recommending calcium channel blockers as the preferred initial therapy for most people over the age of 55 years, the exception being people with evidence of heart failure or at higher risk of heart failure, for whom the sensitivity analysis suggested a thiazide-like diuretic should be preferred as initial therapy. That calcium channel blockers are also less likely to cause glucose tolerance, electrolyte disturbances, and gout and have been reported to be particularly effective at reducing blood pressure variability (which has recently been suggested as a predictor of risk, especially for stroke) further strengthened the rationale for this recommendation. Another consideration was that the only trial to directly evaluate two drug combinations of treatments with a renin-angiotensin receptor system blocker, consistent with step two of the NICE treatment algorithm, also showed that combination with a calcium channel blocker was better than with a thiazide diuretic for preventing cardiovascular outcomes [48]."

Although the rationale for the demotion of diuretics from their long-held top position by NICE may be valid, the use of appropriately small doses of a thiazide remains an attractive way to start therapy for many patients. Cost is no longer a factor, but a number of attributes favor their use as first choice: They reduce the risk of heart attack as well as of stroke better than most other classes; their side effects—in low doses—are minimal; they enhance the efficacy of all other classes save CCBs (which have a mild natriuretic effect of their own); they are widely available in combinations; they are particularly needed for most patients who continue to consume large amounts of sodium; and they thereby prevent volume expansion.

Despite our enthusiasm, even low doses of thiazide diuretics may induce side effects, including hypokalemia and erectile dysfunction. Hyponatremia can be an issue, mainly in older patients. Gout may be precipitated, but the danger is lessened when either the ARB losartan or CCB are also taken [49].

The preference for chlorthalidone as the choice of diuretic has been vigorously advocated [50], and since it is being marketed in combinations, its use will certainly increase.

Chlorthalidone lowers blood pressure for a full 24 h compared with only 12 h for HCTZ; thus, 12.5–25 mg of chlorthalidone was found to be the equivalent of hydrochlorothiazide (HCTZ) 25–50 mg in reducing office blood pressure, but nocturnal blood pressure was lowered twice as much with the longer-acting chlorthalidone [51].

The Deletion of Beta-Blockers

The 2011 NICE guidelines further state: "In the updated meta-analysis for this guideline, as in previously published independent meta-analyses, beta-blockers were the least cost effective treatment for hypertension and notably less effective than the recommended first line drugs. Law and colleagues' meta-analysis also found them to be significantly worse at preventing stroke than other drugs (relative risk 1.18 (1.03–1.36)) [46]. This may be a function of β-blockers inferiority to calcium channel blockers or of less effective blood pressure reduction, but whatever the cause it is difficult to ignore when making recommendations for treating hypertension."

The deletion of beta-blockers in the NICE guidelines refers to standard beta-blockers for uncomplicated hypertension. Beta-blocker–thiazide combinations increase the risk of new-onset diabetes and should be avoided in patients with impaired fasting glucose. On the other hand, beta-blockers are clearly indicated for hypertensive patients with heart failure or CHD. The newer vasodilating beta-blockers such as carvedilol or nebivolol are very effective blood pressure-lowering agents and have neutral effects on glucose metabolism.

The Hazard of Combining Renin–Angiotensin System-Inhibiting Drugs

Since ACEIs, ARBs, and more recently direct renin inhibitors (DRIs) have become mainstays of antihypertensive therapy, they have been combined, particularly by nephrologists in order to further reduce proteinuria. Unfortunately, these combinations are harmful. In the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), there was more hypotension and worsening of renal function with the combination of the ACEI and ARB, likely from too marked blood pressure lowering [52]. More recently, combination of the DRI aliskiren with either an ACEI or an ARB has been shown to significantly increase hyperkalemia and acute kidney injury [53]. In addition, the nephrology trial that had provided the main evidence in favor of "dual RAS blockade" now has been retracted by the editors of Lancet on the basis of scientific fraud [54]. The final line is: ACEIs, ARBs, and DRIs should not be combined.

Revelations About ACEIs

Although ACEIs (and to a lesser extent, ARBs) have been widely thought to have special renoprotective effects, the overall evidence is that they are no better than other classes of drugs [55]. ACEIs do have a protective effect on the most common side effect of dihydropyridine CCBs: vasogenic ankle edema [56].

Perhaps more commonly than appreciated, the original studies of drugs that are done to obtain FDA approval may not reveal the side effects which become obvious when they are used in larger and more diverse populations than the small number of otherwise healthy subjects enrolled in the initial trials. A striking example is the currently reported 11.5 % incidence of cough associated with ACEI use whereas the incidence is stated to be 1.3 % in the marketer's printed information accompanying the drug [57].

The Resurgence of Aldosterone Receptor Blockers

The aldosterone blocker spironolactone and the more recently available, more specific eplerenone have become the favorite fourth choice of therapy as noted in the 2011 NICE guidelines (Fig. 32.2). These agents have previously been shown to be cardioprotective in patients after an acute myocardial infarction or with heart failure. Their use as antihypertensive "rescue" therapy followed the demonstration of their efficacy as fourth-line therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT) trial [58]. The addition of low-dose

spironolactone—25–50 mg—provided an average 21.9/9.5-mmHg fall in blood pressure among 1,411 patients with uncontrolled hypertension despite their use of three antihypertensive drugs. Adverse effects were few: gynecomastia or breast discomfort in 6 %, hyperkalemia in 2 %.

This remarkable alleviation of resistant hypertension has been repeatedly demonstrated [59]. Therefore, the suggestion has been made that an aldosterone receptor blocker be additionally used (in low dose) much earlier, along with a diuretic as first choice therapy in most hypertensives [50].

General Recommendations

With whatever drug(s) used, three additional general recommendations are appropriate: (1) Start with a low dose and gradually titrate upward; (2) use low-dose combinations, whenever appropriate; and (3) use a once-a-day, long-acting formulation.

Low Starting Doses

Many patients and most physicians are in a hurry to bring hypertension under control. The motives are usually good: Reduce the time and money needed to control the disease, thereby more quickly protecting the patient from the dangers of untreated hypertension. Unfortunately, the consequences are often bad: Fast and marked falls in blood pressure often provoke symptoms of tiredness, fatigue, and dizziness, likely a consequence of reduced perfusion to the brain when systemic pressure is lowered even to levels that are not "hypotensive" and that are well tolerated by normotensive people [60]. Autoregulation maintains normal cerebral blood flow over a range of arterial blood pressure from as low as 90/50 to 180/120 mmHg in normotensives. In hypertensives, the autoregulatory curve is shifted to the right as thickened vessels are able to maintain perfusion despite pressures that could not be tolerated in normotensives. On the other hand, if blood pressure is lowered in hypertensives below a mean pressure of 100–110 mmHg, i.e., 140/90 mmHg, cerebral blood flow falls. Fortunately, over time, treated patients shift their curve toward the left so that lower pressure can be tolerated.

Other organs may also be under-perfused if blood pressure is abruptly lowered. These include the heart, kidneys, and perhaps most bothersome to many men, the penis. Penile blood flow must increase almost ten-fold to achieve and maintain an erection. Particularly when blood flow to the genitals is already compromised by artherosclerotic narrowing, an abrupt fall in systemic pressure may induce impotence, whereas a slower and less marked fall in pressure may be tolerated.

By "starting low and going slow," good control should be achieved within a few months, with fewer if any symptoms related to tissue hypoperfusion. If patients monitor their own blood pressure with home devices, manipulations of therapy can easily be made without the need for repeated office visits. For patients who are in no acute distress, the regimen should be intensified only after enough time has passed to enable the full effectiveness of the current drug (s) to be expressed, typically 3–6 weeks.

Low-Dose Combination Therapy

Failure of physicians to appropriately intensify the regimen (clinical inertia) remains one reason why many patients still do not have their hypertension controlled [61]. The regimen can be intensified either by dose-escalation or combination therapy. Fixed-dose combinations of two or more antihypertensive drugs will be used increasingly for a number of reasons: (1) Most patients need at least two or three drugs from different classes to control their hypertension, which is a multifactorial disease; (2) whatever the starting drug, adding a second drug from a different class provides a five times greater reduction in BP than doubling the dose of the first drug [62]; (3) low-dose combinations provide added efficacy while minimizing dose-dependent side effects; (4) the fewer pills prescribed, the more likely they will be taken; (5) each prescription filled often requires a co-payment so that one pill with two ingredients will cost less than separate pills; and (6) more rational and effective combinations are being marketed.

Until recently, most combinations were a thiazide with another class. Particularly since the most popular (also best studied and longest-acting) CCB amlodipine became generic, a number of combinations with it and a RAS-blocking drug have been marketed. As mentioned earlier, amlodipine–ACE inhibitor combinations have performed well in recent clinical trials, providing better cardiovascular outcomes than a thiazide combined either with a beta-blocker or with an ACE inhibitor. Moreover, three drug combinations, usually a thiazide, a CCB, and a renin inhibitor, are now available.

Once-a-Day Dosing

Long-acting formulations of drugs that provide 24-h efficacy are preferred over short-acting agents for many reasons: (1) Adherence is better with once-daily dosing; (2) for some agents fewer tablets incur lower cost; (3) control of hypertension is persistent and smooth rather than intermittent (reduced variability may offer greater protection against stroke); (4) 24-h blood pressure coverage reduces nocturnal hypertension, which seems to be the strongest predictor of hypertensive complications; and (5) protection may be provided against the risk for sudden death, heart attack, and stroke that is due to the abrupt increase of blood pressure

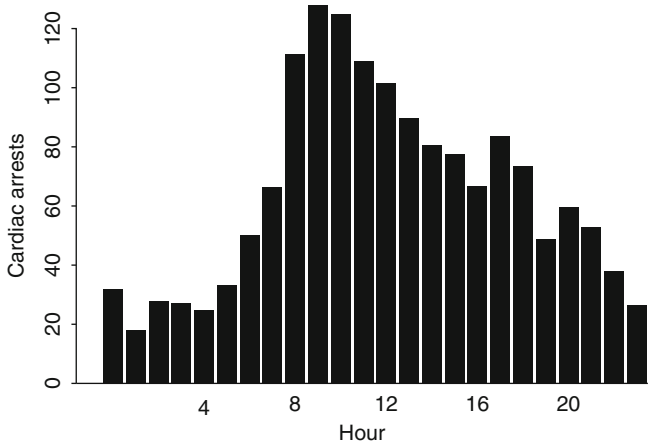

Fig. 32.3 Distribution of time of dispatch for 1,558 unwitnessed, untreated cardiac-etiology episodes of cardiac arrests (Adapted from Peckova et al. [64])

after arising from overnight sleep, i.e., the morning surge. Agents with a duration of action beyond 24 h, such as amlodipine and telmisartan, are attractive because many patients inadvertently miss at least one dose of medication each week.

The first three reasons are obvious. The fourth is based on comparison of conventional clinic measurements vs. 24-h ambulatory blood pressure on over 5,000 patients [63]. The fifth deserve additional comment, as all cardiovascular catastrophes occur at a greater frequency in the first few hours after arising from sleep [64] (Fig. 32.3). If drugs with less than full 24-h efficacy are taken only once a day in the morning, the patient's blood pressure will be poorly controlled in the hours just before and after arising from sleep when the need for control is most critical. Therefore, drugs with full 24-h effectiveness should be chosen, hopefully to thereby provide full protection from early morning catastrophes. There may be added protection by taking at least one antihypertensive drug in the evening thereby further aborting the morning surge and in those whose nighttime BP does not fall, i.e., non-dippers, providing additional BP lowering during the night. However, if as is true of many formulations, the maximal effect occurs within 2–6 h, bedtime dosing could induce nocturnal tissue hypoperfusion in the majority of patients whose blood pressure falls spontaneously during sleep. The author's preference is to give all antihypertensive drugs with 24-h efficacy as early in the morning as possible.

Management of Resistant Hypertension

Resistant hypertension is defined as BP above 140/90 mmHg despite adequate doses of three or more antihypertensive medications, including a diuretic or hypertension requiring four or more drugs regardless of BP level achieved [65]. The prevalence is about 10 % of the overall hypertensive population, higher among those who are poor, diabetic, obese, and with target organ damage (in particular chronic renal disease) [66]. Much apparent resistant hypertension is office only and is not present with out-of-office BP measurements [67]. An even larger proportion is related to inadequate dosing of medication, i.e., physician inertia.

Multiple causes may be responsible including pseudoresistance, nonadherence to therapy, drugs, comorbidities, endocrinopathies, renal disease, and volume overload. The most likely is volume overload, often from use of the short-acting diuretic furosemide only once a day. However, as obesity has increased, sleep apnea has become more common. A long list of drugs, both legal and illegal, may be responsible [68]. In one study, primary aldosteronism was recognized in 11 % of patients with resistant hypertension [69].

Beyond more adequate antihypertensive drug therapy (which should include an aldosterone blocker) and correction of an identifiable (secondary) cause, two investigational procedures hold promise to lower BP in patients with resistant hypertension: baroreceptor activation by an implanted device [70] and catheter-based renal artery denervation [71]. Pending results of the US pivotal trial which is underway, the latter procedure may well become widely used for those patients who remain refractory to appropriate medical therapy.

Therapy of Hypertensive Emergencies

Hypertension emergencies may occur in the setting accelerated malignant hypertension, cerebrovascular and cardiac events, renal disease, excess catecholamine state, surgeries, and others. The small number of patients who present with a hypertensive emergency almost always should receive parenteral therapy in an intensive care facility where careful monitoring is feasible. The choice of drug will usually be based on the experience of the caregiver, but certain types of emergencies are best treated with specific parental agents such as diuretics (furosemide), vasodilators (nitroprusside, nitroglycerin, fenoldopam, nicardipine, hydralazine, enalaprilat), and adrenergic inhibitors (phentolamine, esmolol, labetalol) [9].

Many patients with markedly elevated blood pressure but no advancing target organ damage or other features of a true hypertensive emergency have been considered to have a hypertensive "urgency," i.e., to be in need of immediate reduction of blood pressure but not requiring parenteral therapy. The prudent physician will treat such patients immediately until their blood pressure is at a safer level, likely below 180/110 mmHg. Several oral agents are available that begin working within 30–60 min and bring the blood pressure down in 2–6 h, not so fast as to induce ischemia but fast enough to allow the patient to be sent home on a regimen of

long-acting medications with close follow-up to ensure that control is achieved and necessary evaluation is performed. These agents include fast-acting oral furosemide, propranolol, captopril, nicardipine, felodipine, or nifedipine.

Treatment of Special Populations

Page limitations preclude coverage of all the special populations that clinicians may encounter, including children and patients with a variety of comorbid conditions. Additional attention will be given to three groups of hypertensives because they are both common and in need of special considerations: the elderly, those with diabetes, and those with coexisting cardiac diseases.

Pregnant women with preexisting hypertension can be safely continued on drugs used before pregnancy with the exception of ACEIs, ARBs, and DRIs which must be stopped as soon as the pregnancy is recognized. Since no trials have documented the safety of newer drugs for the fetus as has been shown with methyldopa, this drug is still chosen by most US obstetricians, along with parental hydralazine if needed.

The Elderly Hypertensive

The largest and most rapidly expanding portion of the hypertensive population is those over age 65. More than half are hypertensive, and almost two-thirds have isolated systolic hypertension (ISH). ISH is a serious risk factor for all cardiovascular complications, particularly stroke but including myocardial infarction. Fortunately, treatment of the elderly including those over age 80 [39] with either ISH or combined systolic and diastolic hypertension provides excellent protection against all these morbidities. However, despite the impressive results found in HYVET, caution is needed in the elderly, both as to when antihypertensive therapy should be started and as to what level it should be lowered [72]. Whereas therapy in those over 80 has been shown to reduce cardiovascular morbidities, neither cardiovascular nor all-cause mortality has been shown to be reduced. Moreover, there are no proper trials of patients over age 65 with systolic BP between 140 and 160 mmHg, the largest group of these patients, to document benefits of therapy. Furthermore, the goal of therapy in HYVET was only to a systolic BP of 150 mmHg (or perhaps 145 mmHg if measured at home), and that level seems an appropriate goal for treatment of those over age 80 deemed in need of drug therapy [40].

Avoid Risks of Therapy

The elderly are more susceptible to a variety of potential risks from antihypertensive drug therapy (Table 32.3). In particular, they frequently have postural and postprandial hypotension, which may be converted from an occasional but tolerable nuisance to a frequent intolerable danger by the addition of antihypertensive therapy. Often, their supine and seated hypertension can be treated only after their postural and postprandial hypotension is managed by a variety of helpful maneuvers including slow rising, elevation of the head of the bed with 6-in. cinder blocks, isometric exercise, and frequent small low-carbohydrate meals. If postural hypotension is accompanied by significant supine hypertension, a short-acting agent, in particular nitroglycerin paste, could be used for nighttime effect without carry over to ambulatory time.

Table 32.3 Possible contributors to increased risk from drug treatment of hypertension in elderly persons

Factor	Potential complications
Diminished baroreceptor activity	Orthostatic hypotension
Impaired cerebral autoregulation	Cerebral ischemia with small falls in systemic pressure
Decreased intravascular volume	Orthostatic hypotension, volume depletion, hyponatremia
Sensitivity to hypokalemia	Arrhythmia, muscle weakness
Decreased renal and hepatic function	Drug accumulation
Polypharmacy	Drug interaction
Central nervous system changes	Depression, confusion

Since the only medical condition more frequent than hypertension in the elderly is osteoarthritis, many use nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs with the possible exception of celecoxib may interfere with the antihypertensive efficacy of all antihypertensives, with the probable exception of CCBs. Therefore, whenever possible, other analgesics including acetaminophen should be used instead of NSAIDs.

Since the elderly are susceptible to both over- and undertreatment, home blood pressure self-monitoring is particularly useful for them. Thereby, the white-coat effect and masked hypertension, which are both quantitatively greater in the elderly, can be recognized and assurance provided that therapy is enough but not excessive [73].

Diabetic Hypertensives

Diabetics are more likely to have hypertension than nondiabetics, and more hypertensives than normotensives have diabetes. The combination may be lethal: All diabetic micro- and macrovascular complications are accelerated by the presence of hypertension. As diabetics survive longer, they are prone to develop cardiomyopathy and nephropathy, both worsened by hypertension and now the leading causes of mortality. Previous guidelines have recommended (largely based on

expert opinion) that antihypertensive therapy should be started in diabetics at a BP above 130/80 mmHg and the goal of therapy is to lower systolic pressure below 130 mmHg [74–76]. In the recent ACCORD trial, further reduction reduced strokes but did not afford further protection against heart attack or other cardiovascular complications and caused more adverse drug reactions [77]. While there is strong evidence to support a systolic blood pressure goal of 130–140 mmHg in patients with diabetes, the risks and benefits of further blood pressure reduction should be weighed individually. Since most diabetics are obese, weight reduction must be vigorously pursued by caloric restriction and physical activity. If drugs are needed, therapy should be initiated with an ACEI or ARB, perhaps in low-dose combination with amlodipine or a diuretic. Although widely recommended, ACEIs and ARBs may not protect the kidneys of diabetic hypertensives better than do CCBs or other drugs [55].

Hypertensives with Cardiac Diseases

Since these various diseases are extensively covered elsewhere in this book, only a few specific issues relative to the coexistence of hypertension will be highlighted.

Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) is recognized by electrocardiography in perhaps 25 % of hypertensives and by echocardiography in more than half. As an independent risk factor for coronary mortality in hypertensives, LVH is being more diligently looked for and its regression is being used as a surrogate endpoint for effective therapy. Data still do not document that knowledge of either the presence of the regression of LVH adds enough useful information to make routine echocardiography worthwhile.

Nonetheless, numerous studies have examined the relative ability of various antihypertensive drugs to regress LVH with the assumption that regression in itself is beneficial beyond the value of simply lowering the bold pressure. All lifestyle modifications and antihypertensive drugs except direct vasodilators will regress LVH.

Heart Failure

LVH is often the progenitor of heart failure. In the Framingham study population, hypertension was a factor in more than 90 % of patients with heart failure. The role of hypertension may not be recognized because as cardiac output falls, systemic blood pressure may fall despite the activation of vasoconstrictor neurohormonal mechanisms. For prevention of heart failure, diuretics are best followed by renin–angiotensin inhibitors [78]. Once heart failure has developed, therapy will usually include a diuretic, an ACEI or an ARB in those who cough, the α–β-blocker carvedilol, and an aldosterone blocker. If needed to treat angina or hypertension in patients with heart failure, the long-acting dihydropyridine calcium antagonist such as amlodipine has been found to be generally safe. Beyond the particular ability of β-blockers and long-acting CCBs to treat both angina and hypertension, β-blockers, ACEIs, and aldosterone blockers have been shown to be protective in patients with systolic dysfunction after an acute myocardial infarction.

The blood pressure level achieved needs to be individualized when treating patients with heart failure; the goal is to reduce left ventricular afterload and other myocardial oxygen demands without causing hypoperfusion of the heart, brain, or kidneys (see Chaps. 18 and 19). While thiazide can be combined with a loop diuretic to overcome diuretic resistance in patients with decompensated heart failure, this approach can cause over-diuresis with hypotension and acute renal decompensation. The EPHESUS and CHARM trials achieved a BP of 125/75 mmHg and showed improved cardiovascular outcomes without harm [79, 80].

Coronary Heart Disease

Two caveats are needed in hypertensives with coronary heart disease (CHD). First, the diastolic blood pressure should not be lowered below 65 mmHg because of the likely presence of a J-curve. The earlier AHA recommendation of lowering blood pressure to below 130/80 mmHg in patients with CHD recently has been replaced by a less stringent goal of below 140/90; two or more medications should be prescribed if BP is not at goal [81]. Second, short-acting calcium antagonists should be avoided since they may abruptly lower blood pressure and thereby stir up the sympathetic nervous system, further stressing the already compromised myocardium.

The Need to Improve Adherence to Therapy

As noted at the beginning of this chapter, most hypertensives in the USA and elsewhere are not being treated adequately. A good deal of the blame can be laid on physicians who are noncompliant with the need to push therapy to the goal. Even more is due to patient nonadherence to therapy.

Medication adherence varies by drug class, being worst with thiazides and beta-blockers, intermediate with CCBs, and best with ACE inhibitors and especially ARBs; but even with ARBs, over one-third of patients will discontinue therapy [82].

Adherence is worst to the type of drug most frequently recommended—a low-dose thiazide—with one major side effect being erectile dysfunction [83]. Obviously, care should be taken to recognize any sexual dysfunction related to the treatment of hypertension. Fortunately, the most widely used treatments for erectile dysfunction, phosphodiesterase-5 inhibitors, do not react adversely with most oral antihypertensive drugs but should be used carefully in

combination with either an alpha-blocker or with amlodipine (which releases a small amount of nitric oxide). In a controlled study, addition of sildenafil to 5–10 mg of amlodipine caused an addition reduction in supine BP of −8/−7 mmHg [84]; these drugs should be used with caution in patients with coronary artery disease and not used at all in patients on nitrates.

Only a few interventions are effective in improving patient adherence to therapy. These include less complex and more convenient care, home self-monitoring of blood pressure, and special staff who provide reminders, support, feedback, and reinforcement. These maneuvers may cost a bit more and require greater involvement of physician and staff, but the benefits outweigh the costs. Easier-to-use medications help. The quality of life has been shown to be improved by once-a-day, effective drug therapy as well as by weight loss and increased physical activity.

The best results have been seen with a team approach that includes a clinical pharmacist, who can work with physicians to optimize medical therapy and work with patients to enhance medication adherence [85, 86].

The Past and the Future

The treatment of hypertension has improved greatly over the past 40 years. Despite the evidence that only 71 % of current US hypertensives are being treated and only 48 % are well controlled [1], recognition should be given to the fact that these figures are much improved over those from 1980. These improvements have clearly played a significant role in the marked decreases in mortality from CHD and stroke in the US population.

Just as clearly, more needs to be done. Even among presumably well-treated hypertensives, long-term rates of cardiovascular disease remain higher than among normotensives [87]. More intensive antihypertensive therapy always pushed to the appropriate goal of therapy must be provided. As noted by Law et al. [46]: "Blood pressure lowering drugs should be offered to anyone with high risk, because a given blood pressure reduction lowers risk of CHD and stroke by a constant proportion irrespective of pretreatment blood pressure." New and hopefully better antihypertensive drugs are being developed so that it may be easier to accomplish good blood pressure control. Beyond that, greater attention to other cardiovascular risk factors must be given so that the full benefits of health care can be provided to all hypertensive patients.

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Cardiomyopathies and Myocarditis

33

Colleen M. Harrington and Edward K. Kasper

Introduction

Cardiomyopathies are diseases of the heart muscle characterized by abnormal chamber size, wall thickness, or functional contractile abnormalities such as systolic or diastolic dysfunction in the absence of coronary artery disease, hypertension, valvular disease, or congenital heart disease [1]. Primary cardiomyopathies consist of disorders that are confined to the heart muscle, whereas secondary cardiomyopathies are caused by myocardial damage from a systemic disease process [2]. The World Health Organization/International Society and Federation of Cardiology task force on the definition and classification of cardiomyopathies has defined five subtypes of cardiomyopathy [3]: dilated, hypertrophic, restrictive, arrhythmogenic right ventricular dysplasia, and unclassified cardiomyopathies. Table 33.1 lists echocardiographic characteristics of the major types of cardiomyopathy.

Dilated Cardiomyopathy

Dilated cardiomyopathy is the most common form of cardiomyopathy, accounting for more than 90 % of cases. Left ventricular enlargement and decreased contractility are the defining elements of this condition. Right ventricular dilation and dysfunction are often present as well. It can occur at any age, in either sex, and in people of any ethnic origin [2]. The most common presentation is with signs and symptoms of heart failure, although perhaps as many as 50 % of the cases are asymptomatic or undiagnosed.

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Causes of Dilated Cardiomyopathy

A variety of insults can cause dilated cardiomyopathy. In population-based studies, coronary disease and hypertension are the major causes of cardiomyopathy. We have had a long-standing interest in the causes of cardiomyopathy. Table 33.2 reviews the causes of initially unexplained cardiomyopathy in our tertiary care referral center experience [4, 5]. All patients underwent a complete evaluation for the etiology of the cardiomyopathy, including endomyocardial biopsy, laboratory studies, and cardiac catheterization if appropriate. In our referral cohort of 1,278 patients, no etiology was identified in 51 % of the cases. Myocarditis occurred in about 9 % of the cases, a finding similar to that seen in the Myocarditis Treatment Trial [6]. A more complete list of the causes of dilated cardiomyopathy can be found in Table 33.3.

Familial cardiomyopathy is a more common finding than reported in our series, as we did not evaluate first-degree relatives of patients with idiopathic dilated cardiomyopathy with echocardiography. When this was done by Michels and colleagues, 20 % of patients with idiopathic dilated cardiomyopathy had first-degree relatives with the disease [7]. Currently, the clinical screening of first-degree family members reveals familial dilated cardiomyopathy (FDC) in 20–35 % of those family members [1]. Familial cardiomyopathy is defined as having at least two closely related family members meeting criteria for idiopathic dilated cardiomyopathy [8]. Family studies of patients with dilated cardiomyopathy have demonstrated autosomal dominant, autosomal recessive, X-linked, and mitochondrial modes of inheritance [9]. Autosomal dominant is the most common. The first causative gene that was discovered was actin; now more than 40 disease genes have been identified. Causative genes predominantly encode two major subgroups of proteins, cytoskeletal and sarcomeric proteins; however, other mutated genes encode a wide variety of cellular components [10]. The cytoskeletal proteins identified are dystrophin, desmin, lamin A/C, delta-sarcoglycan, beta-sarcoglycan, and metavinculin. The sarcomere-encoding

C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_33, © Springer Science+Business Media New York 2013

Table 33.1 Echocardiographic findings in cardiomyopathy

	Dilated	Hypertrophic	Restrictive
Ventricular volume	Increased	Decreased	Decreased or normal
LV contractility	Decreased	Increased	Usually normal
Atrial size	Increased	Usually normal	Markedly increased
Other findings	Often MR	LVOT gradient	Diastolic dysfunction

Table 33.2 Final diagnoses in 1,230 patients with initially unexplained cardiomyopathy

Diagnosis	Number (%)
Idiopathic cardiomyopathy	616 (50)
Myocarditis	111 (9)
Ischemic heart disease	91 (7)
Infiltrative disease	59 (5)
Amyloid	36
Sarcoidosis	14
Hemochromatosis	9
Peripartum cardiomyopathy	51 (4)
Hypertension	49 (4)
HIV	45 (4)
Connective tissue disease	39 (3)
Scleroderma	12
Systemic lupus erythematosus	9
Marfan's syndrome	3
Polyarteritis nodosa	3
Dermatomyositis or polymyositis	3
Nonspecific connective tissue disease	3
Ankylosing spondylitis	2
Rheumatoid arthritis	1
Relapsing polychondritis	1
Wegener's granulomatosis	1
Mixed connective tissue disease	1
Substance abuse	37 (3)
Alcohol	28
Cocaine	9
Doxorubicin therapy	15 (1)
Other causes	117 (10)
Restrictive cardiomyopathy	28
Familial	25
Valvular heart disease	19
Endocrine dysfunction	
Thyroid disease	7
Carcinoid	2
Pheochromocytoma	1
Acromegaly	1
Neuromuscular disease	7
Neoplastic heart disease	6
Congenital heart disease	4
Complication of coronary bypass surgery	4
Radiation	3
Critical illness	3
Endomyocardial fibroelastosis	1
Thrombotic thrombocytopenic purpura	1
Rheumatic carditis	1
Drug therapy (not including doxorubicin)	
Leukotrienes	2
Lithium	1
Prednisone	1
Total	1,230 (100)

Adapted from Felker et al. [4]. With permission from Massachusetts Medical Society. © 2000

Table 33.3 Causes of cardiomyopathy

Dilated cardiomyopathy	Connective tissue disease
Idiopathic	Systemic lupus erythematosus
Familial/genetic	Polyarteritis nodosa
Myocarditis/immune (*see* Table 33.4)	Scleroderma
Drug toxicity	Rheumatoid arthritis
Alcohol	Dermatomyositis/ polymyositis
Antidepressants	Muscular dystrophies and neuromuscular disorder
Catecholamines	Tachycardia
Cobalt	Hypertension
Cocaine	Radiation
Doxorubicin	Sepsis/critical illness
Interferon	Hypertrophic cardiomyopathy
Lithium	Familial/genetic
Prednisone	Aortic stenosis
Metabolic	Renal failure
Thyroid disease	Hypertension
Diabetes mellitus	Fabry's disease
Carcinoid	Restrictive cardiomyopathy
Pheochromocytoma	Idiopathic
Acromegaly	Familial/genetic
Hypocalcemia	Metastatic tumors
Infiltrative disease	Infiltrative
Amyloid	Amyloid
Sarcoidosis	Sarcoidosis
Hemochromatosis	Storage diseases
Storage diseases	Endocardial
Nutritional	Endomyocardial fibrosis
Beriberi	Hypereosinophilic syndrome
Carnitine	Radiation
Pellagra	Carcinoid heart disease
Selenium	Arrhythmogenic right ventricular dysplasia
	Noncompacted myocardium

This is a relatively complete list

genes are the same as those responsible for hypertrophic cardiomyopathy including beta-myosin heavy chain, myosin-binding protein C, actin, alpha-tropomyosin and cardiac troponin T and C, and titin. TTN is the gene that encodes the sarcomere protein titin. In a study performed by Herman et al., analyzing titin mutations included 312 subjects with dilated cardiomyopathy, 231 subjects with hypertrophic cardiomyopathy, and 249 controls using next-generation or dideoxy sequencing. The frequency of TTN mutations was significantly higher among patients with dilated cardiomyopathy (27 %) than among patients with hypertrophic cardiomyopathy (1 %) or controls (3 %) [11]. However, mutations in the genes encoding these contractile protein result in functional changes in dilated cardiomyopathy that are opposite of the changes caused by mutations in the same contractile genes that cause hypertrophic cardiomyopathy [9]. A new group of sarcomeric genes encoding Z-disc proteins has been identified. Finally, there are several distinct phenotypes, including dilated cardiomyopathy, dilated cardiomyopathy with conduction system disease, dilated cardiomyopathy with skeletal myopathy, and dilated cardiomyopathy with hearing loss.

Natural History of Clinical Course

In this disease, the left ventricle is dilated and more spherical than normal with raised wall stress and depressed systolic function [12]. Mitral regurgitation and ventricular arrhythmias can develop as well as other rhythm disturbances such as atrioventricular block and supraventricular tachycardia. Signs and symptoms include shortness of breath at rest or with exertion, orthopnea, exercise intolerance, abdominal pain, and edema. Cachexia is usually a late finding. On exam, sinus tachycardia, gallop rhythm, jugular venous distension, pallor, cool extremities, hepatomegaly, abdominal distension, ascites, and a murmur of mitral regurgitation can be appreciated. Diagnosis is based on history and physical and echocardiographic findings. Chest radiographs can show pulmonary vascular congestion, and an ECG can demonstrate rhythm or conduction abnormalities as mentioned above. Biomarkers such as B-type natriuretic peptide and N-terminal pro-brain natriuretic peptide can be used in the diagnosis, management, and prognosis. Endomyocardial biopsy generally reveals areas of interstitial and perivascular fibrosis and occasionally areas of necrosis with cellular infiltrate. Myocytes can vary from appearing atrophied to hypertrophied [13]. Prognosis is tied to the underlying cause of dilated cardiomyopathy [4]. As compared to patients with idiopathic cardiomyopathy, patients with peripartum cardiomyopathy had better survival. Patients with infiltrative cardiomyopathies, HIV infection, or a cardiomyopathy caused by chemotherapy agents such as daunorubicin and doxorubicin had significantly worse survival when compared with idiopathic cardiomyopathy (Fig. 33.1). The mechanism of the latter is multifactorial but is associated with

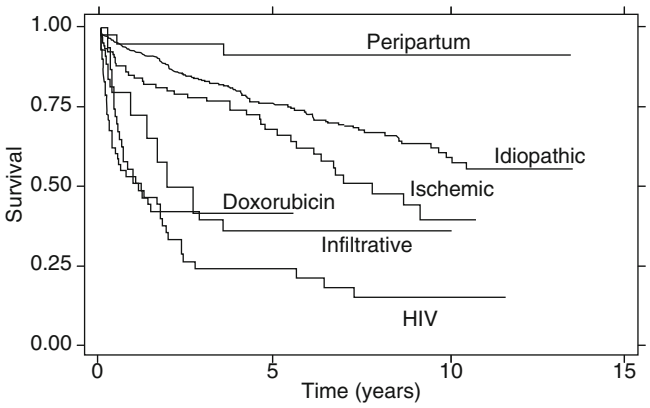

Fig. 33.1 Kaplan-Meier estimates of survival according to underlying cause of cardiomyopathy (Reprinted from Felker et al. [4]. With permission from Massachusetts Medical Society. © 2000)

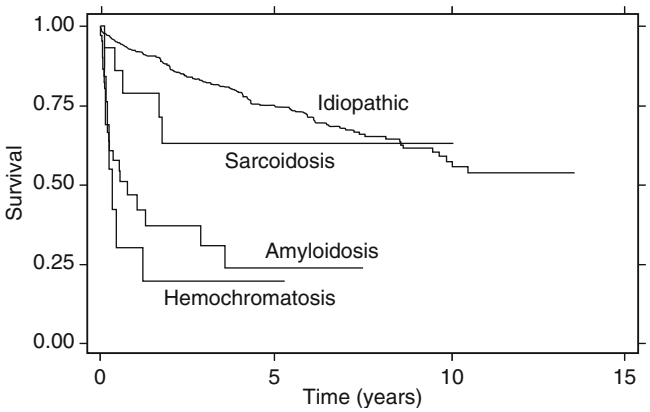

Fig. 33.2 Kaplan-Meier estimates of survival among patients with infiltrative cardiomyopathy (Reprinted from Felker et al. [4]. With permission from Massachusetts Medical Society. © 2000)

reactive oxygen species, disruption of the mitochondria, and uncoupling of the electron transport chain. Use of dexrazoxane might be cardioprotective and has been shown to attenuate the formation of free oxygen species [13]. Not all infiltrative cardiomyopathies are associated with equally poor survival. Patients with a cardiomyopathy due to sarcoidosis have better survival than do patients with either hemochromatosis or amyloidosis and a cardiomyopathy (Fig. 33.2). With the exception of peripartum cardiomyopathy, the natural history of dilated cardiomyopathy is one of progressive heart failure, arrhythmia, and eventual death or heart transplantation. Current therapies for heart failure including angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and aldosterone antagonists have improved this prognosis [14].

Evaluation of Dilated Cardiomyopathy

The ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult suggest that physicians should focus their evaluation of the etiology

of dilated cardiomyopathy on those diagnoses with the potential for improvement [14]. A complete history and physical examination, including a family history of cardiomyopathy, heart failure, and early sudden death, is the foundation. The history should focus on possible causes such as hypertension, coronary disease, diabetes, valvular disease, rheumatic fever, chest irradiation, cardiotoxic agents, illicit drugs, alcohol, systemic disorders, and possible infectious etiologies. The predominant viral etiology has changed with every decade, with coxsackievirus in the 1980s, adenovirus in the 1990s, and parvovirus B19 since 2000. Screening for thyroid disease with a TSH level is suggested, while laboratory screening for specific cardiomyopathies rests on clinical suspicion. ECG should be done to look for evidence of prior infarct and the presence of rhythm and conduction disturbances. Echocardiography is the most cost-efficient means to evaluate the cardiac anatomy, including left ventricular function as well as valvular and pericardial pathology. Coronary arteriography may be important if revascularization is being considered. Endomyocardial biopsy has a limited role in the diagnosis of infiltrative diseases when clinically suspected.

Treatment of Dilated Cardiomyopathy

Diagnosis, severity of disease, and, if possible, cause of the dilated cardiomyopathy should be identified so that therapy can be as precise as possible [13]. Therapy is directed at treatment of heart failure symptoms, prevention of disease progression, and related complications such as end-organ dysfunction such as stroke. Treatment rests on the diagnosis of a specific disorder: for example, replacement of thyroid hormone in hypothyroidism. In general, the treatment for dilated cardiomyopathy is outlined in the chapter on heart failure.

Hypertrophic Cardiomyopathy

The findings in hypertrophic cardiomyopathy include left or right ventricular hypertrophy which is often asymmetric and involves the ventricular septum. A maximal left ventricular wall thickness greater than or equal to 15 mm is the usual diagnostic finding, but abnormal genotypes are associated with almost any degree of LV wall thickness. Mildly increased LV wall thickness (13–14 mm) can also be seen in highly trained athletes and must be differentiated from hypertrophic cardiomyopathy. Obstructive and nonobstructive forms of hypertrophic cardiomyopathy exist, with an obstructive component present in 30–50 % of patients [15]. The term *hypertrophic cardiomyopathy* is now preferred over previous terms, such as hypertrophic subaortic stenosis, that tended to emphasize the obstructive component.

Hypertrophic cardiomyopathy is one of the more common inherited cardiac disorders, with the phenotypic expression occurring in 1 of every 500 adults in the general population [15]. It is the second most common subtype of cardiomyopathy after dilated cardiomyopathy and a frequent cause of sudden death in competitive athletes [16].

Left Ventricular Outflow Tract Obstruction

Outflow tract obstruction is caused by hypertrophy of the basal portion of the septum in association with an elongated mitral valve leaflet and systolic anterior motion of the mitral valve. This leads to a narrowed outflow tract, an outflow tract gradient, and often mitral regurgitation as the mitral valve leaflets fail to coapt. The obstruction can be labile, absent at rest but provoked with changes in preload, afterload, and contractility. The obstruction causes an increase in left ventricular systolic pressure which prolongs ventricular relaxation and increases left ventricular diastolic pressure which lead to myocardial ischemia and decreased cardiac output [15]. The pressure gradient is responsible for the murmur that is usually described as harsh, located along the lower left sternal border, and intensifies by release of Valsalva strain or standing from a squat position. In 5 % of the cases, the obstruction is midventricular rather than subaortic. The diagnosis is confirmed by continuous-wave Doppler echocardiography. The pressure gradient is often dynamic, made worse by increased contractility and decreased ventricular volume. Therefore, the gradient, usually defined as 30 mmHg or more, may be present in the resting state, elicited by provocative maneuvers or absent entirely. Patients should undergo 48-h Holter monitoring and exercise testing which provides prognostic information about the risk of sudden death.

Causes of Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is a disease of the sarcomere. Mutations in nine genes encoding sarcomeric proteins have convincingly been shown to cause hypertrophic cardiomyopathy. Disease-causing mutations are found in up to two-thirds of patients. Mutations in *MYHC7* encoding beta-myosin heavy chain and *MYBPC3* cardiac myosin-binding protein are the most common encoding for one-fourth to one-third of the disease. The mutations generally cause single amino acid substitutions in proteins that become incorporated into the sarcomere. Analysis of in vitro and in mouse models has shown increased contractility of mutant myofilaments that induce cardiac hypertrophy and contribute to diastolic dysfunction. Changes in calcium handling may confer a

predisposition to arrhythmias [10]. The extent of left ventricular hypertrophy varies between different genes. Hypertrophy confined to the apex (apical hypertrophic cardiomyopathy) has been associated with cardiac troponin I mutations. Prognosis can vary with the type of mutation, with beta-myosin heavy chain mutations presenting early in life and cardiac myosin-binding protein C mutations presenting in the elderly. However, not all individuals with an abnormal genotype will express the phenotype of hypertrophic cardiomyopathy.

An important management point is the importance of family screening of new cases of hypertrophic cardiomyopathy. All first-degree family members should be screened by obtaining a history and physical examination, 12-lead ECG, and two-dimensional echocardiography at annual evaluation during the adolescent years [16]. Adults with normal screening evaluations should be reevaluated every 5 years, as hypertrophic cardiomyopathy may not be appreciable until the sixth to seventh decade of life [15]. Genetic analysis remains a research tool but may allow for more directed screening in the future.

Natural History and Clinical Course

The prognosis and clinical course of patients with hypertrophic cardiomyopathy is likewise variable. The majority of patients remain asymptomatic throughout their life, while some present with dyspnea, angina, syncope, and sudden cardiac death. In general, patients who are symptomatic follow one or more of several pathways: (1) sudden death; (2) progressive dyspnea, chest pain, and presyncope/syncope in the face of normal or hyperdynamic LV function; (3) progression to LV systolic dysfunction and a dilated cardiomyopathy; or (4) atrial fibrillation with associated clinical deterioration or stroke [16]. Management is directed at each of these possible clinical pathways. The overall mortality is approximately 1 % per year [15].

Treatment of Hypertrophic Cardiomyopathy

Treatment is directed at reduction of the outflow obstruction to relieve symptoms and assessment of the risk of sudden death. Asymptomatic patients should be instructed to avoid dehydration, strenuous exertion, repeated isometric exercise, and competitive athletics in addition to reporting symptoms of presyncope/syncope immediately. Pharmacological therapy is usually initiated with the onset of disabling symptoms. β-Blockers such as propranolol, atenolol, or metoprolol are first line, enhancing diastolic filling time. If β-blockers are not effective, a trial of verapamil may be warranted. However, verapamil has been associated with death in patients with severe symptoms, severe LV outflow tract gradients, and pulmonary hypertension [15]. Both agents have negative inotropic actions and slow heart rate. The response to such drugs is variable; few clinical trials have examined treatment in hypertrophic cardiomyopathy, so therapy remains somewhat of a "trial and error" event. If a patient develops a dilated cardiomyopathy, he or she should be treated with appropriate heart failure medications and verapamil should be discontinued. Patients with LV outflow tract obstruction or intrinsic mitral valve disease warrant infective endocarditis prophylaxis.

For patients with severe drug refractory symptoms and marked LV outflow tract gradients (>30 mmHg), surgical myectomy or catheter-based alcohol septal ablation is often performed. Dual-chamber pacing is not as effective in alleviating symptoms and reducing LV outflow gradients. Myectomy is considered the gold standard. Postoperatively, many patients are able to exercise to full capacity, and 90 % are free of symptoms. Heart block, aortic regurgitation, and ventricular septal defects occur in less than 3 %, and operative mortality for surgical myectomy is 1–2 %. Alcohol septal ablation produces a confined myocardial infarction in the basal septum. It can decrease the gradient substantially and improve symptoms, but it is generally not as effective as septal myectomy. This procedure cannot be performed in patients that do not have a perforator artery that supplies the critical area of septal hypertrophy [15]. For both surgical myectomy and alcohol septal ablation, it is recommended that both procedures be confined to centers with experience. For patients with severe drug refractory symptoms but no LV outflow tract gradient, heart transplantation may be necessary.

Those who survive sudden cardiac death have an automatic implantable cardioverter-defibrillator implanted. The difficult issue is risk stratification to prevent sudden death. The highest risk has been associated with patients with prior cardiac arrest, sustained ventricular tachycardia, family history of sudden cardiac death, nonsustained ventricular tachycardia on Holter monitoring, abnormal blood pressure response on stress testing, extreme LV hypertrophy (wall thickness 30 mm or more), left ventricular outflow obstruction, microvascular obstruction, and the presence of a high-risk genotype. Annual evaluation for patients with hypertrophic cardiomyopathy at risk for sudden death should include a history directed toward presyncope and syncope, an echocardiogram, a stress test, and possibly a Holter monitor for 48 h [16].

Atrial fibrillation can result in severe hemodynamic compromise due to tachycardia and loss of atrial contraction. This can be life threatening, justifying aggressive attempts at maintenance of sinus rhythm. Treatment should include prompt cardioversion [15]. Warfarin is indicated for those with both paroxysmal and permanent atrial fibrillation.

Restrictive Cardiomyopathy

This rare form of cardiomyopathy is characterized by impaired ventricular filling and reduced diastolic ventricular volumes associated with mild-to-moderate increase in cardiac mass. Biatrial enlargement is common, and thrombi are often present in the left atrial appendage. The cavity size and wall thickness of the ventricles tend to be normal, with normal or reduced global systolic function [17].

Causes of Restrictive Cardiomyopathy

Amyloidosis is probably the most frequent cause of restrictive cardiomyopathy. Cardiac involvement is more commonly found in primary amyloid which is caused by the production of immunoglobulin light chains by plasma cells. Secondary amyloidosis is caused by the deposition of proteins other than immunoglobulin and is familial and senile or due to chronic inflammatory process. Restrictive cardiomyopathy is thought to be due to damage of the normal contractile apparatus by infiltrative interstitial deposits. Forty different mutations of transthyretin (prealbumin) cause inherited forms of amyloidosis. The majority of these mutations are autosomal dominant and associated with ascending peripheral neuropathy [17]. Other infiltrative causes of restrictive cardiomyopathy include carcinoid, hemochromatosis, sarcoidosis, Gaucher's and Fabry's disease, and a variety of other uncommon disorders. Endomyocardial fibrosis and Loeffler's endocarditis are restrictive obliterative cardiomyopathies associated with eosinophilia. It is thought that that the intracytoplasmic granular content of activated eosinophils is toxic to the myocardium. It can involve the atrioventricular valve apparatus leading to valve stenosis or regurgitation. Endomyocardial fibrosis is more common in parts of Africa, India, South and Central America, and Asia. Finally, radiation, metastatic tumors, and familial inheritance may also cause restrictive cardiomyopathy.

Natural History and Clinical Course

Patients present with signs of left- and right-sided heart failure. Angina can be the presenting symptom in amyloidosis. Cardiac conduction abnormalities are common in amyloidosis and sarcoidosis. The initial diagnostic approach is to rule out constrictive pericarditis which has similar signs and symptoms [17]. Prognosis varies with the cause of the restrictive cardiomyopathy. Amyloidosis is associated with a poor prognosis. Others causes of restrictive cardiomyopathy such as endomyocardial fibrosis are associated with a prolonged course. Often right-side symptoms predominate with elevated jugular venous veins, ascites, and edema. Dyspnea is often present as well, due to left atrial hypertension.

Treatment of Restrictive Cardiomyopathy

Treatment is limited and is directed at the underlying cause. Diuretics relieve congestion in the pulmonary and systemic circulations. Aggressive diuresis can reduce ventricular pressure and create a low cardiac output state. Digoxin is arrhythmogenic in patients with amyloidosis and should be avoided. Sinus rhythm is maintained because atrial fibrillation can exacerbate diastolic dysfunction and lead to hemodynamic compromise. Constrictive pericarditis needs to be excluded, as this treatable disorder is easily confused with restrictive cardiomyopathy.

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular dysplasia (ARVC) is characterized by an enlarged right ventricle due to fibrofatty infiltration of the right ventricular free wall [18]. The left ventricle can also be involved. The fibrofatty replacement of myocardium makes these patients susceptible to arrhythmias and can present with ventricular tachycardia of left bundle branch morphology or sudden death. The disease is familial and involves five mutations that encode desmosomal proteins (desmoplakin, plakoglobin, plakophilin 2, desmoglein 2, and desmocollin 2). Desmosomes mediate intercellular attachments and anchor cytoplasmic domains of membrane proteins to the intermediate desmin filaments of cardiomyocytes. Other mutations that encode nondesmosomal genes include transforming growth factor beta-3 and transmembrane protein 43 [10]. A diagnosis of ARVC should be suspected in young patients resuscitated from sudden death without overt left ventricular dysfunction or underlying congenital heart disease.

Evaluation and Treatment of ARVC

The evaluation includes echocardiography, magnetic resonance imaging, and sometimes endomyocardial biopsy (EMB). Asimaki et al. showed that reduced immunoreactive signal levels of plakoglobin on routine EMBs at intercalated disks is a consistent feature in patients with ARVC and not in other forms of cardiomyopathy [19]. In general, an enlarged, hypocontractile right ventricle is seen with evidence of fat infiltration on magnetic resonance imaging. Cardiac sarcoid may present in a similar manner. Definite diagnosis requires the presence of two major criteria, one major plus two minor criteria, or four minor criteria from different categories. The categories include global or regional dysfunction of the right ventricle, fibrofatty replacement of the myocardium on biopsy, depolarization/conduction abnormalities, repolarization abnormalities, arrhythmias, and family history. Treatment

Table 33.4 Causes of myocarditis

Infections
Viral: coxsackievirus, echovirus, poliovirus, influenza, vaccinia, cytomegalovirus, adenovirus, parvovirus, herpes simplex, respiratory syncytial virus, Epstein-Barr virus, hepatitis, varicella zoster, human immunodeficiency virus
Bacterial: *Streptococcus pyogenes, Staphylococcus aureus, Salmonella, Leptospira, Borrelia burgdorferi*, *Mycoplasma pneumoniae, Chlamydia, Rickettsia*
Fungi: *Aspergillus, Candida*
Parasites: *Trypanosoma cruzi, Toxoplasma*
Smallpox vaccination
Peripartum
Giant cell
Eosinophilic
Chemical or drug hypersensitivity
Multiple antibiotics, diuretics, anticonvulsants, interferon
Radiation

includes screening of family members and the placement of an automatic implantable cardioverter-defibrillator. Given the rarity of ARVC, referral to a center with expertise in this disorder is warranted.

Myocarditis

Myocarditis is an inflammatory disease of the myocardium, which can lead to a dilated cardiomyopathy. It usually occurs after a respiratory or gastrointestinal infection and has been associated with a variety of infectious organisms, including bacteria, parasites, and fungi, as well as hypersensitivity drug reactions and autoimmune diseases (*see* Table 33.4). The incidence in the community is not well known, but there is a slight male predominance [20]. Myocarditis may present with a wide range of symptoms, ranging from mild dyspnea or chest pain that resolve without specific therapy to cardiogenic shock and death. The key concept is that some form of myocardial injury, usually viral, leads to an autoimmune reaction. Dilated cardiomyopathy with chronic heart failure is the major long-term sequela of myocarditis [20]. Myocarditis can occur concomitantly in patients with cardiomyopathy and can adversely affect outcome. This section will concentrate on primary myocarditis, which most believe is a post-viral autoimmune disease.

Causes of Myocarditis

As early as the 1800s, it was recognized that cardiac symptoms could be associated with mumps. Around 1929, cardiac inflammation was found in association with influenza. Enteroviruses, particularly the poliomyelitis virus, were associated with myocarditis in the late 1920s. Since then, a number of viruses have been identified in association with myocarditis including both DNA and RNA core viruses (Table 33.4), but cardiotropic strains of coxsackieviruses were felt to be the most common cause of myocarditis. By polymerase chain reaction (PCR), viral genome was recently found in 38 % of 624 patients with myocarditis and only 1.4 % of control samples [21]. The myocardial samples came from endomyocardial biopsy, autopsy, and explanted hearts. The most common virus genome identified in both children and adults with myocarditis was adenovirus followed by enterovirus, cytomegalovirus, parvovirus B19, influenza A, human herpesvirus 6, Epstein-Barr virus, hepatitis C, and respiratory syncytial virus. Myocarditis is the most common finding in patients with human immunodeficiency virus (HIV) with prevalence of 50 %. Cardiomyopathy in HIV patients can be caused by inhibition of cardiac contractility by HIV type 1 glycoprotein 120, coinfections, or antiviral medications.

That adenoviruses and enteroviruses, such as coxsackie, cause myocarditis should not be too surprising as both use common cellular receptors for entry into myocardial cells, and differences in affinity for the receptor may account for differences in susceptibility and pathogenesis. In addition, myocarditis has recently been confirmed following smallpox vaccination in US military personnel [22, 23]. Other etiologies include infection from *Borrelia burgdorferi*, and these patients can be coinfected with ehrlichia or babesia.

Pathogenesis

The acute phase of the disease is triggered by the entry and proliferation of the myocardium by the causative virus. Various cytokines are activated. Circulating levels of plasma tumor necrosis factor and various interleukins are elevated. The acute phase is characterized by myocyte necrosis and cellular infiltrates, whereas in chronic myocarditis, myocyte necrosis is absent but cellular infiltration remains. Kuhl et al. demonstrated that patients with persistent viral genomes detected by myocardial biopsy showed progressive impairment of left ventricular (LV) function, whereas spontaneous viral elimination was associated in improvement of LV function [24]. The innate immune system is essential in the development of myocarditis. Viruses, streptococcal M protein, and host proteins trigger toll-like receptors and pattern recognition receptors in patients with tissue injury. The development of myocarditis requires MyD88, a key protein in the dendritic-cell toll-like receptor signaling. Coxsackievirus B infection upregulates toll-like receptor 4 on macrophages, stimulates maturation of antigen-presenting cells, leads to pro-inflammatory cytokine release, and decreases regulatory T cell function. The increased levels of type 1 helper T and type 2 helper T cytokines are associated with the development of cardiomyopathy. CD4+ T lymphocytes are key mediators of cardiac damage in experimental autoimmune myocarditis. In

Table 33.5 Clinicopathologic forms of myocarditis

	Fulminant	Acute	Chronic active	Chronic persistent
Onset	Distinct	Indistinct	Indistinct	Indistinct
LV function	Severe dysfunction	Moderate dysfunction	Moderate dysfunction	Normal
Biopsy	Multiple foci active	Active or borderline	Active or borderline	Active or borderline
Clinical prognosis	Complete recovery or death	Dilated cardiomyopathy	Restrictive cardiomyopathy	Normal
Histologic prognosis	Resolution	Resolution	Ongoing inflammation and fibrosis	Ongoing myocarditis

addition, autoantibodies to a variety of cardiac antigens are common, streptococcal M protein and coxsackievirus B share epitopes with cardiac myosin, and cross-reactive antibodies may result in the production of autoantigens because of this antigenic mimicry. After viral clearance, cardiac myosin may cross-react with laminin which could provide an endogenous source of antigen in chronic myocarditis and stimulate chronic inflammation [20].

Natural History and Clinical Course

The natural history is variable; the prognosis is dependent on the cause. The majority of patients probably have subclinical cardiac inflammation that clears spontaneously [25]. A much smaller percentage presents with overt disease. Four clinicopathologic forms of myocarditis have been described (Table 33.5). Patients with *fulminant myocarditis* are usually young and have a distinct onset with a recent, recognizable viral illness. They present abruptly with poor left ventricular function and near-normal-sized left ventricles. Ventricular walls are often thick due to a combination of lymphocytic infiltration and edema. Patients either spontaneously recover completely or die of cardiogenic shock or ventricular arrhythmias [26, 27]. We do not believe that immunosuppression has a role in the management of these patients. Patients with *acute myocarditis* have an indistinct onset of symptoms, moderate-to-severe left ventricular dysfunction, and active or borderline myocarditis on endomyocardial biopsy. Such patients may respond to immunosuppression. *Chronic active myocarditis* has an indistinct onset and progressive left ventricular dysfunction, resulting in a restrictive picture. Endomyocardial biopsy shows inflammation and severe fibrosis, which does not respond to immunosuppression. Patients with *chronic persistent myocarditis* present with atypical chest pain or ventricular arrhythmias. Left ventricular dysfunction is not present. Endomyocardial biopsy shows inflammation.

Fulminant lymphocytic myocarditis has a distinct onset with a viral prodrome within 2 weeks before the onset of symptoms and hemodynamic compromise but generally has a good prognosis. They may require intravenous inotropes and mechanical support. Acute lymphocytic myocarditis does not usually have a distinct onset and hemodynamic compromise but more frequently results in death or the need for cardiac transplantation. Both of these entities are rare, so data on heart transplantation in those with myocarditis is limited [20]. Giant-cell myocarditis has a particularly poor prognosis, with a median survival of 5.5 months after the development of symptoms as documented in the largest registry of such patients [28]. The course is characterized by progressive heart failure with refractory ventricular arrhythmias. Patients tend to present in their and many have had a previous autoimmune disease. It is known to recur in transplanted hearts, but heart transplantation is the only therapy likely to offer a significant survival advantage. Endomyocardial biopsy shows a diffuse, aggressive lymphocytic infiltrate with myocyte necrosis and the presence of giant cells without well-formed granuloma. Giant-cell myocarditis is different from cardiac sarcoidosis. The pathology is different, with cardiac sarcoidosis presenting with a patchy infiltrate and well-formed granuloma. The prognosis of cardiac sarcoid is better, and patients with sarcoid are more likely to present with heart block and a long duration of symptoms [29]. Hypersensitivity myocarditis can be caused by anticonvulsants, antibiotics, and antipsychotics with improvement after the withdrawal of the offending agent [20].

Clinical symptoms are variable and subtle, making this a diagnosis that can be missed. They include dyspnea, fatigue, decreased exercise tolerance, palpitations, chest pain, and syncope. Chest pain can be due to associated pericarditis or from coronary artery spasm. Rash, fever, and eosinophilia with or without the introduction of new medications could suggest hypersensitivity myocarditis. Eosinophilic myocarditis shows predominant eosinophils in the myocardium and may be associated with Churg-Strauss syndrome, Loffler's endomyocardial fibrosis, and parasitic, helminth, and protozoal infections. Giant-cell myocarditis should be considered in a patient with new onset of dilated cardiomyopathy associated with a thymoma or other autoimmune conditions with ventricular arrhythmias or high-grade heart block. Cardiac sarcoid should be suspected in chronic heart failure with a dilated cardiomyopathy, ventricular arrhythmias, and high-grade heart block.

Evaluation of Myocarditis

Cardiac biomarkers are elevated in myocarditis. Troponin I has high specificity of 89 % but limited sensitivity [20]. In an autopsy study performed by Carniel et al., only 18 % of patients with myositis had elevated levels of creatine kinase [30]. The electrocardiogram may show sinus tachycardia with nonspecific ST segment and T wave abnormalities. Traditional echocardiographic findings are LV regional or global dysfunction and left ventricular dilation. Felker et al. found that patients with fulminant myocarditis had near-normal LV dimensions (5.3 ± 0.9 cm) but increased septal thickness at presentation, while those with acute myocarditis had increased diastolic dimensions but normal septal thickness [31]. Mendes et al. assessed the predictive value of right ventricular involvement in 23 patients with biopsy-proven myocarditis. Patients with RV involvement had more depressed LV function compared with patients with normal RV function ($p = 0.01$) as well as higher likelihood of an adverse outcome defined as death or need for cardiac transplantation [32]. The gold standard is endomyocardial biopsy, but the sensitivity of this has been reported to be low ranging 25–40 % [24]. Recent recommendations suggest that endomyocardial biopsy should be considered when there is a high chance of finding specific treatable disorders [20]. The standard Dallas pathological criteria remain the benchmark for histologic diagnosis, requiring that inflammatory cellular infiltrate with or without associated myocyte necrosis is present on conventional stained heart tissue sections. This is limited by variability in interpretation and low sensitivity. Alternate classifications have been used relying on cell-specific immunoperoxidase stains for surface antigens such as anti-CD3, anti-CD4, anti-CD20, anti-CD68, and anti-human leukocyte antigen. These criteria may improve sensitivity and prognostic value [20]. Borderline myocarditis is diagnosed if there is no evident myocyte damage. Myocarditis can be suspected in patients who present with a nondilated, hypocontractile heart and an antecedent viral syndrome.

Cardiac magnetic resonance imaging may provide a noninvasive method to diagnose acute myocarditis. This technique can analyze inflammation, edema, and necrosis in additional to functional parameters such as left ventricular function, regional wall motion, and dimensions. Using both T1-weighted and T2- weighted images has the best combination of sensitivity and specificity. Regions of myocarditis are reported to correlate closely with regions of abnormal signaling signal on cardiac MRI [20] and can be used to localize sites for endomyocardial biopsies. Jeserich et al. found that in 44 patients with myocarditis, STIR sequence provided specificity of 90 %, positive predictive value of 93.3 % for the diagnosis of myocarditis compared to controls. Late gadolinium enhancement of the subepicardial/midmyocardial late contrast enhancement is highly predictive of myocarditis [24]. The role of MRI in chronic myocarditis is less clear. Multidetector CT is another noninvasive tool for detecting myocarditis and in small studies where delayed enhancement has correlated well with cardiac MRI in detecting myocarditis [24].

Treatment of Myocarditis

The mainstay of therapy for acute myocarditis is largely supportive therapy. Most will improve with a standard heart failure regimen of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, and diuretics. Arrhythmia therapy should also be supportive since they usually resolve after the first few weeks of treatment. Temporary pacemakers may be required in symptomatic bradycardia or complete heart block. Antiviral therapy is limited to murine models and small case series. The largest trial of immunosuppressive therapy for myocarditis did not support the use of such agents. There was no significant difference in survival [6]. Since then, a number of reports have suggested that patients with cardiac inflammation may respond if the correct patients are chosen. In a trial of 22 patients with PCR-proven enteroviral or adenoviral genomes and persistent left ventricular dysfunction, treatment with interferon-β for 6 months resulted in the elimination of viral genomes in all patients and improvement in left ventricular function in 15 of 22 patients [33]. In another study of 112 patients with a histologic diagnosis of myocarditis, patients with circulating cardiac autoantibodies and no viral genome were most likely to respond to immunosuppression [34]. Wojnicz et al. showed no difference in survival in 84 patients with dilated cardiomyopathy and increased myocyte HLA expression randomized to 3 months of immunosuppression versus placebo [12]. Approximately 27 % of patients in this trial had myocarditis as diagnosed by the Dallas Criteria. Intravenous immunoglobulin did not augment left ventricular function when compared to placebo in adult patients with recent-onset dilated cardiomyopathy [35]. However, left ventricular function did improve to a similar degree, about 16 EF units, in both groups. Only about 16 % of patients in this trial had myocarditis as defined by the Dallas Criteria.

Currently, the treatment of myocarditis is in evolution. Patients with a fulminant presentation usually will not need immunosuppression. In patients with chronic active myocarditis and chronic persistent myocarditis, immunosuppression is usually ineffective. Patients with giant-cell myocarditis are treated with immunosuppression, which can be effective, and transplantation. In the future, we should be able to predict which patients with acute myocarditis will respond to immunosuppression and likely tailor therapy to the stage of the disease. Patients recovering from acute myocarditis

should initially refrain from aerobic exercise based on animal studies which showed an increase in death during sustained exercise [19].

Peripartum Cardiomyopathy

Peripartum cardiomyopathy is included here because in our experience 62 % of patients had myocarditis on endomyocardial biopsy [36]. In the United States, this occurs in 1 of every 1,300–4,000 deliveries. It is defined as left ventricular systolic dysfunction developing in the final month of pregnancy or within 5 months postdelivery in the absence of preexisting heart disease. Affected women present with typical signs and symptoms of heart failure; signs of thromboembolism are also frequent. In our experience, recovery of left ventricular function occurs in the majority of patients, and the 5-year survival is excellent. Subsequent pregnancies have been associated with a reoccurrence of left ventricular dysfunction [37]. In 28 women whose left ventricular function had returned to normal, there was no mortality, but 21 % of patients developed symptoms of heart failure. In 16 women whose heart function had failed to normalize, the mortality was 19 and 44 % of the women developed heart failure. These data are helpful in counseling women regarding future pregnancies.

Left Ventricular Noncompaction

The ACC/AHA for the first time recognized left ventricular noncompaction as a form of cardiomyopathy. A substantial percentage of these patients have a dilated left ventricle with systolic dysfunction mimicking dilated cardiomyopathy. The abnormality is thought to represent an arrest in the normal process of myocardial compaction, the final stage of myocardial morphogenesis. This results in the persistence of many prominent ventricular trabeculations and deep intratrabecular recesses. Signs, symptoms, and outcomes of these patients are similar to those with dilated cardiomyopathy. The prognosis is worse in children compared to than those with dilated cardiomyopathy.

Conclusion

Diseases of the myocardium, cardiomyopathies, leading to heart failure represent fertile ground for further research. I expect molecular techniques to substantially affect our ability to diagnose and care for patients with cardiomyopathy. The next decade will likely see the advent of biologically based therapies to both prevent the phenotypic development of cardiomyopathy and to manage the disease once present.

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Pericardial Disease

34

Bernhard Maisch

Anatomy and Function of the Pericardium

The normal pericardium is a double-layered membrane which consists of an outer fibrous and an inner serous membrane. The inner serous pericardium or epicardium covers the heart and the great vessels. The pericardium fixes the heart in its proper anatomical place, prevents sudden dilatation of the cardiac chambers during exercise and hypervolemia and facilitates atrial filling during ventricular systole. It is a natural barrier against infection and the infiltration of malignant cells [1].

Fat can be found either outside the parietal pericardium as pericardial fat or underneath the visceral layer, the epicardium, as epicardial fat. In effusion it can be visualised as "halo phenomenon" and serves as a hallmark for access to the pericardial sac [2]. Pericardial innervation functions over the phrenic nerves' vagal fibres. Nerves can also transmit painful stimuli in acute pericarditis. Lymphatic drainage occurs mainly to the anterior mediastinal, tracheobronchial, lateropericardial and posterior mediastinal lymph nodes and not into the hilar nodes [2, 3].

The normal small amount (15–50 mL) of pericardial fluid is a serous ultrafiltrate of plasma with an osmolarity less than plasma. If increased, it is called hydropericardium [2].

Pericardiocentesis in patients with an effusion gives access to the space between the epicardium and the parietal serous layer of the fibrous pericardium.

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Pericardial Syndromes

The guidelines of the European Society of Cardiology were the first document worldwide to provide a systematic and practical clinical tool for the diagnosis and treatment of pericardial syndromes based on studies or expert consensus [4]. In general practice, idiopathic pericarditis or pericardial effusion is still the most frequently made diagnosis, but it only demonstrates our inability to make an aetiologically correct diagnosis. Table 34.1 gives an overview of the aetiology, pathogenesis and pathophysiology of the pericardial syndromes in a tertiary referral centre, which provides all diagnostic measures for a correct diagnosis.

Assessment of Pericarditis and Pericardial Effusion

In acute pericarditis, the diagnostic pathway follows the sequence of diagnostic measures in Table 34.2 according to the ESC guidelines [4]. Figure 34.1 illustrates the sequence of diagnostic and therapeutic measures (according to [4], taken from [2], p. 34).

Indications for Pericardiocentesis and Drainage

Indications for pericardiocentesis and drainage are listed in Table 34.3 and Figure 34.1. Each cardiac tamponade except in aortic dissection must undergo life-saving pericardiocentesis [2, 4, 5, 7–9]; also every suspected bacterial or purulent pericardial effusion is a class I recommendation according to

C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_34, © Springer Science+Business Media New York 2013

Table 34.1 Aetiology, incidence and pathogenesis of pericardial syndromes with effusion undergoing pericardiocentesis ($n = 300$) in the Marburg Registry (2nd column) [2] and from the ESC guidelines [4] or literature (*)

Pericardial effusions undergoing pericardiocentesis – aetiology	Incidence of pericardiocentesis from the Marburg Registry in % [2]	Incidence of pericarditis ± effusion in the respective aetiological syndrome or disease (%) [2, 4]*
Infectious	All 21	Pericarditis in myocarditis: ~ 25 in viral my
Viral (CVB A9, B1-4, echo B, CMV, EBV, HHV6, Parvo B19, HIV and others)	14	
Bacterial	7	~10 in endocarditis
Fungal	0	Unknown
Parasitary	0	Unknown
Systemic autoimmune disorders	All 1.5	
Systemic lupus erythematosus	0.5	~30
Rheumatoid arthritis	0.5	~30
Systemic sclerosis	0.5	~50
Type 2 (auto)immune process	All 24	
Rheumatic fever	0	20–50
Postcardiotomy syndrome	1	<20 after operation
Postmyocardial infarction syndrome	0.5	<5 after infarction
Autoreactive pericarditis (or idiopathic)	22.5	~25 in autoreactive my
Pericardial effusion in diseases of surrounding organs		Tamponade is rare
Myocarditis	14.5 (see infectious aetiology)	~25
Aortic aneurysm	Contraindicated	~5
Lung infarction	0	<1
Hydropericardium in CHF	4	Rare in heart failure & pulmonary hypertension
Paraneoplastic/malignant	43	~5–10,
Pericarditis in metabolic disorders		Rare
Uraemia/renal failure	1	Frequent in uraemia
Myxoedema	0.3	~30
Addison's disease	0	Rare
Diabetic ketoacidosis	0.3	Rare
Cholesterol pericarditis	0.3	No data available
Pregnancy	0	Rare, mostly hydropericardium
Traumatic pericarditis		
Direct penetrating injury	0.15	No data available
Indirect injury (by mediastinal irradiation)	5	No data available
Neoplastic pericardial disease	41.5	
Primary tumours	0.5	
Secondary metastatic tumours	41	40
Lung carcinoma	25	22
Breast carcinoma	15	15
Leukaemia and lymphoma	0.5	Rare
Other tumours	0.5	No data available
Idiopathic pericarditis	4.0; in other publications often >50 %	

Based on data from Ref. [2, 5]
my myocarditis, *DCM* dilated cardiomyopathy

the ESC guidelines [4]. Clinical features such as pulsus paradoxus and echocardiographic criteria and the underlying pathophysiology can be derived from Fig. 34.2. In purulent pericardial effusion, extensive saline rinsing by large lumen catheters or surgical drainage is advisable [2, 4, 5, 9, 10]. Cytology of the fluid reveals the underlying tumour in suspected neoplastic pericardial effusion in most cases. Together with epicardial biopsy targeted by pericardioscopy, cytology helps to differentiate neoplastic from radiation-induced effusions in patients with breast and bronchial cancer [2, 11, 12]. Pericardiocentesis is also advisable in large effusions of unknown origin (class II a) without tamponade [2, 4, 13, 14]. In patients with smaller pericardial effusions of unknown origin, the rationale for pericardiocentesis lies in the

Table 34.2 Diagnostic pathway and sequence of performance in acute pericarditis (level of evidence B for all procedures)

Technique	Characteristic findings
Obligatory (indication class I):	
Auscultation	Pericardial rub (mono-, bi-, or triphasic)
ECG[a]	*Stage I*: anterior and inferior concave ST segment elevation. PR segment deviations opposite to P polarity
	Early stage II: ST junctions return to the baseline, PR deviated
	Late stage II: T waves progressively flatten and invert
	Stage III: generalised T wave inversions
Echocardiography	*Stage IV*: ECG returns to prepericarditis state
	Effusion types B-D (Horowitz [23])
	Signs of tamponade
Blood analyses	(a) ESR, CRP, LDH, leukocytes (inflammation markers)
	(b) cTnI, CK-MB (markers of myocardial lesion)[b]
Chest x-ray	Ranging from normal to "water bottle" heart shadow. Revealing additional pulmonary/mediastinal pathology
Mandatory *in* tamponade (*indication class I*), optional in large/recurrent effusions or if previous tests inconclusive (*indication class IIa) in small: effusions (indication class IIb):*	
Pericardiocentesis and drainage	Pericardial fluid cytology, and cultures, PCRs and histochemistry for determination of infection or neoplasia
Optional or if previous tests inconclusive (*indication class IIa):*	
CT	Effusions, peri-, and epicardium
MRI	Effusions, peri-, and epicardium, myocarditis MRI-criteria
Pericardioscopy, pericardial and epicardial biopsy	Establishing the specific aetiology

Reprinted from Ref. [4]. With permission from Oxford University Press

[a]Typical lead involvement: I, II, aVL, aVF, and V3–V6. The ST segment is always depressed in aVR, frequently in V1, and occasionally in V2. Occasionally, stage IV does not occur and there are permanent T wave inversions and flattenings. If ECG is first recorded in stage III, pericarditis cannot be differentiated by ECG from diffuse myocardial injury, "biventricular strain," or myocarditis. ECG in early repolarization is very similar to stage I. Unlike stage I, this ECG does not acutely evolve and J-point elevations are usually accompanied by a slur, oscillation, or notch at the end of the QRS just before and including the J point (best seen with tall R and T waves - large in early repolarisation pattern). Pericarditis is likely if in lead V6 the J point is >25 % of the height of the T wave apex (using the PR segment as a baseline)

[b]cTnI - cardiac troponin is detectable in 32.2–49 %, more frequently in younger, male patients, with ST-segment elevation, and pericardial effusion at presentation. An increase beyond 1.5 ng/mL is rare (7.6–22 %), and associated with CK-MB elevation. cTnI increase is not a negative prognostic marker regarding the incidence of recurrences, constrictive pericarditis, cardiac tamponade or residual LV dysfunction

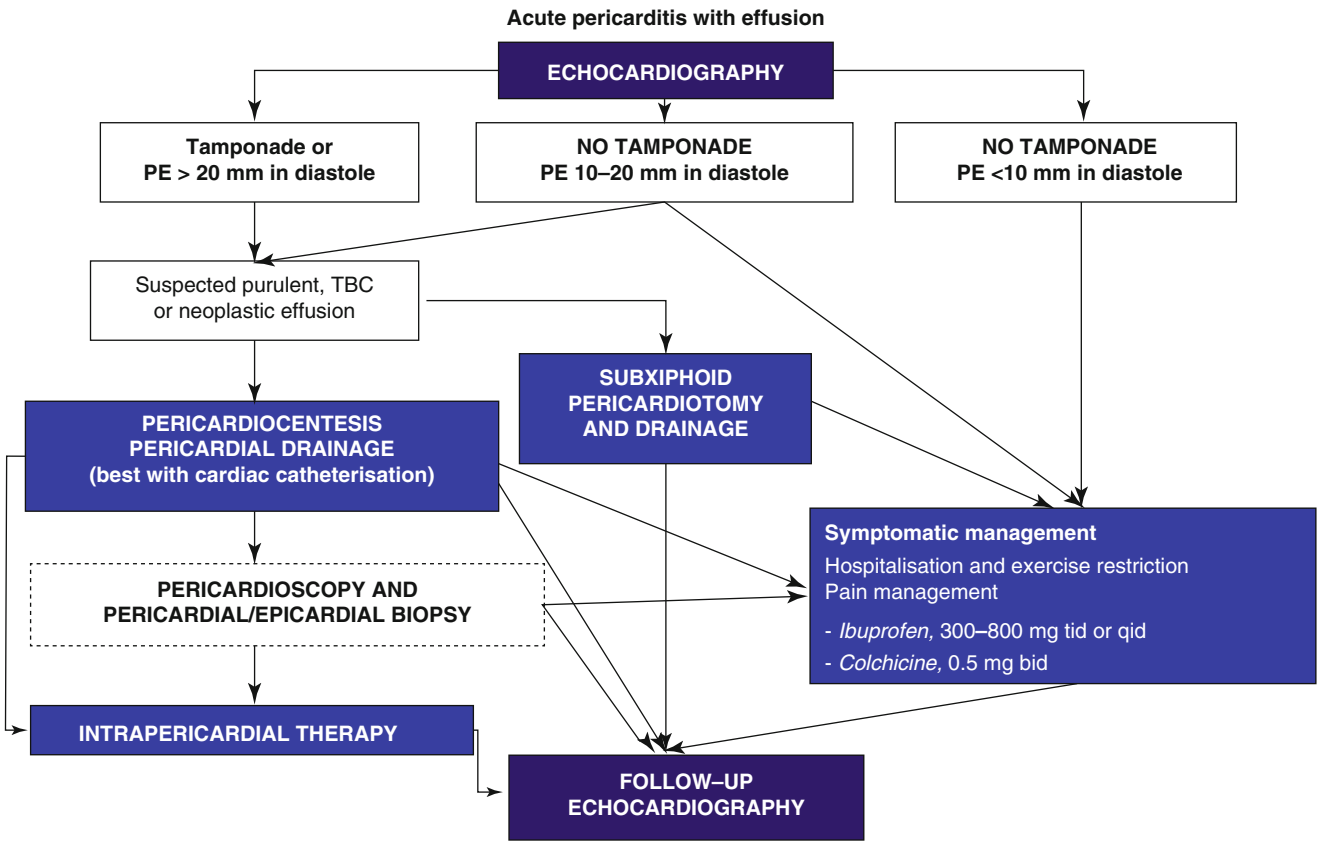

Fig. 34.1 Diagnosis and management in acute pericarditis with effusion (Adapted from Ref. [4, 6])

Table 34.3 Indications for pericardiocentesis independent from access site or method

Class I indications
Cardiac tamponade.
Effusions >20 mm in echocardiography (diastole).
Suspected purulent or tuberculous pericardial effusion.
Class IIa indications
Effusions 10–20 mm in echocardiography in diastole for diagnostic purposes other than purulent pericarditis or tuberculosis (pericardial fluid and tissue analyses, pericardioscopy, and epicardial/pericardial biopsy).
Suspected neoplastic pericardial effusion.
Class IIb indications
Effusions <10 mm in echocardiography in diastole for diagnostic purposes other than purulent; neoplastic, or tuberculous pericarditis (pericardial fluid and tissue analyses, pericardioscopy, and epicardial/pericardial biopsy).
Contraindications (Class III)
Absolute contraindication
Aortic dissection, myocardial rupture (e.g. in transmural infarction)
Relative contraindications
Relative contraindications include uncorrected coagulopathy, anticoagulant therapy, thrombocytopenia <50,000/mm^3, small, posterior, and loculated effusions.

Adapted from Refs. [2, 4]

possibility to clarify the underlying aetiology [2, 5, 9, 11, 12, 14–18] and to keep this access for intrapericardial therapy [2, 4, 5, 9, 12, 15, 19–21]. If the effusion exceeds 1,000 mL, it is advisable to evacuate it in two steps to avoid left ventricular failure [22].

The diagnosis of cardiac tamponade is based on the algorithm described in Table 34.4 [2, 4] and is illustrated in Figs. 34.1 and 34.2.

Since many pregnant women develop a minimal to moderate clinically silent hydropericardium by the third trimester, special conditions apply, particularly because tamponade is rare (Table 34.5). Echocardiographically guided pericardial puncture should be considered only in cardiac compression. Of note, NSAIDs may induce early closure of an open ductus arteriosus and should not be administered. Colchicine is also contraindicated in pregnancy.

Standard Techniques for Pericardiocentesis

Pericardiocentesis should be guided either by fluoroscopy or by echocardiography. Guidance by fluoroscopy is much more frequent in Europe, whereas echocardiography is more

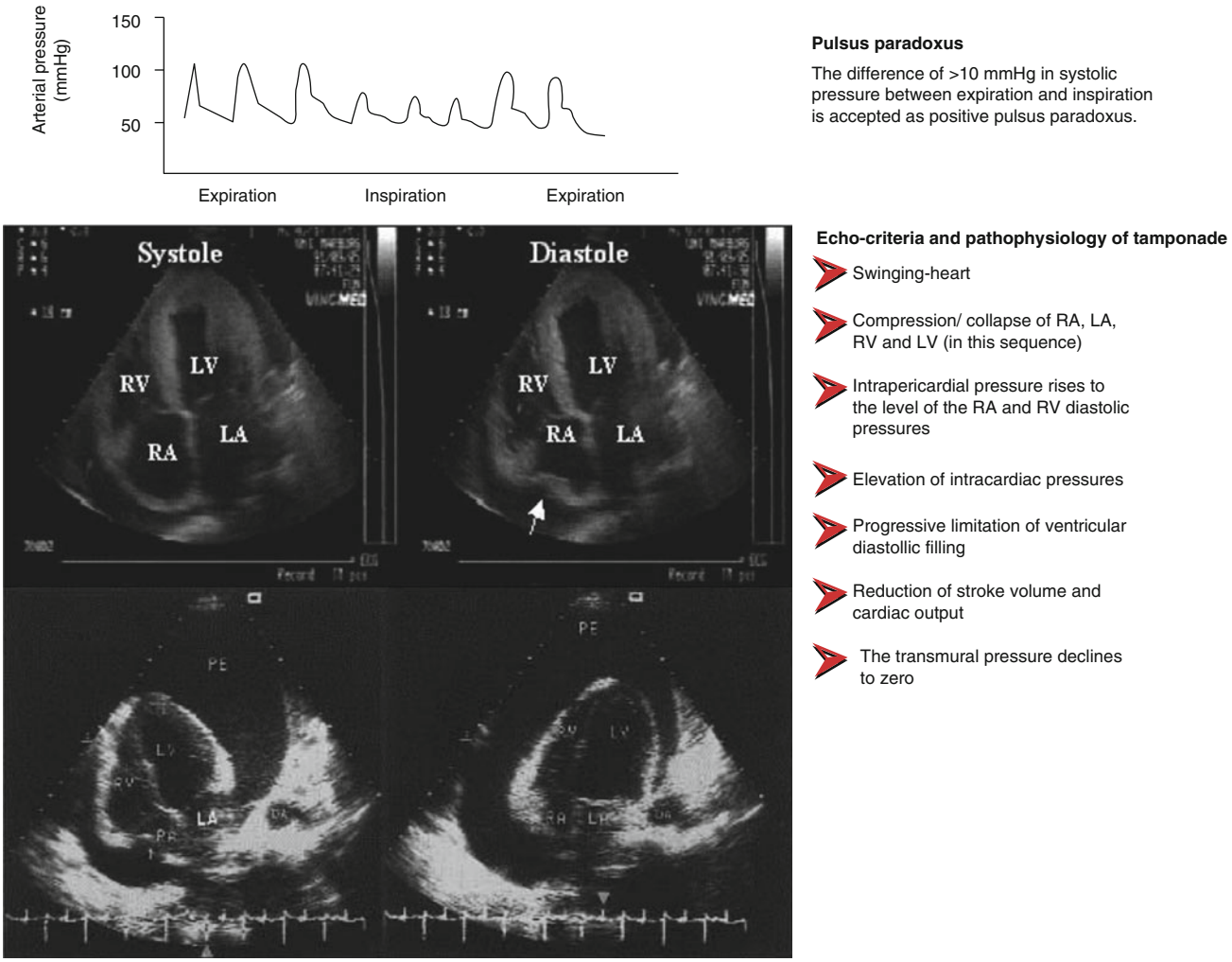

Fig. 34.2 Pulsus paradoxus, 2D echocardiographic criteria underlying the pathophysiology of tamponade (Adapted from Ref. [6])

Table 34.4 Diagnosis of cardiac tamponade

Clinical presentation:	Elevated systemic venous pressure,[a] hypotension,[b] pulsus paradoxus,[c] tachycardia,[d] dyspnoea or tachypnoea with clear lungs
Precipitating factors:	Drugs (cyclosporine, anticoagulants, thrombolytics, etc.), recent cardiac surgery, indwelling instrumentation, blunt chest trauma, malignancies, connective tissue disease, renal failure, septicaemia[e]
EKG:	Can be normal or non-specifically changed (ST-T wave), electrical alternans (QRS, rarely T), bradycardia (end-stage), Electromechanical dissociation (agonal phase)
Chest x-ray:	Enlarged cardiac silhouette with clear lungs ("bocksbeutel heart").
M mode/2D echocardiogram:	Diastolic collapse of the anterior RV free wall[f], RA collapse, LA and very rarely LV collapse, increased LV diastolic wall thickness "pseudohypertrophy", VCI dilatation (no collapse in inspirium), "swinging heart"
Doppler:	Tricuspid flow increases and mitral flow decreases during inspiration (reverse in expiration) Systolic and diastolic flows are reduced in systemic veins in expirium and reverse flow with atrial contraction is increased
M-mode colour Doppler:	Large respiratory fluctuations in mitral/tricuspid flows
Cardiac catheterisation:	1. *Confirmation of the diagnosis and quantification of the haemodynamic compromise*: RA pressure is elevated (preserved systolic x descent and absent or diminished diastolic y descent) Intrapericardial pressure is also elevated and virtually identical to RA pressure (both pressures fall in inspiration) RV mid-diastolic pressure elevated and equal to the RA and pericardial pressures (no dip-and-plateau configuration) Pulmonary artery diastolic pressure is slightly elevated and may correspond to the RV pressure. Pulmonary capillary wedge pressure is also elevated and nearly equal to intrapericardial and right atrial pressure. LV systolic and aortic pressures may be normal or reduced. 2. *Documenting that pericardial aspiration is followed by haemodynamic improvement*[g] 3. *Detection of the coexisting haemodynamic abnormalities* (*LV failure*, *constriction*, *pulmonary hypertension*) 4. *Detection of associated cardiovascular diseases* (*cardiomyopathy*, *coronary artery disease*).
RV/LV angiography:	Atrial collapse and small hyperactive ventricular chambers.
Coronary angiography:	Coronary compression in diastole.
Computer tomography:	No visualisation of subepicardial fat along both ventricles, which show tube-like configuration and anteriorly drawn atrias

Adapted from Refs. [2, 4, 5]
LA left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle, *VCI* inferior vena cava
[a]Jugular venous distension is less notable in hypovolemic patients or in "surgical tamponade". An inspiratory increase or lack of fall of the pressure in the neck veins (Kussmaul sign), when verified with tamponade, or after pericardial drainage, indicates effusive-constrictive disease
[b]Heart rate is usually >100 beats/min, but may be lower in hypothyroidism and in uremic patients
[c]The blood pressure cuff is inflated above the patient's systolic pressure. During slow deflation, the first Korotkoff sound is intermittent. Correlation with the patient's respiratory cycle identifies a point at which the sound is audible during expiration, but disappears when the patient breathes in. As the cuff pressure drops further, another point is reached when the first Korotkoff sound is audible throughout the respiratory cycle. The difference of >10 mmHg in systolic pressure between these two points is accepted as positive pulsus paradoxus. For quick clinical orientation the sign can be also investigated by simply feeling the pulse, which diminishes significantly during inspiration, when the patient is breathing normally. Pulsus paradoxus is absent in tamponade complicating atrial septal defect and in patients with significant aortic regurgitation. Caution: the patient should breathe normally – no deep inspirations
[d]Occasional patients are hypertensive especially if they have pre-existing hypertension
[e]Febrile tamponade may be misdiagnosed as septic shock
[f]Right ventricular collapse can be absent in elevated right ventricular pressure and right ventricular hypertrophy or in right ventricular infarction
[g]If after drainage of pericardial effusion intrapericardial pressure does not fall below atrial pressure, the effusive-constrictive disease should be considered

often used in the USA. In any case immediately before the procedure, transthoracic echocardiography should be carried out, and the operator performing the pericardiocentesis has to see the echocardiogram himself [2, 4]. Precise echocardiographic time motion criteria have been established already by Horowitz et al. [23], a classification still worth to be used nowadays (Fig. 34.3).

Strict aseptic conditions, EKG and blood pressure monitoring and local anaesthesia are minimal conditions which have to be provided. Then pericardiocentesis is performed under sedation with midazolam or 5–10 mg diazepam i.v. and under pain management with morphine preceded by metoclopramide.

Pericardiocentesis Guided by Fluoroscopy

Fluoroscopically guided pericardiocentesis is performed in the cardiac catheterisation laboratory with premedication as described above. The patients should lie in supine

Table 34.5 Diagnostic approach to pericardial effusion in pregnancy

Procedure	Indications	Interpretation in pregnancy
Pulsus paradoxus	Diagnosis of cardiac tamponade	Can be also noted in:
		Normal late pregnancy with no pericardial effusion
		Chronic constrictive pericarditis (~ 50 %)
		Bronchial asthma/emphysema
		Pulmonary embolism
		Extreme obesity
		Hypovolemic shock
Electrocardiogram	Acute pericarditis	ECG changes of acute pericarditis should be distinguished from changes in normal pregnancy:
	Myopericarditis	QRS axis shift to left or right
		ST-segment depressions and T-wave changes
		A small Q wave and an inverted P wave in lead III that vary with respiration, greater R-wave amplitude in V2
		Sinus tachycardia, atrial and/or ventricular premature beats
Chest radiography[a]	Suspected cardiac tamponade or haemopericardium in aortic dissection if echocardiography is not available	The heart may seem enlarged (horizontal positioning)
	Chest trauma	An increase in lung markings may simulate a pattern of flow redistribution (LV failure in perimyocarditis)
	Suspected tuberculous/neoplastic disease	Small pleural effusion is often found early post partum resolving spontaneously 1–2 weeks after delivery
Echocardiography	Pericardial effusion/tamponade	Enlarged right chambers (left lateral position)
	Haemopericardium in aortic dissection	LV systolic dimensions unchanged/slightly increased
Magnetic resonance imaging[b]	Haemopericardium in aortic dissection	
Swan-Ganz catheterization	Confirmation of cardiac tamponade or constriction	
Cardiac catheterisation[c]	Constrictive pericarditis[d]	Brachial approach preferred (to minimize radiation exposure)
	Haemopericardium in aortic dissection	Appropriate shielding (exposure kept to a minimum)
Pericardiocentesis	Only in tamponade or diagnostic pericardiocentesis in critically ill patients	Echocardiography guidance to avoid foetal radiation exposure whenever possible
Pericardioscopy and epicardial/pericardial biopsy	Only in vital indications	Foetal radiation exposure similar as during cardiac catheterisation

Adapted from [6]

[a]Estimated radiation to the uterus is low (0.2–43.0 mrad) but is best avoided in pregnancy

[b]Safety has not been fully established

[c]High dose of radiation (~500 mrad to the conceptus, even with an appropriate pelvic shield)

[d]When cardiac decompensation occurs during pregnancy in patients with constrictive pericarditis, particularly if cardiac surgery is being considered, cardiac catheterisation is required to: (1) confirm the diagnosis and (2) to exclude accompanied coronary artery disease in patients with several risk factors for coronary artery disease and of age >35 years

position, with his thorax elevated 45 % to increase accumulation of the fluid in lower and frontal portions of the pericardium [2, 4, 24], which may be unnecessary in large effusions. With the subxiphoid approach, a long needle, best the Tuohy needle with a rounded tip, is directed towards the left shoulder at a 30° angle to the skin (Fig. 34.4) [2]. During puncturing, its sharp side is turned to the sternum. It is twisted by 180° after entry into the pericardial sac to permit the introduction of the guidewire. The needle approaches the pericardium slowly and under steady manual aspiration (negative pressure) and is stopped as soon as the effusion is aspirated. The orientation of the puncturing needle is best when both the lateral and the anterior-posterior view are available. In the lateral view, the halo phenomenon clearly marks the epicardial fatpat best [2, 25] (see Fig. 34.4). After the first aspiration of pericardial fluid, a soft J-tip guidewire is introduced into the pericardial space. Dilatation of the entry with a 5 or 7 French introducer set follows, and then a multi-holed pigtail catheter is advanced. The procedural success of pericardiocentesis is high (>90 %) in patients with an anterior effusion and an echocardiographically measured pericardial free space of 10 mm or more in diastole [23]. The Marburg Registry reports an overall procedural success of more 98 % in 587 patients with effusions of different sizes, including also small effusions [2]. We had no fatal complication, only 6 chamber

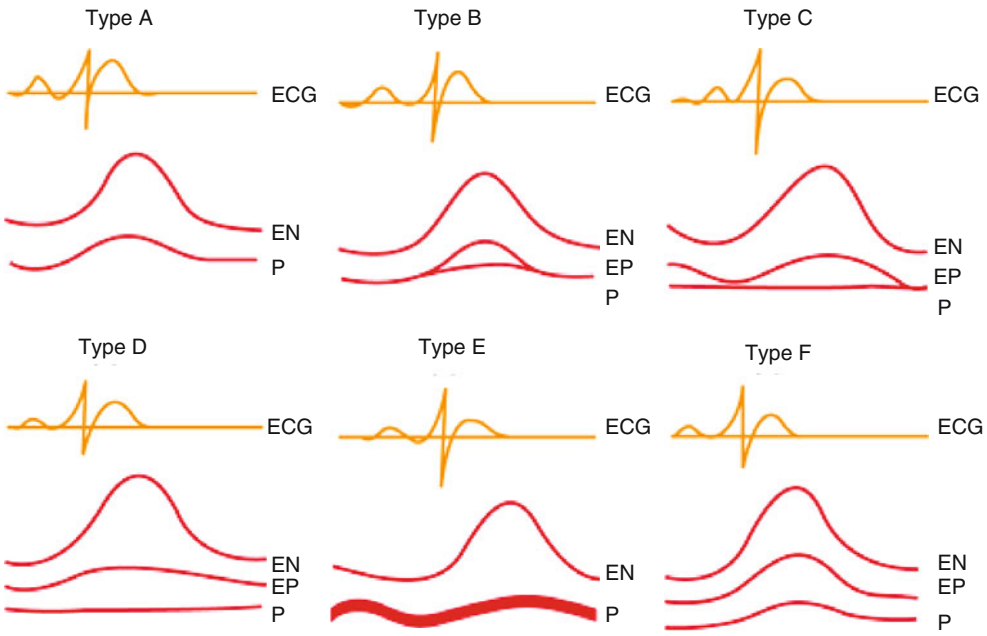

Fig. 34.3 Horowitz classification [23] of pericardial effusion. Type A: no effusion; Type B: separation of epicardium (*EP*) and pericardium (*P*) (3–16 mL effusion); Type C: systolic and diastolic separation of EP and P (small effusion >16 ml); Type D: pronounced separation of EP and P with large echo-free space; Type E: pericardial thickening (>4 mm). *EN*: endocardium (Modified from Ref. [6])

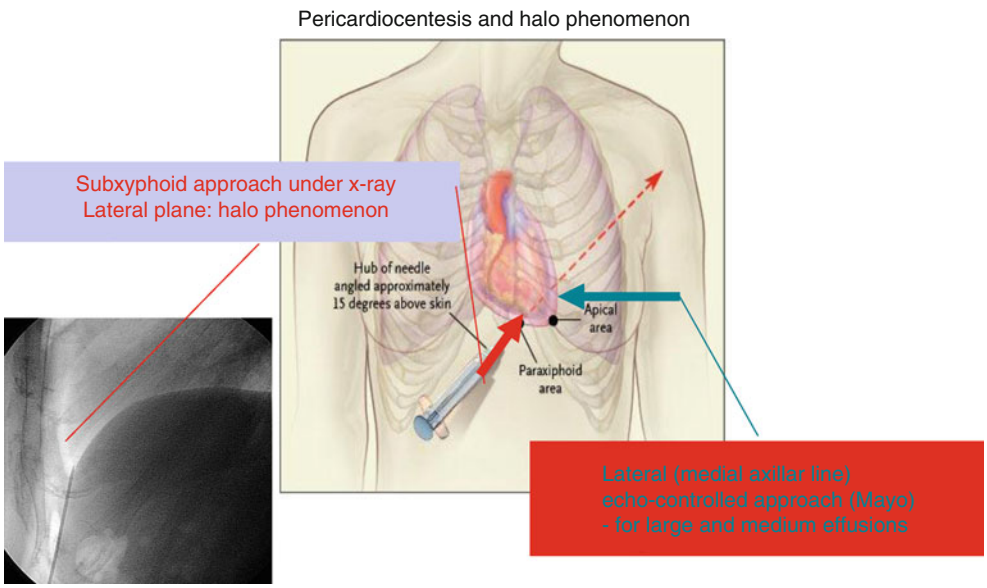

Fig. 34.4 Subxiphoid x-ray controlled and lateral echocardiographically controlled approaches to pericardiocentesis (Adapted from Ref. [6])

lacerations out of the 587 procedures, which required a second and then successful puncture.

Pericardiocentesis Guided by Echocardiography

The Mayo Clinic has been the most experienced centre performing pericardiocentesis guided by echocardiography since the late 1970s with a high success rate [2, 26]. By echocardiography the shortest route to enter the pericardium intercostally is usually in the sixth or seventh intercostal space in the anterior axillary line. From the selected entry side, a polytef-sheathed Deseret needle ("intracath", 16–18 gauge, 5.1–3.3 cm length) is advanced connected with an attached syringe filled with agitated saline solution. From a remote window, the position of the needle can be followed when agitated saline as echo-contrast is injected. After insertion of the needle in the pericardium, the polytef sheath is advanced over the needle, and the steel core is withdrawn so that only the polytef sheath remains in the fluid space. Via a guidewire a pigtail catheter is introduced into the pericardial sac.

There were only very few major (1.2 %) and minor complications (3.5 %) in the Mayo experience such as chamber lacerations requiring surgery and pneumothoraces requiring

chest tube placement in five patients each, injury to an intercostal vessel necessitating surgery, ventricular tachycardia and bacteraemia related to pericardial catheter placement in one patient each [26].

Emergency Pericardiocentesis

If a perforation of cardiac chambers occurs during pericardial puncture, the perforating catheter should be kept in place. Then another percutaneous puncture can be then attempted. If successful, the perforating catheter can be withdrawn, and surgery can be avoided by drainage and autotransfusion of pericardial blood into the femoral vein [2, 4]. Another practical approach could be to close the perforation with a collagen device such as angioseal (personal communication by Dr. Kuck, Hamburg). Autotransfusion should be avoided in suspected malignant pericardial effusions.

Prolonged Pericardial Drainage

In chronic pericardial effusion prolonged pericardial drainage is required until the volume of effusion obtained by intermittent pericardial aspiration (every 6 h) falls to <25 mL per day [2, 4, 5]. Since the pigtail catheter is left in place, i.v. antibiotic prophylaxis (e.g. cephalosporin, ampicillin and/or vancomycin) and, in selected cases also, antimycotic treatment are necessary. After the first evacuation, all patients receive 80 mg gentamicin intrapericardially for sclerosing and antibiotic therapy. With any further evacuation, the removal of the local antibiotic has also to be taken into account, and half the initial dose of gentamicin should be added intrapericardially. The extracted fluid should be controlled for any change of colour or an increase in leukocyte count to avoid bacterial superinfection. If purulent pericarditis is complicating further treatment, surgical drainage and extensive rinsing is warranted.

Surgical Drainage of the Pericardium

In aortic dissection or rupture of a ventricle in transmural infarction, surgical drainage is unavoidable. If the heart cannot be reached by a needle, surgical drainage is also mandatory. In purulent pericarditis, surgical treatment is recommended. In loculated pericardial effusion, the surgeon can break up adhesions, which is important in purulent pericardial effusion. McDonald et al. [10] compared outcomes in a single institution study with 96 patients undergoing pericardial catheter drainage and 150 patients with subxiphoid surgical drainage. In either condition no procedural mortality occurred. However, the in-hospital mortality was higher in the percutaneous group (22.9 %) when compared to surgical patients (10.7 %), in whom general anaesthesia is needed, which is a disadvantage. Recurrence rates were seen more frequently (16.5 %) in the percutaneous when compared to the surgical group (4.6 %). Another advantage of surgical drainage in this study and the one by Allen et al. [24] is that larger samples of tissue were available for diagnosis and that a larger pleuropericardial or abdominopericardial window could be created. These advantages of surgical drainage are nowadays compensated by pericardial and epicardial biopsy sampling under pericardioscopical control [2].

Alternative Techniques for Pericardiocentesis: PerDUCER and PeriAttacher

In specialised centres even small effusion or dry pericardium can be entered with the Tuohy needle, the PerDUCER® or the Marburg PeriAttacher [2, 4, 11, 25]. The pericardial approach has been recently selected for patients in whom epicardial ablation therapy has to be carried out ([3], overview in [2]) or in cases where intrapericardial therapy with little or no systemic side effects is preferable such as in severe forms of fulminant virus negative myocarditis, in eosinophilic myocarditis or in giant cell myocarditis [2, 9]. In these patients intrapericardial triamcinolone instillation can cure the disease [15].

Pericardioscopy

Pericardioscopy as a new window to the heart for the interventional cardiologist was introduced by Maisch et al. in 1994 from the subxiphoid access site [11]; experience both from cardiologists [14] and cardiac surgeons followed [21]. Nowadays by flexible fibroscopic 16 and 14 F devices (e.g. by Storz Co), the peri- and epicardial surfaces can be visualised, and the targeted sampling of pericardial and epicardial tissue can be performed (see Fig. 34.5 for representative images). The fibroscope is moved along a first guidewire, which runs through the endoscope itself, to avoid any perforation of the cardiac tissue. The bioptome is operated via a second working channel and controlled both by the fibre optics itself and by x-ray (details are elaborated in [2]). In the rare case of a perforation during an epicardial biopsy, a second guidewire positioned outside of the fibroscope can be helpful in order to introduce immediately a pigtail catheter to perform the evacuation of blood and to permit autotransfusion from the pericardial space into the femoral vein [2, 5].

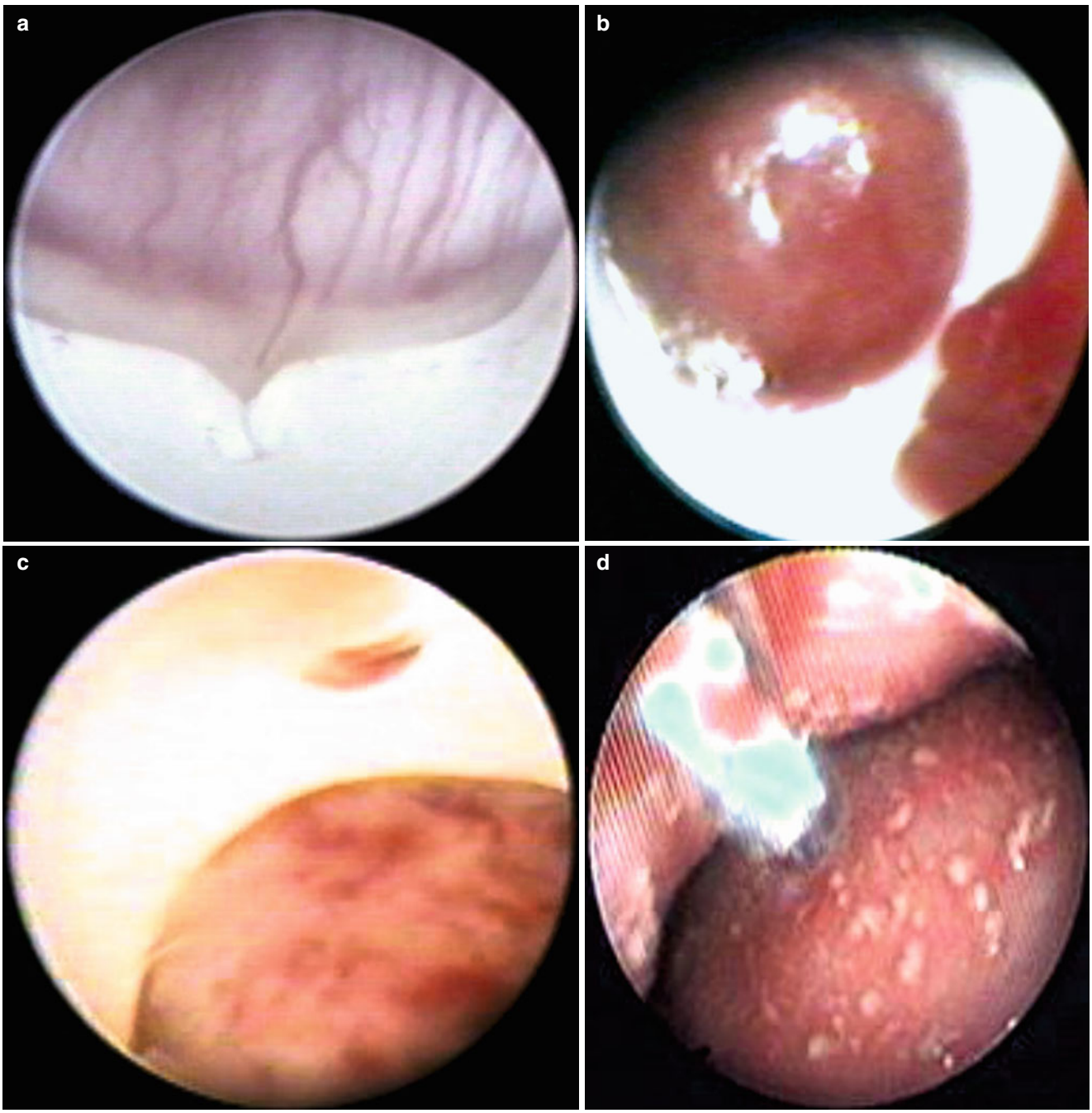

Fig. 34.5 Pericardioscopy demonstrating. (**a**) Normal uninflamed pericardium in hydropericardium. (**b**) Epicardial petechiae in malignant effusion. (**c**) Calcification in tuberculous (epi-) and pericarditis. (**d**) Epicardial biopsy in fibrinous pericarditis (Adapted from Ref. [6])

Pericardial Fluid Analysis

Pericardial fluid should be analysed for protein content, haemoglobin, electrolytes, cardiac enzymes, selected biomarkers or mediators, cytological abnormalities, bacteriology, virology and immunology [2, 4, 5, 9, 11, 27].

The indications in the ESC guidelines [4] for tests have been recently reiterated [2]:

Class I Indication:

- Suspected malignant disease.
- Suspected tuberculosis to assess acid-fast bacilli staining, mycobacterium culture and PCR for TBC; adenosine deaminase (ADA (>40 IU/L) [23]), interferon (IFN)-gamma (≥200 pg/L) and pericardial lysozyme levels (≥6.5 μg/dL) provide additional diagnostic information [27].

- Suspected bacterial infection; at least three cultures of pericardial fluid for aerobes and anaerobes as well as three blood cultures are mandatory.

Class IIa Indication:

- PCR analyses for the RNA or DNA of cardiotropic viruses to discriminate viral from autoreactive pericarditis or a simple hydropericardium
- Tumour markers (e.g. carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), carbohydrate antigens CA 125, CA 72-4, CA 15-3, CA 19-9, CD30, CD25) for additional information on suspected neoplastic pericarditis even when cytology for neoplastic cells is unequivocal
  The combination of epithelial membrane antigen, CEA and vimentin immunocytochemical staining can distinguish reactive mesothelial and adenocarcinoma cells.

Class IIb Indication:

- Analyses of the pericardial fluid specific gravity (>1,015), protein level (>3.0 g/dL; fluid/serum ratio >0.5), LDH (>200 mg/dL; serum/fluid >0.6) and glucose (exudates vs. transudates = 77.9 ± 41.9 vs. 96.1 ± 50.7 mg/dL) can separate exudates from transudates but are not directly diagnostic [4].

Pericardial and Epicardial Biopsy

Pericardial [17] and epicardial biopsy [2] can add, similar to endomyocardial biopsy in inflammatory heart muscle disease or (peri)myocarditis [9], relevant information for the aetiology and pathogenesis of the underlying disease [2, 4]. Since the pericardial effusion in perimyocarditis is by itself diagnostic for inflammation, the biopsy tissue should target on the specific aetiology, either by specific stainings for bacteria (Gram, acid-fast) and fungi (fungal staining) or by PCR for cardiotropic agents (e.g. enterovirus, Coxsackie A9 in particular, echovirus, adenovirus, influenza, hepatitis C, human immunodeficiency, Parvo B19, herpes humanus 6, herpes simplex, Epstein-Barr, cytomegalovirus or Borrelia burgdorferi, Rickettsia burnetii), by the infiltration of malignant cells or specific forms of inflammation (e.g. eosinophilic heart disease, Churg-Strauss syndrome, giant cells, granuloma-forming cells, immune complex binding to cardiac structures) [2, 4, 5, 9].

Intrapericardial Therapy

After the evacuation of the pericardial fluid, saline rinsing and subsequent intrapericardial therapy should follow [12, 15, 19]. For sclerosing treatment we introduce 80 mg gentamicin in the pericardial space. In contrast to tetracyclines, gentamicin neither causes any pain nor does it increase cardiac enzymes. It has additional local bactericidal effects.

Specific intrapericardial and systemic treatment can be derived from Table 34.6.

Table 34.6 Specific intrapericardial and systemic treatment of pericardial effusions

Disease/effusion	Intrapericardial Tx	Systemic Tx	Comment
Bronchus carcinoma PE	Cisplatin 50 mg/m^2 or Thiothepa	Antineoplastic Tx	Prevents recurrence in 85 % of cases
Breast cancer PE	Cisplatin 50 mg/m^2 or Thiothepa	Antineoplastic Tx	Prevent recurrence in 80–85 % of cases
Autoreactive PE	Triamcinolone 500 mg/m^2	NSAIDs for symptomatic Tx or colchicine 0.5 mg 3x/d	Prevents recurrence in 85 % cases
Giant cell PE, sarcoid PE	Triamcinolone 500 mg/m^2 or systemic therapy	Azathioprine 50–100 mg/m^2 initial dose, tapering of to 50 mg for 6 m or more	Life saving is corticoid treatment
Bacterial PE	Intensive rinsing with saline, repeated intrapericardial gentamicin	Systemic i.v. antibiotics (e.g. vancomycin 1 g bid, ceftriaxone 1–2 g bid, and ciprofloxacin 400 mg/day)	Surgical drainage is advisable
Tuberculous PE	Intensive rinsing with saline, repeated intrapericardial gentamicin or surgery	Systemic tuberculostatic antibiotics (e.g. isoniazid 300 mg/day, rifampicin 600 mg/day, pyrazin-amide 15–30 mg/kg/day, and ethambutol 15–25 mg/kg/day). After 2 months most patients can be switched to two-drug regimen (isoniazid and rifampicin) for the total of 6 months	Check for accompanying HIV infection. In this case add systemic antiretroviral therapy, consider corticoid treatment
Uremic PE	Extensive rinsing, triamcinolone 500 mg/m^2		
Fibrotic PE	Urokinase 250–500 U, repeatedly		Only case report available

Adapted from Refs. [2, 5, 12, 15]
Tx treatment, *PE* pericardial effusions

Medical Treatment

In addition to the specific intrapericardial treatment listed in Table 34.6, systemic antineoplastic treatment should accompany malignant pericarditis. Drugs with negative effects on cardiac function or arrhythmogenic potential must be avoided. In tuberculous pericarditis, adequate long-term tuberculostatic treatment is necessary possibly accompanied with corticosteroids in double infections with HIV [2, 4, 28, 29]. In bacterial pericardial effusion, surgical drainage and systemic antibiotic treatment of at least 3–4 weeks are recommended [2, 4].

The mainstay of symptomatic treatment of precordial pain in acute pericarditis are nonsteroidal anti-inflammatory drugs (NSAID) [2, 4, 18, 30–32]. Indomethacin should be avoided in elderly patients due to its flow reduction in the coronaries. Ibuprofen (300–800 mg tid) is preferred for its rare side effects, favourable impact on the coronary flow and the large dose range. Colchicine (0.5 mg bid) can be added to an NSAID. It appears to be effective for the initial attack and the prevention of recurrences [30] as shown in the COPE-Trial [31, 32]. It is well tolerated with fewer side effects than long-term NSAIDs. Systemic corticosteroids should be restricted to connective tissue diseases and autoreactive or uremic pericarditis [4, 5] after exclusion of viral or bacterial genomes. Intrapericardial application of triamcinolone is effective and avoids systemic side effects [15].

When corticosteroids are administered, it is a common mistake to use a dose too low to be effective or to taper the dose too rapidly. The recommended regimen by the ESC guideline is prednisone starting with 1–1.5 mg/kg, for at least 1 month. If patients do not respond adequately, azathioprine (75–100 mg/day) or cyclophosphamide can be added. Corticoids should be tapered over a 3-month period [2]. In chronic or recurrent pericarditis apart from intrapericardial treatment outlined above, balloon pericardiotomy or pericardiectomy may be considered [2]. In all other cases, particularly those in whom the aetiology was not established ("idiopathic"), long-term colchicine is recommended. In patients with "idiopathic" pericarditis who have been treated with oral corticoid therapy, recurrences appear to be more frequent. In these underdiagnosed patients, low-dose oral cortisone prevents recurrences more effectively than high dose [32].

Constrictive and Effusive-Constrictive Pericarditis

In constrictive pericarditis the diastolic expansion of the heart is impaired by a rigid, chronically inflamed or simply thickened, sometimes calcified pericardium. Pericardial thickening may be lacking (*constriction with normal pericardial thickness*) [33]. The predominant form is *chronic constriction* without pericardial effusion. *Effusive-constrictive forms* [34] are equally important. *Acute/subacute forms*, *transient constrictive pericarditis* [35], *epicardial constriction* [36] *and occult/subclinical forms* are rather rare. Additional systolic dysfunction by myocardial fibrosis or atrophy can be found [37, 38]. Symptoms comprise fatigue, peripheral oedema, breathlessness and abdominal swelling and, in decompensated patients, venous congestion, hepatomegaly, pleural effusions and ascites. Physical findings, chest radiography echocardiography [37], computer tomography, magnetic resonance imaging, haemodynamics and endomyocardial biopsy contribute to establishing the diagnosis (for details, see [2]).

Effusive-constrictive pericarditis can be best characterised in patients with tamponade whose elevated intracardiac pressure remains high after removal of pericardial fluid [1, 2, 4, 33, 39–41]. The aetiology is diverse, tuberculosis being a main aetiological finding. The clinical presentation overlaps with other pericardial syndromes. Although a significant number of patients will require pericardiectomy, a certain proportion of patients have a predominantly inflammatory and reversible pericardial reaction, which may be followed up by MRI as they improve with treatment of the underlying cause and use of anti-inflammatory medications before advocating pericardiectomy. Pericardiectomy, if necessary, requires removal of the visceral pericardium in them.

For permanent constriction pericardiectomy is the only treatment.

Perioperative mortality of pericardiectomy is 6–12 % in experienced centres [39–41] but can be up to 40 % if patients with extensive myocardial atrophy/fibrosis are not excluded [38]. If surgery is carried out early, long-term survival after pericardiectomy corresponds to that of the general population [2, 39–41]. Predictors of poor survival are prior radiation, worse renal function, higher pulmonary artery systolic pressure, abnormal left ventricular systolic function, lower serum sodium level and older age [39]. In a controlled study of 143 patients with constrictive tuberculous pericarditis, prednisolone therapy as an adjunct to streptomycin, isoniazid, rifampicin and pyrazinamide reduced the 2-year mortality (4 % vs. 11 %) and decreased the need for repeated pericardial drainage or surgery (21 % vs. 30 %) and the incidence of late constriction (8 % vs. 12 %)[41].

Other Pericardial Diseases

Congenital pericardial cysts are uncommon [42]. *Inflammatory* cysts comprise pseudocysts and encapsulated, loculated pericardial effusions. *Echinococcal cysts* usually originate from ruptured hydatid cysts in the liver or lungs. Most patients with small cysts are asymptomatic, however, but if they become symptomatic, they can be treated by

percutaneous aspiration and ethanol sclerosis [2, 41, 43] or surgical resection. Percutaneous aspiration and instillation of ethanol or silver nitrate after pretreatment with albendazole is effective for echinococcal cysts [43].

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Pulmonary Vascular Disease

35

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Abbreviations

ABG	Arterial blood gas
ACCP	American College of Chest Physicians
ACE	Aangiotensin-converting-enzyme
AHA	American Heart Association
ANCA	Anti-neutrophil cytoplasmic antibody
BNP	Brain natriuretic peptide
CCB	Calcium channel blocker
CHD	Congenital heart disease
CI	Cardiac index
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CTPA	Computed tomography pulmonary angiography
CTD	Connective tissue disease
CTEPH	Chronic thromboembolic pulmonary hypertension
CUS	Compression ultrasonography
CXR	Chest radiograph
DLco	Decreased diffusion capacity for carbon monoxide
dsDNA	Double-stranded DNA
DVT	Deep vein thrombosis
ELISA	Enzyme-linked immunosorbent assay
ERA	Endothelin receptor antagonist
ESC	European Society of Cardiology
ESR	Erythrocyte sedimentation rate
ET-1	Endothelin-1
HIV	Human immunodeficiency virus
INR	International normalized ratio
IPAH	Idiopathic pulmonary arterial hypertension
IPF	Idiopathic pulmonary fibrosis
i.v.	Intravenous
IVC	Inferior vena cava
LMWH	Low molecular weight heparin
LV	Left ventricular
mPAP	Mean pulmonary arterial pressure
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
NIH	National Institute of Health
NT-proBNP	N-terminal proBNP
PaO_2	Arterial oxygen pressure
PAP	Pulmonary arterial pressure
PASP	Pulmonary arterial systolic pressure
PCH	Pulmonary capillary hemangiomatosis
PCWP	Pulmonary capillary wedge pressure
PDE5	Phosphodiesterase type-5
PE	Pulmonary embolism
PEA	Pulmonary endarterectomy
PFO	Patent foramen ovale
PH	Pulmonary hypertension
PVOD	Pulmonary veno-occlusive disease
PVR	Pulmonary vascular resistance
RA	Right atrial
RCT	Randomized control trial
RHC	Right heart catheterization
rt-PA	Recombinant tissue plasminogen activator
RV	Right ventricular
SaO2	Saturation level of oxygen in hemoglobin
s.c.	Subcutaneous
SLE	Systemic lupus erythematosus
SSc	Systemic sclerosis
STEMI	ST-elevation myocardial infarction
TR	Tricuspid regurgitation
UFH	Unfractionated heparin
VKA	Vitamin K antagonist
V/Q	Ventilation/perfusion
VTE	Venous thromboembolism
WHO-FC	World Health Organization functional class
6MWT	Six-minute walk test

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_35,

Introduction

Pulmonary hypertension (PH) and pulmonary embolism (PE) are well-recognized manifestations of pulmonary vascular disease. Significant progress has been made in understanding the pathophysiology of these disorders and in improving diagnostic and therapeutic interventions.

This chapter focuses on the two most widely encountered manifestations of pulmonary vascular disease – PH and PE. In addition to defining these diseases in terms of etiology and epidemiology, this chapter will highlight diagnostic and therapeutic approaches in the context of recently published evidence-based guidelines.

Pulmonary Hypertension

Definition

PH is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest, as measured by right heart catheterization (RHC) [1, 2]. Normal mPAP is considered to be 8–20 mmHg at rest, while the natural history of borderline PH (mPAP of 21–24 mmHg) remains to be determined [1]. PH only documented during exercise is currently not recognized as a valid diagnostic entity.

Classification

While a hemodynamic classification of PH exists (Table 35.1), the clinical classification has changed a number of times since its first endorsement by the World Health Organization (WHO) in 1973 [3]. The 1998 (Evian) and 2003 (Venice) WHO-sponsored meetings radically modified the classification of PH, by classifying the various clinical conditions associated with PH into five groups according to shared pathological, pathophysiological, and therapeutic characteristics [4]. Additional modifications were made to the Evian-Venice classification at the 4th World Symposium on PH held in Dana Point, California, in 2008 (Table 35.2) [5]. Heritable pulmonary arterial hypertension (PAH) includes PAH with germline mutations (mainly bone morphogenetic protein receptor type 2 (*BMPR2*) gene but also activin receptor-like kinase 1) and familial cases with or without identified germline mutations. Associated PAH (APAH) includes conditions with a similar clinical presentation and histological findings to idiopathic PAH (IPAH). Schistosomiasis and chronic hemolytic anemias (e.g., sickle cell disease) have been included in this category due to similar clinical and pathological characteristics.

Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are uncommon but well-recognized causes of PH. They share a number of similarities with PAH, including histological change (intimal fibrosis and medial hypertrophy in the small pulmonary arteries), an often indistinguishable clinical presentation, a similar risk factor profile, e.g., systemic sclerosis (SSc), familial occurrence, and documented cases of *BMPR2* mutations [4–6]. However, there are a number of important reported clinical differences between PVOD and PAH, including crackles and clubbing on physical examination, septal thickening and mediastinal adenopathy on CT scanning, hemosiderin-laden macrophages on bronchoalveolar

Table 35.1 Hemodynamic definitions of pulmonary hypertension[a]

Definition	Characteristics	Clinical group(s)[b]
Pulmonary hypertension (PH)	mPAP ≥ 25 mmHg	All
Precapillary PH	mPAP ≥ 25 mmHg	1. PAH
	PCWP ≤ 15 mmHg	3. PH due to lung diseases
	CO normal or reduced[c]	4. CTEPH
		5. PH with unclear and/or multifactorial mechanisms
Postcapillary PH	mPAP ≥ 25 mmHg	2. PH due to left heart disease
	PCWP > 15 mmHg	
	CO normal or reduced[c]	
Passive	TPG ≤ 12 mmHg	
Reactive (out of proportion)	TPG > 12 mmHg	

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mPAP mean pulmonary arterial pressure, *PCWP* pulmonary capillary wedge pressure, *CO* cardiac output, *CTEPH* chronic thromboembolic pulmonary hypertension, *TPG* transpulmonary pressure gradient, *mPAP* mean PCWP
[a]All values measured at rest
[b]According to Dana Point classification Table 35.2
[c]High CO can be present in cases of hyperkinetic conditions such as systemic-to-pulmonary shunts (only in the pulmonary circulation), anemia, and hyperthyroidism

lavage, a lower DLCO and PaO_2, and poor clinical outcomes following treatment with PAH-specific therapy [6]. Due to these shared similarities as well as distinct differences, PVOD/PCH is now classified as group 1, a distinct but not completely separate category from PAH [5].

Another notable change in the current classification concerns chronic thromboembolic pulmonary hypertension (CTEPH). This is a frequent cause of PH, occurring in up to 4 % of patients after an acute PE [7]. CTEPH was previously classified into proximal (accessible to pulmonary endarterectomy surgery (PEA)) and distal groups based on the level of obstruction of the pulmonary arterial vessels. However, this distinction may be difficult to elucidate in clinical practice, so CTEPH has been reclassified as a single category (group 4) (Table 35.2). The heterogeneous groups of diseases that cause PH by unclear and/or multifactorial mechanisms are detailed in group 5. These include hematological disorders (e.g., myeloproliferative disorders, splenectomy), systemic disorders (e.g., sarcoidosis, vasculitis), metabolic disorders (e.g., Gaucher disease, thyroid disorders), and other causes (e.g., fibrosing mediastinitis, chronic renal failure on dialysis) [5].

Table 35.2 Dana point (2008) clinical classification of pulmonary hypertension

1. Pulmonary arterial hypertension (PAH)
1.1 Idiopathic
1.2 Heritable
1.2.1 BMPR2
1.2.2 ALK-1, endoglin (with or without HHT)
1.2.3 Unknown
1.3 Drugs and toxins induced
1.4 Associated with (APAH)
1.4.1 Connective tissue diseases
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.4.6 Chronic hemolytic anemia
1.5 Persistent pulmonary hypertension of the newborn
1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
2. Pulmonary hypertension due to left heart disease
2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed obstructive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension
5. PH with unclear and/or multifactorial mechanisms
5.1 Hematological disorders: myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, CRF on dialysis

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PAH pulmonary arterial hypertension, *BMPR2* bone morphogenetic protein receptor, type 2, *ALK-1* activin receptor-like kinase 1 gene, *HHT* hereditary hemorrhagic telangiectasia, *APAH* associated pulmonary arterial hypertension, *HIV* human immunodeficiency virus, *PH* pulmonary hypertension, *CRF* chronic renal failure

Epidemiology

The prevalence of PH in the population appears to vary according to etiology. Based on epidemiological data from recent registries, the prevalence of PAH in the general population is estimated to be in the range of 15–50 cases/million adults in the population [8, 9]. In the French national registry, IPAH (39.2 % of all causes of PAH) was the most common type of PAH, and IPAH was more prevalent in women [8]. Connective tissue diseases (CTD) were the most cause of APAH (15.3 %).

A meta-analysis of patients with SSc showed that 9 % of patients had precapillary PH with two-thirds having PAH and to the remaining third having PH associated with interstitial lung disease [10]. Congenital heart disease (CHD) is associated with the development of PAH, especially in those who have not had surgical correction. Results from a pediatric PH registry showed that 36 % of patients with PAH had CHD and that 93 % of these patients had systemic-to-pulmonary shunts [11]. Eisenmenger's syndrome is a common cause of PAH associated with congenital systemic-to-pulmonary shunts.

Left heart disease is the most frequent cause of PH, and the prevalence of PH in patients with chronic heart failure increases with progression of functional class impairment [5]. Up to 60 % of patients with severe left ventricular systolic (LV) dysfunction and up to 70 % of patients with isolated LV diastolic dysfunction have evidence of PH [12], and most patients with severe mitral valve disease or symptomatic aortic stenosis will have PH [13].

The true prevalence of PH associated with lung disease is unknown. However, PH appears to be most prevalent in patients with advanced lung disease. While a number of definitions of PH have been used in different studies, using the current hemodynamic definition of PH, 36 % of patients

Table 35.3 World Health Organization functional classification of pulmonary hypertension

Class I	Patients in with pulmonary hypertension, but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope
Class II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. Patients are comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. Patients are comfortable at rest, but less than ordinary physical activity cause undue dyspnea or fatigue, chest pain, or near syncope
Class IV	Patients with pulmonary hypertension who have an inability to perform any physical activity without symptoms. Patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present at rest, and discomfort is increased by any physical activity

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with advanced COPD and over 30 % of patients with advanced IPF were found to have PH [14, 15].

Diagnosis

Clinical Presentation

The earliest symptoms of PH (exertional dyspnea, fatigue, and lethargy) are caused by an inability to increase cardiac output (CO) with exercise. As the disease progresses and right ventricular (RV) failure develops, exertional chest pain (usually related to RV subendocardial hypoperfusion), syncope, and peripheral edema may develop. An enlarged pulmonary artery (especially when the diameter is ≥40 mm) may contribute to anginal symptoms by compressing the left main coronary artery or may cause hoarseness by compressing the left recurrent laryngeal nerve (Ortner's syndrome). Patients may experience anorexia and right upper quadrant abdominal pain due to hepatic congestion. Other less common symptoms include cough and hemoptysis. The degree of symptomatic involvement can be assessed by using the WHO functional class system, which grades symptoms I through IV (Table 35.3).

A thorough physical examination may provide information on the severity of the underlying PH. An accentuated pulmonary component of the second heart sound provides evidence for increased pulmonary arterial pressure (PAP), while further clinical signs can be elucidated as RV hypertrophy, dilation and RV failure develops (Table 35.4).

Physical examination may also suggest the underlying cause of the PH. For example, digital clubbing may suggest CHD, pulmonary venopathy (e.g., PVOD), or liver disease. SSc may be identified by cutaneous telangiectasias, Raynaud's phenomenon, and sclerodactyly. The presence of fine crackles may suggest pulmonary parenchymal disease, while significant systemic hypertension may suggest underlying obstructive sleep apnea or LV diastolic dysfunction. Pulmonary vascular bruits may suggest CTEPH, while splenomegaly, palmar erythema, icterus, and spider nevi are suggestive of underlying portal hypertension secondary to liver disease.

Electrocardiogram

ECG is not sensitive and/or specific enough to be used as a screening tool for detecting PH [17]. However, the majority of patients with PH have an abnormal ECG which often supports a diagnosis of PH by demonstrating RV hypertrophy, RV strain, and right atrial (RA) dilatation (p pulmonale).

Chest Radiograph

The chest radiograph (CXR) is frequently abnormal (up to 90 % of cases with IPAH) in PH [18]. Typical findings include enlarged central pulmonary arteries with attenuation of peripheral blood vessels. RV enlargement and RA dilatation may be seen with more advanced disease. The CXR may also indicate the underlying etiology of PH, e.g., parenchymal changes suggestive of interstitial lung disease.

Pulmonary Function Tests

Pulmonary function testing may identify underlying lung disease causing or contributing to PH. Interstitial lung disease with PH may be suggested by a low DLCO and reduced lung volumes, while irreversible airway obstruction with increased residual volume and reduced DLCO is suggestive of chronic obstructive pulmonary disease (COPD). It should also be noted that PAH can itself cause a mild to moderate reduction in lung volumes and a reduced DLCO [2].

Arterial Blood Gas Testing and Polysomnography

Arterial oxygen tension is usually normal or slightly reduced at rest in PAH, and arterial carbon dioxide tension is usually decreased due to alveolar hyperventilation. This contrasts with advanced lung diseases associated where hypoxia (e.g., COPD, interstitial lung disease) and hypercarbia (e.g., COPD, obesity hypoventilation syndrome) may be seen. Nocturnal hypoxemia is common in patients with PAH. Therefore, overnight oximetry may identify those who require nocturnal supplemental oxygen therapy or identify those who should be referred for polysomnography for possible sleep-related breathing disorders.

V/Q Scan

A ventilation/perfusion (V/Q) scan is recommended to exclude CTEPH, which is a potentially curable form of PH

Table 35.4 Features of the physical examination pertinent to the evaluation of pulmonary hypertension

Sign	Implication
Neck veins	
Increased jugular "a" wave	Poor RV compliance
Increased jugular "v" waves	Tricuspid regurgitation
Distension of jugular veins	RV dysfunction or tricuspid regurgitation or both
Palpation	
Left parasternal lift	High RV pressure and hypertrophy present
Hepatomegaly	RV dysfunction or tricuspid regurgitation or both
Pulsatile liver	Tricuspid regurgitation
Hepatojugular reflux	High central venous pressure
Peripheral edema (in 32 %)	RV dysfunction or tricuspid regurgitation or both
Ascites	RV dysfunction or tricuspid regurgitation or both
Low blood pressure, diminished pulse pressure, cool extremities	Reduced cardiac output, peripheral vasoconstriction
Auscultation	
Accentuated pulmonary component of S_2 (audible at apex in over 90 %)	High pulmonary pressure increases force of pulmonic valve closure
Early systolic click	Sudden interruption of opening of pulmonary valve into high-pressure artery
Midsystolic ejection murmur	Turbulent transvalvular pulmonary outflow
Right ventricular S_4 (in 38 %)	High RV pressure and hypertrophy present
Holosystolic murmur that increases with inspiration	Tricuspid regurgitation
Diastolic murmur	Pulmonary regurgitation
RV S_3	RV dysfunction

Adapted from McLaughlin et al. [16]. With permission from Elsevier
PH pulmonary hypertension, *RV* right ventricular

[2]. A normal or low-probability V/Q scan excludes CTEPH with a sensitivity and specificity ≥90 % [19]. Unmatched and non-segmental perfusion defects can also be seen in a variety of other conditions, e.g., sarcoidosis. CT angiography is recommended when the V/Q scan is indeterminate or when perfusion defects are seen.

CT Imaging

Contrast CT pulmonary angiography (CTPA) is helpful in determining the extent of pulmonary arterial disease in CTEPH (e.g., complete obstruction, stenoses, and strictures) and in assessing whether the disease is surgically accessible [2]. However, formal pulmonary angiography is still required to determine the feasibility of surgery [20]. It may also be helpful in the evaluation of pulmonary vasculitis and arteriovenous malformations. High-resolution CT thorax should be performed when there is clinical suspicion of underlying parenchymal lung disease, such as COPD or interstitial lung disease. It may also be useful in identifying rarer pulmonary disorders, such as PVOD.

Cardiac MRI

Cardiac magnetic resonance imaging (MRI) accurately assesses the size, morphology, and function of the RV. It enables cardiac parameters such as stroke volume, CO, RV mass, and distensibility of the PA to be noninvasively assessed. Decreased stroke volume, increased RV end-diastolic volume, and decreased LV end-diastolic volume measured at baseline have all been shown to be associated with poorer prognosis in PAH [21].

Laboratory Tests

The diagnostic evaluation of all patients with suspected PH should include routine biochemistry, hematology, thyroid function tests, and HIV serology. Serological testing is useful in the diagnosis of CTD, and antinuclear antibodies, dsDNA, rheumatoid factor, and ANCA tests are recommended. As SSc has a high prevalence of PAH, anti-centromere (limited cutaneous SSc) and anti-DNA topoisomerase (diffuse cutaneous SSc) antibody levels should be performed, and elevated anti-U3-RNP antibody levels are associated with increased prevalence of PAH. Anticardiolipin antibodies should be performed in suspected cases of SLE and as part of a thrombophilia screen in cases of CTEPH. Liver function tests are required in all cases, and abnormalities may warrant further investigation with hepatitis serology and an abdominal ultrasound and Doppler of the portal vein.

Echocardiogram

Transthoracic echocardiography should be performed when PH is suspected. Doppler echocardiography can provide information on the anatomical and physiological sequelae of PH, such as an estimate of RV systolic pressure and RV structure. Common echocardiographic findings in PAH include RA and RV enlargement, flattening of the interventricular septum, and underfilled left heart chambers [16]. The presence of one or

more of these findings or an estimated RV systolic pressure >40 mmHg generally warrants further evaluation in patients with unexplained dyspnea [16]. PAP estimations are based on the peak velocity of the jet of tricuspid regurgitation (TR). The TR signal can be enhanced with contrast (e.g., agitated saline or encapsulated microbubble agents) where the peak TR velocity is difficult to measure [16].

Transthoracic echocardiography can also be used to identify the cause of PH. Congenital or acquired valvular heart disease, LV systolic or diastolic dysfunction (e.g., hypertensive heart disease), and CHD with shunt (e.g., VSD) may all be identified by echocardiography. Findings suggestive of specific etiologies include left-sided valve changes (SLE or anorexigen use) or pericardial effusions (CTD) [16].

PH is considered "likely" in patients with a TR velocity >3.4 m/s and a resting PASP > 50 mmHg (with or without additional echocardiographic variables suggestive of PH) and "unlikely" in patients with a TR velocity ≤2.8 m/s, a PASP ≤36 mmHg, and no additional echocardiographic variables suggestive of PH [2]. However, echocardiography has been shown to both underestimate and overestimate PAP measurements, and its results should be interpreted with caution [22].

Right Heart Catheterization and Vasoreactivity Testing

RHC is required to definitively diagnose PH, determine the severity of the disease, and to test for vasoreactivity of the pulmonary circulation [2, 16]. Accurate pulmonary capillary wedge pressure (PCWP) measurements (a surrogate for left atrial pressure) are essential for characterizing PH due to left heart disease, and direct measurement of LV end-diastolic pressure by left heart catheterization is recommended in patients in whom left heart disease is the likely etiology [16]. CO must be measured by the Fick method in the presence of a systemic-to-pulmonary shunt [2].

Vasoreactivity testing should be performed in patients suspected of having PAH at the time of diagnostic RHC [2, 16]. The acute vasodilator response identifies those likely to have a sustained response to treatment with calcium channel blockers and a better long-term prognosis [23]. The best agent for vasodilator testing is inhaled nitric oxide [23]. A positive acute response is defined as a reduction of mPAP ≥10 mmHg to reach an absolute value of mPAP ≤40 mmHg with an increased or unchanged CO [23]. Unfortunately, less than 10 % of patients with IPAH will meet these criteria, and the number is lower again with other forms of PAH. Acute vasodilator testing is not recommended in clinical groups 2, 3, 4, and 5 [2].

Diagnostic Algorithm

The key to the current diagnostic algorithm in PH is to firstly exclude the common causes of PH (clinical groups 2 and 3) (Fig. 35.1). If these diseases are not found, or if the level of PH seems "out of proportion" to their severity, then groups 4, 5, and 1 should be considered [2].

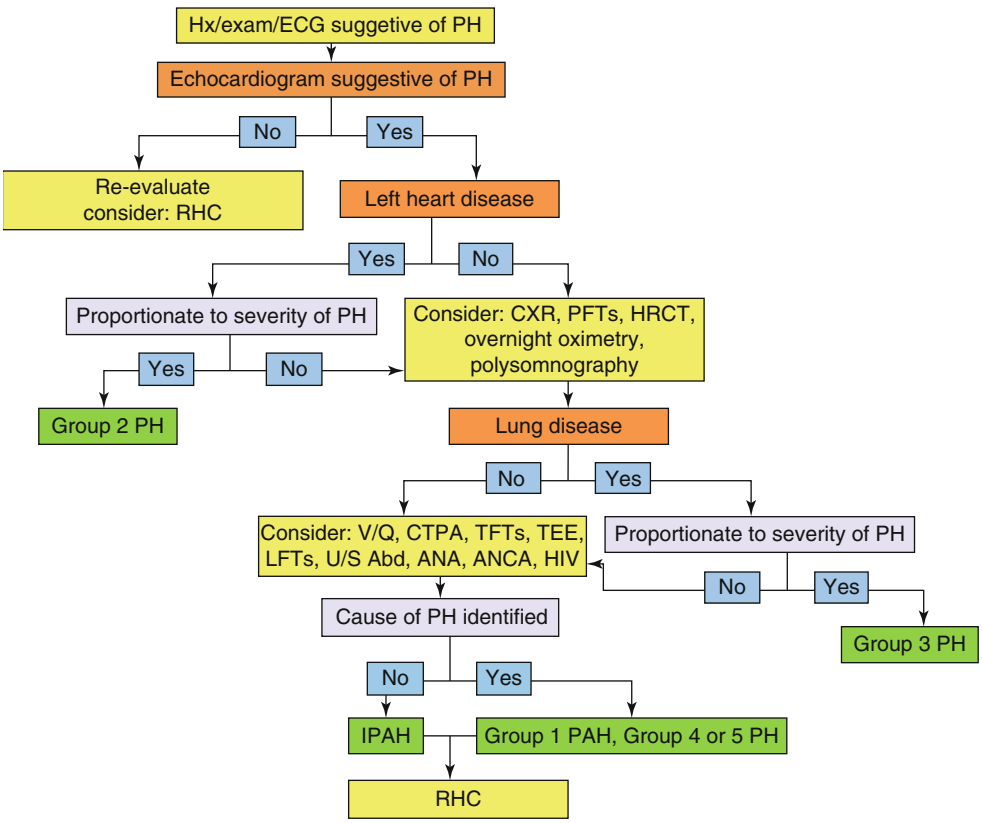

Fig. 35.1 Suggested algorithm for evaluation of suspected pulmonary hypertension. *Hx* clinical history, *Exam* clinical examination, *ECG* electrocardiogram, *PH* pulmonary hypertension, *CXR* chest radiograph, *PFTs* pulmonary function tests, *V/Q* ventilation/perfusion scintigraphy, *CTPA* computed tomography pulmonary angiography, *TFTs* thyroid function tests, *TEE* transesophageal echocardiogram, *LFTs* liver function tests, *U/S abd* ultrasound of the abdomen, *ANA* antinuclear antibody, *ANCA* anti-neutrophil cytoplasmic antibody, *HIV* human immunodeficiency virus serology, *IPAH* idiopathic pulmonary arterial hypertension, *RHC* right heart catheterization

Management

The management of PH is based on treatment of the underlying cause, supportive and general measures, and the use of targeted PH therapies in appropriate patients. A baseline assessment of functional (e.g., 6-mi walk test (6MWT), WHO-FC) and hemodynamic impairment (e.g., mPAP, pulmonary vascular resistance (PVR)) is performed so that response to treatment can be assessed. Ongoing management is guided by regular patient evaluation (e.g., clinical assessment, 6MWT) [2].

Primary Therapy

The first step in the management of PH is to identify and treat the underlying cause (i.e., primary therapy). Clinical improvement has been reported in patients with PAH associated with SLE or mixed CTD treated with intensive immunosuppressive therapy [24]. Management of PH due to left heart disease (group 2) requires optimal medical treatment (e.g., ACE inhibitors, β-adrenoceptor blockers, diuretics, nitrates, inotropic agents) or interventional approaches (e.g., valvular surgery, resynchronization therapy). Optimization with bronchodilators and corticosteroids, as well as long-term supplemental oxygen therapy, is recommended for PH associated with underlying hypoxemic lung disease (group 3) [2]. A survival benefit has been demonstrated with long-term oxygen therapy in COPD [25]. PEA in the setting of experienced multidisciplinary care is the treatment of choice for CTEPH (group 4) [2, 16]. Patients with proximal organized thrombi have the most successful outcomes, and effective procedures may produce a near normalization of pulmonary hemodynamics [2].

General Measures

Regardless of the underlying etiology, a multidisciplinary approach to care is recommended for patients with PH. As with any chronic disease, advice should be given to assist the patient with their daily functioning. Patients should also be advised to avoid potentially precipitating factors such as tobacco smoking and drug use (e.g., anorexigen use). Appropriate and timely referral to a psychologist or psychiatrist is recommended in cases of anxiety or depression. Patients should be vaccinated against influenza and pneumococcal pneumonia [2]. Although results from a recent multinational registry show improved outcomes in treated patients with PAH [26], maternal mortality rates of 30 % (IPAH) to 56 % (PH) have been reported [27]. Therefore, current guidelines recommend that pregnancy is avoided in PAH, and appropriate methods of birth control should be utilized [2, 16]. In-flight supplemental oxygen should be considered in patients with a $PaO_2 < 60$ mmHg (8 kPa) and in those patients with WHO-FC III or IV symptoms [2]. If possible, epidural anesthesia should be used for elective surgical procedures [2].

Supportive Therapy

The following therapies should be considered in all patients with PH.

Oral Anticoagulants

Patients with all forms of PH are at increased risk of thrombosis and thromboembolism as a result of RV dilatation, reduced CO, venous stasis, and reduced mobility. PAH is also associated with thrombotic lesions, endothelial dysfunction, vasoconstriction, and structural remodeling of the pulmonary artery. It is therefore recommended that oral anticoagulation is considered in all patients with IPAH, heritable PAH, and PAH due to anorexigens [2, 28]. Oral anticoagulation should also be considered when there are concomitant risk factors for thromboembolism (e.g., atrial fibrillation), in CTEPH, in specific clinical diseases (e.g., antiphospholipid syndrome), or in PAH patients receiving intravenous prostaglandins [2, 16]. Warfarin is the anticoagulant of choice, and the target INR is 1.5–2.5 (North America) and 2.0–3.0 (Europe) [2, 16]. The potential risks and benefits of anticoagulation should always be considered prior to commencement of therapy, especially when there is an increased risk of hemorrhage (e.g., esophageal varices secondary to portal hypertension).

Diuretics

Diuretics are used to treat PH-associated RV volume overload, which commonly manifests as peripheral edema and ascites [2, 16]. Serum electrolytes and renal function should be closely monitored. Intravenous dopamine or dobutamine can help where renal function is poor and right heart failure progressive.

Supplemental Oxygen Therapy

Long-term data on the effects of supplemental oxygen therapy for PAH does not exist. However, as hypoxia is a potent pulmonary vasoconstrictor, it is generally accepted that continuous long-term oxygen therapy should be used in hypoxemic patients to achieve a $PaO_2 > 60$ mmHg (8 kPa) or a $SaO_2 > 90$ % [2, 16]. Supplemental oxygen therapy should be used to correct resting, ambulatory, or nocturnal hypoxemia in all patients with PH. However, nocturnal oxygen therapy has not been shown to modify the natural history of patients with Eisenmenger's syndrome [29].

Digoxin

Digoxin can be considered as part of the medical management of patients with symptomatic LV systolic failure [30]. However,

while digoxin can acutely increase CO in IPAH, its long-term efficacy is uncertain. Digoxin may be considered in PAH patients who develop RV failure and low CO and to slow ventricular rate in patients with atrial tachyarrhythmias [2, 16].

Exercise Training

Exercise training and rehabilitation have been shown to have beneficial effects (e.g., hemodynamic function and exercise tolerance) in patients with underlying cardiac and pulmonary disease, and it is recommended as an adjunctive therapy for ambulatory symptomatic heart failure patients [30]. Pulmonary rehabilitation has been shown to improve dyspnea, health-related quality-of-life outcomes, health-care utilization, and psychosocial outcomes in patients with COPD [31]. Exercise training (as an add-on to targeted medical therapy) has been shown to improve exercise capacity, quality of life, peak oxygen consumption, and WHO functional class in patients with different forms of PH [32]. Patients should be carefully supervised, and excessive physical activity leading to distressing symptoms should be avoided [2].

Advanced Therapies

Significant progress has been made in recent years in the treatment of PAH. Given the complexity in identifying suitable patients and managing treatment, it is advised that PAH-specific therapy should be administered by suitably experienced clinicians in specialized centers.

Patient Selection

PAH therapy is indicated in WHO-FC II–IV patients with PAH (group 1) who do not respond to vasoreactivity testing or fail to achieve a sustained adequate response to calcium channel blocker (CCB) therapy [2, 28]. The use of PAH-specific drugs is not recommended in patients with PH secondary to left heart disease (group 2) [2]. However, PAH-specific therapy has been shown to produce some improvement in persistent PH following valve replacement or reconstruction for mitral valve disease [13]. Therefore, in certain circumstances where a precapillary disease component is present, PAH-specific therapy may be considered following evaluation in a specialized center and after a detailed diagnostic work-up [33].

Similarly, the general use of PAH-specific drugs is not recommended in patients with PH secondary to lung disease (group 3) [2, 16], as PAH-specific therapies may worsen hypoxemia by increasing V/Q mismatch through nonselective vasodilatation [16]. However, PAH-specific therapies have been shown to improve clinical function in selected patients with PH secondary to lung disease [34]. Current guidelines therefore suggest that patients with "out of proportion" PH (i.e., dyspnea insufficiently explained by the extent of lung mechanical disturbances and mPAP ≥40–45 mmHg at rest) due to lung disease should be referred to specialized centers and considered for enrollment in clinical trials of PAH-specific therapies [2]. PAH-specific drug therapy may also have a role in selected CTEPH (group 4) patients, such as those not considered candidates for PEA, to improve hemodynamics preoperatively or to treat symptomatic or recurrent PH postoperatively [2]. PAH-specific therapy has also been shown to improve clinical and hemodynamic function in small studies of sarcoidosis (group 5) patients, but further trials are needed to assess this role.

Calcium Channel Blockers

CCBs improve functional status, hemodynamics, and survival, in a small number of patients with group 1 PAH with a positive response to vasoreactivity testing [23]. Low initial doses should be titrated upwards with caution, and abrupt discontinuation can lead to severe rebound PH. Diltiazem is an effective agent for patients with a relative tachycardia at baseline, while nifedipine or amlodipine are also options. Patients should be monitored for systemic hypotension and peripheral edema, and a RHC should be performed at 3–4 months to evaluate the hemodynamic response to treatment. Additional PAH therapy should be considered in patients who have an inadequate response (persistent WHO-FC III or IV symptoms or insufficient hemodynamic improvement) to CCB treatment [2].

PAH-Specific Therapy

Endothelin Receptor Antagonists (ERAs)

Endothelin-1 (ET-1) is a potent pulmonary vasoconstrictor and smooth muscle mitogen that binds to endothelin-A and endothelin-B receptors. ET-1 is increased in PAH patients and its level correlates with disease severity. Selective and nonselective receptor antagonists appear to have comparable efficacy.

Bosentan and Ambrisentan

Bosentan is an oral nonselective endothelin receptor antagonist that improves exercise capacity, hemodynamic function, dyspnea, and WHO-FC in patients with IPAH and APAH (SSc) [35]. Bosentan has also demonstrated efficacy in Eisenmenger's syndrome. Ambrisentan is an oral selective endothelin-A receptor antagonist. Two large randomized control trials (ARIES 1 and 2) showed that ambrisentan improved symptoms, exercise capacity, hemodynamics, and time to clinical worsening in patients with IPAH and APAH (CTD and HIV infection) [36].

ERAs are generally well tolerated. Their most notable adverse effect is hepatotoxicity. Sitaxentan, a selective ERA, was withdrawn in 2010 following cases of fatal hepatotoxicity [37]. Dose-dependant elevations of hepatic transaminase levels have been reported in some patients treated with bosentan. Peripheral edema is the commonest adverse effect of ERAs, and this is managed with diuretics. ERAs are also potent teratogens, and female patients should be counseled

regarding contraception. Macitentan, a new ERA, recently delayed time to clinical worsening in a large PAH trial and is a potential future therapy.

Phosphodiesterase Type-5 Inhibitors (PDE5 Inhibitors)

PDE5 inhibitors act by inhibiting the cGMP-degrading PDE5 enzyme (which is found in substantial amounts in the pulmonary vasculature), thereby prolonging the vasodilator effects of nitric oxide.

Sildenafil and Tadalafil

Sildenafil, an orally active selective PDE5 inhibitor, was shown to improve exercise capacity, WHO-FC, and hemodynamic function in symptomatic patients with PAH [38]. An uncontrolled open-label 3-year extension of this study (SUPER-2) showed that the drug was generally well tolerated, with improved or maintained WHO-FC (60 %) and exercise capacity (46 %) [39].

Tadalafil is an oral selective PDE5 inhibitor. In the PHIRST study, tadalafil (40 mg) was shown to be well tolerated and to improve exercise capacity, quality of life, and time to clinical worsening [40]. PDE5 inhibitors are generally well tolerated, with headache, myalgia, and flushing the most common side effects. Vardenafil is another PDE5 inhibitor which has also been studied in PAH.

Prostanoids

Prostacyclin is a potent endogenous vasodilator that inhibits platelet aggregation. Stable prostacyclin analogues known as "prostanoids" have been developed for use in PAH.

Epoprostenol

Intravenous (i.v.) epoprostenol (synthetic prostacyclin) improves symptoms, hemodynamic function, and exercise capacity in IPAH [41] and in patients with PAH associated with the SSc spectrum of disease [42]. Furthermore, it improved survival in patients with severe IPAH [41] and can serve as a bridge to lung transplantation. Epoprostenol has a short half-life (3–5 min). It is therefore administered continuously through a permanently implanted central venous catheter using an infusion pump. Doses are increased incrementally as tolerated.

Treprostinil

Treprostinil is a synthetic long-acting tricyclic benzidine analogue. It can be administered by the subcutaneous (s.c.), i.v., and inhalational routes. A large RCT showed that s.c. treprostinil improved symptoms, exercise capacity, and hemodynamic function in patients with IPAH and APAH, with the greatest improvements seen in sicker patients and at higher doses [43]. Sustained improvement in exercise capacity and hemodynamics was also seen in IPAH and CTEPH patients treated with s.c. treprostinil over 26 months [44]. Patients can be safely transitioned from epoprostenol to either i.v. or s.c. treprostinil for ease of administration [45]. Inhaled treprostinil is also approved for group 1 PAH patients with WHO-FC III symptoms in the United States.

Iloprost

Iloprost is a chemically stable prostacyclin analogue that can be administered via the oral, i.v., and inhalational routes. The effects of oral iloprost have not been adequately assessed in PAH, but i.v. administration appears to be as effective as epoprostenol in PAH and CTEPH [46]. Inhaled iloprost improved exercise capacity, hemodynamic function, WHO-FC, and quality of life in a RCT (AIR study) of patients with severe PAH and CTEPH [47]. This treatment requires frequent administration (6–9 inhalations/day).

Adverse events reported with prostanoid use include headache, flushing, diarrhea, jaw pain, and arthralgia. Patients should also be monitored for complications associated with the drug delivery system, such as local infection, sepsis, malfunction, or obstruction. Abrupt interruption of infusions should be avoided as rebound PH and associated clinical deterioration can occur [2].

Combination Therapy

In the PACES trial, the addition of sildenafil to long-term i.v. epoprostenol therapy was shown to improve exercise capacity, quality of life, hemodynamic function, and time to clinical worsening in patients with group 1 PAH [48]. In the BREATHE-2 study, the addition of bosentan to PAH patients already receiving epoprostenol produced nonstatistically significant improvements in hemodynamic status, exercise capacity, and WHO-FC after 16 weeks of treatment [49]. The TRIUMPH study demonstrated that the addition of inhaled treprostinil to symptomatic PAH patients already treated with oral bosentan or sildenafil improved exercise capacity and quality of life [50], with the treatment benefit persisting up to 24 months [51].

The effect of combining inhaled iloprost and bosentan is less clear. In the STEP-1 study, combination therapy produced only a marginal increase in exercise capacity and failed to produce an improvement in hemodynamic function [52]. Time to clinical worsening was improved however. The COMBI trial was stopped early as no beneficial effects were observed with this form of combination therapy [53]. A subgroup analysis of combination tadalafil and bosentan therapy in the PHIRST study showed improvements in exercise capacity of borderline significance [40]. Combination therapy with tadalafil and ambrisentan is currently being evaluated in a RCT (AMBITION study).

Choice of Therapy and Patient Follow-Up

Given the increasing number of available PAH-specific therapies, selection of appropriate therapy may be complex. A suggested approach to treating PH is shown in Fig. 35.2. Combination therapy is reserved for patients with PAH who are optimized on background therapy and who have an inadequate

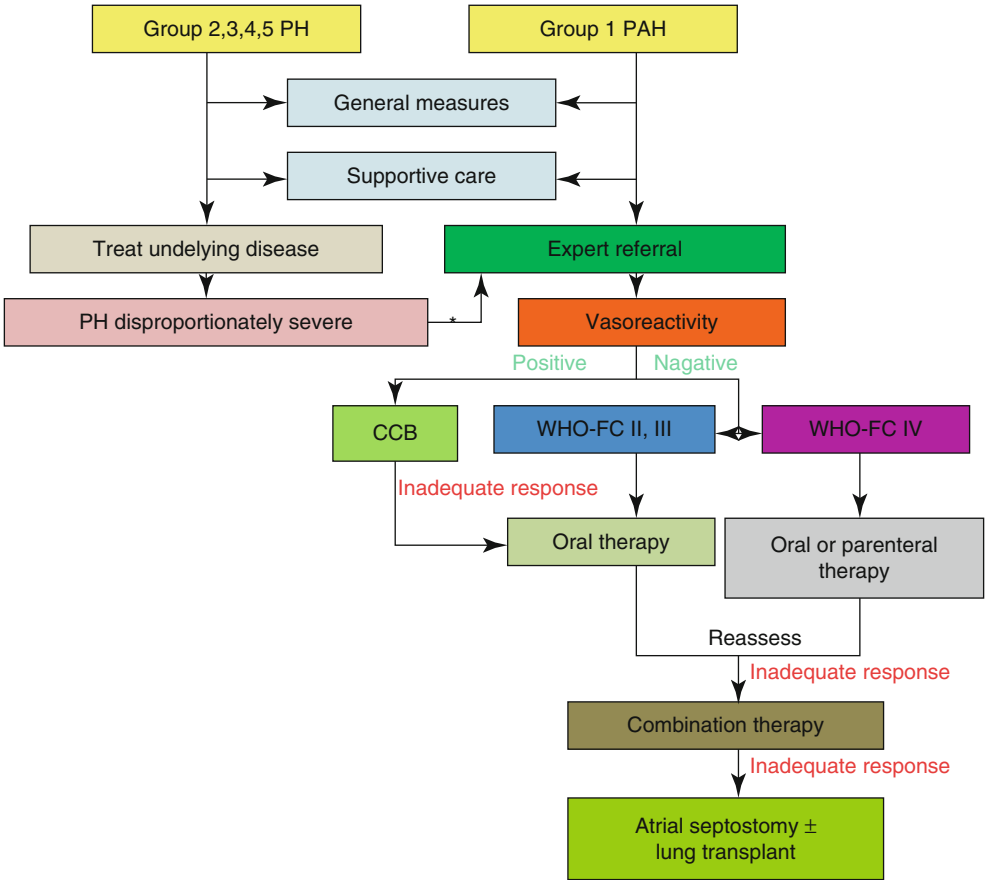

Fig. 35.2 Suggested approach to treatment of pulmonary hypertension. See Table 35.2 for classification of pulmonary hypertension; General measures that may be considered include smoking cessation, influenza and pneumococcal vaccinations, psychosocial support, and pregnancy avoidance in appropriate cases; Supportive care that may be considered includes oral anticoagulants, diuretics, supplemental oxygen therapy, digoxin, and supervised rehabilitation/exercise training; *Patients with "out of proportion" PH following treatment of underlying diseases may be referred to expert centers for consideration for enrolment in trials of PAH-specific therapies; *PAH* pulmonary arterial hypertension, *Vasoreactivity* vasoreactivity testing during right heart catheterization, *CCB* calcium channel blocker, *WHO-FC* World Health Organization functional class (see Table 35.3); Oral, parenteral, and combination therapy refers to PAH-specific agents (Adapted from Galie et al. [2]. With permission from Oxford University Press)

response to PAH-specific monotherapy [2]. Patients with PH who are treated with PAH-specific agents should be followed-up on a frequent basis in order to evaluate efficacy of treatment and potential adverse events. Patients who are clinically unstable and have evidence of RV failure should be evaluated on a 1- to 3-month (or more frequent) basis [2, 16].

Atrial Septostomy

An atrial septostomy creates a right-to-left interatrial shunt, thereby decompressing the right heart chambers, increasing LV preload and CO, and reducing the likelihood of syncope. Graded balloon dilatation is regarded as the procedure of choice. Atrial septostomy is considered in severe intractable RV failure, despite maximal medical therapy (including PAH-specific agents and inotropes) [2, 16]. Procedural mortality can be significant, although this varies between centers. Atrial septostomy has been shown to improve functional class, hemodynamic function, and exercise capacity and improve survival in PAH patients with severe disease [54]. It can also be used as a bridge to lung transplantation.

Transplantation

Organ transplantation is considered in suitable patients with advanced disease refractory to medical therapy. Patient selection, timing of referral for transplant, type of organ and procedure (heart and/or lung, single or double lung), and outcome will depend on the underlying etiology of the PH. The latest international registry figures show that 3.2 % of all adult lung transplants were performed for IPAH, with over 98 % of these being bilateral lung transplants with a 5-year survival post procedure of approximately 50 % [55]. By way of contrast, COPD accounts for 34.6 % of all adult lung transplants, with a similar 5-year survival and 66.5 % being bilateral transplants [55]. Hemodynamic guidelines suggest that lung transplantation should be considered in patients failing maximal medical therapy with a CI <2 l/min/m^2 and/or a RA pressure >15 mmHg [56].

Prognosis

The long-term outcome of PAH has improved in recent years. This is likely to be due to earlier diagnosis, targeted PAH therapies, and management in specialized centers. Results from the first NIH registry during the 1980s showed a 5-year survival of 34 % for IPAH [57]. This contrasts with a more recent 5-year survival figure of 55 % in patients treated with i.v. epoprostenol [58]. Factors associated with poor outcome include WHO-FC IV, decreased exercise capacity, elevated RA pressures, elevated BNP levels, pericardial effusion on echocardiogram, and PAH associated with CTD or portal hypertension [57, 59]. The outcome of patients with PH from other disease processes is more unclear and often depends on the severity of the PH and the underlying condition.

Pulmonary Embolism

PE is a relatively common and often fatal cardiopulmonary disease. Although it refers to obstruction of the pulmonary arterial vasculature by material that originates elsewhere in the body (i.e., thrombus, air, fat, and tumor), the vast majority of PE cases are caused by the embolization of thrombi originating in the lower limbs. The clinical presentation of PE can be nonspecific, thereby making diagnosis difficult in many cases. Guidelines have been developed and updated in recent years to assist clinicians in the diagnosis and management of this condition.

Epidemiology

The true incidence of PE among the general population is unknown. In a retrospective analysis of approximately 43 million deaths in the USA over the period 1979–1998, PE was diagnosed in 1.3 % of cases [60]. The age-adjusted incidence of PE has increased from 62.3 to 112.3 cases/100,000 since the introduction of CTPA into clinical practice, while the age-adjusted PE mortality and case fatality have improved significantly [61]. These findings may be explained by the increased use of prophylactic measures as well as improvements in treatment and management. Technological advances and increased awareness may account for the reported increase in the incidence of PE.

Pathophysiology

The majority of clinically diagnosed PE's originate in the iliofemoral veins, which are part of the deep venous system. Coexisting deep vein thrombosis (DVT) can be found in the lower limbs in up to 70 % of patients with PE [62]. The thromboembolic process may therefore be seen as a continuum, and DVT and PE are two clinical presentations of venous thromboembolism (VTE), with shared pathophysiological characteristics. Lower limb thrombosis usually develops in the setting of abnormal blood flow, vessel wall integrity, or blood constituents (Virchow's triad). While most DVTs resolve spontaneously, those that do not may propagate and embolize to the lung, typically 3–7 days after the onset [63].

The degree of cardiopulmonary compromise depends largely on the size of the embolic thrombus or thrombi. Large emboli may lodge at the bifurcation of the main pulmonary artery (saddle embolus) or lobar arteries. The PVR may acutely increase due to obstruction of the pulmonary vascular bed and by localized vasoconstriction (caused by hypoxia and inflammatory mediators). If the RV cannot tolerate this increased afterload (e.g., RV systolic pressure of >50 mmHg and a mPAP >40 mmHg in a non-preconditioned heart), then pulmonary perfusion will decrease and RV failure occur resulting in syncope, systemic hypotension, and death. Smaller and more distal emboli may cause alveolar hemorrhage, inflammation adjacent to the parietal pleura, leading to hemoptysis, pleuritis, and small pleural effusions. Pulmonary infarction occurs in 10 % of cases.

Hypoxia may be caused by several factors during a PE. Disproportionate lung perfusion within the pulmonary vascular bed results in V/Q mismatch and hypoxemia. Areas of atelectasis caused by surfactant dysfunction and localized bronchoconstriction may develop distal to the embolic obstruction resulting in shunt. Furthermore, an inverted pressure gradient between the right and left atria may open a PFO leading to a right-to-left shunt and hypoxemia.

Risk Factors

DVT and PE have shared predisposing factors, and both are considered to result from an interaction between temporary (setting-related) and permanent (patient-related) risk factors [63, 64] (Table 35.5). The PIOPED II study looked specifically at patients with suspected acute PE, and 94 % of all patients with confirmed PE (92 % of patients with no prior cardiopulmonary disease) had one or more identifiable risk factor for the condition [65]. Immobilization (bed rest within the past month for most of the day for ≥3 consecutive days) was the most common cause of PE, and surgery was the most common cause of immobilization.

Diagnosis

Clinical Presentation

Clinical evaluation does not enable reliable exclusion or confirmation of PE. However, a thorough clinical evaluation

Table 35.5 Predisposing factors for venous thromboembolism

Predisposing factor	Patient-related	Setting-related
Strong risk (*OR* > *10*)		
Fracture (hip or leg)		
Hip or knee replacement		
Major general surgery		
Major trauma		
Spinal cord surgery		
Moderate risk (*OR 2–9*)		
Arthroscopic knee surgery		
Central venous lines		
Chemotherapy		
Chronic heart or respiratory failure		
Hormone replacement therapy		
Malignancy		
Oral contraceptive therapy		
Paralytic stroke		
Pregnancy/postpartum		
Previous VTE		
Thrombophilia		
Weak risk (*OR*<*2*)		
Bed rest >3 days		
Immobility due to prolonged sitting		
Increasing age		
Laparoscopic surgery		
Obesity		
Pregnancy/antepartum		
Varicose veins		

Adapted from Torbicki et al. [63] and Anderson and Spencer [64]
OR odds ratio, *VTE* venous thromboembolism

may increase the index of suspicion for PE and hence will guide the diagnostic strategy in suspected cases [63].

Symptoms

In PIOPED II, dyspnea was the most common presenting symptom in patients with confirmed PE (79 %) [65] Table 35.6. The onset of dyspnea is typically acute, occurring within minutes (26 %). The triad of dyspnea, cough, or pleuritic chest pain was present in 92 % of patients with PE. Hemoptysis was uncommon.

Signs

The most common clinical signs in PIOPED were tachypnea (>50 %), tachycardia (~25 %), rales, and reduced breath sounds [65] Table 35.6. Signs of PH (accentuated pulmonic component of the second heart sound), RV pressure overload or enlargement (RV lift) or elevated RAP (jugular venous distension), were found in 22 % of all patients.

Chest Radiograph

The CXR (anterior and lateral) is an important initial test in the investigation of suspected PE [66]. The main role of the CXR in cases of suspected PE is to out rule other potential causes of acute dyspnea or chest pain (e.g., pleural effusion, pneumonia). Furthermore, a CXR is also required to facilitate accurate interpretation of an abnormal V/Q scan. Common abnormalities in PE include atelectasis, increased parenchymal opacification, or pleural effusion.

D-dimers

Plasma D-dimers are cross-linked degradation products of fibrin. Due to simultaneous activation of coagulation and fibrinolysis, D-dimer levels are elevated during the presence of an acute thrombus. Hence, the negative predictive value and sensitivity of D-dimers are high. However, as fibrin is produced in a variety of clinical conditions (e.g., cancer, inflammation, infection), D-dimers have a low specificity (40–68 %) for diagnosing PE, regardless of the assay used [67]. This specificity decreases even further with increased age, hospitalized patients, and pregnancy [63].

The sensitivity of D-dimers for diagnosing PE varies according to the type of assay used. For example, D-dimer levels are abnormal in patients with PE in approximately 95 % of cases when measured by ELISA, quantitative and semiquantitative rapid ELISA [67]. Hence, these assays can be used to exclude PE in patients with either a low or moderate probability of PE (see below) [63]. In contrast, quantitative latex-derived assays and whole-blood assays are only considered moderately sensitive as their sensitivity is less than 90 % [63, 67].

Laboratory Tests

ABG results are not specific for PE, but hypoxemia, hypocarbia, and respiratory alkalosis are frequently seen. BNP is a marker of myocardial stretch and ventricular dysfunction. Although it has a relatively low sensitivity and specificity in suspected PE, elevated levels of BNP and its precursor NT-proBNP are associated with short-term mortality in hemodynamically stable patients with PE [68]. Similarly, elevated cardiac troponin levels (troponin I and troponin T) are nonspecific for diagnosing PE, but elevated plasma levels are associated with short-term mortality and adverse outcome events [69].

Electrocardiography

Electrocardiography has a low sensitivity for diagnosing PE but can be used to identify patients at risk of adverse outcomes in acute PE. In addition to a RV strain pattern (≥1 of right bundle branch block, S1Q3T3 pattern, or negative T wave in leads V1–V4), atrial arrhythmias, inferior Q waves, and precordial ST segment changes are associated with increased short-term mortality [70].

Table 35.6 Prevalence of symptoms and signs in patients with suspected pulmonary embolism

	No prior CPD (%)	All patients (%)
Symptoms		
Dyspnea (rest or exertion)	73	79
Dyspnea (rest only)	55	61
Dyspnea (exertion only)	16	16
Orthopnea (≥2 pillow)	28	36
Pleuritic pain	44	47
Chest pain (not pleuritic)	19	17
Cough	34	43
Wheeze	21	31
Calf or thigh swelling	41	39
Calf and thigh swelling	7	8
Calf or thigh pain	44	43
Calf and thigh pain	17	16
Signs		
General		
Tachypnea (>20/min)	54	57
Tachycardia (>100/min)	24	26
Diaphoresis	2	4
Temperature >38.5 °C	1	2
Cardiac examination (abnormal)	21	22
Increased P2	15	15
RV lift	4	5
Jugular venous distension	14	13
Pulmonary examination (abnormal)		
Crackles	18	21
Decreased breath sounds	17	21
Rhonchi	2	5
Pleural friction rub	0	1
DVT		
Calf or thigh	47	47
Calf and thigh	14	12

Adapted from Stein et al. [65]. With permission from Elsevier
CPD cardiopulmonary disease, *P2* pulmonic component of the second heart sound, *RV* right ventricular, *DVT* deep vein thrombosis

Compression Ultrasonography

Compression ultrasonography (CUS) of the lower limbs is widely used to diagnose DVT. CUS has a sensitivity of over 90 % and a specificity of approximately 95 % for diagnosing proximal DVT and diagnoses DVT in 30–50 % of patients with PE [71, 72]. CUS can be used to reduce the overall false-negative rate when using single-detector CT to diagnose PE or can be performed to avoid CT when positive in patients with contraindications to contrast dye or irradiation [63, 66]. Diagnosis of proximal DVT in patients with suspected PE is also sufficient to support the commencement of anticoagulation without further testing [63, 73]. Furthermore, CUS may identify patients at higher risk of subsequent PE, as proximal DVT increases the risk of recurrent VTE in patients with PE [63].

Ventilation-Perfusion Scintigraphy

In recent years, the increased use of CTPA has led to a reduction in the use of V/Q scanning in the routine diagnostic evaluation of suspected PE. However, the V/Q scan remains a safe, well-established diagnostic test in cases of suspected PE. A gamma camera is used to acquire lung images following intravenous injection of radioactive technetium macroaggregated albumin (Tc99m-MAA) (perfusion phase) and inhalation of a gaseous radionuclide, e.g., xenon-133 (ventilation phase). Areas of hypoperfusion with corresponding normal ventilation (i.e., V/Q mismatch) are seen in PE. The sensitivity and specificity of the scan may be increased further by using single photon emission computed tomography (SPECT).

V/Q scan results are generally categorized according to criteria established in the initial PIOPED trial, as a normal/near-normal, low, intermediate (nondiagnostic), or high probability of a PE [74]. Results from the PIOPED II study support the results of previous studies, by showing a specificity of 97.7 % in the case of a normal scan (PE absent) and a sensitivity of 77.4 % in the case of a high-probability scan (PE present) [75]. A normal scan is therefore considered to safely exclude PE [63]. A high-probability scan establishes the diagnosis with a high degree of probability, although further tests may be required in patients with a low clinical probability [63]. PE may also be excluded in patients with a low clinical probability and a nondiagnostic scan, although evidence for this is less well validated [63]. Further testing is required in all other combinations of V/Q and clinical probability.

Computed Tomography

Multidetector CTPA is widely employed in assessment of patients with suspected PE [63, 66]. Technological advancements facilitating the acquisition of higher resolution images of the pulmonary arteries down to subsegmental levels have led CTPA to become the primary imaging modality in the diagnostic evaluation of this disease. Multiple previous studies have shown that CTPA is a highly sensitive and specific test. Results from the PIOPED II study showed a sensitivity of 83 % and a specificity of 96 % [76]. A concomitant preclinical probability assessment (e.g., Wells' score) has also been shown to influence the predictive accuracy of CTPA. In PIOPED II, high, intermediate, and low clinical probability scores were associated with positive predictive values of 96, 92, and 58 %, respectively, and negative predictive values of 96, 89, and 60 %, respectively [76]. The addition of CT venography to clinical assessment did not yield significantly different predictive values when compared to CTPA alone.

A negative multidetector CTPA in patients with a non-high clinical probability of PE can therefore be used to exclude PE [63]. Patients with a high clinical probability and a negative scan may require further investigation, e.g., lower limb CUS, V/Q scan, or pulmonary angiography. The sensitivity of CTPA in diagnosing PE is reduced at subsegmental levels, although this is also a finding with pulmonary angiography. A positive CTPA at segmental (or more proximal) levels in non-low clinical probability patients adequately diagnoses PE, while further testing may be required in patients with a low clinical probability and a subsegmental clot [63, 76].

Overall, multidetector CTPA is an accurate, widely available, and efficient test for diagnosing PE. It is a safe procedure but is contraindicated in cases of renal insufficiency and contrast allergy. In addition to PE evaluation, CTPA may also diagnose other thoracic pathologies that may explain the patient's symptoms. By showing the extent of PE and/or RV dysfunction, CTPA can also be used to guide treatment, e.g., the need for thrombolysis or conventional anticoagulation. The recently developed "triple rule-out" CT angiography to evaluate patients with chest pain simultaneously for coronary artery disease, PE, and aortic dissection has not produced any substantial clinical or diagnostic benefits to date.

Pulmonary Angiography

Pulmonary angiography facilitates the visualization of subsegmental thrombi as small as 1–2 mm in diameter, although substantial interobserver variation exists at this level [74]. In recent years, pulmonary angiography has been largely replaced by CTPA, as this noninvasive procedure now provides similar or better information. Pulmonary angiography is therefore generally performed in cases where PE is strongly suspected and noninvasive tests are equivocal [63] or prior to certain interventional procedures, e.g., PEA for CTEPH. The procedure is generally well tolerated, although bleeding, contrast reactions, and arrhythmias may occur.

Echocardiography

Echocardiography is only moderately sensitive in diagnosing PE [77]. Echocardiographic criteria have been used to diagnose PE, such as RV hypokinesis, RV dilatation, increased TR velocity, and regional wall motion abnormalities that spare the RV apex ("McConnell's sign") [78]. However, its main role is prognostic stratification, as echocardiographic evidence of RV dysfunction in such patients is associated with increased mortality [79]. In hemodynamically unstable patients with suspected acute PE, the absence of echocardiographic signs of RV dysfunction or overload practically excludes PE as the cause of the hemodynamic deterioration [63]. Furthermore, it may help in identifying an alternative cause of this deterioration, e.g., cardiac tamponade or acute valvular dysfunction.

Magnetic Resonance Angiography and Perfusion Imaging

MR angiography (MRA) and MR perfusion imaging can provide rapid and noninvasive evaluation of the central and pulmonary arteries. MR perfusion imaging has been shown to be highly sensitive for detection of PE and is most useful when combined with MRI and MRA [80]. These diagnostic modalities are not routinely indicated in the evaluation of suspected PE. However, technological improvements and greater availability and expertise may lead to increased use in future years.

Diagnostic Strategy

The outcomes of acute PE vary substantially according to patient characteristics at the time of presentation. Over the past number of years, efforts have been made to tailor the diagnostic and therapeutic approach to patients with suspected PE according to initial presenting characteristics.

Clinical Probability of PE

Assessing the clinical probability of PE has become a key step in diagnostic algorithms for suspected cases of PE. In order to standardize this assessment, a number of clinical prediction rules have been developed in recent years. One of the most frequently used and widely studied of these is the Wells score, which has been validated using both a three-category (low, moderate, high clinical probability) and a two-category scheme (PE likely or unlikely) [81, 82] (Table 35.7). The revised Geneva score which is based entirely on clinical variables has also been validated [83]. In general, patients have a probability of PE of approximately 10, 30, and 65 % in the low-, moderate-, and high-probability categories, respectively [63].

Risk Stratification

Once a diagnosis of PE has been confirmed, the initial management can be guided by stratifying patients according to the severity of PE and the risk of early (in-hospital or 30-day) mortality [63]. Immediate bedside clinical assessment for the presence or absence of clinical markers facilitates stratification of patients into high- and low-risk groups (Table 35.8). High-risk patients represent a medical emergency and have a short-term mortality >15 % [85]. The terms "massive," "submassive," and "low risk" have also been used for risk stratification purposes, and new definitions of these terms have been recently proposed [84].

An efficient initial evaluation of mortality risk and clinical probability of PE will facilitate the subsequent management of patients with suspected PE according to recognized local and international algorithms. The current ESC guide-

Table 35.7 Clinical prediction rules for PE: Wells score and revised Geneva score

Wells score		Revised Geneva score	
Variable	Points	Variable	Points
Symptoms		*Symptoms*	
Hemoptysis	+1	Unilateral lower limb pain	+3
		Hemoptysis	+2
Clinical signs		*Clinical signs*	
Heart rate		Heart rate	
>100 beats/min	+1.5	75–94 beats/min	+3
		≥95 beats/min	+5
Clinical signs of DVT	+3	Pain on lower limb deep vein at palpation and unilateral edema	+4
Predisposing factors		*Predisposing factors*	
Previous DVT or PE	+1.5	Age > 65 years	+1
Recent surgery or immobilization (≥3 days)	+1.5	Previous DVT or PE	+3
Malignancy	+1	Surgery or fracture within 1 month	+2
		Active malignancy	+2
Clinical judgement			
Alternative diagnosis less likely than PE	+3		
Clinical probability (*3 levels*)		*Clinical probability*	
Low	0–1	Low	0–3
Intermediate	2–6	Intermediate	4–10
High	≥7	High	≥11
Clinical probability (*2 levels*)			
PE unlikely	0–4		
PE likely	>4		

Adapted from Torbicki et al. [63], Le Gal et al. [73], and van Belle et al. [81]
DVT deep vein thrombosis, *PE* pulmonary embolism

lines on the diagnosis and management of acute PE suggest a diagnostic approach based the level of risk and the clinical probability of PE [63].

Suspected High-Risk PE

Emergency CTPA or bedside echocardiography is indicated in high-risk cases of suspected PE [63]. The diagnosis of PE may be accepted on the basis of compatible echocardiographic findings alone (e.g., RV overload, PH), in these patients when other tests, e.g., CTPA, are unavailable [63] (Fig. 35.3).

Suspected Non-High-Risk PE

Most patients with suspected PE are in the non-high-risk category. Plasma D-dimer level (preferably using a higher sensitivity assay) should be performed in patients with a low or intermediate clinical probability, as this may avoid the need for further testing (Fig. 35.4).

D-dimer levels are not recommended in patients with a high clinical probability of PE, and these patients should have a multidetector CTPA. Negative multidetector CTPA safely excludes PE in cases of intermediate probability, but further testing may be required if the clinical probability is high or if subsegmental thrombi are seen [63]. CUS showing a proximal DVT confirms PE in suspected cases, while further testing may be required in distal DVT cases. In centers where CT is unavailable, or in patients where it is contraindicated, a normal V/Q scan will exclude PE. Low-probability V/Q scan combined with low clinical probability will also exclude PE, while high clinical and V/Q scan probability will confirm it.

Treatment

In recent years, evidence-based clinical guidelines (ESC 2008, AHA 2011, and ACCP 2012) have been published to assist clinicians in the management of PE [63, 84, 86]. The focus of therapy is stabilization of the patient, initiation of appropriate treatment, and prevention of recurrence.

Resuscitation and Supportive Care

Patients presenting with acute high-risk (or massive) PE require immediate supportive care. Rapid intravenous fluid administration (e.g., 500–1,000 mL of normal saline) may improve hemodynamics. However, fluids should be administered with caution as excess may exacerbate RV failure [87]. Clinicians should

Table 35.8 Risk stratification according to expected pulmonary embolism-related early mortality rate and type

PE mortality risk		PE type	Risk markers: Shock or hypotension	Risk markers: RV dysfunction	Risk markers: Myocardial injury	Potential treatment
High		Massive	+	(+)[a]	(+)[a]	Thrombolysis or embolectomy
Non-high	Inter	Submassive	–	+	+	Hospital admission
			–	+	–	
			–	–	+	
	Low	Low risk	–	–	–	Early discharge or home treatment

Adapted from Torbicki et al. [63] and Jaff et al. [84]
Massive PE is defined as acute PE with sustained hypotension (systolic blood pressure <90 mmHg for ≥15 min or requiring inotropic support, not due to other causes), pulselessness, or persistent profound bradycardia (heart rate <40 beats/min with sign/symptoms of shock); Jaff et al. [84] RV dysfunction means ≥1 of RV dilatation or RV systolic dysfunction on echocardiography, RV dilatation on CT, elevation of BNP (>90 pg/mL), elevation of NT-proBNP (>500 pg/mL), or electrocardiographic changes [68]; Myocardial necrosis is defined as either elevation of troponin I (>0.4 ng/mL) or elevation of troponin T (>0.1 ng/mL) Jaff et al. [84].
PE pulmonary embolism, *RV* right ventricular, *Inter* intermediate
[a]When shock or hypotension is present, it is not necessary to confirm RV dysfunction/myocardial injury to classify as high risk of PE-related early mortality

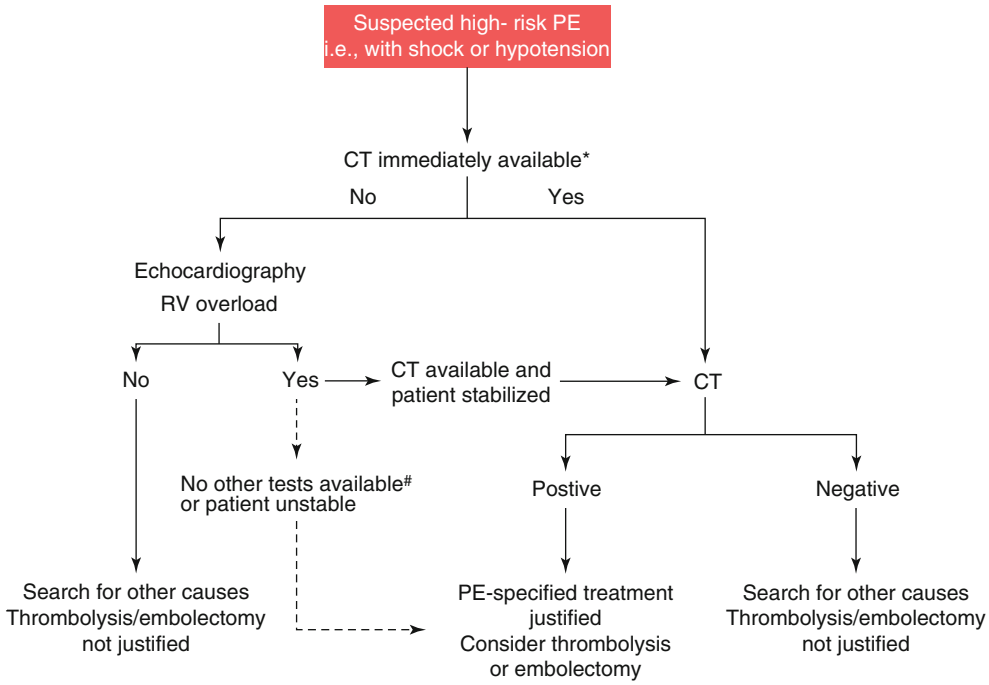

Fig. 35.3 Proposed diagnostic algorithm for patients with suspected high-risk PE, i.e., presenting with shock or hypotension. *CT is also considered not immediately available if the critical condition of a patient allows only bedside diagnostic tests. #Transesophageal echocardiography may detect thrombi in the pulmonary arteries in a significant proportion of patients with RV overload and PE that is ultimately confirmed by spiral CT; confirmation of DVT with bedside CUS might also help in decision-making; *PE* pulmonary embolism, *CT* computed tomography, *RV* right ventricular (Reprinted from Torbicki et al. [63]. With permission from Oxford University Press)

have a low threshold for initiating vasopressor/inotropic support in hypotensive or shocked patients [87].

Supplemental oxygen should be given to hypoxemic patients. Noninvasive or mechanical ventilation is infrequently required. When required, positive end-expiratory pressure should be applied with caution as this may exacerbate RV failure [63].

Initial Anticoagulation

The aim of initial anticoagulation in cases of confirmed or suspected PE is to prevent death and recurrence of PE and to avoid bleeding complications where possible. In patients without contraindications and with confirmed PE or with a high or intermediate clinical probability of PE, parenteral anticoagulation (i.v. UFH, s.c. LMWH, or s.c. fondaparinux) should be initiated without delay while awaiting definitive diagnostic confirmation [63, 84, 86]. The recent ACCP guidelines also suggest parenteral anticoagulation if diagnostic test results are expected to be delayed >4 h in intermediate clinical probability cases, and not treating patients with a low clinical suspicion provided test results are expected within 24 h [86].

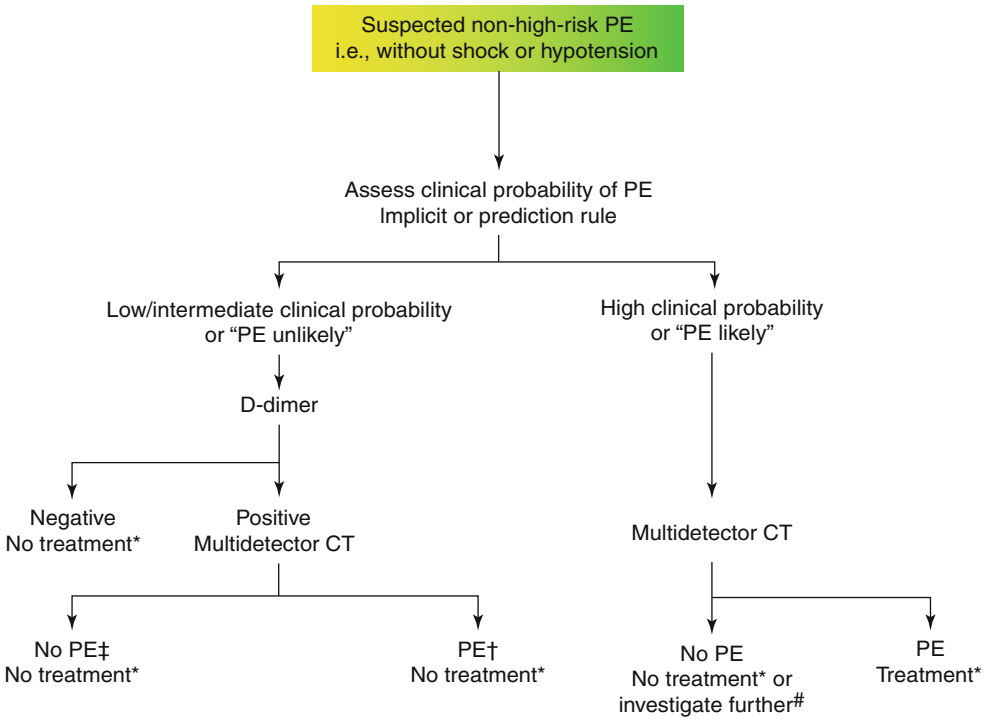

Fig. 35.4 Proposed diagnostic algorithm for patients with suspected non-high-risk PE (i.e., without shock and hypotension). Two alternative classification schemes may be used to assess clinical probability: a three-level scheme (clinical probability low, intermediate, or high) or a two-level scheme (PE unlikely or PE likely). When using a moderately sensitive assay, D-dimer measurement should be restricted to patients with a low clinical probability or a "PE unlikely" classification, while highly sensitive assays may be used in patients with a low or intermediate clinical probability of PE. Plasma D-dimer measurement is of limited use in suspected PE occurring in hospitalized patients. *Anticoagulant treatment for PE. †CT is considered diagnostic of PE if the most proximal thrombus is at least segmental; ‡If single-detector CT is negative, a negative proximal lower limb venous ultrasonography is required in order to safely exclude PE. #If multidetector CT is negative in patients with high clinical probability, further investigation may be considered before withholding PE-specific treatment; *PE* pulmonary embolism, *CT* computed tomography (Reprinted from Torbicki et al. [63]. With permission from Oxford University Press)

Intravenous UFH is recommended in hemodynamically unstable high-risk patients, as there is insufficient evidence to support the use of other parenteral agents in this setting. As it is not renally excreted, i.v. UFH is recommended as the initial anticoagulant of choice in patients with severe renal impairment and also in patients at high risk of bleeding because its anticoagulant effect can be rapidly reversed [63].

LMWH and fondaparinux have been shown to be as effective and as safe as i.v. UFH for the initial treatment of acute PE [88, 89] and are the preferred initial anticoagulants in all other cases of suspected PE [63, 86]. Doses should be weight-adjusted and routine monitoring is not required. However, monitoring of anti-factor Xa levels should be considered in patients receiving LMWH with severe renal failure or in pregnant patients [63]. Monitoring for heparin-induced thrombocytopenia is required in patients being treated with i.v. UFH or LMWH. A once rather than twice-daily administration is suggested in patients being treated with LMWH [86].

Patients should also be commenced on an oral VKA as soon as possible. Parenteral anticoagulation should be continued for a minimum of 5 days and until the INR is ≥2.0 for a minimum of 1–2 days [63, 86].

Thrombolysis

Thrombolytic therapy is generally reserved for patients with significant hemodynamic compromise following an acute PE. Thrombolytics can improve hemodynamic function (e.g., pulmonary perfusion, mPAP, and RV function) [84, 90] and may also reduce mortality and recurrent PE [86, 90]. Therefore, therapy is recommended for patients with acute high-risk (massive) PE and an acceptable risk of bleeding complications [63, 84, 86]. It can also be considered in patients without hypotension and with a low risk of bleeding whose initial clinical presentation or clinical course after starting anticoagulant therapy suggests a high risk of developing hypotension [86]. The optimal choice of thrombolytic agent (i.e., streptokinase, rt-PA, or urokinase) has not been established. When used in patients with acute PE, short infusion times (e.g., over 2 h) via a peripheral vein are recommended [86].

Approximately 92 % of patients can be classified as responders to thrombolysis [91], with the maximal benefit occurring within the first 48 h of treatment. Thrombolysis is associated with a significant risk of major bleeding (13 % cumulative rate) and a 1.8 % risk of intracranial/fatal hemorrhage [63]. The assessment of bleeding risk with throm-

bolytic therapy is similar in patients with PE and with acute STEMI [86], and absolute contraindications may become relative in patients with immediately life-threatening high-risk PE [63].

Embolectomy

The removal or fragmentation of pulmonary thrombi may be performed surgically or by interventional percutaneous methods. Both approaches may be considered in high-risk patients with acute PE who have shock that is likely to cause death before systemic thrombolysis can take effect (e.g., within hours), who have failed thrombolysis or have contraindications to thrombolysis [63, 84, 86]. The choice of procedure will depend on the level of expertise and resources available [86]. Surgical embolectomy is suited to patients with acute PE who require excision of a right atrial thrombus, paradoxical arterial embolism, or closure of a PFO [86]. Percutaneous techniques may be considered an alternative to surgical treatment and include mechanical fragmentation of thrombi using a standard pulmonary artery catheter, pigtail rotational catheter embolectomy, and rheolytic embolectomy. Catheter techniques should only be used in the proximal pulmonary arteries, and the procedure should be stopped when hemodynamic improvement is seen, regardless of the angiographic result [63].

Long-Term Treatment

The long-term treatment of VTE with anticoagulant therapy is to prevent recurrence. Although most of the available data is based on studies of patients with DVT, recommendations for long-term treatment are similar both DVT and PE [86]. It is important to establish if the risk factors for the VTE event were reversible (transient) or unprovoked. The recurrence rate of PE after treatment discontinuation is lower with reversible risk factors compared to unprovoked cases (2.5 % versus 4.5 %/year) [92]. Reversible risk factors include surgery, trauma, medical illness, estrogen therapy, and pregnancy [63]. Anticoagulation for 3 months is recommended in these patients [63, 86]. Decisions in unprovoked PE are more complex. Anticoagulation for at least 3 months (with a risk-benefit evaluation for extended therapy after 3 months) is recommended in patients with a first (low or moderate bleeding risk) or second (low bleeding risk) unprovoked VTE and is suggested in patients with a second unprovoked VTE and a moderate bleeding risk [86]. Anticoagulant therapy for 3 months is recommended in patients with a first VTE and high bleeding risk and is suggested in those with a second VTE and high bleeding risk [86]. The continuing use of treatment in patients on extended therapy should be reassessed at regular intervals.

In patients with PE (without active malignancy), VKA therapy (with a target INR of 2.5, range 2.0–3.0) is suggested as the long-term anticoagulant of choice [86]. There is emerging data to support the use of newer agents, e.g., dabigatran (an oral direct thrombin inhibitor) and rivaroxaban (an oral factor Xa inhibitor), for the treatment of VTE, and these agents may be incorporated into treatment guidelines over the coming years.

Vena Cava Filters

In the PREPIC study, IVC filters reduced the risk of recurrent PE but increased the risk of recurrent DVT with no overall effect on survival, in patients with PE who were also treated with anticoagulants [93]. However, IVC filters were associated with a benefit in mortality and recurrence in the ICOPER registry [87]. IVC filters are therefore recommended in patients with acute PE where serious contraindications to anticoagulation exist [84, 86]. A conventional course of anticoagulation should be resumed if their bleeding risk resolves. IVC filters may also be considered in pregnant patients who develop thrombosis in the weeks prior to delivery [63] or in patients with recurrent acute PE despite therapeutic anticoagulation [84]. Retrievable IVC filters can be placed where there is a short-term contraindication to anticoagulation and can be removed as soon as it is safe to start anticoagulation [63].

Outpatient Treatment

While initial outpatient treatment is recommended in acute lower limb DVT [86], outpatient treatment of acute PE is not a common practice. Results from a large RCT of low-risk patients with acute symptomatic PE showed that outpatient treatment with LMWH is not inferior to inpatient treatment in terms of efficacy and safety [94]. Mortality risk was calculated using the Pulmonary Embolism Severity Index (PESI), which includes patient characteristics (e.g., age, gender, cancer, lung disease) and hemodynamic parameters. A systematic review of previous observational studies reported a low frequency of complications in low-risk patients treated partially or entirely at home [95]. Therefore, in low-risk patients with acute PE and adequate home circumstances, early discharge is currently suggested [86].

Specific Clinical Conditions

Malignancy

Malignancy is associated with a hypercoagulable state, and patients have a fourfold higher risk (6.5-fold higher risk in patients receiving chemotherapy) of VTE than the general population [96]. Active cancer is also a major risk factor for recurrence of VTE [63]. LMWH is associated with a reduction in recurrence of VTE and improvement in survival (in patients without metastatic disease) relative to VKA therapy [86, 97]. Extended anticoagulation is there-

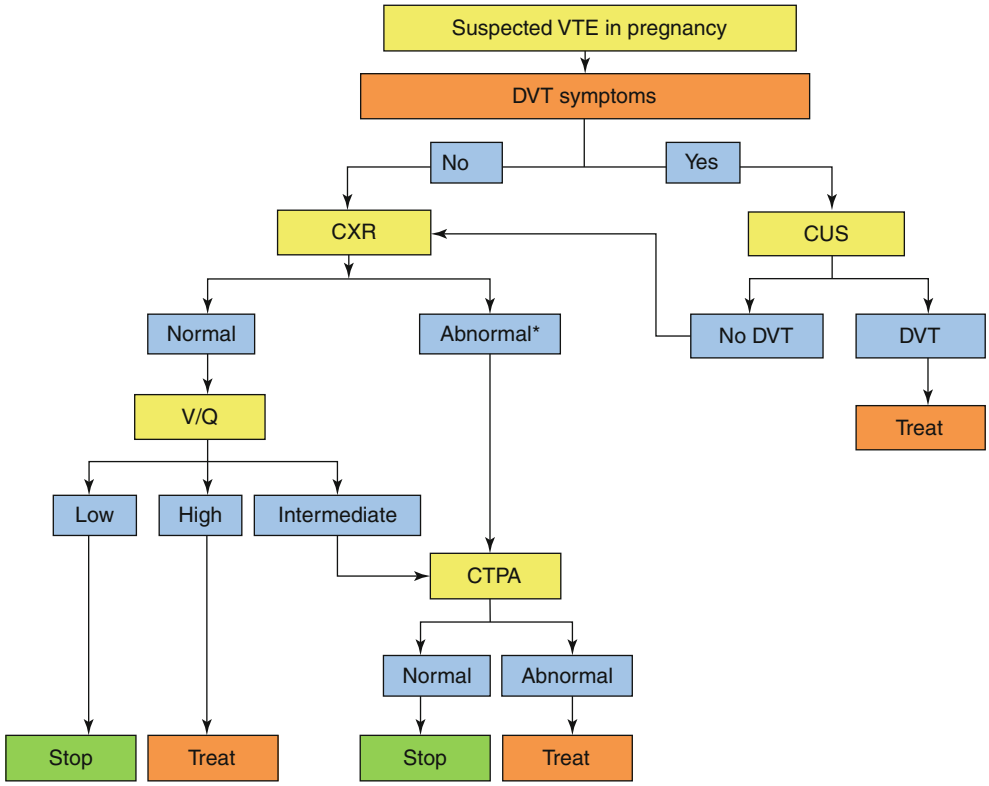

Fig. 35.5 Potential diagnostic algorithm for suspected venous thromboembolism in pregnancy. *VTE* venous thromboembolism, *DVT* deep vein thrombosis, *CXR* chest radiograph, *CUS* compression ultrasonography (of the lower limbs), *V/Q* ventilation-perfusion scintigraphy, *CTPA* computed tomography pulmonary angiogram, Low, high, intermediate refers to the probability of VTE on V/Q scan

fore recommended in patients with active cancer with VTE [63, 86].

Pregnancy

PE is a leading cause of morbidity and mortality in pregnancy. The estimated incidence of PE is 10.6/100,000, increasing to 159.7/100,000 in the postpartum period [98]. The clinical features of VTE are similar in pregnant and non-pregnant patients. Guidelines on the evaluation of suspected PE in pregnancy have been recently published [99]. Patients with suspected PE and symptoms of lower limb DVT should have a bilateral lower limb CUS. A CXR is recommended as the initial radiation-associated procedure in patients with a negative CUS or absent lower limb symptoms. The presence or absence of CXR abnormalities will guide the need for subsequent V/Q scan or CTPA (Fig. 35.5).

Heparin is the cornerstone of treatment of confirmed VTE in pregnancy, as it does not cross the placenta and is not found in breast milk. LMWH is recommended over UFH [100]. Treatment should be continued throughout the entire pregnancy, and guidelines suggest that it should be continued for a minimum of 6 weeks postpartum (with a minimum duration of treatment of 3 months) [100]. Adaptation according to anti-Xa monitoring may be considered in women at the extremes of body weight or with renal disease [63]. VKA are teratogenic and are not recommended during the first and third trimesters and may be considered with caution during the second trimester [63]. Antepartum administration of prophylactic or intermediate-dose UFH or prophylactic LMWH combined with low-dose aspirin is recommended in patients who fulfill the laboratory and clinical (≥3 pregnancy losses) criteria for antiphospholipid antibody syndrome [100].

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Diseases of the Aorta

36

David M. Dudzinski and Eric M. Isselbacher

Introduction

The largest artery in the body, the aorta, receives blood directly from the left ventricle and distributes it distally to the branch arteries. While the aorta is one continuous vessel, its segments have been distinguished anatomically and by location. The aorta begins in the anterior mediastinum above the aortic valve as the ascending aorta, the most proximal portion of which is also called the aortic root. This is followed in the superior mediastinum by the aortic arch, which gives rise to the brachiocephalic arteries (including the left common carotid and subclavian arteries). The descending thoracic aorta then courses in the left posterior mediastinum to the level of the diaphragm, after which it becomes the abdominal aorta and rapidly tapers in size before bifurcating distally into the common iliac arteries. From the descending thoracic aorta arise the intercostal, lumbar, esophageal, bronchial, and mediastinal arteries, while the abdominal aorta is the origin of major visceral branches including celiac, mesenteric, renal, and gonadal arteries.

Because the aorta and its branches transport blood to every vital location in the body, virtually any organ system may be affected by diseases of the aorta, and it is therefore prudent to consider aortic diseases in many diverse clinical contexts. Approximately 40,000–50,000 people die annually in the United States due to diseases of the aorta, and unfortunately, the diagnosis of these syndromes is often difficult or delayed.

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Aortic Aneurysms

Introduction

Aortic aneurysms, defined as pathologic dilatation of the aorta, are one of the most commonly encountered aortic diseases. Aneurysms may involve any part of the aorta, but occur much more commonly in the abdominal than in the thoracic aorta. Abdominal aortic aneurysms have a prevalence of at least 3 % in a population greater than 50 years old and up to 5 % in population greater than 65 years old [1]—although the exact prevalence varies with the age and risk of the population studied—and are five to ten times more common in men than in women. The infrarenal aorta is the segment most often involved. Among thoracic aortic aneurysms, aneurysms of the ascending aorta are most common. When aneurysms involve the descending thoracic aortic aorta, they often extend distally and involve the abdominal aorta as well, producing a *thoracoabdominal* aortic aneurysm.

Etiology

Multiple pathogenic factors—chief among them atherosclerosis, smoking, and inflammation—interact to cause aneurysmal degeneration of the aortic wall. There is also a genetic basis underlying aneurysm formation as suggested by observations that 13–32 % of first-degree relatives of those with abdominal aneurysms may be similarly affected, compared with the 2–5 % risk in the general population; numerous candidate genes being studied involve structural and matrix proteins, proteases, and immunomodulators [2, 3]. Atherosclerosis and factors that promote atherosclerosis, such as smoking, thicken the aortic intima and impair its vasculoprotective functions, which together result in reduction of diffusion of oxygen and nutrients from the aortic lumen to the media, in turn causing degeneration of the elastic elements of the media and a weakening of the aortic wall [4]. Nevertheless, atherosclerosis is an intimal problem, and the

C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_36,

pathophysiologic processes involved in aortic aneurysm formation lie chiefly in the vessel media and adventitia, owing to a pathologic milieu of inflammation, oxidative stress, matrix degradation, and smooth muscle cell apoptosis [5]. Inflammatory cell infiltrates and consequent upregulation of proteolytic enzymes (e.g., matrix metalloproteinases 2, 8, and 9) result in deterioration of the elastin and collagen components of the aortic media extracellular matrix. Signaling kinases such as JNK may play key roles in the pathogenesis of aneurysms by controlling release of inflammatory cytokines and matrix metalloproteinases [6]. Reduced integrity of the fibrous matrix of the aortic media manifests as reduced aortic wall thickness; the weakening of the wall leads to aortic dilatation, and, as the vessel dilates, wall tension increases (in accordance with the law of Laplace), thereby promoting further expansion of the aneurysm. Infection is an uncommon cause of aneurysms, but when it occurs, it is generally a bacterial or mycobacterial infection of an existing aneurysm, or otherwise structurally abnormal vessel segments [7].

While similar atherosclerotic and inflammatory processes also cause aneurysms of the descending thoracic aorta, a history of long-standing hypertension is a common risk factor for thoracic aortic aneurysms. In contrast to aneurysms of the abdominal and descending thoracic aorta, the most important etiology of *ascending* thoracic aortic aneurysms is *medial degeneration*, which appears histologically as smooth muscle cell loss and dysregulation of the elastin fiber network, with resultant mucoid infiltration and degeneration of elastic layers within the aortic media. The process was formerly termed "cystic medial necrosis," but that term is a misnomer, as neither are there true cysts (there are instead subintimal spaces filled with proteoglycan) nor is necrosis necessarily present. Medial degeneration and elastin fragmentation are found in almost all patients with Marfan syndrome, placing this group at very high risk for aortic aneurysm formation at a relatively young age. The abnormal glycoprotein in Marfan syndrome, fibrillin-1, has structural roles in integrity of the extracellular matrix and microfibrils supporting the elastin fibers of the aortic media. More recently recognized is the signaling role of fibrillin-1 as a latent TGF-β-binding protein, whereby it downregulates activity of TGF-β, a molecular switch intimately involved in differentiation, fibrosis, and development [8, 9]. Primary missense mutations in the TGF-β receptor are responsible for Loeys-Dietz syndrome, an autosomal dominant condition characterized by aortic aneurysm and other findings similar to Marfan but with distinct features including hypertelorism, bifid uvula or cleft palate, and arterial tortuosity [8]. Aortic dissections in Loeys-Dietz syndrome tend to occur at much smaller aortic diameters than in Marfan syndrome.

Among patients without overt evidence of connective tissue disorders, ascending thoracic aortic aneurysms occur commonly among those with an underlying bicuspid aortic valve. Bicuspid aortic valve is the single most prevalent congenital cardiac anomaly, found in 1–2 % of the population and with a male–female ratio of greater than 3:1 [10]. Bicuspid aortic valve is associated with ascending aortic aneurysms, aortic dissection, and coarctation. Though the genetic causes of bicuspid aortic valve remain elusive, medial degeneration is found histologically and likely explains the association with aneurysm and dissection. The mechanism of aortopathy was historically thought to be a hemodynamic consequence of congenital aortic stenosis and therefore referred to as "post-stenotic dilatation," but this theory was weakened with the observation that the aortopathy is associated with medial degeneration and completely independent of aortic valve hemodynamics (i.e., equally prevalent among those with normally functioning bicuspid aortic valves). Ascending thoracic aortic aneurysms that are familial but occur in the absence of any other cardiovascular syndrome are referred to as "familial thoracic aortic aneurysm syndromes." These may be related to mutations in myosin heavy chain and vascular smooth muscle actin genes [11]. Less common causes of thoracic aortic aneurysms include Ehlers-Danlos syndrome type IV, Turner syndrome, aortitis (see section "Aortic Dissection"), other autoimmune disease-associated aortitis syndromes (e.g., inflammatory bowel disease, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus), aortic trauma, and chronic aortic dissection. Syphilis was historically also a common cause of saccular thoracic aneurysms but is now a rarity. Often thoracic aortic aneurysms are idiopathic.

Nearly all aortic aneurysms are true aneurysms, involving of all three layers of the vessel wall (intima, media, adventitia). False aneurysms represent a contained rupture of the aorta, in which blood from the aortic lumen is contained by the outer vessel wall (adventitia). Most aneurysms are fusiform, or symmetric, in shape. A minority are saccular in shape, with more localized outpouchings of the aortic wall, likely due to focal atherosclerosis, inflammation, ulceration, or trauma.

Clinical Manifestations

The large majority of patients with abdominal and thoracic aortic aneurysms are asymptomatic, and their aneurysms are discovered incidentally. When patients with abdominal aortic aneurysms experience symptoms, the most frequent complaint is of pain in the hypogastrium or lower back. The pain typically has a steady gnawing quality and may last for hours or days. New or worsening pain may herald aneurysm expansion or impending rupture. Rupture of an abdominal aneurysm is often accompanied by the triad of pain, hypotension, and the presence of a pulsatile abdominal mass. Those with thoracic aortic aneurysms may experience chest or back pain

from aneurysm expansion or symptoms from compression of adjacent structures (such as the recurrent laryngeal nerve, trachea, esophagus, or superior vena cava). Aneurysms of the ascending aorta often produce aortic insufficiency (due to incomplete aortic valve closure secondary to leaflet tethering by the dilated aorta), so patients with large aortic root or ascending aortic aneurysms may present with a diastolic murmur or even congestive heart failure.

Diagnosis

Abdominal aortic aneurysms may be palpable on physical examination, although even large aneurysms are sometimes obscured by body habitus [12]. Typically abdominal aortic aneurysms are difficult to size accurately by physical examination alone, as adjacent structures often make aneurysms feel larger than they actually are. Thoracic aortic aneurysms, on the other hand, cannot be palpated at all on physical examination.

The definitive diagnosis of an aortic aneurysm is made by an imaging study. Abdominal aortic aneurysms can be detected and sized by either abdominal ultrasonography or computed tomography (CT). Ultrasound is extremely sensitive and is the most practical method to use in screening for abdominal aortic aneurysms. The United States Preventive Services Task Force recommends a one-time screening abdominal ultrasound for males age 65–75 who have ever smoked [13]; screening for males >75 and for women has not been demonstrated to be cost-effective. In 2009, England began an ultrasound screening program for males age 65 or above [14].

Abdominal aortic ultrasonography is limited in its ability to characterize suprarenal aortic aneurysms and the aortic branch vessels. CT is more accurate (Fig. 36.1) and can clearly map branch vessel anatomy, although its cost, the risks of iodinated contrast medium, and radiation exposure need to be considered.

Thoracic aortic aneurysms are frequently recognized on chest radiographs, often producing widening of the mediastinal silhouette, enlargement of the aortic knob, or displacement of the trachea from midline (Fig. 36.2). In contrast to abdominal aortic aneurysms, there are presently no population screening recommendations for thoracic aortic aneurysms. Nevertheless, the recent ACC/AHA guidelines [11] suggest that clinicians should have a low threshold for evaluating patients for thoracic aortic disease using CT or magnetic resonance imaging (MR) given that aortic disease is usually asymptomatic and cannot be excluded by physical examination. CT is an excellent modality for detecting and sizing thoracic aneurysms and for following the growth over time of a known aneurysm. Transthoracic echocardiography, which generally visualizes the aortic root and ascending aorta well, is most useful for screening patients with Marfan syndrome because they are at particular risk for aneurysms in this location.

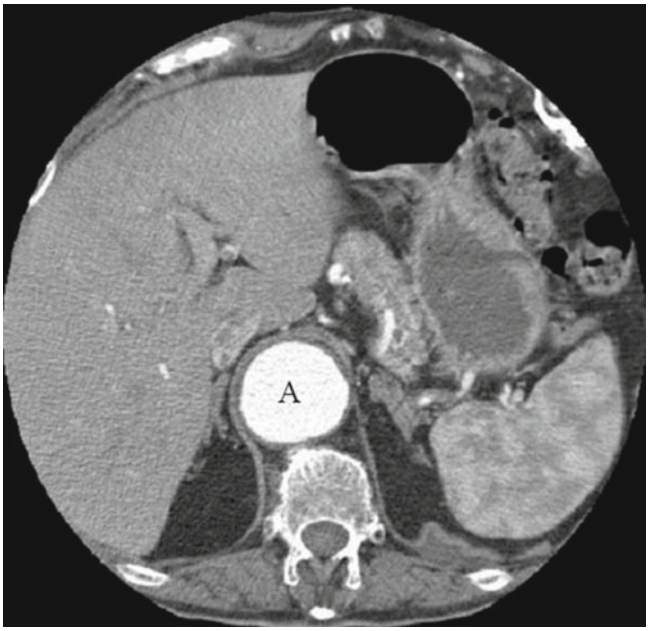

Fig. 36.1 A contrast-enhanced CT scan of the abdomen showing a 5.1 × 5.6 cm suprarenal abdominal aortic aneurysm (*A*)

Prognosis

The natural history of aortic aneurysms is that they expand over time and their rate of growth tends to increase with increasing aneurysm size. The major risk associated with an aortic aneurysm in any location is that of rupture. The risk of rupture rises with increasing aneurysm size because as the diameter of the aorta increases its wall tension rises according to Laplace's law (which states that wall tension is proportional to the product of intraluminal pressure and vessel radius and inversely proportional to wall thickness). Abdominal aortic aneurysms of less than 4.0 cm in size have only a 0.3 % annual risk of rupture, those 4.0–4.9 cm have a 1.5 % annual risk of rupture, and those 5.0–5.9 cm have a 6.5 % annual risk of rupture [15]. The risk of rupture rises sharply for aneurysms 6.0 cm or greater, although an exact risk is difficult to estimate. The overall mortality from rupture of an abdominal aortic aneurysm is >80 %, with a mortality of 50 % even for those who reach the hospital, as these patients present in hemorrhagic shock. It is therefore imperative to repair aneurysms prophylactically when certain size thresholds are reached. Thoracic aneurysms of less than 5.0 cm in size typically expand slowly and rarely rupture, but the rate of growth and risk of rupture increase significantly (to ~7 % annually) when the aneurysms are 6.0 cm or larger

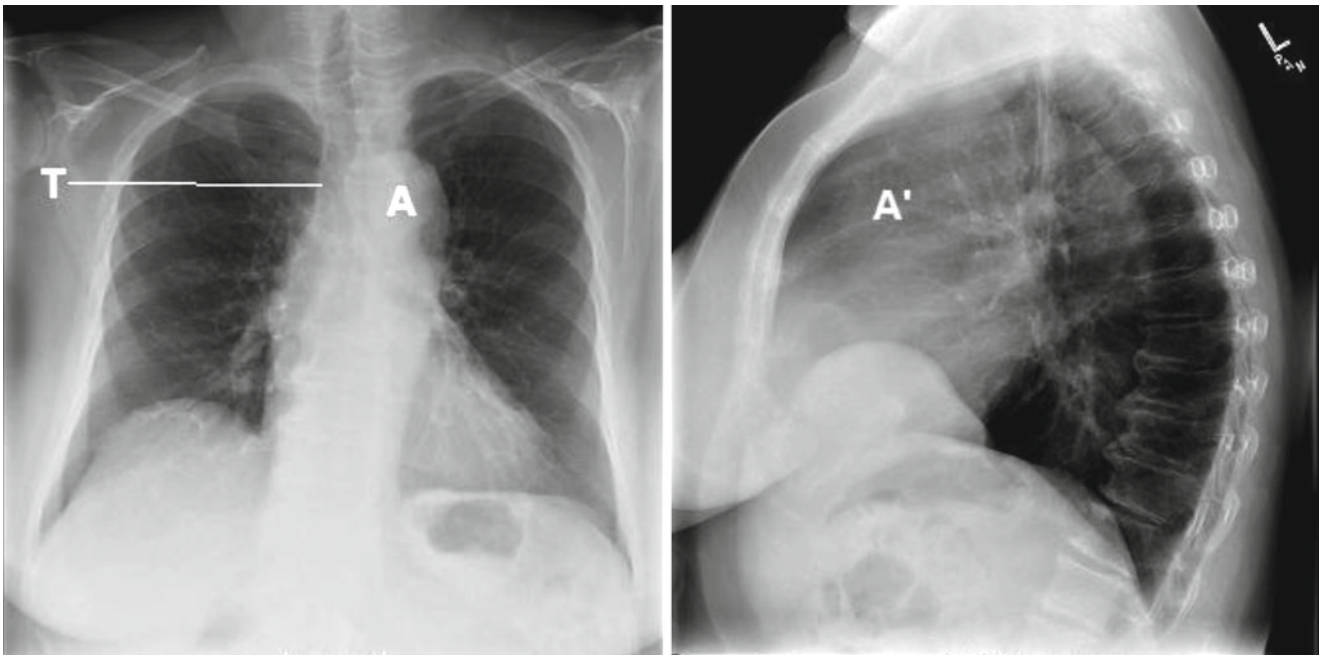

Fig. 36.2 A chest roentgenogram with posteroanterior and lateral views (*left* and *right panels*, respectively), showing a 5.7-cm ascending aorta in both the posteroanterior film (*A*) and the lateral film (*A′*). Though the aortic knob is enlarged when examined in posteroanterior view (A), the size relationship of the ascending aneurysm within lung and chest cavity is best depicted in the lateral view (A′). The trachea (*T*) is deviated rightward in the chest by the aneurysm

[16]. Rupture of thoracic aneurysms carries an early mortality of 76 % at 24 h [17].

The presence of an aneurysm in one location confers increased risk of an aneurysm in another location. About one-quarter of patients with a thoracic aortic aneurysm will have an abdominal aortic aneurysm; similarly, one-quarter of patients with an abdominal aortic aneurysm will have a thoracic aneurysm [18], although women are three times more likely than men to have a concurrent thoracic aortic aneurysm. Popliteal and iliac artery aneurysms are also commonly found in patients with any aortic aneurysm. Screening is advisable for first-degree relatives of patients with thoracic aneurysms, and the screening should be extended to second-degree relatives should any first-degree relative manifest an aortopathy.

The volume of mural thrombus within an abdominal aortic aneurysm, as measured by CTA, has been shown to correlate with cardiovascular events and also aneurysm growth [19].

Treatment

Patients whose aneurysms are not at significant risk of rupture should be managed medically to decrease wall stress and thereby reduce the rate of aneurysm expansion and risk of future rupture. dP/dt is an index that characterizes the impulse or shear stress of blood ejecting from the left ventricle into the aorta; beta-blockers effectively reduce dP/dt and have therefore become the mainstay of medical treatment of aneurysms, although additional antihypertensive agents are often required to control arterial blood pressure as well. Angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists may exhibit pleiotropic salutary benefits in addition to that of direct blood pressure reduction. Patients with abdominal aortic aneurysms treated with angiotensin-converting enzyme inhibitors were less likely to present with rupture [20]. In a mouse model of Marfan syndrome, the use of losartan, which happens to act as a TGF-β antagonist, was associated with a slowing of aortic growth to a rate no different from unaffected control mice [21]. In a small cohort study of humans with Marfan syndrome, the use of angiotensin receptor blockers was associated with a significant slowing of aortic root growth (from a rate of 3.5 mm/year down to 0.5 mm/year) [22]. Both thoracic and abdominal aortic aneurysms should be followed closely with serial imaging studies (such as CT) to detect progressive enlargement over time that may indicate need for a surgical repair. Surveillance imaging is most often performed annually, but the optimal interval is dependent on the location of the aneurysm, its size, and its historic rate of growth [11].

Size is the major indication for surgical or endovascular repair of aortic aneurysms. Abdominal aortic aneurysms larger than 5.5 cm should be repaired in suitable operative candidates, though a lower size threshold may be considered in patients of smaller body stature, in women (whose aneurysms tend to rupture at smaller diameters), and in patients

with family history or other risk factors [23]. Patients with ascending thoracic aortic aneurysms of greater than 5.5 cm in size should undergo surgical repair, while those with Marfan syndrome or bicuspid aortic valve should have repair when the aneurysm is ≥5.0 cm in size and those with Loeys-Dietz when the aneurysm is ≥4.4 cm by CT [11]. While the size thresholds above apply to patients of average size, for patients with a large or small body habitus, the thresholds should be adjusted accordingly. For patients with Marfan syndrome, bicuspid aortic valves, or other genetic syndromes, elective aortic root or ascending aortic aneurysm repair is recommended when the ratio of the maximal cross-sectional area of the aorta (in square centimeters) divided by patient height (in meters) exceeds 10 [11]. Aneurysms of descending thoracic aorta should be repaired at a diameter of ≥6.0 cm [11]. Rapid aortic growth, defined as a rate of >0.5 cm/year, is also an indication for surgical repair. In patients undergoing cardiac surgery for another indication, concomitant aortic repair should be considered if the aortic root or ascending aorta is ≥4.5 cm in diameter [11].

Surgical repair consists of resection of the aneurysmal portion of the aorta and insertion of a synthetic prosthetic tube graft. When aneurysms involve aortic segments with branch arteries, such branch arteries either may need to be reimplanted into the graft, or a multi-limbed prosthetic graft may be deployed (e.g., aortic arch graft with prostheses for great vessels or bifurcating graft prosthesis for aortoiliac aneurysms). For example, when a dilated aortic root must be replaced in the repair of an ascending thoracic aortic aneurysm, the coronary arteries must be reimplanted. Historically, repair of aortic root aneurysms required sacrificing the aortic valve (since the leaflets are attached to the wall of the aortic root) and the placement of a valved conduit or composite aortic graft (also known as the Bentall procedure). In modern practice, repair of an aortic root may be accomplished with placement of an aortic root graft followed by resuspension of the aortic valve within the graft (the David procedure). In a registry of Marfan patients undergoing root replacement, there was no difference in 30-day mortality between these two approaches [24].

A less invasive alternative approach for repair of many abdominal and some descending thoracic aortic aneurysms is endovascular aortic repair (EVAR), in which an expandable endovascular stent-graft is deployed within an aneurysm via a percutaneous catheter-based approach. The device consists of a collapsible prosthetic tube graft that is inserted remotely (e.g., via the femoral artery), advanced transluminally across the aneurysm under fluoroscopic guidance, and then secured at both its proximal and distal ends with an expandable stent attachment system. Once deployed, the stent-graft serves to bridge the normal regions of aorta on either side of the aneurysm, thereby excluding the aneurysm from the circulation while allowing aortic blood flow to continue distally through the prosthetic stent-graft lumen. However, only approximately half of patients with abdominal aortic aneurysms—and fewer with descending thoracic aortic aneurysms—have aneurysm anatomy suitable for endovascular repair. The factors that determine anatomic suitability for endovascular repair include axial length of aneurysm, the shape of aneurysm neck, the diameter and length of proximal and distal landing zones, the caliber of the iliac arteries, aortic tortuosity, and presence of intraluminal calcification or thrombus [25, 26].

The up-front success rate of stent-graft implantation has been high, and EVAR has been associated with a reduction in short-term operative bleeding, postoperative hospital stays, and 30-day mortality [27]. Studies of long-term outcomes of endovascular repair versus conventional surgical repair show that up to 5 % of patients are left with *endoleaks*, indicative of residual blood flow into the aneurysm sac because of failure to completely exclude the aneurysm from the aortic circulation. Following EVAR surveillance imaging is recommended at 1, 6, and 12 months in order to detect endoleaks, as well as to confirm stent-graft position and assess the size and geometry of the excluded aneurysm sac [28]. The complications of endoleaks, including ongoing aneurysm expansion, translate into an approximately 10 % higher reintervention rate at 6 years after EVAR than after open surgery [29]. The EVAR-1 and DREAM trials showed that by 2–3-year post-procedure, the early advantages of EVAR are not sustained and that overall and aneurysm-related mortality are not different than from open surgical repair [24]. Due to the short-term benefits, EVAR is preferred for the subset of patients at high risk from operative repair, typically older patients or those with significant comorbidities. However, among very high-risk aneurysm patients who are ineligible for open repair, EVAR did not reduce mortality when compared with medical management alone [30]. The choice of any therapeutic strategy must be individualized and factor in both patient preferences and comorbidities; ACC/AHA guidelines classify endovascular repair as class IIb for patients at high risk for intervention (although the optimal management of these patients remains unclear) [27].

Surgical repair of descending thoracic aortic aneurysms, which has historically performed via left thoracotomy, is associated with significant mortality and the risk of paraplegia due to of spinal cord ischemia. Thoracic endovascular aortic repair (TEVAR) offers a less invasive alternative with lower surgical morbidity and mortality, provided the aortic anatomy is favorable [31]; in analogy to EVAR, endoleak is again a known complication (with a 12–18 % incidence) that necessitates surveillance imaging at 1-, 6-, and then 12-month intervals [32, 33]. There have been no randomized trials of TEVAR versus open repair, but both a large registry [34] and a large meta-analysis of mixed descending thoracic aorta disease have documented reduced periprocedural morbidity and

mortality, TEVAR is now frequently utilized for treating descending thoracic aortic aneurysms [11, 31]. Five-year follow-up of a Medicare population treated by TEVAR versus open repair for mixed descending thoracic aortic disease revealed no difference in late survival [35].

Vasculoprotective and anti-atherosclerotic measures are essential in patients with aortic aneurysm syndromes. Medication should be prescribed to reduce d*P*/d*t* and blood pressure. Patients must quit smoking entirely. Lipids should be well controlled, with a target low-density lipoprotein of <70 mg/dL [7]. Meta-analyses of trials of statins in abdominal aortic aneurysm suggest a possible reduction in aneurysm growth [36] or improvement in post-repair survival [37], but no randomized trials exist to support this hypothesis.

There are no controlled clinical trials that document a benefit of aspirin for patients with aortic aneurysm. Several studies have investigated macrolide and tetracycline antibiotics based on their anti-inflammatory properties, inhibitory effects on tissue matrix metalloproteinases, and a possible link between vessel inflammation and infectious agents such as *Chlamydia*. Small short-term studies suggest reduction in rates of aneurysm growth, but more robust clinical evidence is needed before introduction of these antibiotics into more widespread practice [38].

All patients with aortic aneurysms should also avoid activities that could acutely and markedly raise aortic wall stress, termed "burst activities." Such precautions include restrictions on heavy lifting or pushing (for employment or for isometric exercise), straining, and jumping.

Aortic Dissection

Introduction

While far less common than aortic aneurysms, aortic dissection is a highly lethal acute condition with an early mortality believed as high as 1–2 %/h. Prompt early diagnosis and treatment is essential. With recognition of dissection, survival can be dramatically improved. Importantly, dissections may occur in segments of aorta even without overt aneurysm. The process of aortic dissection begins with a tear in the aortic intima that exposes a diseased medial layer to the forces of systemic pressure of blood within the aortic lumen. The systolic force of aortic blood flow may cleave the media longitudinally into two layers, producing a blood-filled false lumen within the aortic wall that propagates distally (or sometimes retrograde) a variable distance. The result is the presence of both a true and a false lumen separated by an intimal flap.

Aortic dissections are classified according to location, based on one of several systems as depicted in Fig. 36.3. The classification schemes are intended to distinguish

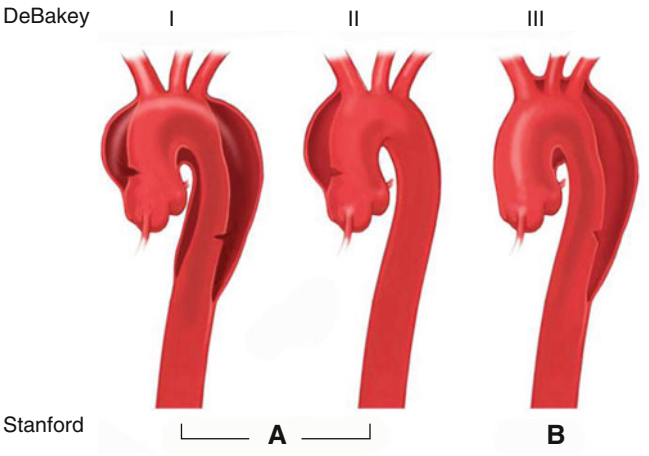

Fig. 36.3 Classification systems for aortic dissection: the DeBakey system characterizes aortic dissections into types I–III (involving both ascending and descending aorta, ascending aorta only, and descending aorta only, respectively), and the Stanford system classifies all dissections involving the ascending aorta as type A and all other dissections as type B (©Massachusetts General Hospital Thoracic Aortic Center, used with permission)

those dissections that involve the ascending aorta (type A) from those that do not (type B). Two-thirds of aortic dissections are type A and the remainder are type B. The distinction is clinically important because involvement of the ascending aorta carries a higher risk of early aortic rupture and death from cardiac tamponade, while those not involving the ascending aorta carry a much lower risk. Prognosis and management therefore differ according to the extent of aortic involvement.

Etiology

Disease of the aortic media, with degeneration of the medial collagen and elastin, is the most common predisposing factor for aortic dissection. Patients with Marfan syndrome have classic medial degeneration and are particularly high risk of aortic dissection at a relatively young age. The peak incidence of aortic dissection in patients without Marfan syndrome is in the sixth and seventh decades of life, with men affected twice as often as women [39]. Other connective tissue syndromes such as Ehlers-Danlos type IV (a defect in procollagen type III) and Loeys-Dietz also predispose to dissection. On a population level, a bicuspid aortic valve is as common as, if not more common than, Marfan syndrome in terms of overall cause of aortic dissection, due to its much higher prevalence [40]. A history of hypertension is present in the large majority of aortic dissection cases. Iatrogenic trauma from catheterization procedures, intra-aortic balloon counterpulsation, or cardiac surgery can also cause aortic dissection.

Clinical Manifestations

The most common presenting symptom of aortic dissection is severe pain, occurring in 90 % of cases [38]. The pain is typically retrosternal or interscapular, but it may also appear in the neck or throat, in the lower back, in the abdomen, or in the lower extremities, depending on the location of the aortic dissection. In fact, the pain may migrate as the dissection propagates distally and compromises flow to other organs. The pain of aortic dissection is often of abrupt onset and maximum at the start, in direct contrast to pain in acute coronary syndrome which may build over several minutes to its maximum. The pain in aortic dissection is most often characterized as "sharp" or "stabbing," or alternatively as "tearing" or "ripping," in quality [38]. On the other hand, the description of the pain is sometimes relatively nonspecific. Less typical presentations include congestive heart failure (due to acute aortic insufficiency), syncope, stroke, acute coronary syndrome (due to dissection involving the coronary artery), mesenteric ischemia, or limb ischemia.

Hypertension on presentation is a common finding, especially among most of those with type B aortic dissection. Hypotension, particularly among those with type A dissections, suggests the presence of rupture into the pericardium (causing cardiac tamponade), coronary ischemia, or the presence of severe aortic insufficiency. It is essential to recognize the presence of *pseudohypotension*, which represents a falsely low measure of blood pressure due to involvement of the affected extremity's subclavian artery by the dissection. Pulse deficits are a common finding on physical examination when there is involvement of any of the subclavian, carotid, or femoral arteries. Acute aortic insufficiency may occur in up to one-half of those with type A dissection. While the presence of congestive heart failure or a widened pulse pressure should raise one's suspicion of acute aortic insufficiency, the diastolic murmur is often difficult to appreciate.

Involvement of branch arteries by the aortic dissection may produce a variety of vascular complications. Compromise of the ostium of a coronary artery—the right coronary artery is most often involved—may cause myocardial ischemia or acute infarction. Involvement of the brachiocephalic or left common carotid arteries may produce a stroke or coma. When a dissection extends into the abdominal aorta, it may compromise flow to one or both renal arteries producing acute renal failure with an exacerbation of hypertension. Another consequence may be mesenteric ischemia presenting as abdominal pain. Finally, an extensive dissection may compromise one of the common iliac arteries, causing femoral pulse deficits or lower extremity ischemia.

The findings on chest roentgenography are typically nonspecific and rarely diagnostic. An enlarged mediastinal silhouette is present in 62 % of cases [38] and is often the factor that first prompts suspicion of aortic dissection among patients with chest pain. A small left pleural effusion (a transudate produced by the inflamed aortic wall) is commonly seen when there is involvement of the descending thoracic aorta. It should be emphasized that under no circumstances does a normal chest roentgenogram exclude the diagnosis of aortic dissection, as the chest roentgenogram is indeed normal in 12 % of cases [38].

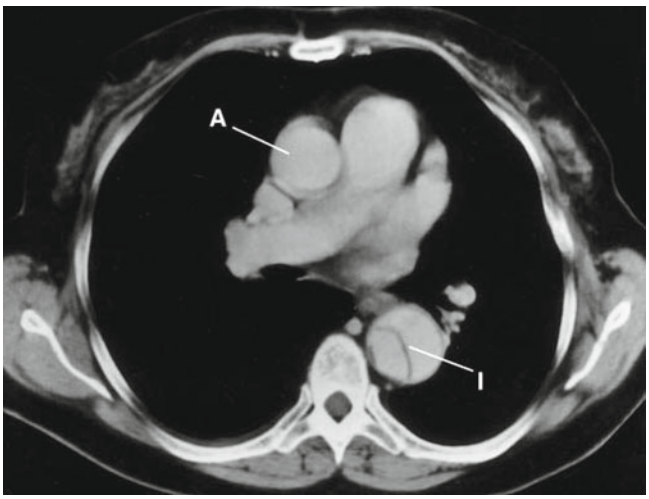

Fig. 36.4 A contrast-enhanced CT scan of the chest showing an intimal flap (*I*) separating the two lumens of the descending thoracic aorta in a type B aortic dissection. Note that there is no evidence of a dissection flap in the ascending aorta (*A*)

Diagnosis

When the possibility of aortic dissection is being considered, it is essential that one promptly confirms or excludes the diagnosis with an appropriate imaging study [41]. Computed tomographic angiography (CTA), magnetic resonance angiography (MRA), transesophageal echocardiography (TEE), and catheter-based aortography can diagnose the presence of aortic dissection. CTA (Fig. 36.4) is the modality of choice in most cases, as it is has a high sensitivity, is readily available in most emergency departments, is quick to obtain, and provides excellent anatomic detail. TEE (Fig. 36.5) is less readily available and is semi-invasive but preferred when there is a contraindication to CTA or if the anatomy of the aortic valve needs to be assessed. MRA is less convenient in the emergency setting, given that it is often not readily available and poorly suited to the management of unstable patients, but it is useful in patients with contraindications to CTA. Aortography is the least sensitive of the imaging modalities and is also invasive and time consuming, so it is rarely used for diagnostic purposes.

At present biomarkers are not sufficient to definitively exclude aortic dissection when there is a reasonable pretest probability. The D-dimer, studied with a cutoff value of <500 ng/mL

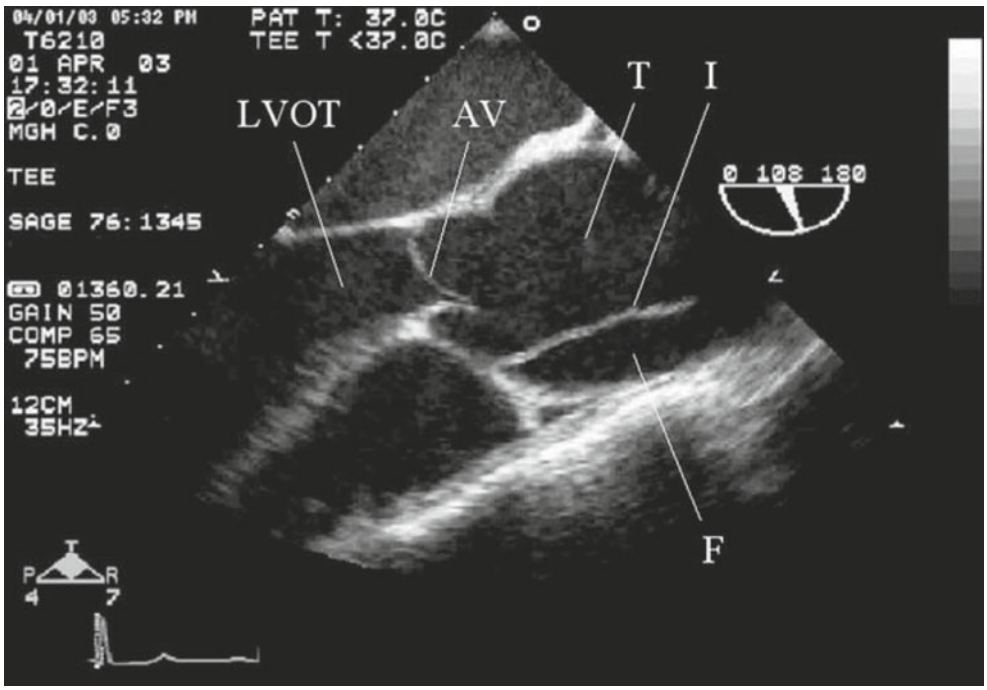

Fig. 36.5 A transesophageal echocardiogram of the ascending aorta in long axis in a patient with a type A aortic dissection. The left ventricular outflow tract (*LVOT*) and aortic valve (*AV*) are on the left, and the ascending aorta extends to the right. Within the aorta is an intimal flap (*I*) that originates at the level of the sinotubular junction. The true (*T*) and the false (*F*) lumens are separated by the intimal flap

in those presenting within 24 h of symptom onset, has a negative predictive value of only 97.6 % [42]. Given the lethality of acute aortic syndromes, coupled with the fact that D-dimer may not be elevated in cases of intramural hematoma (see section "Intramural Hematoma of the Aorta") or when there is not a patent false lumen, D-dimer is not recommended in the diagnostic algorithm to exclude aortic dissection [11]. Biomarkers with future promise include smooth muscle myosin heavy chain, calponin, and soluble elastin fiber degradation products [43].

Treatment

Whenever there is a suspicion of aortic dissection, medical therapy should be instituted immediately while imaging studies are ordered rather than waiting for the diagnosis to be confirmed. The primary goal of medical therapy is to reduce the systolic force of blood ejected from the heart into the aortic lumen by reducing dP/dt, as a means to halt any further progression of the aortic dissection and to reduce the risk of rupture. dP/dt is partly heart rate dependent, and overall shear stress on the aorta is reduced with a lesser number of left ventricle ejections per minute, and so the suggested HR goal is <60 beats/min. The secondary goal is to reduce systolic blood pressure to 100–120 mmHg, or to the lowest level that maintains adequate cerebral, cardiac, and renal perfusion. Beta-blockers are the first-line therapy to achieve these goals, and intravenous agents such as propranolol, metoprolol, or esmolol (ultrashort acting) should be administered. Intravenous labetalol, which acts as both an alpha- and a beta-blocker, may be particularly useful in aortic dissection for reducing both dP/dt and hypertension. Finally, after beta-blockers have been initiated, intravenous vasodilators such as nitroprusside may be added to control hypertension more precisely on a minute-by-minute basis; starting vasodilators without prior beta-blockade may result in reflex tachycardia and increased dP/dt. Analgesics are an important adjunct as a means to inhibit the intense sympathomimetic responses to pain from acute aortic dissection.

When a patient first presents with aortic dissection, the physician must always document which arm has the higher blood pressure and then use only that arm for subsequent hemodynamic monitoring. Moreover, when patients present with significant hypotension, *pseudohypotension* should be carefully excluded by measuring arterial pressure in all extremities. When true hypotension occurs due to hemopericardium and cardiac tamponade, patients should be treated with volume expansion and taken to surgery without delay, as early mortality in this setting is extremely high. Pericardiocentesis should only be performed as a last resort in this setting as it may precipitate exsanguination, hemodynamic collapse, and death [44].

After the diagnosis of aortic dissection has been confirmed, one must choose a strategy of either medical therapy or a combined medical and surgical/endovascular approach. Whenever an acute dissection involves the ascending aorta, immediate surgical repair is indicated in order to minimize the risk of life-threatening complications such as rupture, cardiac tamponade, or severe aortic insufficiency. Conversely, if the dissection spares the ascending aorta, patients have been generally found to fare as well with medical therapy as with surgical repair. However, when a type B dissection is associated with a serious complication, such as refractory hypertension, intractable pain, rapid expansion of the false lumen, or malperfusion with

evidence of end-organ ischemia due to compromise of a major branch artery, intervention is indicated. Endovascular approaches are now advocated for the treatment of complicated acute type B dissection patients, as they appear to have mortality comparable with open surgical repair [45, 46]. Nevertheless, the long-term effects of stent-graft deployment in an acutely dissected aorta remain unknown, and long-term follow-up clinical data are needed [47]. The potential benefits of stent-grafting for uncomplicated type B aortic dissection are also uncertain. In the INSTEAD (the INvestigation of STEnt Grafts in Aortic Dissection) trial of patients with uncomplicated type B aortic dissection who were enrolled more than 2 weeks after the sentinel dissection, when compared with optimal medical therapy, stent-grafting offered no survival benefit at 2 years of follow-up, although there was a beneficial effect on aortic remodeling in terms of thrombosis of false lumen and reconstitution of the true lumen [48]. The ADSORB (Acute Dissection Stent-Grafting or Best Medical Treatment) trial is designed to assess anatomic and clinical outcomes of stent-grafting versus medical management in the acute phase (less than 2 weeks) following uncomplicated type B dissections, with data expected by 2015. Finally, although randomized trial data is not available, there is consensus that the endovascular approach is superior for traumatic thoracic aortic injuries [49] and for ruptured descending thoracic aortic aneurysms [50].

Prognosis

Whether treated medically or surgically, patients with acute aortic dissection who survive the initial hospitalization generally fare well thereafter. However, potential late complications include aneurysm formation (and possible rupture), recurrent dissection, and aortic valve insufficiency. Partial thrombosis of the false lumen in type B dissections (as opposed to either a patent or completely thrombosed false lumen) confers a 2.7 relative risk of mortality at 3-year follow-up [51]. Medications to reduce dP/dt and control hypertension can dramatically reduce the incidence of late complications and should therefore be continued indefinitely [52]. Beta-blockers are the drug of choice in both acute treatment of dissection and chronic therapy and are associated with a reduction in mortality [53], but typically additional medications are needed to sufficiently control systolic blood pressure. In addition to beta-blockers, calcium channel blockers and angiotensin-converting enzyme inhibitors may be beneficial, although the data on these agents is mixed.

Patients are at highest risk of complications during the first 2 years after aortic dissection. Progressive aneurysm expansion typically occurs without symptoms, so patients must be followed closely with serial aortic imaging. This can be done using CT, MR, or TEE, although most clinicians prefer CT. All patients should have a baseline imaging study prior to hospital discharge, with follow-up examinations performed at 1, 3, 6, and 12 months following the dissection and then annually thereafter, provided that the anatomy remains stable.

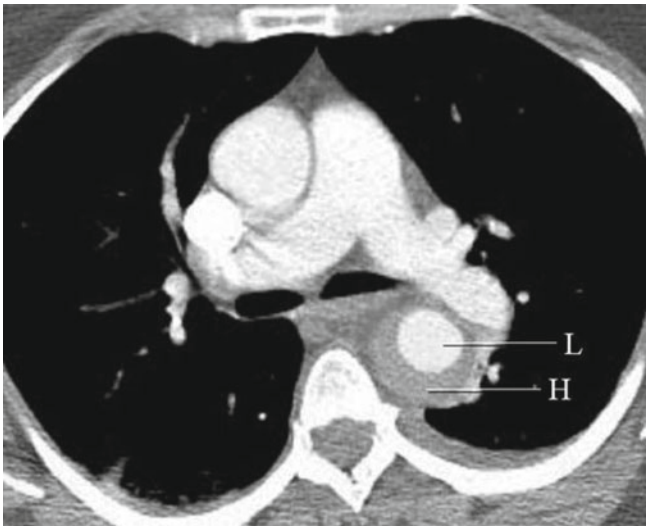

Fig. 36.6 Intramural hematoma of the aorta. A contrast-enhanced CT scan of the chest demonstrates crescentic thickening of the descending thoracic aorta wall consistent with an intramural hematoma (*H*). Note that there is no intimal flap within the lumen (*L*) nor does any contrast enter the hematoma. A small left pleural effusion is also present

Intramural Hematoma of the Aorta

Intramural hematoma of the aorta, which represents approximately 6 % of acute aortic syndromes, is best defined as an atypical form of classic aortic dissection. Its etiology is not entirely certain: Some cases may involve rupture of the vasa vasorum within the aortic media, resulting in a contained hemorrhage within the aortic wall, whereas others appear to arise from microscopic tears in the aortic intima the that allow blood to seep into the aortic media but without free communication with the true lumen. This hematoma may then propagate longitudinally along a variable length of the aorta, but without any distal communication with the aortic lumen. In contrast to classic aortic dissection (which more often involves the ascending aorta), intramural hematoma affects the descending aorta in 60 % of cases. In addition, intramural hematoma is less frequently associated with preexisting aneurysms, murmurs of aortic insufficiency, an abnormal electrocardiogram, myocardial ischemia, leg pain, or pulse deficits [54]. On cross-sectional imaging, intramural hematoma appears as a crescentic thickening around the aortic wall (Fig. 36.6) rather than as true and false lumens separated by an intimal flap, although approximately one-sixth of patients with intramural hematoma will ultimately demonstrate findings consistent with classic aortic dissection on

follow-up radiography. It is important to note that the presence of an intramural hematoma may go undetected on aortography. The prognosis and management of intramural hematoma is essentially the same as that of classic aortic dissection [55], and a similar strategy for follow-up surveillance imaging is indicated.

Takayasu's Arteritis

Introduction

Takayasu's arteritis is a chronic inflammatory disease of unknown etiology that involves the aorta and its branches. It typically affects young women, with a mean age of onset of 29, and women affected eight times as often as men [56]. It occurs more often in Asia and Africa than in Europe or North America. Takayasu's arteritis typically has two stages. The first is an early stage in which there is active inflammation involving the aorta and its branches. This then progresses at a variable rate to a later sclerotic stage, in which there is intimal hyperplasia, medial degeneration, and obliterative changes of the aorta and affected arteries. The majority of the resulting arterial lesions are stenotic, but aneurysms may occur as well. The aortic arch and brachiocephalic vessels are most often affected, but the abdominal aorta is also commonly involved. The pulmonary artery may occasionally be involved. The disease may be diffuse or patchy, with affected areas separated by lengths of normal aorta. The patchy nature can frustrate attempts to render a diagnosis based on biopsy.

Clinical Manifestations

Most patients present initially with symptoms of a systemic inflammatory process, such as fever, night sweats, arthralgias, and weight loss. The nonspecific nature of these symptoms creates a frequent delay, often of months to years between the onset of symptoms to the time the diagnosis of arteritis is made. Indeed, at the time of diagnosis, 90 % of patients have already entered the sclerotic phase and manifest symptoms of vascular insufficiency, typically with pain in the upper (or less often lower) extremities [57]. The subclavian artery is the most commonly affected vessel in Takayasu's arteritis (>90 %). There will often be absent pulses and diminished blood pressures in the upper extremities, and there may be bruits audible over affected arteries. Significant hypertension due to renal artery involvement occurs in more than half of patients, but the presence of hypertension may be difficult to recognize due to the diminished pulses. Aortic insufficiency may result from proximal aortic involvement. Congestive heart failure may result from either the hypertension or aortic insufficiency. Involvement of the coronary artery ostia may cause angina or myocardial infarction, and carotid artery involvement may cause bruits, cerebral ischemia, or stroke. Abdominal angina may result from mesenteric artery compromise. The overall 15-year survival for those diagnosed with Takayasu's arteritis is 83 %, with the majority of deaths due to stroke, myocardial infarction, or congestive heart failure [58]. The survival rate for those with major complications of the disease is as low as 66 %, while it may be as high as 96 % for those without a major complication.

Diagnosis

During the acute phase, coincident with a systemic inflammatory state, laboratory abnormalities include an elevated erythrocyte sedimentation rate, mild leukocytosis, anemia, and elevated immunoglobulin levels. The diagnosis is most accurately made, however, by the angiographic findings of stenosis of the aorta and stenosis or occlusion of its branch vessels, often with post-stenotic dilatation or associated aneurysms. Specific clinical criteria have been proposed for making a definitive diagnosis of Takayasu's arteritis and include subclavian bruit, reduced brachial pulses, and intermittent claudication [59].

Treatment

The primary therapy for those in the acute inflammatory stage of Takayasu's arteritis is corticosteroids, which reduce inflammation and may be effective in improving the constitutional symptoms and slowing disease progression [60]. When steroid therapy is ineffective, other immunosuppressive agents such as cyclophosphamide or methotrexate may be added, typically in conjunction with a rheumatologist. Nevertheless, it remains unknown whether medical therapy actually reduces the risk of major complications or prolongs life. Surgery may be necessary to bypass or reconstruct segments of the aorta or branch arteries. Most commonly surgery is performed to bypass the coronary, carotid, or renal arteries, or to treat aortic insufficiency. More recently, as an alternative to surgery, balloon angioplasty has been used to successfully dilate stenotic lesions of either the aorta or renal arteries.

IgG4 Aortopathy

The most newly recognized of the noninfectious aortitis syndromes occurs in association with IgG4-related systemic disease. IgG4-related systemic disease involves proliferation of plasma cells and increased serum IgG4, with resultant

inflammation and fibrosis that can insidiously strike numerous organ systems including pancreas, submandibular glands, and lymph nodes [61]. Transmural lymphoplasmacytic inflammatory cell infiltrate in the aorta wall is believed to exert a role in aneurysm pathogenesis. IgG4-related systemic disease seems to primarily involve the ascending, arch, and abdominal aorta, and in a single-center experience, it represented the etiology of 9 % of noninfectious thoracic aortitis, and overall was present in 0.5 % of resected thoracic aortas [62].

Conclusion

Diseases of the aorta arise from a variety of acute and chronic pathophysiologic processes and may produce signs and symptoms involving any organ system. The protean manifestations of aortic diseases make it essential that physicians and other providers have a high index of suspicion in appropriate clinical contexts. Early recognition is essential to initiation of timely treatment and improved outcomes in patients with diseases of the aorta.

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Cardiovascular Disease in Women

37

Benjamin D. Mackie and Nanette Kass Wenger

Introduction and Background

Gender differences in health and disease have emerged as a focal point of research throughout the global healthcare community during the past decade. The landmark report by the Institute of Medicine in 2001 commonly referred to as "Does Sex Matter?" brought gender-based health issues to the forefront of the healthcare landscape [1]. Women were traditionally dramatically underrepresented in clinical trials, specifically those dedicated to CVD. This participation has shown steady improvement over the past 10 years through concerted efforts within the cardiovascular community [2, 3]. In 1997, only 30 % of US women were aware that cardiovascular diseases were the major cause of female mortality; this had improved to 54 % by 2009 [4].

Epidemiology CVD

Cardiovascular disease is the leading cause of death among women in the United States and in most countries worldwide. Among females, CVD accounts for more deaths than cancer, Alzheimer disease, chronic lower respiratory disease, and accidents combined [5]. Based upon 2007 statistics, there is approximately 1 CV death per minute among women in the United States, a total of 421,918 female deaths from CVD annually, with approximately half attributable to coronary heart disease (CHD). This is a stark decrease from 1980 with three times the number of annual deaths in women from CHD compared to the present (Fig. 37.1) [5]. Half of this improvement results from more extensive and aggressive secondary prevention therapies, treatment for acute coronary syndromes (ACS) and heart failure, and revascularization for stable or unstable CHD by coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). The remaining risk reduction resulted from primary preventive strategies for CV risk reduction. An unsettling observation in the same data set is that obesity and diabetes accounted for a net increase of 59,500 deaths women versus men from CHD in the year 2000 [6]; diseases that are increasing rapidly in incidence and prevalence. Similar trends are seen globally; internationally, CVD remains the leading cause of death among women in both developed and developing countries. By 2040, women are predicted to represent a higher proportion of CVD deaths than men [7].

Within the United States, substantial racial and ethnic disparities exist among CVD rates in women. The prevalence of CVD among black women is 286.1/100,000 compared to 205.7/100,000 in white women. Despite increases in overall awareness of CVD as the leading cause of death among US women in the past decade [4], disparity of CVD awareness persists being less among black versus white women.

Ischemic Heart Disease

Ischemic heart disease (IHD) encompasses not only CHD in the classic form of an obstructed epicardial coronary artery but also coronary vasospasm, microvascular dysfunction, coronary artery dissection, stress-induced cardiomyopathy, and plaque erosion [8]. CHD is the most common pathophysiological entity, accounting for one-half of all female CVD-related deaths in the USA in 2007. In general, CHD onset occurs 10 years later in females compared to males, with the percentage of men with CHD at any given age being higher than that of women.

The prevalence of CHD in females increases after menopause and approaches that seen in men by the seventh decade of life. Although not fully understood, favorable estrogen effects on high-density lipoprotein cholesterol (HDL-C) and

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_37, © Springer Science+Business Media New York 2013

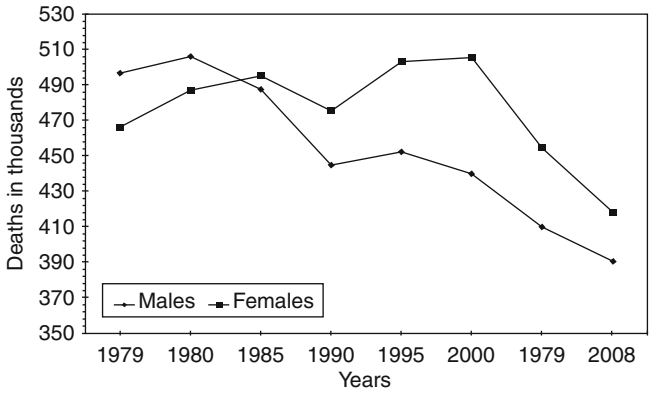

Fig. 37.1 Cardiovascular disease mortality trends for males and females (United States: 1979–2008). Cardiovascular disease excludes congenital cardiovascular defects (International Classification of Diseases, 10th Revision [ICD-10] codes I00–I99). The overall comparability for cardiovascular disease between the International Classification of Diseases, 9th Revision (1979–1998) and ICD-10 (1999–2008) is 0.9962. No comparability ratios were applied (Reprinted from Roger et al. [5]. With permission from Lippincott Williams & Wilkins)

vascular endothelial function may be mechanistically responsible for the cardioprotective effects of endogenous estrogens. Environmental and lifestyle factors play a paramount role in the development of CHD in women. Women who live in countries with a high incidence of CHD (Eastern Europe) have up to six times the rate of disease compared to men living in countries with traditionally less CHD (France, Italy, Japan) [9].

Overall mortality in women from CHD has decreased since 1980, initially lagging and recently outpacing CHD mortality decreases seen in men over the same time period [5]. Worrisome is a trend toward increased CHD mortality in young women ages 35–44, 1.3 % annually since 1997. Much of this increase is attributed to rapidly increasing rates of obesity with diabetes and dyslipidemia playing a major role [6].

Women have higher rates of myocardial ischemia and IHD-related mortality compared to men of similar age, especially pronounced in the diabetic population. Paradoxically, women tend to have preserved left ventricular systolic function and less obstructive coronary artery disease (CAD). Complex pathophysiological mechanisms beyond those traditionally associated with obstructive CAD likely play a role. Data from the Women's Ischemia Syndrome Evaluation (WISE) study [10] propose a paradigm of *microvascular angina* in women (Fig. 37.2), a model that provides explanation for the increased incidence of nonobstructive coronary atheroma in women experiencing myocardial ischemia and angina. The increased microvascular dysfunction can be partially explained by the higher prevalence of hypertension in women. Systemic metabolic, hormonal, and inflammatory factors convey increased thrombotic risk in women which can predispose to plaque erosion and thrombosis which is twice as likely in women compared to men [11]. Abnormal coronary reactivity coupled with nonobstructive atheroma is an emerging hypothesis to explain the pathophysiological mechanisms of ischemia in women with nonobstructive IHD [8] (Fig. 37.3). Evaluation of 50 women presenting with ACS and nonobstructive CAD showed that 40 % had plaque disruption when evaluated by IVUS; however, the distribution of plaque disruption with IVUS did not correlate with ischemia patterns on cardiac MRI. These data suggest that relief of spasm or spontaneous endogenous fibrinolysis plays a role in ACS in women with nonobstructive CAD [12].

IHD Risk Factors and Risk Assessment

The Framingham Risk Score (FRS) is the traditional tool used to calculate a patient's 10-year risk of CAD, death, or myocardial infarction (MI). It is widely accepted that the FRS underestimates the IHD risk in women, classifying >90 % of women as being low risk [13]. Limitations of the FRS primarily result from the focus on short-term risk, lack of inclusion of family history, the prevalence of subclinical CHD in women who score in the low-risk category, and over- or underestimation of risk in nonwhite populations [14]. The Reynolds Risk Score (RRS) adds family history and hsCRP to calculate 10-year sex-specific cardiac risk score using an equation. The RRS reclassified 40 % of women who were deemed intermediate risk by FRS into the high-risk category [15]. An updated Framingham Risk Profile was published in 2008 that is sex specific with a primary end point of CVD risk and allows for the separation of individual risk components (congestive heart failure, intermittent claudication, and stroke) [16]. The 2011 American Heart Association Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women, emphasizing lifetime risk, newly categorized women as high risk (established CV disease or coronary risk equivalents), at risk, or at ideal CV health based on multiple risk factors (Fig. 37.4) [17]. Incorporated into the "at-risk" category were a history of pregnancy-induced complications (gestational diabetes, preeclampsia, or pregnancy-related hypertension) and a history of systemic autoimmune collagen vascular disease. Of all pregnancy-induced complications, preeclampsia is the most reliable predictor of future CVD risk [18]. A pregnancy history was recommended as a routine component of a woman's CV risk assessment.

Differences exist between women and men in regard to traditional CVD risk factors. Diabetes is highly prognostic in women (a 3.3-fold increased risk) conferring a higher risk of CHD in women than in men [19, 20]. Female diabetics are a population without a decrease in CHD mortality over the past 30 years, contrasted with a 43 % mortality reduction among diabetic men during the same time period [21]. A similar risk disparity is seen with smoking; women who

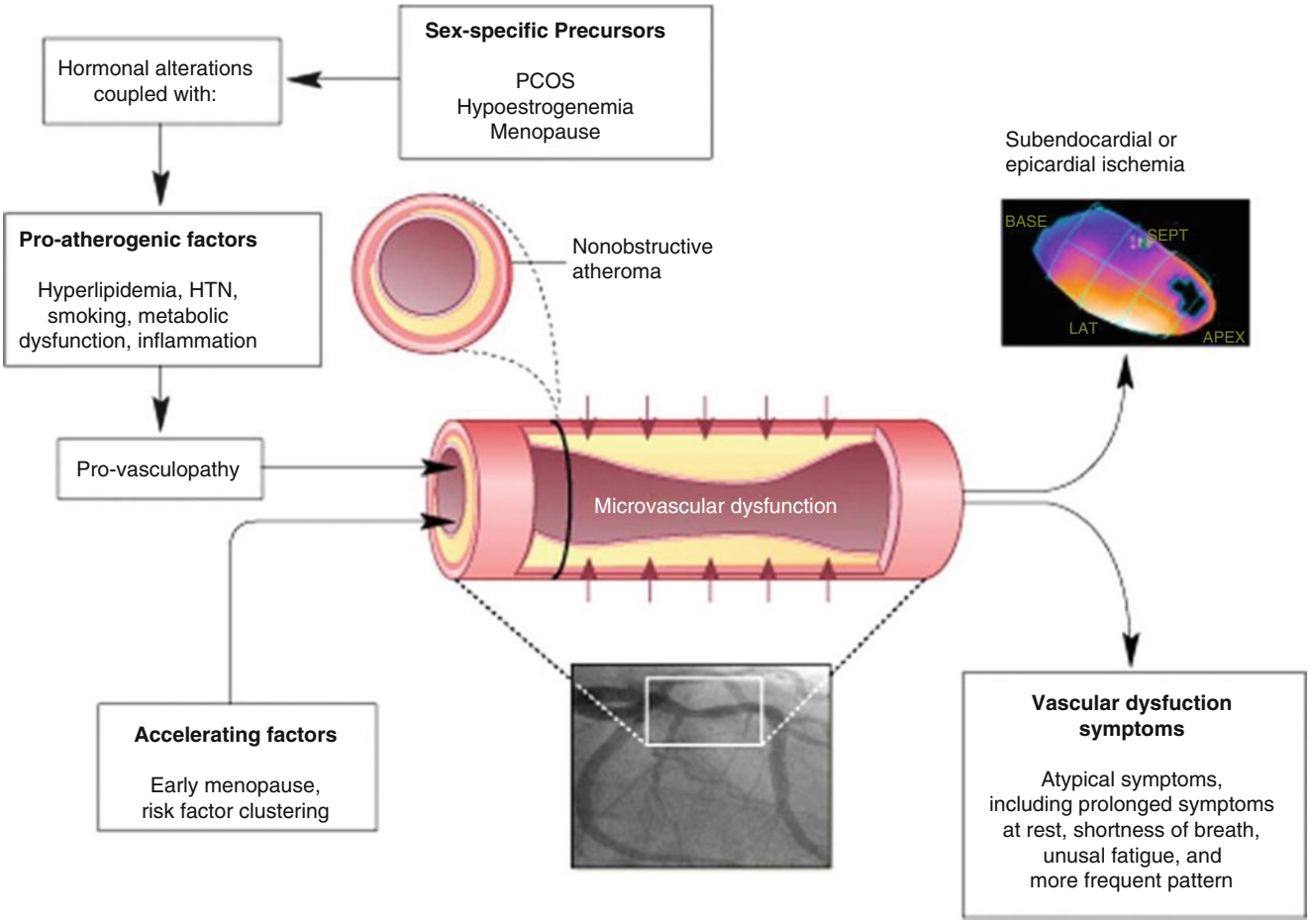

Fig. 37.2 Model of microvascular angina in women (Figure illustration by Rob Flewell) *HTN* hypertension, *PCOS* polycystic ovary syndrome (Reprinted from Shaw et al. [8]. With permission from Elsevier)

smoke have a 25 % greater risk of MI than men who smoke, with smoking linked to almost 50 % of all IHD events in women [22, 23]. While low-density lipoprotein cholesterol (LDL-C) is the most reliable predictor of CHD in men, low levels of high-density lipoprotein cholesterol (HDL-C) and the ratio of total cholesterol (TC) to HDL-C are highly predictive of cardiovascular events in women (a TC/HDL > 3.2 indicates increased risk IHD). An absolute level of HDL-C < 30 mg/dl is strongly associated with cardiovascular mortality in women, and increased TG with low HDL-C imparts increased risk. A premature family history of CHD is more common in women than men with CHD, defined as a first-degree male relative with CHD before age 55 or a female relative with CHD before age 65 [24].

Clinical Presentation

The clinical presentation of IHD in women most frequently involves a chest pain syndrome commonly including atypical features. In general, women are more likely than men to have chest pain syndromes that are not related to the presence of hemodynamically significant atherosclerosis in large epicardial coronary arteries [25]. Women with stable angina and imaging evidence of ischemia described their chest pain as more intense, different in character (usually sharp or burning), often with radiation of the pain to the neck or throat or described some type of discomfort in their throat; were more likely to report pain elsewhere in the body; and were more likely to report palpitations compared to men [26]. Women may present with milder symptoms or atypical prodromes such as fatigue. Women presenting to the emergency department for evaluation of chest pain were more likely than men to report dyspnea, nausea vomiting, diaphoresis, indigestion, and arm or shoulder pain [27]. Mental stress, rest, and sleep are also more likely to induce angina in women than in men. Of women with known CHD, 37 % present with SCD, compared to 56 % of men. In patients without known CHD, more women than men present initially with SCD (63 vs. 44 %).

Data from the Women's Ischemia Syndrome Evaluation (WISE) study documented the absence of obstructive coronary disease in over 50 % of women presenting with anginal

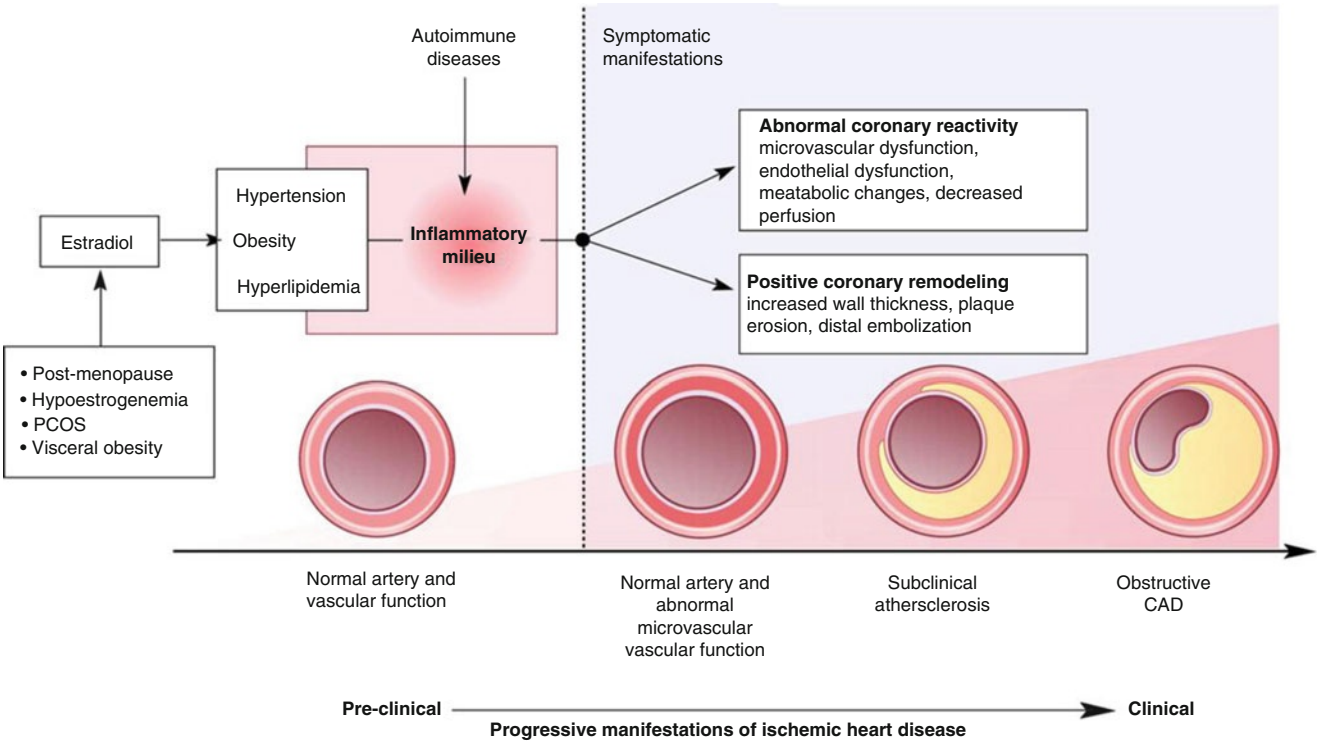

Fig. 37.3 Overarching working model of ischemic heart disease pathophysiology in women (Reprinted from Shaw et al. [8]. With permission from Elsevier)

symptoms and myocardial ischemia at noninvasive testing. Thirty-three percent had completely normal angiographic appearance of their coronary arteries [28]. Women are more likely to present without chest pain in the setting of acute MI and have higher inhospital mortality. These gender differences are most pronounced in younger patients and are attenuated with older age [29]. Ten to twenty-five percent of women presenting with acute coronary syndrome (ACS), including ST-segment elevation MI, have nonobstructive CAD at angiography, compared to 6–10 % of men. Paradoxically, women have worse ACS clinical outcomes despite having less obstructive CAD and less severe MI [30–32]. Women with ACS without obstructive CHD are less likely to receive guideline-based ACS therapies [33]. Advanced age, underutilization of coronary angiography and revascularization, and advanced comorbidities are plausible explanations for this gender difference; this mortality gap, although lessening, persists among young women [34–36].

Diagnostic Testing for Suspected IHD
(See Chaps. 9, 12, and 14)

Recommendations for noninvasive diagnostic imaging in women parallel those for men, with stress imaging generally recommended in women at intermediate to high risk for CAD [37]. Making the diagnosis of IHD can be challenging in women, given their lower prevalence of obstructive CHD and thus lower pretest probability, resulting in a higher likelihood of a false-positive test for obstructive CHD. On average, women are exposed to higher cumulative yearly doses of radiation from medical imaging, and thus radiation exposure should be taken into account when selecting a cardiac imaging modality [38].

Often the first-line test in the evaluation for IHD is an exercise ECG. A recent report from the Women's Study [39] showed initial ETT as a cost-effective option in women able to exercise when compared to SPECT imaging; however, myocardial perfusion imaging tests are diagnostically and prognostically more reliable than exercise ECG testing in women. The use of cardiac specific positron emission tomography (PET) has dramatically increased over the past decade and has proven to be highly accurate in women. It has the highest sensitivity and specificity of all noninvasive cardiac tests for the detection of obstructive CAD [40, 41]. Stress echocardiography is another reliable noninvasive modality to assess for obstructive CAD in women. There are no differences in diagnostic accuracy between women and men evaluated with either exercise stress or dobutamine stress echocardiography. Exercise stress echocardiography has the additional benefits of exercise data to quantify functional capacity, echocardiographic images to define cardiac anatomy, and the absence of radiation exposure.

Risk status	Criteria
High risk (≥1 high-risk states)	Clinically manifest CHD Clinically manifest cerebrovascular disease Clinically manifest peripheral arterial disease Abdominal aortic aneurysm End-stage or chronic iodney disease Diabetes mellitus 10-year Predicted CVD risk ≥10 %
At risk (≥1 major risk factor[s])	Cigaretie smoking SBP ≥120 mmHg, DBP ≥80 mmHg, or treated hypertension Total cholesterol ≥200 mg/dL, HDL-C <50 mg/dL, or treated for dyslipidemia Obesity, particulary central adiposity poor diet Physical inactivity Family history of premature CVD occuming in first-degree relatives in men <55 year of age or in women <65 year of age Metabolic syndrome Evidence of advanced subclinical atherosclerosis (e.g., coronary calcification, carotid plaqua, or thickned IMT) Poor exercise capacity on tredmil test and/or abnormal heart rate recovery after stopping exercise Systemic autoimmune collagen-vascular disease (e.g., lupus or rheumatoid arthritis) History of preeclampsia, gestational diabetes, or pregnancy-induced hypertension
Ideal cardiovascular health (all of these)	Total cholesterol <200 mg/dL (untreated BP <120/<80 mmHg (untreated) Fasting blood glucose <100 mg/dL (untreated) Body mass index <25 kg/m^2 Abstinence from smoking Physical activity at goal for adults >20 year if age: ≥150 min/week moderate intensity, ≥75 min/week vigorous intensity, or combination Health (DASH-like) diet (see appendix)

CVD indicates cardiovascular disease, CHD ciribart heart disease, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL-C* high-density lipoprotein cholesterol, *IMT* intima-media thickness, *BP* blood pressure, and *DASH* Dietary Approaches to stop Hyperetension

Fig. 37.4 Classification of CVD risk in women (Reprinted from Mosca et al. [17]. With permission from Lippincott Williams & Wilkins)

Management of IHD in Women

Risk Factor Prevalence and Management

The traditional risk factors for IHD (age, tobacco use, dyslipidemia, diabetes mellitus, and hypertension) are integral for the development of CHD in women as in men. However, the weight of these factors differs substantially between women and men, particularly the risks associated with tobacco use and diabetes mellitus. In general, guidelines for the prevention of IHD in women do not significantly differ from those for men. Despite these recommendations, women tend to receive less aggressive evaluation of and medical therapy for the treatment of IHD risk factors [42]. Underutilization of guideline-based therapies for IHD in women is also present in the clinical setting of acute coronary syndromes.

Tobacco Use

Smoking is the most important IHD risk factor for both genders. One-half of all coronary events in women are associated with smoking. There is a direct relationship between the amount of smoking and degree of conferred IHD risk. Women who smoke even 1–5 cigarettes/day have a 2.5 increased incidence of MI, which increases substantially (74.6) in those who smoke 40 cigarettes/day [43]. Smoking confers a higher relative risk of IHD in women (2.95) versus men (1.55) [23, 44]. Although there has been an overall decrease in the rate of smoking in the USA, this decrease has been much greater in men. This is especially concerning given the higher associated CHD risk in women. There is a rapid and robust exponential decrease in AMI risk following the cessation of smoking that is inversely proportional to time. The risk reduction curve flattens out after 50-month post-smoking cessation, while the relative risk of AMI remains slightly above 1 [45].

Counseling and multiple pharmacological therapies are available to aid patients in their efforts toward smoking cessation. Nicotine replacement products, bupropion, and varenicline all improve smoking cessation rates among women and men. None of these therapies are gender specific, and they are discussed in detail in Chap. 23.

Hypertension

At younger ages, women have lower blood pressure levels than men. Following menopause, this gap begins to narrow, and by age 60 years, women are more likely to have hypertension than men. The estrogen-depleted state following menopause is postulated to induce vasoconstriction via the renin-angiotensin-aldosterone and sodium sensitive pathways; however, menopausal hormone therapy does not have any beneficial effect on blood pressure and may worsen preexisting HTN. HTN in younger women is rarely attributed to oral contraceptive use with an absolute risk of 41.5 cases per 10,000 person years. The risk of oral contraceptive-associated HTN is further increased in female smokers [46]. Isolated systolic hypertension predominates in women. Multiple studies have shown cardiovascular benefit in controlling blood pressure in women; the most dramatic cardiovascular benefit is stroke reduction [47]. Thiazide diuretics are well tolerated, have minimal side effects, and may improve bone mineral density in older women [48]. Gender-dependent biochemical responses to drugs exist, with women experiencing a higher prevalence of hyponatremia and hypokalemia and men more likely to develop gout with thiazide diuretic therapy. Women are two to three times more likely than men to develop ACE-I-induced cough and more likely to experience peripheral edema related to calcium channel blocker use [46]. Special consideration must be given to the treatment of hypertension in women of childbearing age. ACE-Is and angiotensin receptor blockers should be avoided in pregnancy given their documented teratogenic effects. The development of hypertension during pregnancy confers increased maternal and fetal risk; preeclampsia during pregnancy carries an increased long-term risk of hypertension, ischemic heart disease, stroke, and venous thromboembolism. In one study, there was an increased risk of overall mortality, 1.49, 14.5 years after preeclampsia [49].

Dyslipidemia

IHD risk is well correlated with elevated levels of LDL-C and decreased levels of HDL-C in both women and men. Significant gender differences exist in LDL-C and HDL-C levels prior to menopause. Women have a lower cardiovascular risk at any given total cholesterol level compared to men. Many consider low HDL-C to be a stronger predictor of CHD than high LDL-C in women [50, 51]. The target HDL-C in women is 50 mg/dl in the ACC/AHA 2011 guidelines. Both lifestyle modification and pharmacotherapy are reasonable approaches to achieve the goal of HDL-C > 50 mg/dl [17]. However, the recent AIM-HIGH trial showed no cardiovascular benefits associated with high-dose niacin (in addition to a statin) and a small increased incidence of ischemic stroke despite the increase in HDL-C [52].

Many clinical trials have shown clear cardiovascular benefit in lowering LDL-C in women for both primary and secondary prevention strategies. The Scandinavian Simvastatin Survival Study (4S) and Treating to New Targets (TNT) studies showed the benefit of LDL-C reduction with statin therapy for secondary prevention [9], with similar cardiovascular event risk reductions in women and men. The JUPITER trial evaluated the efficacy of rosuvastatin 20 mg in older women and men for the primary prevention of cardiovascular events. At 2 years, there was a 46 % reduction in the hazard ratio (1.36–0.56, CI 0.46–0.69) for the composite end point of MI, stroke, hospitalization for unstable angina, or cardiovascular mortality in women. A similar but less robust reduction in composite end points was seen in men [53].

Similar to LDL-C, hypertriglyceridemia is not common in women during the premenopausal years, unless diabetes mellitus is present. After menopause, triglyceride levels begin to rise in women and equal those in men at about age 70 years. The treatment of hypertriglyceridemia in women should parallel that in men. Importantly, there continues to be less aggressive lipid management in women compared to men, despite multiple clinical trials showing equal efficacy in treatment of dyslipidemias in both genders [54].

Diabetes Mellitus

Diabetes is the most prognostically adverse IHD risk factor in women. Over the past decade, IHD mortality rates have decreased among nondiabetic women, diabetic men, and nondiabetic men, but IHD mortality increased by 23 % in diabetic women [47]. A meta-analysis of 450,000 patients with type 2 diabetes mellitus showed an increased relative risk for fatal IHD in women (3.5) and men (2.1) [55]. The greater increased risk in women may reflect the high percentage of IHD risk factor clustering in women with diabetes mellitus, particularly an atherogenic lipid profile. Diabetes mellitus in women completely negates the premenopausal protective effects of female gender. Diabetes should be aggressively managed in women; there are no major recommended differences in the treatment in women compared to men. Possibly the most important intervention is preventive. Recognizing women at risk to develop diabetes mellitus can provide the opportunity for lifestyle modification and pharmacotherapy that can delay or prevent the onset of diabetes mellitus [56]. Patients at risk are defined as having glucose intolerance or the metabolic syndrome per the Third Report of National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol [57]. Obesity, specifically visceral adiposity, has a strong correlation with insulin resistance, a dysmetabolic state, and an increased risk of acute MI [58].

Menopausal Hormone Therapy and Oral Contraceptive Use

Multiple clinical trials, particularly the Women's Health Initiative (WHI), have shown an increased risk of cardiovascular events in healthy women treated with menopausal

hormone therapy (MHT) [59, 60]. In women with CHD, multiple studies have shown beneficial effects on lipid profile, blood pressure, diastolic parameters of cardiac function, and rates of progression of carotid intimal thickness with MRT in women [60], but no clinical trial has shown beneficial cardiovascular outcomes. MRT cannot be endorsed to protect against the development of IHD in women. MRT currently carries a class III recommendation (no evidence of benefit and potential harm) by the American Heart Association for the prevention of IHD and in multiple ACC/AHA clinical practice guidelines [4]. The decision to initiate MRT for menopausal symptoms must be made on an individual basis weighing the non-cardiovascular benefits versus cardiovascular risks [61].

Oral contraceptive (OCP) use poses a low but not insignificant cardiovascular risk in women, principally because most women taking oral contraceptives are young and healthy and their absolute baseline risk of CHD is low (less than 1 %) [62]. The newer-generation OCPs have a lower estrogen content than their predecessors and are associated with lower risk of MI, CVA, and other thrombotic events. It is recommended that women who smoke and are over the age of 35 years seek alternative forms of contraception because of a clinically significant and meaningful increased risk of thrombotic events that may outweigh the benefits of preventing an unwanted pregnancy.

Management of Stable Angina and Acute Coronary Syndromes

Stable Angina

Stable angina is less aggressively managed in women compared to men. Evidence-based therapies are similar for women and men [63]. Despite this, women are less likely to undergo evidence-based revascularization procedures and receive less evidence-based pharmacotherapy for secondary prevention. Proposed reasons for this discrepancy include: increased rate of complications and poorer outcomes with some revascularization procedures, gender differences in description of clinical symptoms, and physician bias [54].

USA/NSTEMI

Treatment of biomarker-positive ACS in women mirrors that in men. However, significant gender differences occur in the recommendations for biomarker-negative ACS in the 2011 ACC/AHA guidelines. In a recent large meta-analysis, there was a nonsignificant 35 % higher odds of death or MI (OR, 1.35; 95 % CI, 0.78–2.35; *P* for interaction = 0.08) in women with biomarker-negative ACS treated with an initial invasive strategy compared to those treated with a conservative strategy; there was no difference among men in the composite end point [64]. The same study documented clearly that women with biomarker-positive ACS benefit from an early invasive strategy with revascularization when appropriate. One possible explanation for this difference is the lower prevalence of obstructive CAD in women (24 % in the above study) who underwent an invasive treatment strategy. In these women, benefits of revascularization are minimized, and potential risks of the procedure outweigh the benefits of revascularization. An additional difference is that glycoprotein IIb/IIIa inhibitors in women with biomarker-negative ACS showed a significant increase in the primary end point of death or MI (11.5 vs. 10.4, OR 1.14, 95 % CI 1.01–1.3) compared to a benefit in men [65].

STEMI

The recommended treatment of STEMI ACS in women is the same as for men [66]. There is no significant difference in mortality reduction between women and men treated for acute STEMI with either fibrinolysis or PCI, although women have a higher overall mortality rate at 30 days compared to men [67]. On average, women presenting with STEMI and all types of ACS are older and have more comorbidities (diabetes, hypertension, heart failure, and renal insufficiency) than their male counterparts. Due to these factors, women have poorer outcomes following acute MI and treatment with fibrinolysis or PCI, specifically, higher rates of mortality, target vessel revascularization, and major adverse cardiac events [68]. The underutilization of early aggressive reperfusion strategies and appropriate pharmacotherapy in women with STEMI, especially in the first 24 h after presentation, increases adjusted 30 day mortality compared with men of similar clinical presentation [69]. However, after adjustment for age and comorbidities, female sex is not an independent predictor of 30-day or long-term mortality in patients with STEMI undergoing acute revascularization. Despite these favorable mortality comparisons in the stent era, women continue to have an increased risk of bleeding, vascular complications, and renal failure post-PCI. The increased bleeding risk is in part due to a lack of dosage adjustment for body weight and renal function in women. Women have a higher rate of intracerebral hemorrhage compared to men, and this difference persisted after correction for advanced age and other comorbidities [70].

Recent data reinforce the long described trend of women receiving less aggressive medical therapy than men at discharge following admission for ACS. Women are less likely to receive aspirin, beta-blockers, or statins despite clear evidence-based guidelines supporting their use [71, 72].

Percutaneous Coronary Intervention

Women requiring PCI have more comorbidities and are older than men. Older studies suggested increased female mortality associated with PCI; however, recent studies have not shown sex to be an independent risk factor for increased mortality in the DES era [73]. Women have smaller body habitus and thus smaller diameter coronary arteries, which is correlated with increased restenosis and need for target vessel revascularization after PCI [74]. PCI for the treatment of specific clinical scenarios is discussed above and in detail in Chaps. 11, 24, 25, and 26.

Coronary Artery Bypass Graft Surgery in Women (CABG)

Women account for 20–30 % of all CABG procedures performed in the United States each year and have higher operative and short-term mortality compared to men. The gender gap in mortality is most pronounced in younger women; older female mortality more closely resembles that in males. The reasons for the gender difference in operative mortality are not well understood, especially the greatest mortality gap among young women which challenges the assumption that less favorable outcomes occur in women because of advanced age and increased burden of comorbidities [75, 76]. Women are more likely to present acutely and require CABG either urgently or emergently and are less likely to receive arterial grafts, differences that may partially explain the observed mortality differences [77]. Women also have smaller coronary artery diameters, which many postulate makes CABG surgery more technically difficult. Recent data suggest that off-pump coronary artery bypass (OPCAB) grafting narrowed the mortality gap between women and men compared to on-pump CABG technique [78]. Further study will help determine the best technical approach to CABG in women and help elucidate other factors that may play an integral role in patient selection in efforts to decrease CABG mortality in women.

Other Cardiovascular Conditions in Women

Congestive Heart Failure

Since 1980, the US incidence of heart failure has increased in both women and men. Almost five million Americans are affected by heart failure, and 50 % of cases occur in women. Significant gender differences exist in etiology, pathophysiology, anatomy, and prognosis. The lifetime risk of developing heart failure among women and men, when ischemic cardiomyopathies are included, is 20 % at age 40 years [5]. Women are twice as likely to have heart failure with preserved left ventricular systolic function and have a lower associated mortality from heart failure than men. Women are less likely to develop ischemic cardiomyopathy, more likely to develop diastolic dysfunction, and to have better left ventricular systolic function than men. Eighty percent of patients over age 65 years with heart failure and preserved left ventricular ejection fraction are women [79]. Women are also more likely to develop heart failure secondary to hypertension and valvular heart disease compared to men. Women are more likely to have cardiomyopathy associated with autoimmune conditions and are more susceptible to the cardiotoxic effects of ethanol and other cardiac toxins. Despite this, the incidence and prevalence of alcohol-induced cardiomyopathy is higher in men reflecting the higher prevalence of alcoholism in men. Female gender is an independent risk factor for development of cardiotoxicity related to anthracyclines, when used for the treatment of childhood cancers. This increased risk has not been identified in the adult female population.

The treatment of systolic heart failure in women closely parallels that of men. Women have been underrepresented in clinical heart failure trials, especially trials focusing on patients with decreased left ventricular systolic function. The ACC/AHA heart failure guidelines class I level of evidence B recommendation is that “groups of patients including (a) high-risk ethnic minorities (e.g. blacks), (b) groups underrepresented in clinical trials, and (c) any groups believed to be underserved should, in the absence of specific evidence to direct otherwise, have clinical screening and therapy in a manner identical to that applied to the broader population” [80]. The IMPROVE HF trial showed equivalency in guideline-based therapies for heart failure in women and men, including greater benefit among women with cardiac resynchronization therapy and implantable cardiac defibrillators (ICDs) compared to men [81].

Yet, medical device therapy has been underutilized for the treatment of systolic heart failure in women. With cardiac resynchronization therapy, women have more dramatic improvement in LVEF, larger reductions in all-cause mortality, and reduced recurrences of heart failure exacerbations. These results were associated with increased reverse cardiac remodeling when evaluated with echocardiography [82]. Women derive slightly more benefit from ICDs than do men; despite this, women are less likely than men to receive ICD therapy when clinically indicated. Notably, women are more likely than men to have a complication post ICD implantation [83]. One study showed that only 35.4 % of eligible women received an ICD post-MI [84]. The reasons for this are not fully understood; possibilities include patient preference for ICD therapy, system inequities, and physician bias toward white men, given their robust representation in clinical trials.

Stress-Induced Cardiomyopathy

Women, especially postmenopausal women, are more likely than men to present with stress-induced cardiomyopathy or "takotsubo" cardiomyopathy. Stress cardiomyopathy is typically caused by a strong emotional or psychological stressor, although in an estimated one-thirds of cases, no stressor can be identified, while one-third of cases are associated with an acute medical illness or surgery. The exact etiology is unknown but is thought related to catecholamine excess leading to myocardial stunning. The left ventricle has a characteristic appearance where the base of the heart is hyperdynamic and the apex is akinetic, causing apical ballooning. This distinct and unique pattern of wall motion abnormality attracted the name "takotsubo" cardiomyopathy, also referred to as "broken heart syndrome" and "apical ballooning syndrome." The Japanese word takotsubo refers to an octopus trap sharing a similar shape to the heart with apical ballooning during systole. Takotsubo cardiomyopathy clinically mimics an acute coronary syndrome with the presence of chest discomfort, dynamic ECG changes (ST elevation, depression, and/or dramatic T wave inversions), and elevated cardiac biomarkers The diagnosis can be confirmed with cardiac echocardiography, coronary angiography, magnetic resonance imaging, or a combination thereof. Chronic therapy with beta-blockers and ACE inhibitors is appropriate if there are no contraindications. Left ventricular systolic dysfunction is usually transient and normalizes over 1–3 months; however, data regarding recurrences are sparse [85].

Peripartum Cardiomyopathy

An entity specific to women is peripartum cardiomyopathy (PPCM) defined as the development of heart failure with systolic dysfunction during the last month of pregnancy or within the first 5-months postpartum without known preexisting cardiac conditions. PPCM is partially a diagnosis of exclusion as other etiologies of heart failure must be eliminated. The incidence in the United States is an estimated 1 case per 4,000 pregnancies [86]. Risk factors are advanced maternal age, increased parity, history of PPCM with a prior pregnancy, multi-gestation pregnancies, African descent, prolonged tocolysis, and poverty [87]. Anticoagulation therapy should be strongly considered in women with evidence of systemic embolization, severely depressed LVEF (<35 %), or presence of a left ventricular thrombus. Caution must be used when administering warfarin to the pregnant patient because of its teratogenic effects and small risk of spontaneous intracerebral hemorrhage in the fetus during the 2nd and 3rd trimesters [88]. Fifty percent of women regain normal systolic function within 6 months, while 20 % progressively deteriorate and die or require cardiac transplantation, and the remaining 30 % usually improve slightly from baseline but never fully normalize their systolic function. Recovery is more likely in patients with less severe left ventricular systolic dysfunction. Treatment is conventional heart failure medical therapy. Women should be counseled against subsequent pregnancies once diagnosed with peripartum cardiomyopathy [89]. Recent research has suggested bromocriptine to be effective in preventing deterioration of left ventricular systolic function in subsequent pregnancies; however, these data require confirmation [90].

Valvular Heart Disease and Congenital Heart Disease (See Chaps. 20 and 38)

Marked shifts have occurred in the etiologies of valvular heart disease over the past three decades. Western countries have experienced a decline in rheumatic heart disease and an increase in degenerative valve disease among the aging population. However, rheumatic heart disease remains the most frequent etiology of valvular heart disease in developing nations. Valvular heart disease is discussed extensively in Chap. 29. Congenital heart disease is of great importance in women, particularly related to pregnancy and the complex decision making involved in the care of women who are pregnant or desire to get pregnant and are affected by congenital heart disease. These issues are discussed in detail in Chaps. 20 and 38.

The most frequent acquired valvular lesion in young women is mitral stenosis (MS) with rheumatic disease being the most common etiology. Seventy percent of patients with MS are female, 40 % of patients with rheumatic heart disease have MS. MS is poorly tolerated in pregnancy and should be adequately treated as recommended in the AHA valvular heart disease guidelines [91].

Mitral valve prolapse is more common in women and has been associated with mitral valve prolapse syndrome, the validity of which is controversial. Mitral valve prolapse syndrome is defined by the presence of MVP on echocardiography and various clinical symptoms (atypical chest pain, exertional dyspnea, palpitations, syncope, and anxiety) and clinical findings (low blood pressure, leaner build, and electrocardiographic repolarization abnormalities) [92]. MVP is the most common etiology of chronic mitral regurgitation in developed countries. In some, MVP appears to have a familial pattern of inheritance. There is no clear association of increased arrhythmic risk or sudden cardiac death in patients with MVP and trace to mild mitral regurgitation [93, 94].

Acquired calcific aortic stenosis is diagnosed later in women compared to men. Moderate and severe aortic stenosis is more common in women given their longer life expectancy [95]. Older age of diagnosis has treatment implications

as surgical risk increases with advancing age and higher degrees of frailty. Recent developments in transcatheter aortic valve replacement appear to be safe in women, possibly safer than for men [96]. Transcatheter approaches to aortic stenosis may prove very useful in elderly women given their advanced age at presentation, frequent comorbidities, and smaller aortic annular size.

Arrhythmias and Sudden Cardiac Death

Many gender differences exist in the incidence, prevalence, and prognosis of cardiac arrhythmias, particularly tachyarrhythmias. There are clear intrinsic differences in the native conduction systems between women and men (Fig. 37.5). It was first recognized in 1920 that the average female resting heart rate was 3–5 beats/min faster than that in males. The reasons are not completely understood, but proposed mechanisms are differences in exercise tolerance, unique intrinsic properties of the sinus node, and differences in autonomic tone. Intrinsic differences in sinus node properties are the most likely explanation given that gender differences in resting heart rate persist after autonomic blockade and that women have shorter sinus node recovery times [97]. This same pathophysiology may explain the higher incidence of inappropriate sinus tachycardia in women.

Shorter QRS and longer QT interval duration are additional gender differences unique to the female ECG. The QT interval averages 10–20 ms longer in women. This difference does not exist until after puberty, at which time the male QT interval shortens. This is likely an androgen-mediated occurrence; however, the precise mechanism is unknown. Likely because of this baseline difference, women are at higher risk of developing torsade de pointes from acquired long QT syndrome. In multiple studies, women account for 60–70 % of adverse cardiac events associated with class Ia and class III antiarrhythmic drugs. A similar pattern is seen with non-antiarrhythmic medications such as erythromycin. There is also an unexplained female predominance of congenital long QT syndrome, which cannot be explained by genetic transmission as the inheritance patterns for congenital long QT syndrome are not sex linked. Women are more likely to have their first cardiac event related to congenital LQTS later in life, whereas men are more likely to experience events before puberty, and these events are more likely to be fatal [98].

Arrhythmia	Description
Inappropriate sinus tachycardia	Occurs almost exclusively in women
AVNRT	More frequent in women (2:1 ratio)
AVRT and WPW	More frequent in men (2:1 ratio)
Atrial fibrillation	Men have a 1.5-fold higher risk of developing AF Total prevalence and complication rates are higher in women Ablation is similarly effective in both sexes
LQTS (congenital and acquired)	More common in women SCD in LQTS is more common in boys and adult women
SCD	More frequent in men, VT and VF are more common in men, whereas asystole and PEA are more common in women
Brugada syndrome	More common in men

AF atrial fibrillation, *AVNRT* atrioventricualr nodal reentrant tachycardia, *AVRT* atrioventricular reentrant tachycardia, LQTS long QT syndrome, *PEA* pulseless electrical activity, *SCD* sudden cardiac death, *VF* vebtricular fibrillatio, *VT* ventricular tachycardia, *WPW* Wolff-Parkinson-White syndrome.

Fig. 37.5 Sex differences in arrhythmias (Reprinted from Yarnoz and Curtis [97]. With permission from Elsevier)

Supraventricular Tachycardias

AVNRT, AVRT, and WPW

Women are more prone to develop arrhythmias of supraventricular origin, specifically AV nodal reentrant tachycardia (AVNRT) which has a 2:1 female to male predominance. A shorter refractory period of the slow pathway of the AV node is described in women and likely accounts for this increased prevalence [99]. Atrioventricular reentrant tachycardia and Wolff-Parkinson White syndrome also occur in women, but occur more commonly in men. Acutely, AVNRT can be terminated with intravenous adenosine if the patient is stable and with electrical cardioversion if the patient is unstable. Non-dihydropyridine calcium channel blockers and beta-blockers are the pharmacological agents of choice for the chronic treatment of AVNRT. Catheter ablation is a safe treatment option, is well tolerated, and is usually definitive with a success rate of 96–98 % [100].

As previously mentioned, inappropriate sinus tachycardia is more common in women, is a diagnosis of exclusion, and is thought to be a result of unique intrinsic properties of the sinus node and some degree of increased autonomic tone or possibly an immunological disorder of cardiac beta-adrenergic receptors [101]. Sex hormones also appear to influence the occurrence of SVT in women. Cyclical variations in the number and severity of SVT episodes have been observed throughout the menstrual cycle with more symptomatic SVT occurring during the luteal phase when progesterone levels are elevated. Additionally, cyclical variation in the inducibility of SVT has been observed throughout the menstrual cycle [97]. In one study, the most common trigger of right ventricular outflow tract tachycardia in women was hormonal flux, specifically in the premenstrual period when progesterone levels are elevated [102]. Increased incidence and severity of SVT is also seen during pregnancy with AVNRT and AVRT being the most commonly observed arrhythmias (refer to Chap. 38 for a more detailed discussion of cardiac arrhythmias).

Atrial Fibrillation

Atrial fibrillation (AF) is the most common supraventricular tachycardia seen in clinical practice. The incidence of AF increases with age, and the absolute number of women with AF is greater than that of men because of their longer life expectancy. While more women than men have AF, the Framingham Heart Study found men to have a 1.5-fold higher risk of developing AF compared to women [103]. Women more often than men had hypertension and diabetes as risk factors for AF, while extensive coronary artery disease was more common in men. Recently, the European Heart Survey on atrial fibrillation found that women with AF are more likely to be older with more significant comorbidities, to have a lower quality of life, to have preserved left ventricular systolic function, and to have more associated symptoms than men. Additionally, women have both a higher risk of stroke (2.2 % vs. 1.2 %, $p=0.011$) and risk of major bleeding events (2.2 % vs. 1.3 %, $p=0.028$) at 1 year compared to men on a similar anticoagulation regimen [104]. Women also have poorer mortality outcomes with AF compared to men. The Framingham Heart Study showed the odds ratio for death in subjects with AF to be 1.5 in women and 1.9 in men [105]. A recent study correlated AF with increased all-cause, cardiovascular, and non-cardiovascular mortality in women with a low burden of cardiovascular disease at baseline [106]. Women are treated for AF somewhat less aggressively than men; they are less likely to be cardioverted or have a catheter ablation procedure. Women are anticoagulated at similar rates to men. They are more likely to develop QT prolongation and malignant arrhythmias from antiarrhythmic drugs, especially amiodarone, as well as significant bradyarrhythmias requiring pacemaker implantation [107]. When used, catheter ablation procedures for AF appear to be equally efficacious in both genders [97]. Rivaroxaban and dabigatran are new anticoagulation agents for TIA and stroke prevention in patients with non-valvular atrial fibrillation. There are no reported gender inequities in the efficacy of these agents. There is a statistically significant higher bleeding risk in men with the use of rivaroxaban [108, 109].

Sudden Cardiac Death and Ventricular Arrhythmias

Ventricular Arrhythmias

Long QT syndrome is more common in women, as discussed above, and is an important cause of ventricular arrhythmias. Right ventricular outflow tract ventricular tachycardia is equally prevalent among women and men; however, there are gender differences in the triggering of the arrhythmia. The premenstrual state is the most common trigger in women; exercise and stress are the most common in men. This is important for counseling and educating patients on trigger avoidance. Brugada syndrome is more common in men (70 % of cases), with men having more severe cases, more significant ECG changes, more easily inducible ventricular arrhythmias, and experiencing higher rates of SCD [110]. Ventricular arrhythmias are more common during pregnancy, but are rare in women with structurally normal hearts. Malignant ventricular arrhythmia during pregnancy should raise the suspicion of an underlying structural abnormality or channelopathy that is unmasked by pregnancy.

Sudden Cardiac Death

Sudden cardiac death (SCD) accounts for an estimated 325,000 deaths annually in the United States. Women have a significantly lower incidence of SCD compared to men across all age groups and overall are half as likely to experience SCD as men. When women experience SCD, they are more likely to present with asystole or pulseless electrical activity, whereas ventricular tachycardia and ventricular fibrillation are more common in men. A similar delay of onset of 10 years is seen in women compared to men. Two-thirds of women with SCD have no previous diagnosis of IHD, and 10 % have structurally normal hearts. Importantly, the risk of SCD in women can be correlated to the presence of CHD risk factors, and thus the aggressive modification of these risk factors should confer some protection from SCD [111].

Peripheral Arterial Disease (See Chap. 44)

Atherosclerotic peripheral arterial disease affects women at least as commonly as men and is associated with equal morbidity and mortality as CHD and ischemic stroke. Gender-based differences in pathophysiology, clinical presentation, and treatment are currently unknown and should be the focus of future investigation [112].

Summary

Gender issues in CV disease are now more widely appreciated. Clear gender differences exist in the incidence, prevalence, presentation, diagnosis, treatment, and prognosis of cardiovascular diseases and should translate into gender differences in treating the female patient. Cardiovascular disease is the leading cause of mortality in women, and physicians must be familiar with gender differences to better deliver personalized patient care. Special attention should be paid to women of childbearing age in prescribing drugs with potential teratogenicity. Research efforts should continue to further define the ideal approaches to women with cardiovascular diseases, and it is incumbent upon the physician to aggressively utilize evidence-based therapies in their female patients to minimize their risk of CVD morbidity and mortality.

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Pregnancy and Heart Disease

38

T.P.E. Ruys, Mark R. Johnson, and J.W. Roos-Hesselink

Introduction

We will present an overview of the interaction between pregnancy and heart disease in this chapter. After discussing the epidemiology and hemodynamic changes of normal pregnancy, we will consider the most prevalent cardiac conditions: congenital heart disease, valvular heart disease, cardiomyopathy, acute coronary syndrome, aortic pathology, pulmonary hypertension, and hypertensive disorders, followed by management strategies including counseling, diagnosis, treatment, and delivery.

Epidemiology

Although women with heart disease are rare in the obstetric population, they are the main cause of maternal mortality and morbidity [1, 2]. In the developed world, more women with congenital heart disease are reaching childbearing age and deciding to become pregnant. These women now make up the majority of pregnant women with heart disease. In contrast, in the developing world, women with rheumatic heart disease remain the largest group [3]. Pregnancy increases the risk of acute coronary syndrome (ACS) three- to fourfold [4]. The overall incidence of pregnancy-related ACS is reported to be between 2.7 and 6.2 per 100,000 deliveries, and this figure seems to be increasing, probably due to changes in lifestyle, greater rates of obesity, and older age at pregnancy [4, 5].

The incidence of peripartum cardiomyopathy varies between different populations, but in developed countries is thought to be between 1:2,300 and 1:4,000. Rates are higher in Haiti and in a specific area of Nigeria where they are estimated to be 1:299 and 1:100, respectively [6].

Hemodynamic Changes in Pregnancy

The majority of the cardiovascular changes associated with pregnancy occur in the first 20 weeks, with a decline in total peripheral vascular resistance (TPVR) of 40–70 %, a fall in blood pressure and an increase in blood volume of around 1.5 l (30–50 %). The increase in plasma volume is relatively greater than the increase in red blood cells resulting in a physiological hemodilution [7].

The fall in TPVR reduces cardiac afterload and the greater blood volume increases cardiac preload; together these changes result in an increase in cardiac output of 30–50 % in association with greater left ventricular dimensions and increased ejection fraction. The heart rate also rises by 10–20 beats/min, mainly during the third trimester. During labor, cardiac output increases again by 25 % mainly as a result of uterine contractions and maternal effort [8].

Pregnancy is a hypercoagulable state, with a decrease in releasable tissue plasminogen activator (tPA) and increases in fast-acting tPA inhibitor and factors V, VII, VIII, IX, X, XII, and von Willebrand factor [9]. Protein S is increased and there is an increased resistance to activated protein C [10]. During delivery the placenta and myometrium release tPA inhibitors leading to a further increase in the hypercoagulable state [11]. All pregnancy-induced hemodynamic changes return to baseline levels within 3–12 months. Major hemodynamic changes also occur during the puerperium (from birth until 6–8 weeks after delivery) (see Fig. 38.1).

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_38, © Springer Science+Business Media New York 2013

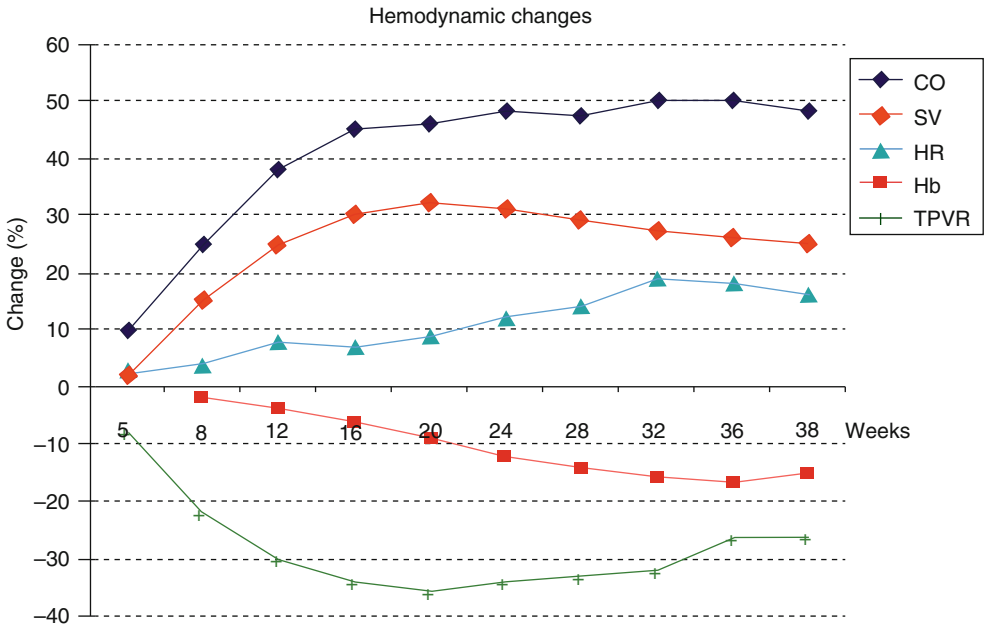

Fig. 38.1 Hemodynamic changes in pregnancy. *CO* cardiac output, *SV* stroke volume, *HR* heart rate, *Hb* blood levels hemoglobin, *TPVR* total peripheral vascular resistance

Congenital Heart Disease

Shunts ASD/VSD/AVSD

The most common congenital heart diseases are atrial septal defects (ASD) and ventricular septal defects (VSD) consisting of 20 and 30 %, respectively, of the congenital heart disease patients. Atrial ventricular septal defect (AVSD) accounts for 3 % of the congenital heart diseases.

Closed Shunts

Yap et al. described 243 pregnancies in 133 patients with repaired ASD and 55 patients with unrepaired ASD. Another study by the same group described 202 pregnancies in 104 repaired VSD patients and 43 unrepaired VSD patients. They showed that pregnancy was well tolerated by most women with a repaired ASD and repaired VSD [12, 13]. In the Canadian guidelines, the only contraindication for pregnancy in ASD or VSD patients is the presence of pulmonary arterial hypertension or Eisenmenger syndrome. For AVSD patients after correction, pregnancy is usually well tolerated when residual valve regurgitation is not severe and ventricular function is normal. Drenthen studied 29 AVSD patients with 62 pregnancies, and he described increases in arrhythmia and deterioration of both AV-valve regurgitation and NYHA class and suggested that in the presence of moderate to severe left AV-valve regurgitation, operative correction should be considered pre-pregnancy [14].

Unoperated Shunts

Yap et al. reported a higher risk of neonatal events in women with unrepaired versus repaired ASD. In addition, women with an unrepaired ASD or VSD had a higher risk of preeclampsia. Similarly, arrhythmias were more common in ASD patients, especially when the ASD was unrepaired or closed at an older age and the pregnant woman was older [12, 13]. Pre-pregnancy surgery in patients with a hemodynamically significant ASD or VSD may prevent these complications. The European guidelines on pregnancy and heart disease advice considering prophylactic low molecular weight heparine (LMWH) administration in case of prolonged bed rest after delivery, because of the increased risk of paradoxical embolism [3].

Fallot

Tetralogy of Fallot (ToF)

Tetralogy of Fallot (ToF) is the most common cyanotic congenital heart defect and accounts for 5–6 % of congenital heart malformations. In a retrospective study, 74 women had 157 pregnancies and cardiovascular events occurred during 8 % of these pregnancies, mainly (supra) ventricular arrhythmias [15]. Patients with severe pulmonic regurgitation are at risk for progressive RV dilation; in these patients, pre-pregnancy surgery should be considered. Patients with ToF have an increased risk of fetal loss [16].

Uncorrected ToF

Patients presenting as adults without correction of ToF are rare. Veldtman et al. reported the cases of 8 women (with 20 pregnancies) and unrepaired ToF was an independent predictor for the occurrence of low birthweight [16]. An additional 7 pregnancies in women with unrepaired ToF are described in the literature, but there were no specific complications reported [17].

Coarctation

Aortic coarctation accounts for 6–9 % of all congenital heart disease. In most cases aortic coarctation is discovered and treated during childhood. In women with a repaired coarctation, pregnancy is associated with a high miscarriage rate, and in 54 women with 126 pregnancies, 22 miscarriages and six abortions were found [18]; in addition, rates of gestational hypertension were increased [19]. Occasionally aortic dissection has been reported [19]. The greater risk of pregnancy-induced hypertension is suggested to be a result of residual abnormalities in aortic compliance, or as a result of an increased cardiac output in patients with a residual coarctation. Over rigorous blood pressure treatment may reduce placental blood flow, thereby compromising fetal growth and development; consequently, treatment is challenging. If maternal health is compromised during pregnancy due to residual coarctation, percutaneous intervention is possible, although it is associated with a higher risk for aortic dissection. This risk may be reduced by the use of covered stents [3]. Aortic dissection is a life-threatening complication, which appears to be more common during pregnancy [3, 20].

Uncorrected coarctation in adult patients is rare and the risks unknown, although the incidence of intrauterine growth restriction and premature labor is held to be increased [19].

Transposition of the Great Arteries (TGA)

In women with atrial repair (*Mustard/Senning*) for complete TGA long-term complications such as sinus node dysfunction, atrial arrhythmias and dysfunction of the systemic right ventricle may occur. In a recent report by Drenthen et al., many patients had arrhythmias during pregnancy (22 %); also high rates of miscarriage (25 %) and fetal and neonatal combined mortality (11 %) were reported [21]. Cannobio et al. reported 70 pregnancies in 40 atrial switch patients and found that one patient suffered from heart failure and died suddenly 1 month after delivery and another needed heart transplantation after pregnancy [22]. Guedes et al. described NYHA class deterioration in approximately one-third of the pregnancies, which was irreversible in 10 % of the patients [23].

Since the *arterial switch operation* was only introduced as the method of choice for TGA in the 1980s, not many pregnancies have been described. In a case series, of 9 women with 17 pregnancies, one patient had a non-sustained ventricular tachycardia and another had a mechanical valve thrombosis [24]; consequently, more data are needed to define whether pregnancy is safe in this group.

There is only one small case series of pregnancy in congenitally corrected TGA (CCTGA). This reported that pregnancy-related congestive heart failure was the most frequent complication [25]. Also of note complete heart block, due to a malpositioned AV node and an inherently abnormal conduction system, is common in CCTGA patients; consequently, beta- blockers must be used with caution [26].

Complex Heart Disease

Fontan

The majority of patients with a univentricular or tricuspid atresia heart survive well into adulthood because of advances in the cardiothoracic surgery and neonatal critical care. An increasing number of women with Fontan palliation are contemplating pregnancy. However, late complications, such as thromboembolism, atrial arrhythmias, ventricular dysfunction, increased pulmonary vascular resistance, and hepatic failure develop more frequently. Even in women with "optimal" Fontan physiology, fetal complications are common including high miscarriage rates up to 50 %, premature rupture of membranes, preterm delivery, fetal growth restriction, and fetal cardiac malformations [27].

In *Eisenmenger syndrome* patients, the Canadian recommendations for the Management of Adults with Congenital Heart Disease is to advice against pregnancy and to offer a termination if pregnancy occurs, because of high maternal mortality rates of up to 50 % [28].

Valvular Heart Disease

Mitral Stenosis

Rheumatic heart disease remains the major burden of heart disease during pregnancy in developing countries and is still seen in western countries, especially in immigrants. The most common lesion is mitral stenosis. Pregnancy is poorly tolerated by women with moderate or severe mitral stenosis (valve area $<1.5\ cm^2$) [29]. The increase in heart rate reduces ventricular filling time. In a study by Silversides et al., heart failure (31 %) and arrhythmias (11 %) mainly occurred during the second and third trimesters [30]. Hameed et al. showed an increase in prematurity (22 %), intrauterine growth retardation (24 %), and stillbirth (4 %) [31]. The American guidelines advise patients with moderate or severe MS to avoid pregnancy until after a corrective procedure has been performed [29, 32].

Aortic Stenosis

Aortic stenosis in young women is most often due to congenital bicuspid aortic valve, but it may also be rheumatic in origin. According the AHA/ACC guidelines for valvular disease, symptomatic patients with moderate to severe obstruction (jet velocity >3.0 m/s) or decreased LV function should be advised

Table 38.1 Anticoagulation regimes in pregnancy

Regime	Valve thrombosis[a]	Valve thrombosis[b]	Maternal mortality	Fetal risk
OAC throughout	3.9	2.4	2	Risk of fetal abnormalities (especially in warfarin > 5 mg)
UFH 1rst trim and OAC 2nd and 3rd trim	9.2	10.2	4	Risk of fetal mortality in case of maternal event
UFH throughout	33		15	Risk of fetal mortality in case of maternal event
LMWH first trimester OAC 2nd and 3rd trim		3.6		Risk of fetal mortality in case of maternal event
LMWH throughout		7.1		Risk of fetal mortality in case of maternal event

OAC oral anticoagulation, *UFH* unfractionated heparin, *LMWH* low molecular weight heparin
[a][76].
[b][75].

to have a corrective procedure prior to pregnancy [32, 33]. In asymptomatic patient with mild or moderate AS, pregnancy is generally well tolerated. In contrast, congestive heart failure was reported in 44 % and arrhythmias in 25 % of patients with an aortic valve <1.5 cm^2. This group also experience increased rates of preterm birth and intra uterine growth retardation [31].

Pulmonary Stenosis

Pulmonary valve stenosis is most often congenital, and patients with an isolated lesion are at low risk during pregnancy [32]. However, Hameed et al. described 2 of 17 patients with PS, who experienced a deterioration in NYHA class during pregnancy [31]. Drenthen et al. described 108 pregnancies in 51 women and found 21 miscarriages (19%) and 6 elective abortions and the occurrence of hypertension-related disorders (15%), fetal mortality (4.8 %) and fetal heart disease (3.7 %) were all increased [34]. Furthermore, Greutmann et al. found that 9 % of women went into right heart failure, predicted by the presence of moderate-to-severe pulmonary regurgitation, right ventricular dilatation and hypertrophy, in a series of 76 pregnancies [35]. Therefore, pre-pregnancy surgery should be considered in women with compromised RV function prior to pregnancy [3].

Mitral or Aortic Regurgitation

During pregnancy regurgitant lesions are usually well tolerated, although the risk of heart failure is increased. The degree of regurgitation is often reduced in pregnancy, secondary to decreased systemic vascular resistance [32]. Lesniak et al. published on 44 patients with mitral regurgitation and 22 with aortic regurgitation, 16 % deteriorated in the mitral regurgitation group (3 patient heart failure and 4 patients with supraventricular tachycardia), and 14 % in the aortic regurgitation group (dyspnea after slight physical effort). All symptomatic patients had either an enlarged left ventricle or a depressed cardiac function (EF < 55 %) at baseline [36]. Therefore, such patients should be advised to have surgery before pregnancy, preferably undergoing a valve repair or implantation of a homograft/bioprosthesis [3].

Valve Replacement

The choice of prosthesis in a young woman needing a valve replacement should be made after a full discussion, including the desire for pregnancy.

Bioprosthetic valves are much less thrombogenic and so have the significant advantage of not needing anticoagulation, but young patients will almost certainly need another operation later in life [3]. During pregnancy, several studies have reported deterioration of bioprosthetic heart valves, but this has not been confirmed by others [37].

Mechanical valves have long-term durability, but the need for anticoagulation increases fetal and maternal mortality and morbidity. Although hemodynamically pregnancy is well tolerated, anticoagulation increases the risk of hemorrhage and fetal complications. These risks have to be balanced with those of valve thrombosis. Each anticoagulant regimen has its own risks, and it is not clear which is best. The options should be discussed with both future parents [3]. The known risks are presented in Table 38.1.

When a patient with a mechanical valve becomes dyspneic, valve thrombosis should be excluded as a matter of urgency. If the diagnosis is confirmed and the patient is stable, then the treatment of choice is intravenous heparin in addition to oral anticoagulation. In a critically ill patient with an obstructive thrombosis or when anticoagulation treatment fails, surgery should be considered immediately. However, if this option is not available, then fibrinolysis should be urgently considered [3].

Cardiomyopathy

Peripartum Cardiomyopathy

Peripartum cardiomyopathy (PPCM) is relatively rare and defined as "peripartum cardiomyopathy is an idiopathic cardiomyopathy presenting with HF secondary to LV

systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of HF is found. It is a diagnosis of exclusion. The LV may not be dilated but the LVEF is nearly always reduced below 45 %." [6] Although it is rare, maternal mortality is high; it is the second most common cardiac cause for mortality in the large Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom [2]. The incidence varies from 1:100 to 1:4,000 pregnancies. The etiology and pathophysiological mechanisms of this disease are not completely understood. In several studies, proposed risk factors include multiparity, extremes of reproductive age, prolonged tocolysis, smoking, hypertension, and low socioeconomic status. African ancestry has been associated with PPCM [6].

The clinical course varies between complete recovery to rapid progression into end-stage heart failure or death. Standard heart failure treatment is the treatment of choice. New disease-specific therapies including prolactin blockade (e.g., by bromocriptine) are being tested, first results are promising, but the outcome of a large randomized controlled trial is awaited [38].

Women with a history of PPCM who become pregnant again are at risk of relapse. Elkayam et al. conducted a retrospective survey of PPCM patients in the USA in which a subset of 44 patients had 60 subsequent pregnancies. All 44 patients experienced reduction in LVEF during subsequent pregnancy [39]. Patients with a persistently reduced LVEF were more likely to become symptomatic in the next pregnancy. Therefore, those women with PPCM who have a persistently reduced LVEF are advised not to become pregnant again [6].

Dilated Cardiomyopathy (DCM)

DCM is defined as the presence of typical symptoms of heart failure, LV dilation, and LV systolic dysfunction of unknown origin [3]. Women with dilated cardiomyopathy (DCM) are at high risk for complications and even mortality during pregnancy. Grewal et al. studied 32 women with DCM with 36 pregnancies and found that 39 % of the pregnancies were complicated by one or more maternal cardiac events, mainly heart failure (in 9 patients) and arrhythmias (in 7 patients). Moderate or severe LV dysfunction (LVEF < 45 %) and/or NYHA III/IV at baseline were independent predictors for the occurrence of cardiac events. By comparing women who did and did not become pregnant, this study showed that pregnancy had an adverse affect on women with DCM [40]. Hemodynamic monitoring of the mother should continue for at least 48 h after delivery, because volume redistribution during this time period can precipitate decompensation [41].

Hypertrophic Cardiomyopathy (HCM)

HCM is the most common genetic cardiac disease [42]. Women with HCM without left ventricular outflow tract obstruction (LVOTO) generally tolerate pregnancy well, but women who are symptomatic before pregnancy and those with a high outflow tract gradient are at risk of heart failure during pregnancy. In a study by Autore et al., 199 pregnancies in 100 women were described in which 2 patients who had been symptomatic before pregnancy died suddenly [43]. In another study, Thaman et al. described 271 pregnancies in 127 women and found that approximately 28 % of women reported cardiac symptoms during pregnancy; most of these women had been symptomatic before pregnancy [44].

Ischemic Heart Disease

Preexisting Coronary Disease

Only limited data exist about the chance of a recurrence during pregnancy have been published: none of the 18 women with previous ACS had a recurrence [45]. However, generally women are advised against pregnancy if they have left ventricular dysfunction and an ejection fraction of below 40 % or have a dilated left ventricle [46].

Evaluating a pregnant woman with chest pain in a pregnant woman can be challenging. Most often chest pain is caused by benign causes such as gastroesophageal reflux, but also the possibility of a life-threatening disease such as aortic dissection, pulmonary thromboembolism, or acute coronary syndrome has to be kept in mind.

The overall incidence of pregnancy-related *acute coronary syndrome* (*ACS*) was reported between 2.7 and 6.2 per 100,000 deliveries and seems to have increased in the last decade [4, 5]. Probably because both advanced maternal age and obesity are becoming more prevalent in the pregnant population. However, mortality rates have declined over the last decades from 19 to 5 %, as a result of improvements in treatment modalities [47]. ACS in pregnancy is not only caused by coronary artery stenosis, Roth and Elkayam found that this was the cause in only 40 % of ACS patients (41 of the 103 patients); the others had acute thrombus (8 %), coronary artery dissection (27 %), vascular spasm (2 %), and normal coronary arteries (13 %) [47].

Coronary artery disease in the *peripartum period* differs from ACS in the antepartum period in terms of coronary abnormality, cause, treatment options, and mortality rate. Coronary dissection was the cause of half of the events in the peripartum period and 34 % in the postpartum period. Probably this is the result of the vessel wall stress during labor and hormonal changes during the last trimester. The mortality rate in patients with ACS in the peripartum period is twice as high as in the antepartum period (18 % versus 9 %) [47]. In the

postpartum period, some cases of ACS have been associated with the administration of bromocriptine and ergotamin [47].

Aortic Disease

Marfan

Marfan syndrome is an autosomal dominant hereditary disorder; in 80 % of the patients some cardiovascular involvement is found, including aortic dilatation, aortic regurgitation, and mitral and tricuspid valve prolapse. During pregnancy, patients with Marfan syndrome and a normal aortic root diameter have a 1 % risk of aortic dissection or other serious cardiac complications. Even in healthy women due to hormonal changes, the aortic wall may become more vulnerable to dissection; this makes pregnancy a high-risk period [48]. Risk factors for dissection are an increase in aortic root diameter during pregnancy and an aortic root diameter >40 mm [20]. According to the current European guidelines, pregnancy in women with an aortic root >45 mm should be discouraged. The use of beta-blockers in patients with Marfan syndrome during pregnancy is recommended, despite of lack of evidence, and delivery by cesarean section is advised in women with an aortic root >45 mm [3].

Other Aortic Disease

Bicuspid Aortic Valve (BAV)

Although a dilated aortic root occurs less frequently in women of childbearing age than in Marfan patients, the association of BAV and aortic dilatation does increase the risk of dissection [20]. Therefore, pre-pregnancy surgery is advised in patients with an aortic root over 50 mm [3].

Women with *Turner's syndrome* are often not fertile, but assisted reproductive technologies now allow Turner patients to become pregnant through the use of donated oocytes. However, pregnancy is high risk in women with Turner's syndrome, with four deaths from aortic dissection in 87 pregnancies and pregnancy-associated hypertensive disorders occurring in 67 % reported [49].

Ehlers–Danlos Syndrome Type IV

One study reported that the mortality rate was 11.5 % in one series of 183 pregnancies [50]. For this reason alone, Ehlers–Danlos syndrome type IV is considered to be a contraindication for pregnancy, but there is also an increased risk of spontaneous uterine rupture [3].

Pulmonary Arterial Hypertension

A mean PAP ≥25 mmHg at rest is indicative of pulmonary arterial hypertension. Pulmonary arterial hypertension (PAH) is a complex disorder with multiple possible causes. PAH can worsen during pregnancy because of an increase in right ventricle preload and a decrease in systemic vascular resistance. In a recent systematic review, the maternal mortality rate was 17–33 % in 73 pregnancies complicated by severe PAH (idiopathic, congenital heart disease or other causes), and neonatal survival rates were 90–93 % [51]. The high-risk period is in the last trimester and the first months after delivery, because of pulmonary thrombosis and refractory right heart failure (caused by autotransfusion after delivery). Pregnancy is contraindicated in women with PAH, and if pregnancy occurs, termination should be offered [3, 52].

Hypertensive Disorders in Pregnancy

Women develop hypertension during pregnancy are at increased risk for developing cardiovascular events later in life. Hypertension complicates 15 % of the pregnancies and accounts for about a quarter of all antenatal admissions. The definition of hypertension in pregnancy is a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg taken on two occasions greater than 6 h apart. Preeclampsia is defined by the "de novo" appearance of hypertension, accompanied by new onset of significant proteinuria >0.3 g/24 h, and is a pregnancy-specific syndrome that occurs after 20 weeks of gestation. Eclampsia is defined as the occurrence of a grand mal seizure in association with preeclampsia [53]. High maternal age, elevated blood pressure, dyslipidemia, obesity, positive family history, thrombophilia, and glucose intolerance are all risk factors for the development of hypertensive disorders [54].

A recent meta-analysis found that women with a history of preeclampsia or eclampsia had twice the risk (odds ratio 2.47, 95 % CI 1.22–5.01) of early cardiac, cerebrovascular, and peripheral arterial disease and cardiovascular mortality [55]. Therefore, early intervention using lifestyle modifications, regular blood pressure monitoring/treatment, and control of metabolic factors should be initiated in women whose pregnancy has been complicated by preeclampsia or eclampsia [54].

Management of Pregnancy in Women with Heart Disease

Pre-pregnancy Counseling

Ideally all women of reproductive age with cardiac disease should undergo thorough evaluation and counseling before becoming pregnant. Pre-pregnancy evaluation should focus on identifying and quantifying risk to the mother and the potential pregnancy. Risk for persistent deterioration of heart function may influence the choice whether to become pregnant. An exercise test and echocardiogram provide essential information for risk stratification. The use of medication

should be discussed and if necessary changed. Genetics and inheritance will be of special interest in some patient groups (such as with congenital heart disease, Marfan syndrome, and hypertrophic cardiomyopathy). Life expectancy and ethical aspects of parenthood should also be discussed during the pre-pregnancy consultation.

Over the years several risk stratification models have been described. Siu et al. published the CARPREG risk score in 2001; in this study, women with mainly congenital and valvular heart disease were included. Prior cardiac events (heart failure, transient ischemic attack, stroke before pregnancy or arrhythmia), baseline NYHA functional class >II or cyanosis, left heart obstruction (mitral valve area <2 cm^2, aortic valve area <1.5 cm^2, peak LV outflow tract gradient >30 mmHg by echocardiography), and reduced systemic ventricular systolic function (ejection fraction <40 %) were significant predictors for adverse maternal and neonatal outcome [33]. Khairy et al. found that a history of smoking and also pulmonary regurgitation were additional predictors for adverse outcome [56]. The ZAHARA investigators showed in a large cohort of congenital heart disease patients that a history of arrhythmic events or a mechanical valve were independent predictors for maternal and neonatal complications [57].

The World Health Organisation (WHO) made a risk score based on diagnosis and comorbidity. WHO class 1 indicates low risk, WHO class 2 indicates an intermediate risk, WHO class 3 indicates high risk, and WHO class 4 indicates a contraindication for pregnancy. In Table 38.2, this classification can be found [58].

Table 38.2 The different diagnoses with corresponding WHO class are depicted

WHO I
Uncomplicated, small or mild
Pulmonary stenosis
Patent ductus arteriosus
Mitral valve prolapse
Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage)
Atrial or ventricular ectopic beats, isolated
WHO II (*if otherwise well and uncomplicated*)
Unoperated atrial or ventricular septal defect
Repaired tetralogy of Fallot
Most arrhythmias
WHO II–III (*depending on individual*)
Mild left ventricular impairment
Hypertrophic cardiomyopathy
Native or tissue valvular heart disease not considered WHO I or IV
Marfan syndrome without aortic dilatation
Aorta <45 mm in aortic disease associated with bicuspid aortic valve
Repaired coarctation
WHO III
Mechanical valve
Systemic right ventricle
Fontan circulation
Cyanotic heart disease (unrepaired)
Other complex congenital heart disease
Aortic dilatation 40–45 mm in Marfan syndrome
Aortic dilatation 45–50 mm in aortic disease associated with bicuspid aortic valve
WHO IV (pregnancy contraindicated)
Pulmonary arterial hypertension of any cause
Severe systemic ventricular dysfunction (LVEF <30 %, NYHA III–IV)
Previous peripartum cardiomyopathy with any residual impairment of left ventricular function
Severe mitral stenosis, severe symptomatic aortic stenosis
Marfan syndrome with aorta dilated >45 mm
Aortic dilatation >50 mm in aortic disease associated with bicuspid aortic valve
Native severe coarctation

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Diagnosis in Pregnancy

During pregnancy diagnosis of or worsening of an existing cardiac condition may be challenging since cardiopulmonary signs and symptoms reported during normal pregnancy closely mimic heart disease.

Physical Examination

In a healthy pregnant woman, a mild increase in resting heart rate, a widened pulse pressure, peripheral edema, and a slight elevation of venous pressure are normal. The first heart sound (S1) is increased, and during the later stages of pregnancy, there is a physiological fixed splitting of the second heart sound (S2). Murmurs develop in nearly all women during pregnancy and are secondary to the increased cardiac output. Diastolic murmurs are unusual and therefore call for further evaluation [46].

Electrocardiogram (ECG)

The electrocardiogram (ECG) changes as a result of the upward shift of the diaphragm caused by the growing uterus. There is left axis deviation, Q waves in lead III and aVF, and inverted T waves in lead III, V1, and V2 are seen in the third trimester. In case of a cesarean section with general anesthesia, ST depression is seen [46].

Doppler Echocardiography

Echocardiography is a safe and fast diagnostic tool. In a normal pregnancy, a significant increase in cardiac output, cardiac index, left ventricular end-diastolic volume, and left ventricular wall thickness is often encountered [46].

Chest Radiography

When needed, a chest X-ray should be performed as the radiation is relatively low. Interventional procedures in the chest do not necessarily (and are probably not likely to) deliver

Table 38.3 Medication during pregnancy

Medication	FDA	Safe during breast-feeding	Extra information
Atenolol	D	No	IUGR and premature birth
Other beta-blockers	C	Yes	Low birth weight, hypoglycemia, and bradycardia in the fetus
ACE inhibitors	D	Yes	High-incidence fetal death and fetotoxic effect: renal failure, renal dysplasia
Amiodarone	D	No	Thyroid insufficiency
ARB	D	No data	High-incidence fetal death and fetal renal failure
Aspirin	B	Yes	Low-dose aspirin is safe (large database)
Calcium channel antagonists	C	Yes	Diltiazem: an increase in major birth defects have been reported
Clopidogrel	B	No	The benefits of using clopidogrel in some high-risk pregnancies may outweigh the potential fetal risks
Digoxin	C	Yes	No reports of congenital defects, monitor serum levels
Loop diuretics	C	Yes	Hypovolemia can lead to reduced uterine perfusion
LMWH and UFH	C	Yes	Factor Xa should by measured weekly, levels may fluctuate during pregnancy
Nitrates	B	No data	Careful titration is advised to avoid maternal hypotension
Spironolactone	D	Yes	Potential antiandrogenic effects on the developing male fetus
Statins	X	No	Animal studies demonstrated increased skeletal abnormalities, fetal and neonatal mortality
Thiazide diuretics	B	Yes	Hypovolemia can lead to reduced uterine perfusion

Food and drug administration (FDA) classification: Category A: Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters). Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Category X: Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits

dangerous doses of radiation to the fetus, and in emergency care, such procedures are justified. However, the lowest possible dose should be given and when possible echo-guidance should be used. The uterus receives radiation scattered from the irradiated area, which is more important than the direct exposure. For low doses to the fetus, the principal risk is radiation-induced cancer (stochastic effects). The actual risk depends on the dose and stage of development of the fetus. Radiation dose to the fetus higher than 50–100 mGy places the child at risk for growth retardation, malformation, or miscarriage [59].

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging may be useful in diagnosing complex heart disease or pathology of the aorta. MRI is considered to be safe after 12 weeks of pregnancy, although no fetal abnormalities have been reported with its use earlier in pregnancy to date [60].

Medication During Pregnancy

Table 38.3 shows the safety profile of commonly used cardiovascular drugs during pregnancy and breast-feeding.

Complications During Pregnancy

Heart Failure

The incidence of heart failure during pregnancy is highly depended on the preexisting diagnosis and pre-pregnancy systemic ventricle function. In a large review by Drenthen et al. focusing on congenital heart disease patients, heart failure was encountered in 4.8 % (ranging from 0 to 20 % in different diagnostic groups). In women with heart failure during pregnancy, diuretics are considered to be first choice [61]. In patients with atrial fibrillation, digoxin can be given; the dose necessary to reach adequate blood levels is higher

than outside pregnancy due to the higher circulating blood volume. Patients with heart failure during pregnancy should be admitted to hospital for bed rest.

Arrhythmias

Pregnancy may increase the incidence of arrhythmias. Ectopic beats are present in one-third of healthy pregnant women and are generally benign; treatment should consist of reassurance. Tachyarrhythmias are rare (supraventricular tachycardia in 3 %) [46]. Nakagawa et al. studied 11 patients with new-onset ventricular arrhythmia during pregnancy, 73 % of the arrhythmias originated from the right ventricular outflow tract; post-pregnancy, the arrhythmia disappeared completely in all patients [62]. Electrical cardioversion can be performed safely and is the treatment of choice for all drug-refractory maternal arrhythmias [63]. If prophylactic drug therapy is needed, then beta-blockers or digoxin is the first choice. Bradyarrhythmias are uncommon and are usually well tolerated. Pacemaker implantation may be necessary in some patients [46].

Interventions During Pregnancy

Cardiac Surgery

Although maternal mortality is not influenced, fetal mortality rates are as high as 30 % as a consequence of cardiac surgery during pregnancy. Predictors for adverse fetal outcome are severity of maternal illness, total operative time, emergency surgery, reoperation, advanced maternal age, and gestational age [64]. Placental perfusion can be monitored by using the fetal heart rate, although Doppler assessment of uterine blood flow may be better, as an indicator to guide bypass pump flow [65]. Uterine contractions are associated with significant fetal loss and should be controlled if necessary. Hypotension, hypothermia, embolic complications, and inadequate placental flow are related to adverse neonatal outcome [64].

Percutaneous Coronary Intervention (PCI)

There is only limited information available on PCI during pregnancy. PCI is the primary treatment for ST-elevation myocardial infarction patients. Roth and Elkayam reviewed 38 patients who underwent PCI, all with bare metal stenting [47]. Bare metal stenting is preferred over drug-eluting stents, because of the risks of dual antiplatelet treatment around the time of delivery.

Percutaneous Balloon Valvuloplasty

In patients with valve stenosis, balloon valvuloplasty may be considered if conservative management fails. There is some experience with mitral, aortic, and pulmonary valve balloon valvulopasty. Mitral valvuloplasty can be done with very limited fluoroscopy (less than 2 min exposure with both pelvic and abdominal shielding) and using echocardiographic guidance. Recently, the outcome of 71 patients who had undergone mitral balloon valvuloplasty was reviewed, 13 % had a preterm delivery, and 2 had thromboembolic events [66]. In women with severe aortic stenosis, a percutaneous approach can be considered with noncalcified lesions. A recent case series by Radford et al. described 8 successful cases [67], although the risk of developing severe aortic regurgitation needing surgical intervention should be discussed. Pulmonary stenosis can be approached with percutaneous valvotomy under echocardiographic guidance when necessary [32].

Delivery

Cardiac output increases by another 25 % during delivery as a result of the greater maternal oxygen consumption (caused by uterine contractions and maternal distress).

Planning

Timing and mode of delivery should be discussed in a multidisciplinary team consisting of at least an obstetrician, an anesthesiologist, and a cardiologist. The patient's preference has to be taken into account, and all potential complications should be discussed prior to delivery.

Timing

When patients are asymptomatic and doing well, a spontaneous delivery can be awaited. However, in patients with heart failure, delivery from 34 weeks may be appropriate to allow early optimization of treatment modalities for the mother [3].

Mode of Delivery

The mode of delivery depends mainly on obstetric factors and the maternal hemodynamic situation. Generally, vaginal delivery is preferred in women with adequate cardiac output, but cesarean section may be the best option in selected high-risk patients. According to the guidelines, cesarean section should be considered for the patients on oral anticoagulants (OAC) in preterm labor, patients in acute intractable heart failure (European guidelines), patients with Marfan syndrome and an aortic diameter >45 mm, and patients with acute or chronic aortic dissection [3, 32, 68].

Vaginal Delivery

Spontaneous vaginal delivery in patients with heart disease shows good results in most patients, with the most important benefit of less blood loss. To study whether vaginal delivery

or cesarean section has lowest complication rate, a prospective randomized controlled trial would be optimal, but this kind of study would be unethical. Second best option would be a case control study from a large registry of pregnant patient with heart disease. Assisted vaginal delivery (by vacuum or forceps extraction) is recommended in some women to avoid excessive maternal efforts and prolonged labor. Adequate pain relief is very important, but epidural anesthesia is contraindicated when the patient is taking anticoagulant treatment. In women with LVOT obstruction, regional anesthesia should be used with caution, because it could cause a decrease in peripheral vascular resistance [32]. Oron et al. showed that induction of labor was a relatively safe procedure in women with cardiac disease. It is not associated with a higher rate of cesarean section or with more maternal and neonatal complications [69].

Cesarean Section

During cesarean section, stress and pain can be relieved and a stable environment can be created. However, blood loss during cesarean section has been shown to be more than during vaginal delivery. In addition cesarean section has been associated with a higher risk of venous thromboembolism, infection, and peripartum hemorrhage. In some cases general anesthesia will be necessary with some risk of complications, such as hypotension during induction [70]. A recent study suggests that pregnant women with cardiac disease may safely deliver by cesarean section under regional anesthesia [71].

Fetal Outcome

Predictors

Neonatal outcome is strongly correlated with maternal outcome. Several predictors for neonatal outcome have been described. Maternal predictors of neonatal events in women with heart disease are baseline NYHA class >II or cyanosis, left heart obstruction, smoking during pregnancy, the use of oral anticoagulants during pregnancy, mechanical valve prosthesis, and multiple gestation. Fetal mortality is high in cardiac surgery during pregnancy (as high as 30 %) [64].

Inheritance

In most studies describing patients with congenital heart disease, the recurrence risk for congenital heart disease in the offspring is around 3–5 % [72]. Marfan syndrome and HCM are autosomal dominant with a recurrence risk of 50 %. Fetal echocardiographic screening at 18–22 weeks of gestational may be advised for early recognition of fetal abnormalities, although good views of the fetal heart may only be achieved later in pregnancy. Second-trimester screening should be performed by appropriately experienced specialists [3].

Monitoring

In addition to second-trimester screening, serial growth scans assessing fetal biometry, amniotic fluid, and fetal blood flow (umbilical, cerebral, ductus venosus) provide a noninvasive measure of the fetoplacental hemodynamic state and should be performed at 4 weekly intervals after 20 weeks gestation [3]. In fetuses with compromised growth, the fetal heart rate pattern may be abnormal with a tachycardia, loss of variability, and an absence of accelerations of the fetal heart rate, decreased body movement, and breathing, hypotonia, and, less acutely, decreased amniotic fluid volume [73].

Postpartum Period

Postpartum Changes

The volume shifts caused by autotransfusion the first days after delivery can be dangerous in patients with diminished left ventricular function. Close monitoring until 5 days after delivery is advisable in high-risk women by close monitoring of symptoms of signs of heart failure and early investigation and treatment [3]. A routine ECHO at 5 days postdelivery in high-risk women is advised paying careful attention to the aortic root in women with Marfan syndrome or aortic valve disease. Prophylaxic diuretics may be advised in high-risk patients with severe systemic ventricular dysfunction. A second risk during the postpartum period consists of thromboembolic events caused by the hypercoagulable state of pregnancy exacerbated by even higher tPA inhibitor levels immediately after delivery, and in some cases prolonged prophylactic LMWH (6 weeks) may be advisable [11].

Mother and Child

Early bonding of mother and child is very important; therefore, ideally monitoring should be done in a unit with neonatal care. In patients with low risk for heart failure and with a normal ventricular function, close monitoring in-hospital for only 1 day after delivery will be sufficient.

Breast-Feeding

The maternal cardiovascular function is influenced by breast-feeding caused by circulating hormones (mainly oxytocin). In a study by Mezzacappa et al., cardiac output during breast-feeding was found to be higher than in bottle-feeding mothers. During the first minutes of breast-feeding, a decrease in heart rate and a small increase in systolic blood pressure were shown [74]. With the production of breast milk (around 800 ml of milk daily), large-volume shifts take place; these may cause a problem in patients with reduced left ventricular function. Lactation is also associated with a risk of bacteremia secondary to mastitis. Although breast-feeding is considered safe in most patients, bottle-feeding should therefore be considered in high-risk patients. Some patients are in need

of medication during the postpartum period. Some medicine is not compatible with lactation (found in Table 38.3); in these patients, bottle-feeding is the only option [3].

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Recommend Reading

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Heart Disease in the Elderly

39

Michael W. Rich

The next several decades will witness an explosive growth in the size of the older adult population in the USA [1], with the number of Americans 65 years of age or older increasing from about 40 million in 2010 to about 72 million in 2030. As a result, the proportion of the population ≥65 years of age will increase from 13.0 to 19.3 %; that is, by 2030 nearly 1 in 5 Americans will be in this age group.

Cardiovascular disease is the leading cause of death and major disability in the USA, and a disproportionate number of individuals with cardiovascular disease are over 65 years of age. The prevalence of cardiovascular disease (including hypertension) increases progressively with age, exceeding 70 % in men and women 60–79 years of age and 80 % in those 80 years of age or older [2]. In addition, 82 % of all deaths attributable to cardiovascular disease occur in patients over age 65, and 67 % are in patients over the age of 75 [2]. Older adults also account for 61 % of all cardiovascular hospitalizations, as well as an increasing proportion of all cardiovascular procedures (Table 39.1) [2, 3].

For these reasons, it is important for the practitioner to have an understanding of the effects of aging on the cardiovascular system, a working knowledge of cardiovascular therapeutics in the elderly, and an appreciation of the limitations of currently available data relevant to the treatment of older cardiac patients.

Effects of Aging on the Cardiovascular System

Aging is associated with diffuse changes in cardiovascular structure and function (Table 39.2) [4, 5]. From the clinical perspective, the principal effects of aging are as follows:

- Increased vascular stiffness, resulting in increased impedance to left ventricular ejection
- Impaired ventricular filling due to altered relaxation and decreased ventricular compliance
- Diminished responsiveness to beta-adrenergic stimulation
- Reduced capacity to augment adenosine triphosphate (ATP) production in response to increased demands
- Impaired endothelial function
- Progressive decline in sinus node function
- Decreased baroreceptor responsiveness

These changes affect disease expression, clinical manifestations, and response to therapy in older patients. Thus, increased vascular stiffness contributes to the progressive rise in systolic blood pressure with advancing age. In turn, systolic hypertension is a key risk factor for coronary heart disease, heart failure, and stroke in the elderly.

Impaired diastolic filling, a hallmark of cardiovascular aging, is caused by increased interstitial collagen deposition, compensatory myocyte hypertrophy, and altered calcium flux leading to impaired relaxation during early diastole. These changes result in decreased filling during early and mid-diastole and are accompanied by increased reliance on atrial contraction to optimize left ventricular end-diastolic volume. Clinical implications of these alterations include a progressive rise in the prevalence of both atrial fibrillation and the syndrome of heart failure with normal left ventricular systolic function and a diminished capacity to augment stroke volume via the Frank-Starling mechanism [6].

The effects of reduced responsiveness to beta-adrenergic stimulation include a linear decline of approximately 10 beats per decade in the maximum attainable heart rate, reduced ability to augment contractility, and impaired $beta_2$-mediated vasodilation. Taken together, these effects greatly reduce the capacity of the older heart to increase cardiac output in response to increased demands, and this capacity is further diminished by the inability of cardiac mitochondria to maximally upregulate ATP production in response to increased energy requirements.

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_39, © Springer Science+Business Media New York 2013

Table 39.1 Major cardiovascular procedures by age

	Age, years					
	<45		45–64		≥65	
	No.[a]	Percent	No.[a]	Percent	No.[a]	Percent
Cardiac catheterization	91	8.6	453	42.7	517	48.7
Percutaneous coronary revascularization	67	5.7	501	42.5	610	51.8
Coronary bypass surgery	9	2.2	165	40.7	231	57.0
Valve procedures	15	10.9	34	24.6	89	64.5
Permanent pacemaker	11	3.1	59	16.5	288	80.4
Implanted cardioverter defibrillator	8	6.9	43	37.1	65	56.0
Carotid endarterectomy	–	NA	21	22.6	72	77.4

Adapted from Roger et al. [2] and Hall et al. [3]
[a]In thousands

Impaired endothelial function contributes to the development of atherosclerosis and limits coronary artery vasodilation, thereby reducing maximum coronary blood flow. These changes predispose older adults to the development of coronary heart disease and also lower the coronary ischemic threshold.

Degenerative changes in the sinus node and atrial-conducting tissues result in a rising prevalence of "sick sinus syndrome" with advancing age and predispose older individuals to the development of supraventricular tachyarrhythmias, especially atrial fibrillation. As shown in Table 39.1, over 80 % of permanent pacemakers are implanted in individuals over 65 years of age, and sinus node dysfunction is the most common indication for pacemaker insertion.

Diminished baroreceptor responsiveness increases the susceptibility of older individuals to dizziness, falls, and syncope. This proclivity is often aggravated by many of the medications commonly used to treat cardiovascular disorders, including diuretics, beta-blockers, and vasodilators.

In addition to age-related changes in the cardiovascular system, there are important changes in renal, pulmonary, neurohumoral, and hemostatic function that have important implications for older patients with cardiovascular disease (Table 39.3). Older patients are also subject to numerous medical, behavioral, psychosocial, and financial influences which may impact upon symptomatology, adherence to prescribed therapy, and overall prognosis. Finally, aging is associated with significant changes in the absorption, distribution, metabolism, and elimination of virtually all medications.

Cardiovascular Risk Factors

In general, the major risk factors for cardiovascular disease are similar in older and younger patients, but the relative importance of some risk factors (e.g., smoking, total cholesterol) declines with age. However, since the prevalence of cardiovascular disease increases with age, the clinical significance of these risk factors is maintained or even increases with age.

Relative Versus Attributable Risk

Relative risk refers to the likelihood that an individual with a given "risk factor" will develop a specific disease, as compared to an individual without that risk factor. Attributable risk refers to the actual number of cases of a disease than can be attributed to the presence of a specific risk factor. As such, the attributable risk reflects both relative risk and disease prevalence, and it provides a more accurate estimate of the potential impact of risk factor modification (i.e., the number of cases prevented by the eradication of a given risk factor). Stated another way, since older individuals are at higher risk for developing cardiovascular disease, the potential benefit of treating a specific risk factor is often greater in older than in younger patients, even though the relative risk may be lower in the elderly.

Hypertension

As shown in Fig. 39.1, systolic blood pressure increases with age in both men and women, whereas diastolic blood pressure tends to peak and plateau in middle age, then declines slightly at older age [7]. As a result of these age-related changes in blood pressure, isolated systolic hypertension accounts for over 90 % of prevalent hypertension among individuals ≥70 years of age [7]. Although systolic and diastolic blood pressures are each independent risk factors for cardiovascular disease in the elderly, systolic hypertension is more common, and it is also a more powerful risk factor.

Table 39.2 Effects of aging on the cardiovascular system

Gross anatomy
Increased left ventricular wall thickness
Decreased left ventricular cavity size
Endocardial thickening and sclerosis
Increased left atrial size
Valvular fibrosis and sclerosis
Increased epicardial fat
Histology
Increased lipid and amyloid deposition
Increased collagen degeneration and fibrosis
Calcification of fibrous skeleton, valve rings, and coronary arteries
Shrinkage of myocardial fibers with focal hypertrophy
Decreased mitochondria, altered mitochondrial membranes
Decreased nucleus: myofibril size ratio
Biochemical changes
Decreased protein elasticity
Numerous changes in enzyme content and activity affecting most metabolic pathways, but no change in myosin ATPase activity
Decreased catechol synthesis, esp. norepinephrine
Decreased acetylcholine synthesis
Conduction system
Degeneration of sinus node pacemaker and transition cells
Decreased number of conducting cells in the AV node and HIS–Purkinje system
Increased connective tissue, fat, and amyloid
Increased calcification around conduction system
Vasculature
Decreased distensibility of large- and medium-sized arteries
Aorta and muscular arteries become dilated, elongated, and tortuous
Increased wall thickness
Increased connective tissue and calcification
Autonomic nervous system
Decreased responsiveness to β-adrenergic stimulation
Increased circulating catecholamines, decreased tissue catecholamines
Decreased α-adrenergic receptors in left ventricle
Decreased cholinergic responsiveness
Diminished response to Valsalva and baroreceptor stimulation
Decreased heart rate variability

Table 39.3 Effects of aging on other organ systems

Kidneys
Gradual decline in glomerular filtration rate, ~8 cc/min/decade
Impaired fluid and electrolyte homeostasis
Lungs
Reduced ventilatory capacity
Increased ventilation/perfusion mismatching
Neurohumoral system
Reduced cerebral perfusion autoregulatory capacity
Diminished reflex responsiveness
Impaired thirst mechanism
Musculoskeletal system
Decreased muscle mass and strength (sarcopenia)
Decreased bone density (osteopenia)
Hemostatic system
Increased levels of coagulation factors
Increased platelet activity and aggregability
Increased inflammatory cytokines and C-reactive protein
Increased inhibitors of fibrinolysis and angiogenesis

Numerous prospective, randomized, placebo-controlled clinical trials have evaluated the effects of antihypertensive therapy in the elderly (Table 39.4) [8]. These studies provide compelling evidence that treatment of systolic and diastolic hypertension substantially reduces the incidence of stroke, coronary heart disease, and cardiac failure in older adults. Moreover, the benefits of treating diastolic hypertension persist at least up to the age of 80, while the benefits of treating systolic hypertension are apparent at least up to the age of 90 [9].

Treatment of hypertension is generally similar in older and younger patients [8]. However, a recent consensus document recommends that a systolic blood pressure treatment threshold of 150 mmHg is reasonable in people ≥80 years of age and that a target systolic blood pressure of 140–145 mmHg is reasonable for this age group. In addition, because older patients are more susceptible to adverse drug reactions, therapy should usually be initiated with lower drug dosages, and close follow-up is essential to assess efficacy and tolerability.

Hyperlipidemia

In men, population mean total cholesterol levels increase until late middle age, and then level off. In the absence of estrogen replacement, population mean total cholesterol levels rise rapidly after menopause in women and average 15–20 mg/dl higher than those in men after the age of 60. Low-density lipoprotein (LDL) cholesterol levels track with total cholesterol levels in men and women, while high-density lipoprotein (HDL) cholesterol levels average 10 mg/dl higher in women than in men throughout adult life. In the Framingham Heart Study, the importance of total cholesterol as a risk factor for coronary heart disease declined with age, but the ratio of total cholesterol to high-density lipoprotein cholesterol (HDL-C) remained a strong independent risk factor in both men and women at older age [10]. Similar findings from other studies confirm the importance of hyperlipidemia as a cardiovascular risk factor in the elderly.

In the Heart Protection Study, simvastatin 40 mg daily was associated with significant reductions in death, myocardial infarction, and stroke in patients 40–80 years of age with vascular disease or diabetes, and the benefits were similar in older and younger patients [11]. In the PROSPER study (PROspective Study of Pravastatin in the Elderly at Risk),

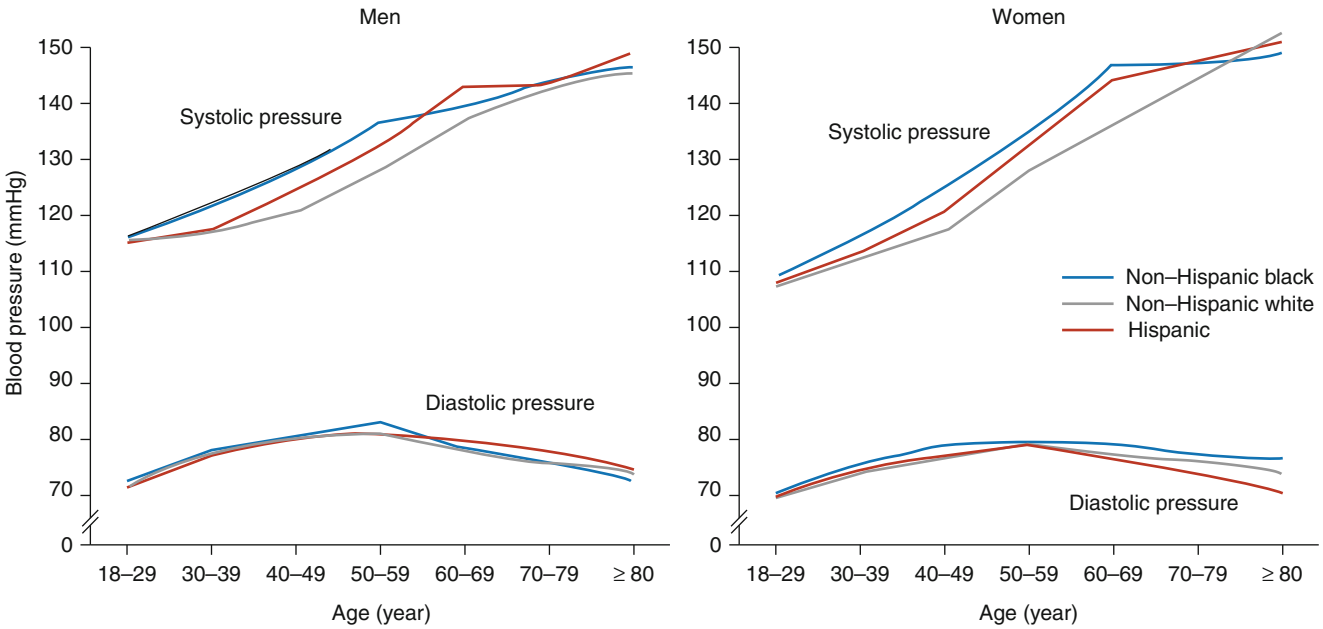

Fig. 39.1 Mean systolic and diastolic blood pressures in the US population by age, sex, and race: NHANES III (Reprinted from Chobanian [7]. With permission from Massachusetts Medical Society)

Table 39.4 Trials of antihypertensive treatment in the elderly

			Risk reduction (%)			
Trial	*N*	Age	CVA (%)	CAD (%)	CHF (%)	All CVD (%)
Australian	582	60–69	33	18	NR	31
EWPHE	840	>60	36	20	22	29
Coope	884	60–79	42	−3	32	24
STOP-HTN	1,627	70–84	47	13	51	40
MRC	4,396	65–74	25	19	NR	17
HDFP	2,374	60–69	44	15	NR	16
SHEP	4,736	≥60	33	27	55	32
Syst-Eur	4,695	≥60	42	26	36	31
STONE	1,632	60–79	57	6	68	60
Syst-China	2,394	≥60	38	33	38	37
HYVET	3,845	≥80	30	28	64	34

CAD coronary artery disease, *CHF* congestive heart failure, *CVA* cerebrovascular accident, *CVD* cardiovascular disease, *EWPHE* European Working Party on High Blood Pressure in the Elderly, *HDFP* Hypertension Detection and Follow-up Program, *HYVET* Hypertension in the Very Elderly Trial, *MRC* Medical Research Council, *NR* not reported, *SHEP* Systolic Hypertension in the Elderly Program, *STONE* Shanghai Trial of Nifedipine in the Elderly, *STOP-HTN* Swedish Trial in Old Patients with Hypertension, *Syst-China* Systolic Hypertension in China, *Syst-Eur* Systolic Hypertension in Europe

pravastatin 40 mg/day reduced the risk of myocardial infarction, stroke, or coronary heart disease death by 15 % in patients 70–82 years of age with established vascular disease, diabetes, hypertension, or current smoking [12]. More recently, subgroup analysis from the JUPITER study (Justification for the Use of statins in Prevention: an International Trial Evaluating Rosuvastatin) demonstrated that among 5,695 patients ≥70 years of age (median 74 years, 51.5 % women) with LDL cholesterol <130 mg/dl and high-sensitivity C-reactive protein (hsCRP) ≥2.0 mg/l, rosuvastatin reduced the risk of the composite endpoint of cardiovascular death, MI, stroke, arterial revascularization, or hospitalization for unstable angina by 39 % relative to placebo ($p<0.001$) [13]. All-cause mortality was 20 % lower in the rosuvastatin group, but this difference was not statistically significant ($p=0.09$). However, because overall event rates were low in this relatively low-risk population, 130 patients would need to be treated for 1 year to prevent one primary endpoint event, and 244 patients would need to be treated for 1 year to prevent one death [13]. Serious adverse events were slightly

but not significantly more common among rosuvastatin-treated patients. Based on available evidence, an HMG-CoA reductase inhibitor, in conjunction with an appropriate low fat diet, is recommended for older individuals with manifest coronary heart disease, peripheral arterial disease, or prevalent risk factors in the absence of other major life-limiting illnesses. However, the value of statins for primary prevention of cardiovascular disease in older adults, especially those over 80–85 years of age, remains unproven. In addition, recent data suggest that long-term use of statins may be associated with impaired cognition and memory loss, and it is likely that older patients are at increased risk for these adverse events.

Diabetes

The prevalence of diabetes increases with age, approaching 20 % in persons over age 65. Diabetes is somewhat more common in older men than in older women, and it is significantly more common in African-Americans and Hispanics than in whites. Diabetes remains a potent independent risk factor for coronary heart disease and other cardiovascular diseases at older age. In the Framingham Heart Study, the relative risk for coronary heart disease in diabetic men over age 65 was 1.4, while in women diabetes conferred a relative risk of 2.1. In both men and women, the excess risk for coronary heart disease in diabetics is greater in persons over 65 years of age than in younger individuals.

Management of diabetes is similar in younger and older patients. In addition to maintaining effective glucose control, hypertension should be treated in accordance with current guidelines [14], the LDL cholesterol should be reduced to <100 mg/dl [15], weight should be maintained in a desirable range (body mass index <25 kg/m^2), regular exercise should be encouraged, and tobacco use should be strongly discouraged. As noted above, the Heart Protection Study provides strong evidence that statin therapy reduces mortality and nonfatal vascular events in older diabetics [11, 16]. In addition, data from the Heart Outcomes Prevention Evaluation (HOPE) indicate that ramipril 10 mg once daily is particularly effective in reducing cardiovascular morbidity and mortality in diabetic patients over age 55 [17].

Smoking

Smoking prevalence declines with age due to smoking-related mortality and successful smoking cessation. Nonetheless, continued smoking remains an important risk factor for myocardial infarction and stroke in older individuals. Moreover, there is strong evidence that smoking cessation is beneficial at all ages. In the Coronary Artery Surgery Study (CASS) Registry, for example, coronary patients over 70 years of age who continued to smoke had a 3.3-fold higher risk of death and a 2.9-fold higher risk of death or myocardial infarction during a 6-year follow-up period compared to those who stopped smoking [18].

The efficacy of smoking cessation programs, nicotine replacement therapy, and other medications (e.g., bupropion, varenicline) in elderly smokers is unknown, but older smokers tend to be more receptive to counseling interventions than younger individuals. In addition, the motivation to quit smoking often peaks following an index cardiovascular event, and the importance of smoking cessation should be strongly emphasized in individuals of all ages who suffer such an event.

Other Risk Factors

Left ventricular hypertrophy, physical inactivity, severe obesity, and elevated levels of C-reactive protein, fibrinogen, and homocysteine are all associated with increased risk for cardiovascular disease in older men and women. In addition, data from the Cardiovascular Health Study indicate that increased carotid artery intima-media thickness and an ankle-arm blood pressure index less than 0.9 or greater than 1.4 are predictive of an increased risk for incident cardiovascular events in older adults [19]. Coronary artery calcium scores ≥100 (Agatston method) are also associated with an increased risk for incident coronary events, and higher scores portend progressively higher risk. However, despite the plethora of risk factors, the impact of treating many of these factors in elderly patients remains unknown. Nonetheless, the presence of a constellation of these risk factors may identify older patients likely to benefit from more aggressive management.

Coronary Artery Disease

Acute Myocardial Infarction

The incidence of acute myocardial infarction (MI) increases with age in both men and women. In 2004, 62.8 % of patients hospitalized with acute MI in the USA were over 65 years of age, 35.5 % were over 75 years of age, and 17.1 % were 85 years of age or older [20]. Case fatality rates increase with age, and 81 % of deaths due to acute MI occur in patients over age 65 [2], while more than 50 % occur in patients over age 75. Median survival following an MI is approximately 15 years in patients age 55–64, 9 years in patients age 65–74, and 3 years in patients 75 years of age or older [2]. In addition, women comprise nearly half of all patients with acute MI over age 65, and MI is the leading cause of death in both men and women in this age group.

Table 39.5 Effect of fibrinolytic treatment on 35-day mortality in patients with ST-elevation or left bundle branch block myocardial infarction presenting within 12 h of symptom onset: Reanalysis of data from the fibrinolytic therapy trialists' overview

Age, years	*N*	Mortality, control (%)	Mortality, fibrinolysis (%)	Relative risk reduction (%)	Lives saved/1,000 patients
<55	10,047	5.4	3.8	29.6	16
55–64	12,252	10.7	8.1	24.3	26
65–74	10,053	19.0	15.0	21.1	40
75	3,322	29.4	26.0	11.6	34

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Clinical Manifestations

After age 75, patients with acute MI are less likely to present with typical ischemic chest discomfort, and shortness of breath is the most common initial symptom in patients over the age of 80. Diaphoresis occurs less frequently at older age, whereas nonspecific neurological symptoms, such as light-headedness, confusion, or syncope, are more common in the elderly and may be the presenting manifestation in up to 20 % of MI patients over the age of 85.

Older MI patients often present with nondiagnostic electrocardiograms (ECGs), due to the presence of preexisting ECG abnormalities (e.g., paced rhythm, left bundle branch block, or left ventricular hypertrophy) and a high prevalence of non-ST-elevation MI (NSTEMI). The combination of atypical symptomatology and a nondiagnostic ECG may obfuscate the diagnosis unless a high index of suspicion is maintained. Lack of diagnostic certainty is also an important factor contributing to reduced utilization of reperfusion therapy and other interventions in older patients.

In addition to increased mortality, older patients with acute MI are more likely to develop heart failure, hypotension, atrial fibrillation, conduction abnormalities, myocardial rupture, and cardiogenic shock. Although ventricular arrhythmias are also more common in the elderly, older patients are less likely to develop primary ventricular fibrillation.

Reperfusion Therapy

Fibrinolytic therapy reduces mortality in patients with ST elevation or left bundle branch block MI across the age spectrum, but the relative risk reduction associated with fibrinolytic therapy declines with age (Table 39.5) [21]. However, absolute mortality reduction is similar in patients ≥75 years of age as in those 55–74 years of age, and twofold greater than in patients <55 years of age [21].

Intracranial hemorrhage (ICH) occurs in 0.3–0.5 % of patients receiving fibrinolytic therapy for acute MI, but the risk increases with advancing age, exceeding 1 % after age 75 [22]. The risk of ICH in the elderly is also higher with fibrin-selective agents, such as alteplase or reteplase, than with the nonselective agent streptokinase. Other major bleeding complications occur slightly more frequently in patients receiving fibrinolysis, but the risk is not age dependent.

Percutaneous coronary intervention (PCI), when performed within 90–120 min of the patient's arrival to the hospital, is more effective than thrombolytic therapy in achieving reperfusion and reducing mortality in ST-elevation MI, at least in patients up to 85 years of age [23]. PCI is also associated with lower risk for ICH. For these reasons, PCI has become the preferred reperfusion strategy in patients of all ages with ST-elevation MI [24, 25].

Aspirin

In the ISIS-2 trial, aspirin 162.5 mg daily was associated with a 21 % mortality reduction at 35 days in patients ≥70 years of age [26]. Moreover, the *absolute* benefit of aspirin increased with advancing age, from 1.0 % in patients under age 60 to 4.7 % in those age 70 or older. Long-term aspirin use following MI also reduces the incidence of death, reinfarction, or stroke by approximately 25 % in patients of all ages.

Other Antiplatelet Agents

The addition of clopidogrel to aspirin reduces the risk of cardiovascular death, MI, or stroke by about 20 % compared to aspirin alone during the 12-month period following hospitalization for unstable angina or NSTEMI, with similar absolute benefits in patients younger or older than age 65 [27].

Prasugrel is associated with improved outcomes relative to clopidogrel in patients with acute coronary syndromes undergoing PCI [28]. However, subgroup analysis from the TRITON-TIMI 38 trial (TRial to assess Improvements in Therapeutic Outcomes by optimizing platelet iNhibition with prasugrel – Thrombolysis In Myocardial Infarction) revealed that among patients ≥75 years of age, those with body weight <60 kg, or individuals with a history of stroke or transient ischemic attack, prasugrel was not superior to clopidogrel and there was a trend to increased risk of major bleeding [28]. As a result, prasugrel is not recommended in patients ≥75 years of age except for high-risk situations (diabetes or prior MI), and the dosage should be reduced in patients weighing <60 kg.

Ticagrelor is a new adenosine diphosphate receptor P2Y12 inhibitor that has been shown to be more effective than clopidogrel in patients with acute coronary syndromes, with or without ST-segment elevation [29]. Although there

was no significant interaction with age, patients ≥75 years of age comprised only 15.5 % of the study population, and the benefit of ticagrelor appeared to be attenuated in this subgroup.

Glycoprotein IIb/IIIa inhibitors improve clinical outcomes in selected patients up to the age of 75, but the value of these agents in older patients is less clear. For example, in a trial involving over 10,000 patients, eptifibatide reduced the risk of death or nonfatal MI in patients up to the age of 80, but there was an increase in event rates among patients over 80 years of age receiving eptifibatide [30]. The value of these agents in older adults receiving dual antiplatelet therapy in conjunction with systemic anticoagulation is also uncertain, while the risk of major bleeding is increased. Therefore, judicious use of these agents in elderly patients is warranted.

Antithrombotic Agents

Although older patients with acute MI often receive intravenous heparin, the value of this treatment is unproven. In a study involving 6,935 Medicare patients hospitalized with acute MI, heparin use was associated with more bleeding complications and an increased length of hospital stay, but there was no evidence of a beneficial effect on mortality or reinfarction [31].

Low molecular weight heparins (LMWH) such as enoxaparin and dalteparin offer several advantages over conventional unfractionated heparin (UFH), and these agents are associated with improved clinical outcomes in patients with unstable coronary syndromes, including the elderly [32]. Based on these findings, subcutaneous LMWH is now considered an acceptable alternative to intravenous UFH in the management of patients with acute MI or unstable angina [24]. Importantly, enoxaparin is not recommended in patients with creatinine clearance <30 cc/min, and UFH is the preferred antithrombotic agent in these cases.

Bivalirudin, a direct thrombin inhibitor, and fondaparinux, a factor Xa inhibitor, have been associated with improved clinical outcomes and fewer major bleeding complications than either UFH or LMWH, with similar benefits in younger and older patients [33–36]. Bivalirudin is approved for patients undergoing PCI; dosage reduction is required in patients with impaired renal function. Fondaparinux is not currently approved for treatment of acute coronary syndromes, and it is contraindicated in patients weighing <50 kg and in individuals with creatinine clearance <30 cc/min. Dosage reduction is also required in patients ≥75 years of age. The role of newer antithrombotic agents, including rivaroxaban and apixaban, is currently under investigation.

Long-term warfarin following acute MI reduces the risk of death, reinfarction, and stroke in elderly patients, and in one large trial, the combination of aspirin and full-dose warfarin was superior to aspirin alone in reducing recurrent events after MI [37]. However, combination therapy was associated with an increased risk of bleeding, and very few patients over age 75 were included in the trial. For these reasons, warfarin use in the very elderly is generally restricted to those who have clear indications for long-term anticoagulation (e.g., chronic atrial fibrillation).

Beta-Blockers

Intravenous beta-blockade reduces mortality and recurrent ischemic events in hemodynamically stable low-risk patients, but may be associated with an early adverse effect on mortality in higher-risk patients, including the elderly [38]. Therefore, current guidelines recommend prompt initiation of oral beta-blocker therapy in patients with acute MI in the absence of contraindications (i.e., heart rate <45–50 bpm, systolic blood pressure <100 mmHg, advanced heart block, moderate or severe heart failure, active bronchospasm) [24]. Since older MI patients are more likely to present with heart failure or shock, a smaller proportion will be suitable candidates for early treatment with a beta-blocker. However, age per se should not be considered a contraindication to beta-blocker therapy.

Long-term beta-blockade following acute MI is at least as effective in reducing mortality and reinfarction in older patients as in younger patients, including patients over 85 years of age [39]. In addition, since event rates are higher in the elderly, beta-blocker therapy is more cost-effective in older than in younger patients.

Nitrates

Nitrates can be administered safely to most elderly patients with acute MI, and data from the GISSI-3 trial (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico) indicate that early treatment with transdermal nitroglycerin is associated with favorable trends in mortality and in the combined endpoint of death, heart failure, or severe left ventricular dysfunction in patients over 70 years of age [40]. The value of long-term nitroglycerin therapy following MI is unknown.

Angiotensin-Converting Enzyme (ACE) Inhibitors

In the GISSI-3 trial, treatment with lisinopril within 24 h of symptom onset reduced the combined endpoint of death, heart failure, or severe left ventricular dysfunction by 17 % in patients over 70 years of age [40]. Similarly, in patients with anterior MI not receiving a thrombolytic agent, early treatment with zofenopril reduced the incidence of death or severe heart failure by 34 %, and the absolute benefit was threefold greater in patients over 65 years of age than in younger patients [41].

In patients with acute MI complicated by heart failure or left ventricular dysfunction (ejection fraction ≤40 %), long-term ACE inhibitor therapy reduces mortality, hospitalizations, and heart failure progression, and the benefits of

treatment are at least as robust in older as in younger patients. Indeed, in the Acute Infarction Ramipril Efficacy (AIRE) trial, the mortality benefit of ramipril was limited to older patients [42]. Since older patients are at greater risk for drug-induced hypotension and renal dysfunction, the use of these agents must be carefully monitored.

Angiotensin Receptor Blockers (ARB)

In the OPTIMAAL study (Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan), which included 5,477 patients 50 years of age or older with acute MI complicated by heart failure or left ventricular dysfunction, mortality was nonsignificantly higher with the ARB losartan than with the ACE inhibitor captopril, and these findings were consistent across age groups [43]. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), 14,703 patients with acute MI complicated by left ventricular systolic dysfunction or heart failure were randomized to valsartan, captopril, or a combination of both drugs and followed for a median of 24.7 months [44]. Overall mortality did not differ between the three groups, nor did the composite endpoint of fatal and nonfatal cardiovascular events. Side effects were more common in patients receiving the combination of valsartan and captopril than in the other two groups. There were no significant differences in outcomes between patients ≥65 years of age compared with those less than age 65. Based on these findings, ACE inhibitors remain the preferred agents in post-MI patients. However, ARBs are an acceptable alternative in patients who are unable to take an ACE inhibitor.

Aldosterone Antagonists

Eplerenone is a selective aldosterone antagonist that has been shown to reduce mortality and cardiovascular hospitalizations following acute MI in patients with left ventricular dysfunction and heart failure, with similar benefits in younger and older patients [45]. Based on these findings, long-term treatment with an aldosterone antagonist is recommended following MI in patients with an ejection fraction ≤40 %, either symptomatic heart failure or diabetes, relatively preserved renal function (serum creatinine <2.5 mg/dl in men, <2.0 mg/dl in women), and serum potassium ≤5.0 meq/l. However, older patients are at increased risk for both worsening renal function and hyperkalemia with aldosterone antagonists, especially when used in conjunction with an ACE inhibitor or ARB. Therefore, therapy should be initiated at low dose with close monitoring of renal function and potassium levels.

Antiarrhythmic Agents

Antiarrhythmic agents have not been shown to reduce mortality or improve clinical outcomes in elderly MI patients, and the routine use of these agents is not recommended.

Non-ST-Elevation MI

NSTEMI increases in frequency with advancing age and accounts for over 50 % of all MIs in patients over the age of 70 [46]. Although the short-term prognosis following NSTEMI is somewhat more favorable than that following ST-elevation MI, NSTEMI patients are at increased risk for reinfarction and death during follow-up.

The treatment of NSTEMI in older patients is generally similar to that in younger patients, and several studies indicate that early coronary angiography followed by percutaneous or surgical revascularization is associated with improved outcomes relative to conservative management in high-risk patients, including the elderly [46]. Nonetheless, the potential benefits and risks of invasive management vary widely, mediated in part by prevalent comorbid conditions, particularly renal insufficiency, cognitive impairment, and frailty, so that the decision to pursue aggressive treatment must be considered on an individual basis, taking into account overall health status, goals of care, and personal preferences.

Chronic Coronary Artery Disease

Coronary artery disease (CAD) is highly prevalent in the elderly, and older patients account for more than half of hospital admissions for angina pectoris. Older CAD patients usually have more diffuse disease than younger patients, and they are more likely to have multivessel and left main coronary disease. Because older patients tend to be more sedentary than their younger counterparts, they are more likely to be asymptomatic or minimally symptomatic despite having more severe CAD. Older patients also have a higher prevalence of silent ischemia and infarction than younger patients.

The treatment of chronic CAD is similar in older and younger patients and will not be reviewed here. However, a brief discussion of revascularization procedures is in order.

Percutaneous Coronary Intervention (PCI)

As shown in Table 39.1, over 50 % of PCIs in the USA are performed in patients over 65 years of age [2]. Compared to younger patients, older patients referred for PCI are more likely to be female, have more severe symptoms, more comorbidity, and more complex "target" lesions. These factors, in conjunction with age-related reductions in cardiovascular reserve, result in increased procedure-related morbidity and mortality in older patients, particularly those over the age of 80, and hospital mortality following elective PCI in octogenarians ranges from 1 to 7 % [47]. In addition, although late survival following successful PCI in older patients is good, there is a higher incidence of recurrent angina than in younger patients, primarily due to incomplete revascularization.

Coronary Bypass Surgery

Over 50 % of all coronary artery bypass graft (CABG) operations in the USA are performed in patients over age 65 [2]. As with PCI, older patients referred for CABG are more likely to be female, have more advanced coronary disease, are more symptomatic, and have more comorbidity than younger patients. Perioperative mortality rates range from 5 to 10 % in patients over age 80 undergoing isolated CABG, as compared to 1–2 % in patients under age 65 [47]. Older patients also have a higher incidence of perioperative complications, including atrial fibrillation, heart failure, stroke, bleeding, cognitive dysfunction, respiratory disorders, and renal insufficiency. As a result, postoperative length of stay is substantially longer in older patients.

Perioperative cognitive dysfunction and postoperative functional decline are common following cardiac surgery in older patients, especially those over 80 years of age. Preoperative cognitive and functional impairments are the strongest predictors of postoperative decline in each of these domains [48]. In addition, preoperative assessment of gait speed has recently been shown to be an independent predictor of postoperative morbidity and mortality in older patients undergoing cardiac surgery [49]. However, whether preoperative testing of gait speed, cognition, or functional status will lead to the development of interventions that reduce the risk of adverse postoperative outcomes remains to be determined.

Long-term results following CABG in older patients are excellent, with up to 90 % of patients experiencing sustained symptomatic improvement, and the majority reporting improved functional capacity and quality of life. In addition, a recent meta-analysis demonstrated 1-, 3-, and 5-year survival rates of 86, 78 and 68 %, respectively, among octogenarians undergoing CABG [47]. Notably, long-term survival rates were similar among octogenarians undergoing PCI or CABG [47].

Valvular Heart Disease

Aortic Valve

Aortic stenosis severe enough to warrant surgical consideration occurs in 2–3 % of individuals over the age of 75, and aortic valve replacement is the second most common major cardiac operation in this age group (after CABG). Age-related degenerative changes occurring on a normal tri-leaflet aortic valve account for the majority of cases. Other causes include bicuspid aortic valve and rheumatic disease.

Aortic stenosis in the elderly is often occult because sedentary older individuals may experience few symptoms, or they may attribute their symptoms to "old age." Similarly, the physician may ascribe the symptoms of aortic stenosis to other causes. In addition, the murmur of aortic stenosis in older patients may be less prominent due to changes in chest wall geometry (increased anteroposterior diameter) and reduced stroke volume. An S_4 gallop is a nonspecific finding in older individuals, but the *absence* of an S_4 during sinus rhythm makes the diagnosis of severe aortic stenosis unlikely. The A_2 component of the second heart sound is frequently diminished in older patients with severe aortic stenosis, but this may be difficult to appreciate on routine examination. As a result of decreased vascular compliance, the carotid upstrokes may be well preserved in older patients with severe aortic stenosis. In addition, although the electrocardiogram usually shows left ventricular hypertrophy with ST-segment and T-wave changes, these findings may be attributed to longstanding hypertension or other causes. For these reasons, echocardiography should be performed in all elderly patients with unexplained symptoms that could potentially be due to aortic stenosis. Cardiac catheterization should also be performed in patients with severe aortic stenosis who are suitable candidates for intervention.

At the present time, aortic valve replacement remains the treatment of choice for the majority of older patients with severe aortic stenosis. However, many elderly patients are at high risk for surgery due to frailty or major comorbidity. Recently, percutaneous or transapical insertion of an aortic valve bioprosthesis has been shown to be associated with improved outcomes compared to medical therapy in patients who are not candidates for surgery [50], and with comparable outcomes compared to surgery in patients at high (but not prohibitive) surgical risk [51]. Vascular complications and stroke are more common following transcatheter aortic valve replacement, whereas major bleeding and atrial fibrillation are more common after surgery [51]. At one-year follow-up, symptomatic improvement is similar with transcatheter or conventional valve replacement [51]. Based on the results of these studies, the transcatheter aortic valve has now been approved for use in the USA.

The results of aortic valve replacement in lower risk patients, including octogenarians, are excellent, with several series reporting perioperative mortality rates of 4–7 % for isolated valve replacement. Mortality rates are somewhat higher when valve replacement is combined with CABG. The majority of patients experience marked improvement in symptoms and functional capacity following the procedure [52], and long-term survival is comparable to the general population at similar age.

The prevalence of aortic regurgitation increases with age, but most cases are of insufficient severity to require surgery. Causes of acute aortic regurgitation in the elderly include type A aortic dissection, infective endocarditis, prosthetic valve dysfunction, and sinus of Valsalva rupture. Causes of chronic aortic regurgitation include rheumatic or calcific aortic valve disease, healed endocarditis, and aneurysms of the

aortic root due to atherosclerosis, syphilis, or other disorders. Treatment of aortic regurgitation is similar in older and younger adults. Whether transcatheter aortic valve replacement will be a suitable alternative to surgery in high-risk patients with severe aortic regurgitation remains to be established.

Mitral Valve

Mitral stenosis in the elderly may be due to rheumatic heart disease or severe mitral valve annular calcification. As in younger patients, the symptoms of mitral stenosis are often insidious, and it is not unusual for the diagnosis to be clinically unsuspected until echocardiography is performed. In most elderly patients with mitral stenosis, the valve apparatus is heavily calcified or there is significant mitral regurgitation, thus precluding percutaneous valvuloplasty or open commissurotomy. However, in those elderly patients who are suitable candidates for valvuloplasty, the procedure can be performed safely, and it produces significant hemodynamic and clinical improvement in the majority of cases. In other patients with severe symptoms, mitral valve replacement offers the only viable therapeutic option. As with aortic valve replacement, mitral valve surgery in elderly patients is associated with increased morbidity and mortality. The perioperative mortality rate for elective mitral valve surgery in elderly patients is 5–15 %.

Mitral regurgitation is the most common valvular lesion in elderly patients, but in most cases it is not severe enough to require surgical intervention. Common causes of mitral regurgitation in the elderly include ischemic mitral valve dysfunction, ischemic or nonischemic dilated cardiomyopathy, mitral valve prolapse, rheumatic heart disease, and mitral valve annular calcification. Less commonly, mitral regurgitation may be due to infective or noninfective endocarditis, prosthetic valve dysfunction, or hypertrophic cardiomyopathy. In patients with mild-to-moderate mitral regurgitation, medical management with afterload reduction (e.g., ACE inhibitors, hydralazine) is appropriate. In patients with severe symptomatic mitral regurgitation and satisfactory left ventricular function, surgical treatment should be considered. As in younger patients, mitral valve repair, when feasible, is associated with more favorable outcomes. Long-term results following successful mitral valve repair or replacement in elderly patients are generally favorable, with significant symptomatic improvement occurring in the majority of cases. More recently, percutaneous mitral valve repair has been shown to be associated with satisfactory 1-year outcomes in elderly patients with severe mitral regurgitation not amenable to surgery [53].

Infective Endocarditis

The incidence of infective endocarditis increases progressively with age, reflecting age-related changes in valve structure, the increasing prevalence of specific valvular pathologies in the elderly, and the increased prevalence of potential sources of bacteremia (e.g., poor dentition, respiratory and urinary tract infections, and procedures such as cystoscopy) [54]. The diagnosis of endocarditis in the elderly is often difficult, since the clinical manifestations are usually nonspecific and protean. The classical peripheral manifestations of endocarditis, such as Roth spots, Osler nodes, and Janeway lesions, are also uncommon in elderly patients.

In general, the causative organisms of endocarditis are similar in older and younger patients, with streptococci, staphylococci, and enterococci being the most common agents, followed by gram-negative bacilli and other less common pathogens. In addition, up to 10 % of cases may be culture negative, usually due to the initiation of antibiotic therapy prior to obtaining an adequate number of blood cultures. As in younger patients, vegetations are visualized with transthoracic echocardiography in less than 50 % of cases, but the yield is substantially higher with the transesophageal approach [54]. The treatment and complications of endocarditis are similar in older and younger patients, although mortality is higher in the elderly. In patients with endocarditis complicated by heart failure, early surgical intervention appears to be associated with more favorable outcomes [55].

Heart Failure

The effects of aging on the cardiovascular system markedly reduce cardiovascular reserve and predispose the older patient to the development of heart failure (HF) [56]. Since the prevalence of cardiovascular disease, particularly hypertension and CAD, also increases with age, these factors combine to produce an exponential rise in HF with advancing age. Thus, HF is relatively uncommon in younger adults, but the prevalence doubles with each decade after age 45, and HF affects 1 in 10 individuals over the age of 80. As a result, HF is the most common indication for hospitalization and rehospitalization in persons over age 65, and it is the most costly diagnosis-related group (DRG) by a factor of almost 2. HF is also a major cause of chronic disability in the elderly, and mortality rates from HF increase progressively with age.

Hypertension is the most common antecedent illness in elderly patients with HF, and 70–80 % of cases can be attributed to either hypertension or CAD. Valvular disease is the third most common cause of HF in the elderly, followed by nonischemic cardiomyopathy. Importantly, the prevalence of HF with preserved ejection fraction (HFPEF) increases with age, accounting for over 50 % of cases after the age of 70.

HF in the elderly is both overdiagnosed and underdiagnosed. The cardinal symptoms of HF – shortness of breath, edema, fatigue, and exercise intolerance – are common in the elderly, and these symptoms are often attributed to HF even when caused by other disorders. Conversely, sedentary elderly individuals may not report exertional symptoms, and neurological symptoms, such as altered sensorium or irritability, or gastrointestinal disturbances, such as anorexia or bloating, may be the only overt manifestations of HF. Similarly, the physical findings are often nonspecific, and the chest radiograph may be difficult to interpret in patients with mild HF.

Plasma B-type natriuretic peptide (BNP) and n-terminal pro-BNP (nt-proBNP) levels aid in distinguishing dyspnea due to HF from that related to other causes, such as pulmonary disorders [57]. These natriuretic peptide levels tend to be elevated in both systolic and diastolic HF, and they also correlate with response to therapy and prognosis. However, BNP levels also increase with age in healthy individuals without HF, particularly women, and, as a result, the specificity and predictive accuracy of BNP levels decline with age [58]. Nonetheless, in cases of diagnostic uncertainty, a low or normal BNP or nt-proBNP level effectively excludes acute HF, whereas markedly elevated levels provide strong evidence in support of the diagnosis.

Management

The principal goals of HF management in elderly patients are to maximize quality of life, reduce medical resource utilization, and extend functional survival. In the past several decades, there have been major advances in the treatment of HF, but older HF patients have been underrepresented in clinical trials and are less likely than younger patients to receive evidence-based therapy. In addition, management of older HF patients is often complicated by multiple comorbid conditions and by a variety of behavioral, psychosocial, and economic factors that contribute to poor outcomes and the high rate of repetitive hospitalizations. For these reasons, current guidelines advocate utilizing a multidisciplinary disease management strategy for optimizing medication prescribing practices, enhancing compliance with medications and diet, and providing appropriate follow-up for older HF patients [59]. Multiple studies and systematic reviews have documented the efficacy of this approach in reducing hospitalizations and cost of care, while improving quality of life and overall compliance [60].

Medical Therapy

In general, the pharmacologic treatment of patients with systolic HF is similar in older and younger patients. Considerations specific to the elderly are discussed briefly in the following paragraphs.

ACE Inhibitors

Although none of the ACE inhibitor trials have specifically targeted older patients, the average age of patients in CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) was 71 years, and the beneficial effects of enalapril were also similar in older and younger patients enrolled in the SOLVD (Studies of Left Ventricular Dysfunction) trials [61, 62]. Moreover, in the post-MI ACE inhibitor trials, the benefits of ACE inhibitors were, if anything, greater in older patients [42]. Nonetheless, few patients over 75 years of age were enrolled in the ACE inhibitor trials, and a large meta-analyses of the ACE inhibitor studies suggested that the benefit of ACE inhibitors may be attenuated at elderly age [63]. Despite these concerns, ACE inhibitors are recommended for all individuals with significant left ventricular systolic dysfunction (ejection fraction <40–45 %), whether or not overt HF symptoms are present [59]. As in younger patients, the ACE inhibitor dosage should be gradually titrated to achieve a target daily dose of captopril 150 mg, enalapril 20 mg, lisinopril 20 mg, or equivalent. ACE inhibitors are usually well tolerated in older adults, but hyperkalemia and renal dysfunction occur more frequently than in younger patients.

ARBs

ARBs have a more favorable side effect profile than ACE inhibitors, and both valsartan and candesartan have been shown to improve clinical outcomes in patients with symptomatic HF and reduced left ventricular systolic function [64–67]. In all of these studies, the beneficial effects were similar in older and younger patients [64–68]. Based on these findings, ARBs are an acceptable alternative to ACE inhibitors in patients intolerant to the latter class of agents due to cough, gastrointestinal side effects, or allergic reactions [59].

Other Vasodilators

The combination of hydralazine and isosorbide dinitrate increased survival relative to placebo in V-HeFT-I (Veterans Administration Heart Failure Trial) [69], but was less effective than enalapril in V-HeFT-II [70]. More recently, the combination was shown to improve outcomes in African-Americans with moderate-to-severe HF when added to standard therapy [71]. Although few elderly patients were enrolled in these trials, this combination is an acceptable alternative to ACE inhibitors or ARBs in appropriately selected patients.

Beta-Blockers

Beta-blockers improve ventricular function and reduce mortality and hospitalizations in patients with symptomatic systolic HF, including those with New York Heart Association

class IV symptoms and persons up to 80 years of age [72, 73]. Use of beta-blockers in older patients may be limited by a higher prevalence of bradyarrhythmias and severe chronic lung disease, and older patients may also be more susceptible to the development of fatigue and impaired exercise tolerance during long-term beta-blocker administration. Nonetheless, beta-blockers should be considered standard therapy in older patients with stable systolic HF and no contraindications, especially those with underlying coronary heart disease or an elevated resting heart rate.

Digoxin

Digoxin improves symptoms and reduces hospitalizations in patients with symptomatic systolic HF treated with ACE inhibitors and diuretics, but has no effect on total or cardiovascular mortality [74]. The effects of digoxin are similar in younger and older patients, including octogenarians [75].

The volume of distribution and renal clearance of digoxin decline with age. In addition, recent data indicate that the optimal therapeutic concentration for digoxin is 0.5–0.9 ng/ml [76]. For most older patients with preserved renal function (est. creatinine clearance ≥60 cc/min), digoxin 0.125 mg daily provides a therapeutic effect. Lower dosages should be used in patients with renal insufficiency. Although older patients are often thought to be at increased risk for digitalis toxicity, this was not confirmed in an analysis from the Digitalis Investigation Group (DIG) trial [75].

Diuretics

Although conventional diuretics such as furosemide may not improve long-term outcomes in HF patients, diuretics remain a cornerstone of therapy due to their efficacy in relieving congestive symptoms and edema. Elderly patients are more susceptible to dehydration and to diuretic-induced electrolyte disturbances, so older patients receiving chronic diuretic therapy should be monitored closely with daily weights and periodic electrolyte assessments.

Aldosterone Antagonists

Spironolactone 12.5–50 mg daily added to standard therapy has been shown to reduce mortality by 30 % in patients with class III–IV systolic HF, with similar benefits in older and younger patients [77]. Eplerenone, a selective aldosterone antagonist, has also been shown to reduce mortality and sudden cardiac death in patients with left ventricular dysfunction following acute MI [45]. Spironolactone is contraindicated in patients with severe renal insufficiency or hyperkalemia, and up to 10 % of patients develop painful gynecomastia. In addition, older patients receiving spironolactone in combination with an ACE inhibitor may be at increased risk for hyperkalemia, particularly in the presence of preexisting renal insufficiency or diabetes and at doses in excess of 25 mg/day.

Device Therapy

Device therapy is playing an increasingly important role in the management of patients with advanced systolic HF, including the elderly. In the USA, more than half of implantable cardioverter defibrillators (ICDs) are inserted in patients 65 years of age or older (Table 39.1) [2, 3], and 10–15 % are implanted in patients ≥80 years. Notably, however, several recent analyses suggest that the life-prolonging benefits of ICDs are markedly reduced in older patients [78–80], in part because elderly patients are at increased risk of dying from other causes. Conversely, cardiac resynchronization therapy (CRT) appears to improve symptoms, exercise tolerance, and quality of life to a comparable extent in younger and older patients, including octogenarians [81]. More recently, an increasing proportion of older patients with advanced systolic HF are being considered as potential candidates for continuous-flow ventricular assist devices (VADs), and preliminary data indicate favorable outcomes up to 2 years in carefully selected patients [82]. Finally, many centers now consider patients in their early 70s as potential candidates for orthotopic heart transplantation.

Heart Failure with Preserved Ejection Fraction

As noted previously, up to 50 % of older HF patients have HFPEF. However, despite the high prevalence of this disorder in older adults, to date no treatment has been shown to reduce mortality. Patients with HFPEF have a somewhat more favorable prognosis than those with systolic HF [83], but symptoms, exercise tolerance, and hospitalization rates are similar in systolic HF and HFPEF.

Diuretics are effective in relieving congestion and edema, but they must be used cautiously because patients with HFPEF are dependent on sufficient preload to maintain adequate stroke volume. Such patients are often "volume sensitive" and are prone to develop pulmonary edema with modest volume overload, while volume contraction and pre-renal azotemia may occur in response to overdiuresis.

Several trials evaluating specific pharmacologic interventions in patients with HFPEF have now been reported. In the CHARM-Preserved (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity) trial, candesartan reduced HF hospitalizations but had no effect on mortality in patients with class II–IV HF and an ejection fraction >40 % [84]. In the largest study to date, the ARB irbesartan had no effect on mortality or other secondary outcomes among patients 60 years of age or older with class II–IV HF and an ejection fraction ≥45 % [85]. Smaller studies with the beta-blocker nebivolol and the ACE inhibitor perindopril in patients with HFPEF have demonstrated modest reductions in HF hospitalizations but no effect on mortality [86, 87].

Finally, in the DIG ancillary trial, digoxin had no effect on mortality or all-cause hospitalizations in HF patients with an ejection fraction >45 % [88].

Prevention

Given the high rates of morbidity and mortality in older patients with established HF, prevention of this disorder is clearly desirable. At the present time, the best preventive measures include aggressive treatment of hypertension and other known coronary risk factors. In the Hypertension in the Very Elderly Trial, for example, among hypertensive patients 80 years of age or older, diuretic-based treatment with indapamide led to a 21 % reduction in all-cause mortality, 30 % reduction in stroke, and 64 % reduction in incident HF [9].

Arrhythmias and Conduction Disorders

Supraventricular, ventricular, and bradyarrhythmias all increase in frequency with advancing age, as do supranodal, nodal, and infranodal conduction abnormalities. Each of these disorders is discussed briefly in the following paragraphs.

Supraventricular Arrhythmias

Atrial fibrillation is the most common and clinically important sustained arrhythmia in older adults. The prevalence of atrial fibrillation increases from less than 1 % in individuals under age 40 to more than 10 % in those over the age of 80, and the median age of patients with atrial fibrillation is 75 years. Atrial fibrillation is more common in men than in women at all ages, but the proportion of women increases with age.

Atrial fibrillation in the elderly is almost always associated with significant underlying cardiac disease, with hypertension, CAD, valvular heart disease, and sick sinus syndrome being the most common precursors. Hyperthyroidism, alcoholism, nonischemic cardiomyopathies, chronic lung disease, and electrolyte disturbances (esp. hypokalemia) are also important causes of atrial fibrillation in the elderly. In addition, atrial fibrillation frequently complicates major cardiac and noncardiac surgery in older patients.

The symptomatology of atrial fibrillation in the elderly is highly variable. Many patients are asymptomatic or experience only mild palpitations. Other patients describe fatigue, shortness of breath, or poor exercise tolerance, while still others present with acute pulmonary edema or stroke. In the Framingham Heart Study, the proportion of strokes attributable to atrial fibrillation increased from 1.5 % in patients 50–59 years of age to 23.5 % in patients over the age of 80 [89], thus demonstrating the importance of atrial fibrillation as a cause of stroke at older age.

Although it is clear that the risk of stroke in patients with atrial fibrillation increases with age, particularly after age 75, the management of atrial fibrillation in the very elderly remains somewhat controversial. The greatest effect of warfarin in reducing the absolute risk of thromboembolic stroke occurs in patients over age 75, but the risk of major bleeding complications, including intracranial hemorrhage, is also highest in this age group. However, despite concerns about bleeding risk, current guidelines recommend that patients over age 75 with chronic atrial fibrillation and no major contraindications be treated with warfarin to maintain an international normalized ratio (INR) in the range of 2.0–3.0 [90].

Recently, dabigatran and rivaroxaban have been approved for stroke prophylaxis in patients with atrial fibrillation [91, 92]. Although both of these agents have significant advantages compared to warfarin, limited data are available in patients over 75–80 years of age. In addition, there have been reports of increased serious bleeding complications with dabigatran in the very elderly and in patients weighing less than 60 kg. Therefore, dabigatran should be used with caution in these populations.

Aspirin is a less effective alternative to systemic anticoagulation in patients who are ineligible for warfarin. The addition of clopidogrel to aspirin provides additional protection against stroke, but this benefit is limited to patients less than 75 years of age [93].

In patients with recent onset atrial fibrillation, that is, within 6–12 months, many clinicians attempt cardioversion at least once, with or without antiarrhythmic drug therapy to maintain sinus rhythm following successful cardioversion. However, data from the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial and other studies indicate that a strategy of anticoagulation and rate control is associated with equivalent or superior outcomes in patients with atrial fibrillation who are minimally symptomatic [94].

In patients who continue to experience significant symptoms despite medical therapy, catheter-based or surgical ablation may be considered [90]. Ablation of the atrioventricular node with implantation of a permanent ventricular pacemaker is effective in controlling heart rate and alleviating symptoms related to tachycardia but does not obviate the need for systemic anticoagulation, as patients undergoing this procedure remain in atrial fibrillation [90]. Catheter ablation along the margins of the pulmonary veins in the left atrium is effective in restoring and maintaining sinus rhythm in over 70 % of selected patients [90]. However, the efficacy of pulmonary vein isolation appears to be lower in older patients with persistent atrial fibrillation, and limited data are available in patients

over 75–80 years of age. Surgical ablation using the Cox maze procedure restores sinus rhythm in over 90 % of patients, including the elderly, and may be considered in patients undergoing cardiac surgery for other reasons (e.g., CABG) in centers with expertise in performing the procedure [90].

The treatment of other supraventricular arrhythmias, including atrial flutter, is generally similar in older and younger patients, but the risk of antiarrhythmic drug toxicity is greater in the elderly.

Ventricular Arrhythmias

The prevalence and complexity of ventricular ectopic activity increase with age, with men being affected more often than women. As in younger patients, the prognostic significance of ventricular arrhythmias is primarily related to the underlying cardiac disease. Therefore, therapy should be directed at the primary disorder (e.g., CAD, hypertension), and the arrhythmias should only be treated if they are highly symptomatic or life threatening. When indicated, treatment is similar in older and younger patients. In particular, age is not a contraindication to an implanted cardioverter defibrillator (ICD), and the majority of ICD recipients are over age 65 (Table 39.1). Nonetheless, as previously discussed, the value of ICDs in patients over age 80 is controversial, as none of the major ICD trials enrolled individuals in this age group [95]. In addition, elderly patients are more likely than younger patients to die of noncardiac causes (e.g., pneumonia, hip fracture), and therefore less likely to die from ventricular arrhythmias.

Bradyarrhythmias and Conduction Disturbances

Aging is associated with degenerative changes throughout the conduction system, and the prevalence of virtually all bradyarrhythmias and conduction abnormalities increases with age. From the clinical perspective, "sick sinus syndrome" is the most important disorder of the conduction system in older adults [96]. Increasing age is associated with a decline in the number of functioning pacemaker cells in the sinus node, and by age 75 only about 10 % of the cells remain capable of initiating an impulse. In addition, conduction of the impulse from the sinus node to the atrial tissues may be impaired (sinus exit block), and conduction within the atria and through the AV node may also be delayed. Sick sinus syndrome thus represents a generalized disorder of sinoatrial function that is often manifested by both bradyarrhythmias and supraventricular tachyarrhythmias (tachy-brady syndrome). Importantly, most medications used to treat the tachyarrhythmias, including beta-blockers, diltiazem, verapamil, and antiarrhythmic agents, may exacerbate the bradyarrhythmias.

Bradyarrhythmias commonly associated with the sick sinus syndrome include marked sinus bradycardia, sinus pauses and sinus arrest, sinus exit block, advanced AV-nodal block, and atrial fibrillation with slow ventricular response. These arrhythmias can produce a spectrum of symptoms ranging from fatigue, shortness of breath, angina, or reduced exercise tolerance to dizziness, impaired cognition, or syncope. In patients with major symptoms directly attributable to bradycardia, permanent pacemaker implantation is indicated. In the USA, over 80 % of all pacemakers are inserted in older individuals (Table 39.1), and sick sinus syndrome is the most common underlying disorder. For patients in sinus rhythm, dual-chamber pacing is associated with a lower risk for developing atrial fibrillation, fewer hospitalizations for HF, and an improved quality of life compared to single-chamber ventricular pacing [97].

Cardiopulmonary Resuscitation

The value of cardiopulmonary resuscitation (CPR) in elderly patients remains a matter of debate. Fewer than 10 % of older patients who suffer cardiac arrest and receive CPR survive beyond 30 days with favorable neurological outcomes. In addition, there is little difference in outcome whether the arrest occurs in a hospital, nursing home, or community setting. Despite these grim statistics, a subgroup of older patients with substantially better outcomes can be identified. For example, previously healthy individuals who receive prompt CPR for a witnessed cardiac arrest and who are subsequently found to be in ventricular fibrillation have a 25–40 % likelihood of surviving with a good neurological outcome. Thus, although the decision to initiate CPR must be based on both clinical and psychosocial considerations, the results of CPR can be gratifying in selected patients, even at elderly age.

Exercise and Cardiac Rehabilitation

As in younger patients, physical inactivity is a risk factor for cardiovascular events in older adults, and regular physical exercise is associated with improved health status and sense of well-being in the elderly. In addition, the benefits of cardiac rehabilitation following myocardial infarction or cardiac surgery are comparable in older and younger patients [98]. Despite these considerations, physicians are less likely to recommend regular exercise or cardiac rehabilitation for older patients with or without cardiovascular disease. Nonetheless, the dictum "use it or lose it" is most applicable in the elderly, and maintaining a physically, intellectually, and emotionally active lifestyle is perhaps the best approach for preserving independence and ensuring a high quality of life in older individuals.

Ethical Issues and End-of-Life Care

As discussed throughout this chapter, older patients with cardiovascular disease are at increased risk for a multitude of complications, including death. Elderly individuals maintain widely divergent views about the use of life-sustaining interventions and other invasive medical procedures, as well as what constitutes an acceptable quality of life in the face of chronic or terminal illness [99]. Moreover, studies have shown that patient surrogates, including spouses and physicians, are unable to reliably predict a patient's preferences in specific end-of-life scenarios. In order to ensure that a patient's wishes are honored if and when the patient is no longer capable of communicating his or her preferences, the physician should make an effort to address these issues at a time when the patient is still competent and lucid. The patient should also be encouraged to develop a living will and appoint a durable power of attorney. In addition, in patients with a progressive illness such as HF, it is helpful to discuss where the patient wishes to spend his or her final days. Potentially suitable environments include the home, a chronic care facility, or a hospital. Palliative care and hospice should be considered in older patients with terminal cardiovascular disease [100].

Summary and Conclusions

Aging is associated with extensive changes in cardiovascular structure and physiology, many of which have a direct impact on the clinical manifestations, response to treatment, and prognosis of cardiovascular disease in older adults. As a general principle, older patients are at increased risk for adverse outcomes, and the potential benefits to be derived from specific therapeutic interventions are therefore greater in older than in younger patients. Although additional research is needed to define the precise role of many therapies in older patients, the available evidence indicates that age alone is not a sufficient justification for withholding treatment. Similarly, it is evident that more effective preventive strategies are needed to reduce the tremendous physical, emotional, and financial burden imposed on our society by cardiovascular disease in our ever-expanding elderly population.

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Cardiovascular Complications in Patients with Renal Disease

40

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How the Kidney Affects the Heart: Chronic Kidney Disease

Clinical Importance

CKD is a worldwide health problem with rising incidence and prevalence, associated with high morbidities and mortalities [1]. As a result of the high prevalence of traditional and nontraditional cardiovascular risk factors, CKD is associated with accelerated cardiovascular disease [2], which is a major preventable cause of morbidity and mortality. In patients undergoing dialysis, the cardiovascular mortality rate was 10–30 times higher than in the general population [3, 4]. In post myocardial infarction patients with an estimated GFR (eGFR) <60 but >45 mL/min/1.73 m^2, total mortality was 25 % higher [5] than with an eGFR >60 mL/min/1.73 m^2. In addition, following an acute coronary artery syndrome, a fall in GFR was associated with worse cardiovascular outcomes [6].

Based on the strong association between CKD and cardiovascular disease, the National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Renal Disease recommended inclusion of all patients with CKD in the highest-risk group for cardiovascular events [7]. These recommendations are supported by other professional guidelines, including the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) and the NKF-K/DOQI dyslipidemia guidelines [8].

In addition to the prevention, early detection, and rigorous management of cardiovascular risk factors, early identification and treatment of CKD and its associated comorbidities are also important to improve cardiovascular outcomes. This is supported by a position statement from the American Heart Association that recommended screening for proteinuria and estimation of GFR in the routine evaluation of patients with cardiovascular disease or at high risk for cardiovascular disease [9]. For instance, blockade of the renin-angiotensin aldosterone system (RAAS) is associated with less renal progression [10] and therefore potentially with better cardiovascular outcomes in patients with proteinuric CKD.

Epidemiology of CKD

A cross-sectional analysis of the most recent National Health and Nutrition Examination Surveys (NHANES 1999–2004) reported that approximately 13 % of American adults have a low GFR defined as <60 mL/min; most of these (8 %) were stage 3 CKD with an eGFR of 30–60 mL/min. Another 3–4 % have normal GFR but have abnormal albuminuria [11]. A low GFR has been associated with a greater risk of cardiovascular events in observational data [12] and also in randomized controlled trials [13]. Albuminuria has also been associated with a greater risk of cardiovascular death in observational studies, rising almost logarithmically with higher levels [14]. This is also true in randomized controlled trials; for example, in people with diabetes the presence of albuminuria almost doubles the risk of total mortality in patients whether they are treated with an ACE inhibitor or not [15]. Therefore, the presence of a low GFR and abnormal albuminuria are markers for greater cardiovascular risk.

CKD is usually classified into the following categories: glomerular diseases (including diabetic glomerulosclerosis), vascular diseases, vascular diseases, tubulointerstitial disease, cystic diseases, and diseases in transplant patients.

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DOI 10.1007/978-1-4614-6705-2_40,

Cardiac Diagnostic Issues in CKD

Contrast-Induced Nephropathy

Patients with CKD are at high risk for atherosclerotic disease and may benefit from diagnostic and interventional vascular procedures. The use of iodinated contrast agents in coronary angiography may be complicated by contrast-induced nephropathy (CIN), commonly defined as an increase in serum creatinine by more than 0.5 mg/dL or 25 % from baseline within 48 to 72 h after contrast administration. A simple risk score of CIN after percutaneous coronary intervention (PCI) has been developed by Mehran, incorporating the following risk factors [16]. See Table 40.1.

The pathogenesis of CIN is not completely understood but thought to be related to contrast-induced hemodynamic and direct cytotoxic effects on renal structures [17]. Careful patient selection, limiting the amount of contrast exposure, and adequate peri-procedural hydration are the only preventive measures with demonstrated efficacy [18]. The roles of other agents, such as N-acetylcysteine (NAC) and sodium bicarbonate, are controversial.

While high-osmolar contrast media is known to cause nephrotoxicity, there has been conflicting data on the role of low-osmolar and iso-osmolar contrast media in the prevention of CIN. Previous studies have shown significantly reduced incidence of CIN and cardiovascular outcomes associated with the use of the iso-osmolar contrast agent iodixanol compared with the low-osmolar contrast agent iopromide in patients with renal insufficiency undergoing coronary angiography [19]. In contrast, more recent larger randomized trials have revealed similar incidences of CIN and cardiac events following the administration of iodixanol or iopromide during coronary angiography, both in patients with renal insufficiency [20, 21] and in unselected patients undergoing primary PCI for STEMI [22]. The CIN risks from different contrast media were thought to be affected by other factors (such as ionicity) than can be attributed to osmolarity alone. Based on these findings, the ACC/AHA 2009 Focused Updates on Guidelines on Percutaneous Coronary Intervention expanded the choice of contrast media during coronary angiography to either iso-osmolar media or low-osmolar media other than ioxaglate or iohexol [23].

Previous studies have shown conflicting results on the efficacy of NAC in the prevention of CIN in patients undergoing coronary angiography. The benefit of NAC 600 mg orally twice daily in reducing the risk of CIN was demonstrated in patients with moderate renal insufficiency (creatinine clearance <60 mL/min) undergoing elective coronary angiogram in a prospective randomized trial [24]. In contrast, multiple subsequent prospective randomized trials in patients with renal impairment undergoing coronary angiography showed no benefit of NAC over placebo in reducing the risk of CIN [25–27]. Compared with ascorbic acid, high-dose NAC 1,200 mg orally twice daily for four doses resulted in less elevation of serum creatinine in patients with renal insufficiency (creatinine clearance <60 mL/min or serum creatinine ≥1.1 mg/dL) undergoing coronary angiography in a recent prospective randomized trial [28]. While NAC was shown to significantly reduce the risk of CIN compared with ascorbic acid among patients with diabetes, the benefit was not statistically significant in the overall population. Another study in patients with diabetes and CKD (serum creatinine ≥1.5 mg/dL for men, ≥1.4 mg/dL for women) undergoing elective coronary angiography failed to any benefit of oral NAC 600 mg twice daily over aggressive hydration in reducing the risk of CIN [25]. A meta-analysis of 14 prospective trials demonstrated that NAC resulted in a 43 % reduction in the risk of CIN in patients with CKD undergoing contrast procedures [29] and another supported higher dose at 1,200 mg bid [30], but there are questions about publication bias [31]. While the use of NAC has been recommended for some due to its low-cost and side-effect profile, the cost effectiveness of this approach is unclear. Presently with almost as many meta-analyses as studies, the role of NAC to prevent CIN is unclear [32–52].

The efficacy of sodium bicarbonate in preventing CIN is also controversial due to significant heterogeneity across studies and publication bias. Most of the studies were performed in a general population undergoing contrast procedures. Multiple meta-analyses have shown a superiority of peri-procedural hydration with sodium bicarbonate over normal saline in decreasing the risk of CIN, with odds ratios ranging from 0.37 to 0.54 [47, 53–55]. This finding was also confirmed in patients with mild preexisting renal impairment receiving contrast procedures in a meta-analysis [56]. The benefit disappears when NAC was used in addition to hydration. Another systematic review of 23 randomized trials in the general population also demonstrated the benefit of sodium bicarbonate in preventing CIN (relative risk 0.43 in published studies and 0.78 in unpublished studies), with overestimation of the benefit in smaller earlier studies and neutral results in larger, more recent studies [55]. Because of the heterogeneity of previous studies, larger high-quality

Table 40.1 Risk factors for contrast-induced nephropathy

Diabetes
Anemia (hematocrit <0.39 for men and <0.36 for women)
Age >75 years
Hypotension, the need for inotropic support for hypotension
Intra-aortic balloon pump within 24 h of the procedure
CHF class III or IV by New York Heart Association or pulmonary edema
Underlying CKD (creatinine >130 umol/L(>1.5 g/dL))
Volume of contrast

randomized controlled trials in patients with CKD undergoing coronary angiography are needed to assess the benefit of sodium bicarbonate before recommendation for routine use can be made.

The efficacy of combination therapy of sodium bicarbonate plus NAC in reducing the risk of CIN (relative risk reduction 0.65) was shown in a meta-analysis of ten randomized trials of low to intermediate risk patients undergoing coronary angiogram [35]. In patients at high risk for CIN (GFR ≤ 30 mL/min/1.73 m^2 or a high contrast nephropathy risk score), a novel approach to the prevention of CIN has been developed using the RenalGuard System, a real-time matched fluid replacement device that aims to maintain a high urine output and cause prompt elimination of nephrotoxic contrast media. Hydration with saline and NAC controlled by the RenalGuard System and furosemide was shown to be superior to sodium bicarbonate plus NAC in the Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II) [57].

While we await the conduct of larger prospective trials, we suggest the following interim approach for management as it appears the single common thread among these studies is that putting patients into some sort of protocol is protective. Based on the work of Mehran, we suggest dividing patients into low-risk, at-risk, high-risk, and very-high-risk groups. Using a simplification of Mehran's work, the presence of a creatinine of >130 umol/L with or without one of the following indicates a patient at risk (risk of need for dialysis of only 0.1 % and risk of contrast-induced nephropathy of around 10 %). Thus, the presence of a creatinine >130 umol/L is sufficient to justify at-risk status alone. A creatinine >130 umol/L with any two other risk factors from Table 40.1 indicates a patient at high risk (risk of dialysis of 1 % and risk of contrast-induced nephropathy of more than 25 %). Anyone with a creatinine of 130 umol/L or greater with three risk factors is at very high risk (risk of dialysis approximately 10 %). We also suggest arbitrarily including any patient with an estimated GFR of <30 mL/min as equivalent to very high risk. The following are suggestions only on how these different risk groups might be managed and should be updated as new evidence becomes available. See Table 40.2

Gadolinium

Gadolinium compounds are safe and useful as MRI contrast agents. Although free gadolinium is neurotoxic, when complexed to one of a variety of chelates, it is safe for use in adults and children. These hydrophilic gadolinium-chelated agents have pharmacokinetic properties very similar to those of iodinated X-ray contrast media. Like iodinated contrast agents, gadolinium contrast agents have a plasma half-life of about 2 h in patients with normal renal function and are nearly completely cleared from the bloodstream within 24 h. However, the elimination half-life is increased to 6 h in patients with GFR of 10–30 mL/min [58] and 34 h in patients with a GFR of 2–10 mL/min [59].

Nephrogenic systemic fibrosis (NSF) is a recently recognized entity associated with the use of gadolinium-based magnetic resonance (MR) contrast agents in patients with advanced renal disease. It is a potentially debilitating and fatal disease that typically presents with skin induration affecting the extremities and fibrosis of internal organs. In an analysis of 229 cases of NSF reported in the literature, all patients with known baseline renal function had a GFR <30 mL/min/1.73 m^2, while GFR <15 mL/min/1.73 m^2 was present in 85 % of cases [60]. There is no effective treatment for NSF. Supportive measures to improve renal function and physiotherapy are the mainstay of therapy. A wide range of experimental therapies have been used with variable efficacy, including renal transplantation, sodium thiosulfate, extracorporeal photopheresis, imatinib mesylate, plasmapheresis, pentoxifylline, IVIG, steroids, and cyclophosphamide [61].

For patients with renal disease, careful patient selection, limitation of the dose of contrast agent, and avoidance of gadolinium-based contrast media for advanced renal failure (GFR < 30 mL/min/1.73 m^2) are recommended to reduce the risk of NSF [62]. If the benefit of gadolinium-enhanced MRI outweigh the risk of NSF and no other imaging modalities are available to answer the clinical question, contrast-enhanced imaging may be performed with caution, using a more stable agent or an agent with cyclic structures [61].

Blood Pressure Target in CKD With and Without Diabetes

The previous target blood pressure <130/80 mmHg for patients with CKD with or without diabetes was endorsed by multiple professional guidelines [63–66], based on studies suggesting a benefit of aggressive blood pressure control on

Table 40.2 Proposed management of CIN for each risk level

Treatment	At risk	High risk	Very high risk
Hold NSAID (except cardiac ASA) and hold metformin. Avoid hypovolemia	√	√	√
N-acetylcysteine 1,200 mg bid day before and day of contrast procedure (this remains controversial)	√	√	√
Bicarbonate infusion 3 A of sodium bicarbonate added to 1,000 mL of D5W (total volume 1,150 mL) 3.5 mL/kg over 1 h then 1 mL/kg/h for up to 6 h		√	√
Admission day before contrast procedure			√

renal outcomes especially in proteinuric CKD. Lower BP targets were first proposed for patients with nondiabetic CKD based on a secondary analysis of the modification of diet in renal disease (MDRD) study. The MDRD study was a multicenter prospective randomized trial in 840 patients with CKD that showed no impact of intensive blood pressure control on the change in GFR, cardiovascular events, or death compared with usual blood pressure control [67, 68]. A post hoc subanalysis of the MDRD study showed a slower decline in GFR in patients with over 3 g/day of proteinuria receiving intensive blood pressure control (mean achieved blood pressure 126/76 mmHg) compared to usual blood pressure control (mean achieved blood pressure 134/81 mmHg) [69]. However, this benefit of intensive blood pressure management was only demonstrated in a non-prespecified endpoint in 32 patients. The renoprotective effect of lower blood pressure target was also suggested by a meta-analysis of 11 randomized trials that revealed a 4.5 times increased risk of decline in renal function observed with higher target systolic blood pressure (130–139 mmHg vs. 110–129 mmHg) in patients with nondiabetic CKD and proteinuria ≥1 g/day [70]. This risk was decreased by the use of ACE inhibitors independent of its effect on blood pressure and urine protein excretion.

The target blood pressure in nondiabetic CKD has recently been raised to <140/90 mmHg in the 2008 NICE chronic kidney disease guidelines [67] as a result of several recent randomized studies that failed to demonstrate renoprotective benefits of aggressive blood pressure control. The Blood Pressure Control for Renoprotection in Patients with Nondiabetic Chronic Renal Disease (REIN-2) study showed no difference in the risk of progression to ESRD between intensive blood pressure control (target <130/80 mmHg) and usual care (target diastolic blood pressure <90 mmHg) in patients with nondiabetic CKD and proteinuria more than 1 g/day [71]. All patients were treated with ramipril and received felodipine and other agents as needed to achieve blood pressure targets. However, the lack of benefit in the intensive treatment arm may be explained by similar blood pressure achieved between the groups (134/82 mmHg in the usual care group vs. 130/80 mmHg in the intensive group) [71].

The African American Study of Kidney Disease and Hypertension (AASK) trial is a randomized trial of 1,094 African Americans with hypertensive CKD that failed to demonstrate a reduction in the rate of GFR decline in patients receiving aggressive blood pressure control with a target MAP of 92 mmHg compared with a target MAP of 102–107 mmHg, even in patients with proteinuria [72]. In contrast to the absence of renal protection in the group randomized to aggressive blood pressure control, a significantly lower risk of ESRD or death was observed in patients who achieved the low blood pressure target in each group in a post hoc subgroup analysis, independent of the amount of urinary protein excretion [73]. The conflicting findings may be explained by confounding factors such as comorbidities and poor adherence, as well as limitations inherent in the use of a secondary endpoint in the post hoc analysis [74].

Given the insufficient level of evidence from randomized trials supporting aggressive blood pressure lowering in patients with nondiabetic CKD, even in those with proteinuria, the blood pressure target for this population has been changed to <140/90 mmHg.

For patients with diabetes and hypertension, the blood pressure target is <130/80 mmHg including patients with diabetes and CKD [63]. In patients with diabetes, intensive blood pressure control to <120 mmHg is still controversial. In the ACCORD-BP study, a randomized study of 4,733 patients with type 2 diabetes, intensive blood pressure lowering <120 mmHg did not reduce the composite outcome of cardiovascular events and cardiovascular death but did reduce the risk of stroke, a prespecified secondary endpoint by 41 % at 4.7 years compared with standard blood pressure control <140 mmHg [75]. Blood pressure targets following an acute coronary syndrome or with heart failure are <140/90 mmHg [63].

Blood Pressure Control

The benefit of blood pressure control in preventing adverse cardiovascular and renal events is well established. Lowering blood pressure leads to regression of LVH [76]. In the double-blind randomized Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study in 9,193 patients with essential hypertension and LVH, regression of electrocardiographic LVH during antihypertensive treatment with losartan or atenolol was associated with decreased cardiovascular morbidity and mortality [77].

In diabetic or nondiabetic proteinuric CKD, RAAS blockade using an ACE inhibitor or an ARB is effective in reducing cardiovascular risks and delaying the progression of renal disease [78, 79] and has become a cornerstone of the treatment of hypertension in these patients [80]. Thiazide diuretics or chlorthalidone are often added to RAAS blockade to achieve target blood pressure. Loop diuretics may be used as an alternative for CKD patients with volume overload to achieve euvolemia.

In patients with type 2 diabetes and hypertension, an ACE inhibitor and CCB combination therapy (benzapril/amlodipine) is associated with a 21 % reduction in cardiovascular events compared with an ACE inhibitor and diuretic combination (benzapril/thiazide) in the Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension (ACCOMPLISH) trial, a randomized trial of 6,946 patients with diabetes [81]. Additionally in a renal subanalysis, the combination of the ACE inhibitor and CCB slowed the progression of nephropathy to a greater

extent than the ACE inhibitor diuretic combination [82]. Combination of a beta-blocker and a nondihydropyridine CCB should be used with great caution due to risk of additive chronotropic effects [63]. The safety of long-acting calcium channel blockers (both dihydropyridine and nondihydropyridine) was recently evaluated in patients with coronary artery disease, and they were associated with a reduction in the risk of stroke, angina pectoris, and heart failure, but a similar outcome for mortality [83].

Drug Therapy to Reduce the Calcium × Phosphate Product

Derangements in calcium and phosphorus metabolism in ESRD and dialysis patients are highly prevalent and are associated with accelerated vascular calcification which is a major nontraditional risk factor for cardiovascular disease. Before the 1990s aluminum was used for phosphate binding but was then switched to calcium compounds (usually calcium carbonate). However, with the finding that vascular calcification was linked to excess coronary artery disease, explaining in part the greater CV risk in patients with CKD, the use of excessive doses of calcium carbonate has come into question [84, 85]. There are increasing randomized trial data within the past few years supporting the role of calcium-based phosphate binders in the pathogenesis of accelerated vascular calcification in ESRD [86].

Sevelamer is an alternative, non-calcium-based phosphate binder used in patients with ESRD. Unlike calcium-based phosphate binders, sevelamer may have beneficial cardiovascular effects. Several studies have shown slower progression of vascular calcification associated with the use of sevelamer compared with calcium-based phosphate binders [87]. Data on the survival benefit of sevelamer found a benefit in a small randomized trial but no difference in all-cause and cardiovascular mortality between sevelamer and calcium-based phosphate binders in a larger multicenter randomized trial of 2,103 hemodialysis patients [88].

Given the potential risk of vascular calcification accelerated by calcium supplementation in the healthy population as well as in patients with ESRD, cautious use of these agents and vascular risk factor reduction are essential to reduce the risk of adverse cardiovascular outcomes.

QT Interval in CKD

A prolonged QT(c) interval has been recognized as an independent marker of risk for overall and cardiovascular mortality in dialysis patients [89–91]. There is an associated increased risk of torsade de pointes, particularly with antiarrhythmics like sotalol, a class III antiarrhythmic used for atrial fibrillation and heart failure [92, 93]. Close monitoring of serum potassium level, renal function, and QT interval, avoidance of polypharmacy with other potassium antagonists, and control of heart failure are important to reduce the risk of proarrhythmia [94].

Antiplatelet Therapy in CKD

The benefit-risk balance of aspirin use for primary prophylaxis in CKD is unclear, given the elevated cardiovascular and potentially bleeding risks in this population. There is a scarcity of data, most of which are from subgroup analyses. In a post hoc analysis of the randomized trial HOT (Hypertension Optimal Treatment), treatment with low-dose aspirin therapy for 3.8 years resulted in a significant reduction in major cardiovascular events (HR 0.34) and mortality in 3,619 hypertensive patients with eGFR <45 mL/min/1.73 m^2 (HR 0.34) but not those with eGFR ≥60 mL/min/1.73 m^2, with no significantly increased risk of major bleeding in the CKD population [95]. In addition, the safety of aspirin in CKD was supported by the UK-HARP-I study comparing the efficacy of aspirin vs. placebo and simvastatin vs. placebo with a 2×2 factorial design. In this study of 448 patients with CKD, 100 mg of modified-release aspirin use did not significantly increase the risk for a major bleeding event, but the impact of aspirin on cardiovascular outcome was not addressed [96].

In patients with diabetic renal disease, a subanalysis of the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial demonstrated a benefit of low-dose aspirin therapy in cardiovascular outcomes limited to patients with stage 2 CKD. In this prospective randomized trial of 2,523 diabetes patients without a history of cardiovascular diseases, low-dose aspirin therapy for 4.4 years resulted in a 43 % reduction in the risk of cardiovascular events and mortality in patients with an eGFR of 60–89 mL/min/1.73 m^2, but not in those with eGFR ≥90 mL/min/1.73 m^2 or <60 mL/min/1.73 m^2 [97]. While this post hoc subgroup analysis may suggest cardiovascular protective effects of aspirin in stage 2 CKD, it is largely hypothesis generating. In the absence of more evidence, the indications for aspirin use as primary or secondary prevention in CKD should be extrapolated from the recommendations for the general population at high risk for cardiovascular disease.

Lipid-Lowering Therapy in CKD

The National Kidney Foundation Clinical Practice Guidelines recommend that all patients with CKD be included in the highest-risk group, justifying a target LDL cholesterol level

below 2.0 mmol/L [98]. Observational studies have not shown a consistent relationship between dyslipidemia and increased cardiovascular events in CKD [99]. Some studies reported a negative association between total cholesterol level and mortality in hemodialysis patients with very low cholesterol levels and lack of an association in patients with average cholesterol levels [100]. This anomalous finding may be partly attributed to increased risk of mortality associated with the malnutrition and other chronic illnesses for which low cholesterol level was a surrogate marker. Previous multicenter randomized trials failed to demonstrate the benefit of statins on cardiovascular outcomes in hemodialysis patients (AURORA, 4D) but did show a benefit in renal transplant patients (ALERT) [101–103]. However, a secondary analysis of the JUPITER trial among healthy patients with moderate CKD and elevated high-sensitivity C-reactive protein showed efficacy of rosuvastatin 20 mg with a 45 % reduction in cardiovascular events and a 44 % reduction in all-cause mortality [104].

The Study of Heart and Renal Protection (SHARP) trial was the first randomized trial to demonstrate the benefit of LDL lowering on major vascular events in patients with CKD. In this large-scale multicenter randomized trial in 9,270 patients with advanced CKD, simvastatin 20 mg and ezetimibe 10 mg daily safely decreased the incidence of major atherosclerotic events by 17 % compared with placebo, irrespective of the severity of renal disease or dialysis status [105]. The combination of simvastatin and ezetimibe was used to maximize the lipid-lowering effect while reducing side effects associated with statin therapies. The study was not powered to demonstrate a benefit in overall survival or renal outcomes. Because the SHARP study demonstrated the benefit in patients with CKD at baseline rather than on dialysis and considering the disproportionate number of sudden cardiac deaths (related to arrhythmia or cardiomyopathy, "dead in bed") compared to coronary artery disease in dialysis patients [106], the role of initiating aggressive LDL lowering therapy (e.g., statin and ezetimibe) in prevalent dialysis patients is still unclear but should be a standard of care for patients with CKD.

Glycemic Control in CKD

The National Kidney Foundation KDOQI Guidelines Work Group recommended adherence to the American Diabetes Association guidelines on the assessment of glycemic control in patients with diabetes and CKD. There is insufficient data on the benefits and risks of intensive glycemic control in advanced CKD or in patients undergoing dialysis. HbA1c is a significant predictor of survival for patients on dialysis [107]. The accuracy of HbA1c as a measurement of glycemic control may be affected by a variety of factors: reduced red blood cell life span, hemolysis, and iron deficiency may render the HbA1c value falsely low, whereas acidosis may render it falsely high.

Glycemic control to achieve target HbA1c <7.0 % prevents the development of microalbuminuria and may slow the progression of existing CKD in patients with stage 1 and 2 CKD. In patients with more advanced CKD including patients on dialysis, there is reduced clearance of insulin and certain oral hypoglycemics, and decreased renal gluconeogensis. There is insufficient data on the benefits and risks of intensive glycemic control in these patients [108].

Metformin is contraindicated in patients with stage 4 CKD (GFR <30 mL/min) due to a greater risk of lactic acidosis [99]. First-generation sulfonylureas and glyburide should be avoided in patients with stage 3–5 CKD and those undergoing dialysis due to the risk of hypoglycemia, while gliclazide and glipizide are the preferred second-generation sulfonylureas with no need for dose adjustment. Alpha-glucosidase inhibitors are not recommended in patients with serum creatinine >2 mg/dL and should be avoided in dialysis. Some DPP-4 inhibitors require dose reduction in patients with stage 3–5 CKD and on dialysis. Thiazolidinediones, repaglinide, and the incretin mimetic exenatide do not require dose adjustment in CKD and dialysis, although thiazolidinediones should be used with caution due to risk of fluid retention and adverse cardiac outcomes.

When to Refer to Nephrology

There is no consensus on the optimal time for a referral for nephrology consultation and management. A recent literature review revealed conflicting recommendations from different guidelines, which may cause confusion for referring physicians [109]. Major professional guidelines in different countries included some or all the following criteria to guide appropriate referral to nephrology (Table 40.3).

The UK guidelines provide the most comprehensive list of criteria that also include electrolytes and parathyroid hormone abnormalities, hematuria, and systemic illness [110]. Studies have shown that earlier referral to nephrology may lead to improved outcomes in patients with CKD, including delayed onset of ESRD, improved survival, and reduced complications such as anemia, hypertension, diabetes, and cardiovascular

Table 40.3 Criteria to guide referral of patients to the nephrology clinic

1. Estimated GFR <30–60 mL/min/1.73 m^2
2. Progressive fall in GFR over time (e.g., 30 % fall over 1 year)
3. The presence of proteinuria
4. Severe or refractory hypertension
5. Anemia <110 g/L

disease [111–113]. Most guidelines recommend referral of patients who have progressed to CDK stage 4.

Joint management of the increasingly prevalent CKD population [114] with interprofessional and multidisciplinary teams is recommended [115–117]. The level of nephrology involvement in shared care will vary based on local practice patterns and CKD stage and rate of progression [118].

Clinical Importance and Epidemiology of Heart Disease and CKD

In the Framingham Heart Study, the prevalence of an elevated level of creatinine (136 umol/L (1.5 mg/dL) for men and 120 umol/L (1.4 mg/dL) for women) was 8.9 % in men and 8.0 % in women and was associated with older age, treated hypertension, and diabetes [119]. At least 35 % of patients with CKD have evidence of an ischemic event at the time they present to a nephrologist [120]. In the (Trial to Reduce Cardiovascular Events With Aranesp Therapy) TREAT study of patients with chronic kidney disease, diabetes, and anemia, 25 % of patients had a cardiovascular event in the 2.4-year mean follow-up of the study [121]. CKD is highly prevalent in patients with heart failure, present in 45 % of the 7,788 patients in the Digitalis Investigation Group trial [122] and 30 % of >105,000 hospitalized patients with heart failure in the Acute Decompensated Heart Failure National Registry (ADHERE) [123]. Compared to the general population, the prevalence of LVH is much higher in patients with CKD, ranging from 25 to 50 % in stage 3–4 CKD to 75 % in stage 5 CKD [124–126]. In hemodialysis patients, the annual incidence of new congestive heart failure and ischemic heart disease was found to be 7–3 %, respectively [126]. Most dialysis patients (70–80 %) develop abnormalities of left ventricular size, shape, and function, and LVH is associated with higher mortality rates in dialysis patients as it is in the general population and in patients with hypertension [127–131]. Regression of left ventricular abnormalities has also been shown to be associated with improved cardiac outcomes in dialysis patients [131].

Pathophysiology of Heart Disease and CKD

Patients with CKD are at increased risk of cardiovascular disease due to a higher prevalence of traditional cardiovascular risk factors and the presence of nontraditional risk factors. These risk factors lead to arteriosclerosis, left ventricular diastolic dysfunction, and hypertrophy [132].

In an analysis of data from the NHANES 1 epidemiologic follow-up study, there was no independent association between moderate renal insufficiency and total mortality or cardiovascular mortality after adjustment for traditional cardiovascular risk factors [133]. In contrast, both the Hypertension Optimal Treatment (HOT) study and a post hoc analysis of the Heart Outcomes and Prevention Evaluation (HOPE) trial have identified renal insufficiency (serum creatinine >1.5 mg/dL in the HOT study, creatinine 1.4–2.3 mg/dL in the HOPE study) as an independent predictor for significantly increased risks of cardiovascular morbidity and mortality and total mortality after adjustment for known cardiovascular risks [13, 134].

In addition to traditional risk factors, complications of CKD (such as anemia and mineral metabolism abnormalities) as well as novel biomarkers have been identified in recent years as potential nontraditional cardiovascular risk factors in patients with renal disease. Many of these are linked to the abnormal bone physiology of ESRD leading to medial as well as intimal vascular calcification, with the medial calcification of small vessels playing an important role [135].

The finding of microalbuminuria is recognized as a marker for cardiovascular risk both in people with and without diabetes [15, 136, 137]. Multiple complications and comorbidities of CKD contribute to the development of LV remodeling and cardiomyopathy, including hypertension, arterial stiffness, and anemia, and in patients with ESRD, hypervolemia, arteriovenous fistula, abnormal calcium and phosphorus metabolism, and uremia [130]. Pressure overload from hypertension, arteriosclerosis, and aortic stenosis results in the development of concentric LVH with increased wall thickness and reduced cavity volume. Wall stress from pressure overload stimulates the proliferation of sarcomeres in parallel and increased myocyte width. Concentric LVH decreases diastolic compliance, resulting in increased LV end-diastolic pressure and left atrial pressure that may lead to pulmonary congestion. Increased oxygen demand from concentric LVH may predispose to the development of ischemia even in the absence of atherosclerotic disease. With prolonged pressure overload, the heart may no longer compensate for the increased afterload by concentric LVH alone and undergo LV dilatation. Volume overload and high cardiac output states such as anemia and arteriovenous fistulas may result in lengthening of sarcomeres and LV dilatation to increase stroke volume. The increased wall tension resulting from LV dilatation is compensated by an adaptive increase in wall thickness leading to eccentric LVH [130, 138].

Arteriosclerosis is prevalent in patients with CKD and is characterized by remodeling of large arteries and arterial stiffness from pressure overload, flow overload, arterial calcification, and oxidative stress. The reduction in arterial compliance may cause increased pulse pressure and decreased coronary perfusion resulting in ischemic heart disease. Aortic stiffness [139, 140], increased pulse pressure [141], and arterial medial calcification [142] have all been shown to be independent predictors of cardiovascular

and all-cause mortality in patients on hemodialysis. While aortic pulse wave velocity and impedance are used in clinical trials to measure arterial compliance, other surrogate markers of arteriosclerosis include increased pulse pressure, media calcification, and more indirectly, LVH. While intimal calcification may lead to atherosclerotic plaques, medial calcification is complicated by arteriosclerosis and increased arterial stiffness. In addition, concentric LVH may result from aortic valve calcification and stenosis which occurs in 28–55 % of patients receiving dialysis [143]. In the TREAT study, the predictors of the composite of cardiovascular death, myocardial infarction, stroke, and hospitalization for MI or CHF were prior heart failure, age, urinary protein excretion, higher CRP level, and also the biomarkers N-terminal pro B-type natriuretic peptide and troponin T [121].

The Role of Echo for Diagnosing LVH in CKD

While LVH is a histological entity requiring biopsy for definitive documentation of the pathophysiological process of fibrosis, echocardiography provides a simpler, noninvasive alternative through measures of LV size, geometry, and function [130]. One caveat in patient with ESRD is the dependence of LV mass index calculation upon the extracellular fluid volume status, as the calculated mass index may decrease by 26 g/m^2 following fluid removal from dialysis [144]. Echocardiographic LV mass index should therefore be interpreted with caution and preferably measured post dialysis when the patients are close to dry weight. In patients with ESRD, echocardiography may overestimate the LV mass and volume compared with MRI especially due to abnormal LV geometry and changing intravascular volume [145].

Echocardiographic abnormalities such as LV mass index and fractional shortening are highly prevalent in patients starting dialysis and are associated with the development of heart failure and death. Serial regression of these echocardiographic abnormalities has been observed in approximately half of patients 1 year following dialysis and has been shown to be an independent predictor of improved cardiac outcome in a prospective cohort study [131].

Management of Extracellular Fluid Volume in CKD

Increased interdialytic weight gain due to extracellular fluid retention is associated with increased cardiovascular mortality in ESRD patients receiving long-term hemodialysis [146]. A post hoc analysis of the HEMO study also demonstrated increased cardiovascular morbidity and mortality associated with high ultrafiltration rates during hemodialysis [147]. Sodium and fluid restriction and increasing frequency of hemodialysis may reduce interdialytic weight gain and ultrafiltration rates and potentially improve cardiovascular outcomes.

Management of Abnormal Bone–Mineral Metabolism and Vitamin D in CKD

Secondary hyperparathyroidism is a serious complication of CKD that may lead to abnormal bone development and renal osteodystrophy. It often occurs when GFR falls below 60 mL/min/1.73 m^2 and is present in virtually all patients requiring dialysis. Contributing factors to the development of secondary hyperparathyroidism include deficiency of 1,25-dihydroxy-vitamin D, hypocalcemia, and skeletal resistance to PTH. Elevated PTH and elevated serum calcium, phosphorus, and the calcium–phosphorus product have all been identified as independent risk factors for death and cardiovascular events in patients undergoing dialysis in multiple studies [148–150]. Hence, chronic kidney disease–mineral and bone disorder (CKD–MBD) is increasingly recognized as an important nontraditional cardiovascular risk factor that may lead to adverse cardiac events via vascular calcification, arterial stiffness, hypertension, and LVH [141, 151–153]. As potentially modifiable cardiovascular risk factors, these biochemical abnormalities associated with CKD–MBD are good targets for therapeutic interventions to further reduce cardiovascular risk in CKD. However, the benefit of correcting these metabolic disturbances on cardiovascular outcomes has not been demonstrated in any prospective trials.

Frequency of Hemodialysis and the Heart

Increased frequency of dialysis in the form of short daily hemodialysis and nocturnal home hemodialysis are associated with reduced duration of exposure and peak concentration of uremic toxins and may lead to improved cardiovascular outcomes. In addition, improved cardiovascular outcomes associated with frequent hemodialysis may occur as a result of better control of blood pressure and extracellular fluid volume, regression of LVH, and improved mineral metabolic profile [154]. In a systematic review of 14 uncontrolled studies of daily hemodialysis, 10 of 11 studies showed improvement in blood pressure control compared with conventional intermittent hemodialysis, and all 4 studies that measured LVH demonstrated improvement with daily dialysis [155]. The Frequent Hemodialysis Network (FHN) short daily hemodialysis trial in 245 patients with ESRD demonstrated a 39 % reduction in the composite outcome of 1-year mortality and increase in LVM in patients randomized to in-center hemodialysis six times per week compared with three times per week [156]. Significant regression of LV

mass has also been shown in a randomized controlled trial of 52 ESRD patients undergoing frequent nocturnal hemodialysis six times per week compared with a small increase of LV mass in conventional hemodialysis three times per week [157]. This finding was not reproduced in the Frequent Hemodialysis Network (FHN) Nocturnal Trial [158] designed to assess the impact of nocturnal hemodialysis on LVH and mortality. While a trend towards regression of LV mass was observed in patients randomized to the frequent nocturnal hemodialysis group, it did not reach statistical significance. The study was underpowered to detect a significant difference between the groups, since only 87 patients were recruited, while 250 were required according to the sample size calculation.

Prognosis of Patients with Both Heart Disease and CKD

Serial changes of echocardiographic abnormalities such as LV mass index and fractional shortening has been identified as independent predictors of cardiac outcome in a prospective cohort study of 227 patients with ESRD initiating dialysis [131].

In a propensity matched study of 2,399 pairs of heart failure patients with or without CKD, mortality rate was significantly higher in those with CKD. CKD-associated mortality was higher in patients with diastolic heart failure than those with systolic heart failure (adjusted p for interaction = 0.034), with a graded relationship between mortality and LVEF [122]. It is therefore important to evaluate for CKD in patients with diastolic HF.

Summary

In summary, the finding of either a low GFR defined as less than 60 mL/min or abnormal albuminuria defined as the presence of microalbuminuria identifies the patient as being at high cardiovascular risk. There is sufficient evidence to recommend the combination of achieving blood pressure targets of <140/90 mmHg, RAAS blockade (monotherapy with the maximal recommended dose of an ACE inhibitor or ARB), aggressive LDL lowering, management of diabetes, as well as lifestyle changes including diet, exercise, and smoking cessation. Together these therapies represent "optimal medical therapy" and are particularly effective when managed by an interprofessional and interdisciplinary team. For the practicing clinician, the finding of a low GFR or abnormal albuminuria should constitute an "action item" for pursuing the evaluation and diagnosis of potentially unsuspected cardiac involvement and the initiation of multimodal therapy to lower cardiovascular and renal risk.

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Diabetes and the Cardiovascular System

41

Paul Cohen and Jorge Plutzky

Overview

Coupled with the increase in obesity and physical inactivity, diabetes has become a worldwide epidemic. Nearly 26 million people in the United States now have diabetes, and another 79 million are estimated to have prediabetes. In China and India, the world's two most populous nations, over 30 million people are estimated to have diabetes and this rate is expected to rise dramatically over the next generation [1]. In addition, diabetes is most prevalent in poor and underserved populations, suggesting it may be underdiagnosed. Although diabetes is defined as a disease by blood glucose levels, the majority of the morbidity and mortality of patients with diabetes results from cardiovascular disease. As such, increased attention to the interaction between diabetes and the cardiovascular system is warranted.

Diabetes is marked by either insufficient production of insulin or a failure to respond appropriately to insulin, both of which result in hyperglycemia. Diabetes can be diagnosed based on any of the following criteria: fasting plasma glucose ≥126 mg/dl, plasma glucose ≥200 mg/dl 2 h following a standard oral glucose tolerance test, nonfasted plasma glucose ≥200 mg/dl with symptoms of hyperglycemia, or a glycosylated hemoglobin (A1c) level ≥6.5 % [2]. Diabetes is broadly divided into type 1 diabetes, in which there is absolute insulin deficiency, and type 2 diabetes, in which there is insulin resistance and insufficient insulin. The great majority of cases are type II diabetes.

Diabetes is closely associated with microvascular complications such as nephropathy, neuropathy, and retinopathy. However, the majority of patients with diabetes ultimately die of macrovascular disease, specifically from complications of coronary heart disease (CHD). Data from the Framingham Heart Study shows that patients with diabetes have a nearly threefold increased risk of cardiovascular mortality [3]. Patients with diabetes have an increased risk of myocardial infarction. In fact, in patients with diabetes without a prior history of myocardial infarction, the 7-year incidence of myocardial infarction is equivalent to or even exceeds the incidence in patients with prior myocardial infarction who do not have diabetes [4]. For these reasons, diabetes has been considered a coronary disease equivalent. In a multitude of trials, diabetes is associated with worse outcomes across all acute coronary syndrome (ACS) events [5]. In addition to CHD, diabetes is associated with elevated risk of cerebrovascular and peripheral arterial disease. Moreover, diabetes portends an increased risk for heart failure, with worse outcomes. However, clinical trials have not demonstrated a clear benefit of aggressive glycemic control in preventing these outcomes. Therefore, a deeper understanding of the links between diabetes and cardiovascular disease is becoming increasingly important for the care of the cardiovascular patient. Some of the seminal studies in this area were done in patients with type 1 diabetes and are highlighted here. However, the preponderance of the data comes from studies of patients with type 2 diabetes. As such, unless otherwise specified, use of the term diabetes here will in general refer to type 2 diabetes. This chapter will review the data illustrating the effects of diabetes on the cardiovascular system and will highlight clinical data relevant to the management of this growing patient population.

Pathophysiology

The mechanisms responsible for macrovascular disease, and specifically atherosclerosis, in diabetes are incompletely understood, but a number of processes have been implicated (Table 41.1). Hyperglycemia is certainly a major culprit, as it results in oxidative stress and the formation of advanced glycation end products. It may promote vascular complications

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_41,

Table 41.1 Mechanisms implicated in diabetic macrovascular disease

Cellular players	Mechanisms
Endothelium	NF-κB activation
	Decreased NO production
	Increased reactive oxygen species
	Increased harmful metabolites (peroxynitrite, nitrotyrosine)
	Increased lipid peroxidation products
	Impaired endothelial-dependent relaxation
Immune cells	Increased IL1β, IL6, CD36, MCP-1, CRP, TNFα, SAA
	Induction of protein kinase C
Vascular smooth muscle	Increased proliferation
	Increased migration into intima
	Altered matrix components
	Increased matrix degradation
	Increased nonenzymatic collagen glycation

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via effects on endothelial cells, vascular smooth muscle, or circulating immune cells such as macrophages and T cells [6]. The disease process may differ somewhat from that involved in diabetic microvascular disease, which is characterized by thickening of the capillary basement membrane and results in diabetic microangiopathy. The pathologic differences between microvascular and macrovascular disease are an area of active research. Understanding this biology may help explain why microvascular complications improve with glycemic control, while the same relationship has been more difficult to establish for macrovascular outcomes [7]. Small and large vessel disease could be mechanistically linked by changes in the vasa vasorum, a network of small vessels supplying the outer layer of large arteries. Microangiopathy in the vasa vasorum may in turn contribute to the development of large vessel atherosclerosis.

Inflammation plays an important role in atherosclerosis, which may be particularly relevant in diabetic macrovascular disease. Chronic, low-level inflammation is associated with endoplasmic reticulum stress, mitochondrial dysfunction, insulin resistance, endothelial dysfunction, and hypercoagulability. These processes, in turn, may contribute to the development of metabolic diseases including obesity, diabetes, hypertension, and atherosclerosis [8, 9]. The relevant inflammatory markers and mediators are under active investigation but likely include acute-phase proteins such as C-reactive protein (CRP) and serum amyloid A and chemokines and cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor alpha [10].

There are other important pathologic determinants of diabetic macrovascular disease, which may be difficult to disentangle from hyperglycemia. Diabetes is associated with a dyslipidemia characterized by elevated triglycerides (TG), low concentration of high-density lipoprotein (HDL) cholesterol, elevated apolipoprotein B (apoB), and small, dense low-density lipoprotein (LDL) particles. This atherogenic lipid abnormality is predictive of CHD and is particularly common in the setting of obesity [11]. The association between obesity and diabetes may also reflect dysfunctional adipose tissue as well as ectopic lipid deposition in tissues like muscle and liver, a process which may drive the development of atherosclerosis [12]. Finally, the elevated insulin levels seen in most type 2 diabetics may actually promote atherosclerosis [13]. This may have therapeutic relevance, given the widespread use of exogenous insulin in the treatment of diabetes.

Treatment of Symptomatic Coronary Heart Disease in Diabetes

Given the elevated risk associated with diabetes, an increasing proportion of patients hospitalized for ACS will have diabetes. In addition, in many cases the diagnosis of diabetes is first made during index hospitalization for symptomatic CHD. One small prospective study from Sweden found that among patients with previously undiagnosed diabetes hospitalized for acute myocardial infarction, 25 % have diabetes and 40 % have impaired glucose tolerance [14]. Similar trends have been documented in patients undergoing coronary artery bypass graft surgery, and patients with undiagnosed diabetes may have worse outcomes [15]. The management of patients with diabetes presenting with ACS should generally follow that for patients without diabetes, as detailed in published practice guidelines. Numerous ACS trials have evaluated outcomes in predefined subgroups of patients with diabetes. Some of the salient findings from these studies are reviewed below.

Antiplatelet Therapy

The cornerstone of ACS management involves the use of antiplatelet drugs, such as aspirin and thienopyridines. Diabetes is associated with platelet dysfunction, with both increased activity and aggregation [16]. Therefore, choosing the most appropriate antiplatelet regimen is particularly relevant. A number of clinical trials have demonstrated the benefit of adding a thienopyridine to aspirin in patients with ACS. The CURE trial randomized over 12,000 patients with non-ST elevation ACS to either clopidogrel or placebo in addition to aspirin. The primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or stroke was more frequent in patients with diabetes,

regardless of treatment. However, the addition of clopidogrel provided a similar risk reduction in the diabetic subgroup to that of the entire study population [17]. The Triton-TIMI 38 trial compared prasugrel, a new thienopyridine, to clopidogrel in over 13,000 patients with moderate- to high-risk ACS. Prasugrel was associated with significantly fewer primary outcome events, at the expense of increased bleeding complications [18]. Prasugrel was also more effective in the diabetic subgroup, and interestingly, the rate of bleeding was not increased among these patients [19]. Finally, the PLATO trial compared ticagrelor, a direct and reversible platelet P2Y12 inhibitor, to clopidogrel in patients with ACS. Ticagrelor was associated with a significant reduction in events in both the entire study population and in the prespecified diabetic subgroup, without an increase in major bleeding events [20, 21]. In sum, these studies provide strong support for dual antiplatelet therapy in ACS patients with diabetes. However, given that these findings come from subgroup analyses, there is no clear consensus on the optimal choice of antiplatelet medications in this high-risk population.

Glycoprotein IIb/IIIa (GpIIb/IIIa) inhibitors interfere with platelet aggregation and are often employed in the management of patients with ACS. At present, eptifibatide and tirofiban are approved for use in ACS, and abciximab is approved for use in percutaneous coronary intervention (PCI). A meta-analysis of over 6,000 diabetic patients from six ACS trials showed a significant mortality reduction with GpIIb/IIIa inhibitors that was greatest in those patients undergoing PCI [22, 23]. However, these studies predated the routine use of thienopyridines. When used as part of triple antiplatelet therapy, data support the provisional rather than routine early use of eptifibatide in the overall study population and in the diabetic subgroup [23].

Medical Management

The medical management of ACS in patients with diabetes should also include ACE inhibitors or ARBs, aldosterone blockade in patients with reduced systolic function, and beta-blockers. Blockade of the renin-angiotensin-aldosterone pathway has pleiotropic effects in the setting of ACS, with benefits on ventricular remodeling and endothelial function. A meta-analysis of over 100,000 patients from trials of ACE inhibitors in acute myocardial infarction showed an overall 30-day survival benefit that was larger in high-risk populations such as patients with diabetes [24]. Retrospective analysis of the diabetic subgroup from the TRACE trial showed that ACE inhibitors also have long-term benefits including a significant reduction in the risk of death and reduced progression to heart failure [25]. For patients who are intolerant of ACE inhibitors, ARB medications are a reasonable choice, though there is a less substantial evidence base to support their use. The VALIANT trial compared the ARB valsartan to the ACE inhibitor captopril following acute myocardial infarction complicated by ventricular dysfunction. In the study as a whole and in the diabetic subgroup, valsartan was as effective as captopril in reducing all-cause mortality [26]. However, the OPTIMAAL trial, which compared the ARB losartan to captopril in patients with acute myocardial infarction and heart failure, showed a trend toward increased mortality with losartan [27]. Aldosterone blockade also provides benefits that extend to the patients with diabetes. The EPHESUS trial evaluated eplerenone in patients following myocardial infarction with reduced ventricular function. Study inclusion required that patients also had symptoms of congestive heart failure, unless they had diabetes, since such patients are already at increased risk following ischemic events. Eplerenone reduced morbidity and mortality in this study [28]. Finally, beta-blockers are a recommended therapy for all patients with ACS, regardless of diabetes. However, analysis has shown that ACS patients with diabetes are less likely to receive beta-blockers, as well as other guideline-based therapy [29].

Glycemic Control

Intensive glycemic control during ACS events has not been specifically evaluated in a large clinical trial. A number of studies have examined intensive glucose control in intensive care unit (ICU) populations, though relatively few ACS patients were included. With the exception of one study showing a mortality benefit in surgical ICU patients, the others have shown either no benefit or even increased mortality with intensive glycemic control [30–34]. This lack of benefit has been ascribed to the increased incidence of hypoglycemia associated with intensive glucose control. The normal counterresponse to hypoglycemia, with induction of glucagon and catecholamines, would be unfavorable for ischemic myocardium. Retrospective analyses of ACS patients have shown increased mortality associated with episodes of hypoglycemia [35, 36]. However, another retrospective study found that the mortality risk associated with hypoglycemia seems to be restricted to those patients who develop spontaneous, rather than iatrogenic, low blood glucose [37]. The link between hypoglycemia and mortality was further complicated by data from the NICE-SUGAR trial [34]. Out of several published randomized trials using insulin infusions for intensive glucose control in critically ill patients, this was the only one to show increased mortality, but at the same time had the lowest incidence of hypoglycemia. Based on these trials, the most recent guidelines recommend less stringent glycemic control in the setting of ACS, with treatment for hyperglycemia only recommended for glucose levels >180 mg/dl [38].

These studies of targeted glycemic control differ from studies using insulin infusions to manipulate myocardial metabolism. The heart preferentially uses free fatty acids for fuel under normal physiological conditions. However, during periods of ischemia, metabolism switches to glucose, and cardiomyocytes can develop relative insulin resistance [39]. Glucose-insulin-potassium (GIK) therapy was developed in an attempt to favorably modulate myocardial metabolism during periods of ischemia. While several smaller studies suggested possible benefits of this approach, a large trial of over 20,000 patients showed no benefit [40, 41]. As a result, GIK therapy is no longer commonly employed.

Revascularization

When patients with type 2 diabetes require coronary revascularization, several points are germane to clinical decision-making. These patients represent a growing proportion of the population undergoing percutaneous coronary intervention (PCI) and have a higher incidence of stent restenosis [42]. A meta-analysis has shown that the use of drug-eluting stents (DES) results in a marked reduction in stent restenosis and need for target revascularization in patients with diabetes [43]. Registry data and propensity-score matching with long-term follow-up found that, relative to bare metal stents (BMS), DES in patients with diabetes are associated with decreased mortality, myocardial infarction, and need for revascularization [44]. These data and other studies support the use of DES in patients with diabetes requiring PCI. The optimal DES for this population is not yet clear.

Patients with diabetes are more likely to have more extensive and/or diffuse coronary atherosclerosis, and thus, the question of appropriate revascularization often involves balancing the risks and benefits of PCI relative to coronary artery bypass graft surgery (CABG). The BARI trial was the first study to show a benefit of CABG relative to balloon angioplasty in patients with diabetes and multivessel coronary disease [45]. In the subset of patients with diabetes, at 10 years of follow-up, CABG had a significant survival benefit relative to angioplasty (57.8 % vs. 45.5 %) [46]. A meta-analysis of over 7,000 patients compared outcomes with PCI relative to CABG. This included trials using balloon angioplasty and BMS, but none with DES. While long-term mortality was not different in patients without diabetes, those with diabetes had a significant survival benefit with CABG [47]. There is comparatively less data comparing PCI with DES, along with contemporary medical therapy, to CABG in patients with diabetes. The SYNTAX trial compared PCI to CABG in patients with three-vessel and/or left main disease [48]. This trial was done on the background of modern medical therapy and used DES. Approximately 25 % of the patients in the trial had diabetes, and overall the study showed a significant increase in major adverse cardiac or cerebrovascular events (MACCE) with PCI, mainly driven by a need for repeat revascularization. Three year follow-up from this study showed that patients with diabetes with less complex coronary disease had equivalent outcomes with PCI with DES and CABG. However, with more complex disease (as measured by the SYNTAX score), patients with diabetes had significantly reduced MACCE with CABG [49].

For stable coronary disease, in most cases the literature supports intensive medical therapy over revascularization in those with diabetes. The COURAGE trial shifted many clinical-decision paradigms in showing that optimal medical therapy (OMT) plus PCI did not reduce death or myocardial infarction relative to OMT alone [50]. Nearly one-third of the patients in this study had diabetes. In this prespecified subgroup, OMT remained equivalent to OMT plus PCI [51]. This treatment decision was further investigated in the BARI-2D trial in which patients with diabetes and stable coronary disease were randomized to receive either intensive medical therapy alone or intensive medical therapy with revascularization [52]. The mode of revascularization was left to the discretion of the treating physicians, so the study was not designed to compare PCI to CABG. The study found no differences in death or major adverse cardiovascular events (MACE) between medical therapy and revascularization. Subgroup analyses based on mode of revascularization showed no difference between medical therapy and PCI, with a reduction in MACE between CABG and medical therapy.

Despite the rapidly advancing treatment options for treatment of CHD, the use of these therapies and subsequent secondary prevention remains underused in the diabetic population. A large study of over 45,000 patients hospitalized in the United States for non-ST elevation ACS compared adherence to treatment guidelines between patients with and without diabetes. Individuals with insulin-treated diabetes in this analysis were less likely to receive aspirin and beta-blockers [29]. This underutilization of therapies was also noted in the Munich Myocardial Infarction Registry. Importantly, with the coordinated intensification of therapy, 24-h and in-hospital mortality declined [53]. The ongoing development of new drugs to treat diabetes along with new FDA guidelines that require that antidiabetic therapies establish their cardiovascular benefits has fostered numerous clinical trials, including those involving patients with ACS. Agents under study in this regard include glucagon-like peptide 1 (GLP-1) agonists, dipeptidyl peptidase-IV (DPP-IV) inhibitors, and dual PPAR α/γ agonists [54, 55].

Primary Prevention of Coronary Heart Disease in Patients with Diabetes

Given the rising incidence of diabetes and associated cardiovascular complications, emphasis has shifted toward preventive care. The initial pathogenic changes in atherosclerosis occur during childhood, providing a rationale for early intervention to prevent atherosclerosis [56]. These have the potential to reduce morbidity and mortality from diabetic macrovascular disease and thereby reduce the growing burden that the care of these patients places on our healthcare system. In the sections that follow, the data in support of a primary prevention strategy are presented. The goals for each risk factor are summarized in Table 41.2.

Lifestyle modification is a central, and often overlooked, intervention to reduce atherosclerotic complications from diabetes. Recommendations by the American Diabetes Association include avoidance of cigarette smoking, medical nutrition therapy, at least 150 min of moderate intensity aerobic exercise each week, and moderate weight loss (7 % body weight) for patients who are overweight or obese [2].

Lipids

Diabetic dyslipidemia is considered a major risk factor for macrovascular disease. This pattern of elevated triglycerides (TG), low concentration of high-density lipoprotein (HDL) cholesterol, elevated apolipoprotein B (apoB), and small, dense low-density lipoprotein (LDL) particles is predictive of CHD [11]. Although those with diabetes often do not have a particularly elevated LDL level, LDL still emerges as a significant risk factor predictive of future events in this group [57]. As with the population as a whole, statin drugs should be the main element of lipid-lowering therapy in this population. In the CARDS study, atorvastatin 10 mg daily in patients with diabetes, but no prior history of cardiovascular disease, significantly reduced the risk of a first cardiovascular event [58]. Moreover, a meta-analysis of patients with diabetes in statin trials showed a similar reduction in mortality and vascular events to that seen in nondiabetics [59]. Practice guidelines recommend a statin for all patients with diabetes with overt CHD and for those without overt CHD who are over age 40 and have at least one cardiovascular risk factor. In those at lower risk, statins are recommended for patients with an LDL greater than 100 mg/dl [2].

Table 41.2 Primary prevention goals for patients with diabetes

Risk factor	Goal
Sedentary lifestyle	≥150 min/week moderate intensity aerobic exercise
Overweight/obesity	At least moderate weight loss
Dyslipidemia	LDL < 100 mg/dl HDL > 50 mg/dl TG < 150 mg/dl
Hypertension	<130/80 mmHg
Hyperglycemia	HbA1c < 7.0 %

Recommendations summarized from Ref. [2]
The above recommendations are general, with more specific recommendations made according to an individual patient's risk factors

Once LDL treatment targets have been reached on statin therapy, secondary goals can be addressed that might further reduce cardiovascular risk. ApoB is the predominant lipoprotein in chylomicrons and LDL and may be more predictive of risk. Non-HDL cholesterol (total cholesterol – HDL cholesterol) correlates well with ApoB levels. Targets for non-HDL are 30 mg/dl greater than the corresponding LDL target. Elevated triglycerides are also a target, with elevated levels also correlating with non-HDL levels. When patients have elevated triglyceride levels, secondary causes of hypertriglyceridemia must be considered, including thyroid abnormalities, nephrotic syndrome, drug effects, obesity, and undiagnosed or undertreated diabetes. Triglyceride lowering can be achieved with the use of additional agents, though the data supporting benefits from this approach are less robust. Omega-3 fatty acids, commonly as fish oil preparations, can significantly reduce TG, with minimal effects on HDL and total cholesterol and only modest raising of LDL. Benefits of fish oils were seen in a subanalysis of patients with diabetes or impaired fasting glucose in the JELIS trial [60]. In this randomized study, the addition of eicosapentaenoic acid to simvastatin resulted in a significant reduction in cardiovascular endpoints.

Fibrates are another class of drugs that can lower TGs and modestly increase HDL. They work as agonists of the transcription factor peroxisome proliferator-activated receptor alpha (PPARα). Older prevention trials showed reduced adverse outcomes with fibrates, though many of these were done in the pre-statin era and relatively few diabetics were included [61, 62]. The VA-HIT trial showed a reduction in cardiovascular events with fibrates among patients with known cardiovascular disease, in the absence of any concomitant statin use [63]. The FIELD trial randomized nearly 10,000 patients with diabetes with elevated cholesterol to either fenofibrate or placebo. The majority of the subjects had no known cardiovascular disease. Patients randomized to fenofibrate had no significant reduction in the primary endpoint of coronary death or nonfatal myocardial infarction [64]. However, this trial was limited by a substantial 17 % drop-in of lipid-lowering agents in the placebo arm, relative to an 8 % rate in the fenofibrate arm, which may have masked a treatment effect. The role of fibrates in combination with a statin was more recently examined in the ACCORD Lipid trial. Over 5,500 patients with diabetes at

risk of cardiovascular disease and already on simvastatin were randomized to fenofibrate or placebo. The addition of fenofibrate did not reduce the incidence of fatal or nonfatal cardiovascular events [65]. Subgroup analysis found a lower event rate in men and a higher rate in women, though neither was significant. Additionally, the patients in the lowest tertile of HDL and highest tertile of triglycerides showed a signal of benefit with fenofibrate ($p=0.06$). With the caveat of overinterpreting data from subgroup analyses, this suggests that men with diabetes on statin therapy with an HDL <35 mg/dl and TG >200 mg/dl may benefit from fenofibrate.

Niacin is the most effective currently available drug at increasing HDL and also lowers triglycerides. A meta-analysis showed a 27 % reduction in cardiovascular events with niacin, though these studies were not done on the background of statin therapy and did not contain a large number of diabetics [61]. The incremental benefit of adding niacin to background statin therapy was evaluated in the AIM-HIGH trial. Patients with known cardiovascular disease were treated with simvastatin, and ezetimibe if necessary, for aggressive LDL lowering, with patients in the study having a baseline LDL of approximately 76 mg/dl. Despite significant improvements in HDL and TG, the trial was stopped early because niacin crossed the boundary for futility [66]. Niacin-treated patients also had an unexplained higher number of ischemic strokes, though it is not clear that there is a causal relationship. Prior studies and meta-analyses have not shown an increase in stroke. The results of this trial do not support niacin add-on therapy. However, the much larger HPS2-THRIVE trial of niacin add-on therapy is currently ongoing and is expected to be completed in 2013 [67]. Other HDL-raising drugs are also under investigation in patients at risk of cardiovascular disease, including a substantial number of patients with diabetes [68].

Blood Pressure

Hypertension is highly prevalent in individuals with diabetes and is closely associated with adverse outcomes. The JNC 7 report noted an increase in cardiovascular risk with blood pressure >115/75 mmHg, doubling with each 20/10 mmHg increment [69]. In the UKPDS, a prospective observational study of patients with diabetes, each 10 mmHg reduction in systolic blood pressure (SBP) was associated with reduced risk of death from diabetes, microvascular endpoints, stroke, amputation, and myocardial infarction [69]. In this cohort, the lowest risk was associated with systolic blood pressure below 120 mmHg. The ACCORD study evaluated a strategy of aggressive blood pressure lowering to SBP <120 mmHg in subjects with diabetes at risk for cardiovascular events. Relative to standard therapy targeting SBP <140 mmHg, more stringent control did not reduce a composite endpoint of fatal and nonfatal cardiovascular events and was associated with increased adverse events [70]. However, it did reduce the secondary endpoint of stroke and nonfatal stroke. Of note, the mean SBPs achieved were 119.3 mmHg in the intensive treatment group and 133.5 mmHg in the standard group. Based on the existing data, current guidelines recommend targeting a blood pressure goal of less than 130/80 mmHg in patients with diabetes.

Blood pressure lowering in patients with diabetes should include an ACE inhibitor or ARB medication. These medications protect against diabetic nephropathy and may also have beneficial effects on glucose metabolism [71]. The HOPE trial evaluated the ACE inhibitor ramipril in patients at risk for cardiovascular events. Relative to placebo, ramipril significantly reduced the rate of death, myocardial infarction, and other cardiovascular outcomes [72]. This benefit was also noted in an analysis of over 3,500 patients with diabetes in this study [73]. Data in support of ARB medications to reduce cardiovascular outcomes in diabetics is less impressive. The TRANSCEND trial assessed the effects of the ARB telmisartan in high-risk patients who were intolerant of ACE inhibitors. Telmisartan had no effect on the primary outcome, which was a composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure. It did significantly reduce a secondary composite outcome of cardiovascular death, myocardial infarction, or stroke [74]. Approximately one-third of the patients in this trial had diabetes, and analysis of this subgroup found no benefit of telmisartan for primary or secondary outcomes. Based on these data, ARBs should be considered in patients with diabetes who are unable to take ACE inhibitors.

Data also supports benefits with blood pressure lowering using other classes of medications in patients with diabetes. In an analysis of 27 randomized trials, the effects of different blood pressure lowering on cardiovascular outcomes were analyzed in subjects with and without diabetes. This analysis showed that ACE inhibitors, ARBs, calcium channel blockers, beta-blockers, and diuretics can be similarly effective in both groups [75]. Prior literature has suggested that beta-blockers and thiazide diuretics might adversely impact glucose metabolism. There has also been concern that beta-blockers might mask symptoms of hypoglycemia. Posttrial follow-up of the UKPDS cohort showed no differences in diabetes-related outcomes between patients treated with beta-blockers and ACE inhibitors [76]. Beta-blockers with alpha-receptor blocking activity might have metabolic benefits relative to cardioselective beta-blockers, though it is not yet clear if their use will alter clinical outcomes [77]. Data from the ALLHAT trial showed an increase in fasting glucose and incident diabetes in patients randomized to chlorthalidone, but this was not associated with more frequent cardiovascular events [78].

While data supports blockade of the renin-angiotensin-aldosterone system as the preferred initial treatment strategy, the majority of hypertensive patients require more than one medication to achieve target blood pressure. The ASCOT-BPLA trial compared regimens of amlodipine adding perindopril as needed to atenolol adding bendroflumethiazide as needed in patients with hypertension and cardiovascular risk factors. The amlodipine-based regimen was not associated with a significant reduction in the primary endpoint but did significantly reduce mortality and cardiovascular events [79]. Nearly 1/3 of the patients in this study had diabetes, and this subgroup showed similar benefit. The ADVANCE trial assessed the combination of an ACE inhibitor and diuretic added on to existing therapy in over 11,000 patients with diabetes. This combination resulted in a significant reduction in death and major vascular events [80]. More recently, the ACCOMPLISH study compared the combination of benazepril and amlodipine to benazepril and hydrochlorothiazide in patients with hypertension and cardiovascular risk factors. Benazepril and amlodipine were associated with significantly fewer cardiovascular events in the trial as whole and in a prespecified diabetic subgroup [81].

Antiplatelet Therapy

Diabetes is known to be associated with dysfunctional platelets, which may contribute to the association with increased atherothrombotic events [16]. Despite this pathophysiological connection, data supporting the use of antiplatelet therapy for primary prevention is not especially convincing. Two randomized trials of aspirin used for primary prevention in patients with diabetes found no significant reduction in cardiovascular events [82, 83]. A meta-analysis of 95,000 individuals from six primary prevention trials showed a significant reduction in vascular events with aspirin, driven mainly by reduced nonfatal myocardial infarction. However, there was no difference in vascular mortality and a significant increase in bleeding [84]. The subgroup of patients with diabetes in this analysis showed no benefit with aspirin. A meta-analysis confined to patients with diabetes found no difference in cardiovascular events or mortality with aspirin. Aspirin was associated with a significant reduction in myocardial infarction in men, but not in women with diabetes [85]. In addition to the uncertain benefits of aspirin, the appropriate dose and contribution from aspirin resistance remain to be clarified. There are no trial data available on the use of thienopyridines, such as clopidogrel, for primary prevention. Current guidelines recommend using aspirin for primary prevention in individuals with diabetes with 10-year cardiovascular risk estimated at >10 %. This would typically include men over 50 or women over 60 with at least one additional risk factor. Clopidogrel is suggested for those who require aspirin but have an allergy to it [2]. At least three randomized, controlled trials of aspirin for primary prevention in patients with diabetes are currently underway and may provide more certainty regarding this highly debated question [86].

The central element of diabetes treatment is the management of hyperglycemia. While diet and exercise have indispensable roles, medical therapy is often indicated. In addition to exogenous insulin, several classes of oral glucose-lowering drugs are presently in clinical use. Broadly, these medications work either by stimulating endogenous insulin production, improving insulin sensitivity, or reducing carbohydrate absorption. These agents have been efficacious at lowering blood glucose and in reducing microvascular complications from diabetes. Comparatively less data exists on the effects these drugs have on macrovascular complications. Given the increased cardiovascular risk associated with diabetes, a familiarity with the available data and unanswered questions is important.

Glucose-Lowering Medications

Metformin is a biguanide drug that decreases hepatic glucose output and improves insulin sensitivity. Its mechanism of action remains a subject of investigation. Metformin is also associated with weight loss and a low risk for hypoglycemia. The main side effects are diarrhea and nausea [87]. An earlier biguanide, phenformin, was associated with lactic acidosis and has since been taken off the market. Fortunately, extensive clinical experience with metformin has found no association with lactic acidosis [88]. It remains contraindicated in the setting of chronic kidney disease and 48–72 h after the administration of iodinated contrast.

The main data on cardiovascular outcomes with metformin comes from the UKPDS study. In one arm of this study, overweight patients with newly diagnosed diabetes were randomized to dietary management or metformin and followed for a median of over 10 years. Metformin resulted in a greater reduction in HbA1c (7.4 % vs. 8.0 %) and had significant reductions in diabetes-related endpoints, myocardial infarction, and mortality [89]. Posttrial monitoring for an additional 10 years found that although the glycemic difference did not persist, significant reductions in diabetes-related endpoints, myocardial infarction, and mortality persisted [90]. Based on these data and its overall safety, metformin is recommended as first-line therapy for type 2 diabetes [2].

Sulfonylureas inhibit ATP-dependent potassium (K-ATP) channels in pancreatic beta cells resulting in increased insulin production. These drugs are associated with hypoglycemia and weight gain [87]. In an early trial comparing different treatment strategies for diabetes, tolbutamide was associated with increased cardiovascular mortality [91]. However,

subsequent trials with newer sulfonylureas have not shown such safety concerns. In fact, in the UKPDS study, sulfonylurea use was associated with improved outcomes [90, 92]. K-ATP channels serve an important role in the heart. Based on animal models, there is concern that sulfonylureas might inhibit ischemic preconditioning, though it is not clear whether this has any relevance to clinical trials data [93]. For oral agents, sulfonylureas are generally second-line recommendations after metformin.

Thiazolidinediones (TZDs) lower glucose levels by improving the insulin sensitivity of target tissues. They act as ligands for the nuclear receptor PPAR-γ. These drugs have been associated with weight gain, edema, bladder cancer, and bone loss [87]. The PROactive study assessed the effects of the TZD pioglitazone on macrovascular complications. The primary composite endpoint of mortality, nonfatal myocardial infarction, and a number of other cardiovascular outcomes was reduced in patients on pioglitazone, but this was not statistically significant [94]. A composite secondary endpoint, consisting of more objective and traditional cardiovascular endpoints, was reduced in a statistically significant manner. There was no increase in adverse events associated with pioglitazone. Another TZD, rosiglitazone, has been associated with increased cardiovascular events and is now under restriction by the Food and Drug Administration. Two meta-analyses found that rosiglitazone significantly increased the risk of myocardial infarction, and in one of these studies, it was also associated with a borderline significant increased risk of death [95, 96]. Thus, while pioglitazone may protect against macrovascular events, rosiglitazone appears to increase the risk of adverse cardiovascular outcomes. Both drugs are associated with peripheral edema and have the potential to precipitate or worsen heart failure. For that reason, they are contraindicated in patients with class III or IV heart failure [97].

Several less widely used glucose-lowering medications have also been found to have effects on cardiovascular endpoints. Glucosidase inhibitors lower postprandial blood glucose by decreasing carbohydrate absorption from the gut. The STOP-NIDDM trial randomized patients with impaired blood glucose to receive either acarbose or placebo. Acarbose was associated with a statistically significant reduction in cardiovascular events, though 24 % of the subjects discontinued the study early [98]. Given that these agents need to be taken multiple times each day and can cause unpleasant gastrointestinal side effects, glucosidase inhibitors are not widely used. Bromocriptine is a D2 dopamine receptor agonist that can also lower blood glucose. In a 52-week safety trial of a quick-release formulation used in conjunction with usual diabetes therapy, bromocriptine use was associated with a 40 % relative risk reduction in cardiovascular events, without any apparent safety concerns [99]. This may represent a new class of therapies, though additional studies will be required.

Incretin modulators are a newer class of medication that lowers glucose levels by acting on an endogenous pathway, in which oral glucose enhances the insulin response. Incretin hormones such as glucagon-like peptide 1 (GLP1) are released in response to nutrients and act on peripheral receptors in the pancreas and a host of other peripheral tissues including adipocytes, cardiomyocytes, endothelial cells, and vascular smooth muscle cells. GLP1 is normally degraded by the enzyme dipeptidyl peptidase-IV (DPP-IV). Approved medications now include GLP1 analogs (such as exenatide and liraglutide) and DPP-IV inhibitors (such as saxagliptin and sitagliptin). These drugs are associated with weight loss and may have beneficial effects on inflammation and the vasculature [54]. While preclinical data suggests that these drugs may protect against atherosclerosis, macrovascular outcome data is not yet available. A number of large clinical trials are currently underway, which should clarify this question over the next few years.

Given the epidemiological association between diabetes and macrovascular complications, it was reasonable to presume that intensive glucose control might protect against cardiovascular events. The DCCT trial investigated the effects of intensive glucose control in type I diabetes. At a mean follow-up of 6.5 years, more stringent control significantly reduced microvascular complications [7]. Long-term, 20-year follow-up of these patients found that intensive glycemic control significantly reduced the risk of cardiovascular events [100]. These studies suggest that similar benefits might also be seen with more rigorous control of type 2 diabetes and also raise the prospect that this may take longer term studies to confirm. The UKPDS trial compared intensive glucose control over 10 years with sulfonylureas or insulin to dietary management in newly diagnosed type 2 diabetes. In a separate arm, overweight subjects in the intensive control group could also be randomized to metformin. In the sulfonylurea and insulin arm, the mean HbA1c was 7.0 % in the intensive group and 7.9 % in the conventional group. Intensive control significantly reduced microvascular complications and showed a trend toward decreased myocardial infarction that did not quite reach statistical significance ($p = 0.052$) [92]. In the metformin arm, the mean HbA1c was 7.4 % in the intensive group and 8.0 % in the control group. Metformin significantly reduced diabetes-related endpoints, including the risk of myocardial infarction, and decreased overall mortality [89]. Posttrial monitoring showed that the glycemic benefits were lost within the first year of the study's termination. Despite this, 10 years later, patients who had been randomized to intensive control with either sulfonylureas and insulin or metformin had significantly reduced microvascular disease, myocardial infarction, and death [90].

These data provided a rationale for randomized trials to assess the effects of intensive glucose control on

Table 41.3 Effect of intensive glucose lowering on macrovascular complications

	ACCORD [102]	ADVANCE [103]	VADT [104]	Meta-analysis [105]
Primary outcome	Nonfatal MI, nonfatal stroke, CV death	Nonfatal MI, nonfatal stroke, CV death	MI, stroke, CV death, CHF, surgery for vascular disease, inoperable coronary disease, amputation	Nonfatal MI, CHD events, stroke, mortality
Hazard ratio for primary outcome (95 % CI)	0.90 (0.78–1.04)	0.94 (0.84–1.06)	0.88 (0.74–1.05)	Nonfatal MI 0.83 (0.75–0.93) CHD events 0.85 (0.77–0.93) Stroke 0.93 (0.81–1.06)
Hazard ratio for mortality (95 % CI)	1.22 (1.01–1.46)	0.93 (0.83–1.06)	1.07 (0.81–1.42)	1.02 (0.87–1.19)

Modified from Plutzky [101]. With permission from Elsevier
ACCORD Action to Control Cardiovascular Risk in Diabetes, *ADVANCE* Action in Diabetes and Vascular Disease, *VADT* Veterans Affairs Diabetes Trial

macrovascular outcomes in patients with diabetes at increased risk for cardiovascular disease. Three such trials were published in the last few years and showed no cardiovascular benefit from stringent diabetes control [101]. The results of these three trials and a subsequent meta-analysis are summarized in Table 41.3. The ACCORD trial compared intensive control (goal HbA1c <6.0 %) to standard control (goal HbA1c 7.0–7.9 %) in over 10,000 subjects with diabetes and either known cardiovascular disease or increased cardiovascular risk. This trial was stopped early due to increased mortality in the intensive control group, with no difference in the primary composite outcome of cardiovascular events [102]. The ADVANCE trial compared intensive control (target HbA1c <6.5 %) with gliclazide and other agents as needed to standard control in over 11,000 patients with cardiovascular disease or risk factors. After a median of 5 years, HbA1c was 6.5 % in the intensive group and 7.3 % in the standard group. Intensive control resulted in no difference in macrovascular events, cardiovascular death, or overall death [103]. Finally, the VADT trial randomized nearly 1,800 veterans with poorly controlled diabetes to intensive or standard glucose control strategies. After a median of 5.6 years, HbA1c was 6.9 % in the intensive group and 8.4 % in the standard group. Despite this difference, intensive control did not reduce cardiovascular events or death [104].

A number of factors may account for the lack of benefit from intensive glucose control that was common to these three large trials. More aggressive glucose lowering was associated with a higher incidence of hypoglycemia. Both clinically evident and silent hypoglycemia could contribute to adverse events. In addition, the majority of the patients in these studies had long-standing diabetes. The benefit from intensive control may be restricted to earlier phases in the disease process. This conclusion is supported by the benefit seen in the UKPDS trial, which studied patients with a new diagnosis of diabetes [90]. The UKPDS study also took far longer than the more recent trials to show benefit. Perhaps, effects on macrovascular outcomes simply take longer to become apparent. Also of relevance, a sizable number of patients in these studies received TZDs, including rosiglitazone, and it is possible this may have reduced benefit or contributed to harm. A meta-analysis of over 33,000 patients from trials of intensive glucose control found that this was associated with a significant reduction in coronary events, without an increased risk of death [105]. At the present time, uncertainty remains regarding the optimal regimen of medications and magnitude of HbA1c lowering. Current guidelines from the American Diabetes Association recommend a target HbA1c of below 7.0 %. For patients with long-standing diabetes, significant comorbidities, or a history of severe hypoglycemia, less stringent targets may be reasonable [2].

Primary prevention in patients with diabetes at risk of cardiovascular disease typically involves modification of multiple risk factors, including lipids, blood pressure, and glucose control. Most of the studies described above have focused on individual risk factors on the background of contemporary therapy for other comorbidities. The Steno-2 trial was a relatively small study that evaluated the effects of multifactorial risk factor modification in subjects with type 2 diabetes at risk of cardiovascular disease. 80 patients each were randomized to either conventional therapy or multifactorial intensive treatment including behavioral modification and medication targeting dyslipidemia, hypertension, hyperglycemia, and microalbuminuria. After a mean follow-up of nearly 8 years, patients in the intensive therapy group had a nearly 50 % reduction in cardiovascular events [106]. Extended follow-up of these patients for an additional

5.5 years after the original trial ended showed that intensive risk factor modification was associated with significantly decreased overall and cardiovascular mortality and decreased cardiovascular events [107].

Prediabetes and Obesity

In parallel with the increasing incidence of diabetes worldwide, clinicians are now placing increasing focus on patients at risk for diabetes. Patients with elevated plasma glucose who do not meet the threshold for diabetes can be defined as having prediabetes if they meet one of the following criteria: fasting plasma glucose 100–125 mg/dl, HbA1c 5.7–6.4 %, or 2-h plasma glucose in the 75 g oral glucose tolerance test of 140–199 mg/dl [2]. Prediabetes is associated with a markedly increased risk of developing diabetes. In one large analysis, individuals with HbA1c in the range of 6.0–6.5 % had a 25–50 % risk of developing diabetes over 5 years [108]. Prediabetes is closely associated with visceral obesity, dyslipidemia, and hypertension, all of which contribute to cardiovascular disease. Analysis of subjects from the ARIC study showed that HbA1c in the prediabetic range was associated with an increased risk of cardiovascular disease [109]. A meta-analysis showed that different measures indicative of prediabetes were associated with a modest roughly 20 % increase in risk for cardiovascular disease [110]. Given this association and the negative results from trials of intensive glucose lowering in patients with long-standing diabetes, earlier intervention, even before patients develop frank diabetes, may be the most effective means to prevent macrovascular complications.

Most primary prevention studies in patients with prediabetes have employed lifestyle modifications focused on weight loss and exercise. Three long-term studies have each shown decreased progression to diabetes when at-risk individuals follow a strategy of lifestyle intervention. There was a 43 % reduction at 7 years in the Finnish Diabetes Prevention Study, a 43 % reduction at 20 years in the Da Qing Diabetes Prevention Study, and a 34 % reduction at 10 years in the US Diabetes Prevention Program Outcomes Study (DPPOS) [111–113]. A number of studies have also used oral agents in an attempt to decrease the development of diabetes. The DPP and DPPOS trials both showed that metformin could reduce the incidence of diabetes, though neither was as effective as lifestyle intervention [113, 114]. TZD drugs have also been found to reduce incident diabetes, though there remains the concern that these drugs could cause coronary events [115, 116]. It remains unclear whether prediabetes itself causes atherosclerosis and what the relative contribution is of associated conditions such as obesity, dyslipidemia, and hypertension [116]. Present guidelines endorse weight loss, when indicated, and exercise for all patients with prediabetes. For high-risk patients, metformin might be considered [2]. Clinical trials will be needed to resolve whether lifestyle or pharmacologic intervention in this growing patient population will actually prevent adverse cardiovascular outcomes.

The worldwide increase in the incidence of overweight and obesity, which are closely associated with prediabetes and diabetes, threatens to undermine the progress that has been made in reducing mortality from cardiovascular disease. Obesity is at the center of the metabolic syndrome, which has been shown to increase the risk for cardiovascular disease approximately twofold [117]. While diet and exercise are important elements in reducing cardiovascular disease in these patients, effective and safe therapies are urgently needed. Prior efforts to treat obesity with medical therapy have been complicated, and the hurdles for FDA approval have been high. Earlier agents had either limited effects on obesity or concerning side effects. The effect of sibutramine on cardiovascular outcomes was recently studied in the SCOUT trial. The primary outcome, which was a composite of events, was more common with sibutramine, driven mainly by an increase in nonfatal myocardial infarction and stroke [118]. This medication has since been withdrawn from the market. There has been new movement in this area, however, as lorcaserin was recently approved by the FDA and phentermine/topiramate is under review. It will be of interest to follow the impact of these agents on cardiovascular risk factors and events.

Given the lack of an effective medical therapy, an increasing number of obese individuals are undergoing bariatric surgery. Most of these operations are now performed laparoscopically, and morbidity and mortality from these procedures have declined markedly [119]. Two long-term follow-up studies found that bariatric surgery significantly reduces mortality [120, 121]. A subsequent study showed that bariatric surgery is associated with reduced cardiovascular events and death [122]. Since weight loss surgery ameliorates all of the components of the metabolic syndrome, the mechanism underlying these striking benefits remains uncertain. Correction of diabetes has been proposed as one possible explanation. Weight loss surgery results in a rapid improvement in glycemia, out of proportion to the degree of weight loss. A meta-analysis found that bariatric surgery results in a complete resolution of diabetes in 78 % of patients and an improvement in 87 % [123]. In fact, the American Diabetes Association Guidelines now suggest considering bariatric surgery for adults with BMI >35 and diabetes [2]. Two recent studies randomized overweight and obese patients with diabetes to intensive medical management or bariatric surgery. Both studies found that surgery provided a significant improvement in diabetes [124, 125]. Based on these and emerging data, bariatric surgery may be evolving into a “metabolic” surgery that is likely to play an

increasing role in the management of diabetes [126]. Further studies will be needed to define the durability of these effects and specific predictors of which patients will most benefit from these procedures.

Conclusion

The incidence of diabetes is increasing worldwide and will have a substantial impact on the care of cardiovascular patients. While patients with diabetes are at increased risk of macrovascular complications, advances in medical therapy and percutaneous interventions have improved outcomes in this high-risk population. Given the morbidity and mortality associated with diabetes, more focus has turned to primary prevention. Careful management of the full spectrum of risk factors remains critical to preventing cardiovascular events in patients with diabetes.

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Cancer Therapy-Induced Cardiomyopathy

42

Peter Kim, Pimprapa Vejpongsa, and Edward T.H. Yeh

Introduction

Since the turn of the early twenty-first century, overall cancer survival has increased due to the development of new chemical, biologic, and radiologic therapies. With the shared risk factors of smoking, advanced age, and poor dietary habits, the likelihood of discovering cardiovascular disease in a cancer patient is high. A growing awareness of cardiovascular complications of cancer and its therapies has rapidly grown in the medical community. Accelerated atherosclerosis, congestive heart failure (CHF), pericardial disease, arrhythmias, and hypertension are some of the common disease entities that are encountered in these patients. The management of specific cardiovascular diseases in a cancer patient has provided unique challenges to cardiologists and oncologists. Anticipation of acute and long-term cardiovascular comorbidities in cancer treatments and surveillance is thereby critical in providing optimal care and improving quality of life in patients with oncologic malignancies.

Cancer therapies target cancer cell growth by inducing apoptosis, suppressing cell division, or both. While cell injury is not limited to myocardium, the main clinical manifestations reflect direct and indirect cardiac myocyte damage. Secondary vascular damage may also play an important role in cardiac injury. Although reported incidences vary among institutions, aggregate data have shown clear correlation of cancer therapies and cardiovascular toxicities. The six main reported cardiovascular effects associated with cancer treatment are cardiomyopathy/heart failure, ischemia, hypertension, thromboembolism, QT prolongation, and bradycardia [1]. In this chapter, we will focus predominantly on cancer therapy-induced cardiomyopathy.

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Chemotherapy-Induced Cardiomyopathy

One of the most well-recognized clinical toxicities of cancer treatment is the development of cardiomyopathy. The most commonly recognized chemotherapeutic agents known to cause cardiomyopathy are anthracyclines and tyrosine kinase inhibitors (TKIs). However, newer agents are being implicated in the development of impaired myocardium. Although reported incidences vary from different sources, there is a growing list of therapies that are associated with the development of cardiomyopathy (see Table 42.1). The clinical presentation and prognosis may vary depending on a variety of factors. In cancer patients, the most significant risk factors include cumulative dose of chemotherapy, age of exposure, concomitant cardiotoxic agents, preexisting cardiovascular disease, and chest radiation therapy.

One of the most well-recognized cardiotoxic agents, daunorubicin, originates from the Streptomyces species of fungi [2]. Anthracyclines, such as daunorubicin and doxorubicin, offer effective treatment for a variety of hematologic and solid tumor malignancies. However, cardiotoxicity due to cumulative dose often limits its utilization and may lead to discontinuation. The relationship between the incidence of CHF and the cumulative dose of anthracycline was first recognized by von Hoff and colleagues in 1979 [3]. They explored 4,018 patients in retrospective fashion and subsequently plotted the curve for cumulative probability of developing doxorubicin-induced CHF [3]. The authors suggest that the probability of doxorubicin-induced CHF is likely to occur 3 % at 400 mg/m^2, 7 % at 550 mg/m^2, and 18 % at 700 mg/m^2. The cumulative dose of 550 mg/m^2 of doxorubicin was initially considered as a reasonable dose that balanced the benefits of antitumor with the risk of cardiotoxicity. More recent data suggest that the incidence of CHF after doxorubicin administration is much higher [4]. The estimated cumulative percentage of heart failure was 5 % of patients at a cumulative dose of 400 mg/m^2, 26 % of patients at 550 mg/m^2, and 48 % of patients at 700 mg/m^2. As a result of this data, the cumulative dose of doxorubicin at 400 mg/m^2 is now considered as a rational dose that keeps the

C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_42,

Table 42.1 Incidence of cancer therapy-induced cardiac dysfunction

Cancer therapy agents	Incidence (%)	Frequency of use
Anthracyclines		
Doxorubicin (Adriamycin)	3–26	+++
Idarubicin (Idamycin PFS)	5–18	+
Epirubicin (Ellence)	0.9–3.3	++
Alkylating agents		
Cyclophosphamide (Cytoxan)	7–28	+++
Ifosfamide (Ifex)	17	+++
Antimetabolites		
Clofarabine (Clolar)	27	+
Antimicrotubule agent		
Docetaxel (Taxotere)	2.3–8	++
Monoclonal antibody-based TKIs		
Trastuzumab (Herceptin)	2–28	++
Bevacizumab (Avastin)	1.7–3	++
Small-molecule TKIs		
Sunitinib (Sutent)	2.7–11	+++
Dasatinib (Sprycel)	2–4	++
Lapatinib (Tykerb)	1.5–2.2	+
Imatinib mesylate (Gleevec)	0.5–1.7	+
Proteasome inhibitor		
Bortezomib (Velcade)	2–5	++

Modified from Yeh and Bickford [1]. With permission from Elsevier

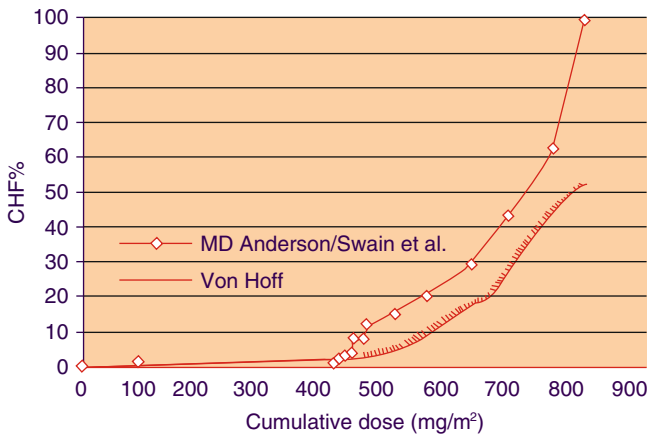

Fig. 42.1 Incidence of CHF vs. cumulative dose (Reprinted from Swain et al. [4]. With permission from John Wiley & Sons, Inc.)

risk of cardiac dysfunction at acceptable levels (see Fig. 42.1). However, this curve does not apply universally. As observed in clinical practice, some patients have received more than 1,000 mg/m^2 of doxorubicin, considered as an unusual high dose, without the development of any cardiac dysfunction. In contrast, some patients without any underlying cardiac conditions developed CHF after only one to two doses of anthracycline administration. Many investigators have attempted to identify high-risk patients who are likely to develop early cardiotoxicity by accounting for cardiac risk factors such as age, hypertension, and previous history of radiation therapy to the chest. Nevertheless, none have been clearly proven to be clinically useful.

The onset of toxicity can be classified into "acute or subacute toxicity," "chronic," and "late onset" [5]. Acute toxicity is rare and may present immediately after treatment with transient ECG changes including nonspecific ST-T wave changes, QT prolongation, or arrhythmias [2]. This form can also present with acute left ventricular (LV) dysfunction, pericarditis, or myocarditis. Chronic cardiotoxicity occurs within 1 year of treatment, while late onset may occur many years after completion of treatment.

Although there are significant advances in imaging modalities and other noninvasive diagnostic techniques, endomyocardial biopsy remains the gold standard for detecting anthracycline cardiac damage [6]. The diagnostic characteristic of anthracycline-induced cardiomyopathy in electron microscope includes vacuoles, myofibrillar disarray and dropout, and myocyte necrosis. The structural abnormalities of cardiac myocytes can even be detected in patients who have received as little as 100 mg/m^2 of doxorubicin. Cardiac biopsy should be considered as a reliable diagnostic tool if the noninvasive diagnostic results are inconclusive.

Major medical advances in chemotherapy have introduced cancer-specific targeted therapy into clinical practice. These agents act directly against tumor-specific molecules and signaling pathways which theoretically should have less toxicity when compared to conventional chemotherapy. Although generally having fewer side effects than many traditional chemotherapeutic agents, some tyrosine kinase inhibitors (TKIs) have been associated with significant cardiovascular side effects. Trastuzumab (Herceptin) is a recombinant, humanized monoclonal antibody directed against the extracellular domain of the human epidermal growth factor receptor 2 (HER2, also known as ErbB2), commonly used in treatment of breast cancer. Trastuzumab-mediated cardiotoxicity was originally described in a phase III randomized clinical trial in metastatic breast cancer [7]. The incidence of severe CHF (NYHA class III or IV) was as high as 16 % when trastuzumab was administered concurrently with anthracyclines but decreased to only 3 % when anthracyclines were administered alone. Interestingly, subsequent adjuvant clinical trials of trastuzumab with anthracyclines have reported a lower incidence of severe CHF to 2–4.4 % [8–10]. These discrepancies may be explained by the difference in chemotherapy scheduling. It has been observed that the incidence of severe CHF seems to be lower if the time interval between the administration of anthracycline and trastuzumab is longer [11].

In comparison to anthracycline-induced cardiomyopathy, trastuzumab-induced cardiotoxicity is not dose related and has overall lower morbidity and mortality [12]. Also, cardiac

dysfunction secondary to trastuzumab generally improves following discontinuation of the agent. If aggressively treated with angiotensin-converting enzyme inhibitors and/or beta-blockers, cardiac function may return to near-baseline levels [13]. A rechallenge of trastuzumab in this group of patients is reasonable if oncologically indicated. Endomyocardial biopsy in patients with trastuzumab-related cardiomyopathy normally reveals minimal myocyte necrosis or replacement fibrosis which correlates with recovery of cardiac function and better clinical outcomes.

Small-molecule tyrosine kinase inhibitors have been approved for the treatment of a variety of malignancies. The broad biological activities of TKIs against multiple tyrosine kinase receptors have raised the concern for off-target toxic effects [14]. Hypertension is a major adverse cardiac side effect in several TKIs agents, occurring 17–43 % in sorafenib and 5–24 % in sunitinib [1]. Moreover, recognition of TKIs-induced cardiomyopathy is emerging as the number of clinical trials with these agents increase.

Mechanisms of Toxicity

The classical paradigm of doxorubicin-induced cardiotoxicity is thought to be from formation of reactive oxygen species, which in turn induce oxidative stress in normal cardiac tissue [15]. The heart is known to be rich in mitochondria accounting for approximately 40 % of the intracellular volume of cardiomyocytes. Doxorubicin is known to have a high affinity for cardiolipin, a negatively charged phospholipid found in the mitochondrial inner membrane. Accumulation of mitochondrial doxorubicin makes the heart a site of redox activity. One-electron reduction of the quinone group of the anthracycline forms a semiquinone radical which reacts with oxygen to form superoxide radicals. The semiquinone then reverts back to quinone to react again, which over time generates large amounts of superoxide radicals. The semiquinone form also triggers the release of iron from ferritin and aconitase. Iron regulatory proteins bind to iron-responsive elements, ultimately destabilizing ferritin mRNA. As iron uptake overtakes iron sequestration, the increased cellular levels of free iron produce hydroxyl radicals through Fenton chemistry, contributing to further oxidative stress.

Despite the molecular contribution of oxidative stress, the use of ROS scavenger treatment has not been promising in preventing cytotoxicity in cardiac myocytes. Another proposed mechanism of toxicity is through the targeting of topoisomerase IIβ. It is well known that doxorubicin kills cancer cells through DNA intercalation and inhibition of topoisomerase II, particularly topoisomerase IIα [16]. Studies have shown that the protective effects of dexrazoxane, an agent used for cardioprotection in anthracycline-induced cardiomyopathy, may be from the antagonistic effects of dexrazoxane in the formation of topoisomerase IIβ-DNA covalent (cleavage) complexes. Also in animal studies, topoisomerase IIβ knockout mice embryonic fibroblasts demonstrated resistance to doxorubicin-induced DNA damage. These findings suggest a possible topoisomerase IIβ-mediated mechanism of cardiotoxicity.

Mechanistic theories of trastuzumab cardiotoxicity are not fully understood but has been partially explained by the disruption of the epidermal growth factor (EGF) signaling system. Of the four isoforms of ErbB receptors, only ErbB2 and ErbB4 were found to be expressed by neonatal and adult ventricular myocytes. These receptors play an important role in cardiomyocyte developmental and survival signaling pathway [17]. Neuregulin-1 (NRG-1) is an EGF ligand secreted in the heart which binds to and activates ErbB4 and subsequently recruits ErbB2 as co-receptor to initiate signaling. This pathway is crucial in the developing heart for synthesis and stabilization of structural proteins as well as attenuating myocyte death. Remarkably, mutations of NRG-1, ErbB2, or ErbB4 gene in adult mice have similar cardiac phenotypes demonstrating cardiomyopathy with left ventricular dysfunction and dilation. When these genes were knocked out, myocardial trabeculae development was arrested in ventricular muscle during mid-embryogenesis [18, 19]. Inhibition of this vital pathway by trastuzumab leads to decreased cardiomyocyte survival and inhibition of repair mechanisms which ultimately causes cardiac dysfunction.

The high incidence of CHF during the concomitant administration of anthracycline and trastuzumab has been investigated [7]. A study by de Korte and colleagues provided a potential mechanistic explanation of this phenomenon [20]. Upregulation of HER2 expression after anthracycline therapy is a compensatory mechanism of the myocardium following stress. This cellular alteration and upregulation increases the vulnerability of cardiac myocytes to concurrent and subsequent damage following the administration of trastuzumab.

Similar to trastuzumab, several small-molecule oral TKIs have been found to cause significant damage to the cardiovascular system. Sunitinib is a small-molecule, multi-targeted tyrosine kinase inhibitor with potent properties against vascular endothelial growth factor receptors (VEGFR), platelet-derived growth factor receptors (PDGFRs), stem cell factor receptors (c-KIT), and FMS-like tyrosine kinase-3 (FLT-3). The mechanism of sunitinib-associated LV dysfunction was previously believed to be solely a consequence of uncontrolled hypertension, a common side effect of sunitinib. Further investigation in PDGFR signaling has provided more insights into the underlying mechanism of the hypertensive stress-induced cardiac dysfunction [21]. PDGFR is known to be expressed on cardiac myocytes; the expression will increase dramatically in response to stress. PDGFR-beta cardiac-specific knockout mice models have demonstrated

Table 42.2 Mechanism of cancer therapy-induced cardiomyopathy

Drug	Mechanism
Anthracycline	Direct cardiac myocyte damage
Trastuzumab	Blunting pro-survival factors
Sunitinib	Blocking stress response

the vital role of PDGFR-beta signaling in regulating cardiac response to pressure overload-induced stress. The maladaptive remodeling in response to stress caused by PDGFR blockage and uncontrolled hypertension ultimately leads to the development of life-threatening cardiomyopathy and heart failure (see Table 42.2).

Management of Cancer Therapy-Induced Cardiotoxicity

Prior to initiation or in the early phases of cancer treatment, every effort must be made to modify risk factors in order to minimize the potential of cardiac complications which could compromise cancer treatment. Serial monitoring of clinical signs and symptoms is necessary to ensure early detection of cardiac dysfunction prior to the development of irreversible change to the myocardium.

When cardiac dysfunction is discovered, immediate initiation of standard heart failure therapy is essential. The risks and benefits of continued use of cardiotoxic chemotherapeutic agents should be evaluated on an individual basis.

Monitoring the long-term consequences of cancer treatment is important to ensure lasting survival and quality of life. Data released by the Centers for Disease Control and Prevention and the National Cancer Institute indicate that the number of cancer survivors in 2007 had risen approximately 20 % from 2001. Not surprisingly, subsequent cardiac mortality was a major cause of non-cancer-related deaths among survivors. Such reports further necessitate attempts to validate diagnostic tools that could provide prognostic value to predict cardiac outcomes. Unfortunately, despite the growing body of literature linking cancer therapy to cardiotoxicity, as of yet there is currently no consensus guideline on the prevention and monitoring of cancer patients exposed to cardiotoxic medications.

Imaging Modalities During Monitoring

Aside from symptom monitoring, baseline imaging assessment of LV function is essential and should be obtained prior to the initiation of chemotherapy. The most common modalities of functional assessment are echocardiography and radionuclide angiography. Both procedures are well validated and commonly used in assessing LV function in cancer patients.

Radionuclide Angiography

Radionuclide angiography, or multiple-gated acquisition scan (MUGA), is a volumetric measurement of the left ventricular ejection fraction (LVEF). In contrast to echocardiographic calculations, it does not use geometric assumptions and is highly reproducible regardless of differences in body size and tissue attenuation [22, 23]. For serial LVEF assessment in ambulatory outpatient cancer centers, MUGA has been shown to demonstrate little variability and is not limited by operator skills or acoustic windows. Although it is a relatively safe and accurate test, radionuclide angiography does have a few limitations. These include the lack of portability, exposure to ionizing radiation, and inaccuracy in the face of arrhythmias. The ionizing radiation is minimal but can raise concern particularly in long-term serial follow-up, particularly in pediatric cancer survivors.

Echocardiography in Cardiac Assessment

Transthoracic echocardiography has been shown to be a useful tool in the diagnosis and serial evaluation of cardiac structure and function for a variety of cardiac conditions. It provides real-time hemodynamic information with minimal risk to the patient. Early detection of subclinical cardiotoxicity from echocardiographic parameters may lead to modification of therapeutic protocols and early initiation of cardioprotective therapy to minimize further myocardial damage [24]. However, current clinical practice using LVEF and fractional shortening is not sensitive for preclinical cardiac damage. Various newer echocardiographic techniques have been investigated in cancer patients for a potential role in monitoring chemotherapy-induced cardiotoxicity. A number of studies have investigated the use of tissue Doppler imaging (TDI) to detect early myocardial injury induced by chemotherapy [25]. Several parameters of systolic and diastolic function from TDI have been found to be abnormal even after exposure to low-dose anthracycline therapy which normally would not be detected by conventional echocardiography LV function assessment [26, 27]. Nevertheless, no single parameter in TDI has consistently demonstrated a good correlation with LVEF and cardiac event rate. Further clinical studies will be necessary to validate clinical application.

Recently, the use of speckle-tracking echocardiography (STE) has emerged as a more sensitive and reproducible method of LV function evaluation (see Fig. 42.2). Strain is a dimensionless parameter of myocardial deformation in response to an applied force or stress during systolic time frame. The sensitivity of strain imaging in detecting late events was assessed in multiple cross-sectional studies which

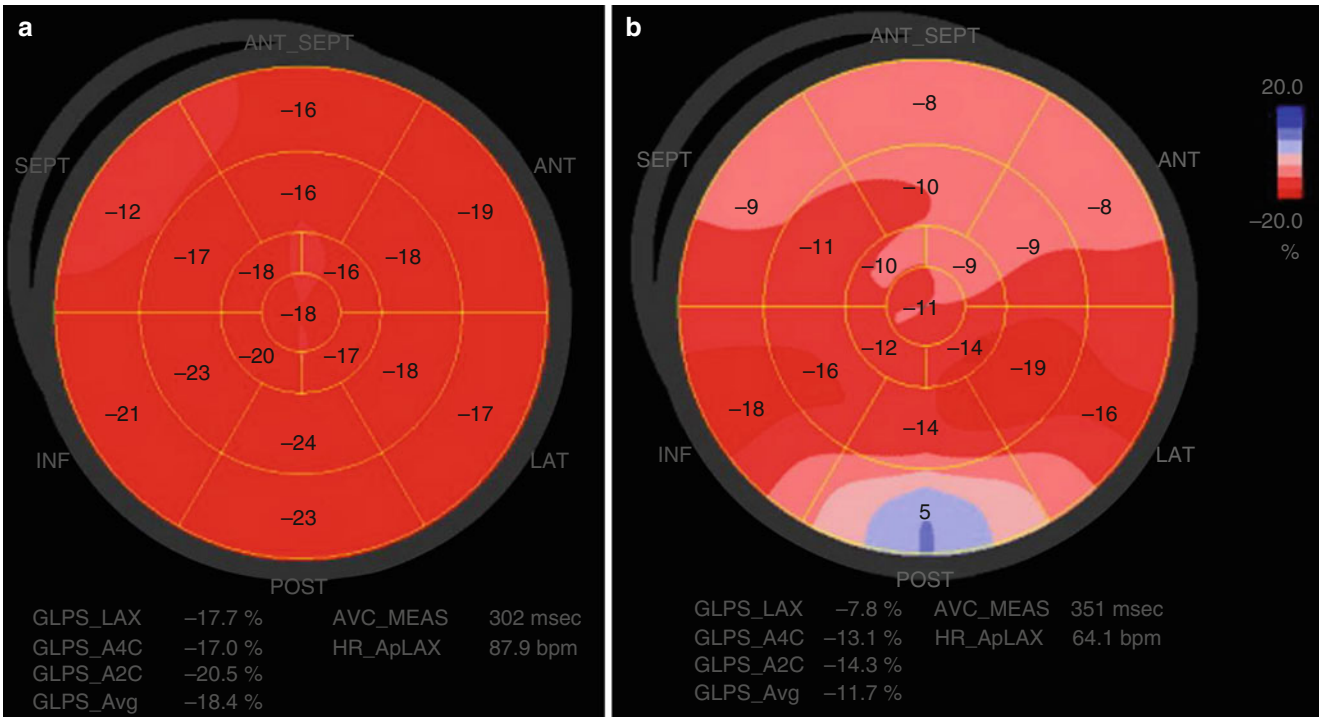

Fig. 42.2 Speckle-tracking echocardiography in the patient prior to and after tyrosine kinase inhibitor therapy. (**a**) Speckle tracking prior to chemotherapy demonstrated normal global longitudinal peak strain average (GLPS avg) (18.4 %) and (**b**) abnormal GLPS avg (11.7 %) following tyrosine kinase inhibitor therapy

demonstrated abnormal strain patterns being detected in asymptomatic cancer survivors even 20 years after their cancer treatment [28, 29]. Subtle changes have been recognized by STE prior to detectable changes in LVEF by conventional methods [30]. However, only a few prospective trials correlated changes in strain imaging with clinical outcomes [31]. Additionally, some data from these studies are conflicting, and none of these findings are sensitive or specific enough to apply in daily clinical practice [32]. Recent trials have proposed utility in combining the strain imaging with cardiac biomarkers in order to provide better positive and negative predictive values [33].

Oftentimes, abnormalities may not be apparent in patients exposed to cardiotoxic chemotherapy on resting echocardiograms. Stress echocardiography can demonstrate abnormalities in cancer survivors with normal resting function. Both exercise and dobutamine stress echocardiography have been used to reveal subtle abnormalities in left ventricular shortening fraction in patients exposed to anthracycline [34, 35].

Cardiac Magnetic Resonance

Over the past decade, cardiac magnetic resonance imaging (CMR) has become a useful imaging modality in assessing cardiac morphology, function, and metabolism. Due to its excellent spatial and temporal resolution, CMR is considered the gold standard for the noninvasive assessment of LV systolic function [36]. An advantage of CMR in cancer patients is not only the precise evaluation of cardiac function but also its unique potential in visualizing functional change in myocardial tissue prior to structural alterations. In one small clinical study, an increase of myocardial contrast enhancement after the first dose of anthracycline chemotherapy was observed to have predictive value preceding a significant loss of LVEF during the first month of treatment [37]. Other studies have demonstrated the pattern changes of late contrast enhancement in the myocardium of patients with chemotherapy-induced cardiomyopathy [38–40]. Due to limited number of patients and inconsistent findings, additional studies are necessary to confirm the benefit and prognostic value of CMR. Although CMR is accurate, highly reproducible, with low intraobserver variability, the high costs of repeated testing and its limited availability in most centers preclude its routine use in monitoring chemotherapy-induced cardiotoxicity.

Utility of Biomarkers During Monitoring

As previously mentioned, the early identification of cardiotoxicity prior to the development of LV dysfunction is a primary goal for cardiologists. Despite their usefulness, routine cardiac imaging alone lacks sensitivity for early detection of

preclinical cardiac disease. Cardiac biomarkers have been evaluated extensively in both animal models and clinical studies. In acute coronary syndromes, troponin is one of the most well-established biomarkers used in the diagnosis, treatment, and prognosis of patients with myocardial injury [41, 42]. However, the utility in monitoring myocardial damage secondary to chemotherapy is still controversial.

Both cardiac troponin subtypes, T (cTnT) and I (cTnI), have been investigated in clinical trials demonstrating correlation in both subtypes but to a lesser degree of clinical correlation from cTnT [43, 44]. Multiple studies reported that elevated cTnI has predictive value for subsequent decrease in LVEF and cardiac events long before the impairment is observed by echocardiogram or symptoms have developed [45]. Elevation in cTnI has shown a positive predictive value of 50–84 % and a negative predictive value of 90–99 % [33, 46]. Furthermore, the peak value and the duration of cTnI elevation have both been found to have a close relationship with the degree of LVEF reduction [47]. A major limitation in the clinical use of cTnI is timing for the most accurate blood sampling. An elevation in cTnI level can be seen immediately after chemotherapy is administered or as late as 1 month after chemotherapy is completed. A limitation for using this marker in daily clinical practice is the need for frequent blood samplings during and after the course of chemotherapy in order to demonstrate the possible early elevation of the biomarker.

Natriuretic hormones, the mediators of volume-expansion natriuresis, are primarily released from the cardiac myocyte during situations of increased wall stress caused by excessive volume or pressure loading conditions of the heart. They have been used in clinical practice to aid in the diagnosis and management of heart failure and cardiomyopathy. Therefore, natriuretic peptides have been considered as possible cardiac biomarkers for early determinant of cardiotoxicity in cancer patients. Potential diagnostic value of brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) prior to development of cardiomyopathy in cancer patients has been demonstrated in a few small prospective studies [48]. Contrarily, atrial natriuretic peptide (ANP) and N-terminal pro-atrial natriuretic peptide (NT-pro-ANP) have shown to be less sensitive and specific to detect subclinical heart failure in this group of patients [49]. Immediately after chemotherapy is administered, transient elevation of BNP and NT-pro-BNP can be seen with a return to baseline levels within 1–2 weeks. It has been suggested that the persistent elevation of BNP and NT-pro-BNP may correlate with the potential development of a decompensated heart during follow-up [50]. Nonetheless, the data reported from these studies are often incomplete and lack crucial information such as the laboratory methods used in measurement of cardiac biomarkers or the cutoff values that show the best diagnostic accuracy. This represents a limitation against the routine use of cardiac natriuretic peptides as predictors for subclinical chemotherapy-induced cardiomyopathy in clinical practice.

Preventive Therapies

Dexrazoxane

Dexrazoxane, a bisdioxopiperazine, is a cyclic derivative of the powerful metal-chelating agent ethylenediaminetetraacetic acid (EDTA). Although it was originally investigated as a potential chemotherapeutic agent, dexrazoxane was found to have utility in its protective activity against anthracycline-induced cardiotoxicity. The American Society of Clinical Oncology 2008 Clinical Practice Guideline recommends that the use of dexrazoxane be considered for adult patients who have received more than 300 mg/m^2 of doxorubicin-based therapy. The data for using dexrazoxane with other anthracycline chemotherapy are limited. There is insufficient evidence to make a recommendation for the routine use of dexrazoxane in pediatric patients. It is also not recommended to use dexrazoxane in patients who are receiving an initial dose of doxorubicin [51].

The cardioprotective effect of dexrazoxane was primarily proposed based on the ability of its hydrolysis products to chelate free and bound iron in anthracycline complexes, thereby preventing the formation of cardiotoxic reactive oxygen radicals in the myocardium [52]. However, other iron-chelating agents failed to demonstrate the same cardioprotective action against anthracycline. Dexrazoxane has a strong inhibition of the catalytic activity of topoisomerase II (Top2) which is a potential biochemical property that protects cardiomyocyte from anthracycline chemotherapy [53]. Additional data to support this theory come from investigative use of ICRF-193, another potent Top2 inhibitor. It has shown to be comparable to dexrazoxane in antagonizing doxorubicin-induced DNA double-strand breaks. Despite the impressive clinical and biochemical evidence of its cardioprotective benefits, dexrazoxane is not routinely administered with anthracycline-based regimen due to a concern that dexrazoxane may interfere with the oncologic efficacy of anthracyclines [54]. In addition, a few studies have raised a concern that dexrazoxane may increase the incidence of secondary malignant neoplasms and acute myeloid leukemia/myelodysplastic syndrome [55]. Nevertheless, the preponderance of evidence indicates dexrazoxane provides long-term cardioprotective effects without compromising oncological activity.

ACE Inhibitors

Angiotensin-converting enzyme inhibitor (ACE inhibitors) therapy and angiotensin receptor blockers (ARB) have been

well established as a treatment for a variety of cardiac conditions with an approximate 20 % relative risk reduction in cardiovascular events [56]. Their utility in preventing cardiotoxicity in cancer patients has been under investigation.

The use of ACE inhibitors and ARB has been shown in animal models as promising agents to prevent chemotherapy-induced cardiomyopathy. Most of the studies focused on anthracycline cardiotoxicity. Coadministration of ACE inhibitors or ARB with anthracycline chemotherapy has been documented in different animal models to attenuate myocardial damage in acute and late-onset cardiotoxicity [57, 58]. Biomarkers, LV function, and survival rate were significantly improved in ACE inhibitors or ARB groups as compared to control groups [59, 60].

To date, only a few prospective studies in humans have been conducted, yielding conflicting results. Two small randomized controlled trials have shown an intriguing benefit of ARB therapy in preventing acute cardiotoxicity from anthracycline-based regimens. ARB therapy was found to suppress the inflammatory process and prevent LV diastolic impairment [61, 62]. Regardless of this finding, there was no significant difference of LVEF between treatment and control groups which may have been attributed to the short follow-up period. Another study randomized 114 patients with an elevated cTnI to receive enalapril 1 month after completion of the last cycle of anthracycline-based chemotherapy. After 1 year, patients in the control group demonstrated a significant reduction in LVEF, an increase in end-diastolic volume, and an increase in end-systolic volumes. None of the patients in the enalapril group experienced a drop in LVEF, but 43 % of patients in the control group without ARB therapy developed a decrease in LVEF > 10 % from baseline with a decline below the normal cutoff value of 50 % [63]. However, another study in 135 pediatric cancer survivors who were previously treated with anthracyclines showed no benefit of enalapril in long-term use on LV function or exercise performance [64]. Due to these discrepancies, current practice guidelines have not made recommendations on pretreatment with ACE inhibitors or ARB.

Beta-Blockers

Beta-adrenergic blockers (BB) have also been proven to reduce cardiac outcomes in a variety of conditions. Like the ACE inhibitors, the utility in pretreatment with BB has been equivocal. The role of BB in hindering the pathogenesis of anthracycline-related cardiac injury has been evaluated in cell cultures and animal models. Carvedilol, a nonselective beta-blocker/alpha-1-blocker with potent antioxidant and anti-apoptotic properties, has demonstrated the ability to reduce oxidative stress, mitochondrial dysfunction, and histopathological lesions induced by anthracyclines [65–67]. In addition to positive effects at the molecular level, both LV function and survival rate in animal models are also significantly improved when carvedilol is administered concurrent with chemotherapy. In contrast, atenolol, a pure beta-adrenergic receptor antagonist, failed to show any benefit [65]. Metoprolol, another cardioselective beta-1 receptor blocker, showed an improvement in functional parameters of the heart but did not result in improved survival [68].

In a small study, 50 patients were randomized to receive carvedilol or placebo for 6 months during the course of anthracycline chemotherapy. At their 6-month follow-up, LVEF was reduced significantly in the control group as compared to the carvedilol group (68.9 vs. 52.3; $p < 0.001$) [69]. With a relatively short follow-up and small sample size of patients, the long-term benefit of BB as preventative treatment appears promising but remains unclear.

Treatment Strategies

The fundamental of treatment for heart failure and LV dysfunction in chemotherapy-induced cardiomyopathy is similar to those without cancer. Subsequently, the current practice guidelines published by the American College of Cardiology, American Heart Association, and the Heart Failure Society of America are recommended as a main reference in the management of these patients. ACE inhibitors and BB are the well-established key elements of heart failure therapy [70]. Extensive investigations with more than 50 published placebo-controlled clinical trials on ACE inhibitors and BB have consistently demonstrated the improvement of clinical status and NYHA functional class, reduction in morbidity and mortality, and reversal of LV remodeling process. Patients with depressed LV systolic function should be started on ACE inhibitors and BB therapy as soon as possible. Those who are intolerant of ACE inhibitors should be changed to ARB therapy. Additional therapies with aldosterone antagonists, vasodilators, and diuretics may also be used in the treatment of the patient's heart failure.

To date, a limited amount of research has been performed to determine the efficacy of standard heart failure therapy specifically in chemotherapy-induced cardiomyopathy. Most of the studies mainly focused on cardiotoxicity of anthracycline, which, in the past, was considered an irreversible condition refractory to treatment (mainly comprising digoxin and diuretics at that time). A few observational and retrospective studies have shown that ACE inhibitors therapy can alleviate symptoms and improve clinical status and LV function in this cohort of patients. All of these trials enrolled patients who already had clinical signs and symptoms of CHF with reduced LVEF (range from18 to 35 %). Therapy with ACE inhibitors was well tolerated without significant hypotensive effects, and most of the patients demonstrated significant clinical and LV function improvement [71, 72].

Moreover, the use of BB in additional to ACE inhibitors has been shown to provide a greater improvement in NYHA class and cardiac function [73]. The most recent prospective trial exploring the efficacy of combined enalapril and carvedilol therapy was conducted in 201 patients with anthracycline-induced cardiomyopathy. In this study, time-to-HF treatment (duration from the end of chemotherapy to the start of HF treatment) and NYHA functional class were independent predictors for LVEF recovery. No participants with time-to-HF treatment greater than 6 months had complete recovery of LV function. Therefore, early detection and prompt initiation of standard HF therapy plays an important role in complete recovery of LV function as well as reduction of cardiac events [24]. Although data on long-term outcomes after heart failure treatment are still lacking, one small retrospective study in pediatric cancer survivors reported short-term improvement of symptoms and LV function after initiation of enalapril but failed to demonstrate a sustain benefit during the follow-up period of 6–10 years [74].

A multidisciplinary approach is advisable when monitoring cancer patients on high-risk therapy. Discussions must be held with the patient and oncologist regarding interruption or cessation of the chemotherapy. Although there are no clear timeframes for LVEF recovery in chemo-induced cardiomyopathy, generally a reassessment may be performed after 3–4 weeks with continued medical therapy.

For high-risk patients and those who have already developed cardiomyopathy, repeat assessment of LV function to assess for further decline is recommended after each subsequent cycle of chemotherapy. If patients become refractory to medical treatment with decompensated heart failure, inotropic support and mechanical support, such as ventricular assist devices, may be required to stabilize patients.

Discontinuation of Therapy

The decision to discontinue cardiomyopathy treatment in patients with recovered LV systolic function is an area that has not been fully investigated in chemo-related toxicity. Data in the general heart failure population have shown worse outcomes in patients who were prematurely discontinued from therapy. The OPTIMIZE-HF study showed longer durations of hospitalization, higher rates of readmission, and worse overall mortality outcomes at 60 and 90 days in patients who were either discontinued on BB or who were never started on BB therapy for heart failure [75]. Only one cohort study has been done to explore the long-term requirement of ACE inhibitors and/or BB in chemotherapy-induced cardiomyopathy. Upon withdrawal of these medications, cardiac function was found to be acutely deteriorated with the mean LVEF decreased to 30.62 % from 49.62 % at baseline. Of note, 9 out of 16 patients died within 6 months after discontinuation of therapy. Furthermore, reinstitution of carvedilol and/or ACE inhibitors improved LVEF to 45 % [76]. Although newer investigations are currently underway to identify the safety of withdrawing heart failure therapy, current data suggest that therapy should continue indefinitely unless there is a compelling contraindication.

Summary

During the past decade, a number of modern anticancer therapies have been introduced that have significantly impacted cancer survival. Despite these successes, cardiac dysfunction as an undesirable consequence of cancer therapy continues to remain a major challenge. Although chemotherapy-induced cardiomyopathy was first recognized as early as in the 1970s, the precise mechanisms remain unclear. Elucidating the pathophysiology of cardiotoxicity from antineoplastic agents continues to be an area of great interest to both cardiologists and oncologists. To supplement traditional monitoring techniques by echocardiography and radionuclide imaging, novel tools in cardiac imaging, such strain rate, and biomarkers, such as cTnI, have shown great promise for earlier detection of cardiotoxicity. Many patients with cancer therapy-induced cardiomyopathy can be treated with ACE inhibitors and BB with recovery of LV function. It remains unknown whether cardioprotective medications can be withdrawn following successful treatment of cardiotoxicity. Further investigation is required to identify potential genetic markers of cancer therapy-induced cardiotoxicity and to determine an optimal protocol for monitoring and treating patients ultimately to improve the mortality and quality of life of cancer patients with cardiovascular disease.

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Recommended Readings

Cardinale D et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol. 2010;55:213–20.

Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. J Clin Oncol. 2005;23:2900–2.

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43 Assessment of Patients with Heart Disease for Fitness for Noncardiac Surgery

Lee A. Fleisher and Joseph S. Savino

The tendency in medicine over the past two decades is to decrease preoperative testing as the evidence for improved outcomes for these often expensive procedures is lacking. Population-based management decisions are often steered by clinical trials, cost-effectiveness analysis, and resource allocation. However, few doctors take care of populations. Most of us care for individuals. Evidence-based paradigms based on "population medicine" define the most effective management scheme for the vast majority of patients, but not every patient. Individual patient decisions by the attending physicians are not consistently based on evidence but often made in the context of "what would I do if it was my mother?" with the premise that more information is better. Should every patient undergoing repair of an abdominal aortic aneurysm undergo dipyridamole or dobutamine stress testing? The evidence supports not. Nonetheless, the practice in many centers has been to obtain a dipyridamole or adenosine thallium stress test even if the patient is asymptomatic. Despite the reassurances provided by large clinical trials, practitioners do not consistently adhere to their recommendations and often rely on tradition, anecdote, and impression in their decision making. If physicians are to remain the dispensers of medical care and resources, then we need to be cognizant of the effects of our decisions on all patients, not just the one sitting in the examination room. Exorbitant sums spent on unnecessary testing exhausts valuable resources that could be diverted to the more needy. Unfortunately, the risk of uncertainty and medicolegal liability results in more testing than is often indicated. However, in the era of healthcare reform and accountable care, it is critical to utilize testing and consultations more appropriately.

The evaluation of the patient scheduled for anesthesia for noncardiac surgery remains a diagnostic dilemma because of competing issues of economics, expediency, and the desire to have a complete knowledge base regarding extent of cardiovascular disease. Multiple medical specialties are involved in the evaluation of the high-risk patient, each of which may have complimentary or redundant contributions. In many institutions, anesthesiologists have established preoperative evaluation clinics, and the surgeon will defer to the anesthesiologist's judgment regarding the need for extensive cardiovascular consultation. However, these same "preoperative clinics" are at a significant cost to the hospital or the physician practices as their activity is not independently reimbursable by payers, and studies on their cost-effectiveness are now old and may be less relevant [1]. Not uncommonly, the surgeon may initiate a cardiology consultation. The most effective paradigm to accomplish the preoperative assessment of cardiovascular fitness may be institution dependent, based on allocation of resources and expertise of staff. A preoperative evaluation clinic and a preoperative medical clearance by the primary physician for all patients seem redundant and unnecessary. Whatever the model, the goal of all individuals involved in the care of the surgical patient with heart disease is to ensure that critical information is attained and communicated to the appropriate personnel so that optimal care can be provided.

Concepts for Preoperative Cardiac Evaluation

The underlying premise for the need for preoperative evaluation is the information will be used to modify perioperative care and improve outcome [2]. The preoperative evaluation will also be used to provide the patient and physicians with information to assess risk and to determine if the benefits of the planned procedure outweigh these risks. The benefits of some elective surgeries may be small or may not accrue for

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_43, © Springer Science+Business Media New York 2013

several years. Alternatives to complex surgery, such as external beam or seed radiation implants for the treatment of prostate cancer, maybe preferable for the patient at high risk of perioperative cardiac morbidity. Preoperative evaluation can influence the choice of operation based upon the cardiovascular risk. Endovascular stents for the treatment of aortic aneurysm have revolutionized the discipline of vascular surgery with lower perioperative risk, although open procedures are still performed but at a higher perioperative risk.

The most important role is the evaluation of patients with unstable symptoms since these patients have been shown to be at prohibitive risk [3]. Management of unstable cardiovascular symptoms is achieved prior to elective surgery since the risk of tachycardia, hypercoagulability, and plaque rupture maybe greater during the perioperative period. Coronary revascularization should be considered for patients with unstable angina, although the culprit lesion for a postoperative myocardial infarction is not reliably the coronary artery with the angiographically most significant stenosis. Alternative treatment strategies need to be considered if the procedure is emergent. The use of invasive monitoring during anesthesia and surgery is not without cost and risks. The use of a pulmonary artery catheter is unlikely to change outcome [4]. The preoperative evaluation should be used to identify those individuals for whom postoperative intensive care is warranted.

Role of the Consultant

As outlined in the recent American Heart Association/American College of Cardiology Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery, the role of the consultant is to define the extent and stability of a patient's cardiac disease and determine if they are in their optimum medical condition [2]. Unfortunately, there is no assurance that optimization of preoperative disease leads to improved outcome, although it appears that postoperative myocardial infarction and death are more likely to occur in patients with preexisting left main or three-vessel coronary artery disease [5]. If these patients can be identified in advance of their surgery, treatment or alternatives to surgery can be sought. There is a small but growing body of data that suggests that risk modification may actually improve outcome in the operative setting. The treatment of active coronary artery disease is efficacious before surgery. The perceived benefit of treatment of heart failure before surgery is based on the increased morbidity associated with NYHA Class III and IV heart failure. Systolic or diastolic dysfunction leading to heart failure my produce the greatest cardiovascular risk, especially if the etiology is ischemic heart disease. The incidence of diastolic dysfunction and abnormal ventricular filling is often ignored during preoperative assessment, despite its marked prevalence in the aged. Although studies in surgical patients are lacking, diastolic dysfunction has been associated with significant increases in "all-cause" mortality during long-term follow-up after adjustment for age, gender, and ventricular ejection fraction. An asymptomatic systolic murmur warrants an echocardiogram to assess aortic and mitral valve function. Occult aortic stenosis can lead to a catastrophic response to the vasodilatory effects of anesthetic induction or neuroaxial blockade and sympathectomy. Mitral regurgitation is typically better tolerated as the vasodilation during anesthesia typically decreases regurgitant fraction and improves forward flow. Rheumatic mitral stenosis is much less common but may become symptomatic during the perioperative period, especially during pregnancy. Severe pulmonary hypertension with mitral disease may lead to right heart failure and circulatory instability. Patients with prosthetic valves need meticulous attention to bacterial prophylaxis, depending on the nature of the operation. A growing population in the United States is adults with corrected congenital heart disease who often present with complex reconstruction of the great vessels of the mediastinum, residual shunts, pulmonary hypertension, and increased risk of endocarditis. Pathophysiology can vary significantly among cohorts of patients that carry the same diagnosis. Their response to intraoperative derangements may differ substantially, not allowing them to be considered under the same rubric. Preoperative assessment often includes echocardiography, electrocardiogram, and chest radiograph. Age-related cardiovascular disorders as well as postoperative cardiac residua need to be considered in their preparation for noncardiac surgery. The benefits of preoperative "optimization" of hypertension, hypercholesterolemia, and smoking cessation are less clear. From the anesthesiologist's perspective, the critical factors necessary that modify intraoperative technique and monitoring are preexisting disease and the complexity of the operative procedure. The guidelines state the specific choice of anesthetic technique, and agents are best determined by the anesthesia providers [2]. The choice of anesthetic technique and agents do not influence cardiovascular outcome. There appears to be no difference evidence to support the use of regional (epidural and spinal) anesthesia over general anesthesia. Hence, the preoperative evaluation should target not the type of anesthetic, but rather the patient condition in the context of the planned operation.

Pathophysiology of Perioperative Cardiac Events

The pathophysiology underlying perioperative cardiac events is multifactorial, which influences the potential value of preoperative cardiac testing. There has been a great deal of attention focused on the association of perioperative myocardial

ischemia and cardiac morbidity. In several large-scale studies, the presence of postoperative ischemia had the strongest association with myocardial infarction and cardiac death [6, 7]. Further analysis has suggested that prolonged ischemia is a critical factor for predicting events [8]. If mismatches of supply/demand in patients with critical coronary stenoses are the underlying substrate for these events, then either coronary revascularization or tight hemodynamic management should reduce morbidity. Maintenance of normothermia significantly decreased the rate of cardiac complications in a randomized clinical trial of intraoperative forced-air warming [9]. Anemia (hematocrit <28 %) was associated with an increased incidence of cardiac morbidity in a small cohort study [10]. However, the FOCUS study was unable to demonstrate any reduction in cardiac events in patients randomized to a liberal or restrictive transfusion protocol after surgery for hip fracture [11]. All of these factors could contribute to ischemia, which if prolonged, may lead to infarction. Yet symptomatic cardiac events and cardiac death may result from acute coronary thrombosis of a noncritical stenosis. Plague rupture and acute coronary thrombosis and occlusion occur in preexisting critical and noncritical coronary lesions. Downstream myocardium in the latter case maybe at greater risk than myocardium supplied by a significantly obstructed coronary artery because there is unlikely to be an established collateral circulation. Preoperative evaluation of significant preoperative coronary disease fails in this instance in identifying a high-risk event. Value may be gained by affecting the coagulation profile of surgery. It is unclear which surgical procedures and which anesthetics are associated with an increased propensity for arterial thrombosis.

Clinical Assessment

Since the original manuscript by Goldman and colleagues in 1977 describing a Cardiac Risk Index, multiple investigators have validated various clinical risk indices for their ability to predict perioperative cardiac complications [12]. The most recent index was developed in a study of 4,315 patients aged 50 years or greater undergoing elective major noncardiac procedures in a tertiary-care teaching hospital. Six independent predictors of complications were identified and included in a Revised Cardiac Risk Index (RCRI): high-risk type of surgery, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative treatment with insulin, and preoperative serum creatinine >2.0 mg/day, with increasing cardiac complication rates noted with increasing number of risk factors [13]. The RCRI has become the standard tool in the literature in assessing the prior probability of perioperative cardiac risk in a given individual and has been used to direct the decision to perform cardiovascular testing and implement perioperative management protocols. It has recently been validated for both short- and long-term cardiovascular outcomes [14]. It has also been shown to predict long-term quality of life [ref]. Therefore, it can be used to help define the long-term risks of cardiovascular disease in the surgical patient.

A primary issue with all of these indices from the anesthesiologist's perspective is that a simple estimate of risk does not help in refining perioperative management, and therefore it is important that the anesthesiologist determines the extent and stability of the patient's coronary artery disease through obtaining information from the primary caregiver or cardiologist or through a thorough history or physical examination.

A thorough history should focus on cardiovascular risk factors and symptoms or signs of unstable cardiac disease states, such as myocardial ischemia with minimal exertion, active congestive heart failure, symptomatic valvular heart disease, and significant cardiac arrhythmias. The presence of unstable angina was associated with a 28 % incidence of perioperative MI [3]. Such patients would benefit from the delay of surgery and stability of the coronary symptoms. For those patients with chronic stable angina, exercise tolerance appears to be a good method of assessing risk. In virtually all studies, the presence of active congestive heart failure preoperatively has been associated with an increased incidence of perioperative cardiac morbidity [15]. Stabilization of ventricular function and treatment for pulmonary congestion are prudent prior to elective surgery. Also, it is important to determine the etiology of the left heart failure since the type of perioperative monitoring and treatments would be different.

Patients with a prior MI have coronary artery disease, although a small group of patients may sustain an MI from a nonatherosclerotic mechanism. Time from a prior MI had traditionally been an important predictor of perioperative risk. The more recent the myocardial infarction, particularly within 3–6 months, the greater the perioperative risk. However, like the Goldman Index, medicine has changed and outcomes are improved. The classic Rao paper published in 1983 cited a reinfarction rate of nearly 30 % if noncoronary surgery occurred within 3 months of a prior infarction. These events had a very high mortality rate. With the advent of dedicated postoperative intensive care units, more vigilant monitoring, and early intervention, the postoperative reinfarction rate has decreased to almost an order of magnitude less. The American College of Cardiology/American Heart Association Guidelines advocate the use of 30 days as the acute period, with high risk continuing up to 6–8 weeks [2]. After that time, a prior MI places the patient in the intermediate clinical risk category, and further evaluation depends upon clinical symptoms. Patients should be evaluated from the perspective of their risk for ongoing ischemia. A recent

Table 43.1 Active cardiac conditions

Condition	Examples
Unstable coronary syndromes	Unstable or severe angina[a] (CCS Class III or IV)[b]
	Recent MI[c]
Decompensated HF	NYHA functional Class IV
	Worsening or new-onset HF
Significant arrhythmias	High-grade atrioventricular block
	Mobitz II atrioventricular block
	Third-degree atrioventricular heart block
	Symptomatic ventricular arrhythmias
	Supraventricular arrhythmias (including atrial fibrillation) with uncontrolled ventricular rate (HR > 100 bpm at rest)
	Symptomatic bradycardia
	Newly recognized ventricular tachycardia
Severe valvular disease	Severe aortic stenosis (mean pressure gradient greater than 40 mmHg, aortic valve area less than 1.0 cm^2, or symptomatic)
	Symptomatic mitral stenosis (progressive dyspnea on exertion, exertional presyncope, or HF)

Adapted from Fleisher et al. [2]. With permission from Wolters Kluwer Health

[a]According to Campeau

[b]May include stable angina in patients who are unusually sedentary

[c]The Acc National Database Library defines recent MI as more than 7 days but within 30 days

Table 43.2 Clinical risk factors

Ischemic heart disease
H/O CHF
H/O cerebrovascular disease
Diabetes mellitus
Preop Cr > 2.0 mg/dl

analysis using Medicare Claims data suggests that the risk of reinfarction remains high for at least 2 months after an MI and that coronary artery bypass grafting (CABG) may reduce that risk while coronary stent placement soon after an MI does not [16, 17].

For those patients without overt symptoms or history, the probability of CAD varies with the type and number of atherosclerotic risk factors present. Diabetes mellitus is common in the elderly and represents a disease that impacts on multiple organ systems. Diabetes accelerates the progression of atherosclerosis, which can frequently be silent in nature, leading many clinicians to assume coronary artery disease in this population and treating them as such. Diabetes is an independent risk factor for perioperative cardiac morbidity, and the preoperative treatment with insulin has been included in the RCRI. In attempting to determine the degree of this increased probability, the treatment modality, length of the disease, and other associated end-organ dysfunction should be taken into account, including autonomic neuropathy. Hypertension has also been associated with an increased incidence of silent myocardial ischemia and infarction. Those hypertensive patients with left ventricular hypertrophy and who are undergoing noncardiac surgery are at a higher perioperative risk than nonhypertensive patients [18]. There is a great deal of debate regarding a trigger to delay or cancel a surgical procedure in a patient with poorly or untreated hypertension. The patient with a sustained diastolic blood pressure greater than 110 mmHg had traditionally triggered a delay in surgery, although the data does not support such an assertion. In fact, none of the patients with "uncontrolled systemic hypertension" sustained a major cardiac event, and the authors simply state that surgery is safe with hypertension up to a diastolic of 110 mmHg [19]. In the absence of end-organ changes, such as renal insufficiency or left ventricular hypertrophy with strain, it would seem appropriate to proceed with surgery. A randomized trial of treated hypertensive patients without known CAD who presented the morning of surgery with an elevated diastolic blood pressure was unable to demonstrate any difference in outcome between those who were actively treated and those in whom surgery was delayed [20]. In contrast, a patient with a markedly elevated blood pressure and the new onset of a headache should have surgery delayed for further evaluation and potential treatment. For the purpose of the guidelines, a list of active cardiac conditions (Table 43.1) and clinical risk factors (Table 43.2) were defined.

Importance of Surgical Procedure (Table 43.3)

The surgical procedure influences the extent of the preoperative evaluation required by determining the potential range of changes in perioperative management. There is little hard data to define the surgery-specific incidence of complications, and the rate may be very institution dependent. Eagle et al. published data on the incidence of perioperative myocardial infarction and mortality by procedure for patients enrolled in the coronary artery surgery study (CASS) [21]. Higher risk procedures for which coronary artery bypass grafting reduced the risk of noncardiac surgery compared to medical therapy include major vascular, abdominal, thoracic, and orthopedic surgery. Ambulatory procedures denote low risk, and the mortality after surgery in the elderly population may actually be lower initially than 30 days after surgery. This may reflect the benefits of a thorough preoperative evaluation and management. Vascular surgery represents a unique group of patients in whom there is extensive evidence regarding preoperative testing and perioperative interventions. Endovascular stent placement is associated with lower perioperative risk, particularly the risk of death, but similar long-term mortality compared to open procedures.

Table 43.3 Risk based upon surgical procedure

Risk stratification	Procedure examples
Vascular (reported cardiac risk often >5 %)	Aortic and other major vascular surgery
	Peripheral vascular surgery
Intermediate (reported cardiac risk generally 1–5 %)	Intraperitoneal and intrathoracic surgery
	Carotid endarterectomy
	Head and neck surgery
	Orthopedic surgery
	Prostate surgery
Low (reported cardiac risk generally <1 %)	Endoscopic procedures
	Superficial procedure
	Cataract surgery
	Breast surgery
	Ambulatory surgery

Adapted from Fleisher et al. [2]. With permission from Wolters Kluwer Health

Table 43.4 Assessment of functional capacity (Mets)

	Can you…		Can you…
1 Met	Take care of yourself?	4 Mets	Climb a flight of stairs or walk up a hill?
	Eat, dress, or use the toilet?		Walk on level ground at 4 mph (6.4 kph)?
	Walk indoors around the house?		Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?
	Walk a block or 2 on level ground at 2–3 mph (3.2–4.8 kph)?		Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football?
4 Mets	Do light work around the house like dusting or washing dishes?	≥10 Mets	Participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing?

Adapted from Fleisher et al. [2]. With permission from Wolters Kluwer Health

Importance of Exercise Tolerance

Exercise tolerance is one of the most important determinants of perioperative risk and the need for invasive monitoring. If a patient can walk a mile without becoming short of breath, then the probability of extensive coronary artery disease is small. Alternatively, if patients become dyspneic associated with chest pain during minimal exertion, then the probability of extensive coronary artery disease is high. Reilly and colleagues demonstrated that the likelihood of a serious complication occurring was inversely related to the number of blocks that could be walked or flights of stairs that could be climbed [22]. Exercise tolerance can be assessed with formal treadmill testing or with a questionnaire that assesses activities of daily living (Table 43.4). There is some suggestion that cardiopulmonary testing is useful for more accurately predicting risk.

Approach to the Patient

The figure presents in algorithmic form a framework for determining which patients are candidates for cardiac testing (Fig. 43.1). Given the availability of this evidence, the AHA/ACC Writing Committee chose to include the level of the recommendations and strength of evidence for many of the pathways. Importantly, the value of adopting the algorithm depends upon local factors such as current perioperative risk and rate of utilization of testing.

Step 1: The individual should determine the urgency of noncardiac surgery. In many instances, patient- or surgery-specific factors dictate an obvious strategy (e.g., emergent surgery) that may not allow for further cardiac assessment or treatment.

Step 2: Does the patient have one of the active cardiac conditions? In patients being considered for elective noncardiac surgery, the presence of unstable coronary disease, decompensated heart failure, or severe arrhythmia or valvular heart disease usually leads to cancellation or delay of surgery until the cardiac problem has been clarified and treated appropriately. Examples of unstable coronary syndromes include previous MI with evidence of important ischemic risk by clinical symptoms or noninvasive study, unstable or severe angina, and new or poorly controlled ischemia-mediated heart failure. Depending on the results of the test or interventions and the risk of delaying surgery, it may be appropriate to proceed to the planned surgery with maximal medical therapy.

Step 3: Is the patient undergoing low-risk surgery? In these patients, interventions based on cardiovascular testing in stable patients would rarely result in a change in management, and it would be appropriate to proceed with the planned surgical procedure.

Step 4: Does the patient have moderate functional capacity without symptoms? In highly functional asymptomatic patients, management will rarely be changed on the basis of results of any further cardiovascular testing, and it is therefore appropriate to proceed with the planned surgery. If the patient has poor functional capacity, is symptomatic, or has unknown functional capacity, then the presence of clinical risk factors will determine the need for further evaluation. If the patient has no clinical risk factors, then it is appropriate to proceed with the planned surgery, and no further change in management is indicated.

If the patient has one or two clinical risk factors, then it is reasonable either to proceed with the planned surgery, with

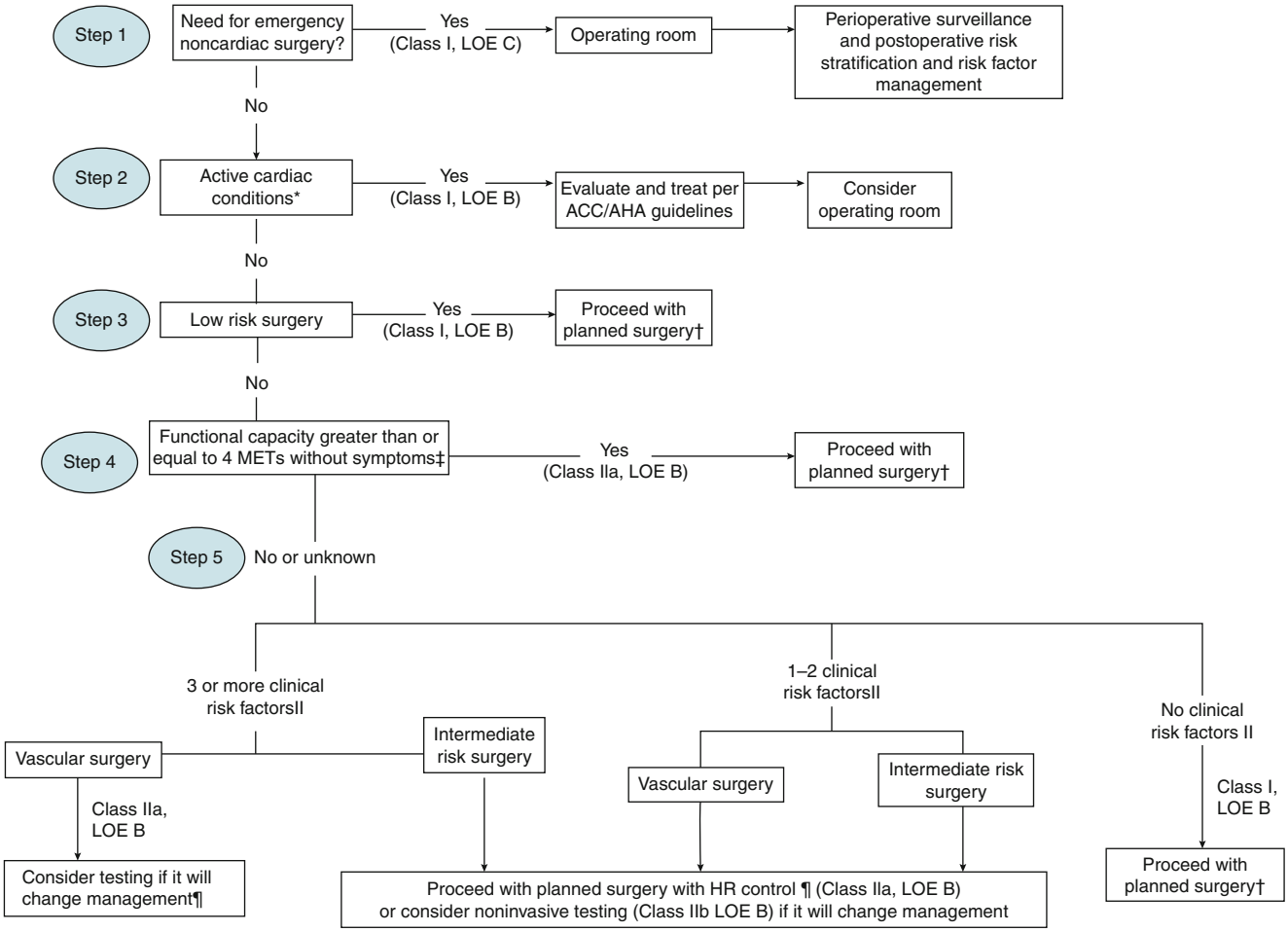

Fig. 43.1 The American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Perioperative Evaluation of Cardiac Patients Undergoing Noncardiac Surgery has proposed an algorithm for decisions regarding the need for further evaluation. The algorithm is based on expert opinion and incorporates six steps. First, the clinician must evaluate the urgency of the surgery and the appropriateness of a formal preoperative assessment. Next, the clinician must determine whether the patient has had a previous revascularization procedure or coronary evaluation. Those patients with unstable coronary syndromes should be identified, and appropriate treatment should be instituted. The decision to have further testing depends on the interaction of the clinical risk factors, surgery-specific risk, and functional capacity. * See Table 43.1 for active clinical conditions. †See Class III recommendations for Noninvasive Stress Testing per AHA/ACCF. ‡See Table 43.4 for estimated MET level equivalent. §Noninvasive testing may be considered before surgery in specific patients with risk factors if it will change management. Clinical risk factors include ischemic heart disease, compensated or prior heart failure, diabetes mellitus, renal insufficiency, and cerebrovascular disease. ¶Consider perioperative beta blockade for populations in which this has been shown to reduce cardiac morbidity/mortality. ACC/AHA indicates American College of Cardiology/American Heart Association; HR, heart rate; LOE, level of evidence; and MET, metabolic equivalent (Adapted from Fleisher et al. [2]. With permission from Wolters Kluwer Health)

heart rate control, or to consider testing if it will change management. In patients with three or more clinical risk factors, if the patient is undergoing vascular surgery, recent studies suggest that testing should only be considered if it will change management. In nonvascular surgery in which the perioperative morbidity related to the procedures ranges from 1 to 5 % (intermediate-risk surgery), there are insufficient data to determine the best strategy (proceeding with the planned surgery with tight heart rate control with beta-blockade or further cardiovascular testing if it will change management).

Choice of Diagnostic Test

There are multiple noninvasive diagnostic tests which have been proposed to evaluate the extent of coronary artery disease before noncardiac surgery. Although exercise electrocardiogram has been the traditional method of evaluating individuals for the presence of coronary artery disease, patients with a good exercise tolerance will rarely benefit from further testing. Therefore, pharmacologic stress testing has become popular, particularly as a preoperative test in vascular surgery patients.

Several authors have shown that the presence of a redistribution defect on dipyridamole thallium imaging in patients undergoing peripheral vascular surgery is predictive of postoperative cardiac events. In order to increase the predictive value of the test, several strategies have been suggested. Lung uptake, left ventricular cavity dilation, and redistribution defect size have all been shown to be predictive of subsequent morbidity [23]. The appearance of new or worsened regional wall motion abnormalities is considered a positive test. The advantage of this test is that it is a dynamic assessment of ventricular function. Dobutamine echocardiography has also been studied and was found to have among the best positive and negative predictive values. Poldermans et al. demonstrated that the group at greatest risk were those who demonstrated regional wall motion abnormalities at low heart rates [24]. The presence of five or more segments of new regional wall motion abnormalities denotes a high-risk group who did not benefit from perioperative beta-blockade in one trial [25]. Beattie and colleagues demonstrate that stress echocardiography has better negative predicative characteristics than thallium imaging [26]. They found that moderate-to-large perfusion defect by either test predicts postoperative MI and death.

Interventions for Patients with Documented CAD

There is increasing evidence that coronary revascularization before noncardiac surgery does not reduce the incidence of perioperative cardiac morbidity. McFalls and colleagues reported the results of a multicenter randomized trial in the Veterans Administration Health System in which patients with documented coronary artery disease on coronary angiography (CARP), excluding those with left main disease or severely depressed ejection fraction (<20 %), were randomized to coronary artery bypass grafting (CABG) (59 %) or percutaneous coronary interventions (PCI) (41 %) versus routine medical therapy [27]. At 2.7 years after randomization, mortality in the revascularization group was not significantly different (22 %) compared to the no-revascularization group (23 %). Within 30 days after the vascular operation, a postoperative myocardial infarction, defined by elevated troponin levels, occurred in 12 % of the revascularization group and 14 % of the no-revascularization group ($P = 0.37$). In a follow-up analysis, Ward and colleagues reported improved outcome in the subset of patients who underwent CABG compared to PCI [28]. Among the patients who underwent coronary angiography in both the randomized and nonrandomized portion of the CARP trial, only the subset of patients with unprotected left main disease showed a benefit with preoperative coronary artery revascularization, while there was a suggestion of benefit in those with 3-vessel disease [29]. Poldermans and colleagues randomized 770 patients having major vascular surgery and considered as having intermediate cardiac risk, defined as the presence of one or two cardiac risk factors to either undergo further risk stratification with stress imaging or proceed right to surgery [30]. All patients received preoperative bisoprolol with a targeted heart rate (HR) of 60–65 initiated before and continued after surgery. The 30-day incidence of cardiac death and nonfatal MI was similar in both groups (1.8 % in the no testing group versus 2.3 % in the tested group). The conclusion of the authors was that further risk stratification in this group of patients considered at intermediate risk based on clinical history alone was unnecessary as long as perioperative beta-blockers were used, and testing only delayed necessary vascular surgery. In a pilot study (DECREASE V), 101 patients with three or more risk factors and a markedly positive stress test were randomized to coronary revascularization versus medical therapy. In those patients in whom there was successful revascularization, there was significant improvement in long-term outcome [31]. There has been recent evidence to suggest that there are issues of quality of the DECREASE studies with respect to protocol adherence and outcome assessment, although the investigative body has determined that no studies require retraction at the time of writing this chapter.

The current evidence does not support the use of percutaneous transluminal coronary angioplasty (PTCA) beyond established indications for nonoperative patients, since the incidence of perioperative complications does not appear to be reduced in those patients in whom PTCA was performed less than 90 days prior to surgery [32]. Coronary stent placement may be a unique issue and several studies suggest that a minimum of 30 days is required before the rate of perioperative complications is low [33–36]. Several reports suggest that drug-eluting stents may represent an additional risk over a prolonged period (up to 12 months), particularly if antiplatelet agents are discontinued [37]. However, a recent case series suggests that an elevated risk continues beyond 1 year [38]. The new guidelines suggest continuing aspirin therapy in all patients with a coronary stent and discontinuing clopidogrel for as short a time interval as possible for patients with bare-metal stents <30 days or drug-eluting stents <1 year. Based upon the non-perioperative literature, there is a suggestion that holds clopidogrel for the traditional 8 days may actually increase risk associated with a hypercoagulable rebound, suggesting a shorter period of time may be optimal. A recent cohort study suggests that withdrawal of antiplatelet agents >5 days is associated with increased major adverse cardiac events.

There is now a great deal of evidence to suggest that perioperative medical therapy can be optimized in those patients

with coronary artery disease as a means of reducing perioperative cardiovascular complications. Multiple studies have demonstrated improved outcome in patients given perioperative beta-blockers, especially if heart rate is controlled, although there is recent concern regarding the quality of the studies from the Erasmus group [39, 40]. Newer studies have demonstrated that beta-blockers may not be effective if heart rate is not well controlled or in lower risk patients [41–43]. The POISE trial was published in which 8,351 high-risk beta-blocker naive patients were randomized to high-dose metoprolol CR versus placebo [44]. There was a significant reduction of the primary outcome of cardiovascular events, associated with a 30 % reduction in MI rate, but with a significantly increased rate of 30-day all-cause mortality and stroke. Patients at intermediate risk were randomized to statin therapy, beta-blocker therapy, both (started on average 30 days in advance), or double placebo. Beta-blocker therapy was associated with significantly decreased cardiovascular events, while statin therapy was not [45]. The current AHA/ACC Guidelines on perioperative beta-blockade advocate that perioperative beta-blockade is a Class I indication and should be used in patients previously on beta-blockers. The new recommendations advocate that beta-blockers titrated to heart rate and blood pressure are probably recommended for patients undergoing vascular surgery who are at high cardiac risk owing to coronary artery disease or the finding of cardiac ischemia on preoperative testing (Class IIa). The ESC Guidelines continue to advocate that both recommendations are Class I. Flu et al. demonstrated that β-blocker treatment initiated >1 week before surgery is associated with improved outcome, compared with treatment initiated <1 week preoperative which is associated with an increased risk of stroke [46]. Wallace et al. reported that perioperative β-blockade administered according to the Perioperative Cardiac Risk Reduction protocol is associated with a reduction in 30-day and 1-year mortality [47]. Perioperative withdrawal of β-blockers is associated with increased mortality. The ACC/AHA Task Force recently reaffirmed their recommendations regarding beta-blockers in light of the questions regarding some of the studies, while the ESC is currently reviewing their recommendations.

Other pharmacologic agents have also been shown to improve perioperative cardiac outcome. Alpha-2 agonists have been shown to improve both perioperative mortality and 6-month event-free survival [48]. Most recently, perioperative statins have been shown to improve cardiac outcome. Durazzo and colleagues published a randomized trial of 200 vascular surgery patients in which statins were started an average of 30 days prior to vascular surgery [49]. A significant reduction in cardiovascular complications was demonstrated using this protocol. Le Manach and colleagues demonstrated that statin withdrawal greater than 4 days was associated with a 2.9 odds ratio of increased risk of cardiac morbidity in vascular surgery [50]. Most recently, a total of 250 patients were assigned to fluvastatin, and 247 to placebo, a median of 37 days before vascular surgery [51]. Perioperative fluvastatin therapy was associated with an improvement in postoperative cardiac outcome. The recent guidelines advocate continuing statin therapy in patients currently taking statins as a Class I indication. A multimodal approach to medical management should be taken in high-risk patients.

Summary

Preoperative evaluation should focus on identifying patients with symptomatic and asymptomatic coronary artery disease and the exercise capacity of the patient. The decision to perform further diagnostic evaluation depends upon the interactions of patients and surgery-specific factors, as well as exercise capacity, and should be reserved for those at moderate risk undergoing major or intermediate surgery with poor exercise capacity. The indications for coronary interventions are the same in the perioperative period as for the nonoperative setting.

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Cardiovascular Gene Therapy

44

Thomas J. LaRocca and Roger J. Hajjar

Introduction

Cardiovascular disease (CVD) continues to be the leading cause of death in the United States with approximately 811,000 individuals succumbing to the illness in 2008, nearly 33 % of deaths from all cause. The economic costs resulting from cardiovascular disease exceed 300 billion dollars annually, approximately 16 % of total health-care costs in the United States. The total direct and indirect costs from health-care expenditures and lost productivity due to CVD are projected to increase threefold by the year 2030. Importantly, there have been significant advancements in promoting cardiovascular health and in understanding molecular pathways enabling development of novel therapeutic modalities. However, with nearly 20 million Americans diagnosed with coronary heart disease and congestive heart failure, we continue to face daunting challenges in public health. Therefore, it is critical to further develop novel cardiovascular therapeutics to meet this growing need.

Cell surface receptors, in particular G-protein-coupled receptors, have proven to be pharmacologically viable targets in small molecule design for treating cardiovascular disease, including β-blockers and angiotensin receptor antagonists. While progress in conventional treatment modalities is making steady and incremental gains to reduce CVD burden, there remains an urgent need to explore new therapeutic approaches. Gene therapy was initially envisioned as a treatment strategy for inherited monogenic disorders. It is now apparent that gene therapy has broader potential including acquired polygenic diseases, such as peripheral vascular disease, ischemic heart disease, arrhythmias, and congestive heart failure. Advances in the understanding of the molecular basis of these conditions, together with the evolution of increasingly safe and efficient gene transfer technologies, has placed cardiovascular disease within reach of gene-based therapies.

This chapter will allow the clinical cardiologist and the basic scientist to understand recent advancements in gene modifying strategies targeting diseases of the cardiovascular system. The efficacy of various gene and vector delivery systems is addressed with results from human clinical trials. While there are many promising strategies in modifying cardiovascular disease, only molecular targets that have progressed to preclinical and human clinical trials are systematically reviewed. The current cardiologist will benefit from further understanding of the techniques and rationale of cardiovascular gene therapy as this therapeutic strategy enters the clinical realm.

Gene Therapy Vectors

The development of gene transfer intervention necessitates addressing several factors to ensure high efficiency while minimizing toxicity. These include understanding target cell and transgene biology, and the temporal and spatial patterns of the specific cardiovascular pathophysiological process. In addition, the choices of gene and vector delivery systems also critically determine clinical outcomes. Answering these questions will dictate the proportion of target cells within the myocardium that need to be successfully gene-modified in order to elicit cardioprotection. For example, the creation of a biological pacemaker or inducing angiogenesis requires the focal genetic modification of only a modest number of cells within a prescribed region in the heart. In contrast, restoring myocardial contractility in the context of heart failure requires the successful gene transfer to a vast majority of cardiac myocytes in the ventricular myocardium to enable a significant impact on ventricular function. Furthermore, the required temporal pattern of transgene expression will determine the choice of gene transfer system that can be employed for

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_44,

efficient and positive results. The strategy of transient expression of angiogenic factors by plasmid-mediated gene transfer may be a useful approach in relieving anginal symptoms and myocardial ischemia. Likewise, the requirement for persistent transgene expression for conditions such as congestive heart failure would likely be necessary in order to improve the long-term survival rate of these patients. Gene delivery systems can be classified into two categories, nonviral physicochemical systems and recombinant viral systems with each having unique profiles in gene transfer expression.

Nonviral Vectors

Nonviral vectors include naked plasmid DNA, liposomal DNA complexes, polymer-carried DNA, and oligonucleotides. Plasmids are double-stranded circular DNA containing transgenes encoding proteins of interest, in addition to having enhancer and promoter sequences. The most common promoters used in plasmid DNA therapeutics include cytomegalovirus (CMV), rous sarcoma virus, and human alpha-actin. Enhancer and promoter sequences allow tissue specificity further selecting gene expression to target cells. There are several benefits to plasmid DNA vector-based systems including ease of manufacturing, low cost, and reduced risk of systemic immunological responses. However, cellular transduction using naked plasmid DNA in vivo is a relatively inefficient process and provides only transient expression, approximately 1–8 weeks. Administration of naked plasmid DNA into the systemic circulation is rapidly degraded by endo- and exonucleases through hydrolytic cleavage of DNA phosphodiester linkages and through robust hepatic clearance, both significantly contributing to reduced bioavailability. In addition, cellular entry of plasmid DNA is further compromised by electrostatic repulsion of the anionic phosphate backbone and the anionic cellular lipid membrane. Plasmid DNA cellular uptake has been shown to use receptor-mediated endocytosis; however, the scavenger receptor class remains undefined. Of the small proportion of DNA gaining cellular entry, a large fraction within the endosome is degraded due to acidification of the endosomal and lysomal compartments. The plasmid DNA must then enter the nucleus via nuclear pores to access the DNA translational machinery. These significant hurdles to efficient naked plasmid DNA transduction have led to development of liposomal and polymer-based DNA vectors.

The use of liposome-DNA complexes provides stability of plasmid DNA in the systemic circulation; however, it is cleared quickly and mainly induces expression in the lungs. Cationic lipids using N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA) and 3β[N-(N′,N′-dimethylaminoethane)-carbamoyl] cholesterol (DC-Chol) allows efficient binding of the negatively charged DNA, protection from systemic degradation, and enhances cellular entry. However, the handling of the liposomal preparation is difficult and of clinical concern. Furthermore, these liposomal complexes do not offer DNA escape mechanisms from the intracellular endosomal complex. Polymer-based DNA complexes involving polyethylenimines (PEI) and poly(amidoamine) (PAA) complexes have shown usefulness in improving gene transduction though enhanced uptake, reduced cytotoxicity, and protection from endosomal degradation [1]. PAA carboxylic modifications have further improved cellular transduction and continued development of PAAs are a promising strategy for gene delivery mechanisms [2]. Oligonucleotides including, siRNA and shRNA, also can be effectively modified or incorporated into plasmids for gene inhibition strategies.

Plasmid DNA transfection leads to transient expression due to transgene silencing induced by de novo methylation, histone modification, and heterochromatin formation. Recently identified matrix attachment region (MAR) elements have been shown to prevent transgene silencing in part by inhibiting DNA methylation leading to long-term expression in vivo [3–5]. It is hypothesized that MAR elements interact with the nuclear matrix, effectively insulating the transgene and creating independent euchromatin domains preventing methylation and heterochromatin formation [3, 6]. Incorporation of MAR elements may be a useful strategy in prolonging transgene expression in nonviral DNA-based gene transfer therapies.

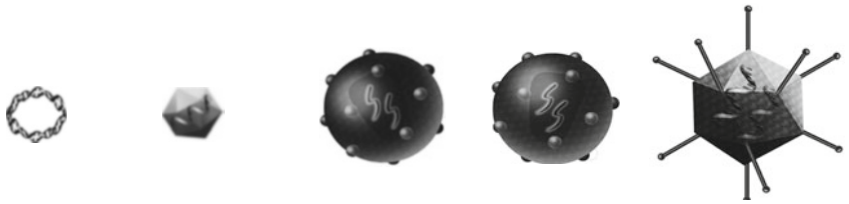
Even though targeted myocardial plasmid-mediated gene transfer is relatively inefficient and leads to transient expression, the reduced immunological response, low cost of plasmid DNA vectors, and novel strategies enhancing transgene expression have made it a common vector system employed in human clinical trials targeting cardiovascular disease (Fig. 44.1).

Viral Vectors

The predominant use of viral vectors in preclinical models of gene therapy and in human clinical trials is a reflection of the superior gene transfer efficiencies achievable with these systems. This efficiency is conferred as a result of utilizing virological elements securing favorable gene expression. The four most developed and clinically relevant viral vector systems in human clinical trials include retrovirus, lentivirus, adenovirus, and adeno-associated virus (Fig. 44.1).

Retrovirus

Viral vectors from the family *Retroviridae* include retrovirus and lentivirus. Retroviruses contain single-stranded positive-sense RNA which utilize a virally encoded reverse transcriptase to generate double-stranded DNA. In order for viral DNA integration into the host cell genome, the host cell



	Plasmid	Adeno-associated virus	Retrovirus	Lentivirus	Adenovirus
Diameter	n/a	20 nM	80–100 nM	80–100 nM	70–90 nM
Genome, size	DNA, n/a	DNA, 4.8 kb	RNA, 8 kb	RNA, 8 kb	DNA, 36 kb
Mitotic/non-mitotic transduction	Y/Y	Y/Y	Y/N	Y/Y	Y/Y
Peak cardiac expression	Days	4 weeks	n/a	Days	Days
Expression duration	-2 months	Long-term	n/a	Long-term	2 weeks
Neutralizing antibodies	-	++++	++	++	++++
Immunogencity	+	+	++++	++++	++++
Preferred myocardial delivery	IM	IC, IV	n/a	In vitro application only	IC

Fig. 44.1 Nonviral and viral vector clinical profiles

nuclear membrane must be broken down as occurs during cell division. Also, in mitotically inactive cells, retroviruses cannot proceed with complete reverse transcription in the cytoplasm due to a limited amount of available dNTPs in the cytoplasm. Therefore, retroviruses are limited to infecting dividing cells and cannot efficiently transduce nondividing cell types such as cardiomyocytes or quiescent endothelial or smooth muscle cells. Retroviruses include *gag*, *env*, and *pol* sequences which encode viral core proteins, transmembrane envelope proteins, and viral reverse transcriptase and integrase, respectively. In addition, retroviruses have a lipid bilayer envelope with transmembrane proteins necessary for cell binding and fusion. Retroviruses must be made replication deficient for gene therapy to prevent viral replication and subsequent host cell lysis and death. The *gag*, *env*, and *pol* are deleted allowing insertion of the gene of interest up to 8–10 kb into the viral genome. Viral production is achieved through the use of helper cell lines such as HEK293T transfected with *gag, env*, and *pol* plasmids. The integration of the gene of interest into the host cell genome allows for long-term expression for therapeutic efficacy. However, a major limitation of retroviruses in clinical gene therapy is insertional mutagenesis [7]. Retroviral DNA integration is a pseudorandom process integrating primarily in promoter and enhancer regions of the host cell genome. Retroviruses based on the Moloney murine leukemia virus have been extensively used in preclinical and clinical trials. In the human clinical trial of gene therapy for X-linked severe combined immunodeficiency (X-SCID), Moloney-based retroviruses encoding for the γc cytokine receptor which is deficient in X-SCID patients resulted in significant immunological improvement; however, 5 out of a total of 20 patients developed T-cell acute lymphoblastic leukemia (T-ALL) approximately 3 years post-gene therapy, with one fatality. This was due to insertion of the viral genome near the T-cell proto-oncogene Lim-only 2 (LMO-2) promoter [8–10]. As a result there has been renewed interest in improving vector biosafety. Modifications such as the use of self-inactivating vectors, the introduction of insulator sequences, and targeting of genome integration sites are potential methods reducing the risk of insertional mutagenesis [8, 9, 11]. The role of retroviruses in cardiovascular gene therapy is currently limited to research applications.

Lentivirus Vectors

Lentiviral vectors, also from the family *Retroviridae*, are similar to MoMLV-based vectors, being ssRNA viruses utilizing reverse transcriptase and genome integration for long-term expression of transgenes. Lentiviral vectors have the same gag, pol, and env genes but also contain six other genes (rev, tat, nef, vpr, vpu, and vif) necessary for binding, fusion, and viral replication. In contrast to gammaretroviruses, such as murine leukemia viruses, lentiviral vectors are capable of transducing mitotically quiescent cells allowing for efficient transduction of cardiomyocytes and do not have the same predilection to activating proto-oncogenes. The lentiviral pre-integration complex contains a nuclear localization signal allowing transport across the nuclear membrane via nuclear pore complexes of nondividing cells [12]. The most commonly used lentiviral vector system is based on the

human immunodeficiency virus type 1 (HIV-1). Vector biosafety concerns associated with HIV-1 have led to viral modifications of associated genes and the development of non-primate lentiviruses such as feline immunodeficiency virus (FIV), bovine immunodeficiency virus (BIV), and equine infectious anemia virus (EIAV). These non-primate lentiviral vectors do not induce seroconversion in humans, allow a large transgene carrying capacity (8–10 kb), and can be manufactured in high titre. Several human clinical trials of lentiviral vectors have shown promise for various disorders including ADA-deficient SCID (Clinical Trial ID: NCT01380990) and HIV infection [13–15]. The safety and efficacy of these human clinical trials and the feature of long-term expression of transgenes in nondividing cells are critical in further developing lentiviral-based therapies for human cardiovascular disease.

Adenoviral Vectors

Adenovirus, from the family *Adenoviridae,* consists of seven species (adenovirus A–G) with 57 serotypes identified. Adenovirus (Adv) is pathogenic in humans and is the cause of 5–10 % of upper respiratory infections in the pediatric population, commonly Adv B and C. Adv also can lead to gastroenteritis, genitourinary infections, and pneumonia, especially in immunocompromised patients. Adv is a non-enveloped, non-integrating virus containing double-stranded DNA with two main transcriptional regions, early and late phase. Early phase encodes E1, E2, E3, and E4 viral proteins which are necessary for activating the S phase of the cell cycle, DNA polymerase, and splicing proteins. Late-phase regions encode proteins involved in capsid coat production resulting in viral particle assembly. However, the E1–4 proteins elicit a significant innate immune response which is the major therapeutic challenge in using adenovirus in human applications. Third-generation "gutless" adenoviral vectors with E1–4 deleted have a lower immunogenicity profile and partially overcome this obstacle. This allows for the packaging of large transgenes, up to 36 kb. Adenoviruses have large protein complexes which bind to CD46 or coxsackie-adenovirus receptor (CAR) depending on the serotype for viral binding and cellular entry. The αv integrin is also a necessary co-receptor for efficient Adv binding and entry [16]. Upon cellular entry via clathrin-mediated endocytosis, the dsDNA is transported to the nucleus across nuclear pores. This allows the efficient transduction of both mitotic and non-mitotic cells. CAR is expressed on the major cell types of the heart, including the cardiac myocyte enabling efficient transduction in the myocardium. However, CAR is present on many other organ systems which lead to significant expression in nontarget organs, such as the liver. Modifying the capsid coat proteins has been shown to enhance cardiac tropism to a degree; however, these attempts have failed to limit the expression of adenovirus in nontarget organs. Importantly, Adv transgene expression is robust, yet transient. Transgene expression levels peak within 2–3 days, but return to undetectable levels by 2 weeks. This imposes therapeutic challenges for chronic pathological processes such as congestive heart failure, but may be appropriate for pro-angiogenic responses needed post-myocardial infarction. Human clinical trials using Adv2 or Adv5 have been primarily focused on transduction of pro-angiogenic factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and hypoxia-inducible factor 1α (HIF1a) to stimulate angiogenesis during myocardial ischemia. These methods are also being extensively studied in peripheral arterial occlusive disease and limb ischemia [17, 18]. The strengths of this vector system are the relative ease of production both in the laboratory and in human applications, ability to generate high functional vector titres, and the stability of developed titres. Particular disadvantages of Adv vectors are the presence of systemic neutralizing antibodies and the highly immunogenic potential of these viruses. Adenovirus elicits robust innate immune responses which can severely compromise organ function and patient health [19]. Third-generation gutless, or helper dependent, Adv have diminished immunogenic potential; however, significant risk remains. Due to these limiting factors, adenoviral-mediated strategies are declining in prevalence for cardiovascular gene therapy trials.

Adeno-Associated Virus (AAV) Vectors

Adeno-associated viruses are members of the family *Parvoviridae* and are non-enveloped, single-stranded DNA viruses. AAV are relatively small (20 nm) and therefore are limited in their genome capacity of 4.7 kb. The AAV genome consists of *Rep* and *Cap* which encode for 4 replication proteins and 3 capsid proteins (VP1, VP2, and VP3) via alternative splicing mechanisms [20, 21]. AAV is not known to cause human pathology and elicits a reduced adaptive and innate immune response as compared to other viral vectors. There are 13 reported serotypes of AAV with varying degrees of tissue tropism depending on capsid protein structure. AAV1, 6, 8, and 9 have been identified as being the most cardiotropic; however, significant transduction in nontarget tissues such as liver, skeletal muscle, and lung persists. Various methods have improved AAV cardiotropism through directed evolution utilizing DNA shuffling of capsid sequences with error-prone polymerases or development of chimeric AAV capsid structures of different serotypes. The novel viral capsid AAV libraries can be purified from myocardial tissue after multiple sequential intravenous inoculations, therefore enriching for the

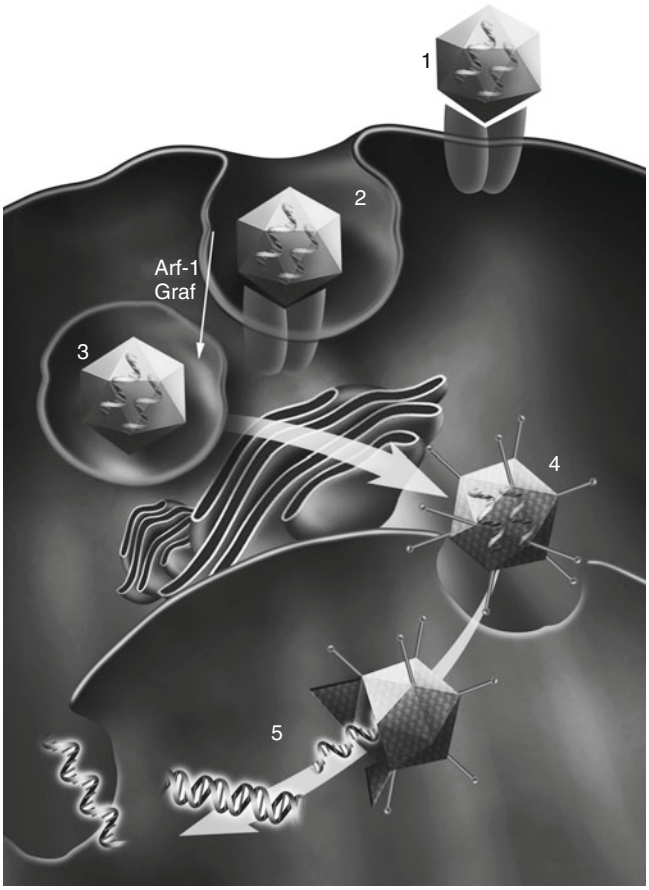


Fig. 44.2 Adeno-associated viral cellular entry and transduction. (*1*) AAV binding to cell surface receptors is primarily mediated by proteoglycan receptors, such as O- or N-linked sugars and often a protein co-receptor including various integrins, hepatocyte growth factor, or laminin for efficient binding and cellular transduction. (*2*) AAV binding induces endocytosis which was originally thought to be mediated by a clathrin-dependent mechanism; however, recent work suggests a clathrin-independent mechanism utilizing cholesterol, cdc42, Arf1, and Graf1. These components comprise the clathrin-independent carriers/GPI-linked enriched endocytic compartment (CLIC/GEEC). (*3*) Upon endosomal entry, AAV are shuttled via retrograde transport through the trans-Golgi network. During this transport process, the acidification of the endosomal compartment induces conformational changes in AAV capsid proteins. (*4*) VP1 N-terminus is exposed revealing a phospholipase A2, BC1, and BC2 domains which may act as nuclear localization signals. (*5*) Upon viral entry into the nucleus, AAV undergoes uncoating and capsid disassembly releasing their genome for DNA double strand synthesis and transcription

most cardiotropic AAV. This strategy not only can be used to enhance tissue tropism but can be utilized to produce AAV to evade naturally occurring neutralizing antibodies [22–26]. Neutralizing antibodies to various AAV serotypes are present in approximately 20–80 % of the population, therefore severely limiting potential therapeutic use of AAV and are major exclusion criteria in many AAV-based clinical trials [27]. Strategies such as directed evolution as well as chemical modification of capsid proteins by conjugation of polyethylene glycol may partially circumvent the presence of neutralizing antibodies. AAV cellular entry is dependent on viral binding to heparin sulfate moieties. Upon binding, endocytosis is mediated by clathrin-independent carriers (CLIC), a high-volume endocytotic mechanism allowing large quantities of virion cellular entry. Internalization is mediated by GPI-anchored protein enriched endosomal compartments (GEEC) and transported to the Golgi apparatus through Arf-1 and Graf (Fig. 44.2). Dynamin-mediated endocytosis also plays a role in internal trafficking of AAV, but to a much lesser degree than CLIC/GEEC pathways [28, 29]. Wild-type AAV integrates at a specific noncoding region called AAVS1 on Chr19q13.3; however, recombinant AAV used for human gene therapy clinical trials is non-integrating. The genomes form episomal concatamers providing long-term transgene expression throughout the life of the host cell. AAV can infect both dividing and nondividing cell types making it an attractive vector for cardiovascular gene therapy. AAV can induce global and stable gene expression throughout the heart which is advantageous for chronic disease such as congestive heart failure.

Transcriptional Regulation of Transgenes

The various vector systems all have different expression kinetics and tissue tropisms which must be taken into account when designing human gene therapy trials. Nonspecific expression and off-target effects are an obstacle for any therapeutic modality. Cytomegalovirus (CMV) promoter sequences are commonly used in human gene therapy trials and allow for rapid and robust expression of the transgene, however, and also lead to nonspecific, off-target transgene expression. Viral promoters are convenient in gene therapy due to their small size and ease of manipulation in the genomic construct. Other nonspecific promoters such as chicken β-actin and eIF1-α have also shown utility in gene therapy producing long-term expression of transgenes. However, the restriction of the transgene to the target tissue is critical, especially due to the wide tissue tropisms of viral vectors, to minimize potential systemic toxicities. One method to enhance specificity of transgene expression is to utilize cell-specific promoter sequences. In regard to cardiac gene therapy, α-myosin heavy chain, myosin light chain kinase-2, and troponin T promoters have shown success in restricting transgene expression to the cardiac myocyte [30, 31]. In addition, the use of human brain natriuretic peptide promoters increases cardiac myocyte specificity and transgene regulation upon increased ventricular wall stress. Strategies utilizing hypoxia response elements and HIF1α promoters can be useful in restricting transgene expression during myocardial ischemia, such as acute MI and/or unstable angina [32, 33]. These ischemia-inducible constructs are

an attractive approach in maintaining and initiating angiogenic responses. Finally, methods to temporally restrict transgene expression using ligand-inducible promoters may be suitable to turn on transgene expression when clinically necessary, including acute decompensated heart failure. This could be achieved through a tetracycline-on (Tet-on) system using the tetracycline resistance operon. The mutant reverse tet-repressors enable the tet-transactivator to bind to the response element and initiate transgene expression upon tetracycline administration [34]. The rapamycin-inducible system using FK-506-binding protein (FKBP) and FKBP12-rapamycin-associated protein (FRAP) dimerization has also been successful in temporally regulating transgene expression [35]. Importantly, cell-specific eukaryotic promoters generally lead to reduced transgene expression levels and delayed onset. In addition, virion packaging constraints must be considered when designing cell-specific promoters and viral vectors. These strategies must be optimized and selected according to the molecular target/transgene of interest and the disease process involved.

Vector Delivery Systems

The selection of the vector delivery modality is critical to proper implementation of therapeutic strategy and to efficient transgene expression in the myocardium. As discussed previously, vectors have unique profiles of bioavailability, transgene expression kinetics, and tissue tropisms, therefore it is vital to choose a vector delivery method which complements the vector as well as the disease process. Importantly, invasiveness of vector delivery method and patient safety need critical assessment prior to initiating gene therapy trials for cardiovascular disease.

Intravenous Injection

The infusion of vectors into the systemic venous circulation is noninvasive and safe to moderately and severely ill patients. The advantages of patient safety and the potential of homogenous myocardial transduction make this an attractive vector delivery method. However, intravenous injection has multiple disadvantages for several vector systems. First, there is significant dilution of vector upon systemic injection necessitating high doses of vector administration. Viral vectors, such as adenovirus and AAV, need to be administered in high titres for sufficient transduction of the myocardium increasing the risk of an immunological response as well as significant transduction of nontarget tissues. Nonviral vectors such as cationic-liposomal DNA complexes or plasmid DNA are rapidly degraded and have high first-pass clearance by liver, lungs, and kidney preventing efficient myocardial gene transfer. However, there are strategies which are improving intravenous vector administration. As discussed previously, enhanced cardiotropic viral vectors improve cardiac transduction and limit nontarget tissue gene transfer. Additionally, application via Swan-Ganz catheter or ultrasound-guided cationic microbubble technique can aid in nonviral targeting of myocardial tissue [36]. Further development of these strategies will ultimately enable noninvasive intravenous administration of nonviral and viral vectors a more efficient and reliable method.

Percutaneous Transluminal Delivery

Percutaneous catheter-based gene delivery is also a safe and minimally invasive strategy in cardiac gene transfer which is advantageous to the hemodynamically unstable patient diagnosed with congestive heart failure. The two cardiac catheterization-based strategies incorporate an antegrade or a retrograde approach to viral vector administration. Antegrade coronary injection of viral vectors through fluoroscopy provides efficient homogenous ventricular myocardial transduction with minimal risk to the patient. This approach provides focused administration of the vector to the ventricles and when given in low-dose and continuous infusion, limits systemic circulation of virus and nontarget effects [37, 38]. However, the endothelium remains a significant barrier for viral transduction of cardiac myocytes. Cardiac catheterization allows higher titres with a focused administration and can be used to prolong coronary perfusion time and myocardial contact. Coronary balloon catheters provide very controlled release and prevent vector dilution to the coronary circulation distal to balloon occlusion. However, this does increase the risk to the patient where episodes of transient ischemia may not be tolerated. In parallel, application of the venous balloon catheter in the coronary sinus impedes coronary flow allowing increased vector contact time to the ventricular myocardium [37]. Additionally, pharmacologic manipulation of the endothelial barrier can improve transduction efficiencies. The concomitant use of vasodilatory agents such as adenosine, VEGF, nitroprusside, and nitroglycerin improves myocardial viral transduction [39, 40]. Nitroglycerin has a rapid onset, short half-life, and minimal action on systemic vasodilation making this suitable in patients with end-stage heart failure. Indeed, studies have clearly shown the utility of coadministration of nitroglycerin and rAAV in enhancing gene transfer [41]. Importantly, antegrade techniques are not suitable when coronary vessels are infarcted due atherosclerosis and thrombosis or with significant coronary artery disease. The retrograde infusion approach resolves this issue. Balloon catheter advancement into the coronary sinus allows for viral vectors to advance unimpeded in healthy coronary veins and prolongs contact

time for efficient transduction. A novel platform for vector administration utilizes an extracorporeal closed circuit enhancing vector myocardial exposure, termed V-focus delivery system. Vector administration via a coronary catheter is perfused into the coronary circulation. The coronary venous outflow is subsequently routed to a small-volume oxygenator and readministered into the coronary catheter for a repeated pass into the coronary circulation. This process limits systemic exposure of vector and significantly increases vector contact time with the myocardium [42, 43].

Direct Intramyocardial Delivery

Direct myocardial injection can be done percutaneously for endocardial delivery or surgically for epicardial application. In percutaneous direct endocardial delivery, vector administration is limited to focal gene transfer to the myocardium. This method of vector delivery and pattern of gene transfer lends itself most readily to applications such as therapeutic angiogenesis and to a lesser extent focal arrhythmia therapy. Gene delivery can be achieved using steerable needle-tip catheters through which vector may be injected to predetermined regions of endocardium. The catheter tip can be guided by fluoroscopy or by intracardiac echocardiography. Importantly, the non-fluoroscopic electromechanical mapping system is highly suited for endocardial gene transfer. The NOGA® system is capable of identifying viable, nonviable, and ischemic myocardium. The electrical map generated by unipolar and bipolar voltages, coupled with local linear shortening (LLS), combines electrical and wall motion properties generating a three-dimensional, high-resolution reconstruction of LV myocardium. This greatly aids in guiding delivery catheters for gene transfer interventions such as therapeutic angiogenesis to ischemic myocardium. The feasibility, safety, and potential efficacy of this approach have been established in human clinical trials of patients with medically refractory severe angina and ischemic heart disease [44, 45].

In contrast, surgically invasive intramyocardial administration of vector is generally unsuitable for many patients in end-stage congestive heart failure due to the strains of anesthesia and surgery and therefore limits its applicability to specific cardiovascular complaints. Direct vector delivery to the myocardium by multiple injections is an established technique and proven to be efficacious and safe in multiple clinical trials. Direct injection into multiple sites, commonly the left ventricular free wall secondary to left anterior descending infarction, results in a mosaic pattern of transgene expression in the epicardium. This method is highly efficacious for plasmid DNA vectors as you can directly target the myocardium without risk of vector degradation or nontarget tissue effects. This also allows vectors to circumvent potential barriers to cardiac myocyte transgene expression such as the endothelium, first-pass clearance, and systemic degradation. In addition, viral vector direct application to the myocardium also provides focused expression of transgenes and eliminates the effects of circulating neutralizing antibodies. However, direct myocardial injection does carry clinical risk. The invasiveness of the procedure increases morbidity and mortality, and an acute inflammatory response to physical injury from sites of injection could impair transgene expression and worsen myocardial dysfunction [46]. In addition, sterile abscess formation is a potential complication with direct myocardial injections [47]. Sterile abscesses are commonly formed at sites of vaccine injection or implantation of a medical device and are treated surgically; however, myocardial sterile abscesses are particularly difficult to treat and a feared complication. Overall, direct myocardial injection is a safe and robust technique in expressing transgenes in the human heart but does carry inherent risks which must be evaluated when determining clinical benefit.

Pericardial Delivery

The human pericardium is easily accessible through a percutaneous approach providing a safe route for vector administration to the epicardium. The human pericardial sac contains about 15–50 ml of fluid providing lubrication of cardiac visceral and parietal layers. Pericardial fluid through its ability to evenly distribute forces across the entire heart helps maintain uniform ventricular contraction. The pericardium also enables vector administration to have prolonged contact time to the epicardium. However, transgene expression efficiency is generally limited to the superficial epicardium and pericardial layers. Novel uses of various substances have increased epicardial transduction such as the development of porcine gelatin granules, termed Gelfoam, which can be treated with viral vectors. Application of slow dissolving, biodegradable gelatin granules provides lasting exposure of vector to the epicardium thereby enhancing transduction [48]. Pericardial delivery provides a safe and minimally invasive approach, yet risks of pericardial effusion, cardiac tamponade, and pneumothorax are serious complications of this method.

Molecular Targets for Therapeutic Intervention

The recent advances in gene therapy vector design and delivery has enabled the development of multiple molecular targets for therapeutic intervention in cardiovascular disease. Promising therapeutic targets discovered on the bench now have an additional therapeutic approach to regulating myocardial function in the clinic. There are several major

myocardial signaling pathways with advanced development through human clinical gene therapy trials including the β-adrenergic cascade, calcium homeostasis, angiogenesis, and chemokine signaling.

The Beta-Adrenergic Signaling Cascade

7-Transmembrane receptors (7TMRs) in the heart are the most abundant class of receptors in the cardiac myocyte and have been targets for the two most widely used and successful pharmacological therapies for congestive heart failure, β-adrenergic and angiotensin receptor blockers (ARB). The progression of a diseased heart to symptomatic cardiac failure is a complex molecular process. β-adrenergic receptors are fundamental in regulating cardiac myocyte contractility and cell survival and underlie many of the mechanisms involved in heart failure progression. β-ARs consist of three subtypes in the heart, including β1, β2, and β3. β1-AR and β2-AR are the predominant isoforms in the heart with a lesser contribution from β3-AR. The Gi-coupled β3-AR has recently been shown to have a cardioprotective function in pressure overload-induced heart failure through promoting eNOS and PKG activity [49, 50]. Further mechanistic insight into β3-AR cardioprotection is only now being addressed. In comparison, the Gs-coupled β1-AR and Gi/Gs-coupled β2-AR are well known to be involved in heart failure pathogenesis. In the healthy myocardium, β1-AR is more prevalent than β2-AR by an approximately 80:20 ratio. In congestive heart failure, β1-AR signaling is excessive due to neurohumoral activation via epinephrine and norepinephrine. The increased β1-AR-Gs pathway yields maladaptive transformation in the cardiac myocyte inducing hypertrophy, diastolic calcium overload, and altered gene expression [51]. This leads to uncoupling of β1-AR from Gs, receptor desensitization, and subsequent reduction in contractility and systolic failure. These remodeling mechanisms lead to increased apoptosis in the heart, fibrosis, and further myocardial dysfunction [52]. In compensation, the cardiac myocyte upregulates the potentially cardioprotective β2-AR. β2-AR couples to both Gs and Gi and switches to mainly Gi to counteract increased Gs activity in CHF. The β1-AR:β2-AR ratio reduces to approximately 50:50 in heart failure. It has been shown that enhanced β2-AR augments cardioprotective anti-apoptotic pathways. Chronically, however, when the cardioprotective effects of β2-AR are overcome, β1-AR is further uncoupled, accelerating ventricular dysfunction and heart failure onset.

Beta-adrenergic receptor density and desensitization is a critical mechanism for decreased neurohumoral responses in the heart leading to worsening of CHF. Therapies aimed at restoring physiological β-adrenergic signaling may mitigate this effect. Upon ligand binding to β1-AR, a conformational change within the receptor alters the cytoplasmic face (intracellular loops 1–3) and C-terminus initiating G-protein activation through the exchange of GDP for GTP. The G-protein is comprised of three subunits, G α, β, and γ. The G αs-GTP monomer activates adenylyl cyclase generating cAMP. Cyclic AMP binds the regulatory subunits of PKA releasing the catalytic subunits to phosphorylate downstream targets including phospholamban (PLB), troponin I, and L-type calcium channels enhancing contractility and relaxation in the cardiac myocyte [53]. Cellular termination of the 7TMR signal is tightly regulated through a series of phosphorylating events of the carboxyl-terminus involving G-protein receptor kinases (GRK) resulting in receptor desensitization, internalization, and intracellular trafficking. GRK phosphorylates specific serine/threonine residues of the carboxyl-terminus leading to the recruitment of β-arrestins [54–56]. β-arrestins are a family of scaffolding proteins which when bound to the 7TMR participate in receptor desensitization through steric hindrance of G-protein activation and function as a key component for receptor internalization. There are 4 β-arrestin subtypes with β-arrestin 1 and 2 the most prevalent in the cardiac myocyte. It has been recognized that certain ligands to a 7TMR, including β1-AR, can recruit β-arrestins without activating G-proteins and initiate cardioprotective extracellular signal-regulated kinase (Erk1/2) signaling pathways via EGFR transactivation [54–56]. This biased agonism, or pluridimensional efficacy, allows for the development of novel pharmacological strategies and potential gene therapeutic targets aimed at the β1-AR signaling system. Pharmacologically based clinical trials are ongoing; however, are outside the scope of this chapter [54–56].

G-protein receptor kinase-2, formerly known as β-adrenergic receptor kinase-1 (βARK1), is the most prevalent of the GRK family in the cardiac myocyte. Studies have shown GRK2 is upregulated in the myocardium in animal models of heart failure as well as in humans with CHF [57]. Investigators determined GRK2 was critical in internalizing β1-AR, and enhancing GRK2 through overexpression techniques induced systolic failure in the cardiac myocyte through enhanced β1-AR desensitization. Small molecule development was challenging due to the intracellular location of GRK2; therefore, peptides were developed to inhibit the function of GRK2 as a possible therapeutic approach to heart failure. βARKct is a carboxyl-terminal peptide sequence of GRK2 binding the βγ-subunit and preventing GRK2-mediated phosphorylation and internalization of β1-AR. As a peptide, βARKct was engineered into an AAV vector construct as a potential candidate for gene therapy for CHF [58]. In preclinical trials using a large animal porcine model of heart failure, administration of AAV6 encoding βARKct to the failing porcine myocardium yielded improved left ventricular hemodynamics and decreased cardiac myocyte apoptosis 6 weeks post-gene transfer [59]. In addition, AAV6.βARKct

induced positive inotropic effects on isolated human failing cardiac myocytes in vitro [60]. Taken together, these results are promising for the development of a human clinical trial involving intracoronary injection of AAV6.βARKct in patients with end-stage congestive heart failure.

Adenylyl cyclases (AC) are also promising therapeutic targets for CHF. There are multiple subtypes of AC in the cardiac myocyte with AC5 and AC6 as the most predominant. AC5 and AC6 have a 65 % sequence homology and were originally thought to have redundant mechanisms in the heart; however, it is now known that they have unique and opposing capabilities in the cardiac myocyte. β1-AR agonism induces cAMP through both AC5 and AC6. However, deletion of AC5 improves cardiac function in pacing models of heart failure in dogs, while AC6 deletion is detrimental to cardiac function. These opposing effects could be due to several mechanisms including differential compartmentalization and unique signaling capabilities independent of cAMP of AC5 and AC6 [61–63]. In parallel, studies have determined that AC6 overexpression yields improvement in cardiac myocyte survival, contractility, and SERCA2a function, and this benefit is independent of cAMP in in vitro and in vivo heart failure models. A catalytically inactive AC6 mutant, which does not produce cAMP, continued to yield benefit on LV function through multiple mechanisms including enhancing Akt phosphorylation, improving contractility via SERCA2a function, and promoting cellular survival [64]. These results have led to the development of AC6 overexpression via gene therapy in patients diagnosed with congestive heart failure. Preclinical studies using intracoronary injection of adenovirus encoding AC6, along with nitroprusside to facilitate transgene expression, promoted left ventricular function and reduced hypertrophy and fibrosis in the myocardium in a porcine model of heart failure [65]. Phase I/II clinical trials using Adv.hAC6 in treating congestive heart failure are currently recruiting patients (*Clinical Trials.gov*: NCT00787059).

Calcium Homeostasis

Cardiac myocyte calcium homeostasis is central to myocyte physiology, and disturbances in calcium handling are one of the major underlying etiologies in congestive heart failure. Briefly, upon cardiac myocyte depolarization, voltage-dependent L-Type calcium channels open allowing calcium movement into the cell down its electrochemical gradient. This small rise in intracellular calcium enables ryanodine receptors to adopt a conformation enabling the release of large sarcoplasmic reticular stores of calcium. Diastolic intracellular calcium is approximately 1uM, but upon Ryr opening, calcium reach peak levels of 1 mM. Calcium binds to troponin C conformationally shifting actin allowing myocyte cross bridging, ATP hydrolysis, and contraction to occur. Relaxation results when calcium is displaced by troponin I and subsequent Ca^{2+} reuptake into the SR by the sarco-endoplasmic reticulum Ca^{2+}-ATPase (SERCA2a). The endogenous SERCA2a inhibitor, phospholamban (PLB), sterically hinders SERCA2a; however, phosphorylation of PLB ser16/thr17 residues by cAMP-PKA relieves inhibition and enhances SERCA2a function. SERCA2a is fundamental to refilling SR calcium stores for further, efficient contractions.

In congestive heart failure, SERCA2a function and content is reduced. In failing human cardiac myocytes, both PLB phosphorylation and SERCA2a protein is diminished leading to depressed calcium reuptake and lower SR calcium stores eliciting reduced contractile responses and subsequent systolic failure. Pharmacological intervention to the SERCA2a-PLB complex has proven difficult, in part, due to small molecule access to intracellular sites. However, SERCA2a gene therapy has been shown to be a viable method in restoring SERCA2a function and SR calcium stores and enhancing myocardial systolic function. Initial gene transfer studies in small animal models of heart failure using adenovirus encoding SERCA2a indicated improvement in peak calcium transients, myocyte contraction, and ventricular function [66]. In addition, isolation of failing human cardiac myocytes also showed improvement in SR calcium load and contractile parameters [67]. However, these studies were limited by only transient expression secondary to adenoviral vector making homogenous and sustained expression difficult to achieve. Aortic cross clamping procedures improved homogenous myocardial SERCA2a gene transfer by creating a closed coronary circuit increasing viral contact time to the myocardium. However, aortic cross clamping is an invasive procedure and in failing myocardium often intolerable and not clinically transferable.

The development and design of new viral vectors was critical in allowing efficient and safe gene transfer in the clinic. In a preclinical porcine model of heart failure, recombinant adeno-associated virus-1 (AAV1) driven by a CMV promoter not only improved expression but allowed for sustained transgene expression after gene transfer which is clinically useful in chronic disease processes such as congestive heart failure. This study employed a clinically transferable vector delivery method utilizing AAV1.SERCA2a intracoronary infusion via a percutaneous approach yielding homogenous myocardial expression with improved ventricular hemodynamics [43, 68]. Importantly, none of the study animals treated with AAV1.SERCA2a suffered from a fatal arrhythmic event [69]. These results led to the design of clinical trials to test AAV1.SERCA2a gene therapy as a treatment modality for congestive heart failure in humans.

The Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID) Trial is

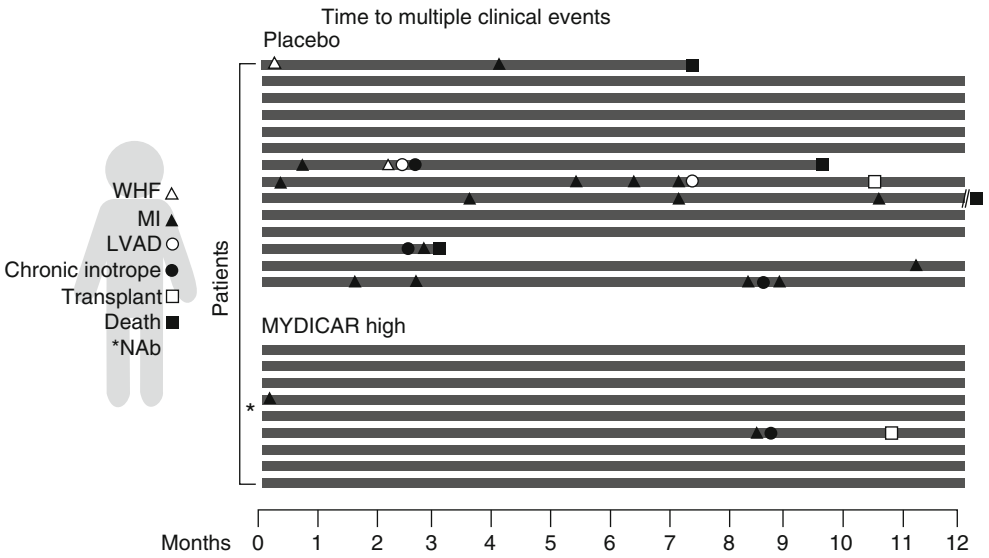


Fig. 44.3 CUPID Trial Phase II study of AAV1.SERCa2A (MYDICAR) in patients diagnosed with NYHA III/IV heart failure. Fourteen patients, each represented by a *line*, received placebo while nine patients received high dose of AAV1.SERCA2a. Patients were monitored for 12 months for time to multiple clinical events as defined by worsening heart failure (*WHF*), myocardial infarction (*MI*), left ventricular assist device placement (*LVAD*), inotrope use, cardiac transplantation, or death. The hazard ratios were calculated using a joint frailty model. The hazard ratios and respective confidence intervals at 12 months versus placebo for recurrent clinical events adjusted for correlated terminal events (left ventricular assist device, transplantation, death) is 0.12 (0.03–0.49) ($P=0.003$) for high-dose (1×10^{13} DNase resistant particles) MYDICAR ($n=9$) AAV1.SERCA2a, with $n=14$ in the placebo control group

an FDA-approved Phase I/II study in determining the safety and efficacy of AAV1.SERCA2a gene therapy in humans (*Clinical Trials.gov: NCT00454818)*. Patient inclusionary criteria included diagnosis of New York Heart Association (NYHA) Class III/IV and, specifically, the absence of circulating AAV1 neutralizing antibodies. The 39 patients enrolled in the study were administered either placebo, low, mid, or high dose of AAV1.SERCA2a. Importantly, patients administered the high dose of AAV1.SERCA2a had significant improvement in the 6-minute walk test as well as reductions in left ventricular end-diastolic volume and brain natriuretic peptide (BNP). Furthermore, individuals administered the high dose of AAV1.SERCA2a had a significant reduction in time to multiple clinical events which included MI, inotrope use, LVAD placement, cardiac transplantation, and death (Fig. 44.3) [70]. These positive results and tolerability data of AAV1.SERCA2a in humans have led to the design of a larger Phase III clinical trial for the treatment of congestive heart failure.

As described, SERCA2a is a central molecular mechanism for cardiac myocyte calcium homeostasis and shown to be a viable therapeutic target. Therefore, endogenous regulators of SERCA2a may have potential therapeutic promise. SERCA2a is posttranslationally modified by several mechanisms including glutathiolation and nitration. Specifically, SUMOylation has been identified as being a critical post-translational modification (PTM) of SERCA2a in cardiac myocytes. SUMO, small ubiquitin-like modifier, is involved in several cellular processes including protein localization, altering binding partners, and, importantly, improving protein stability. In patients with CHF and in animal models of heart failure, SUMOylated SERCA2a is reduced. SUMO1 PTM acts by enhancing SERCA2a ATPase activity by sumoylating lysine residues 480 and 585 in a conserved recognition motif. Additionally, SUMOylation prevents the ubiquitination and degradation of SERCA2a, thereby increasing its stability in the cardiac myocyte. In a therapeutic designed experiment in a small animal model of heart failure, AAV9.SUMO1 administration to animals already in CHF significantly improved ventricular hemodynamics post-gene transfer [71]. Preclinical trials testing AAV1.SUMO1 in porcine models of heart failure have been initiated.

S100A1 is also a primary regulator of contractile and relaxation responses in the cardiac myocyte. S100 proteins are the largest EF-hand superfamily of homodimeric calcium-binding proteins, similar to calmodulin, mediating various processes including calcium homeostasis, inflammation, cell cycle progression, apoptosis, and cellular differentiation [72, 73]. There are over 25 subtypes of S100 proteins with S100A1 being the most prevalent in cardiac myocytes. S100A1 has been shown to be central for normal cardiovascular development via interactions with key proteins involved in cardiac myocyte calcium homeostasis and contractility, as well as being downregulated in human cardiomyopathy [73–75]. S100A1 diminishes diastolic Ryr calcium leak and enhances SERCA2a enzymatic activity in myocyte dysfunction [76]. It also has been shown to promote mitochondrial function and optimize interactions of the sarcomeric contractile

apparatus through associations with titin [77]. In failing human myocardium and various small and large animal models of heart failure, S100A1 is significantly downregulated associated with reduced SR Ca load, decreased peak calcium transients, and contractile dysfunction. Importantly, in isolated failing human cardiac myocytes, adenoviral-mediated gene transfer of S100A1 in vitro restores contractile and relaxation processes through improvement of calcium handling [78]. A preclinical post-ischemic porcine model of heart failure via balloon occlusion of the left circumflex artery utilizing AAV9.S100A1 further showed improved EF, increased d*P*/d*T* max, restored left ventricular dimensions, and reduced circulating BNP [79]. S100A1 is a promising target for gene therapy in part by its positive effect on SERCA2a activity and impact on calcium homeostasis in the cardiac myocyte. A clinical trial Phase I/II for AAV9.S100A1 gene therapy for congestive heart failure in humans is currently being developed.

Angiogenesis

Angiogenic gene therapy is an attractive approach for ischemic disease including peripheral arterial disease as well as coronary artery disease. There have been several clinical trials using plasmid-based gene transfer of many pro-angiogenic factors including VEGF, FGF, Del-1, and HGF [80]. In peripheral arterial disease, many of these factors have progressed through human clinical trials with pHGF as the most promising. pHGF is currently in Phase III clinical trials and given fast-track status by the US FDA for severe PAD with significant improvements observed in vessel formation, walking distance, and time to claudication (*Clinical Trials.gov*: NCT00189540*)* [81, 82]. However, clinical translation into coronary arterial disease has proven more difficult. VEGF, vascular endothelial growth factor, is the only pro-angiogenic factor to be employed in the setting of gene therapy for ischemic heart disease. VEGF, a member of the platelet-derived growth factor family, is comprised of 5 subfamilies of VEGF-A, B, C, D, and E. VEGF-A is the primary pro-angiogenic factor which has been investigated for promoting angiogenesis in CAD. VEGF is composed of 8 exons with alternative splicing producing several isoforms, including the pro-angiogenic VEGF165a. VEGF165a is a homodimeric protein binding primarily to the tyrosine kinase receptor, VEGF-R2/FLK1. VEGF165a expression is regulated by hypoxia-inducible factor (HIF1α) promoting angiogenesis in ischemic microenvironments.

A major obstacle in plasmid-based angiogenic gene therapy is identifying areas of ischemia and nonviable myocardium for efficient gene transfer. Percutaneous electromechanical mapping of the endocardium using a NOGA-based system, as discussed previously, has greatly overcome this barrier and has been used for several human clinical trials for VEGF gene transfer in patients with severe angina or ischemic heart disease. Unfortunately, human clinical trials for plasmid-based VEGF gene therapy have shown not to enhance myocardial perfusion or improve patient functional outcomes. The EuroInject One and NORTHERN clinical trials were the largest gene transfer studies for VEGF in patients with ischemic heart disease. However, both trials determined no clinical improvement in myocardial perfusion using NOGA-guided endomyocardial gene transfer of varying doses of pVEGF, 500 ug (EuroInject One) or 2,000 ug (NORTHERN) [83–85]. The major contributing barrier most likely originates from subtherapeutic VEGF expression for a sufficient duration. It is challenging to quantify VEGF expression in human myocardium, and current clinical doses have been empirically determined through preclinical studies. VEGF remains a viable therapeutic option for ischemic heart disease; however, other mediators of angiogenesis and different delivery modalities may be needed to increase myocardial perfusion efficiently during ischemic events.

The CXCL12-CXCR4 Chemokine Axis

The CXCL12/CXCR4 chemokine axis is well known for its role in chemotaxis during embryonic development and inflammation. CXCL12, also known as stromal cell-derived factor-1 (SDF-1), and its main receptor, CXCR4, are involved in a host of cell-to-cell interactions, including directed cell migration. Chemokines are small polypeptides (7–14 kDa) and are classified according to the number and location of the cysteine residue from the N-terminus: C, CC, CXC, and CXC3. CXCL12 is expressed in almost all tissues of the body including bone marrow, liver, brain, thymus, spleen, and heart. CXCL12/CXCR4 are critically involved in embryogenesis, especially in neural and cardiac development [86]. The CXCL12/CXCR4 chemokine axis is also central in many human pathophysiological processes, including HIV infection and metastatic disease.

CXCL12/CXCR4 have also been shown to play critical roles in recruitment of circulating progenitor cells to areas of myocardial ischemia and infarction. CXCL12 expression increases significantly post-MI yielding a potent chemotactic cue for recruiting circulating CD34+ CXCR4+ progenitor cells to ischemic myocardium. However, the endogenous CXCL12 signal is transient, peaking approximately 24–48 h post-MI and returning to basal levels within 7 days [87]. Preclinical studies aiming to maintain the CXCL12 signal through direct myocardial injections of plasmid, adenovirus, or mesenchymal stem cells engineered to overexpress CXCL12 have all shown to promote ventricular function post-MI [88–91]. CXCL12 augmentation enhances stem cell recruitment potentially aiding cardiac regeneration, preserving

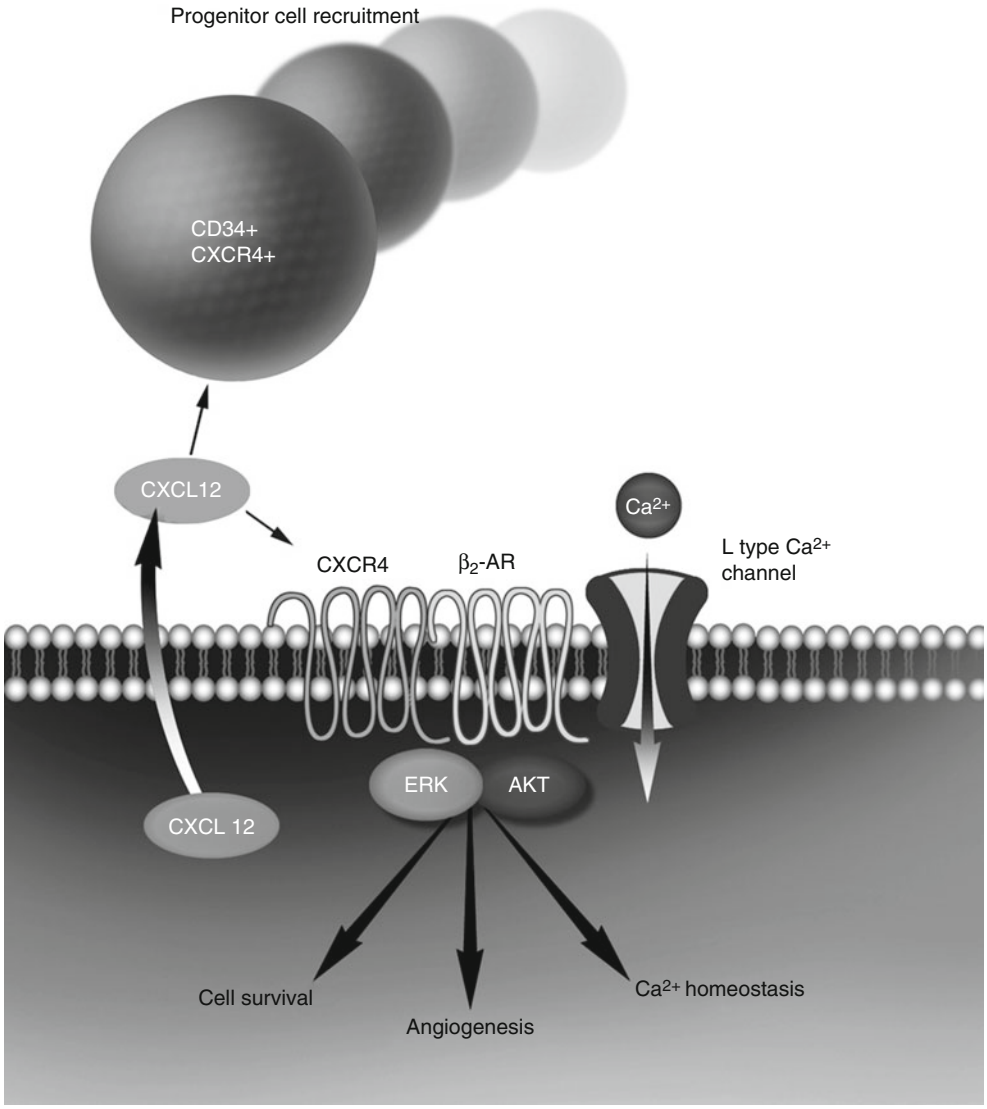


Fig. 44.4 Proposed molecular model of CXCR4-mediated cardioprotection. Upon cardiac myocyte stress from acute ischemia or sustained ventricular wall stresses, CXCL12 is secreted from stored granules in the cardiac myocyte. The secreted CXCL12 creates a chemokine gradient through interactions with glycosaminoglycans (GAG) which induces chemotaxis of circulating CD34+ CXCR4+ progenitor cells enabling myocardial protection and ventricular function through paracrine-mediated mechanisms and possibly regenerative mechanisms. In addition, CXCL12 secretion may act in an autocrine manner and activate cardiac myocyte CXCR4. It has been shown CXCR4 participates in a CXCR4-β2AR-Cav1.2 macromolecular complex which can augment beneficial cardioprotective pathways such as Erk1/2 and Akt impacting calcium homeostasis and calcineurin/NFAT inhibition, VEGF expression and angiogenesis, and prevention of apoptosis. The direct significance of the CXCR4-β2AR-Cav1.2 complex on Cav1.2-mediated calcium dynamics remains unknown

cardiac tissue and function. CXCL12 overexpression also promotes angiogenesis and pro-survival pathways, including Erk1/2 and Akt [90, 92]. A Phase I human clinical trial is currently evaluating the efficacy of direct endocardial injection of naked plasmid CXCL12 driven by a CMV promoter to define the beneficial effects in patients with ischemic cardiomyopathies (*Clinical Trial.gov:* NCT01082094).

CXCR4 is a Gi-coupled 7TMR participating mainly in regulating calcium flux and activating focal adhesion complexes, Erk 1/2-Elk1, and PI3k-Akt-NFkB which are all essential in mediating chemotaxis. Importantly, CXCR4 signaling pathways in the adult cardiac myocyte have yet to be fully elucidated. Recent evidence indicates that CXCR4 modulates β-AR pathways through inhibition of isoproterenol-induced L-type calcium channel (Cav1.2) activity and PLB phosphorylation and limits peak calcium transients and myocyte contraction [93]. Furthermore, CXCR4 has been shown to directly associate with β2-AR in the adult cardiac myocyte and positively influence pro-survival pathways including Akt and Erk1/2 while inhibiting apoptotic p38 pathways [94]. The beneficial signaling profile of CXCR4 and its ability to interact with β2-AR may potentially protect the myocardium from chronic hypertrophic and heart failure processes, independent of acute ischemic events and progenitor cell recruitment. In vitro, adenoviral overexpression of CXCR4 and treatment with CXCL12 both prevented isoproterenol-induced cardiac myocyte hypertrophy via interruption of calcineurin/NFAT signaling. AAV9.CXCR4 gene therapy was subsequently shown to significantly limit ventricular hypertrophy and heart failure progression in a murine model of pressure overload in vivo. It was determined CXCR4 participates in a macromolecular complex with β2-AR and Cav1.2 [95]. The CXCR4-β2-AR-Cav1.2 complex may represent a tightly regulated calcium homeostatic mechanism enabling cardiac myocyte protection from chronic wall stresses. The CXCL12/CXCR4 axis utilizes

multiple mechanisms protecting the myocardium by not only enhancing progenitor cell recruitment and potentially influencing myocardial regeneration but also through autocrine/paracrine modulation of cardiac myocyte beta-adrenergic signaling and Cav1.2 function (Fig. 44.4). The CXCL12/CXCR4 chemokine axis is a viable target for developing nonviral and AAV gene therapies in treating ischemic cardiomyopathies and congestive heart failure.

Conclusion

Since the conceptualization of gene therapy in the early 1970s, the scientific and clinical community has learned a great deal from the successes and, unfortunately, failures of previous gene therapy clinical trials over the past decades. Gene therapy has evolved to be potential first-line treatment in many diseases including cardiovascular, hematological, and immunological disease. Cardiovascular disease continues to grow as a major cause of preventable death and economic burden not only to the United States but to the global community. New therapeutic strategies are needed to complement current pharmacological and mechanical interventions. Cardiovascular gene therapy has advanced immensely by the development of multiple vectors and delivery systems. Along with the identification of novel regulators in cardiac myocyte pathophysiology, cardiovascular gene therapy may significantly expand the therapeutic quiver for cardiologists to effectively treat patients suffering from cardiovascular disease.

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Cardiovascular Cell Therapy

45

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Introduction

A fundamental issue pertaining to the ability of the heart to sustain cardiac diseases of ischemic and nonischemic origin is whether myocardial regeneration occurs in the adult organ or whether this growth adaptation is restricted to prenatal life, severely limiting the response of the heart to pathologic states. The concept of the heart as a terminally differentiated organ incapable of replacing damaged myocytes has been at the center of cardiovascular research and therapeutic development for the last 50 years. The accepted view has been that the postnatal, adult, and old heart reacts to an increase in workload only by hypertrophy of the existing myocytes. This growth process is exhausted when the upper limit in myocyte volume, ~90,000 μm^3, and cross-sectional area, 600–900 μm^2, is reached. No further hypertrophy can occur and senescence supervenes [1]. Enlarged old cardiomyocytes express the senescence-associated proteins p53 and $p16^{INK4a}$ and are prone to undergo apoptosis and necrosis, possibly because of the high intracellular content of reactive oxygen species. Although cell death is restricted to $p16^{INK4a}$-positive myocytes, the process of clearance of old cells is inefficient, resulting in accumulation of poorly functioning myocytes, which are characterized by changes in the expression of contractile protein isoforms, profound alterations of intracellular calcium cycling, and prolongation of the action potential. These defects together with myocyte loss and the development of foci of myocardial scarring inevitably contribute over time to the onset of ventricular dysfunction and its progression to cardiac failure.

The progressive decline in myocyte number as a function of age and the formation of scarred tissue following myocardial infarction have been interpreted as irrefutable proofs of the postmitotic characteristic of the heart [2]. However, the effects of age and pathologic states on the number of parenchymal cells are similar in organs with high and low turnover cell rate. In the bone marrow, lymphoid tissue, retinal epithelium, cochlea, liver, brain, and peripheral nervous system, the number of specialized cells diminishes as a function of age [3]. In these organs, the adaptation to stress involves an increased replicative response that, however, does not preserve tissue homeostasis because cell death exceeds cell division. Numerous findings indicate that the mammalian heart responds in a comparable manner to injury: abnormal elevations in load are accompanied by the activation of the intrinsic growth reserve of the myocardium and enhanced myocyte proliferation [1]. Thus, the behavior of the heart corresponds to a model of tissue growth common to all organs in the organism.

The adult heart is largely composed of a highly specialized compartment of terminally differentiated interconnected myocytes. However, cyclin and cyclin-dependent kinase activity, BrdU incorporation, and expression of Ki67, MCM5, Cdc6, and phospho-histone H3 have been recognized in myocyte nuclei. The identification of the mitotic spindle and contractile ring during karyokinesis and cytokinesis has further demonstrated the existence of a subpopulation of replicating myocytes in the adult heart [1, 4]. In all cases, proliferating myocytes correspond to small poorly differentiated cells that exhibit a thin halo of myofibrils in the subsarcolemmal region (Fig. 45.1). These phenotypical characteristics reflect those of transit-amplifying cells, a population of cells that is typically present in stem cell-regulated organs. Transit-amplifying cells occupy an intermediate position in the hierarchy of cells within an organ and have the unique property to divide and simultaneously differentiate. By this mechanism, amplifying cells increase the number of irreversibly committed cells generated by stem cell growth [5]. In vitro and in vivo findings strongly suggest that replicating myocytes correspond to transit-amplifying cells derived from the lineage determination of primitive cells, supporting the notion that cardiomyogenesis is controlled by a pool of resident cardiac stem cells (CSCs).

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_45,

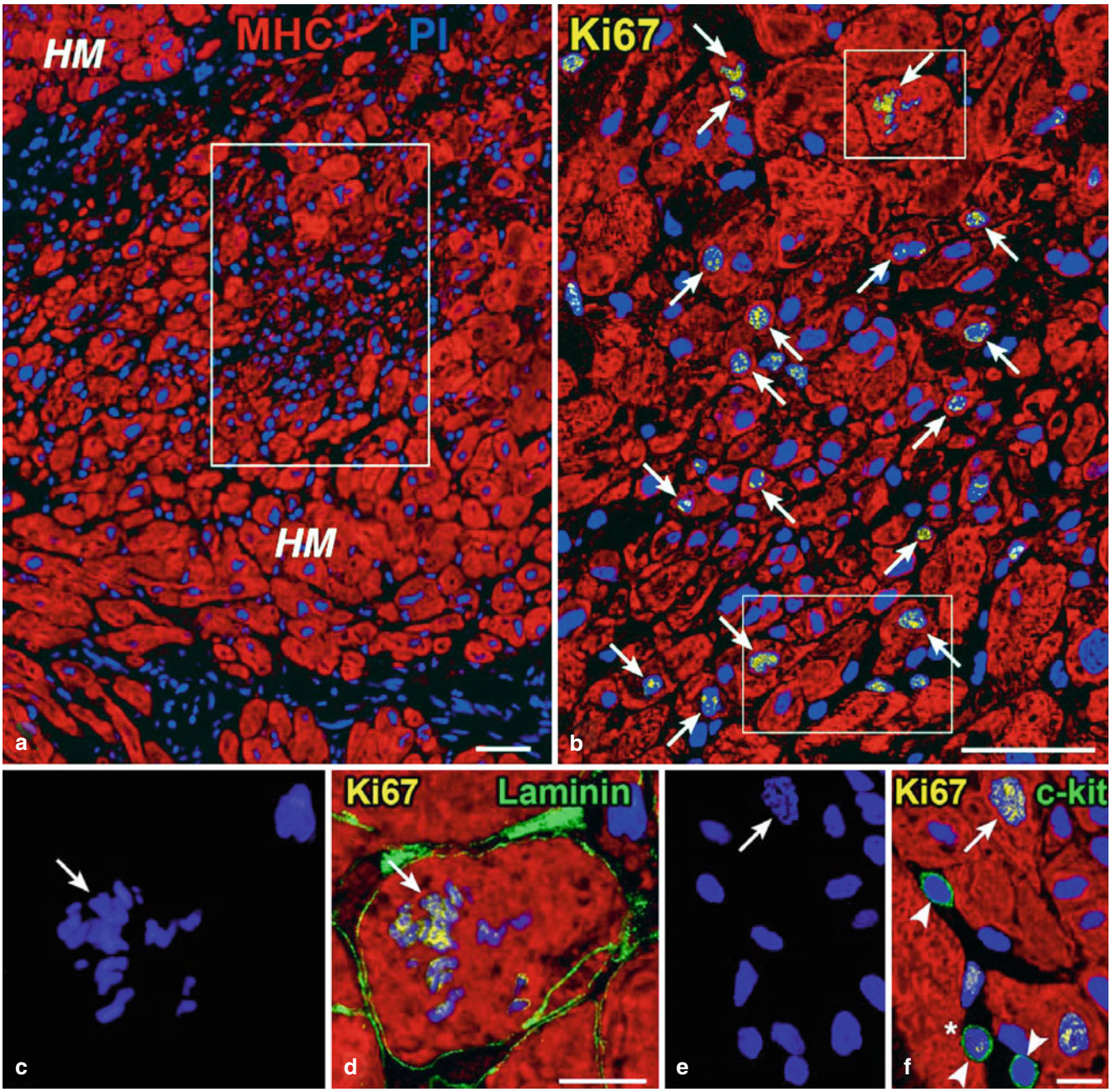


Fig. 45.1 Intense myocyte growth in the hypertrophied heart. The *white rectangle* in panel **a** includes a cluster of small poorly differentiated myocytes within the hypertrophied myocardium (*HM*). Myocytes are labeled by cardiac myosin (*red*) and nuclei by propidium iodide (*blue*). The area in the rectangle is illustrated at higher magnification in panel **b**, in which Ki67 (*yellow*) labels a large number of myocyte nuclei (*arrows*). The two small *rectangles* in **b** delimit myocardial regions shown at higher magnification in panels **c**–**f**. A mitotic nucleus with metaphase chromosomes (**c**, *blue*; *arrow*) is positive for Ki67 (**d**, *yellow*; *arrow*), and the boundary of the cell is defined by laminin (**d**, *green*). Another mitotic nucleus (**e**, *blue*; *arrow*) is labeled by Ki67 (**f**, *yellow*; *arrow*). c-kit-positive CSCs (**f**, *green*; *arrowheads*) are present in proximity of the mitotic myocyte. A dividing Ki67-positive CSC (**f**, *yellow*; *asterisk*) is present

Somatic stem cells are present in most, if not all, adult organs. Tissue-specific stem cells are undifferentiated cells characterized by the ability to self-renew and differentiate to yield all specialized cell types of that tissue or organ [6]. Asymmetric kinetics of growth is essential for the maintenance of the pool of resident progenitors and the formation of a compartment of mature cells. These two processes are maintained in tight equilibrium in organs in a steady state. Stem cell activation is dependent on the needs of the tissue in which they reside; when parenchymal cells are lost and their number decreases, proliferation signals are generated and stem cells leave the niche area and differentiate. Organ mass

in prenatal and postnatal life is controlled by the balance between cell death and cell division, which maintains constant the number of parenchymal cells within the tissue. In pathologic states, cell loss may be compensated by an increase in size of the remaining cells and/or by tissue regeneration. The hypertrophic response can become rapidly maladaptive because of the difficulty of the enlarged cells to perform efficiently their specialized function. A proficient regenerative reaction in self-renewing organs depends on the size of the stem cell and transit-amplifying cell pool, which may be intact early in life and following an acute damaging event but may be severely compromised with aging and chronic disease processes.

Although cellular hypertrophy can reconstitute a correct organ volume, actual repair is achieved through cell regeneration, which results in the replacement of the cells lost following injury with new functionally competent cells. In physiological conditions, this process is highly efficient; cell dropout by normal wear and tear is counteracted by cell regeneration, and organ homeostasis is preserved. Conversely, in the presence of damage, restitutio ad integrum does not occur and healing is associated with the formation of a scar. In spite of the presence of resident stem cells, spontaneous tissue regeneration is a rare event in adult self-renewing organs [1, 3].

The ability of stem cells to continuously replenish the compartment of undifferentiated and lineage-committed cells is a fundamental property of higher organisms with mitotic soma. In these cases, tissues are capable of renewal and repair, and the extent of regeneration positively correlates with animal lifespan [7]. The reduced longevity of lower organisms, including *C. elegans* and *Drosophila*, is linked to the lack of regenerative potential of their postmitotic tissues in adulthood [7]. Dying cells cannot be replaced resulting in a rapid and progressive decline in organ function. Conversely, cell turnover by proliferation and commitment of resident progenitor cells is active in mammals, and old injured cells may be restored by new better functioning cells.

During embryonic-fetal development and physiologic cell turnover in adult tissues, cells divide for a predetermined number of rounds, ultimately reaching terminal differentiation and growth arrest. The process of commitment of primitive cells to specialized cells is characterized by a progressive restriction in proliferative and developmental options that culminates in cell cycle withdrawal and acquisition of the mature phenotype [5]. The precise coordination of cell division is required to ensure the production of a proper number of lineage-committed cells, while cell cycle arrest in terminally differentiated cells is critical for tissue architecture and function. The heart would fail if the majority of its cardiomyocytes would be engaged in cell division with transient disassembly of the myofibrillar apparatus during mitosis. On the other hand, it is biologically unlikely that the heart can survive and exert its hemodynamic function until death of the organ and organism with the same cells which are present at birth. Accumulating evidence offers a dynamic view of the heart in which cell death and regeneration are vital components of the remodeling process that governs cardiac homeostasis, aging, and disease.

Postnatal Cardiac Maturation

The postnatal growth of the myocardium accommodates the increasing demands of the rapidly growing animal and the abrupt changes in the patterns of blood flow and circulatory resistance occurring shortly after birth. Traditionally, myocyte replication is considered to cease abruptly at birth, and the progressive increase in size of the growing heart is viewed primarily as the result of an increase in volume of preexisting cardiomyocytes which were formed prenatally [2]. Based on this notion, the contribution of cell proliferation to the expansion in ventricular mass is restricted to embryonic-fetal life. Approximately 15 years ago, the administration of thymidine analogs to mice revealed that two temporally distinct phases of DNA synthesis characterize the prenatal and early postnatal heart [8]. The first peak in DNA synthesis was observed in the fetal heart and was attributed to cardiomyocyte proliferation. Conversely, the second phase of DNA synthesis, which occurs 4 days after birth and involves 10 % of cardiomyocytes, was arbitrarily associated to binucleation. This claim provided further support to the concept that cardiomyocyte replication ceases before birth and that the network of proteins coordinating cell cycle progression is differentially expressed during fetal and neonatal life.

The search for the molecular mechanisms responsible for the alleged withdrawal of postnatal cardiomyocytes from the cell cycle resulted in the compilation of an endless list of genes that are known to promote growth arrest in multiple systems. Cessation of myocyte proliferation at birth has been linked to the downregulation of cyclins, cyclin-dependent kinases, and E2F transcription factors and to the upregulation of the negative modulators of cell cycle progression Cdkn1a, Cdkn1b, Cdkn1c, and Cdkn2c [2]. Transgenic and knockout mice were developed to document that changes in gene expression can overcome the barrier to myocyte renewal at birth but not in adulthood, when myocytes, in spite of the persistence of the transgene, unexpectedly escape the pro-proliferative effects and exit from the cell cycle [9]. The normalization of cardiac size and myocyte cell number in adult mice was suggested to be the result of an increase in cell death to correct for the early postnatal hyperplasia [9].

In the skeletal muscle, MyoD has been recognized as the master gene that directs the entire program of myoblast differentiation by organizing an interactive circuitry of tissue-specific transcription factors and chromatin-associated proteins. A gene

with similar function remains to be identified in the heart. Recent reports have suggested that Mesp1 acts as a key regulatory switch during cardiovascular specification, but whether this protein has a comparable role postnatally remains to be defined [10]. The homeodomain factor Nkx2.5 occupies an upstream position in the hierarchy of the cardiac regulatory genes, driving directly or indirectly the expression of multiple genes involved in heart formation. Homozygous Nkx2.5 null embryos are characterized by arrest of cardiac growth and death between 9.5 and 11.5 days of prenatal life [11] pointing to the essential role of Nkx2.5 in cardiac morphogenesis. Nkx2.5 continues to be expressed in a subset of postnatal and adult myocytes, raising the question whether Nkx2.5 is required postnatally for cell fate determination [12, 13].

The analysis of chimeric embryos with variable contribution of Nkx2.5-null myocytes demonstrates that the severity of the cardiac abnormality is proportional to the fraction of Nkx2.5-null cells present in the developing heart [11]. The normal phenotype of chimeric hearts including 15 % Nkx2.5-null cells suggests that the concomitant expression of Nkx2.5 in all myocytes is not necessary for cardiac growth prenatally. These findings are consistent with the progressive decrease in the number of Nkx2.5-positive myocytes from the embryonic to the adult heart [12, 13]. The heterogeneous distribution of Nkx2.5 is, however, in conflict with the notion that this transcription factor is indispensable for the maintenance of the differentiated state of cardiomyocytes. To reconcile these conflicting observations, the hypothesis has been advanced that Nkx2.5 may promote the synthesis and secretion of paracrine factors that support the survival and the maturation of the surrounding embryonic myocytes [11]. An alternative interpretation involves the possibility that Nkx2.5 expression is restricted to the pool of early committed myocyte progenitors-precursors and transit-amplifying cells derived from the activation of resident CSCs.

By employing a reporter mouse in which EGFP is placed under the control of the Nkx2.5 promoter, fluorescently labeled cells have been identified in the neonatal and young adult heart. The existence of Nkx2.5-positive cells with an embryonic phenotype suggests that a pool of immature cardiomyoblasts persists after birth and may contribute to cardiomyogenesis during postnatal growth and following injury in the adult heart [14]. Early in life, a significant fraction of myocytes express the senescence-associated protein $p16^{INK4a}$ and undergo apoptosis, indicating that a subset of these cells has a rather short lifespan [15]. These observations corroborate the view that myocyte renewal is an important component of cardiac maturation. The formation of new myocytes mediated by CSC growth may not be a minor phenomenon that undergoes sudden downregulation at birth but may represent a continuous process that conditions the acquisition of the adult heart phenotype, structurally and functionally.

Noninvasive imaging protocols consisting of in vivo cardiac magnetic resonance and ex vivo diffusion tensor imaging have documented that the progressive increase in size of the rat heart from day 2 to day 56 after birth is dictated by two processes that occur concomitantly in early postnatal growth: myocyte hyperplasia and hypertrophy. These findings strongly suggest that the developing heart should be viewed as a dynamic organ in which myocyte hypertrophy, myocyte death, and de novo generation of myocytes dictate the changes in cardiac size and shape that take place shortly after birth until myocardial loading has stabilized in the young adult organism. The origin of postnatal cardiomyocytes was determined by employing a loss of function approach involving the blockade of Notch1 receptor signaling [13]. In the intact early postnatal myocardium, Jagged 1 is present on the myocyte surface and binds to the Notch1 receptor expressed on the membrane of CSCs. This interaction positively modulates the commitment of CSCs to the myocyte lineage. Replicating myocytes derive from translocation of the active fragment of Notch1 (N1ICD) to the nucleus of CSCs and upregulation of Nkx2.5. This process involves the transition from undifferentiated Notch1-positive CSCs to early committed N1ICD-positive myocytes and, then, to functionally competent N1ICD-negative maturing parenchymal cells.

Interference with cardiomyogenesis by inhibition of the Notch1 pathway has a powerful negative effect on the structure and function of the growing heart, resulting in the onset of a dilated cardiomyopathy with high mortality [13]. Importantly, the restoration of cardiomyogenesis reverses the dilated myopathy, promoting the recovery of the functional and structural integrity of the myocardium. These observations in the mouse raise the possibility that Notch1 is involved in the etiology of idiopathic dilated cardiomyopathy (IDC) in children. Dilated cardiomyopathy is the most common cause for cardiac transplantation in children, but its etiology is unknown in ~65 % of cases [16]. Pediatric IDC may involve defects of Notch1 in CSCs with severe attenuation in the generation of cardiomyocytes.

Sustained, constitutive activation of Notch1 signaling or stimulation with the Jagged1 soluble ligand maintains long-term proliferation of in vitro cultured cardiomyocytes, delaying their differentiation into mature beating cells [17]. This phenomenon should not be interpreted as cell dedifferentiation; Notch1 receptor activation does not reprogram newly formed cardiomyocytes into precursor cells but prolongs the proliferative phase of cardiomyocytes, favors their survival, and extends their lifespan [17]. Additionally, N1ICD dictates the acquisition of the cardiomyocyte phenotype in endothelial progenitor cells (EPCs), and this response is enhanced by co-culture with neonatal myocytes secreting Jagged1 [18], strengthening further the relevance of this transcription factor for myocyte renewal postnatally. A similar mechanism is operative in the adult infarcted heart. Activation of Notch1

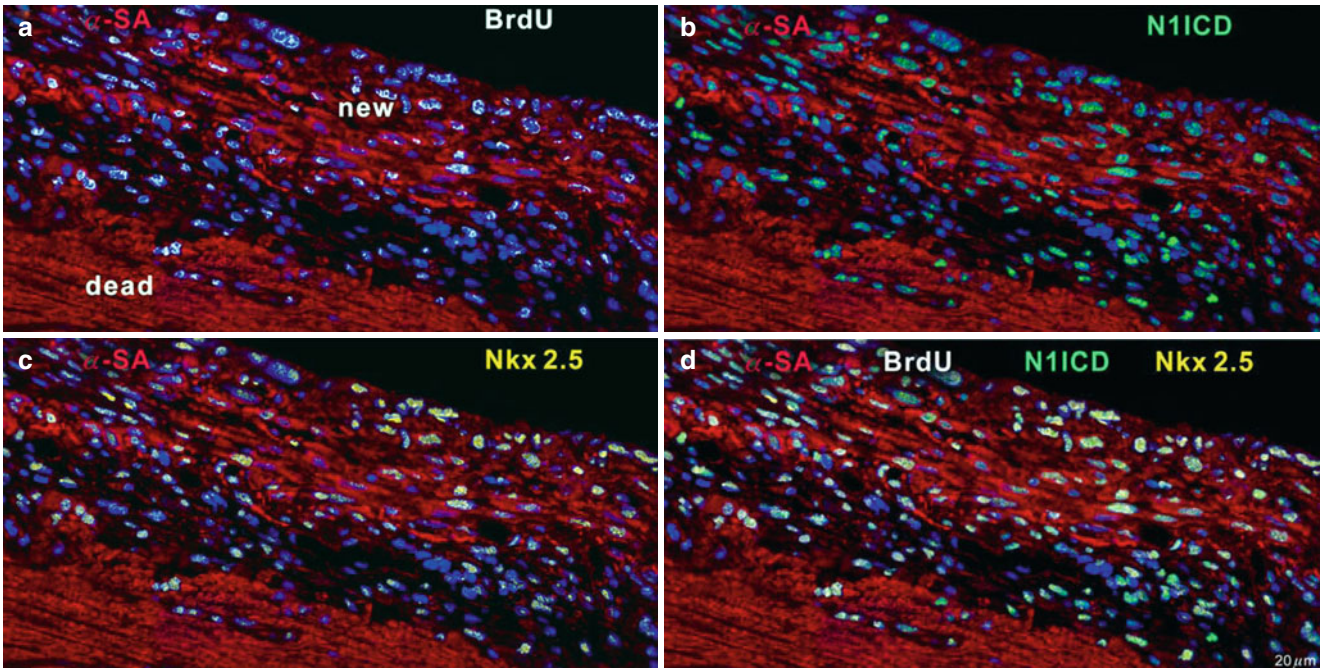


Fig. 45.2 Notch1 activation promotes the commitment of CSCs to the myocyte lineage. Area of regeneration (*new*) located within the infarct (*dead*). New myocytes are *BrdU* positive (**a**, *white*), N1ICD positive (**b**, *green*), and Nkx2.5 positive (**c**, *yellow*). (**d**) Merge of (**a**–**c**). *N1ICD* notch 1 intracellular domain; *α-SA* α-sarcomeric actin (myocytes, *red*)

receptor is a critical determinant of the transition of adult CSCs to the compartment of amplifying myocytes (Fig. 45.2), and inhibition of this pathway has dramatic negative consequences on the adaptation of the heart to ischemic myocardial injury [12].

Cardiomyocyte Turnover

The controversy on the growth reserve of the adult human heart has not been resolved, and the extent of myocyte renewal claimed by different groups varies dramatically. A recent study, based on retrospective carbon 14 (^{14}C) birth dating of cells, has claimed that 1 and 0.45 % replacement of myocytes occurs annually in the human heart at 25 and 75 years of age, respectively [19]. These findings indicate that only 50 % of myocytes are renewed during the entire life of the human heart, from birth to death, whereas an equal number lives as long as the organ and organism, up to 100 years of age and longer. Although the possibility of myocyte regeneration was confirmed, the actual magnitude of the process is in contrast with the level of myocyte apoptosis found in the adult human heart and the progressive increase in myocyte loss that occurs with aging [1].

In a recent study, involving 32 female and 42 male hearts from 19 to 104 years of age, myocyte regeneration in the physiologically aging heart was found to occur at previously unexpected levels [20, 21]. In the female heart, myocyte replacement occurs at a rate of 10, 14, and 40 % per year at 20, 60, and 100 years of age, respectively. Corresponding values in the male heart are 7, 12, and 32 % per year, documenting that myocyte turnover involves a large and progressively increasing number of parenchymal cells with aging. From 20 to 100 years of age, the myocyte compartment was replaced completely 15 times in women and 11 times in men, and essentially none of the myocytes present at birth is preserved in the young adult, middle-aged, and senescent heart. These findings question the contention that 50 % of cardiomyocytes survive and retain their function for the entire lifespan of the organ and organism [19].

Cycling myocytes expressing Ki67, phospho-histone H3, and aurora B kinase were found in male and female hearts, and aging was characterized by a time-dependent increase in the generation of this cell class in both genders. The pool of amplifying myocytes and the fraction of mitotic myocytes were, respectively, 1.7- and 1.5-fold higher in old women than men, pointing to enhanced myocyte renewal in the female left ventricle; the rate of increase in these myocyte categories per year was higher in the female than male myocardium. Importantly, the proportion of mononucleated and binucleated myocytes did not change from 19 to 104 years of age. Thus, Ki67, phospho-histone H3, and aurora B kinase were all markers of cell replication, indicating that cardiac aging is characterized by a significant degree of myocyte regeneration.

The high level of myocyte turnover documented in the mammalian heart is at variance with lineage-tracing studies, suggesting that very little replacement of cardiomyocytes occurs with age in the absence of pathologic states [22]. However, the young adult heart typically shows a degree of myocyte apoptosis of ~300 cells per million or one thirtieth of 1 % [23]. Although this may be seen as inconsequential physiologically, the duration of this form of cell death is at most 4 h [1, 20]. Thus, ~1,800 myocytes/10^6 cells are lost per day in the heart, implying that, over a period of 6 months, ~1.1 million myocytes are lost and have to be replaced by new cells to preserve cardiac function.

Throughout life, myocyte apoptosis is higher in men than in women. In the absence of myocyte formation, only 5 % of cardiomyocytes would persist at 63 and 48 years of age in women and men, respectively, indicating that myocyte regeneration plays a major role in the preservation of tissue mass and function of the aging human heart. Quantitative studies of the aging human heart in women and men have shown that from 17 to 89 years of age, nearly 64×10^6 cardiomyocytes are lost per year in men, whereas myocyte number does not change in the female heart up to 90 years of age [24]. Thus, a perfect balance appears to exist between myocyte renewal and death in women, whereas myocyte loss exceeds cell formation in men.

Origin of Cardiomyocytes

The identification of dividing myocytes raises the important question concerning the origin of the newly formed cells. Studies in rodents have claimed that terminally differentiated myocytes can be coaxed to reenter the cell cycle and divide [2]. However, this work fell short in documenting whether a mature myocyte, ~25,000 μm^3 in volume, increases its size during S phase and G2 phase, reaching ~50,000 μm^3 in volume, and then divides, giving rise to two daughter cells, ~25,000 μm^3 each. This sequence of events does not occur physiologically, and the forced reentry of postmitotic myocytes into the cell cycle results in abortive mitosis with formation of anaphase bridges and apoptotic cell death [25]. Replicating cardiomyocytes are typically mononucleated, have a 60–80 % smaller volume than non-cycling myocytes, and show a disorganized contractile apparatus with modest accumulation of myofibrils in the subsarcolemmal region. Thus, the properties of dividing myocytes are consistent with those of transit-amplifying myocytes in the process of acquiring the adult functionally competent phenotype.

The mammalian heart contains a pool of c-kit-positive undifferentiated cells, pointing to the possibility that resident stem cells are the source of myocyte renewal, physiologically and pathologically [1]. Several lines of evidence have been accumulated in favor of the notion that cardiac cells expressing the c-kit receptor are bona fide stem cells; they include the capacity to self-renew, form multicellular clones, and give rise to a committed progeny in vitro and in vivo [26]. However, differentiation assays of stem cell clones in vitro have inherent limitations including the possibility that culture conditions result in the preferential acquisition of a selective lineage phenotype, masking the full potential of the founder cell. Similarly, the identification of multiple phenotypes in the progeny of transplanted non-clonal stem cell populations does not provide a direct evidence of the multipotentiality of each administered cell. This problem has been overcome by the delivery of single-cell-derived clonal CSCs to the injured myocardium; by necessity, all regenerated structures derive from the individual founder cell that underwent amplification ex vivo [26]. Criticisms, however, have been raised concerning the possibility that serial passaging may modify the original properties of CSCs and that tissue injury may affect in an unpredictable manner the fate of CSCs in vivo. Novel protocols have been introduced to document unequivocally that cardiomyocytes and coronary vessels originate from CSCs in the non-damaged heart and during physiological aging.

Fate mapping strategies, which are commonly employed to track the origin of the cells and their destiny, would represent the ideal prospective assay for the study of cardiomyocyte turnover when the expression of the fluorescent label is placed under the control of the promoter of genes coding for contractile proteins [22]. However, this protocol provides information at the level of populations of cells, which share the reporter gene, but fails to demonstrate in vivo the self-renewal, clonogenicity, and multipotentiality of single stem cells and the clonal origin of the daughter cells. This intrinsic problem makes it impossible to establish with certainty the identity of the ancestors of replicating myocytes. Moreover, genetic manipulations involving transgene constructs placed under the control of the α-myosin heavy chain promoter inevitably affect myocyte precursors and the pool of amplifying myocytes [27].

An alternative prospective protocol is based on the stable integration of proviral genome in the mammalian DNA of the infected cells. The insertion site of the viral integrant is inherited by the entire population derived from the parental cell. The implementation of this methodology to the adult heart is particularly relevant because the recognition whether a resident stem cell pool is present in the myocardium remains partly controversial and questions persist on the ability of the heart to undergo spontaneous tissue repair [1]. Genetic tagging with retroviruses was introduced more than 20 years ago for the characterization of individual hematopoietic stem cells and their progeny. The analysis of the clonality of CSCs and myocyte turnover cannot be performed in humans since it requires genetic tagging of the undifferentiated cells so that the clonal marker of individual mother cells

is traced in the specialized progeny in vivo. c-kit-positive CSCs located in the niches of the atrioventricular groove and apex of the mouse heart were infected with a lentivirus carrying EGFP, and the destiny of the labeled cells was determined 1–6 months later [28], providing the opportunity to assess the behavior of tissue-resident primitive cells in the non-injured heart. Although myocyte turnover in the intact heart is slower than the rapid pace at which cells renew themselves in the presence of damage, the intrinsic properties of CSCs are better characterized when tissue lesions are absent. A common integration site was identified in isolated c-kit-positive CSCs, cardiomyocytes, ECs, and fibroblasts, documenting the multipotentiality of CSCs and the clonal origin of the differentiated cells [28]. During a 6-month period, each EGFP-positive CSC divided ~8 times, giving rise to 230 cardiomyocytes. These findings, together with data obtained with BrdU pulse-chase assays, indicate that activation and differentiation of CSCs is an ongoing process which results in a significant renewal of cardiomyocytes in the adult mouse heart (Fig. 45.3).

Although viral clonal marking represents the only protocol that can establish the multipotentiality of CSCs in situ, limitations involve the low efficiency of CSC infection and the impossibility to collect serial samples of the transduced progeny in small animals. Moreover, whether the insertion site confers a selective advantage or disadvantage to the growth of single cells may be easily assessed in blood cells but cannot be established with certainty in the heart. An additional variable that may influence the assessment of myocyte formation from tagged CSCs involves the insertion of the proviral integrant in repressive regions of the mouse genome [29]. However, silencing of the reporter gene interferes with the recognition of labeled cells by immunohistochemistry but does not affect the analysis of integration sites by PCR.

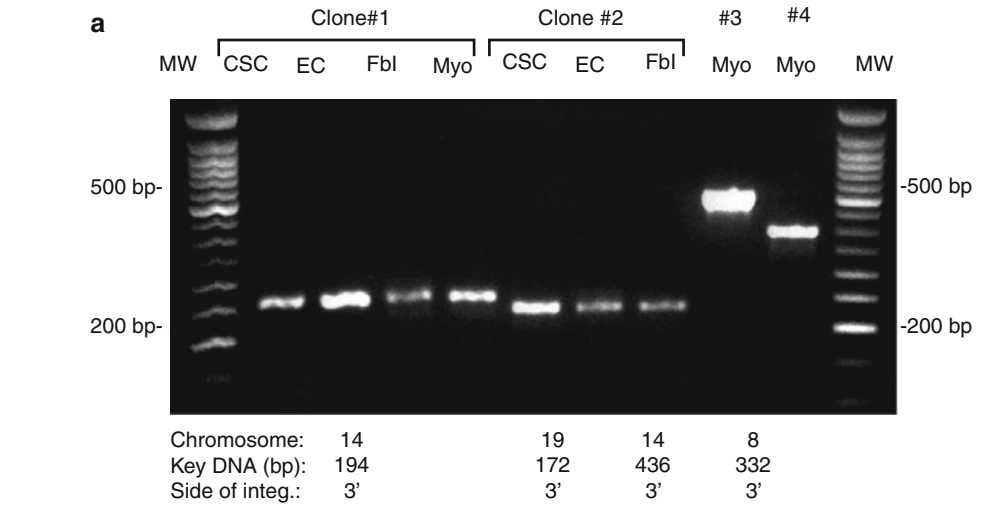
EGFP is a widely used fluorescent tag for the analysis of the fate of progenitor cells in vivo following adoptive transfer, and in lineage-tracing and viral clonal marking assays. The immunogenic potential of this foreign protein has raised questions on the appropriateness of its utilization in long-term studies. Processed peptides derived from EGFP may be presented by the major histocompatibility complex on the cell surface, potentially inducing a T cell immune response against the labeled cells. Cells transduced with genes perceived as foreign proteins by the recipient may actively engraft but may be subsequently cleared by the immune system. The magnitude of immunological rejection of cells carrying EGFP remains controversial and most likely context dependent. Different degrees of bone marrow ablation from sublethal irradiation to minimal conditioning have been employed to prevent rejection of EGFP-infected hematopoietic cells. This phenomenon may result in an underestimation of the number of EGFP-positive CSCs and their tagged progeny.

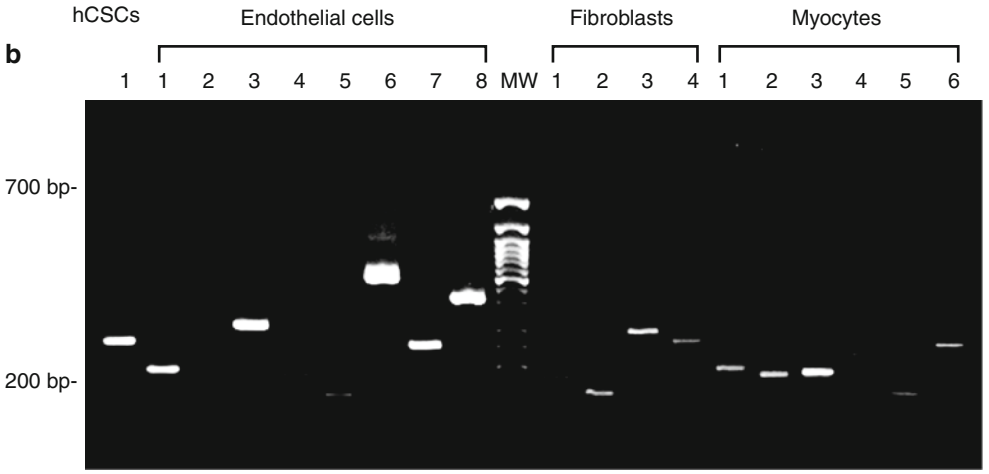
A critical question is whether cardiac repair after injury recapitulates the developmental steps of CSC lineage commitment in the organ in a steady state, in which the invariant growth mechanism preserves the stem cell pool and produces an adequate progeny. Knowledge of the basic principles that regulate the physiological activity of CSCs may help in understanding the response of these cells to pathological states and their ability to initiate a repair process. Viral clonal marking can be applied to the analysis of transplanted clonal EGFP-labeled human CSCs and their progeny in the ischemic myocardium. By this approach, the multipotentiality of hCSCs and the polyclonal origin of myocardial regeneration after infarction have been demonstrated [28]. Clinically, relevant questions of cell therapy for the failing heart may be addressed, including the clonal heterogeneity of hCSCs, the optimal number of hCSCs to be administered, and the repopulation properties of individual hCSCs.

Cardiovascular Cell Therapy: Bone Marrow Progenitor Cells

In the last few years, effort has been made to restore function in the infarcted myocardium by transplanting fetal-neonatal and adult myocytes, skeletal myoblasts, smooth muscle cells (SMCs), fibroblasts, embryonic stem (ES) cells, and induced pluripotent stem (iPS) cells. Fibroblasts, SMCs, and fetal-neonatal myocytes form a passive graft, which, by decreasing the stiffness of the scarred portion of the wall, has a transient positive effect on ventricular remodeling and performance. Totipotent ES cells home to the myocardium but do not undergo long-term engraftment, resulting in rapid and massive disappearance of the allograft because of the lack of vessel formation and immune rejection [3]. Additionally, ES cells and iPS cells give rise to teratomas and teratocarcinomas. Importantly, a residual epigenetic memory of the original parental source in iPS cells leads to a biased differentiation potential of the biologically modified progeny. Incomplete erasure of tissue-specific methylation and aberrant de novo methylation are the molecular bases of this incomplete epigenetic transformation [30]. These currently unresolved molecular and biological problems raise doubts about the appropriateness to use iPS cells as a platform for human disease modeling and drug screening. Even more, the possibility to utilize iPS cells for regenerative purposes is unlikely at present.

The first attempt to replace infarcted myocardium with a patch of skeletal muscle was performed in the 1930s. Fifty years later, large sheets of skeletal muscle tissue were positioned on the epicardial surface of the ischemic area and stimulated to contract with a pacemaker. This surgical procedure, known as dynamic cardiomyoplasty, has prompted





c

hCSCs	chr.	key	side	EC	chr.	key	side	Myo	chr	key	side
#1	6	69 bP	5'	> #1	1	113bP	3'	> #1	1	113 bP	3'
> #2	9	103 bP	3'	#2	5	61 bP	3'	> #2	3	95 bP	3'
#3	19	322 bP	3'	#3	5	232 bP	3'	> #3	9	103 bP	3'
> #4	X	183 bP	3'	> #4	9	103 bP	3'	#4	9	145 bP	3'
Fbl				> #5	16	61 bp	5'	> #5	16	61 bp	5'
< #1	3	95 bP	3'	#6	16	427 bp	3'	> #6	17	176 bp	3'
< #2	16	61 bP	5'	> #7	17	176 bp	3'				
#3	19	207 bP	5'	#8	20	333 bp	3'				
< #4	X	183 bP	3'	#9	und	20 bp	5'				

Fig. 45.3 Genetic tagging and clonal marking of CSCs in vivo. (**a**) Four distinct clones were identified in EGFP-tagged CSCs, ECs, fibroblasts (*Fbl*), and cardiomyocytes (*Myo*) isolated from the LV of one mouse heart, 4 months after the injection of EGFP lentivirus in the atrial and apical niches. The site of insertion of the lentiviral sequence in the mouse genome was detected by nested PCR. Multiple PCR products (bands in agarose gel) were identified. Bands of the same molecular weight correspond to identical sites of integration of the proviral sequence in the host genome of CSCs, myocytes, ECs, and fibroblasts (*Fbl*), documenting a lineage relationship between CSCs and the differentiated progeny. Key corresponds to the mouse DNA sequence adjacent to an integrated provirus. These sequences are ~80 bp shorter than the corresponding clonal bands. (**b**) EGFP-labeled hCSCs were injected in infarcted rats. Following enzymatic dissociation of the regenerated myocardium, EGFP-positive CSCs, myocytes, ECs, and fibroblasts were FACS sorted. Various clones were detected: one clone in c-kit-positive CPCs, eight clones in ECs, four clones in fibroblasts, and six clones in myocytes. (**c**) Mapping of the viral integrant in the human genome is shown. Some clones were common to different cell classes (same color *arrowheads*). Key DNA sequences are ~80 bp shorter than the corresponding clonal bands

investigators to utilize individual myogenic cells. This new approach, or cellular cardiomyoplasty, consists of the direct injection of isolated skeletal myoblasts into the ischemic area. The autologous origin of the cells to be implanted constitutes an obvious advantage of this form of cardiac repair. Moreover, skeletal myoblasts are more resistant to

ischemia than cardiomyocytes, enhancing their possibility of survival in the necrotic myocardium. These considerations have prompted clinicians to use skeletal myoblasts for the treatment of patients suffering from ischemic cardiomyopathy.

The lack of integration of skeletal myoblasts within the myocardium represents a reason of concern for the therapeutic implementation of these cells. Analysis of the graft-host myocardium interface has failed to document any evidence of mechanical or electrical coupling between skeletal and cardiac muscle. Connexin 43 and N-cadherin are consistently absent in injected skeletal muscle cells, and a layer of dense scar tissue often separates the cardiomyocytes from the skeletal muscle further opposing the integration process [3]. As documented in animals, the absence of synchronous contraction may be one of the factors responsible for the arrhythmic, at times lethal, complications observed in infarcted patients subjected to skeletal myoblast transplantation [31]. Regenerative medicine should aim at the restoration of tissue with the same functional and structural properties of the damaged organ. However, transdifferentiation of skeletal myoblast into cardiac myocytes has never been observed. These numerous problems have resulted in an early termination of the enrollment of patients in clinical trials [31], prompting the search for an alternative cell-based intervention.

In recent years, the potential role of bone marrow-derived circulating stem/progenitor cells in tissue repair has been studied extensively. Circulating progenitors with colony formation ability have been detected in the peripheral blood and include hematopoietic, mesenchymal, endothelial, smooth muscle, and skeletal muscle precursors. The physiological relevance of circulating stem and progenitor cells for the implementation of a normal process of hematopoiesis is well known. The constant flux of adult hematopoietic stem cells (HSCs) is likely to provide an immediate source of rapidly recruitable progenitor cells for medullary and extramedullary hematopoiesis in case of catastrophic blood loss. However, it remains controversial whether bone marrow cells (BMCs) and their circulating progeny contribute to physiological homeostasis and regeneration of non-hematopoietic tissues.

Following the discovery of endothelial progenitor cells (EPCs) in 1997 [32], numerous classes of bone marrow-derived, circulating cells have been termed EPCs. The analysis of the surface phenotype of putative EPCs has been challenging and has not provided a definitive answer concerning their identity. Originally, it was assumed that the combination of hematopoietic and endothelial markers was a hallmark of EPCs, but the concomitant presence of these epitopes identifies both blood-forming cells and EC-generating cells. Available data have been analyzed in a recent review, leading to the conclusion that functional EPCs correspond to cells that do not express CD45, CD14, and CD115, do not ingest bacteria, display high proliferative potential at a clonal level, form tubules in co-culture with lung fibroblasts, or generate de novo vessels in vivo [33].

Although there is disagreement concerning the magnitude of the process, migration and homing of EPCs to regions of damage has been shown to contribute to EC turnover and vessel growth, providing an alternative mechanism of vessel repair. EPCs form an endothelial lining in vascular grafts, in denudated arteries, and on the surface of left ventricular assist devices. However, EPCs cannot prevent or correct atherosclerotic lesions or generate conductive and resistance coronary arteries. The beneficial effect of EPCs and unselected bone marrow cells on the evolution of the post-infarcted heart has been attributed mostly to enhanced capillary density and, to a lesser extent, to the formation of SMC-covered vessels and cardiomyocytes [34]. Importantly, EPC number is inversely correlated with cardiovascular mortality, suggesting that these cells may support vasculogenesis. The level of circulating CD34-positive hematopoietic cells and EPCs increases during the early phases of ischemic cardiac disease, although the functional integrity of EPCs in these pathologic conditions was questioned.

Lineage-negative c-kit-positive BMCs, implanted in the border zone of an acute infarct, translocate to the necrotic region of the left ventricular wall and reconstitute myocardium, interfering with scar formation and cardiac decompensation [35]. Numerous small cardiomyocytes and vascular structures develop within the infarct and partially replace the dead tissue (Fig. 45.4). Additionally, coronary arterioles and capillaries are distributed within the regenerated tissue and are functionally connected with the primary coronary circulation. Alternatively, cytokines and growth factors may be employed to mobilize stem cells and promote their migration to damaged organs including the heart. The mobilizing agents stem cell factor (SCF) and granulocyte colony-stimulating factor (G-CSF) markedly increase the number of circulating bone marrow progenitor cells [36]. These progenitors reconstitute the lymphohematopoietic system of lethally irradiated recipient mice and in the presence of myocardial infarction home to the heart and differentiate into myocytes, and vascular ECs and SMCs.

These early studies on BMC transdifferentiation have been challenged, and the therapeutic efficacy of this class of progenitors for the infarcted heart has been questioned. However, shortly after the experimental evidence that HSCs induce myocardial regeneration after infarction, unfractionated mononuclear BMCs and CD34-positive cells have been administered to patients affected by acute and chronic myocardial infarction, dilated cardiomyopathy, and refractory angina. Although the individual outcomes have been inconsistent and variability exists among trials, meta-analyses of

pooled data indicate that BMC therapy results in a 3–4 % increase in ejection fraction [37]. Allogeneic and autologous MSCs have also been employed in small clinical trials with encouraging results [38]. Collectively, these initial data have prompted the development and conduct of larger randomized trials designed to critically evaluate the long-term effects of BMC therapy on a broader patient population. The mechanisms involved in the positive impact of BMC therapy on human beings remain to be identified. Measurements of coronary flow suggest that vasculogenesis may be operative, while the contribution of de novo myocyte formation is uncertain. Additionally, the injected BMCs activate the growth and differentiation of resident stem cells [38]. The recent identification of CSCs has shifted the attention to endogenous progenitors as a novel form of cell therapy for the failing heart.

Cardiovascular Cell Therapy: Endogenous Progenitor Cells

Investigators in several laboratories concur with the notion that the adult heart contains a compartment of stem/progenitor cells [1]. Distinct protocols based on the recognition of surface markers and transcription factors, and functional assays have been employed for the isolation of stem cells from the myocardium. The developing and adult heart contains a pool of cells that have the ability to efflux dyes, or side population (SP) cells. Of interest, a Sca-1-positive, Hoechst 33,342 dye-low, and CD31-negative cardiac SP cell has been shown to form beating cardiomyocytes in vitro and acquire the adult phenotype in vivo through cellular coupling with differentiated cardiomyocytes [39]. The Isl1 transcription factor is associated with the commitment to the myocyte

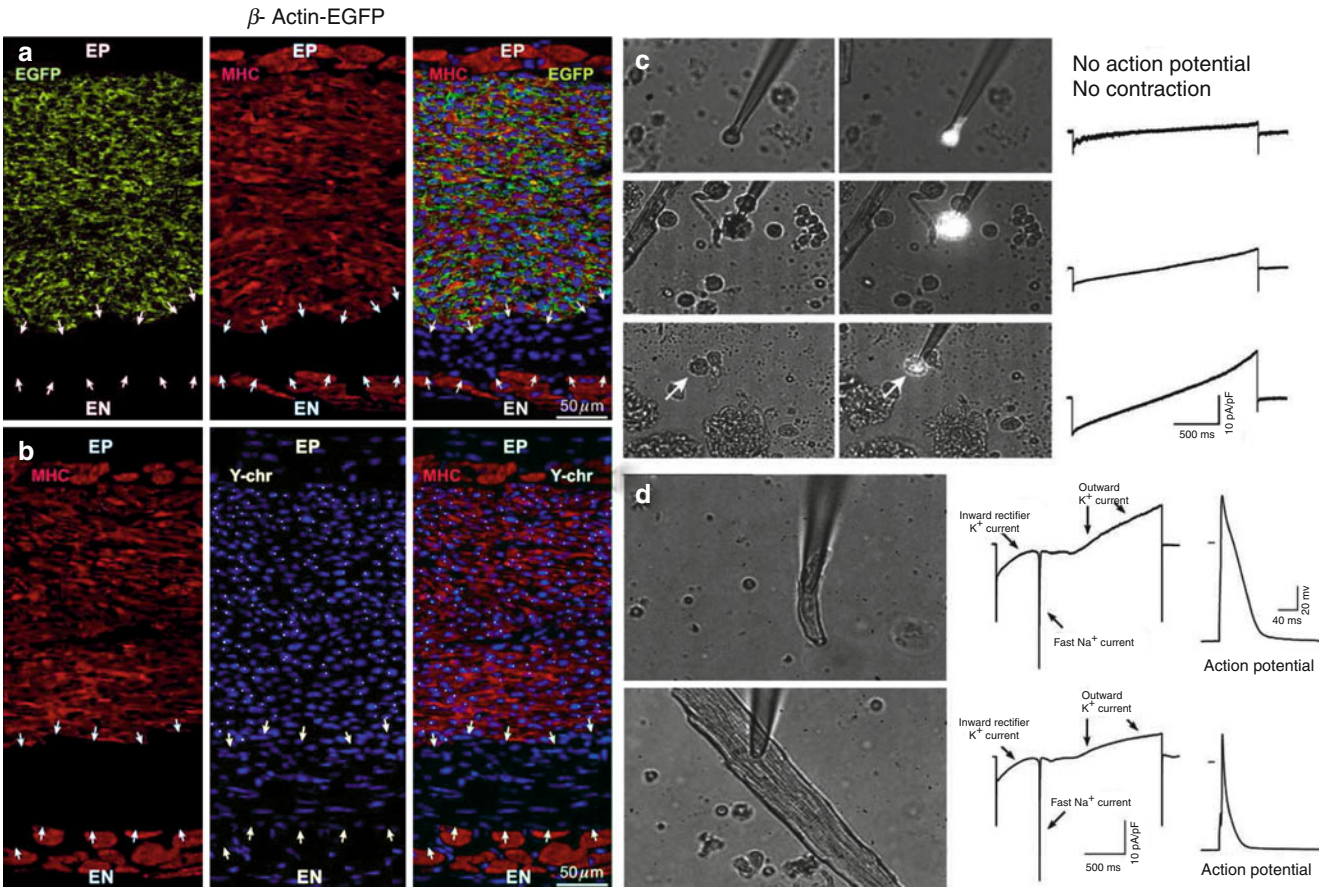
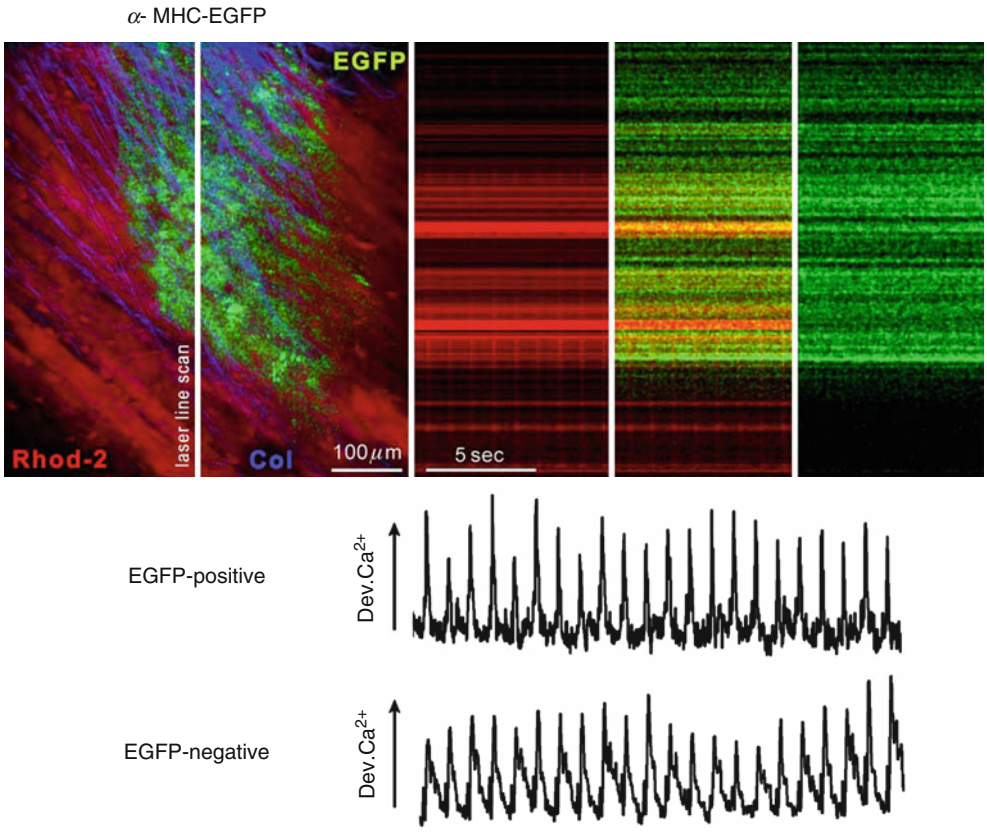


Fig. 45.4 c-kit-positive BMCs transdifferentiate into functionally competent cardiomyocytes. (**a**, **b**) Infarcted female mice were injected with BMCs obtained from male β-actin-EGFP mice. In panel **a**, newly formed myocytes are positive for EGFP (*left*, *green*), α-myosin heavy chain (*center*: *MHC*, *red*). *Right*, merge. *Arrows* indicate non-regenerated infarct. *EP* epicardium; *EN* endocardium. In panel **b**, regenerated myocytes (*left*: *MHC*, *red*) show positivity for Y chromosome (*center*: *Y-chr*, *white*) across the infarct. (**c**) At 2–3 days, EGFP-positive cells (*arrow*) lacked electrical activity. (**d**) Electrical properties of BMC-derived and spared myocytes. (**e**) The functional integration of regenerated EGFP-positive myocytes with the surrounding myocardium was documented by an ex vivo preparation and two-photon microscopy. This example pertains to a mouse heart at 30 days after coronary artery ligation and implantation of BMCs isolated from a reporter mouse in which EGFP is placed under the control of α-MHC. Calcium transient was detected in EGFP-positive BMC-derived myocytes and EGFP-negative recipient myocytes. The synchronicity in calcium transients between these two myocyte populations documents their functional coupling

Fig. 45.4 (continued)



lineage of cardiac cells that have lost their undifferentiated stem cell state. These cells disappear after birth, raising serious questions on the possibility to employ Isl1-positive cells for therapeutic purposes. We will focus on two cardiac-derived cell types that are currently employed in phase 1 clinical trials.

Cell culture in serum-free media has been utilized for the isolation of cardiospheres. These aggregates contain a core of cells positive for the stem cell antigen c-kit and an outer layer composed of cells positive for CD105, a membrane glycoprotein commonly expressed in bone marrow mesenchymal stromal cells [40]. Cardiosphere-derived cells undergo spontaneous maturation toward the myocyte lineage, and this process of commitment can be coaxed by co-culture with neonatal ventricular myocytes. Connexin 43 is expressed between highly dividing cells within the cardiospheres and in the expanded differentiating cardiosphere-derived cells (CDCs). Clinically, CDCs may represent the ideal combination of primitive and early committed cells for the treatment of cardiac diseases. However, the delivery of a partially defined heterogeneous cell preparation may result in a vaster array of unpredictable, undesired effects than a uniform population of identical cells with well-established biological characteristics. In analogy with pharmacological approaches, the combination of different drugs in the same pill is coupled with ease of administration but may not allow dosage flexibility and personalized therapy.

Cardiospheres may recapitulate the microenvironment of the stem cell niche. Mesenchymal-like and committed cells of the external layer may act as supporting cells for the internally distributed c-kit-positive CSCs. It has been suggested that direct implantation of niche-like cardiospheres in the damaged myocardium may be associated with a homing advantage with respect to monolayer-cultured CDCs. The presence of supporting cells may transiently protect the adjacent primitive cells, enhancing their survival in the hostile environment of the damaged myocardium. However, a direct contact between the delivered and recipient cardiac cells is required for actual engraftment in the host tissue and acquisition of the cardiogenic fate. Donor stem cells have to integrate structurally within the surrounding myocardium by forming junctional and adhesion complexes with adjacent myocytes and fibroblasts.

In the prospective, randomized CArdiosphere-Derived aUtologous stem CElls to reverse ventricULar dySfunction (CADUCEUS) trial, patients 2–4 weeks after myocardial infarction with EF of 25–45 % were enrolled. Autologous cells were isolated from endomyocardial biopsies, expanded in vitro, and infused in the infarct-related artery 1.5–3 months after myocardial infarction. The primary endpoint of the

clinical study was the proportion of patients at 6 months who died due to ventricular tachycardia, ventricular fibrillation, or sudden unexpected death or had myocardial infarction after cell infusion, new cardiac tumor formation, or a major adverse cardiac event (MACE; composite of death and hospital admission for heart failure or nonfatal recurrent myocardial infarction). Four treated patients, 24 % in the CDC group, had serious adverse events compared with one control. At 6 months, MRI analysis of patients treated with CDCs showed reductions in scar mass and increases in viable heart mass, regional contractility, and regional systolic wall thickening. Surprisingly, ejection fraction (EF) did not differ between control and treated groups [41].

As discussed above, the c-kit receptor tyrosine kinase identifies a pool of resident cardiac stem cells that are self-renewing, clonogenic, and multipotent in vitro and in vivo [26]. In experimental models of myocardial infarction, human CSCs (hCSCs) replace the necrotic/scarred tissue with functionally competent myocardium composed of cardiomyocytes and vessels, largely restoring ventricular performance [26]. The phase 1 trial SCIPIO (Stem Cell Infusion in Patients with Ischemic cardiOmyopathy) involves the delivery of autologous c-kit-positive lineage-negative CSCs for the treatment of severe chronic heart failure of ischemic origin [42]. Patients with EF lower than 40 % at 4 months after coronary artery bypass grafting were enrolled in the treatment and control groups. Treated patients received a single intracoronary infusion of one million autologous CSCs. The primary endpoint was short-term safety of treatment, and the secondary endpoint was efficacy. Importantly, no CSC-related adverse effects were reported. In 14 CSC-treated patients who were analyzed, EF increased from 30 to 38 % at 4 months after infusion. In contrast, seven control patients, during the corresponding time interval, did not show any change in this functional parameter. The beneficial effects of CSCs were even more pronounced at 1 year. In seven treated patients, in whom cardiac MRI could be done, infarct size decreased 24 and 30 % at 4 and 12 months, respectively. These initial results are highly encouraging and warrant further, larger, phase 2 studies.

Prior to infusion in patients enrolled in SCIPIO trial, c-kit-positive CSCs were extensively characterized by immunolabeling and confocal microscopy, and FACS analysis. In each of the 20 treated patients, the fraction of c-kit-positive cells varied from 75 to 98 %; early markers of commitment to the myocyte, SMC, and EC lineages were found only in 0.1–2.7 % of the entire cell population. Mean telomere length was 7.5 kbp, varying from 6.8 to 8.1 kbp, and telomerase activity was high in all CSC samples, indicating that, after passaging in culture, CSCs retained a significant growth reserve. The characterization of the telomere-telomerase axis should be introduced as standard quality control assay for the evaluation of the functional properties of cells to be administered to patients.

Chronological age and chronic heart diseases lead to telomeric attrition in hCSCs, which generate a progeny that rapidly attains the senescent phenotype. Daughter cells acquire the shortened telomeres of maternal hCSCs and, after a few rounds of division and terminal differentiation, eventually express $p16^{INK4a}$. Telomere length reflects the past replicative history and cumulative oxidative DNA damage occurring during the life cycle of the cell. hCSC function is regulated by telomerase activity and telomere length [26, 42]. Telomerase activity delays but cannot prevent telomere erosion, which is mediated by downregulation of telomerase, reactive oxygen species, and loss of telomere-related proteins. Shortening of telomeres beyond a critical length triggers cellular senescence, which corresponds to irreversible growth arrest in G1 with loss of specialized functions, including cell proliferation, migration, and differentiation. Aging, cardiac hypertrophy, ischemic myocardial injury, and metabolic disorders, together with genetic and environmental factors, dramatically affect the growth and differentiation behavior of resident hCSCs. This raises the important questions whether a compartment of functionally competent hCSCs persists in the decompensated heart and whether these cells have potential therapeutic implications.

Of great relevance, a pool of hCSCs with intact telomeres, 8–12 kbp, was found in the female and male heart at 90–104 years of age [20]. This category of hCSCs with high growth reserve is expected to generate a young myocyte progeny within the senescent heart. Because each division of hCSCs results in the loss of ~130 bp of telomeric DNA [26], an extremely large number of cardiomyocytes can be formed by these cells, before critical telomeric shortening and growth arrest occur (Fig. 45.5). From a clinical perspective, the recognition that a subset of telomerase-competent hCSCs with long telomeres persists at all ages and with chronic cardiac diseases has raised the possibility that autologous cell-based therapy may be feasible in patients with severe heart failure. Recently, a methodology has been developed to isolate this compartment of functionally competent hCSCs from endomyocardial biopsies of patients undergoing cardiac transplantation or left ventricular assist device implantation. After in vitro amplification, a clinically relevant number of hCSCs with high myogenic and vasculogenic potential were obtained. Importantly, expanded hCSCs possessed a significant growth reserve as documented by the short population doubling time, the high telomerase activity, and the relatively long telomeres [43].

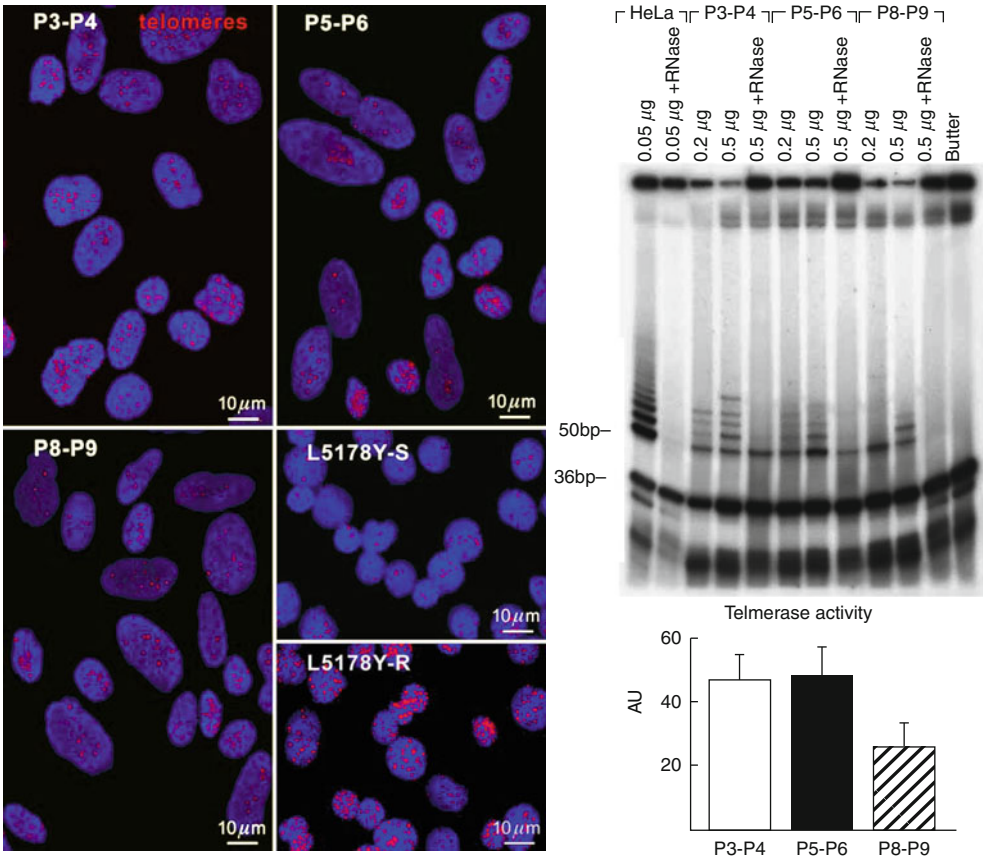


Fig. 45.5 Telomere-telomerase system in hCSCs. (**a**) Nuclei (*blue*) of hCSCs were stained with a telomere probe (*magenta*). Lymphoma cells with short (7-kbp) and long (48-kbp) telomeres are shown for comparison. (**b**) Products of telomerase activity in hCSCs start at 50 bp and display a 6-bp periodicity. Samples treated with RNase and CHAPS buffer were used as negative controls, and HeLa cells were used as positive control. The band at 36 bp corresponds to an internal control for PCR efficiency. Optical density (arbitrary units, AU) is shown as mean ± SD

Conclusions

The human heart is a highly dynamic organ regulated by a pool of resident hCSCs that modulate cardiac homeostasis and condition organ aging. Hopefully, recent findings will resolve the long debate that has divided the scientific community in strong opponents and passionate supporters of the regenerative potential of the human heart, offering a more biologically valid understanding of cardiac growth and repair. A common ground can now be found to translate this different perspective of cardiac biology into the development of novel strategies for the management of the human disease.

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Recommended Reading

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Preventive Cardiology

46

Temilolu O. Aje and Michael Miller

Understanding the Paradigm of CHD Risk

A number of algorithms have surfaced in recent years aiming to identify risk factors that are most predictive of coronary heart disease (CHD) events. For many years, the Framingham Risk Score was relied upon in this assessment, and in 2001, FRS was formally adopted by the National Cholesterol Education Program (NCEP) for evaluating 10-year risk of CHD based upon five factors (age, systolic blood pressure, total cholesterol, HDL-C, and cigarette smoking) [1]. Within this context, they defined three categories of risk: high risk (20 % or greater or 2 % per annum) or CHD or its equivalent (i.e., diabetes mellitus), intermediate risk (10–20 %) or 2+ risk factors, and low risk (<10 %) or 0–1 risk factors with accompanying target goals for LDL-C and non-HDL-C. During the past decade, further refinement to this classification has been suggested, including the addition of family history of CHD and levels of high sensitivity C-reactive protein (hs-CRP), referred to as the Reynolds Score [2]. Others have suggested incorporating additional lipid-based factors (e.g., LDL particle concentration, apolipoprotein B levels) or non-invasive diagnostic measures (e.g., coronary calcium levels, carotid intima-media thickness) [3, 4]. Whether and to what extent any of these additional measurements will be incorporated and/or emphasized in the NCEP Adult Treatment Panel (ATP) IV guidelines will in large part be dependent upon clinical outcome evidence demonstrating that influencing any of these parameters beyond LDL-C lowering translates into improved outcomes.

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Content Considerations in ATP IV

Among the more favorable considerations include (1) reducing the "low-risk" classification to less than 5 % over 10 years [5], (2) inclusion of lifetime risk [6], and (3) adding chronic renal insufficiency (CRI) to the "high-risk" CHD equivalent group [7]. The basis for altering the "low-risk" group as adopted in Europe [8] stems from observational data demonstrating the generalizability of this threshold. However, due to the heavily age-weighted FRS, a 10-year CHD risk score of less than 5 % can only be attained in men and women who have no CHD risk factors and are below age 60 and 75 years, respectively. The importance of maintaining an overall low-risk profile is underscored by the favorable life expectancy rates as compared to agematched men and women who have at least 1 CHD risk factor [9]. In fact, the use of additional tests such as coronary calcium do not appear to enhance reclassification efforts when risk is in the very low range (less than 3 %) [10]. Thus, if a patient is truly at low CHD risk, defined as less than 5 % over 10 years, then the likelihood remains very low that addition of other tests will elevate them to "high-risk" status. As such, "low risk" as defined by FRS (Fig. 46.1) signifies that in the absence of symptoms suggestive of CHD, no further testing is required.

Comparison Between 10-Year Risk and Lifetime Risk

While the 10-year risk of CHD provides useful information in the near term, assessment of lifetime risk provides a more complete picture that not only emphasizes the high prevalence of CHD and that the number of CHD risk factors directly contributes to the acceleration of this process. Individuals with optimal risk factors at age 50 have a very low lifetime risk of CHD. In contrast, the lifetime risk of CHD in the presence of two or more CHD risk factors approximates 50 % in women and 69 % in men [6]. Taken together, knowledge of both short-term and lifetime risk

C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_46,

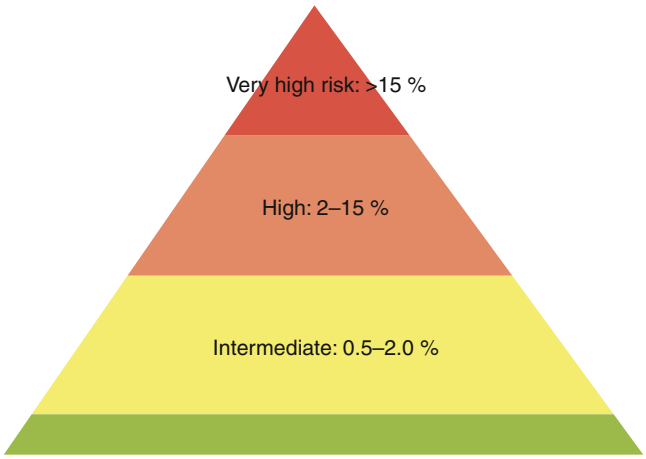

Fig. 46.1 Risk classification with low risk defined as annual CHD event rate less than 0.5 % (Reprinted from Braunwald [5]. With permission from Elsevier)

provides additive information that can be used to direct therapeutic changes that may beneficially impact overall CHD risk.

Importance of CRI in CHD Risk Assessment

Another important element that may garner additional attention in the revised NCEP guidelines might be the addition of CRI as a CHD risk equivalent, in view of the high rate of CHD events [7] and to which the National Kidney Foundation has endorsed an LDL-C target of less than 100 mg/dL irrespective of other CHD risk factors (http://www.kidney.org/professionals/doqi/kdoqi/toc.htm). Despite the inherent limitations of using FRS as a primary and/or sole tool for CHD risk assessment, the overwhelming majority of CHD risk continues to be accounted for by traditional CHD risk factors [11], and therefore it is doubtful that additional testing will be recommended as a primary screening tool in forthcoming NCEP guidelines. Undoubtedly, the focus of intensive therapies will continue to be aimed at reducing LDL cholesterol (LDL-C) and other atherogenic parameters (e.g., non-HDL-C). Among the continuing questions in this regard is how low should LDL-C be treated to?

LDL-C: How Low Should We Go?

Barring monogenic abnormalities that result in inborn errors of lipoprotein metabolism, total cholesterol (TC) and LDL-C approximate 70 and 30 mg/dL, respectively, at birth. These levels nearly double between 6 and 12 months [12], providing the foundation for "physiologic" TC and LDL-C anticipated in humans throughout life. In fact, it has been well established that CHD risk begins to accentuate as TC levels exceed 150 mg/dL with doubling of risk for each 50 mg/dL increment above 200 mg/dL. Conversely, societies at low risk of CHD exhibit LDL-C levels that approximate this physiologic range (e.g., ~50–80 mg/dL). Early statin-based clinical trials consistently demonstrated that lowering LDL-C improved CHD outcomes. This was followed by the demonstration that more intensive LDL-C lowering (on-treatment LDL-C ~ 70 versus 100 mg/dL) was also associated with reduced CHD risk [13–15]. What remains to be established is whether continued lowering of LDL-C to ~50 mg/dL is clinically superior to 70 mg/dL. This is currently being address in the 18,000 patient clinical trial, IMPROVE-IT-Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin (Ezetimibe/Simvastatin) versus Simvastatin (http://clinicaltrials.gov/ct2/show/NCT00202878), scheduled to be completed in 2013.

HDL-C: An Emerging Therapeutic Target

Despite the well-established inverse association between HDL-C and CHD risk, no definitive proof exists to date as to whether raising an isolated low HDL-C (i.e., less than 40 mg/dL) improves clinical outcomes. The most potent HDL-C raising medication, nicotinic acid (niacin), was recently employed to test this hypothesis based upon prior angiographic studies that found that reduced coronary arteriographic progression with niacin-statin combination compared with placebo (i.e., HDL Atherosclerosis Intervention Trial, HATS) [16]. Because the HATS protocol did not include a statin comparator group, a larger clinical outcome trial was designed and funded by NHLBI [17]. Entitled AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health), 3,414 men and women with vascular disease and the metabolic syndrome were assigned to either LDL-C lowering monotherapy (to a range between 40 and 80 mg/dL) or LDL-C lowering and niacin. The study was prematurely halted after a median follow-up of 32 months identified an unanticipated, though nonstatistically significant increase in ischemic stroke rates in the niacin assigned group [18]. In addition, there was no evidence of divergence in the primary endpoint between the groups. Table 46.1 outlines a number of suppositions to explain the failure of AIM-HIGH to meet its primary endpoint. Previously, the secondary prevention Coronary Drug Project (CDP) reported a 25 % reduction in nonfatal MI in men treated with niacin for 5 years and survival benefit 9 years after its discontinuance [19, 20]. Moreover, several clinical trials employing fibrate therapy did not demonstrate reductions in CHD risk until treatment had extended well beyond the AIM-HIGH treatment period [21, 22]. Taken together, the negative results of AIM-HIGH raise the possibility that

Table 46.1 Potential reasons for the failure of niacin-based therapy in AIM-HIGH

1. Underpowered to identify 25 % relative-risk reduction between groups
2. Majority of study participants had received statin (94 %) and/or niacin (20 %) therapy prior to study entry
3. Therapeutic background of statin therapy dilutes effects of other therapies
4. LDL-C levels were intensively matched between groups
5. HDL-C levels were increased in the monotherapy group
6. 32 months was an insufficient follow-up period
7. Niacin is an ineffective strategy in patients with vascular disease and low HDL-C

premature study termination after a 32-month follow-up period, may have been too short to identify differences between the groups. Alternatively, niacin may not be the cardioprotective agent previously touted when added to a background of statin therapy, especially when on-treatment LDL-C is reduced to 70 mg/dL or lower. This may be a primary "take home message" from AIM-HIGH pending results from the larger 25,000 patient trial comparing niacin-statin combination to statin monotherapy (Heart Protection Study 2 THRIVE; http://clinicaltrials.gov/ct2/show/NCT00461630). Until HPS2 THRIVE results are available, our practice is to withdraw niacin-based therapy unless LDL-C and/or non-HDL-C target goals cannot otherwise be attained in combination with statins and other lipid-lowering agents. In addition to niacin, the cholesteryl ester transfer protein (CETP) inhibitors represent another class of HDL-C raising agents that are currently in clinical testing. The first of the CETP inhibitors to be studied was torcetrapib and the randomized clinical trial, ILLUMINATE tested whether HDL-C raising superimposed upon standard of care measures that included statin therapy would improve CHD risk. Unfortunately, the study was prematurely terminated after identifying increased mortality in the torcetrapib treated arm [23]. Specifically, torcetrapib was found to possess side effects that included upregulation of the renin-angiotensin axis (RAAS) with increased aldosterone secretion and associated elevations in blood pressure and electrolyte disturbances [24]. Newer compounds that inhibit (e.g., anacetrapib, evacetrapib) or modulate CETP (e.g., dalcetrapib) [25–27] do not affect RAAS, and early phase clinical trials have been shown to be both safe and effective in raising HDL-C. At least two of these agents (dalcetrapib, anacetrapib) have progressed to large randomized clinical trials to assess whether treatment following an acute coronary syndrome (dal-OUTCOMES; http://clinicaltrials.gov/ct2/show/NCT00658515) or with stable angina (DEFINE; http://clinicaltrials.gov/ct2/show/NCT00685776?term=anacetrapib&rank=1; dal-OUTCOMES 2 http://www.clinicaltrials.gov/ct2/show/NCT01516541?term=dalcetrapib&rank=2) translates into improved clinical outcomes.

Triglycerides and CHD Risk

In 2011, the AHA released a scientific statement outlining the evidence supporting triglycerides as a biomarker of increased CHD risk [28]. While triglycerides represent an important source of energy storage and utilization, they have little, if any, atherogenic potential. Rather, their hydrolyzed by-products (i.e., "remnants") donate cholesterol to macrophages in a manner analogous to modified LDL. In effect, the combination of elevated LDL-C and triglycerides produce a mixed phenotype that is associated with higher risk of CHD than either elevations in LDL-C (barring monogenic abnormalities) or triglycerides alone. What has been less well established, however, is whether combined therapies aimed at lowering triglycerides beyond LDL-C reduction translates into clinical improvement because no studies have specifically addressed this issue in a hypertriglyceridemic population. The closest was a prespecified analysis in the ACCORD trial which found that the combination of statin and fibrate favorably reduced CHD risk ($p=0.057$) compared to statin alone in diabetic patients with elevated triglycerides (>200 mg/dL) and low HDL-C [29]. To more appropriately address this important issue, a large RCT entitled REDUCE-IT is currently underway (http://www.clinicaltrials.gov/ct2/show/NCT01492361?term=reduce+it&rank=1; accessed March 26, 2012).

Hypertension

Hypertension is another major risk factor for heart disease. With a current definition of hypertension as 140/90, roughly a fourth of the United States population can be considered hypertensive [30]. This would suggest that, as an independent risk factor for CHD, all efforts should be made to adequately control elevated blood pressure in patients. Different options are available for therapy and are addressed elsewhere in the book (Chaps. 31 and 32). It is very important to appreciate that with all of these options available for therapy (some as simple as diet and exercise), hypertension remains a ripe target for CHD risk factor modification.

Diabetes Mellitus

The effect of diabetes on cardiovascular disease is well described in a joint statement released by the AHA and American Diabetes Association [31]. Currently, over 25 million Americans are afflicted with this disease – putting a significant portion of the population at increased risk for the cardiovascular complications (http://www.cdc.gov/diabetes/pubs/factsheet11.htm?loc=diabetes-statistics; Accessed April 20, 2012). The increased presence of

microvascular disease in patients with diabetes makes it even more lethal and justifies aggressive management. It is worthy to note that it has, however, been demonstrated that overaggressive management of hyperglycemia in patients with cardiovascular disease is associated with increased mortality [32]. The subject of diabetes is discussed at length elsewhere within this book (Chap. 41), but the complex nature – pathophysiology and management – of this CHD risk factor cannot be overemphasized.

Nonlipid CHD Biomarkers

Though nonlipid biomarkers represent potentially important contributors to enhanced CHD event rates, there are currently limited data demonstrating that reduction of these parameters confer additional benefits beyond that achieved through lifestyle and medications aimed at improving lipids, blood pressure, and glycemic control. The most extensively studied of these atherogenic markers is C-reactive protein. Personality factors such as mental stress and depression have also been evaluated in CHD risk assessment and deserve mention.

C-Reactive Protein

C-reactive protein (CRP) predicts CHD independent of LDL-C [33] and has gained increased recognition in CHD risk assessment. Using high sensitivity assays, 3 categories of risk have been defined: low (<1 mg/L), intermediate (1–3 mg/dL), and high (>3 mg/L).

CRP is synthesized in the liver in response to the upregulation of peripheral cytokines, including IL-6 elaborated by adipocytes. As such, elevated CRP is tightly correlated with body mass index, obesity [34], and other measures of the metabolic syndrome (Table 46.2). Therapies that reduce CRP levels include weight-reducing measures (e.g., diet and exercise) and medications including lipid lowering (statins, niacin), aspirin (325 mg/day), and thiazolidinedione. The extent to which reducing elevated CRP may decrease CHD risk was the subject of the JUPITER trial [35]. This primary prevention trial evaluated normocholesterolemic (median LDL-C = 108 mg/dL) middle-aged and older men and women with high baseline CRP levels (placebo median, 4.3 mg/L). Despite "low" levels of LDL-C, placebo-treated patients exhibited annual event rates (2 %) analogous to high-risk patients (e.g., preexisting CHD). While statin treatment reduced both LDL-C and CRP significantly, resulting in dramatic reduction in CHD risk within 2 years of the follow-up period, it has been difficult to sort out the relative contribution of each of these statin-mediated effects on CHD events. One approach would be to investigate non-statin anti-inflammatory therapies in patients with CHD or CHD risk equivalents as is currently under investigation (http://www.clinicaltrials.gov/ct2/show/NCT01327846?term=hs-crp&rank=13). Until such data become available, the AHA and other governing bodies are not likely to endorse widespread CRP screening [36].

Table 46.2 Criteria defining the metabolic syndrome (presence of three or more of the following)

1. Increased waist circumference (men >40 in., women >35 in.)
2. Elevated triglycerides (≥150 mg/dL)
3. Low HDL-C (<40 in men and <50 mg/dL in women)
4. Elevated blood pressure (≥130/85)
5. Elevated blood glucose (≥110 mg/dL)

Mental Stress

A paradigm of how acute mental stress may lead to CAD events is shown in Fig. 46.2. A paradoxical vasoconstrictor response following intracoronary acetylcholine, an endothelin-dependent vasodilator, was observed in patients asked to perform mental arithmetic [38]. Other studies have extended these findings by demonstrating wall motion abnormalities, transient reduction in ventricular function, and silent ischemia in response to mental stress [39]. More recently, these findings have been extended to include a reduced likelihood of silent ischemia during high positive emotional periods (e.g., happiness) compared with negative emotions such as tension, frustration, and sadness.

Depression

As many as 20 % of MI survivors experience major depression and the risk of mortality quadruples within the first year following a CHD event [40]. A recent meta-analysis suggests that depression may be a predictor of initial CHD events, even after adjusting for other covariates [41]. An overactive hypothalamic-pituitary-adrenocortical axis in depressed subjects leads to enhanced cortisol production and mediation of pro-atherothrombotic activity (e.g., platelet activation and systemic inflammation) [42, 43] coupled with reduced heart rate variability that are believed to contribute to accelerated CHD event rates [44]. Tricyclic antidepressants are often contraindicated in CHD patients owing to potential deleterious CV effects including tachyarrhythmias, prolongation of the QT interval, and orthostatic hypotension. In contrast, selective serotonin reuptake inhibitors (SSRIs) have few, if any, untoward cardiovascular side effects and are the drugs of choice [45].

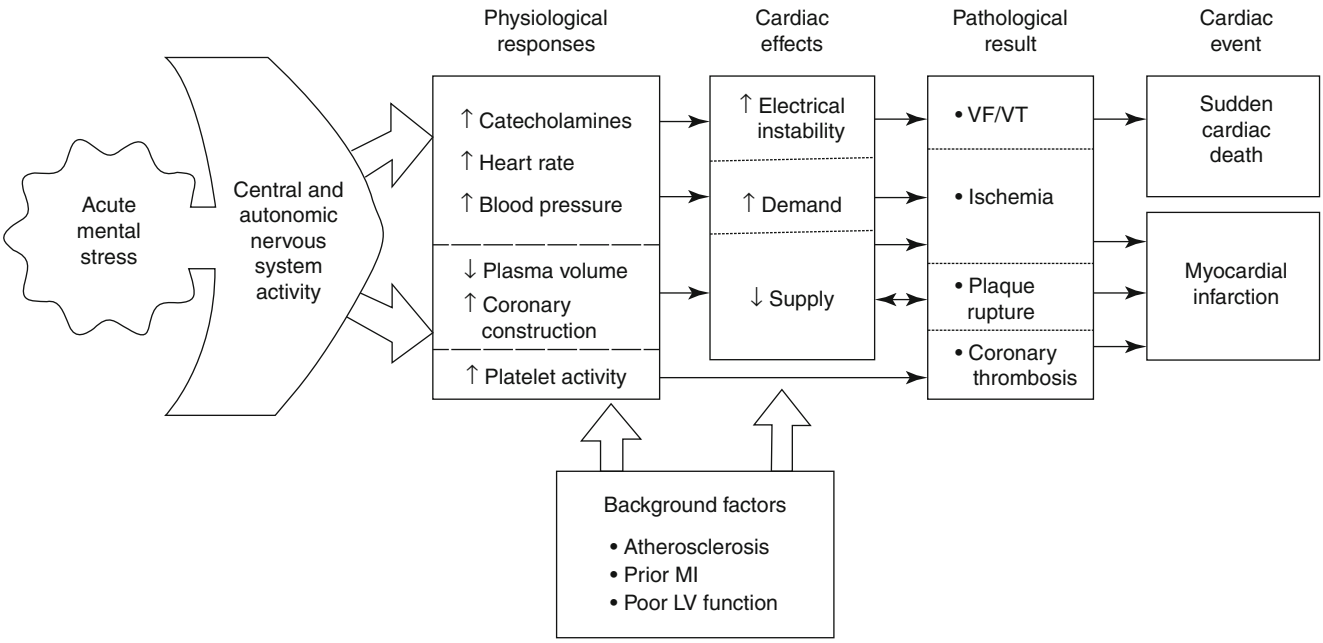

Fig. 46.2 Pathophysiologic model of mental stress as a trigger of myocardial ischemia and infarction (Reprinted from Krantz et al. [37]. With permission from Elsevier)

Diagnostic Strategies

Of the numerous emerging noninvasive diagnostic tools under evaluation, carotid intima-media thickening and coronary calcification have been the most investigated to date.

Carotid Intima-Media Thickness

Measurement of common carotid artery (CCA) intima-media thickness (IMT) remains the most validated noninvasive surrogate for detection of early atherosclerosis because of its high reproducibility and low variability. CCA IMT is highly correlated with existing CHD and predictive of future CHD events in subjects without symptomatic disease [46]. The mean CCA IMT in 55-year-old men and women are 0.70 and 0.64 mm, respectively, with an average annual cross-sectional change approximating 0.008 mm/year [47]. However, high-risk groups such as FH may have up to a five-fold greater rate of CCA IMT progression compared to the lower risk subjects. Statin therapy may reduce or reverse CCA IMT progression, and it appears that the lower LDL (or non-HDL) achieved, the greater the effect, mirroring similar observations using IVUS [48].

Coronary Artery Calcification

Another noninvasive method employed for detection of subclinical CHD is scanning for coronary artery calcification. While the majority of published studies to date have evaluated electron-beam CT, helical or multislice CT scanners are more readily available in hospitals and are being more widely used. Although the degree of calcification correlates with anatomic abnormalities as assessed by coronary arteriography, highly calcified vessels are often stable and are not predictive as the culprit lesion in acute coronary syndromes (ACS) or MI. Nevertheless, high calcium scores (age and gender adjusted calcium exceeding the 75th percentile) are associated with a greater presence of noncalcified, highly thrombogenic lipid-rich lesions at high risk of rupture/erosion, which result in a 4-fold or greater increased likelihood of MI. Because of significant retest variability in calcium scores, a standardized measuring system was recently developed by the International Consortium for Standardization in Coronary Artery Calcium. This new standard uses 100 mg/cc as the threshold for a positive scan and is applicable across the spectrum of devices used to measure coronary calcium. While calcium scanning is presently not recommended as a screening tool for diagnosing CHD based on the 2007 ACC/AHA Consensus Statement, recent data suggest that this test may be most useful in modifying CHD risk prediction with Framingham Risk Scores in the intermediate range (10–20 %) but not at lower risk ranges. Nonetheless, the highest scores (>300) were associated with the greatest likelihood of CHD events across all strata of Framingham risk (Fig. 46.3) [50]. The Multi-Ethnic Study of Atherosclerosis has demonstrated the association between progression of coronary calcium and the development of cardiovascular events [51].

Lifestyle Therapies: The Obesity Epidemic

Deaths attributable to poor diet and inactivity are now responsible for 400,000 deaths in the USA accounting for 1 in 6 deaths and second only to tobacco as the leading preventable cause of mortality [49]. In fact, since 1990, death rates resulting from obesity have climbed 33 % compared to the approximate 9 % increase related to smoking. Likely explanations include fast-food lifestyles, increases in food portion sizes, decline in school physical education programs, and sedentary activities including more weekly hours spent on computers and television. Obesity, defined as BMI >30 kg/m^2, is epidemic in the USA with all states reporting an obesity prevalence of at least 20 % (Fig. 46.4) (http://www.cdc.gov/obesity/data/trends.HTML). Moreover, with aging, intrinsic basal metabolic rate (BMR) defined as energy expenditure at rest falls at an approximate rate of 5 kcal/d per year. Not surprisingly, weight gain in adults has averaged approximately 10 pounds during the past decade. Thus, even before discussing specific dietary measures, reduction in total caloric intake and or increased energy expenditure should be a top priority in CHD risk reduction strategies.

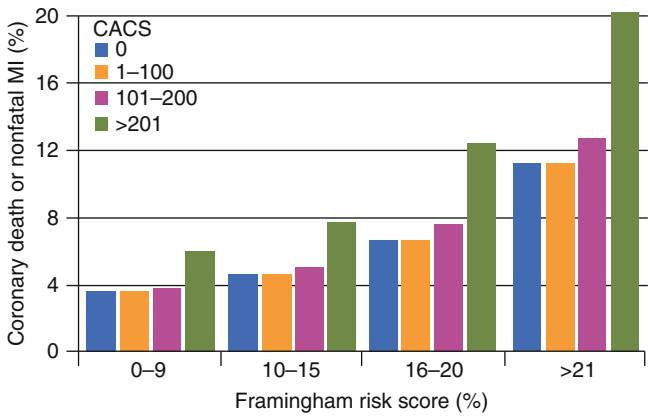

Fig. 46.3 Predicted 7-year event rates from COX regression model for CHD death or nonfatal MI for categories of Framingham Risk Score or coronary artery calcium score (CACS) (Adapted from Mokdad et al. [49], 210–5. With permission from American Medical Association)

Nutritional Aspects of Preventive Cardiology

Important Lessons from Our Paleolithic Ancestors

Barring monogenic abnormalities (e.g., FH), a diet low in saturated and trans fats translates into a low risk of CHD, as exemplified by today's hunter-gatherer societies. A comparison of the dietary composition of the foods consumed by the descendants of modern preliterate societies (e.g., our Paleolithic ancestors) with present Westernized countries is outlined in Table 46.3.

The reduced percentage of fat consumed in Stone Age societies reflects a predominantly low intake of saturated fat and of course no trans fats. Wild game, the primary source of fat, has been found to contain considerably less carcass fat (4 %) compared to domesticated livestock (30 %). Equally important was the absence of dairy products from the diet of our Paleolithic ancestors; the processing of milk products was developed during the agricultural revolution within the past 5,000 years. Harvesting of tobacco also occurred during this period. Thus, not only was the relative intake of fat reduced in these preagrarian societies, but the percentage of saturated fat consumption was also low as reflected in the polyunsaturated to saturated fat (P:S) ratio. It is noteworthy that fiber intake was considerably higher and sodium intake lower compared with modern day societies. Taken together, the earlier dietary habits support the notion that atherothrombosis was an uncommon occurrence.

Fig. 46.4 2010 obesity trends in the United States (Reprinted from Adult Obesity Facts. CDC. 2010. http://www.cdc.gov/obesity/data/trends.HTML)

2010 state obestity rates							
State	%	State	%	State	%	State	%
Alabama	32.2	Illinois	28.2	Montana	23.0	Rhode Island	25.5
Alaska	24.5	Indiana	29.6	Nebraska	26.9	South Carolina	31.5
Arizona	24.3	Iowa	28.4	Nevada	22.4	South Dakota	27.3
Arkansas	30.1	Kansas	29.4	New Hampshire	25.0	Tennessee	30.8
California	24.0	Kentucky	31.3	New Jersey	23.8	Texas	31.0
Colorado	21.0	Louisiana	31.0	New Mexico	25.1	Utah	22.5
Connecticut	22.5	Maine	26.8	New York	23.9	Vermont	23.2
Delaware	28.0	Maryland	27.1	North Carolina	27.8	Virginia	26.0
District of Columbia	22.2	Massachusetts	23.0	North Dakota	27.2	Washington	25.5
Florida	26.6	Michigan	30.9	Ohio	29.2	West Virginia	32.5
Georgia	29.6	Minnesota	24.8	Oklahoma	30.4	Wisconsin	26.3
Hawaii	22.7	Mississippi	34.0	Oregon	26.8	Wyoming	25.1
Idaho	26.5	Missouri	30.5	Pennsylvania	28.6		

Table 46.3 Comparison between late Paleolithic and contemporary American diets

	Late Paleolithic diet	Contemporary American diet
Energy (%)		
Carbohydrate	46	46
Fat	21	42
Protein	33	12
P:S ratio[a]	1.4:1	0.44
Cholesterol (mg)	520	300–500
Fiber (g)	100–150	<20
Sodium (mg)	<700	2,300–6,900

Modified from: Eaton et al. [52] and Eaton et al. [53]
[a]Polyunsaturated/saturated

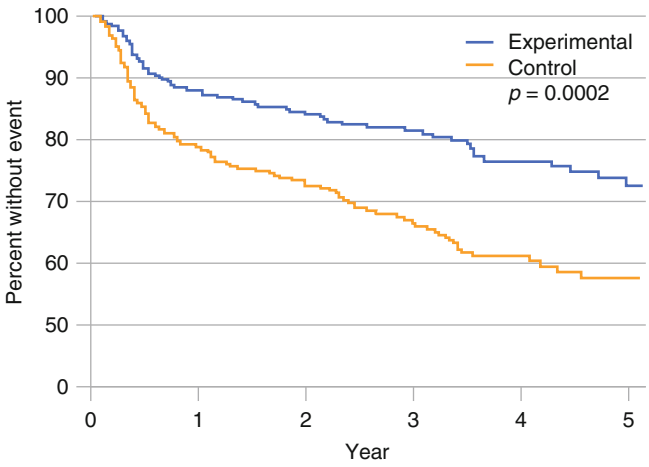

Fig. 46.5 Survival curves between the experimental and control groups in the Lyon Diet Heart Study (Reprinted from de Lorgeril et al. [61]. With permission from Lippincott Williams & Wilkins)

The Impact of Dietary Fat in Cardiovascular Disease Prevention

Saturated Fat

It has been well established that diets high in saturated fat (>40 % of caloric intake) are associated with an increased tendency to atherothrombosis. Over 40 years ago, Connor demonstrated the impact of saturated fatty acids on coagulation and thrombosis [54]. Saturated fatty acids may also inhibit LDL-C receptor activity, thereby raising LDL-C [55]. In general, for each 1 % rise in saturated fat, there is a 2.7 mg/dL increase in total cholesterol. Of the major saturated fats, only stearate is believed to have a neutral effect on cholesterol levels.

Trans Fatty Acids

Trans fatty acids are present in animal and dairy fats and when polyunsaturated vegetable oils, are (partially) hydrogenated to increase product stability and shelf life. Substitution of *trans* fatty acids for *cis* (e.g., oleic acid) raises LDL, TG, and Lp(a) and reduces HDL [56]. Trans fats represent ~20 % of total dietary fat, and common sources include shortening used in baked products (e.g., doughnuts, cookies), packaged foods (e.g., potato chips, crackers), and margarines. There are now data that demonstrate that the link between trans fatty acids and abnormal lipids and lipoproteins extends to enhanced CHD event rates as shown in the Framingham Heart Study [57], Alpha-Tocopherol Beta-Carotene study (ATBC) [58], and Nurses Health Study (NHS) [59]. NHS was the most comprehensive of the *trans* fat studies, and they observed that each 2 % increase in trans fatty acid intake was associated with a near doubling of CHD rates. Since 2006, the FDA has mandated that food manufacturers list the amount of *trans* fats provided the amount exceeds 0.5 g per serving. Hence, a label that states "*trans fat* free" may contain up to 0.5 g of *trans* fat and go undetected, and petitions have been submitted for revision of labeling to include any *trans fats* contained in a product. Denmark became the first country to strictly regulate *trans* fat-containing products, and in recent years, several cities in the USA have also adopted regulatory measures banning *trans* fats in restaurants (e.g., New York City). Maryland and Vermont are considering a statewide ban.

Monounsaturated Fat

The Mediterranean diet gained prominence following publication of the Seven Countries Study which disclosed a significantly lower incidence of CAD in southern European countries (e.g., Italy, Spain) compared with North America. The primary fatty acid, oleate, reduces VLDL-C and LDL-C and may reduce macrophage uptake of LDL-C by inhibiting oxidation. In addition to olive oil, the Mediterranean diet also includes a high concentration of fruits and vegetables (an excellent source of antioxidant vitamins and flavonoids), supplemented with fish, poultry, and, occasionally, red meat. Alcoholic beverages (particularly red wine) and nuts are consumed in the Mediterranean diet. Milk products, when consumed, were often in the form of grated cheese added to pasta. Eggs (up to 4) were also consumed weekly. In addition to its palatability, the Mediterranean diet has been the only diet to demonstrate CHD reduction. In the Lyon Diet Heart Study, subjects randomized to this diet experienced a 73 % reduction in CAD deaths and nonfatal MI and 70 % reduction in overall mortality during the initial 27-month period [60] with benefits extending to 4 years (Fig. 46.5). It has also been suggested that diabetic patients benefit from a Mediterranean rather than a high-carbohydrate, low-fat diet. As carbohydrate intake exceeds 65 % of total caloric intake, VLDL-C production is increased thereby raising plasma TG level. Even 55 % carbohydrate diets have been associated with elevated TG, reduced HDL levels and potential deterioration of glycemic

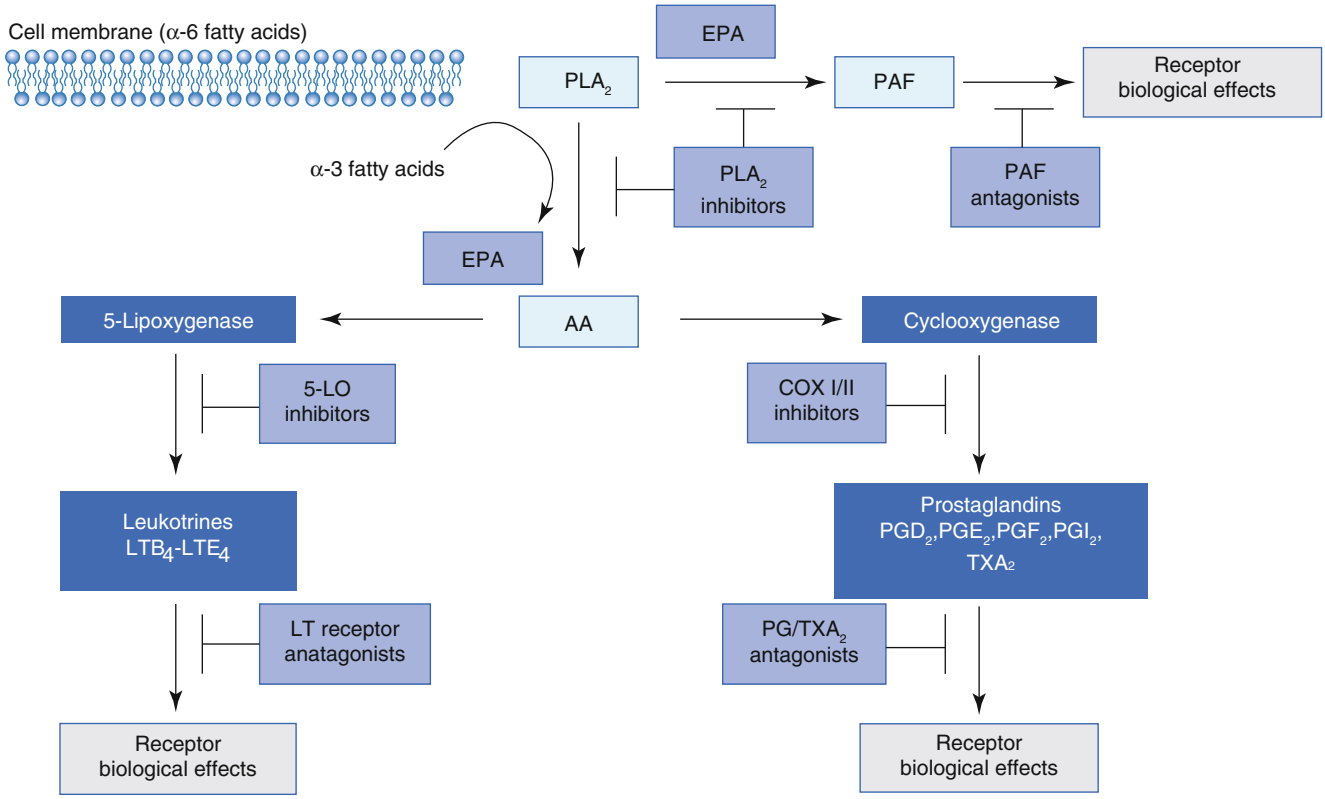

Fig. 46.6 Eicosanoid and platelet-activating factor (Reprinted from Heller et al. [64]. With permission from Springer Science + Business Media)

control [62]. In addition to olive oil, other important sources of monounsaturated fats are avocados and nuts [63]. Avocados are rich in vitamins E and C while nuts provide a rich source of antioxidants, including the phytonutrient ellagic acid (walnuts, pecans), Vitamin E (almonds, peanuts), and omega-3 fatty acids (e.g., walnuts).

Diets Rich in Omega-3 Fatty Acids

Omega-3 fatty acids are long-chain polyunsaturated fats that contain the first double bond at the third position adjacent to the methyl terminal of the molecule. As a precursor of arachadonic acid, they may be incorporated through the cyclooxygenase or leukotriene pathway (Fig. 46.6) providing both antiplatelet and anti-inflammatory effects. The clinical impact of these fatty acids was demonstrated in Greenland Eskimos whose diet of predominantly fatty fish was enriched with omega-3's (e.g., whale, salmon, herring and mackerel). Bang and Dyerberg found that these individuals had an increased bleeding time and a low incidence of CAD and astutely attributed these effects to a high content of omega-3 fatty acids such as eicosapentanoic acid (EPA) (C20:5–3) and dicosahexanoic acid (C22:4–3). In addition, significant TG lowering (20–50 %) was also observed owing to reduced hepatic VLDL-C secretion. Both observational (e.g., Diet and Reinfarction Trial) [65] and randomized clinical trials (e.g., GISSI) [66] of patients with CHD, omega-3 fatty acid supplements significantly reduced CV events (death, nonfatal heart attacks, nonfatal strokes). Omega-3 fatty acids are believed to reduce sudden cardiac death by inhibiting L-type calcium channels and voltage dependent sodium currents [67]. In view of the cardioprotective effects of fish, the AHA/ACC has endorsed consumption of 1 g of omega-3 containing fish daily either in the form of fish oil capsules or consumption of oily fish [68]. Table 46.4 below lists the content of omega-3 among fish consumed in the USA. Generally, for each 1 g of EPA/DHA, there is also a 10 % reduction in TG; often 2–4 g are needed in hyperTG patients. High doses should be used cautiously in CHD patients receiving aspirin (>162 mg/day) and/or clopidogrel, although one recent study in patients with atrial fibrillation did not find excessive bleeding risk with this combination [70]. Fish oil capsules should be refrigerated or frozen after opening to minimize oxidation and fishy odor eructation. Capsules tested by Consumer Reports® are free of mercury and other contaminants.

Table 46.4 Total fat and content of the highest omega-3 containing fish in grams per 3.6 oz serving

Fish	Total fat	Omega-3 content per 100 g
Sardines, in sardine oil	15.5	3.3
Atlantic mackerel	13.9	2.5
Pacific herring	13.9	1.7
Atlantic herring	9.0	1.6
Lake trout	9.7	1.6
Anchovy	4.8	1.4
Chinook salmon	10.4	1.4
Sablefish	15.3	1.4
Bluefish	6.5	1.2
Sockeye salmon	8.6	1.2
Atlantic salmon	5.4	1.2
Pink salmon	8.6	1.2

Based on data from Connor and Connor [69]

Weight Loss Diets: Low Carb Versus Low Fat

Weight loss is most sustainable if performed on a gradual basis. Small changes in diet and exercise patterns will enhance the likelihood of achieving the recommended reductions approximating 1 lb/week. Table 46.5 provides examples of modest lifestyle measures that enable net negative balance of 500 kcal/day in an average 70 kg adult. A primary concern with various weight loss programs is the induction phase, where water loss accounts for the precipitous weight drop. For example, in low-carbohydrate, high-protein diets, weight loss is rapid because for each gram of glycogen depleted, 2–4 g of intracellular water are mobilized, resulting rapid weight (e.g., water) loss. If carbohydrate restriction is severe (less than 60 g), ketosis ensues, leading to nausea, reduced appetite and hyperuricemia as ketones compete with uric acid for renal tubular excretion [71]. Diets low in total and saturated fat were popularized by Pritikin; he reduced his dietary fat intake following an MI and reportedly had minimal evidence of coronary disease on postmortem examination. The Lifestyle Heart Trial also evaluated the efficacy of a very low-fat diet (10 % of caloric intake) in concert with lifestyle changes (aerobic exercise, stress management training, smoking cessation, and group support) on arteriographic progression in patients with preexisting CAD. The dietary component of the treated (experimental) group consisted primarily of fruits, vegetables, grains, legumes and soybean products. Red meat, poultry and fish consumption was not permitted. After 1 year, the experimental group evidenced reduced progression and slight regression of lesions [72]. At the 5-year follow-up, total fat intake represented 8.5 % of calories, LDL-C was reduced 20 %, and reduced coronary arteriographic progression compared to the control group became more apparent. Nevertheless, there were still 25 cardiac events among the 28 experimental patients during the 5-year follow-up period [73]. As the TG level in the experimental group was elevated (mean TG = 258 mg/dL), these results suggest that intensive lifestyle measures may not be sufficient in optimizing CAD event reduction. Other low-fat nonpharmacologic trials including the St. Thomas Arteriographic Regression Study (STARS) (27 % fat) and the Heidelberg Exercise/Diet Study (<20 % fat) also resulted in reduced arteriographic progression of CAD in patients assigned to the intervention group. While evidence supports reduction of total fat intake to less than 40 % of total caloric burden, it remains unclear whether very low-fat diets (<10 % fat) as consumed in the Lifestyle Heart Diet offer any advantages to more palatable diets offered by the Mediterraneans (25–35 % fat), the Paleolithic diet (21 % fat; see above), or an American Heart Association diet supplemented with lipid-lowering therapy. The combination of intensive diet, exercise, and lipid-lowering agents may yield the most favorable responses on TC, LDL, and TG (Fig. 46.7), but the relative impact on CAD event rates has only been established for a Mediterranean approach. In terms of weight loss, macronutrient content appears to be less important than overall adherence to the specified diet [75]. The one exception would be in hypertriglyceridemic subjects where a relatively low-carbohydrate diet is favored due to enhanced VLDL secretion as carbohydrate intake exceeds ~60 % of total energy intake [28].

Table 46.5 Five ways to offset 500 kcal daily in a 70 kg adult

	Eliminate	Add
1	4 oz bagel (250 cal)	45 min walk at 4 mph (250 cal)
2	1 candy bar (250 cal)	55 min yoga (250 cal)
3	16 oz soda (200 cal)	50 min low impact aerobics (300 cal)
4	2 oz whole wheat pretzels (200 cal)	35 min jogging (300 cal)
5	2 slices of bread (150 cal)	40 min stationary bicycling (moderate) (350 cal)

Based on data from: USDA National Nutrient Database (http://www.ars.usda.gov/main/site_main.htm?modecode=12-35-45-00) & DiscoverFitness.Com (http://www.discoverfitness.com/MET_value_table_.html)

Cardioprotective Nutrients

In recent years, polyphenols found in a variety of foods have been linked to cardioprotective health. This broad group of antioxidant compounds includes flavonoids which are plant-derived pigments responsible for bright colored chemical components present in fruits and vegetables. Epidemiologic studies have evaluated the clinical significance 2 flavonoid subclasses, flavan-3-ols (e.g., catechins) and flavonols

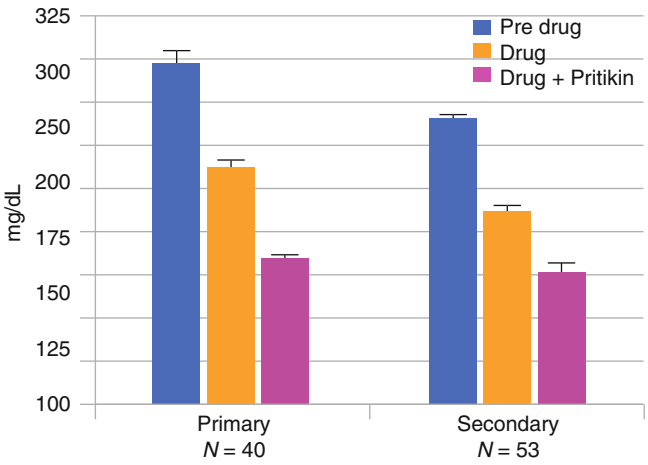

Fig. 46.7 Total serum cholesterol values before and after cholesterol-lowering drug therapy and then with the addition of the Pritikin diet and exercise program for both primary and secondary prevention groups. All three values were significantly different ($P<0.01$) for both groups (Reprinted from Barnard et al. [74]. With permission from Elsevier)

Table 46.6 Selected foods with high flavonoid content from the 2003 USDA database (mg/100 g or /100 mL)

High catechin-containing foods	
Tea, green brewed	133
Tea, black brewed	114
Chocolate bar, dark	53
Blackberries	19
Chocolate bar, milk	13
Red table wine	12
Cherries, raw	12
Apricots, raw	11
Raspberries	9
Apples, with skin	9
High quercetin-containing foods	
Cocoa powder	20
Onions, cooked, boiled	19
Cranberries, raw	14
Onions, raw	13
Lingonberries, raw	12
Spinach, raw	4.9
Apples, with skin	4.4
Barley	3.8
Celery	3.5
Broccoli, raw	3.2
Blueberries	3.1
High myricetin-containing foods	
Cranberries, raw	4.3
Rutabagas	2.13
Black Currant Juice	1.9
Tea, green brewed	1.1
Blueberries	0.82
Red table wine	0.7
Grape Juice	0.6
Grapes, black, green, or white	0.45
Tea, black brewed	0.45

Table 46.7 Flavonoid content in selected nuts (mg/100 mg proanthocyanidins)

Nut	PA
Hazelnut	500.7
Pecans	494.1
Pistachios	237.3
Almonds	184
Walnuts	67.3
Peanuts	15.6
Peanut Butter	13.2
Cashews	8.7

(e.g., quercetin, myricetin), the former of which represent powerful antioxidants with greater potency than vitamins A, C, and E. In the Zutphen elderly prospective study of 800 seniors (65–84 years old), the highest intake of catechins was inversely associated with CHD death after adjustment for other covariates ($RR=0.48$; 95 % CI 0.28, 0.82), so that for each 50 mg intake, there was a corresponding 25 % reduction in CHD events [76]. Rich sources of catechins are listed below. Quercetin and myricetin are also potent antioxidants (Table 46.6). In a prospective study of 10,000 Finnish men and women, a 20 % reduced incidence of type 2 diabetes mellitus coincided with higher quercetin and myricetin intake; quercetin was also found to be inversely related to CHD mortality [77]. A major fraction of the total flavonoid content has been analyzed in more than 40 different foods [78]. In the USA, the mean daily intake of these antioxidants approximated 60 mg/daily with the majority obtained from 3 primary sources, apples (32 %), chocolate (18 %), and grapes (18 %). Examples of the flavonoid content in selected nuts are shown in Table 46.7. In the Nurses Study of 86,000 women aged 34–59, frequent intake of nuts (1 oz or greater at least 5 times weekly) was associated with a 35 % reduction in fatal CAD events and nonfatal MI compared to women who did not (or rarely) consume nuts [79]. Overall, the most concentrated source of antioxidant units was found in cinnamon, and studies suggest that polyphenolic polymers potentiate insulin action, which in turn may improve glycemic control in diabetic patients [80, 81]. Taken together, identification of potential cardioprotective nutrients provides an excellent opportunity to further explore the critical yet underemphasized role of diet in the prevention of CHD.

The Impact of Exercise in Cardiovascular Disease Prevention

Individuals with a high aerobic capacity have a lower incidence of CAD compared with sedentary subjects. While it has been widely touted that the most well-conditioned athletes present with the lowest case-fatality rates

of MI [82], moderate levels of physical activity have also been associated with favorably reduced rates. These activities must persist throughout life; a high school athlete that foregoes exercise in later life is not protected from the subsequent development of CAD [83]. Exercise is beneficial throughout all age groups. In fact, regular exercise in the elderly (walking or cycling for 20 min three times weekly) resulted in a 30 % reduction in CHD and total mortality. In addition, moderate physical activity may also reduce stroke rates. In the Harvard Alumni Health Study, an approximate 50 % reduction in stroke was observed in men (mean age = 58 years) who expended 2–3,000 kcal of energy weekly. This can easily be achieved with 1 h of brisk walking (3–4 miles/h) daily. We also recommend wearing a pedometer with a minimum of 10,000 steps taken daily. Finally, light weight lifting exerts an additional 20–25 % reduction in CHD event rates and is independent of other cardioprotective measures [84].

The ABCs of CHD Prevention

In addition to quitting smoking, physical activity, and weight management (see above), other important considerations in maximizing secondary preventive efforts are antiplatelet agents, ACE inhibitors, beta-blockers, and cholesterol-lowering therapies (covered in more depth in previous chapters).

Antiplatelet Agents

Aspirin reduces the risk of CHD 20–25 % in high-risk patients and remains the first-line antiplatelet drug because of its relative safety, low cost, and cost-effectiveness. However, the FDA denied Bayer's petition for routine aspirin use in primary prevention because of the lack of data demonstrating reduction in CHD mortality or ischemic stroke. Previous studies have indicated that the platelet ADP inhibitor, clopidogrel, reduces CHD events by 10 % compared with aspirin in acute coronary syndromes or non-ST-segment elevation MI [85]. Moreover, in patients undergoing PCI, the combination of clopidogrel and aspirin was shown to be more effective in reducing MI or CHD death than aspirin alone (OR 0.23, 95 % CI 0.11–0.49, $p = 0.0001$). In the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial ($n = 12{,}000$), the combination of aspirin and clopidogrel treated for 9 months (in subjects not having PCI) resulted in a 20 % reduction in the primary endpoint (MI, CVA, CHD death). While risk of bleeding was generally higher, the most favorable combination included use of low-dose (75 mg/day) aspirin. In the smaller subgroup of PCI subjects ($n = 2{,}100$), pretreatment with clopidogrel resulted in a 30 % reduction in the primary endpoint. Continuation of clopidogrel for up to 1 year following PCI continued to show benefit as indicated by 27 % reduction in MI and stroke. Ongoing studies will determine whether longer-term combination treatment (e.g., 1–3 years) remains cardioprotective. In addition to use for ACS and as pre- and post-PCI therapy, clopidogrel (75 mg/day) is a suitable replacement for aspirin in allergic or insensitive patients and in those who have experienced atherothrombotic events on aspirin. Prasugrel is an option as well, with studies showing decreased ischemic events when used for PCI used during ACS. Its use is, however, associated with increased bleeding [86].

Angiotensin-Converting Enzyme (ACE) Inhibitors

Randomized controlled trials in MI survivors have revealed significant reductions in recurrent cardiovascular events and mortality (20–25 %) with ACE inhibitor use. The HOPE study extended the benefit of ACE inhibition using ramipril in high-risk subjects (CHD and diabetics) even without markedly compromised EF (>40 %). Within the past decade, the EUROPA study showed that ACE inhibition resulted in 20 % reduction in CHD death and MI in patients with stable coronary heart disease and without CHF. In this population, ACE inhibition is cost-effective as 4 years of therapy is expected to prevent 1 event for every 50 treated patients [87].

Beta-Blockers

β-Blockers are very effective agents for reducing recurrent MI events (15–25 %), sudden cardiac death (30–35 %), and overall mortality (20 %). Hemodynamically stable post-MI patients with compromised ventricular function (<40 %) also benefit from β-blocker use.

Cholesterol-lowering medication (see above)

Fish oil therapy (see above)

Potential Cumulative Effect of Secondary Preventive Measures

The impact of established strategies on offsetting CHD events is shown in Table 46.8.

Among high-risk patients, defined as an annual CHD event rate of 4 %, employing all of these strategies and cigarette cessation would reduce the risk by an estimated 80 % and thereby reduce event rates to a level observed in low-risk subjects. Overall and with few exceptions, CHD remains

Table 46.8 Potential cumulative impact of four simple secondary-prevention treatments

	Relative-risk reduction (%)	2-year event rate (%)
None	–	8
Aspirin	25	6
β-Blockers	25	4.5
Lipid lowering (50–60 mg/dL)	30	3
ACE inhibitors	25	2.3

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largely avertable in the USA, and even among genetically susceptible individuals, effective strategies are now available to prevent initial and recurrent CHD events [88].

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Peripheral Arterial Disease

47

Giovina Lara Bomba and Jonathan L. Halperin

Background

The most widely recognized peripheral vascular disease in adults is *obstructive atherosclerosis of the extremities* or *peripheral arterial disease* (PAD). The traditional term "arteriosclerosis obliterans" distinguishes the development of obstructive lesions from normal aging by which the arteries increase in diameter, rigidity, and calcium content. The disease was defined in 1958 by the World Health Organization as a "variable combination of changes of the intima of arteries (as distinguished from arterioles) consisting of the focal accumulation of lipids, complex carbohydrates, blood and blood products, fibrous tissue and calcium deposits, and associated with medial changes."

Atherosclerotic peripheral arterial disease refers to a range of non-coronary arterial vascular syndromes with progressive stenosis, occlusion, or aneurysmal dilation, most commonly affecting the lower extremity. Lower extremity PAD involves occlusive disease of the aorta, iliac, femoral, and more distal arteries. Patients with PAD typically carry a substantial burden of systemic atherosclerotic disease. Clinical manifestations associated with lower extremity PAD include decrements in functional capacity and quality of life, including loss of limb.

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Epidemiology

By the time symptoms of obstructive arterial disease develop, there is usually at least 50 % narrowing of the vascular lumen. Based on 26-year longitudinal surveillance of the Framingham Heart Study cohort of 5,209 subjects, the annual incidence of symptomatic ischemic arterial obstructive disease was 0.26 % for men and 0.12 % in women [1]. The incidence increased with age until age 75 years, with about a twofold male predominance at all ages (Fig. 47.1). The peak incidence of symptomatic limb arterial obstructive disease occurred in males in the sixth and seventh decades of life. Fewer than 10 % of nondiabetic cases younger than 60 years were females. The incidence in women beyond menopause rose quickly toward that in men.

The prevalence of arterial obstructive disease exceeds that of symptomatic ischemia [3]. Since patients often present with atypical limb symptoms or without claudication, the frequency of PAD diagnosis is generally considerably lower than the prevalence of the disease. Based on the Ankle Brachial Index (ABI), the prevalence of PAD in unselected populations 25–65 years old was 0.7 % for females and 1.3 % for males. The prevalence depends, however, upon the threshold ABI selected for diagnosis [4]. The national cross-sectional survey of PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) program, in which PAD diagnosis was defined by ABI ≤0.9, detected the disease in 29 % of patients who were either 50–69 years old with risk factors of tobacco smoking or diabetes mellitus or ≥70 years old regardless of risk factors [5]. More than 70 % of the primary care physicians participating in the PARTNERS study were unaware that these patients had PAD before screening.

In elderly patients, gangrene may be the initial symptom because coexisting conditions limit ambulation. In the Rotterdam Study of 7,715 subjects aged ≥55 years, the prevalence of PAD was 19.1 % based on ABI <0.9, yet symptoms of intermittent claudication were reported by only 6.3 % of patients. In an elderly nursing home population, the prevalence of severe obstructive arterial disease (ABI <0.7) was

C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2_47, © Springer Science+Business Media New York 2013

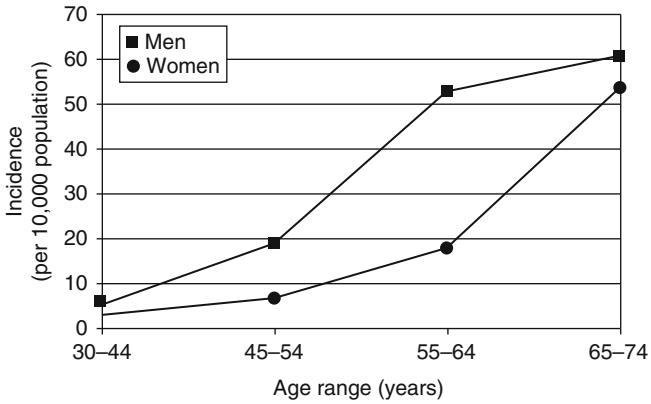

Fig. 47.1 Age-specific annual incidence: intermittent claudication (Adapted from Ref. [2]. With permission from Lippincott Williams & Wilkins)

approximately 50 %, predicting increased mortality compared to patients without signs of disease. Among patients older than 90 years, the second most common surgical operation is lower extremity amputation for limb arterial disease or gangrene.

A meta-analysis of population-based studies found that ABI added predictive value on top of Framingham risk score analysis. Low ABI was associated with twice the mortality and morbidity for each Framingham risk category [6]. A German epidemiological study evaluated the ABI in 6,880 patients 65 years old or older and found asymptomatic or symptomatic PAD in 21 %. Whether symptomatic or not, patients with PAD faced an increased risk of vascular events including mortality [7].

Risk Factors

Hyperlipidemia, diabetes mellitus, hypertension, and tobacco smoking modify the effects of age, gender, and heredity on atherosclerosis. Specific risk factors are additive and better predict relative than absolute risk. Overall, the major cardiovascular risk factors correlate better with intermittent claudication than with clinical manifestations of coronary heart disease.

Hyperlipidemia

The prevalence of hyperlipoproteinemia in patients with PAD ranges in various studies from 31 to 57 %, and intermittent claudication is over twice as common in patients with serum cholesterol levels higher than 260 mg/dl than in those without hyperlipidemia. In the Edinburgh Artery Study, PAD was directly associated with elevated serum cholesterol levels and inversely related to high-density lipoprotein (HDL) levels [8]. The development of PAD is independently associated with elevations in lipid peroxides, such as oxidized low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL) [9, 10]

Diabetes Mellitus

In patients with diabetes, peripheral atherosclerosis has a predilection for the tibial and peroneal arteries, for which revascularization procedures are more difficult. While the incidence of femoropopliteal arterial obstructive disease is similar to that in the nondiabetic population, aortoiliac occlusive disease may occur less frequently in patients with diabetes. The risk of developing PAD appears related to the duration of non-insulin-dependent diabetes mellitus [11]. Diabetes raises the risk of ischemic gangrene 20-fold and that of surgical amputation 4-fold. Coexisting sensory and autonomic neuropathy, lack of reflex hyperemia, loss of pain sensation, and arteriovenous shunting contribute to ischemic complications in diabetic patients.

Hypertension

In the Framingham study cohort, hypertension increased the risk of PAD 2.5- to 4-fold in men and women, respectively. Autopsy studies have demonstrated more extensive atherosclerosis of the aortoiliac arteries in hypertensive men than in age-matched normotensive controls. In women, this difference is more generalized along the course of the arterial tree. Limb arterial obstructive disease occurs twice as frequently as coronary artery disease among hypertensive individuals.

Tobacco Smoking

The Framingham Heart Study found a relationship between the number of cigarettes smoked and the incidence of intermittent claudication. Multivariate analysis found that tobacco smoking was the strongest single risk factor for development of symptomatic obstructive arterial disease. In the Framingham Offspring Study, for each 10-pack year increment in smoking, there was a 1.3-fold greater incidence of PAD [12]. The incidence of intermittent claudication is twice as high in smokers as nonsmokers. Among male patients with symptomatic atherosclerotic disease of the limb vessels, the majority report smoking cigarettes at the onset of the clinical phase of the disease. Smoking is clearly associated with an increase in amputation and bypass graft occlusion. Seventy-three to ninety percent of patients with limb arterial disease are smokers, such that it is rare to encounter a young female with the disease who does not smoke cigarettes. Pathophysiological mechanisms related to

tobacco smoking involve vasoconstriction, lipid metabolism, and thrombogenicity.

While no randomized trials have examined the impact of smoking cessation on cardiovascular events in patients with lower extremity PAD, observational studies suggest that the risk of death, MI, and amputation is greater, and lower extremity and revascularization patency rates are lower in those patients who continue to smoke than in those who quit [13, 14].

Obesity

The National Health and Nutrition Examination survey (NHANES III) found that obese patients were more likely to have PAD defined by ABI <0.9. Obesity more than doubled the odds of developing PAD and peripheral neuropathy. Higher body mass index (BMI) is associated with greater functional decline in people with than in those without PAD [15]. The basis of this association is unclear, but adverse calf muscle characteristics are associated with greater functional impairment and faster functional decline in men and women with PAD [16].

Additional Risk Factors

Hereditary disorders associated with ischemic complications in the limbs include homocystinuria, oxalosis, inhibitors of von Willebrand factor, and inherited states associated with thrombogenicity, though the latter are more closely associated with venous than arterial diseases.

Histopathology

The basic lesion in PAD is the atherosclerotic plaque that produces *localized stenosis* of the lumen with or without areas of complete *arterial occlusion*. Deposition of thrombus and subsequently progressive fibrosis occur in eccentric layers. Fragmentation of the internal elastic lamina typically occurs and areas of intraplaque hemorrhage and calcification characterize the advanced lesion.

Segmental lesions usually produce stenosis or occlusion of large and medium-sized arteries. After the thoracoabdominal aorta, the coronary arteries are most commonly affected by atherosclerosis, followed by the iliofemoral, carotid, renal, mesenteric, vertebrobasilar, tibial-peroneal, subclavian, brachial, radial, and ulnar arteries. Even in advanced cases, smaller arteries of the digits are generally spared, though these may become obstructed by thrombus when there is proximal atherosclerotic disease. Patients with intermittent claudication may have disease at multiple arterial levels. In symptomatic patients, approximately 80 % have *femoropopliteal* disease, approximately 30 % have lesions at the *aortoiliac* level, and up to 40 % have *tibial-peroneal* obstruction. Involvement of the distal vessels is most frequent in diabetics and the elderly.

Natural History and Prognosis

The clinical courses of patients with PAD vary markedly, with abrupt vascular occlusion in some cases and chronic progression in others. In patients with aortoiliac disease, a copious collateral circulation tends to develop with a generally favorable prognosis in terms of limb outcome. Patients with distal tibial-peroneal disease have a distinctly poorer outcome, however, encountering amputation at an annual rate of 1.4 %.

Followed without surgical intervention, yearly mortality averages over 5 %, with death usually due to coronary or cerebral vascular disease. In the Framingham Heart Study, the relative mortality risk imposed by symptomatic PAD without cardiovascular comorbidity was 1.3 for men and 2.1 for women; total mortality ratios were 2.2 and 4.1, respectively. In patients with severely symptomatic PAD, the rate of coronary heart disease (defined angiographically as >70 % stenosis of at least one coronary vessel) was nearly 90 %. About 50 % of patients had impaired left ventricular function. Symptomatic PAD raises the risk of myocardial infarction, coronary and cardiovascular death 5 to 6-fold [17]. In a 15-year study of 2,777 patients with claudication, over 66 % of mortality was attributable to cardiovascular disease [18]. Angina and history of myocardial infarction did not predict mortality. Instead, reduced ABI at rest and following exercise, diabetes mellitus, and age were significant independent predictors.

Remission of intermittent claudication is common. Among patients followed 4 or more years from symptom onset in the Framingham study, 45 % became asymptomatic. In a Mayo Clinic study, 24 % of nondiabetic patients with PAD affecting the superficial femoral artery had symptomatic improvement, while 69 % experienced no progression of symptoms and clinical deterioration developed in only 7 % [19]. According to the Trans-Atlantic Inter-Society Consensus (TASC) working group, only 5 % of patients with intermittent claudication require surgical or endovascular intervention, and approximately 2 % need major amputation over a 5-year period.

Clinical Presentation

Intermittent Claudication

The cardinal symptom of obstructive arterial disease in the lower extremities is *intermittent claudication*. Typically, patients describe calf pain, since the gastrocnemius musculature has the

Table 47.1 Differential diagnosis of exertional calf pain

Obstructive arterial disease
Neurogenic pseudoclaudication
Venous claudication
Muscular disorders

greatest oxygen consumption of any muscle group in the leg during ambulation. Some patients report aching, heaviness, fatigue, or numbness when walking, but distress is usually relieved within a few minutes of rest. Ischemic claudication must be distinguished from other causes of exertional calf pain (Table 47.1). Among 460 patients with PAD evaluated in the Walking and Leg Circulation study, only 32.6 % had intermittent claudication; the remainder had no exertional leg symptoms, atypical leg pain, or rest pain [20]. Diabetic patients with distal tibial or peroneal arterial obstruction may describe ankle or foot pain while walking that is difficult to distinguish from diabetic neuropathy. With proximal aortoiliac disease, thigh, hip, or buttock claudication or low back pain may develop while walking, usually preceded by calf pain. Bilateral "high claudication" accompanying impotency and global atrophy of the lower extremities characterizes the *Leriche syndrome* associated with aortoiliac disease.

Multiple factors contribute to leg discomfort during exercise in patients with PAD. Hemodynamically significant arterial stenosis may reduce pressure and flow minimally at rest while the pressure gradient across the stenosis increases during exercise. Extravascular compression by exercising muscle and lack of flow-mediated vasodilation in atherosclerotic vessels may further blunt limb blood flow. Discomfort may be related to activation of local chemoreceptors due to accumulation of lactate or other metabolites as a result of ischemia.

Critical Limb Ischemia

When the minimal nutritional requirements of resting skin, muscle, nerves, and bone are not met, *ischemic rest pain, ulceration,* and *gangrene* ensue, any of which translate to a poor prognosis. Clinically, limb ischemia at rest is manifested first in the cutaneous tissues of the foot, where factors regulating perfusion differ from those governing calf muscle circulation. Reflexive, sympathetically mediated vasoconstrictor activity may reduce foot blood flow even under conditions of ischemia. With tissue necrosis there is typically severe pain that worsens with limb elevation at night and improves upon standing. With advanced neuropathy, ulceration and gangrene may occur painlessly. Other symptoms of ischemia at rest include hypoesthesia, cold sensitivity, muscle weakness, joint stiffness, and contracture.

Severe ischemia usually demands angiographic examination and therapeutic intervention by percutaneous angioplasty or surgical revascularization. When these are not feasible, gangrene commonly leads to amputation, though remission has been described even at this advanced stage. Critical limb ischemia results in some 150,000 amputations annually in the United States, with perioperative mortality rates of 5–10 % for below-knee and up to 50 % for above-knee amputations.

In the Reduction of Atherothrombosis for Continued Health (REACH) registry, which included a multinational cohort of 7,996 outpatients with PAD enrolled from primary medical clinics in 44 countries in 2003–2004, 1,160 patients (14.5 %) had a prior leg amputation at any level. Systemic (MI, stroke, cardiovascular death) and limb (angioplasty, surgery, amputation) ischemic event rates over 3 years were higher than in PAD patients without amputation. The rate of subsequent amputation was also higher (12.4 vs. 2.4 %, $p<0.001$), while the rate of peripheral angioplasty was lower (8.3 vs. 10.7 %, $p=0.005$), rates of surgical revascularization procedures were similar in the two groups. A nearly 2-fold increase in rates of cardiovascular death (14.5 vs. 7.7 %, $p<.0001$) and all-cause mortality (21.8 vs. 12.6 %, $p<0.001$) were observed. Recent (within 1 year) amputation was associated with higher rates of worsening PAD, subsequent lower extremity surgical revascularization, repeated amputation, nonfatal MI, and hospitalization. Adverse systemic and limb ischemic outcomes were similar regardless of amputation level [21].

Acute Arterial Occlusion

The major causes of acute arterial occlusion are trauma, arterial thrombosis, and arterial embolism. Traumatic occlusion is usually associated with external compression, transection, or laceration. Increasingly, the clinical spectrum of traumatic arterial occlusive disease includes iatrogenic causes, most commonly associated with indwelling intravascular diagnostic or therapeutic cannulation. Atraumatic acute arterial occlusion includes systemic embolism, usually cardiogenic, but occasionally derived from mural thrombus within aneurysms of the aorta, and thrombosis superimposed upon chronic atherosclerosis or other intrinsic arterial disease. Systemic disorders of coagulation associated with arterial thrombosis include those associated with anticardiolipin antibodies, circulating lupus anticoagulants, and heparin-induced thrombocytopenia.

Arterial Embolism

Nearly 85 % of systemic arterial emboli arise from thrombi in the chambers of the left side of the heart. Atrial fibrillation accounts for about half the cases and ventricular thrombi for most of the remainder. Infective (particularly fungal) endocarditis, cardiac tumors, invasive lesions of the pulmonary

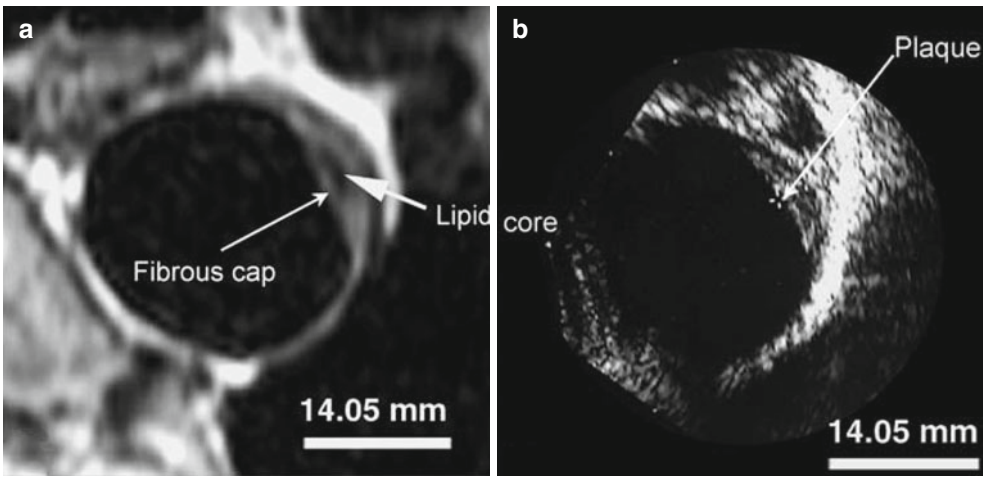

Fig. 47.2 Magnetic resonance, T2-weighted, (**a**) and transesophageal echocardiographic (**b**) images of a 4.5 mm fibroatheromatous aortic plaque showing the eccentric lesion with fibrous cap and lipid-laden core (Reprinted from [22]. With permission from Lippincott Williams & Wilkins)

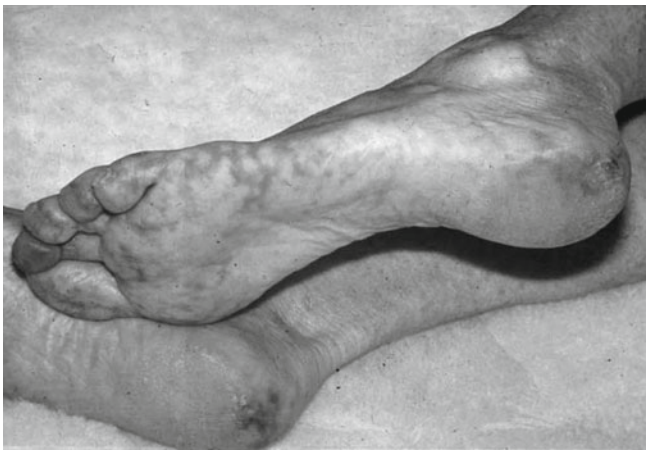

Fig. 47.3 Typical appearance of atheromatous embolism involving the feet. There is livedo reticularis along the lateral aspect of the foot and cyanosis of several toes (Reprinted from Ref. [24]. With permission from Elsevier)

venous system, mural thrombus within aortic aneurysms, ulcerated proximal atherosclerotic lesions, vascular grafts, arteritis, and traumatic arterial lesions represent additional sources of embolism.

Microembolism of atherosclerotic debris consisting of lipid and thrombotic material may originate in the aorta or more distal arteries and lead to occlusion of small distal limb arteries. The source may involve either aneurysmal disease or irregular ulceration of diffusely atherosclerotic vessels. Transesophageal echocardiography and magnetic resonance imaging have identified such atherosclerotic lesions (Fig. 47.2) [23]. The syndrome, designated *atheroembolism*, is often labeled the "blue toe syndrome" when the feet are affected and is characterized by unilateral or bilateral, painful, cyanotic toes in the presence of palpable pedal pulses (Fig. 47.3). The lateral and plantar aspects of the feet are frequently involved and manifest as livedo reticularis and petechiae on the feet and legs. The violaceous parts generally blanch with pressure, and the surrounding skin may appear normally perfused. Calf pain and gastrocnemius muscle tenderness are often present as a result of embolic occlusion of small intramuscular vessels. Fever, eosinophilia, renal failure, and acceleration of the erythrocyte sedimentation rate may signal an inflammatory reaction to atheroembolism, which may be difficult to distinguish from acute vasculitis.

Atheroembolism implies a physically unstable proximal atherosclerotic lesion at risk of acute thrombotic occlusion depending upon the diameter of the arterial segment involved and other factors governing flow. Antithrombotic therapy should be given in the form of platelet inhibitor or anticoagulant medication. Although angioplasty and stent-grafting are sometimes effective, intravascular catheterization may provoke embolism. The most definitive approach is removal or exclusion of the source from the circulation. When the lower limbs are ischemic, aortobifemoral bypass is often required, but an alternative approach is axillobifemoral extra-anatomic bypass with interruption of the external iliac arteries proximal to the point of anastomosis, and endovascular stent-grafting has been successfully employed. When renal embolism occurs, more proximal aortic reconstruction may be necessary. The risks of proximal aortic procedures are considerable, particularly when severe atherosclerosis involves the entire length of the aorta accompanied by a malignant syndrome of cerebral, mesenteric and limb ischemia.

Differential Diagnosis

Exertional calf pain may be produced by both nonatherosclerotic arterial obstructive diseases and conditions unrelated to the arterial circulation (Table 47.1). Among the latter are *neurogenic pseudoclaudication* due to lumbosacral radiculopathy, in which ambulation provokes nerve root irritation with pain referred to the extremity. Characteristic symptoms include pain upon walking just a few steps without progression

to ischemia at rest, relief on bending forward at the waist, and reproduction of symptoms by straight leg raising.

Venous claudication illustrates the role of venous pressure as a factor in regional circulatory resistance. Exertional leg pain (especially near the medial aspect of the leg above the ankle) results from insufficiency of the musculovenous pumping mechanism that normally reduces distal venous pressure during ambulation. Venous hypertension raises local vascular resistance causing exertional ischemia. Venous claudication is uncommon and usually occurs in patients with concomitant arterial insufficiency.

In *McArdle's syndrome,* skeletal muscle metabolites accumulate due to phosphorylase deficiency, evoking exercise intolerance in the absence of ischemia. Similar metabolites, including but not limited to lactic acid, may be responsible for the pain of intermittent claudication due to obstructive arterial disease.

Obstructive arterial diseases other than atherosclerosis that may produce intermittent claudication include *fibromuscular dysplasia* (FMD), *thromboangiitis obliterans* (TAO; *Buerger's disease*) and other arteritides, arterial entrapment syndromes (most commonly caused by the gastrocnemius muscles), extravascular compressive lesions, adventitial cysts and tumors, and thromboembolic lesions (Table 47.2). The most prevalent of these is *fibromuscular dysplasia,* a hyperplastic disorder that usually affects medium-sized and small arteries in Caucasian females [25]. The renal and carotid arteries are most frequently involved, but the disorder has also been described in the mesenteric, coronary, subclavian, and iliac arteries. Three histologic varieties have been delineated, based upon which layer of the arterial wall displays the predominant features of the process. Medial fibroplasia, the most common FMD, is characterized angiographically by a "string of beads" appearance representing multiple thickened fibromuscular ridges alternating with thinning of the arterial wall. The etiology is unknown, but pathogenic concepts include influence of female sex hormones, vascular microtrauma, and genetic factors. The natural history in limb arteries is less well defined than in the renal and carotid arteries, where progression of stenosis occurs over 5 years in a third of cases. Clinical manifestations such as intermittent claudication, rest pain, coldness, and cyanosis of the limb and even microembolism are similar to atherosclerosis. In addition to surgical reconstruction, percutaneous angioplasty has been employed for management of FMD. Balloon dilatation with or without intravascular stenting has been successfully accomplished with relatively low inflation pressures.

Table 47.2 Differential diagnosis of obstructive arterial disease

Arteriosclerosis obliterans
Fibromuscular dysplasia
Vasculitis
Vascular entrapment or compression
Adventitial cysts and tumors
Thrombosis and embolism

Buerger's disease (thromboangiitis obliterans) is a non-atherosclerotic segmental inflammatory obliterative disease most commonly affecting small- and medium-sized arteries and veins in both the upper and lower extremities [26]. Though the disease was once considered confined to young males, in clinical series up to a third of the cases were women. Most patients are heavy users of tobacco, usually cigarette smokers, and antigenic cross-reactivity between type III vascular collagen and a component of tobacco smoke has been considered etiologically important [27]. Distinctive pathological findings distinguish this disorder from other arterial occlusive diseases. Successful therapy requires abstinence from tobacco.

Physical Examination

Trophic signs of chronic limb ischemia include subcutaneous atrophy, brittle toenails, hair loss, pallor, coolness or dependent rubor (Table 47.3). Other visible changes reflect sympathetic denervation and sensorimotor neuropathy. Severe ischemia produces petechiae, regional edema, tenderness, ulceration, or gangrene. The level of arterial obstruction may be judged by palpation of the femoral, popliteal, posterior tibial, and dorsalis pedis pulses. Vascular bruits denote turbulent flow but do not indicate the severity of stenosis.

Cutaneous perfusion may be estimated by the color and temperature of the feet during elevation above heart level at rest and following exercise. The rate of hyperemic color return and venous filling in the foot upon dependency reflect collateral perfusion (Table 47.4). When this does not meet minimal tissue perfusion requirements, cutaneous ulceration is frequent. *Arterial ulcers* caused by arterial disease are often as small as 3–5 mm in diameter, have irregular borders and pale bases, usually involve the tips of the toes or the heel of the foot, and are typically painful on elevation and most bothersome at night. The clinical course is often one of rapid progression to extensive gangrene. *Vasospasm* may produce

Table 47.3 Trophic signs of ischemia in patients with peripheral arterial disease of the extremities

Chronic arterial obstructive disease
Hair loss
Subcutaneous atrophy
Thickened nails
Dependent rubor
Acute ischemia
Ulceration
Petechiae
Calf tenderness
Dependent edema

Table 47.4 Elevation and dependency tests in the evaluation of acral ischemia

	Color return	Venous filling
	(s)	
Normal	10	10–15
Adequate collaterals	15–25	15–30
Severe ischemia	>35	>40

cutaneous ischemia leading to digital ulceration in patients with *Raynaud's phenomenon* or chronic *pernio*. Diabetic patients, who are prone to combined peripheral sensory neuropathy and ischemic disease, often develop deep *neurotrophic ulcers* from trauma or pressure on the plantar surface. In patients with severe hypertension, painful *Hines ulcers* related to arteriolar obliteration tend to occur near the lateral malleoli. *Vasculitic ulcers* are characterized by arteriolar thickening, with or without superimposed thrombosis. Hematologic disorders such as the hemoglobinopathies, hereditary spherocytosis, dysproteinemias, and myeloproliferative diseases may be associated with cutaneous infarction, venous thrombosis, and microvascular occlusion. *Chronic venous stasis* usually produces indolent or recurrent ulceration near the medial malleoli that are more painful during dependency, helping to distinguish them from ulcers due to arterial disease. A host of systemic diseases may also be associated with cutaneous ulceration in the lower extremities, such as tumors (i.e., Kaposi's sarcoma), syphilitic chancre and gumma, tuberculous lupus vulgaris, and pyoderma gangrenosum. Factitious and traumatic ulcers may mimic those induced by obstructive arterial disease.

Noninvasive Evaluation (Table 47.5)

Doppler Sphygmomanometry

Doppler sphygmomanometry has become part of the initial bedside vascular examination for determination of the ABI. Normally, systolic arterial pressure at the ankle exceeds that at the brachial artery. An ABI ≤0.9 at rest indicates hemodynamically significant arterial obstruction proximal to the pneumatic leg cuff. In general, ABI may exceed 0.9 in individuals with obstructive disease in the absence of symptoms; values between 0.5 and 0.9 at rest are typical in patients with intermittent claudication, and values below 0.5 are frequently associated with ischemic rest pain, ulceration, and gangrene threatening limb viability (Fig. 47.4).

Calcific atherosclerosis of vessels beneath the cuff resists compression producing overestimation of regional perfusion pressure. This constitutes the major limitation of sphygmomanometry, and may falsely elevate the ABI in patients with

Table 47.5 Noninvasive laboratory evaluation of peripheral arterial disease

Doppler sphygmomanometry
Segmental pressure measurement
Pulse volume recording
Venous-occlusion plethysmography
Radionuclide mapping
Duplex ultrasound imaging
Magnetic resonance angiography
Computed tomographic angiography

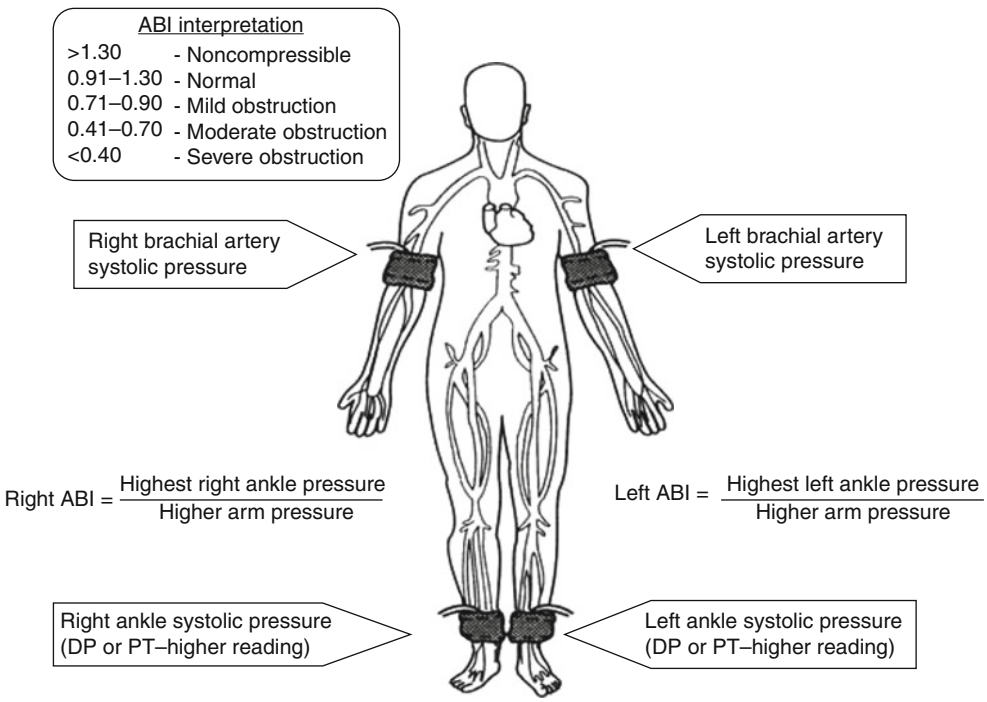

Fig. 47.4 Measurement of ankle brachial index (ABI)

diabetes mellitus or end-stage renal disease. Ankle brachial indices may be normal at rest despite hemodynamically significant arterial stenosis, yet decline following calf muscle exercise. Postexercise systolic ankle pressure readings below 90 mmHg are typical of patients with intermittent claudication, and values below 60 mmHg are typical of ischemia at rest.

Segmental Limb Pressure Measurements

To localize segmental arterial lesions, pneumatic cuffs are applied to determine systolic pressure at several levels, based on the principle that pressure drops distal to the obstruction. *Segmental pressure measurements* are subject to the same limitations as Doppler sphygmomanometry. Segmental compression cuffs combined with the Doppler ultrasound device, *photoplethysmograph,* or other flow detectors are subject to error related to arterial rigidity.

Pulse volume recordings overcome some of these limitations. The amplitude of the pulse volume wave reflects local arterial pressure, vascular wall compliance, the number of arterial vessels beneath the cuff, and the severity of atherosclerotic disease. The normal pulse is characterized by a sharp systolic upstroke which rises rapidly to a peak and then drops off slowly toward the baseline. The downslope curves toward the baseline and usually contains a dicrotic notch and secondary wave midway between the peak and the baseline. The pulse recording distal to an arterial obstruction is more rounded, the anacrotic slope is reduced, the crest is delayed, the catacrotic limb descends more gradually, and the dicrotic wave is lost.

The pulse volume recorder reveals distortions in pulse wave contour even in patients with vascular calcification. The waveforms appear depressed and altered even when arteries are noncompressible. The *pulsatility index*, representing the ratio of pulse amplitude to mean volume obtained by integration of the deflection, is abnormally low even with falsely elevated systolic pressure readings. The value of these observations is enhanced by exercise testing, which also provides a quantitative estimate of functional capacity. In addition, exercise testing helps to distinguish PAD from disorders producing similar symptoms, since the ABI declines following exercise in those with arterial obstructive disease.

Ultrasound Velocity Spectroscopy and Imaging

Doppler velocity analysis of normal arteries reveals a triphasic signal. Rapid acceleration to peak systolic velocity occurs along a narrow frequency spectrum, end-systolic deceleration culminates in protodiastolic flow reversal, and antegrade flow resumes in mid-diastole. Peak systolic velocities diminish with advancing age. Arterial obstruction proximal to the probe transforms the waveform by loss of the reversed flow component and attenuation of the spectrum, with delayed upstroke and decreased amplitude.

Duplex ultrasound scanning combines B-mode and pulsed-Doppler analysis to examine arterial configuration and localize stenosis. Flow through a stenosis is accelerated, and turbulence is detected as spectral broadening of the velocities beyond the narrow band seen with normal flow. Microprocessor-based systems for calculation of blood cell velocities allow accurate estimation of instantaneous pressure gradients and degrees of stenosis [28]. Duplex scanning is more sensitive and specific than segmental blood pressure measurements for detection of restenosis following vascular interventional procedures.

The clinical vascular noninvasive laboratory is subject to misconceptions that predispose to misuse. Among these are that the findings can establish indications for specific therapeutic procedures, since clinical decisions are best based on symptoms and the physical appearance of the limb. Noninvasive vascular measurements reflect the severity of ischemia, the contribution of obstructive arterial factors to symptoms, and the hemodynamic significance of lesions at various points. It is important that in formulating management decisions, noninvasive testing aid rather than replace the medical history, physical examination, and clinical judgment.

Magnetic Resonance Angiography

Magnetic resonance angiography obviates arterial catheterization and exposure to iodinated contrast material and may identify runoff vessels not visualized by conventional angiography [29]. Magnetic resonance (MR) imaging methods can also characterize the arterial wall and atherosclerotic lesions. In the magnetic field, water molecules are excited by a radiofrequency (RF) pulse generating a secondary signal that is detected and measured digitally and displayed as images that distinguish fine details of tissue architecture and composition. Plaque dimensions and composition are assessed using T1-weighted, proton density, and T2-weighted images and techniques of real-time, cine MR angiography. Currently, MR imaging is limited in assessing restenosis in arteries following angioplasty and stenting.

Computerized Tomographic Angiography

Multiplanar high-resolution computerized tomographic angiography (CTA) may be obtained from thin contiguous axial images acquired following intravenous administration of radiographic contrast material. Unlike ultrasonography or

MRA, CTA provides direct imaging of the arterial lumen suitable for evaluation of stenosis. Arterial calcification and, with severe stenosis, the resolution limit of the CT system limit diagnostic accuracy.

Contrast Angiography

Diagnosis of PAD does not generally require invasive techniques, and most patients with claudication should not undergo angiography. *Contrast angiography* is indicated for mapping the extent and location of arterial pathology prior to revascularization. Such testing should be reserved for patients in whom the diagnosis is in doubt or as a prelude to intervention when conservative approaches are inadequate. Aortic injection of contrast material in patients with aortoiliac occlusive disease can be accomplished either by the *retrograde transfemoral*, *translumbar,* or *transaxillary* approach to visualize the aorta and proximal limb vessels, but definition of the circulation distal to the popliteal trifurcations may be compromised by dilution. In patients with femoropopliteal obstructive disease, antegrade or retrograde transfemoral angiography can be confined to the involved extremity with fine definition of the distal vasculature.

Computer-enhanced *digital subtraction angiography* may be useful to minimize the volume of contrast material injected or improve image resolution. The technique may be employed with either intravenous or intra-arterial contrast injection especially for postoperative examination of anastomoses but is not an effective means of visualizing large regions of the arterial tree**.**

Medical Therapy

The principles of management of patients with PAD involve protecting affected tissues, preserving functional capacity, avoiding disease progression or arterial thrombosis, restoring blood flow, and preventing mortality. These can be categorized as local measures, modification of risk factors, drug therapy for claudication, and antithrombotic agents.

Local Measures

Local measures to reduce skin breakdown and infection are particularly important in diabetics and in patients with severely impaired perfusion. The feet should be kept clean. Moisturizing cream applied to prevent fissuring must be selected to avoid irritant effects. Well-fitted shoes reduce the risk of pressure-induced necrosis. Stockings made of absorbent fibers are recommended. The skin should be inspected frequently and minor abrasions promptly tended. Elastic support stockings that restrict cutaneous blood flow should be avoided. In patients with ischemia at rest, conservative measures such as positioning the affected limb below heart level increases oxygen tension in ischemic tissues. When edema is present, the limb should be kept horizontal to enhance healing. The heels should be protected from pressure against bed sheets with sheepskin padding. Blankets should be cradled over a footboard to reduce friction. Separating the toes with cotton protects against friction. Unless purulence is present, dryness is preferred to soaks except for intermittent cleansing. Gentle warmth is recommended to minimize vasoconstriction. Antimicrobial treatment of fungal onycholysis reduces skin breakdown and infection. Topical preparations should be used cautiously to avoid inflammation. Open sores should be cultured and roentgenograms performed on affected limbs to detect osteomyelitis. Antibiotic medication is less effective when delivery to ischemic tissue is impaired. Passive physical therapy may progress to weight bearing and ambulation, with attention to foot care and properly fitted footwear.

Risk Factor Modification

Modification of associated risk factors may prevent progression of atherosclerotic disease, as discussed earlier.

Treatment of Dyslipidemia

The HMG-CoA-reductase inhibitors ("statins") have favorable effects in patients with intermittent claudication [30]. In addition to improving lipid profiles, statins improve walking distance in patients with PAD and decrease the risk of developing intermittent claudication [30–32].

Treatment of Diabetes Mellitus

Control of blood glucose reduces the incidence of microvascular complications, but data are insufficient regarding efficacy against progression and complications of PAD [33]. In the UK Prospective Diabetes Study, aggressive blood-glucose control reduction was not associated with statistically significant reduction in myocardial infarction, amputation, and death associated with PAD [34].

Management of Hypertension

Meta-analysis has shown ~40 % reduction in risk of stroke and 10–15 % reduction in risk of MI with antihypertensive treatment, but effects of therapy on PAD have not been quantified [35]. Treatment with the angiotensin-converting enzyme inhibitor ramipril was associated with a 27 % relative risk reduction in stroke, MI, and death in the subgroup of PAD patients enrolled in the Hope Outcomes Prevention Evaluation (HOPE) trial [36].

Smoking Cessation

Clinical prognosis for those with PAD is related to tobacco use. Among smokers with claudication, 11 % of those continuing to smoke required amputation, while this befell none who quit [14]. Patients with claudication who quit had twice the survival benefit of those who continued to smoke at 5 and 10 years [13]. Physician intervention and frequent follow-up greatly improves success rates [37]. The addition of pharmacologic agents can increase 1-year quit rate to 30 % [38].

Exercise Training

Exercise training improves walking and functional capacity in patients with PAD over several months, but most studies have not identified consistent improvement in perfusion, and data from controlled trials are scant. In animals with arterial obstruction, regular muscular exercise increases collateral development, but in the clinical setting functional improvement may depend upon muscle metabolism or ergonomics.

In the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) trial, 111 patients with aortoiliac PAD were randomized to optimal medical therapy with or without supervised exercise or medical therapy plus percutaneous catheter-based revascularization. At 6-months follow-up, change in peak walking time (the primary endpoint) was greatest for supervised exercise, intermediate for stenting, and least with medical therapy alone. Although disease-specific quality of life improved with both exercise and stenting compared with medical therapy, for most scales improvement was greater with stenting than with exercise without revascularization [39].

Treatment of Hyperhomocysteinemia

Hyperhomocysteinemia is strongly associated with peripheral atherosclerosis. Treatment with B-complex vitamins including folic acid, pyridoxine, and cyanocobalamin reduces homocysteine levels, but there are no conclusive data supporting efficacy for clinical outcomes.

Drug Therapy to Reduce Ischemia and Claudication

Despite advances in surgical and interventional techniques for symptomatic management of patients with PAD, there is an unmet need for better pharmacological treatment. Lifestyle modification such as smoking cessation, exercise, and weight loss and management of risk factors such as diabetes, hypertension, and hyperlipidemia slow the progression of atherosclerosis but typically do not ameliorate symptoms of PAD, except that exercise and certain drugs such as cilostazol increase walking distance in those with claudication.

Vasodilator Drugs

In contrast to their usefulness in patients with angina pectoris, vasodilator drugs have been disappointing for relief of claudication. In patients with limb ischemia, the goal is to increase the work capacity of exercising muscle. Critical stenosis limits blood supply and reduces distal perfusion pressure. Intramuscular arterioles normally dilate in response to exercise. In patients with PAD, flow augmentation is blunted and distal pressure falls during exercise. The distal vasculature virtually collapses under the compressive force of exercising skeletal muscle, and this cannot be mitigated by vasodilator drugs.

History is replete with therapies that achieve popularity for awhile before falling into disrepute when adequate studies confirm their ineffectiveness. *β-Adrenergic agonists, α-adrenergic antagonists, nitrates*, and other vasodilator drugs have been evaluated in clinical trials. No vasodilator agent increases blood flow in exercising skeletal muscle subtended by significant arterial stenosis or improves claudication and objective measures of exercise capacity.

Pharmacological Enhancement of Collateral Flow

An alternative tactic for patients with PAD is augmentation of collateral perfusion, the rationale behind the selective serotonin antagonist, *ketanserin*. In one study this increased collateral flow in patients with PAD. In a multicenter trial of patients with claudication, however, exercise performance was no better a year after treatment than with placebo [40].

Hemorheologic Agents

Abnormal rheology is present in many patients with atherosclerotic disease. Oral *pentoxifylline* is used to improve walking capacity in patients with claudication, based upon salutary results in several clinical trials. In vitro, reduced erythrocyte flexibility of blood obtained from patients with claudication is partially corrected, and skeletal muscle oxygen tension rises at rest following treatment. Improved blood fluidity in vivo has not been conclusively demonstrated, and vascular resistance during reactive hyperemia showed no improvement after administration of pentoxifylline compared with placebo in patients with claudication. This suggests that hemorheologic effects do not reduce impedance to blood flow, and a clinical benefit of pentoxifylline has not been proven [41].

Metabolic Agents

Cilostazol, an inhibitor of phosphodiesterase-III with vasodilator, antiplatelet, and vascular smooth muscle cell inhibitory actions, was approved by the US Food and Drug Administration for treatment of patients with claudication. The mechanism of its effect is not well understood. Cilostazol has been compared to placebo in controlled trials involving over 2,000 patients and in two studies to pentoxifylline (the

only other drug approved in the USA for treatment of claudication). Primary endpoints were the distances walked on a treadmill before onset of claudication (initial claudication distance, ICD) and before pain became intolerable (absolute claudication distance, ACD). In most studies, ICD and ACD improved with cilostazol compared to placebo. In one study, cilostazol was superior to pentoxifylline; in another, neither drug was superior to placebo [42]. In general, cilostazol, 100 mg twice daily, was superior to 50 mg twice daily. There are no data bearing on limb preservation or rate of disease progression during longer-term treatment. Phosphodiesterase inhibitors (such as milrinone and vesnarinone) used as inotropic agents in patients with severe heart failure were associated with mortality, and cilostazol is contraindicated in patients with a history of cardiac failure [43].

Propionyl L-carnitine facilitates transfer of acetylated compounds and fatty acids across mitochondrial membranes leading to enhanced energy storage. Accumulation of acylcarnitines in ischemic skeletal muscle correlates impaired exercise performance and abnormal oxidative metabolism [44]. Increased substrate availability was the purported mechanism by which proprionyl-L-carnitine improved walking capacity in a European multicenter trial of patients with claudication, but results in different populations were contradictory and larger studies are needed [45].

The mechanism by which *prostaglandin* E_1 (PGE_1) and *prostacyclin* (PGI_2), potent vasodilators and inhibitors of platelet aggregation, relieve ischemic rest pain and promote healing of ulcers is controversial. Intra-arterial infusions of PGE_1 and PGI_2 have effects on blood flow and exercise capacity that persist for weeks to months, but intravenous administration has yielded inconsistent results [46]. The major drawback of prostaglandin therapy is the short half-lives of these drugs, but oral analogues are under development. Prostacyclins may provide temporary relief of ischemic rest pain in patients with severe arterial insufficiency when given intra-arterially, but it is unknown whether this prevents amputation in patients not amenable to revascularization.

A few novel agents have been studied to improve walking capacity for PAD patients. L-arginine, a substrate for nitric oxide, increased pain-free and total walking distances in patients with claudication after 2 weeks of administration [47]. Avasimibe, an inhibitor of acyl-coenzyme A-cholesterol acyltransferase (ACAT), 50 mg daily for 52 weeks, demonstrated a trend toward improved walking distances that did not reach statistical significance [48].

Angiogenesis

Therapeutic angiogenesis involves administration of vascular endothelial growth factors (VEGF), usually as recombinant protein or DNA, to augment the collateral blood supply to ischemic tissues. Clinical trials of VEGF have given inconclusive results. In the Therapeutic Angiogenesis with Recombinant Fibroblast Growth Factor-2 for Intermittent Claudication (TRAFFIC) study, intra-arterial administration of recombinant fibroblast growth factor-2 improved walking distance in claudicants [49]. The Regional Angiogenesis with Vascular Endothelial growth factor (RAVE) trial, however, did not show improvement in walking time in patients with PAD treated with intramuscular VEGF [50]. In a later study, injection of bone marrow-mononuclear cells into the legs of patients with PAD improved ABI, tissue oxygenation and peak walking times 24 weeks after implantation [51].

Antithrombotic Therapy

Antithrombotic therapy is part of the management of patients with PAD to reduce coronary and cerebrovascular events and mortality. Following limb revascularization, the objective is to prevent thrombotic complications and preserve patency. In those with acute arterial occlusion, therapy is directed toward preventing propagation of thrombus and recurrent embolism. Available approaches include *anticoagulants*, *platelet inhibitor* and *thrombolytic drugs*, and *direct inhibitors of thrombin*. A combination of approaches is warranted for high-risk patients.

There is no conclusive evidence that antithrombotic therapy alters the course of PAD, although some reports suggest benefit. Recent data indicate that antithrombotic therapy delays the progression of atherosclerotic lesions. In double-blind studies involving several hundred patients, serial angiography revealed less pronounced progression of PAD in those randomized to *aspirin* or the combination of aspirin plus *dipyridamole* than in those given placebo. The role of platelet inhibitor medication in retarding progression of the atherosclerotic plaque has been demonstrated over a longer period in patients with coronary artery disease.

Aspirin has been demonstrated to reduce the risks of MI, ischemic stroke, and vascular death in patients with atherosclerosis. The Antiplatelet Trialists' Collaboration (ATC), a meta-analysis of over 100 randomized clinical trials involving about 70,000 participants concluded that aspirin reduces these vascular events by about 25 %, regardless of dose. Nonfatal MI and stroke was reduced by about one-third and vascular deaths by about one-sixth [52]. The 9,214 patients with PAD had a 23 % reduction in vascular events with antiplatelet therapy [53]. In Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE), clopidogrel (75 mg/day) was compared with aspirin (325 mg/day) over a mean follow-up of 1.5 years in 19,185 patients with clinical atherosclerosis [54]. Participants included survivors of MI or non-disabling stroke as well as those with symptomatic PAD; the primary endpoint was a composite of ischemic stroke, MI, or vascular death. Patients treated with clopidogrel had a 5.32 % annual risk of primary events compared with 5.83 %

for those treated with aspirin (a statistically significant relative risk reduction of 8.7 %). Most benefit was confined to the 6,452 patients entered on the basis of PAD (relative risk reduction 24 %; $p = 0.0028$) (Fig. 47.5).

Studies evaluating aspirin therapy for the prevention of cardiovascular events in patients with PAD have produced mixed results. In the Critical Leg Ischaemia Prevention Study, patients with ABI < 0.85 randomized to aspirin had a lower risk of major cardiovascular events and critical limb ischemia than those given oral antioxidant vitamins, neither, or both [55]. In the larger Prevention of Progression of Asymptomatic Diabetic Arterial Disease (POPADAD) study of patients with asymptomatic PAD, there was no difference in event rate with aspirin or placebo [56]. Similarly in the Aspiring for Asymptomatic Atherosclerosis (AAA) study, which evaluated individuals with ABI <0.95, there was no benefit of aspirin therapy [57]. The Critical Leg Ischemia Prevention Study (CLIPS), which enrolled patients with symptoms and/or ABI <0.85, was stopped due to poor recruitment with only 366 of an intended 2,000 patients enrolled but demonstrated a significant reduction in ischemic events among those randomized to aspirin [55]. Post hoc analysis of the CHARISMA trial found that patients with PAD treated with aspirin and clopidogrel had a lower rate of MI without increased bleeding; there was no difference in the endpoint of death, MI, and stroke [58], and in a subgroup with symptomatic PAD, aspirin and clopidogrel reduced death, MI, or stroke [59].

It is unclear whether aspirin therapy benefits all patients with PAD, but those with symptomatic PAD should probably be treated with aspirin or clopidogrel to prevent cardiovascular events. Whether more recently introduced platelet inhibitor drugs like the P_2Y_{12} inhibitors prasugrel or ticagrelor will provide superior prophylactic value will require relatively large clinical trials that consider both limb outcomes and other cardiovascular events such as MI and stroke. Systemic anticoagulation offers marginal, if any benefit in patients with PAD. The WAVE trial assigned patients with PAD to antiplatelet plus anticoagulant medication versus antiplatelet therapy alone, and the combination did not reduce rates of MI, stroke, or death but increased life-threatening bleeding [60]. The incidence of ischemic events was lower, and survival was greater among selected anticoagulated patients following femoropopliteal bypass surgery than in a control group, in whom the ABI declined more gradually and graft patency was extended over 12 years, but this falls short of confirming delayed progression of PAD.

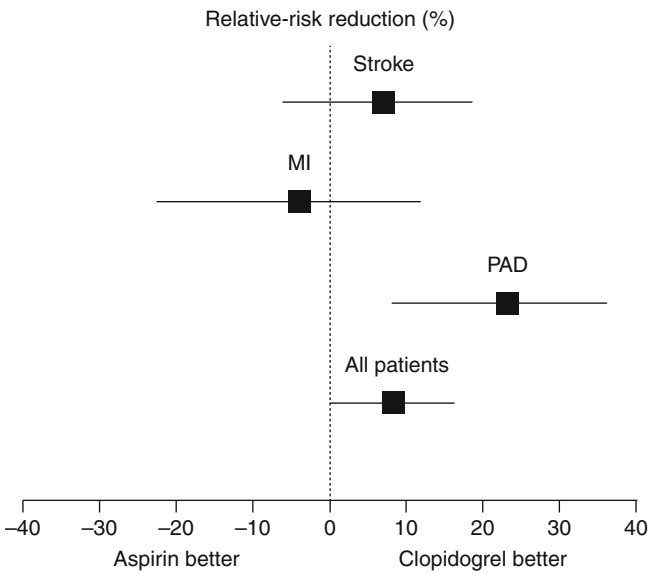

Fig. 47.5 Relative risk reduction and 95 % CI by disease subgroup in the CAPRIE trial. *MI* myocardial infarction, *PAD* peripheral arterial disease(Reprinted from Ref. [54]. With permission from Elsevier)

Interventional Angiography

Considerable success has attended transluminal dilatation for correction of iliac arterial stenoses, but patency rates are lower in the femoral and popliteal arteries. Initial and long-term success is related to the acuity of ischemic symptoms, morphologic features of the atherosclerotic segment (i.e., length of obstruction, relation to anatomic branch points, and condition of the distal artery), and comorbid conditions (i.e., diabetes, active smoking). Experience with obstructions distal to the popliteal trifurcation has been disappointing, but "steerable" devices drawn from coronary catheterization enhance outcome in selected cases. Endovascular techniques used to treat PAD include percutaneous atherectomy, angioplasty, stents, and thrombolysis.

Antithrombotic therapy is advocated prior to angioplasty to reduce thrombus formation and occlusion. Current practice tends toward pre- and post-procedural administration of aspirin plus clopidogrel, intraprocedural heparin, and maintenance therapy with aspirin or clopidogrel. Despite this widespread practice, the benefits of antiplatelet or anticoagulant therapy in conjunction with percutaneous interventions of peripheral arterial lesions have not been proven [61], but meta-analysis found increased patency and lower amputation rates with antiplatelet therapy [62].

Trans-catheter Atherectomy and Endovascular Stents

Extraction of atherothrombotic material using rotational, abrasion, or pulverization methods intends to remove atheromatous material and leave a smooth surface. Atherectomy appears well suited to eccentric atherosclerotic lesions associated with calcification. For stenoses at the femoropopliteal level, angiographic success has been reported in 87–93 % of the lesions removed; recurrent symptoms occurred in 31 % of patients during 6 months of clinical follow-up. Atherectomy for infrapopliteal occlusive disease has demonstrated a high

restenosis rate (91 %) at 6 months post-intervention [63]. Therefore, atherectomy is not recommended for routine peripheral atherosclerotic lesions except possibly for limb salvage.

Patency rates following endovascular stent deployment in iliac arterial stenosis were 92 % at 9 months and clinical benefit has been reported to extend for 2 years. Results with infrainguinal stents have been less favorable, however, with restenosis or re-occlusion rates about 50 % in the femoropopliteal segment. Infrainguinal endovascular angioplasty with or without stents has been an accepted practice for salvage of critically ischemic limbs. The TASC working group recommended endovascular intervention for iliac and femoropopliteal arterial occlusions <3 cm in length (type A) (Fig. 47.6). Percutaneous angioplasty with stenting of long-segment superficial femoral arterial disease has been associated with high rates of restenosis and re-occlusion [65].

Endovascular brachytherapy and drug-eluting stents have been reported to decrease restenosis rates in intervened femoropopliteal and infrapopliteal arterial occlusions [66, 67]. However, long-term prospective clinical trials are needed to assess the utility of these techniques.

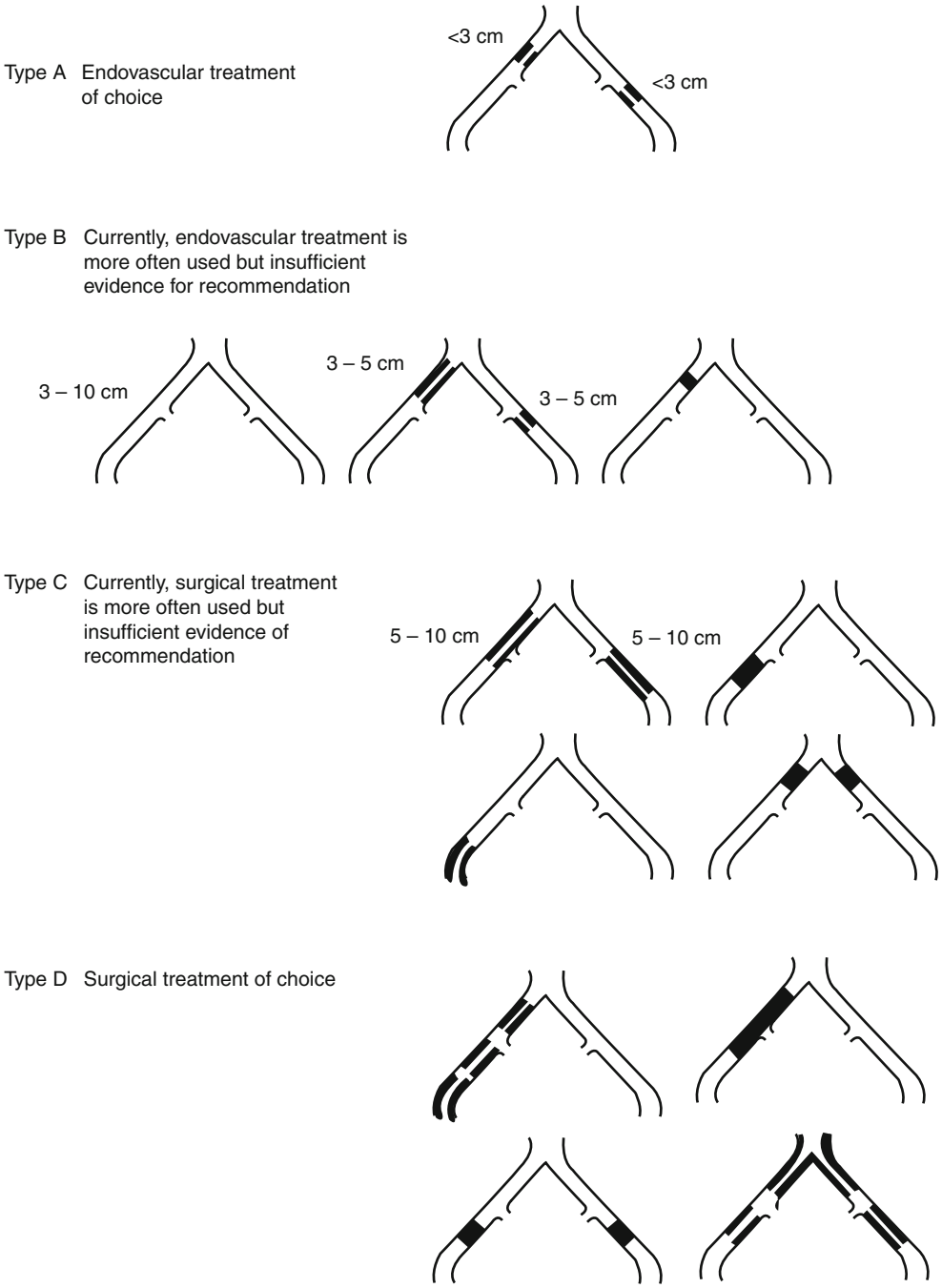

Fig. 47.6 The Trans-Atlantic Inter-Society Consensus (TASC) recommendations in the interventional management of iliac lesions (Reprinted from Ref. [64]. With permission from Elsevier)

Intra-arterial Thrombolysis

Catheter-directed, intra-arterial thrombolytic therapy has been used as an adjunct to revascularization for management of both acute and chronic critical limb ischemia. Several studies have shown comparable rates of mortality and limb salvage with thrombolysis and surgical revascularization in patients with acute arterial insufficiency. In the Thrombolysis or Peripheral Arterial Surgery (TOPAS) trial, urokinase yielded amputation-free survival similar to surgery at 12 months [68]. However, the Surgery versus Thrombolysis for Ischemia of the Lower Extremity (STILE) trial showed higher recurrence of limb ischemia after lysis [69]. In both studies, lysis was equal to or possibly superior to surgery for arterial occlusions <14 days in duration. Although the rate of successful reperfusion (50–80 %) is higher with local intra-arterial than systemic (intravenous) thrombolytic therapy, local infusions allow concurrent angiographic definition of effectiveness so angioplasty may be incorporated to prevent re-occlusion. Bleeding or thromboembolism (up to 20 % of cases) may complicate protracted periods of indwelling arterial catheterization. Thrombolytic therapy may be particularly useful in cases of thrombotic distal arterial occlusion in the forearm, hand, ankle, and foot, where surgical access is difficult.

Surgical Therapy

Surgical intervention is not indicated for most patients with stable claudication who have sufficient collateral supply to meet the nutritional requirement of resting limb tissue. It is indicated if patients fail maximum aggressive medical management and have severe functional impairment. Since most patients with claudication remain stable or improve with time, surgical intervention becomes appropriate when the disease process becomes severely debilitating or progressive. The most pressing indication for revascularization is ischemic rest pain, ulceration, or gangrene amenable to reconstruction when more limited measures, including angioplasty, are insufficient, unsafe, or not feasible.

Beyond severity of ischemic symptoms, anatomic pathology is important in deciding whether surgery should be undertaken. The syndromic approach to disease classification reflects the success of surgical bypass procedures. The TASC working group recommends that diffuse, multiple iliac lesions, and complete common femoral, superficial femoral, popliteal, or proximal trifurcation arterial occlusions (type D) be treated with surgery (Fig. 47.6). Revascularization for aortoiliac obstructive disease is associated with approximately 85 % patency rates at 5–10 years, for femoropopliteal reconstruction around a 70 % patency rate at 5 years, and for distal anastomosis located beyond the popliteal trifurcation a patency rate in the range of 40–60 % after 2 years. This should be interpreted in the context of a patient's overall functional status and medical condition with reference to risk imposed by associated coronary or cerebrovascular disease.

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C. Rosendorff (ed.), *Essential Cardiology*,
DOI 10.1007/978-1-4614-6705-2, © Springer Science+Business Media New York 2013

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