Cardiovascular Disease in the Elderly Patient

Second Edition, Revised and Expanded

edited by
Donald D. Tresch
Wilbert S. Aronow

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Samuel Z. Goldhaber

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As with the first edition of our book, we dedicate this second edition to our elderly patients:

All beginnings are joyous.
Our elderly patients show us that endings
may also be joyous and
they never fail to teach us that life,
even with the struggles of aging and disease,
may be full of meaning and joy.

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Foreword

Once again, as in the initial publication of *Cardiovascular Disease in the Elderly Patient,* edited by Donald D. Tresch and Wilbert S. Aronow, I have the opportunity to keynote the presentation of the field of cardiovascular aging and the interplay between disease and aging. Drs. Tresch and Aronow have their fingers on the pulse of this expansive field and have made this compendium far more comprehensive and useful in clinical medicine.

The basic pathophysiology that exists within the cardiovascular system of the elderly is understood in terms of fundamental principles. This is also the case for the integration between disease and aging. Here, major advances have been made in understanding the limitations of the older individual in terms of adaptation to disease. Disease takes a bigger toll on the elderly in large part because of limited compensation by adaptive mechanisms. In addition, recent data point to the real importance of prevention and proper disease management.

In experimental animals, as well as in humans, it is clear that there are important aspects of the cardiovascular system that show little or no change with age. These aspects include: (1) little or no age-associated change in myocardial perfusion or coronary blood flow in the absence of coronary artery disease and (2) relatively little change in intrinsic myocardial function under normal or even high loading conditions. Myocardium is also normal in terms of the inotropic response to influences that do not involve the sympathetic nervous system. Inotropic response to calcium and postexon systolic potentiation are unchanged with age. Not surprisingly, in humans with normal myocardial blood flow and normal intrinsic function, left ventricular chamber size and ejection fraction at rest are unchanged or nearly unchanged with age. This is, of course, in the absence of disease.

Myocardial cells hypertrophy substantially with age. The age-hypertrophied cells function similarly to cells that hypertrophy at a younger age through increased systolic stress. Their are two primary causes of cellular hypertrophy with aging. First, and most important quantitatively, there is very significant myocardial cell dropout or death with age. Biochemical evidence of programmed cell death or apoptosis with age has been demonstrated in a number of species. Other causes of cell death are also being sought. Second, there is a tendency toward hypertrophy, which results from the age-associated increase in impedance to left ventricular ejection. This hypertrophy results from the first of the major fundamental age changes in the circulation: the increase in vascular stiffness, particularly of the central arterial vessels leading to a higher systolic blood pressure.

The second major physiological change occurring with aging is the decrease in beta sympathetic response, which has recently been demonstrated to include both beta-2 and beta-1 responses. Decreased beta response has been shown to occur with age in many species, including humans. With a decrease in beta sympathetic response, there is the

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well-known decrease with age in the heart rate in response to exercise. There is also a decrease in inotropic response during exercise and other forms of stress. Finally, with decreased beta sympathetic response, there is a striking decrease with age in the major arterial vasodilating response to circulating epinephrine. This leads to an increase in afterload during stress, which is particularly striking during exercise. During exercise, the young individual enjoys a much greater arterial vasodilating response and therefore a much more limited rise in systolic blood pressure and left ventricular load. Many of these issues of response to exercise are discussed extensively in Chapter 1.

It is with this background of decreased beta sympathetic response and increased vascular load on the left ventricle that the insult of disease occurs.

Over the last several years, it has been increasingly recognized that it is not just the increase in vascular stiffness and left ventricular load and the decrease in beta sympathetic response that alter disease severity in the elderly. The adaptive response of the older individual to disease is strikingly altered (i.e., diminished) in the elderly. In experimental animals, the left ventricle of the older animals confronted with increased pressure or volume load hypertrophies less. The hemodynamic signal may be the same, but the genetic and molecular responses that lead to hypertrophy appear to be lessened. In humans, this lack of hypertrophy response is most strikingly seen in the relative lack of hypertrophy of the left ventricle with severe aortic valve obstruction in the elderly. Also, there is broad recognition that acute myocardial infarction, even the first, results in strikingly high mortality and morbidity in the elderly. This higher mortality is seen even after normalizing for infarct size among first infarct patients. There is strong suggestive data that failure of hypertrophy of remaining myocardium is an important factor. Perhaps there is also failure of the initial inflammatory response with age, which may lead to greater infarct expansion or thirsting.

Although far from proven in humans, a third failure of adaptation may be operating in acute myocardial infarction. Data from experimental animals suggest that production and activity of collateral vessels promoting factors such as vascular endothelial growth factor may be reduced in the elderly. Furthermore, there may be a decrease in the growth response of the vascular system to these factors. Such a failure of vascular growth may once more lead in a circumstance of acute myocardial infarction to greater myocardial loss and poorer scar formation. In addition, with multivessel disease and/or diffused disease, the lack of collateralization may hamper adaptation to ischemic heart disease in the elderly.

Appropriately, much of this volume concentrates on disease rates as they manifest in the elderly, including hypertension, heart failure, and atherosclerotic cardiovascular disease, particularly coronary disease. The striking decrease in chest pain associated with myocardial ischemia is emphasized in Chapter 1. There is extensive discussion of the problems of acute myocardial infarction and the response to interventions commonly found in the elderly, including coronary bypass surgery, angioplasty procedures, and valvular replacement and reconstruction. Among cardiac arrhythmias, the most common, atrial fibrillation, is discussed in detail in Chapter 24. The volume proceeds to discussions of anticoagulation, beta-blockers, cardiac arrest, and resuscitation. These are all important clinical problems of the elderly that are given significant attention. In Chapter 33, the focus turns to the use of cardiovascular drug therapy in the elderly. This chapter concentrates on the important issues of increased vascular load in the elderly and the possibly greater importance of lowering systolic arterial blood pressure through active vasodilatation. This strategy of management is of particular significance when left ventricular myocardial dis-

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ease is present. This desire for reduced load is balanced by concern with regard to decreased baroreceptor and beta sympathetic response to induced hypertension. Also, perhaps the elderly are more sensitive to the effects of beta-blockers because of the already decreased response based on aging changes. This chapter does an excellent job of identifying therapeutic principles when data are available and providing an integrated view in areas where we are limited by a lack of therapeutic trials in the elderly. In Chapter 34, comments are presented on ethical and quality-of-life issues in management of cardiovascular disease in the elderly.

Finally, Drs. Tresch and Aronow provide a renewed stimulus toward research to address major issues in cardiac disease and its management in the elderly. It is remarkable, at this date, that there are no data that convincingly address the value of digitalis in the elderly patient with heart failure without atrial fibrillation. More generally, what approaches to treating heart failure reduce mortality and morbidity in the elderly? Gene therapy for cardiac disease is no longer speculation. Do we stimulate hypertrophy and/or collaterals? If so, when, how, and how much?

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Preface

It is only 5 years since the first edition of *Cardiovascular Disease in the Elderly Patient* was published. This might be considered a short time before introducing a new edition. However, the enormous increase in knowledge and the advances in therapy in cardiology, particularly geriatric cardiology, dictate a timely update and revision of our earlier work.

Partially due to this new knowledge and advances in therapy, cardiovascular mortality continues to decline, and the decline has been impressive in older, as well as in younger, persons. Nevertheless, cardiovascular disease remains the number one cause of death in industrial countries and is a major cause of functional impairment, especially in elderly persons. A disproportionate increase in mortality associated with cardiovascular disorders is seen in older persons. For example, patients 70 years or older with acute myocardial infarction are three times more likely to die than younger patients with the disorder. Furthermore, cardiovascular disorders are mainly disorders of the elderly with the prevalence and incidence of these disorders markedly increased with age. Over two million persons in the United States demonstrate atrial fibrillation, and the majority of these persons are over 70 years of age. Three million Americans have heart failure, with the incidence of new cases doubling with each decade from age 45 to age 84. Besides the high prevalence of cardiovascular disorders in elderly persons, the continual increase in the percentage of elderly persons in the general population adds to the significance of the problem.

There is no doubt that a major segment of patients seen by the practicing physician, whether family physician, internist, or cardiologist, are elderly patients with cardiovascular disorders, and this segment of elderly patients will be even larger in the next century as the population continues to age. These elderly patients will present a major challenge to physicians, not only due to the large numbers, but, more importantly, due to the high morbidity and mortality associated with cardiovascular disorders in this age group.

To adequately care for this increasing segment of elderly patients, physicians need to continually be aware of new knowledge in geriatric cardiology and must be able to incorporate new therapies into their daily management of these patients. Unfortunately, elderly cardiovascular patients often are not given the benefit of new and effective therapies. Beta-blockers are not used in many elderly patients who sustain myocardial infarction; thrombolytic therapy is underutilized; and even aspirin has been found to be infrequently prescribed in elderly postmyocardial infarction patients.

The objective of the second edition of *Cardiovascular Disease in the Elderly Patient* is to improve the care of elderly patients with cardiovascular disease by providing the practicing physician with the most current knowledge concerning the pathophysiology of cardiovascular disorders and the newest advances in therapy to treat elderly patients with these disorders.

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To accomplish these objectives, chapters in the previous edition have been rewritten to include all the latest information. In addition, new chapters have been added, which include topics not previously covered. One new chapter (Chap. 9) discusses the most recent concepts concerning pathophysiology of coronary artery disease and provides insight into why stable coronary artery disease suddenly becomes so unstable. This is a phenomenon that has great significance in elderly patients who may have asymptomatic stable coronary artery disease until their eighth or ninth decade. A better understanding of the pathophysiological mechanisms should lead to more effective preventive strategies in these patients and should improve management of the acute coronary artery syndromes, such as unstable angina and acute myocardial infarction, that are so common in elderly patients. Another new chapter (Chap. 32) concerning preoperative evaluation provides a thorough, systematic, and practical approach that should be useful to physicians who are commonly called to quickly evaluate the elderly patient who has been scheduled for noncardiac surgery. Chapter 33, also new, provides an overview of cardiovascular drugs and discusses new information concerning efficacy and adverse reactions of both the commonly used and newly developed drugs. In addition, the authors provide a practical approach to managing the elderly patient in whom these drugs are used. Chapter 34, which concerns the ethical problems facing physicians caring for elderly patients with cardiovascular disease, is especially important. Such issues are perplexing to the practicing physician and easy answers are not available. This chapter gives more insight into the problem, and will provide the physician with a logical and practical approach when confronted with having to make these difficult ethical decisions.

As previously stated, all the chapters of the first edition have been rewritten and the authors have incorporated new information with an emphasis on results of recent multicenter studies that included older patients. In addition, the chapters have been updated to include the most recent advances in therapy. Chapter 24, on supraventricular tachyarrhythmias, now emphasizes atrial fibrillation and provides the newest information concerning management of this perplexing and common disorder. Moreover, Chapter 25 has been updated, with discussion of the new studies that cite the current guidelines for the use of anticoagulation in elderly patients with atrial fibrillation. The revised Chapter 23 thoroughly discusses the issue of ventricular diastolic dysfunction, which has been shown to be so important in elderly patients with heart failure. We think all of the chapters from the previous edition now present the newest information available concerning the specific chapter topic and provide the reader with a practical approach to managing elderly patients with the various cardiovascular disorders.

As with the first edition, the contributors to the second edition all have many years of experience in cardiology, have made valuable contributions to the cardiology literature, and are particularly well qualified to discuss the subject of geriatric cardiology. We thank them for their effort and diligence. The topics are thoroughly covered, and the discussions are concise and pertinent to the elderly patient. For this, we are especially appreciative.

Finally, we know this edition will provide practicing physicians with new information that will be valuable in their daily care of elderly patients with cardiovascular disorders and will continue to serve as a reference when resolving the difficult problems encountered when treating elderly patients with cardiovascular diseases.

Donald D. Tresch
Wilbert S. Aronow

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1

Normal Aging Changes of the Cardiovascular System

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INTRODUCTION

It is not difficult to understand the often held misconception that heart disease is part of ''normal aging'' and that overall cardiovascular function declines with increasing age. This rapidly growing portion of the population often does have heart disease, with hypertension, coronary artery disease, and heart failure being three conditions commonly diagnosed in many elderly patients. Nonetheless, it is not the case that heart disease and impaired cardiac function is a sine que non of the aging process. Healthy elderly persons have normal left ventricular systolic function at rest. Importantly, there are certain cardiovascular changes that occur with aging throughout the animal kingdom which are important to recognize and which are described below. Knowledge of the cardiovascular changes that occur with aging are important for several reasons. First, recognition of these changes allows us to better distinguish normal cardiovascular aging from disease states in the elderly. Second, manifestations of various cardiovascular diseases vary between young and old patients, most likely influenced in part by changes that occur with aging. An example is hypertension, which is manifest as diastolic blood pressure elevation in younger subjects and systolic blood pressure elevation in the elderly. Third, the ability of an individual to compensate for their cardiovascular illness may be age-dependent, and thus the elderly patient may be more symptomatic for any burden of disease and require more aggressive evaluation and therapy than younger subjects. An example includes congestive heart failure, which is one of the most common discharge diagnoses in the Medicare population (1). Fourth, the response to appropriate cardiovascular therapy may also be somewhat age-dependent, such as β-adrenergic receptor blockade. Finally, there have not always been clear distinctions between when an age-related phenomenon becomes a disease-related phenomenon. An example includes the increase in left ventricular mass that occurs with increasing age in disease-free subjects and the known fact that increasing left ventricular mass predicts future cardiovascular morbidity and mortality (2,3). In the sections below, animal and human studies will describe resting cardiovascular function, the response to stress, and ventricular–vascular coupling.

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ANIMAL MODELS OF CARDIOVASCULAR AGING

Cardiac Function

Important information has been obtained about age-associated changes in cardiac function from studies of isolated cardiac muscle. Since coronary disease occurs with low frequency in most animal models, the difficulties of coexistent disease seen in human studies of elderly subjects is not encountered (4). This research has yielded insights into the potential mechanisms for the changes in cardiac function.

Isolated papillary muscle from rats, guinea pigs, and other species shows normal contractile function. Resting tension, peak active isometric tension, and maximal rate of tension development is similar between young and old isolated cardiac muscle (5). The similarity of tension development between cardiac muscle from young and old animals persists across the entire working range of muscle length. There is a small decrease in the velocity of shortening in cardiac muscle from senescent animals, likely due to a decrease in adenosine triphosphatase activity of the myofibrils (6). Similar to isolated muscle, in vivo animal studies demonstrate no difference in resting left ventricular function in aged compared to young animals (7).

The most consistent age-associated change in cardiac muscle function is prolonged contraction duration and prolonged relaxation in senescent cardiac muscle (5,8). There are two mechanisms that contribute to the prolonged active state in senescent myocardium: sarcoplasmic reticulum calcium uptake and the duration of calcium entry during depolarization. In senescent myocardium, there is a prolongation of the action potential (9,10). There is also a decrease in the velocity of sarcoplasmic reticulum calcium uptake from myocardium of aged rats compared to young adult rats (Fig. 1) (11). Since the active

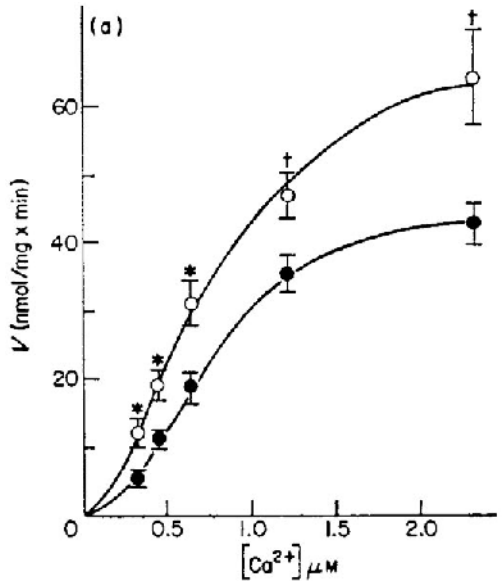

Figure 1 Rates of calcium accumulation in microsomes from young adult (open circles) and senescent (closed circles) hearts. At all calcium concentration tests, the rate of microsomal calcium uptake was significantly lower from the aged hearts. (From Ref. 11.)

uptake of calcium by the sarcoplasmic reticulum from the myofibrils initiates relaxation, this decrease in velocity of sarcoplasmic calcium uptake likely contributes to the prolonged contraction duration in cardiac muscle from aged rats. A similar prolongation in left ventricular relaxation has been demonstrated in the intact senescent dog heart (12). Deconditioning may contribute to this age-associated prolongation in contraction duration and decline in sarcoplasmic reticulum calcium uptake. In experiments evaluating cardiac muscle function in young adult and aged rats who underwent intense exercise training over 20 weeks, cardiac muscle from young rats had no alteration in contraction duration or relaxation time compared to untrained young rats (13). In contrast, exercise-trained aged rats showed significant reductions in contraction duration and relaxation times compared to mechanical properties from cardiac muscle of sedentary aged rats. Indeed, these cardiac parameters were indistinguishable from young rats. The improvements in contraction duration and relaxation time in older exercise-trained rats were due to increases in the rate of sarcoplasmic reticulum calcium uptake in the exercise-trained older rats (14).

An animal model that also demonstrates prolonged relaxation and decreased sarcoplasmic reticulum calcium uptake is the development of pressure overload hypertrophy in young animals following aortic banding. The link to the aging heart may be left ventricular hypertrophy, which occurs with normal aging due to an increase in aortic stiffness and myocardial cell dropout (7). The increase in wall thickness with aging plus myocardial fibrosis may not only impair active relaxation, but also alter passive left ventricular properties by increasing left ventricular chamber stiffness resulting in impairment of left ventricular filling (5).

In summary, animal models demonstrate normal rates and extent of tension development in senescent cardiac muscle, but do show a prolonged contraction duration and decreased rate of relaxation. Experimental data suggest these age-associated changes may be related to myocardial cell hypertrophy that occur with aging and perhaps an increasingly sedentary lifestyle.

Response to Stress

Mechanisms to increase cardiac output in response to stress include the Frank-Starling mechanism, increases in heart rate and myocardial contractility in response to stress-related elaboration of catecholamines, and a decrease in afterload from catecholamine-induced arterial vasodilatation (4). The use of the Frank-Starling mechanism remains intact in animal models of aging. Active length-tension curves from aged rat trabeculae are similar to those obtained from their younger counterparts (5).

Studies in a variety of animal models show a striking decrease in both the chronotropic and inotropic response to catecholamines in older animals. Thus, the heart rate response to isoproterenol is blunted in aged compared to younger dogs (15). Both isolated cardiac muscle and ventricular myocytes from aged animals show a marked decline in the inotropic response to catecholamines (16–18). Figure 2 shows the twitch amplitude responses of isolated rat ventricular myocytes from young adult, middle-aged, and aged rats to increasing concentrations of norepinephrine (18). Twitch amplitude increases significantly compared to baseline in young adult and middle-aged groups, but there was significantly less twitch response to increasing concentrations of norepinephrine in the aged ventricular myocytes. This age difference in the inotropic response to norepinephrine is also present at the maximal rates of tension development. Similar age differences exist in response to other catecholamines and are present in isolated trabecular muscle and in

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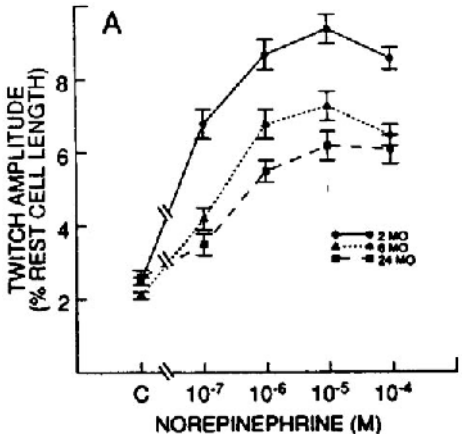

Figure 2 Twitch amplitude of individual ventricular myocytes isolated from the hearts of 2-month (closed circles), 6-month (closed triangles), and 24-month (closed squares)-old rats. The effect of increasing concentrations of superfused norepinephrine on myocyte contractility measured from a phase contrast microscope was determined in 5 to 10 cells from each group. Ventricular myocytes from aged rats show significantly less inotropic response to increasing concentrations of norepinephrine. There were no age differences in the contractile response to increasing calcium concentrations. (From Ref. 18.)

the intact animal. In response to isoproterenol and norepinephrine, aged monkeys have significantly lower heart rate response and less augmentation in left ventricular contractility (the first derivative of left ventricular pressure) compared to younger monkeys, although baseline heart rate and contractility are unchanged with age in this model (19). Importantly, the inotropic response of cardiac muscle to calcium is well sustained across all age groups, suggesting that myofibrillar contractile function and responsiveness are well maintained with aging (16).

The diminished inotropic response to catecholamines in aged myocardium suggests a specific defect in the ability of catecholamines to increase the amount of calcium delivered to the myofilaments (16). This decrease in responsiveness to catecholamines is likely multifactorial. The number and affinity of β-adrenergic receptors in cardiac muscle of aged rats are somewhat decreased compared to younger animals (17). In isolated rat cardiac myocytes, there is an age-associated decline in sarcoplasmic reticulum calcium release in response to catecholamines, which correlates to reduced shortening (20). This reduced calcium transient in response to catecholamines correlates with a reduced catecholamine-induced calcium current. Other mechanisms for the age-associated decline in catecholamine responsiveness of cardiac muscle include postreceptor mechanisms such as a decline of cyclic adenosine monophosphate production and/or G-protein activity (21). In contrast to the inotropic response, catecholamines enhance relaxation similarly in young and aged cardiac muscle (16).

Therefore, another hallmark of aging myocardium is a marked decrease in the chronotropic and inotropic response to catecholamines. This response has been demonstrated in multiple species, in isolated myocytes, cardiac muscle, and the intact animal. Age-associated changes in the excitation-contraction response to catecholamines is likely an important mechanism for this decline.

Vascular Changes

The ability of the left ventricle to increase cardiac output with exercise is strongly coupled to the vascular afterload against which the heart ejects. For any level of left ventricular contractility, higher afterload would limit the exercise cardiac output response. Ventricular afterload is both nonpulsatile and pulsatile. The nonpulsatile component is indexed as the mean systemic vascular resistance, which relates mean aortic pressure to mean aortic flow and is determined by the size of the distal vascular bed and the degree of arteriolar vasoconstriction or dilation (4). The pulsatile component of afterload is determined by the degree of stiffness of the great vessels and the magnitude and timing of pressure and flow waves reflected back to the aortic root (22). The stiffer the arterial tree and the larger the magnitude and more rapid reflection of arterial pressure waves back to the heart, the greater is the pulsatile load against which the heart ejects blood during systole. Various invasive and noninvasive measurements describe this pulsatile component of afterload, such as aortic characteristic impedance (invasive) and pulse wave velocity (noninvasive) (22).

Several age-associated changes in arterial mechanical properties in animal models increase left ventricular afterload. These changes include alterations in the composition and distribution of elastin and collagen in the arteries, resulting in increased stiffness in the central arteries and changes in the distal arterioles (22). These changes in animal models result in age-associated increases in both systemic vascular resistance as well as the characteristic impedance and pulse wave velocity. The hemodynamic effects resulting from left ventricular ejection into a stiffened arterial tree were evaluated by Kass and colleagues in a canine model (23). Left ventricular ejection into a stiff bypass conduit resulted in the expected marked decrease in arterial compliance with resultant fall in diastolic blood pressure (less aortic recoil) and a rise in systolic blood pressure (less aortic elasticity). There was an increase in left ventricular metabolic demand and systolic wall stress. Despite the fall in diastolic blood pressure, coronary blood flow was higher even at matched myocardial oxygen demand due to a marked increase in the systolic contribution to total coronary blood flow when the dogs ejected into the stiff conduit (Fig. 3). These results suggest that the aortic pressure waveform itself may influence coronary blood flow and that systolic blood pressure may have a greater role in myocardial perfusion in older than in younger subjects. Kass and coworkers demonstrated that during transient coronary artery occlusion, there was a significantly greater amount of left ventricular dysfunction and myocardial ischemia with ejection into a stiffened conduit than the native aorta (24). Since in the former condition there is relatively more coronary blood flow occurring during systole, for the same decline in mean arterial and systolic blood pressure which occurs with ischemia, coronary flow is disproportionately reduced in the presence of a stiff aorta. These data suggest that when left ventricular ejection occurs into a stiffened aorta, as with aging, a greater degree of myocardial perfusion occurs during systole, which makes the heart more sensitive to lowering systolic and mean arterial pressure, potentially resulting in a greater amount of ischemia and left ventricular dysfunction. In summary, afterload increases with age in the animal model due to increases in both the nonpulsatile load (systemic vascular resistance) and pulsatile load (aortic compliance). This increased afterload results in more rapid reflection of pressure waves back to the heart, which results in a greater amount of coronary flow occurring in systole. Thus older animals are more sensitive to lowering of systolic blood pressure, which can result in diminution of coronary blood flow and worsening ischemia.

The vascular response to exercise is smooth muscle vasodilation due to catechola-

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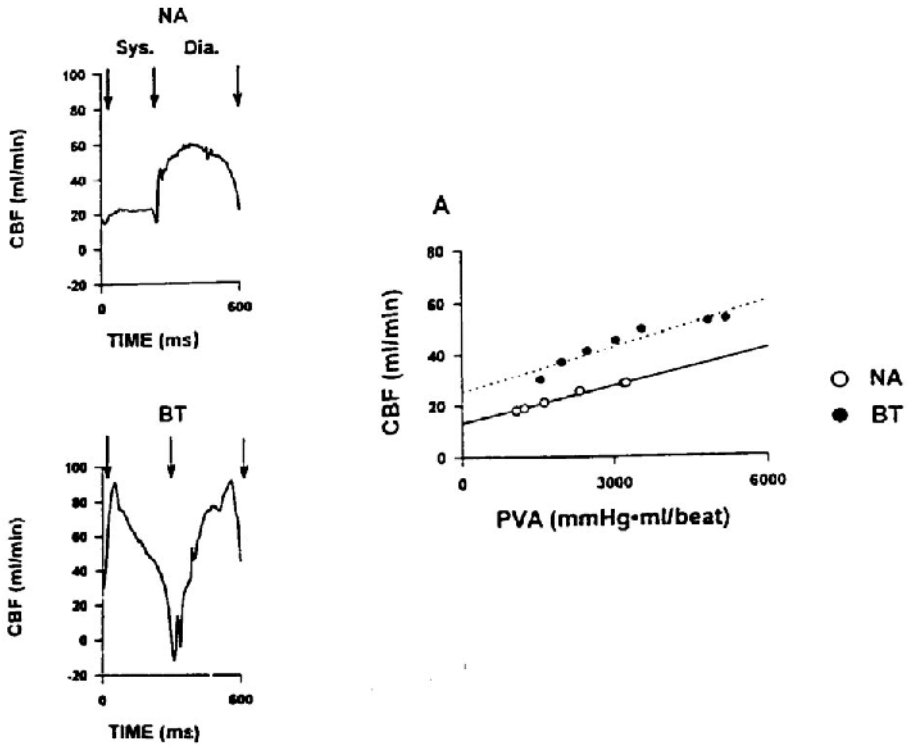

Figure 3 Examples (left) of coronary blood flow (CBF) when dog heart ejected into native aorta (NA) and stiff bypass tube (BT). When the dog heart ejected into the BT, there was a significant increase in CBF during systole. On the right is the CBF work–load relation (pressure-volume area or PVA) with left ventricular ejection into the NA or BT. During ejection into the BT, CBF was higher at every work load. (From Ref. 23.)

mine-induced β-adrenergic receptor stimulation. Similar to cardiac muscle, there is an age-associated decline in the vasodilating response to isoproterenol in rabbit and rat aortae (25). This decline in vasodilation is specific to the β-adrenergic receptor as there are no age differences in aortic vasodilation to the direct smooth muscle vasodilators nitroglycerin and nitroprusside (25). This age-associated decline in arterial vasodilation to catecholamines limits the exercise response in older dogs due to augmented afterload (7). Hemodynamic studies in chronically instrumented dogs show similar resting hemodynamics in young and old animals. During exercise, however, young animals had a progressive increase in stroke volume. The older dogs had no increase in stroke volume, with exercise resulting in a lower peak exercise cardiac output. The aortic impedance differed significantly during exercise between the younger and older dogs, with the increased vascular load during exercise in the older animals likely contributing to the impaired exercise cardiac output response. In a second series of experiments (7), pretreatment with β-adrenergic blocker propranolol abolished the age differences in exercise aortic impedance, suggesting that in young animals catecholamine-induced arterial vasodilation acts to decrease vascular

load to augment left ventricular ejection. This response is not present in older animals, with the resultant increased vascular load likely limiting the exercise response.

CARDIOVASCULAR FUNCTION IN HUMANS

Results of many studies evaluating cardiovascular functional changes with age rely importantly on whether subjects are carefully screened for coronary artery disease that is very prevalent in the elderly and may certainly influence the cardiovascular response to exercise (26,27). Many of the observed age-related changes in cardiovascular function in healthy humans parallel the changes in the animal models described above.

Cardiac Function

Similar to animal studies, resting systolic left ventricular function does not decline with advancing age in healthy humans. Studies utilizing echocardiography and radionuclide scintigraphy show normal systolic function in the elderly (e.g., cardiac volumes, ejection fraction, and fractional shortening) (2,28,29). Similar to animal studies, echocardiographic left ventricular wall thicknesses and left ventricular mass increase with age, due most likely to an increase in afterload with increasing age (2).

Also similar to animal models, there is a slowed and delayed left ventricular relaxation in healthy elderly subjects (30). Thus, noninvasive studies have demonstrated an age-associated decrease in early diastolic left ventricular filling (2,31,32). Although many hemodynamic and structural changes affect left ventricular filling, there are several age-associated changes that probably contribute to the decrease in early diastolic filling in healthy elderly subjects, including a prolongation of the time constant of relaxation (33), an increase in left ventricular mass (2), an increase in afterload (34), an increase in chamber stiffness (35), and an increase in regional heterogeneity in filling among left ventricular segments (36). Resting end diastolic volume is maintained in healthy elderly subjects despite the decline in early diastolic filling by an increased atrial contribution to left ventricular filling (37). Unlike the effects of exercise training on relaxation in animal models, endurance trained elderly subjects have a similar decrease in early left ventricular filling as age-matched sedentary controls in most, but not all, studies (38,39).

In summary, in healthy elderly subjects, there is no significant age-associated change in left ventricular systolic function. Mild left ventricular hypertrophy occurs, which may contribute to the characteristic prolonged relaxation of aging muscle across animal species. Resting end-diastolic volume is maintained because of an increase in atrial contribution to left ventricular filling in this age group.

Response to Stress

Exercise capacity declines with age. An index of aerobic capacity—maximal oxygen consumption—declines about 8 to 10% per decade in sedentary healthy populations (40–44). This decline is secondary to a fall in maximal cardiac output and a decrease in arteriovenous oxygen difference, the central and peripheral components of measured oxygen consumption, respectively (45). The hemodynamic differences in the exercise response between healthy young and older subjects are explained primarily by the decrease in β-

adrenergic responsiveness with increasing age. Therefore, young subjects rely primarily on an increase in heart rate and inotropic state and a decrease in impedance to left ventricular ejection to increase cardiac output with exercise, effects secondary to the cardiac and vascular response to catecholamine stimulation. In contrast, elderly subjects effectively utilize the Frank-Starling mechanism to augment exercise cardiac output due to the decrease in β-adrenergic responsiveness that limits the aforementioned mechanisms utilized in younger subjects. This compensatory mechanism allows healthy elderly subjects to effectively augment exercise cardiac output.

These age differences in the exercise response were determined from a study of 200 sedentary subjects from the Baltimore Longitudinal Study of Aging (46). This healthy population was carefully screened for cardiovascular disease by history, examination, and exercise treadmill testing. Subjects aged 40 and above had normal exercise thallium tests. All subjects underwent rest and bicycle exercise gated blood pool scan imaging to determine cardiac volumes and cardiac output at each level of exercise until exhaustion. The relationship of age (22 to 86 years) and sex (121 men and 79 women) to the cardiovascular response to exercise was evaluated. Figure 4 shows the relationship of rest and peak exer-

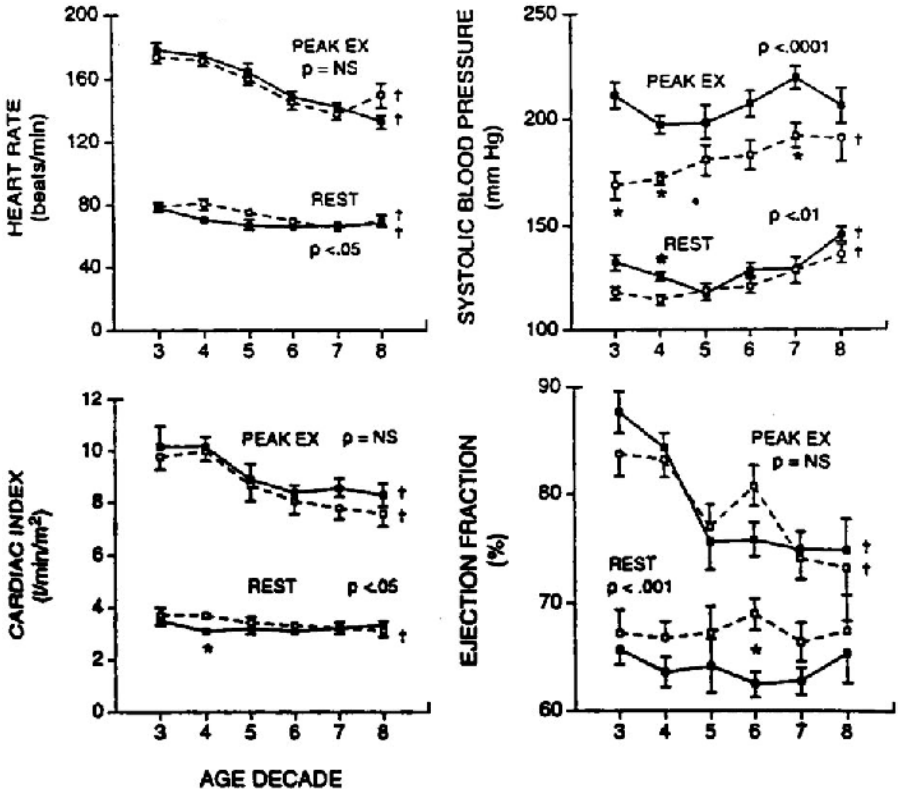

Figure 4 Relationship of age in decades to rest and exercise heart rate (top left), systolic blood pressure (top right), cardiac index (bottom left), and ejection fraction (bottom right) in men (closed squares) and women (open squares). + = significant age regressions within gender exist at rest or peak exercise. Significant *p* values indicate gender differences. (From Ref. 46.)

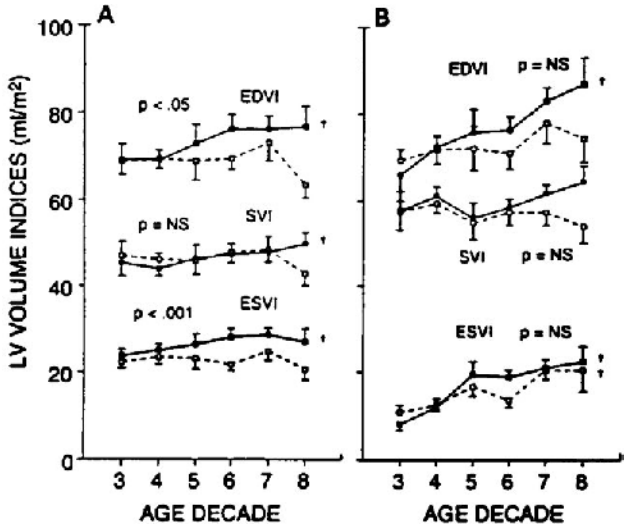

Figure 5 Relationship of age in decades to rest (left) and peak exercise (right) end-diastolic volume index (EDVI), end-systolic volume index (ESVI), and stroke volume index (SVI) in men (closed squares) and women (open squares). + = significant age regressions within gender exist at rest or peak exercise. Significant *p* values indicate gender differences. (From Ref. 46.)

cise heart rate (upper left), systolic blood pressure (upper right), cardiac index (lower left), and ejection fraction (lower right) to age and sex. Figure 5 shows resting and peak exercise cardiac volumes. In both men and women at rest, heart rate declines and systolic blood pressure increases with increasing age. The decrease in resting heart rate in men is compensated by an age-associated increase in resting end-diastolic and end-systolic volume indices (i.e., use of the Frank-Starling mechanism) (Fig. 5, left). In contrast, resting cardiac volumes in women were not age related. Resting ejection fraction in both men and women do not vary with age, consistent with preserved resting systolic contractile function with increasing age.

In this study, peak exercise capacity, indexed by maximal oxygen consumption, declined linearly with age. There are several age-associated hemodynamic changes that occur with peak exercise. First, peak exercise heart rate declines 25% in men and women from the third to eighth decade of life (Fig. 4, upper left). This response is consistent with previous studies demonstrating that the maximal heart rate response to an isoproterenol infusion is blunted in older compared with younger individuals (47). Second, in young subjects, end-systolic volume index diminished with exercise due to catecholamine-induced increase in contractility and decrease in vascular afterload. In contrast, peak exercise end-systolic index rises progressively with increasing age probably a reflection of both a decreased inotropic response and decreased vascular vasodilator response to exercise (Fig. 5, right). Third, there is an increase in end-diastolic volume index from rest to peak exercise in elderly men and women (Fig. 5, right), whereas in younger individuals, end-diastolic volume index does not change from rest to peak exercise. The relationship between rest and exercise end-diastolic volume index and stroke volume index in younger (<40 years) and older (>60 years) individuals is shown in Figure 6. At rest, older men have greater end-diastolic volume indices than older women and younger men and women.

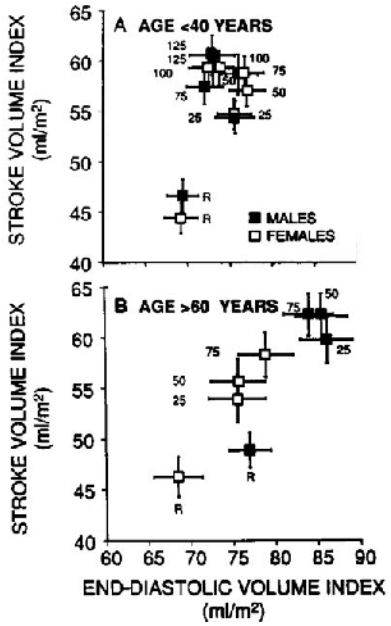

Figure 6 Relationship between end-diastolic volume index and stroke volume index at rest (R) and bicycle work rates of 25 W 125 Watts in men and women under 40 years of age (A) and over 60 years of age (B). Older subjects rely on the Frank-Starling mechanism to augment stroke volume index during exercise, while younger subjects have a decrease in end-systolic volume index that results in an increase in exercise stroke volume index. (From Ref. 46.)

During exercise, end-diastolic volume indices do not change in young subjects, thus younger individuals do not utilize the Frank-Starling mechanism. To augment exercise stroke volume and cardiac index, young subjects rely on an increase in contractility and decrease in afterload that results in a decrease in end-systolic volume with exercise and an increase in stroke volume. Heart rate also increases, resulting in a large increase in cardiac index. In older men and women, with increasing exercise workloads, there is a steady increase in end-diastolic volume index indicating effective utilization of the Frank-Starling mechanism to augment stroke volume and cardiac index (Fig. 5, right). Nevertheless, the lower heart-rate response to exercise in older men and women results in an age-associated decline in peak exercise cardiac index. The increase in peak exercise end-systolic volume indices with increasing age also results in an age-associated fall in peak exercise ejection fraction (Fig. 4).

The critical role of age differences in β-adrenergic responsiveness in determining the age differences in the hemodynamic response to exercise comes from rest and bicycle exercise gated blood pool studies of 25 participants from the Baltimore Longitudinal Study of Aging who were pretreated with intravenous propranolol (48). These results were compared to 70 age-matched controls and show that young subjects who receive β-blockade prior to exercise utilize the Frank-Starling mechanism to augment cardiac index with a large increase in end-diastolic volume during exercise and a marked decrease in the heart-rate response. Older subjects respond less to acute β-blockade. These studies suggest that age differences in the hemodynamic response to exercise (age-related decline in peak

exercise heart rate and compensation with cardiac dilatation) are due to the age-associated reduction in β-adrenergic receptor responsiveness.

Changes in lifestyle, including an increasingly sedentary lifestyle with increasing age, may also contribute to the cardiovascular changes in the elderly. Studies in healthy elderly subjects demonstrate that aerobic exercise conditioning results in a significant increase in maximal oxygen consumption (49–51). Recent studies show significant improvement in bicycle exercise gated blood pool scan cardiac function in sedentary elderly men who undergo exercise training and deterioration in cardiac function in senior master athletes following detraining (49,50). Thus, physical conditioning in healthy sedentary subjects results in an increase in peak exercise ejection fraction, cardiac index, and stroke volume index with a decrease in end-systolic volume index. Senior athletes following cessation of exercise training have deterioration in cardiac function directionally opposite those subjects who have trained. Across a broad range of cardiovascular fitness, indexed as maximal oxygen consumption, there is a linear relationship among indices of cardiac pump performance, including peak exercise ejection fraction and cardiac index, and an inverse relationship to end-systolic volume index (Fig. 7), suggesting an important influence of physical conditioning on left ventricular performance. This improvement in cardiac performance in healthy elderly subjects with exercise training is not due to a change in β-adrenergic responsiveness, which does not appear to change with exercise conditioning (52). A potential mechanism for improved systolic function following exercise training is a reduction in vascular afterload (see below) (53). Noninvasive indices of arterial stiff-

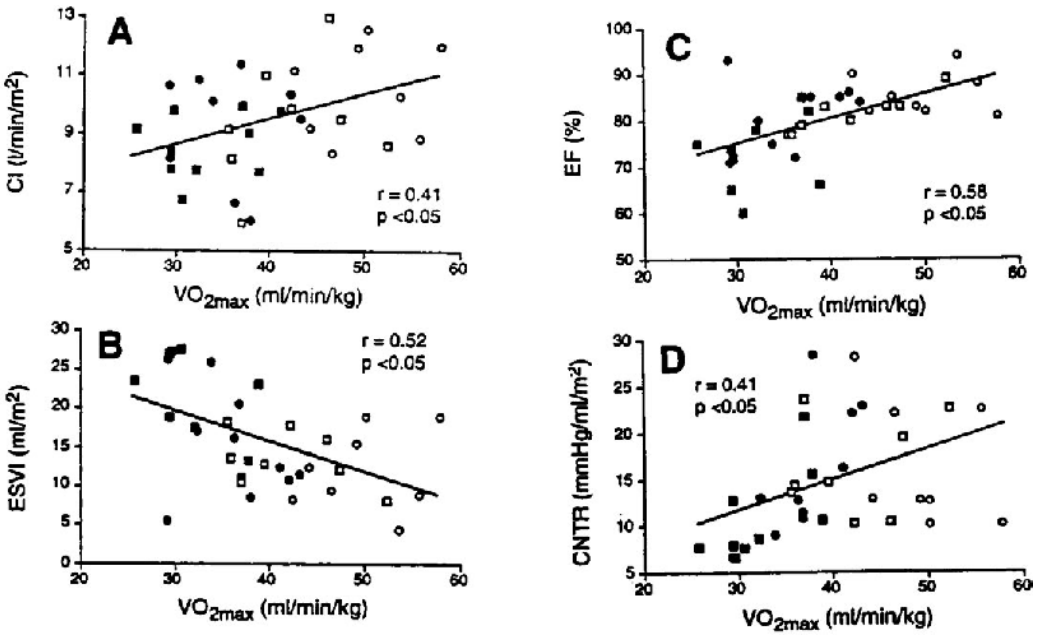

Figure 7 Relationship of maximal oxygen consumption (VO_{2max}) to four indices of left ventricular function: cardiac index (CI); end-systolic volume index (ESVI); ejection fraction (EF); and contractility index (CNTR). There is a linear relationship between cardiovascular fitness and myocardial contractility. (From Ref. 50.)

ness in senior master athletes are significantly reduced compared with those of age-matched, sedentary controls, and similar to arterial stiffness indices of young subjects.

Ventricular–Vascular Coupling

The age differences in the cardiovascular response to exercise relate not only to the decreased β-adrenergic responsiveness of senescent myocardium, but also the decreased β-adrenergic response of the vasculature. The human aorta undergoes changes in composition and distribution of elastin and collagen that cause stiffening of the great vessels (54). The increase in aortic stiffness with age results in predictable hemodynamic changes, including an increase in systemic vascular resistance and an increase in characteristic impedance resulting in an age-associated rise in systolic blood pressure, an increase in the arterial pulse pressure, and an increase in left ventricular wall stress and left ventricular mass (55,2,22). In a noninvasive study of arterial stiffness utilizing pulse wave velocity, Avolio and colleagues demonstrated a linear correlation between pulse wave velocity and age in a group of 524 rural Chinese subjects aged 2 months to 94 years (56) (Fig. 8). In this area of China there is a low prevalence of atherosclerosis and hypertension, so the increase in vessel stiffness is probably a true age effect.

This age-associated increase in vascular afterload may have a key role in limiting peak exercise cardiac index and ejection fraction in healthy elderly subjects. Similar to the animal model, arterial vasodilation to β-adrenergic stimulation is limited in the elderly (52). This diminished vasodilation to catecholamines may result in a greater afterload to left ventricular ejection during exercise in older subjects compared to younger subjects and limit peak exercise cardiac output and ejection fraction. Noninvasive measurements of aortic stiffness are inversely and independently associated with maximal oxygen consumption in healthy subjects consistent with the role of increasing aortic stiffness with

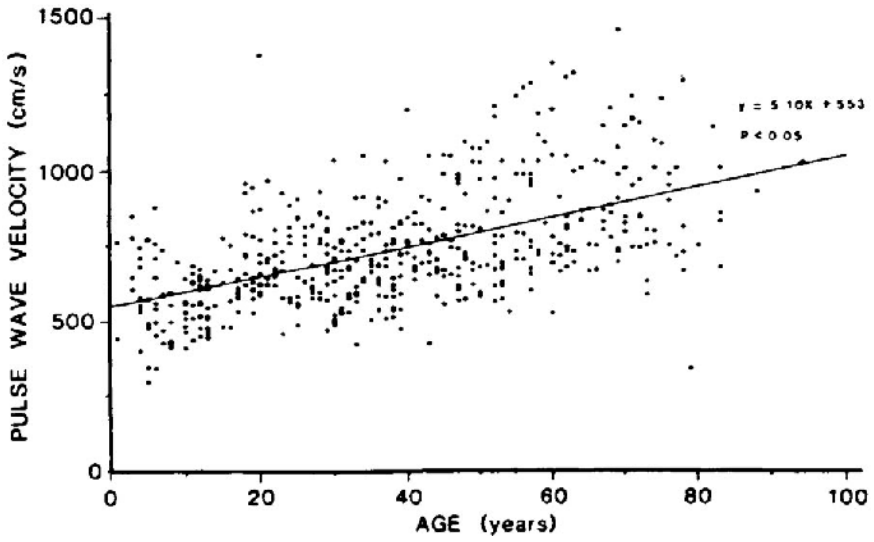

Figure 8 The relationship between pulse wave velocity and age from a larger group of healthy Chinese subjects. Pulse wave velocity increases linearly with increasing age. (From Ref. 56.)

age-limiting exercise capacity in the elderly (53). Reducing arterial stiffness with nitroprusside in older, healthy subjects results in improved cardiac ejection performance during exercise (57). These data are consistent with animal models and suggest that the increase in vascular load in healthy elderly limits the exercise response.

CONCLUSIONS

In conclusion, similar age-associated changes in cardiovascular function are apparent across species, including healthy humans. Both animal models and human studies do not show an age-associated decline in resting myocardial function. Three age-associated changes include prolongation in myocardial relaxation, a decreased responsiveness of myocardium and vascular smooth muscle to β-adrenergic stimulation, and an increase in arterial stiffness with resultant increase in vascular afterload. These cardiovascular changes limit peak exercise cardiac index and ejection fraction. Nonetheless, healthy elderly subjects are able to augment cardiac output during exercise by effective use of the Frank-Starling mechanism with a resultant large increase in end-diastolic volume from rest to exercise. It is likely that some of these age-related cardiovascular changes may not be inherent to aging but due to an increasingly sedentary lifestyle, as exercise training may reverse some of these age-associated changes. Finally, these age-associated changes (impaired diastolic filling, increased afterload, impaired β-adrenergic responsiveness) make the elderly more prone than younger subjects to develop symptoms and decompensate with the burden of disease, such as hypertension, coronary artery disease, or atrial fibrillation. The manifestations and management of these common disorders in the elderly is the subject of the following chapters.

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2

Morphological Features of the Elderly Heart

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INTRODUCTION

As in any body tissue or organ, changes take place in the cardiovascular system as life progresses. Some of these changes allow easy identification of the very elderly heart when examining autopsy cardiac specimens as unknowns. The ''normal'' elderly heart has relatively small ventricular cavities and relatively large atria and great arteries. The ascending aorta and left atrium, in comparison with the relatively small left ventricular cavity, appear particularly large. The coronary arteries increase in both length and width; the former, particularly in association with the decreasing size of the cardiac ventricles, results in arterial tortuosity. (The young river is straight and the old one winding.) The leaflets of each of the four cardiac valves thicken with age, particularly the atrioventricular valves; these have a smaller area to occupy in the ventricles because of the diminished size of the latter. Histological examination discloses large quantities of lipofuscin pigment in myocardial cells; some contain mucoid deposits (''mucoid degeneration''). These changes appear to affect all population groups of elderly individuals regardless of where they reside on the earth or their level of serum lipids. An elevated systemic arterial pressure appears to both accelerate and amplify these normal expected cardiac changes of aging. Both the aorta and its branches and the major pulmonary arteries and their branches enlarge with age. Because the enlargement is in both the longitudinal and the transverse dimensions, the aorta, as the coronary arteries, tends to become tortuous. This process is further amplified as the vertebral bodies become smaller and the height becomes somewhat shorter. The major pulmonary arteries appear to be too short and have too low a pressure to dilate longitudinally.

The amount of information at necropsy in very elderly persons is relatively sparse. In 1983, Waller and Roberts (1) described some clinical and necropsy findings in 40 American patients aged 90 years and over. In 1988, Lie and Hammond (2) reported findings at necropsy in 237 patients aged 90 and older. In 1991, Gertz and associates (3) described composition of coronary atherosclerotic plaques in 18 persons ≥90 years of age. In 1993, Roberts (4) described cardiac necropsy findings in an additional 53 patients ≥90 years of age. In 1995, Shirani et al. (5) described cardiac findings at necropsy in

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366 Americans aged 80 to 89 years, and in 1998 Roberts (6) described cardiac findings at necropsy in six centenarians. Also, in 1998 Roberts and Shirani (7) compared cardiovascular findings in 490 patients studied at necropsy in three age categories: 80–89; 90–99; and ≥100 years. This chapter expands on that previous comparative study.

METHODS

Patients. The files of the Pathology Branch, National Heart, Lung, and Blood Institutes, National Institutes of Health, Bethesda, Maryland, from 1959 to 1993, and those of the Baylor University Medical Center, Dallas, Texas, beginning January 1993, were searched for all accessioned cases of patients aged ≥80 years of age. Of 511 such cases found, adequate clinical information was available in 490 necropsy patients and they are the subject of this chapter. The clinical and cardiac morphological records, photographs, and postmortem radiographs, histological slides, and the initial gross description of the heart were reviewed. All 490 hearts were originally examined by WCR, who recorded gross morphological abnormalities in each case.

Sources of patients. Of the 490 cases, the hearts in 412 were obtained from 12 Washington, DC, area hospitals, and the hearts in the other 78 cases, from hospitals outside that area, including 25 from Baylor University Medical Center. Of the 490 hearts, 37 (8%) were examined in 1970 or before; 153 (31%), from 1971 through 1980; 244 (50%), from 1981 through 1990; and 56 (11%) from 1991 through 1997.

Definitions. Sudden coronary death was defined as death within 6 h from the onset of new symptoms of myocardial ischemia in the presence of morphological evidence of significant atherosclerotic coronary artery disease (≥1 major epicardial coronary artery narrowed >75% in cross-sectional area by atherosclerotic plaque). Most patients who died suddenly did so outside a hospital; a few, however, died shortly after admission to an emergency room. Sudden, out-of-hospital death also occurred in some patients with cardiac disease other than atherosclerotic coronary artery disease. In each case, an underlying cardiac disease generally accepted to cause sudden death was present at necropsy. Acute myocardial infarction was defined as a grossly visible left ventricular wall lesion confirmed histologically to represent coagulation-type myocardial necrosis. Ischemic cardiomyopathy was defined as chronic congestive heart failure associated with a transmural healed myocardial infarct and a dilated left ventricular cavity.

Cardiac morphological data. Hearts were fixed in 10% phosphate-buffered formalin for 3 to 15 days before examination. They were ''cleaned'' of parietal pericardium and postmortem intracavity clot, and the pulmonary trunk and ascending aorta were incised approximately 2 cm cephalad to the sinotubular junction. Heart weight was then measured on accurate scales by WCR (Lipsaw scale before 1971, accurate to 10 g, and Mettler P1210 scale after 1971, accurate to 0.1 g). Heart weight was considered increased if it was ≥350 g in women and >400 g in men. Most hearts were studied by cutting the ventricles transversely at approximately 1-cm-thick intervals from apex to base parallel to the atrioventricular groove posteriorly. In each heart, the sizes of cardiac ventricular cavities (determined by gross inspection), presence of left ventricular necrosis (acute myocardial infarct) and fibrosis (healed myocardial infarct), status of the four cardiac valves, and the maximal degree of cross-sectional luminal narrowing in each of the three major (left anterior descending, left circumflex, and right) epicardial coronary arteries were recorded.

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RESULTS

Number of patients in each of the three groups. Certain clinical and necropsy cardiac findings in the 490 cases are summarized in Table 1 and illustrated in Figures 1 through 19. The 490 patients were divided into three groups: the octogenarians (80–89 years) ($n = 391$[80%]); the nonagenarians (90–99 years) ($n = 93$[19%]); and the centenarians (≥100 years) ($n = 6$[1%]); 248 (51%) were women and 242 (49%) were men.

CLINICAL FINDINGS

The clinical manifestations of the various cardiac disorders probably represent minimal numbers: many patients apparently were unable to provide much clinical information, many came to the hospital from nursing homes, and many had varying degrees of dementia. Nevertheless, angina pectoris was noted in the records of 137 (35%) of the 391 octogenarians, in 5 (5%) of the 93 nonagenarians, and in none of the centenarians. A history of a hospitalization for an illness compatible with acute myocardial infarction was present in 78 (20%) of the 391 octogenarians; in 18 (19%) of the 93 nonagenarians; and in none of the 6 octogenarians. Chronic congestive heart failure was present in 36% (140/391) of the octogenarians; in 25% (23/93) of the nonagenarians; and in none of the 6 centenarians. A history of systemic hypertension was present in 44% (174/391) of the octogenarians; in 54% (50/93) of the nonagenarians; and in none of the centenarians. Diabetes mellitus was present in 14% (56/391) of the octogenarians; in 9% (8/93) of the nonagenarians; and in none of the centenarians.

CAUSES OF DEATH

The causes of death in the 490 patients are summarized in Table 2. A cardiac condition was the cause of death in 51% (198/391) of the octogenarians; in 32% (30/99) of the nonagenarians; and in none of the centenarians. A noncardiac but vascular condition was responsible for death in 13% (52/391) of the octogenarians and in 20% (19/93) of the nonagenarians. A noncardiac and a nonvascular condition was responsible for death in 36% (141/391) of the octogenarians; in 47% (44/93) of the nonagenarians; and in all of the centenarians.

CARDIAC NECROPSY FINDINGS

Cardiac findings at necropsy are tabulated in Table 1.

Heart weight. The mean heart weights were largest in the octogenarians and smallest in the centenarians (449 g vs. 420 g vs. 328 g). Heart weight was increased (>400 g in men; >350 g in women) in 131 (64%) of the 205 men and in 157 (74%) of the women, and the percent was highest in the octogenarians.

Calcific deposits in the heart. Calcific deposits were present in the heart at necropsy in 444 (91%) of the 490 patients and were most common in the coronary arteries—in all cases being located in atherosclerotic plaques and not in the media—81% (398/490); in the aortic valve cusps in 47% (228/490)—heavy enough to result in aortic stenosis

Table 1 Certain Clinical and Necropsy Findings in 490 Patients Aged 80 to 103 Years

Variable	Age group (years)		
	80–89 (n = 391)	90–99 (n = 93)	≥100 (n = 6)
1. Mean age (Years)	84 ± 4	93 ± 4	102
2. Male : female	194(50%) : 197(50%)	52(56%) : 41(44%)	2/4
3. Angina pectoris	137(35%)	5(5%)	0
4. Acute myocardial infarction	78(20%)	18(18%)	0
5. Chronic congestive heart failure	140(36%)	23(25%)	0
6. Systemic hypertension (history)	174(44%)	50(54%)	0
7. Diabetes mellitus	56(14%)	8(9%)	0
8. Atrial fibrillation	57(15%)	35(38%)	0
9. Heart weight (g) : range(mean)	185–900(449)	220–660(420)	240–410(328)
Men	230–830(493)	285–660(436)	335&410(372)
Women	185–900(409)	220–630(406)	240–385(306)
10. Cardiomegaly			
Men > 400 g	103/154(67%)	27/49(55%)	1/2
Women > 350 g	133/165(81%)	23/42(55%)	1/4
11. Cardiac calcific deposits			
None	43(11%)	3(3%)	0
Present	348(89%)	90(97%)	6(100%)
Coronary arteries	304(78%)	89(96%)	5
Aortic valve cusps	164(42%)	59(63%)	5
Heavy (stenosis)	43(11%)	8(9%)	0
Mitral annulus	146(37%)	42(45%)	2
Heavy	52(13%)	11(12%)	0
Papillary muscle	37(9%)	42(45%)	6

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12. Numbers of patients with 0,1,2, or 3 major (right, left anterior descending, left circumflex) coronary arteries ↓ >75% in cross-sectional area			
0	159(41%)	33(35%)	2
1	67	20	2
2	71 } 232(59%)	32 } 60(65%)	2 } 4
3	94	8	0
Mean	1.7	1.5	1.5
13. Number of major coronary arteries (3/patient) ↓ >75% in cross-sectional area by plaque			
0	0/477	0/99	0/6
1	67/201	20/60	2/6
2	142/213	64/96	4/6
3	282/282	24/24	0
Totals	491/1173(42%)	108/279(39%)	6/18(33%)
14. Left ventricular necrosis and/or fibrosis			
Necrosis only	54/(14%)	10(11%)	0
Fibrosis only	101(26%)	20(21%)	2
Both	37 (9%)	5(5%)	0
15. Ventricular cavity dilatation			
Neither	222(57%)	58(62%)	4
One	84(21%)	4(4%)	2
Right ventricle	42	2	2
Left ventricle	42	2	2
Both	85(22%)	31(34%)	0
16. Cardiac amyloidosis (massive)	14 (4%)	8(9%)	0

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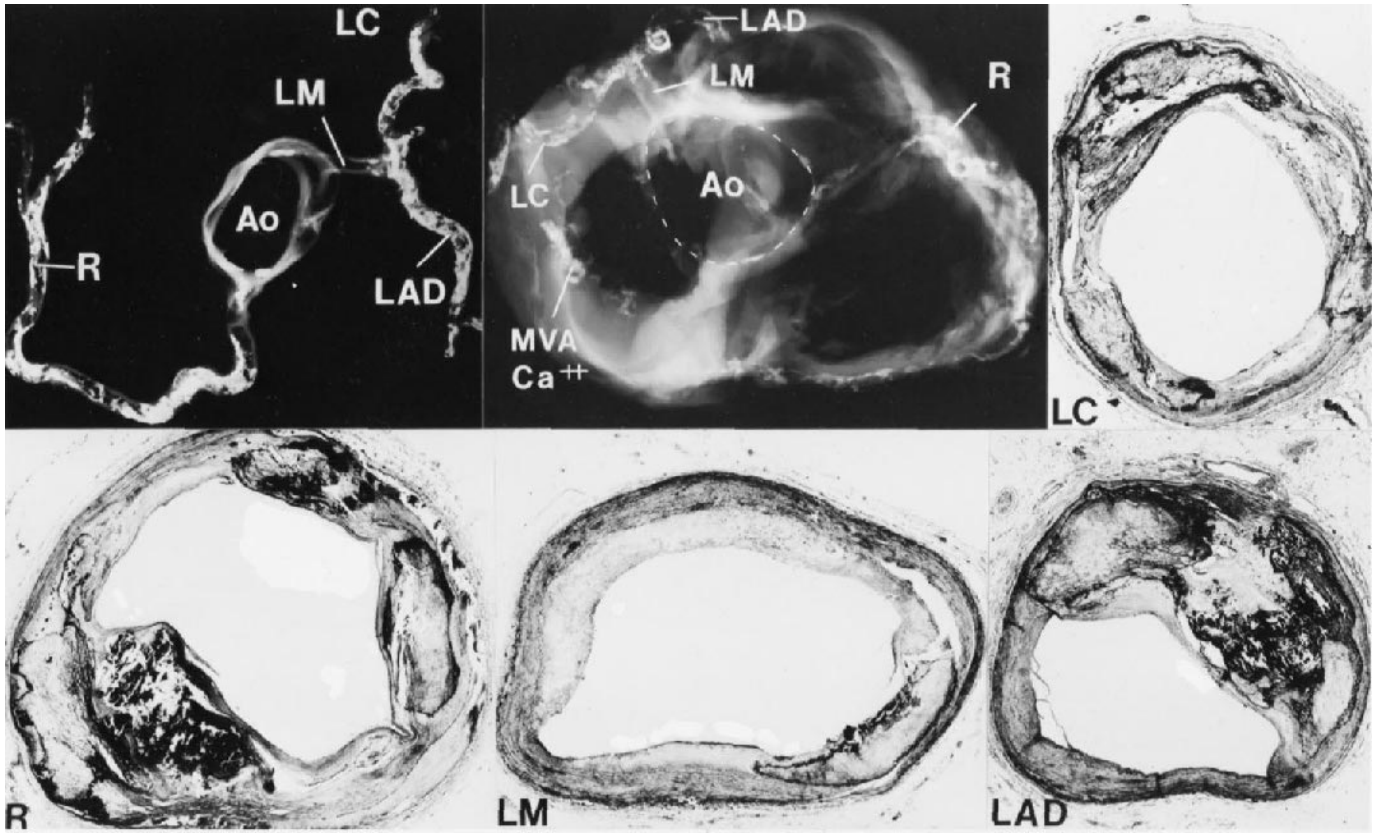

Figure 1 Tortuous and heavily calcified coronary arteries in a 95-year-old woman (SH #A80-74) who never had symptoms of cardiac dysfunction and who died from a perforated gastric ulcer. Top left: postmortem radiogram of the excised right (R), left main (LM), left anterior descending (LAD), and left circumflex (LC) coronary arteries. Top center: radiogram of a portion of the heart after removing the walls of the atria and most of the walls of the ventricles. MVA = mitral valve annulus. Top right and lower panels: photomicrographs of coronary arteries at sites of maximal narrowing by calcified atherosclerotic plaques. (Movat stains; magnification × 17, reduced 40%). This case illustrates extensive calcific deposits in the coronary arteries without significant luminal narrowing.

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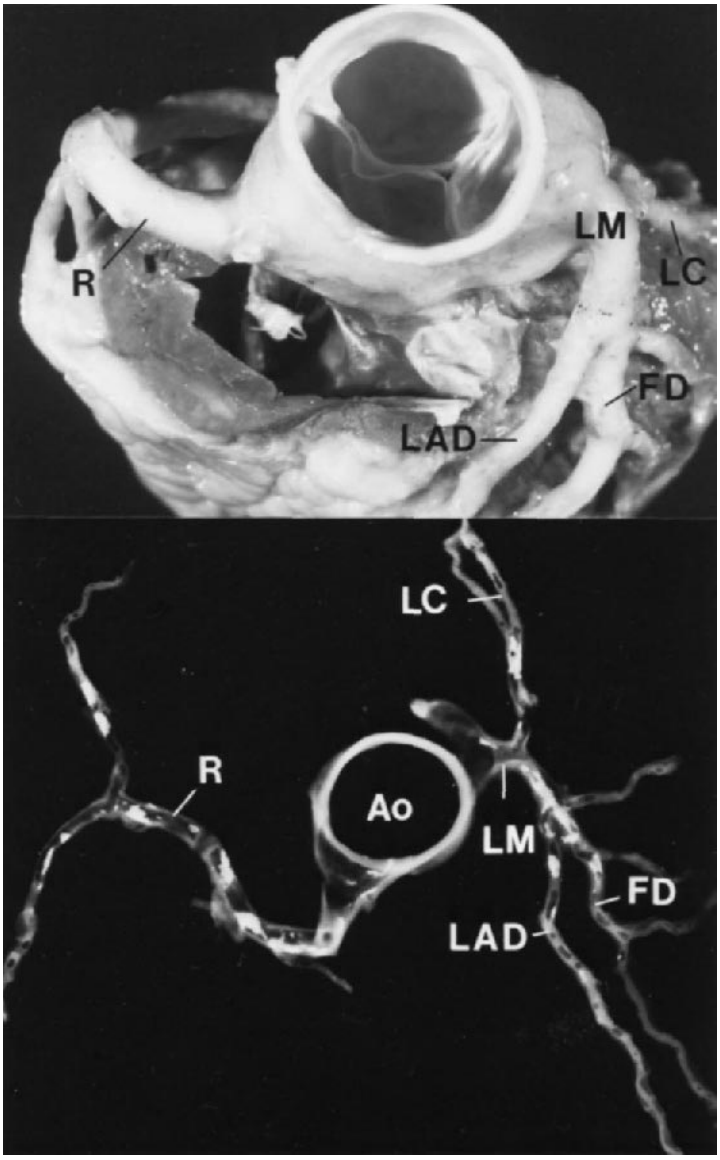

Figure 2 Coronary arteries in a 95-year-old man (SH #A79-77) who never had symptoms of cardiac dysfunction and who died from cancer. Top: aorta and coronary arteries from above. Bottom: radiograms of aortic root (Ao) and excised coronary arteries that contain calcific deposits. FD = first diagonal, LAD = left anterior descending, LC = left circumflex, LM = left main, R = right.

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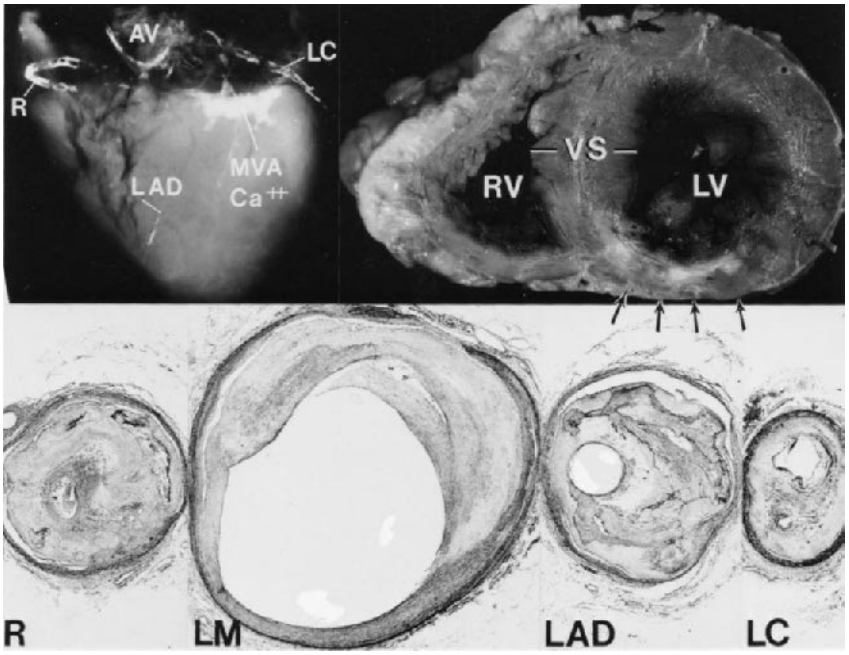

Figure 3 Heart and coronary arteries in a 93-year-old woman who was hospitalized with worsening chronic congestive heart failure. Top left: postmortem radiogram showing calcific deposits in the right (R), left anterior descending (LAD), and left circumflex (LC) coronary arteries and in the mitral valve annulus (MVA) and aortic valve. Top right: view of right (RV) and left (LV) ventricles and ventricular septum (VS) showing a transmural scar (arrows). Bottom: coronary arteries at sites of maximal narrowing. LM = left main. (Movat stains; magnification ± 17, reduced 40%.)

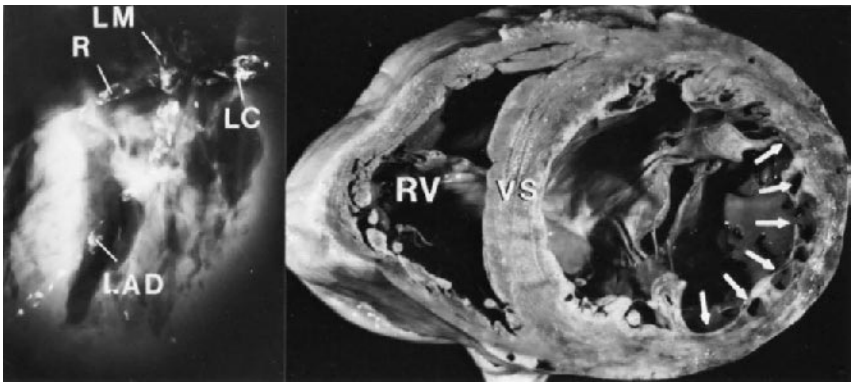

Figure 4 This 91-year-old woman (LRC #3) had a ''typical'' clinical acute myocardial infarct, which was fatal. Left: postmortem radiogram showing calcific deposits in the right (R), left main (LM), left anterior descending (LAD), and left circumflex (LC) coronary arteries. Right, view of the left and right (RV) ventricles showing transmural necrosis and fibrosis (arrows) and dilated ventricles. VS = ventricular septum.

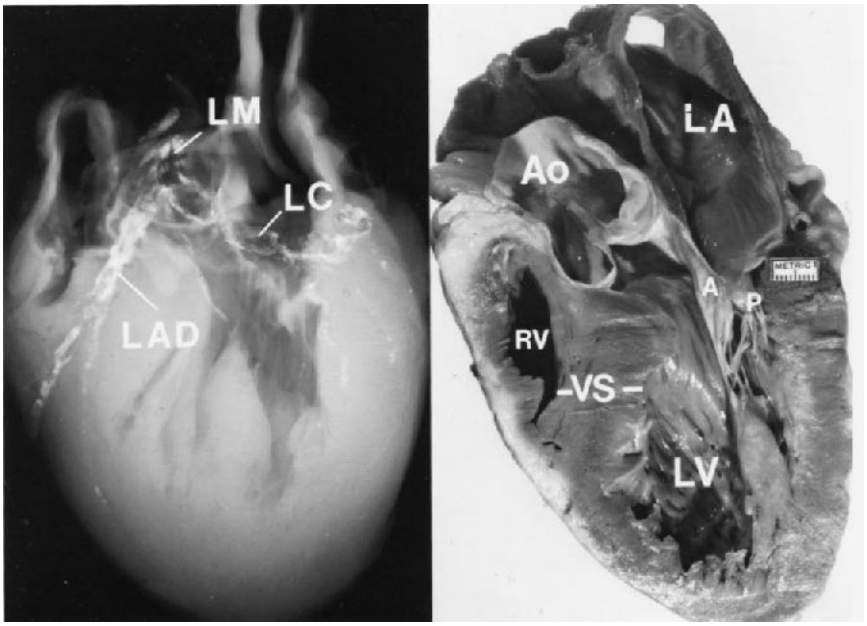

Figure 5 This 90-year-old woman (SH #A82-1) had no symptoms of cardiac dysfunction and died from a ruptured fusiform abdominal aortic aneurysm. Left: postmortem radiogram of the entire heart showing calcific deposits in the left anterior descending (LAD), left circumflex (LC), and left main (LM) coronary arteries. Right: view of heart cut in an anteroposterior fashion (M-mode or long-axix two-dimensional echocardiographic view) showing a dilated left atrium (LA) and left ventricle (LV). A and P = anterior and posterior mitral valve leaflets; Ao = aorta; RV = right ventricle; VS = ventricular septum.

in 10% (51/490); mitral valve annulus in 39% (190/490)—very heavy deposits in 13% (63/490), and in the apices of 1 or both left ventricular papillary muscles in 17% (85/490). The cardiac calcific deposits were more frequent and heavier in the nonagenarians than in the octogenarians.

Numbers of patients with narrowing of 1 or more major epicardial coronary arteries. Among the 490 patients, 194 (40%) had none of the three major (right, left anterior descending, and left circumflex) epicardial coronary arteries narrowed by plaque >75% in cross-sectional area; 89 (18%) had one artery so narrowed; 105 (21%) had two arteries so narrowed; and 94 (19%) had all three arteries so narrowed. The percent of patients in each of the three groups with no arteries and 1, 2, and 3 arteries narrowed >75% was similar.

Numbers of major coronary arteries (three/patient) narrowed >75% in cross-sectional area by plaque. Among the 490 patients, a total of 1470 major epicardial coronary arteries were examined: 865 (59%) arteries had insignificant (<75% in cross-sectional area) narrowing and 605 (41%) had narrowing by plaque >75% in cross-sectional area. The percent of arteries significantly narrowed was similar in each of the three groups (42% vs. 39% vs. 33%).

Acute and healed myocardial infarcts. Grossly visible foci of left ventricular wall

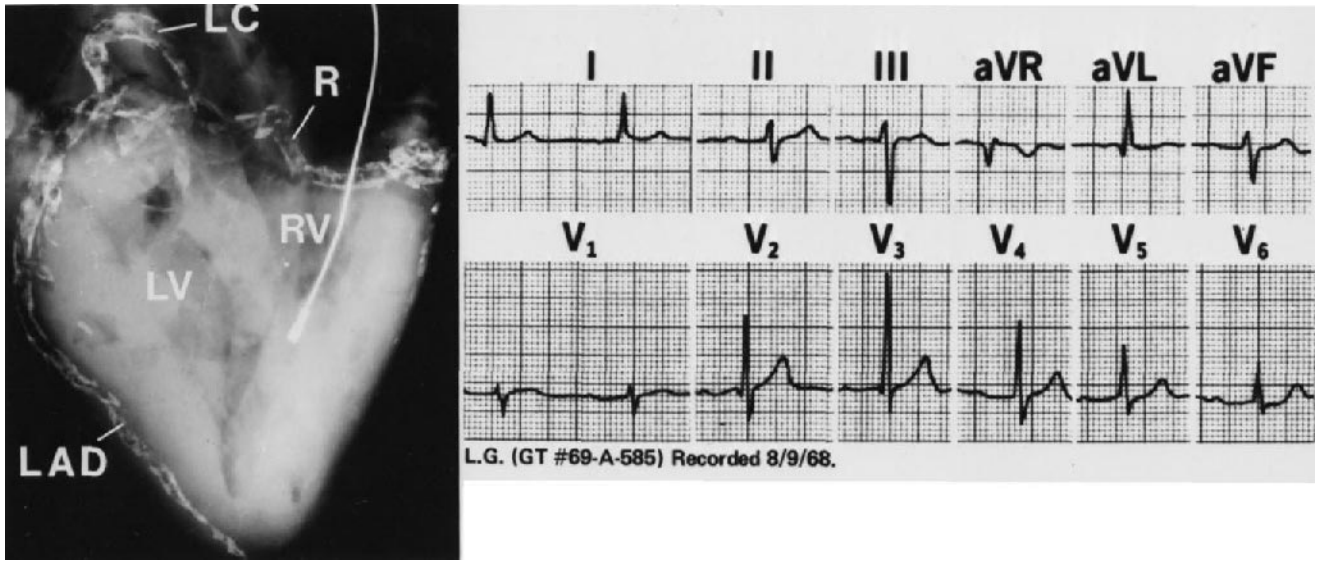

Figure 6 This 97-year-old man (GT # 69A-585) had complete heart block and had a pacemaker inserted when he was 91 years old. Left: radiogram of heart at necropsy showing calcific deposits in the left anterior descending (LAD), left circumflex (LC), and right (R) coronary arteries and a pacemaker wire in the right ventricle (RV). LV = left ventricle. Right: electrocardiogram.

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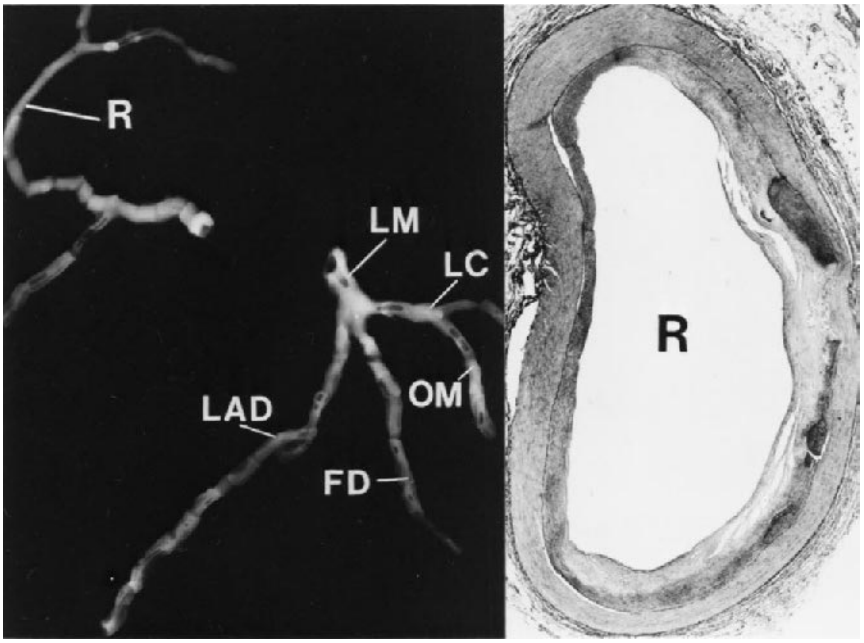

Figure 7 This 96-year-old woman (DCGH #68A80) had chronic congestive heart failure from dilated cardiomyopathy. Her total serum cholesterol level was 108 mg/dl. Left: postmortem radiogram of the right (R), left main (LM), left anterior descending (LAD), left circumflex (LC), first diagonal (FD), and left obtuse marginal (OM) coronary arteries showing no calcific deposits. Right: right coronary artery section devoid of calcium or narrowing. (Movat stain; magnification × 16, reduced 23%.)

(includes ventricular septum) necrosis (acute infarcts) without associated left ventricular scars (healed infarcts) were found in 64 (13%) patients; foci of left ventricular fibrosis without associated necrosis were observed in 123 patients (25%); and foci of both necrosis and fibrous were found in 42 patients (9%). Thus, a total of 229 (47%) of the 490 patients had grossly visible evidence of acute or healed myocardial infarcts or both. The percents of patients with myocardial lesions of ischemia were similar among the octogenarians and nonagenarians.

Ventricular cavity dilatation. One or both ventricular cavities were dilated (by gross inspection) in 218 (44%) of the 490 patients and no significant differences were observed in the three groups.

Cardiac amyloidosis. Grossly visible amyloid (confirmed histologically) in ventricular and atrial myocardium as well as in atrial mural endocardium was present in 22 patients (4%). In these 22 patients, the amyloidosis was symptomatic and fatal. A number of other patients who had no gross evidence of cardiac amyloidosis had small foci in the heart on histological study. These minute deposits did not cause symptoms of cardiac dysfunction. In the 22 patients with fatal cardiac amyloidosis, deposits of amyloid also were present in several other body organs at necropsy.

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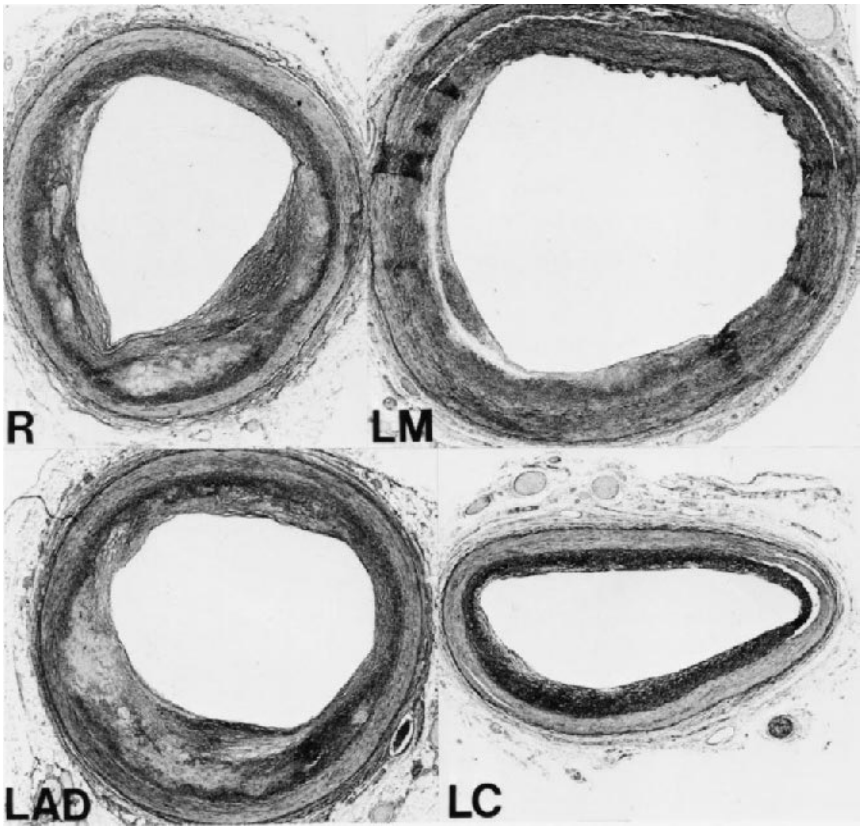

Figure 8 Right (R), left main (LM), left anterior descending (LAD), and left circumflex (LC) coronary arteries at sites of maximal narrowing in a 103-year-old woman (GT #70A301). She never had evidence of cardiac dysfunction and died from complications of a duodenal ulcer. The coronary arteries are devoid of calcium and of significant narrowing. (Elastic-van Gieson's stain; magnification × 16, reduced 31%.)

ELECTROCARDIOGRAPHIC FINDINGS

Information on electrocardiograms was available on 30 of the 99 patients aged ≥90 years. Of the 30 patients, three had electrocardiograms recorded during acute myocardial infarction. The electrocardiograms in all three, however, disclosed only atrial fibrillation and complete left bundle branch block, and these findings in these patients were known to be present before the fatal acute myocardial infarction. The electrocardiograms in the other 27 patients were not recorded during periods of acute myocardial infarction. Of the 30 patients on whom electrocardiographic information was available, 8 had clinical evidence of heart disease and 22 did not; the findings are summarized in Table 2. The total 12-lead QRS voltage ranged from 82 to 251 mm (mean 151; 10 mm = 1 mV). In the 19 women, the total voltage ranged from 82 to 251 mm (mean 158) and, in the 5 men, from

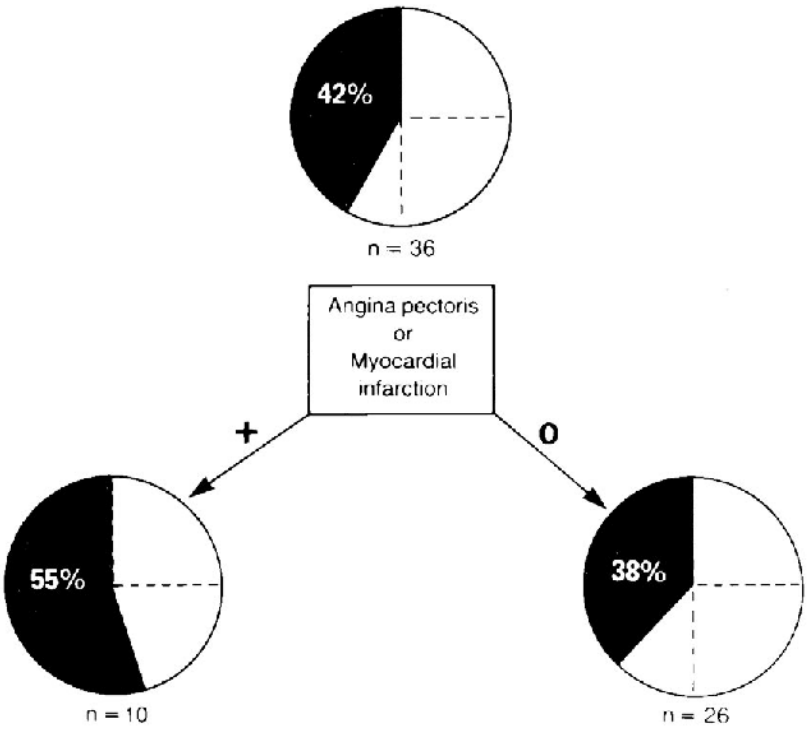

Figure 9 Mean percentage cross-sectional area narrowing by atherosclerotic plaques in 1789 segments (5 mm) of the four major epicardial coronary arteries in 36 necropsy patients aged 90 years and older, 10 of whom had angina pectoris or acute myocardial infarction, or both, and 26 of whom did not. The mean percentage of narrowing for each 5-mm segment differs significantly in the group with clinical evidence of myocardial ischemia (55%) and the group without such evidence.

105 to 154 mm (mean 101; $p < 0.05$). The total 12-lead QRS voltage did not correlate with either heart or body weight. The 24 patients in whom the total 12-lead QRS voltage was measured were separated into two groups: eight patients in whom clinical evidence of cardiac dysfunction was present (coronary heart disease in five, massive cardiac amyloid in two, and aortic valve stenosis in one) and 16 patients without such evidence (Table 3). Comparison of the total QRS voltage in the eight patients with and in the 16 patients without clinical evidence of heart disease disclosed no significant difference (mean 147 mm vs. 152 mm). Breakdown on the eight patients with cardiac dysfunction did show some differences: the total 12-lead QRS voltage in the five patients with angina pectoris or acute myocardial infarction ranged from 123 to 163 mm (mean 143); in the two patients with massive cardiac amyloidosis it was 102 and 117 mm (mean 109); and in the one patient with aortic valve stenosis was 238 mm. Of 29 patients on whom information was available, 18 (62%) received digitalis and only two appeared to have evidence of digitalis toxicity.

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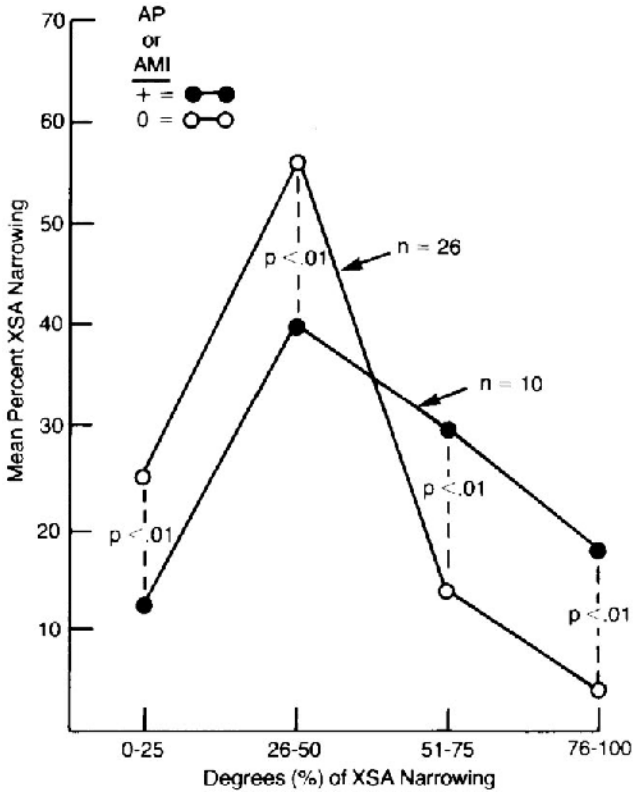

Figure 10 Mean percentage cross-sectional area (XSA) narrowing by atherosclerotic plaques in the 5-mm segments of the right, left main, left anterior descending, and left circumflex coronary arteries in the 36 patients in whom the four major coronary arteries in their entirety were available for examination. The 36 patients were classified into 10 with and 26 without clinical evidence of myocardial ischemia. For each of the four categories of narrowing, a highly significant difference in the amount of narrowing was observed.

COMMENTS

This study describes findings in a large group ($n = 490$) of patients ≥80 years of age studied at necropsy, and it compares certain clinical and necropsy findings in the octogenarians, nonagenarians, and centenarians. Despite study of nearly 500 patients, only 6 (1%) lived 100 years or longer, and only 93 (19%) lived into the tenth decade of life. Nevertheless, the ratio of one centenarian for every 65 octogenarians is much higher than might be expected. In general, it takes 10,000 persons to reach age 85 before one reaches age 100 (8).

Another finding was the high frequency of men: 248 men (51%) and 242 (49%) women. A higher than expected percent of men may have resulted in part from receiving a number of these cases from a Veterans Administration Hospital and from a retirement home filled almost entirely by men.

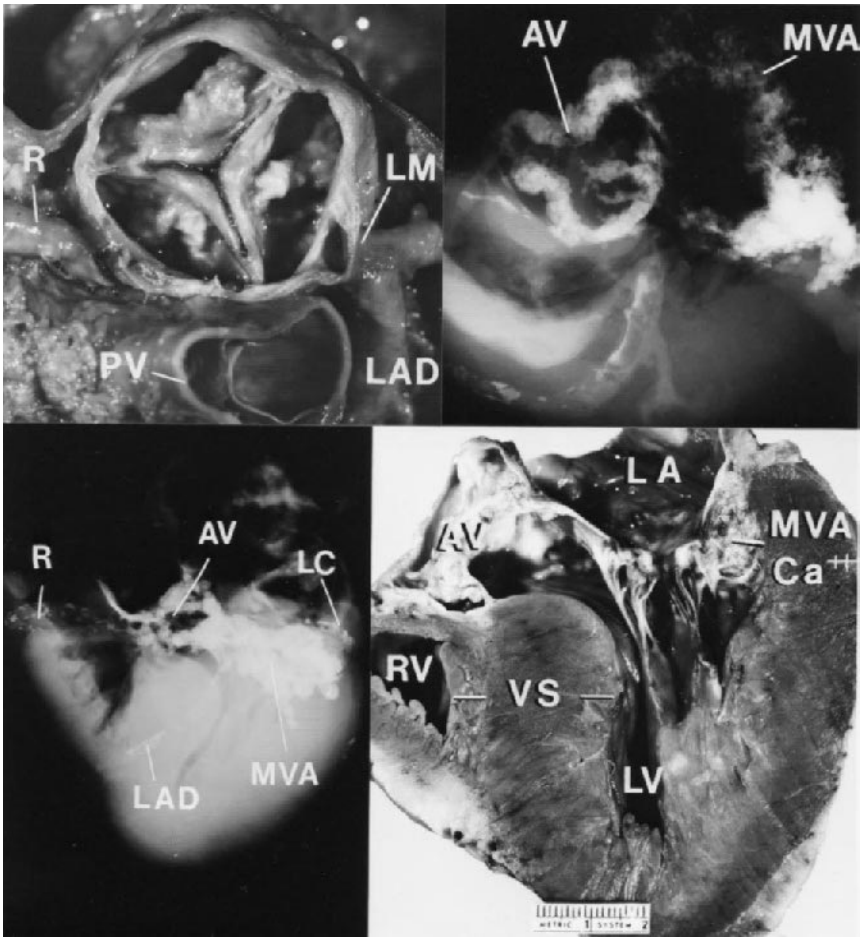

Figure 11 A 92-year-old woman (GT #78A58) with clinically recognized and eventually fatal aortic valve stenosis. Top left: stenotic aortic valve from above. PV = pulmonic valve; R = right; LM = left main; LAD = left anterior descending coronary arteries. Top right: postmortem radiogram showing heavy calcific deposits in the aortic valve (AV) and in the mitral valve annular (MVA) region. Bottom left: radiogram of the heart at necropsy showing calcific deposits in the coronary arteries, in the aortic valve, and in the mitral annular region. Bottom right: long-axis view of heart (M-mode or two-dimensional long-axis view) showing a small left ventricular (LV) cavity, a thickened and ''sigmoid-shaped'' ventricular septum (VS), and the stenotic aortic valve just above the right ventricular (RV) outflow tract. LA = left atrium.

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Figure 12 (a) A 90-year-old woman (GT #80A126) with heavy mitral valve annular calcific deposits that reduced the mitral valve orifice to <1 cm in diameter. The unusual feature of the mitral calcium in this patient was that it not only was located behind the posterior mitral leaflet (mitral annular region) but it also extended across the anterior mitral leaflet, nearly producing a letter O), as has been described previously. She died from rupture of a descending thoracic aortic aneurysm. VS = ventricular septum. (b) View of the left ventricle at the level of the tips of the mitral leaflets, showing a very small cavity.

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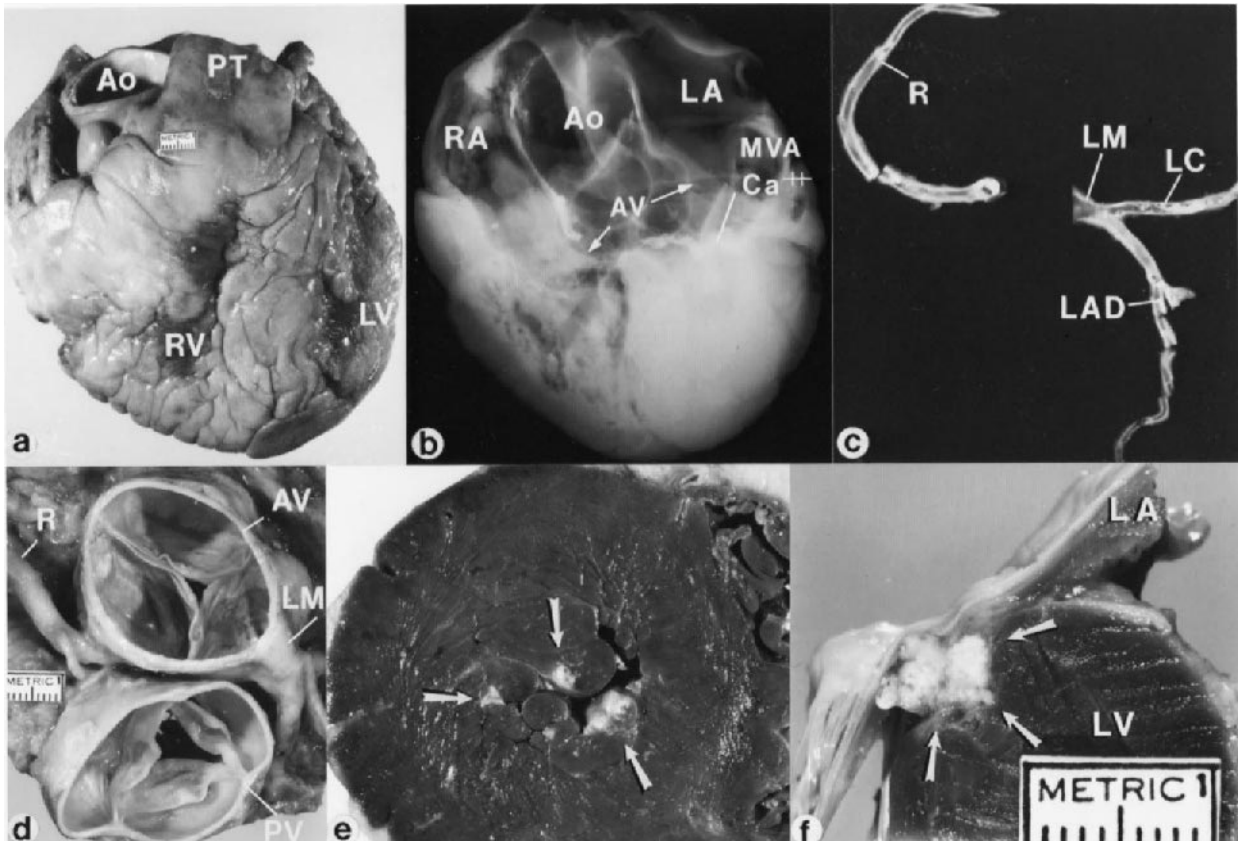

Figure 13 A 97-year-old woman (SH #A81-62) who never had clinical evidence of cardiac dysfunction and who died from cancer. (a) External view of anterior surface of the heart showing and increased amount of subepicardial fat. Ao = aorta, LV = left ventricle, PT = pulmonary trunk, RV = right ventricle. (b) Postmortem radiogram showing calcific deposits in the mitral valve annulus (MVA) an aortic valve (AV). LA = left atrium, RA = right atrium. (c) Radiogram of the excised coronary arteries showing a few calcific deposits. LAD = left anterior descending, LC = left circumflex, LM = left main, R = right. (d) View of aortic valve (AV) and pulmonic valve (PV) from above. (e) View of left ventricle showing clacific deposits (arrows) in the papillary muscles. (f) Calcific deposits in the mirtal annular region (arrows).

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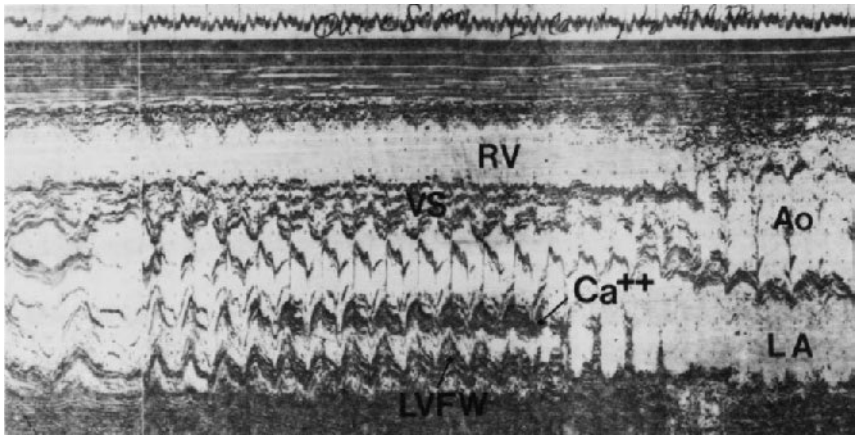

Figure 14 M-mode echocardiogram obtained 10 months before death (SH #80-18). The ascending aorta (Ao) has a larger diameter than the left atrium (LA). The left ventricular (LV) cavity is small. Calcium is present in the mitral annular region. (I thank Dr. Robert Montgomery, Bethesda, Maryland, for allowing me to show this echocardiogram from his patient.)

The causes of death were divided into three major types: cardiac = 228/490 (47%); vascular but noncardiac = 71/490 (14%); and noncardiac and nonvascular = 191/490 (39%). The frequency of a cardiac condition causing death decreased with increasing age groups (51% vs. 32% vs. 0), and the frequency of a noncardiac and nonvascular condition causing death increased with increasing age groups (36% vs. 47% vs. 100%). Among the cardiac conditions, coronary artery disease was the problem in 62% (141/228), and the other cardiac conditions, mainly aortic valve stenosis (36/228[16%]) and cardiac amyloidosis (22/228[10%]), in the other 38%. Stroke, rupture of an abdominal aortic aneurysm, and complications of peripheral arterial atherosclerosis were the major vascular (noncardiac) conditions causing death. Of the noncardiac and nonvascular causes of death, cancer and infection, mainly pneumonia, were the major conditions, 35% (65/185) and 29% (54/185), respectively, among the octogenarians and nonagenarians.

The cardiac necropsy findings focused primarily on calcific deposits in the coronary arteries, aortic valve cusps, and mitral valve annulus and their consequences, and, to a lesser extent, on heavy amyloid deposits in the heart. Calcific deposits were present in the atherosclerotic plaques of one or more epicardial coronary arteries in 81% (398/490) of the patients, on the aortic aspects of the aortic valve cusps in 47% (228/490), in the mitral annular regional in 39% (190/490), and in one or both left ventricular papillary in 25% (122/490). The calcific deposits tended to be less frequent in the octogenarians. The frequent presence of calcific deposits in the coronary arteries, aortic valve cusps, and mitral annular region in the same patient suggests that the cause of the calcific deposits in each of these three locations is the same. The calcific deposits in the coronary arteries indicate the presence of atherosclerosis because calcium occurs in the coronary arteries, with one exception (9), only in the plaques and not in the media. It is reasonable to believe that the calcific deposits in and on the aortic cusps, at least when this valve is three-cuspid, are another manifestation of atherosclerosis. Because mitral annular calcium in this older population is nearly always associated with calcium in the coronary arteries, it is also

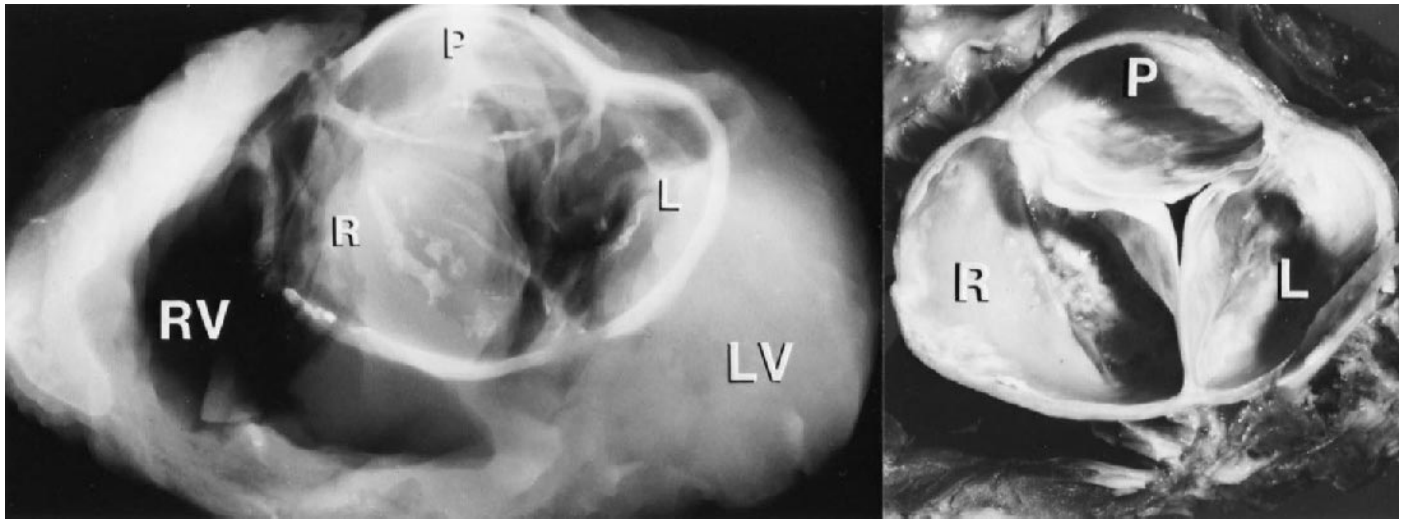

Figure 15 A 95-year-old man (SH #79-77) who never had symptoms of cardiac dysfunction and died from sarcoma. The coronary arteries are shown in Figure 2. Left: radiogram of heart at necropsy showing considerable enlargement of the aorta in comparison to the ventricles. LV = left ventricle, RV = right ventricle, R = right, L = left, and P = posterior sinuses of Valsalva. Right: aortic valve from above. The coronary arteries were excised before the radiogram and photographs were taken.

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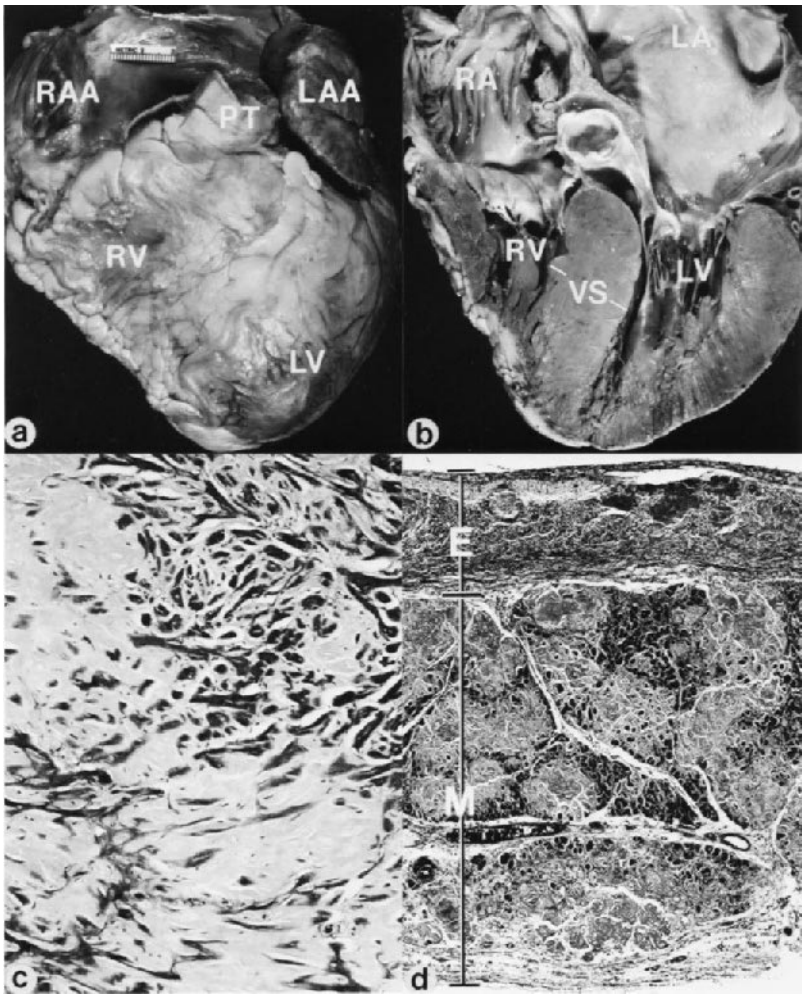

Figure 16 A 90-year-old man (DCGH #69A391) with chronic, eventually fatal, congestive heart failure from clinically unrecognized cardiac amyloidosis. (a) External view of the heart showing prominent left ventricle (LV) and left atrial appendage (LAA). PT = pulmonary trunk, RAA = right atrial appendage, RV = right ventricle. (b) Right-to-left longitudinal cut of the heart (four-chamber, two-dimensional echocardiographic view) showing thickened ventricular walls and dilated right (RA) and left (LA) atria. VS = ventricular septum. (c) Photomicrograph of a portion of the left ventricle showing extensive amyloid deposits. (d) Photomicrograph of LA wall showing amyloid deposits in endocardium (E) and in myocardium (M). (Hematoxylin and eosin; magnification × 100 (c) and × 25 (d), both reduced 35%.)

Figure 17 Electrocardiograms in four patients, each recorded at age 90 years or older. None ever had symptoms of cardiac dysfunction, and each died from noncardiac conditions. Top left: The electrocardiogram was recorded 43 days before death (A66-13), and it is normal (heart weight 270 g). Top right: The electrocardiogram was recorded 11 days before death (GT #68A325), and it shows left QRS axis deviation and a slightly prolonged P-R interval (heart weight 400 g). Bottom left: This electrocardiogram was recorded 28 days before death (A64-62), and it shows left axis deviation and complete left bundle branch block (heart weight 320 g). Bottom right: This electrocardiogram was recorded 128 days before death (SH #A80-74), and it shows atrial fibrillation, left axis deviation, and complete right bundle branch block (heart weight 440 g).

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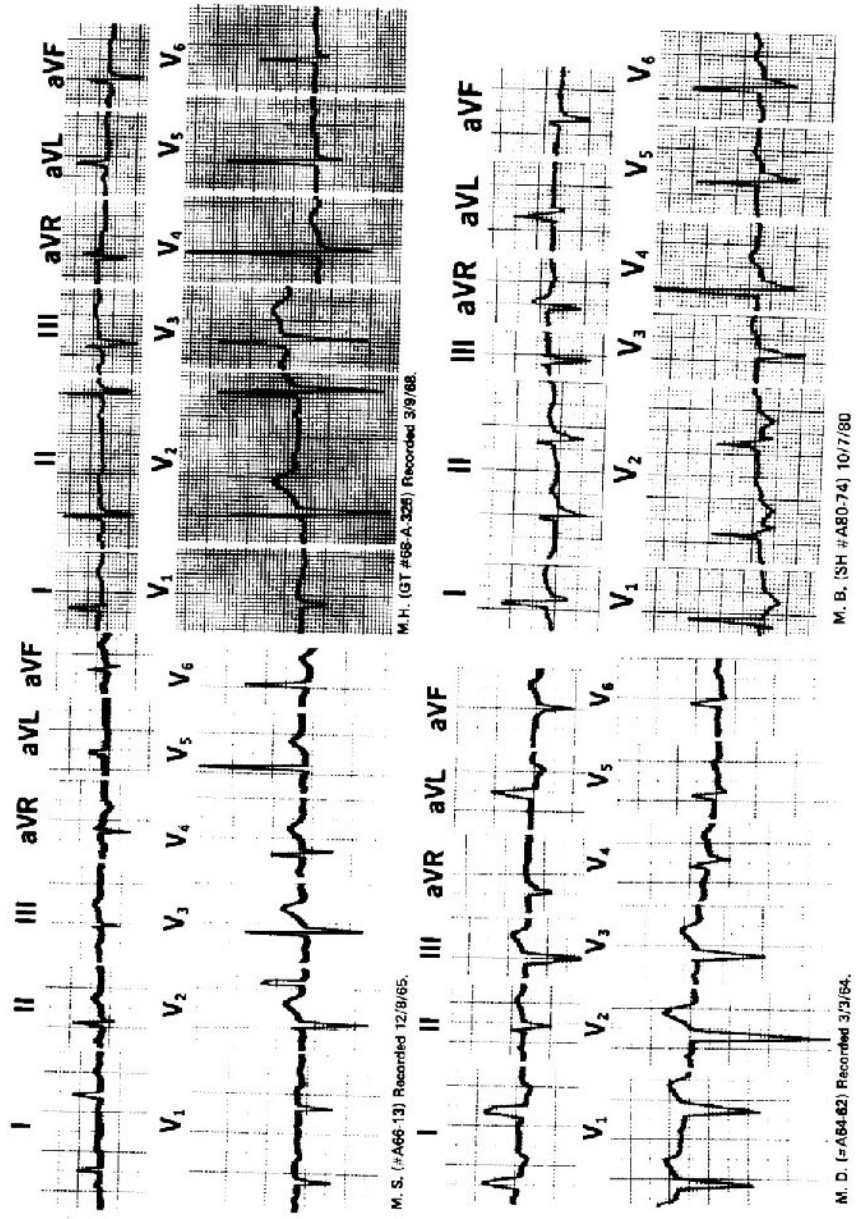

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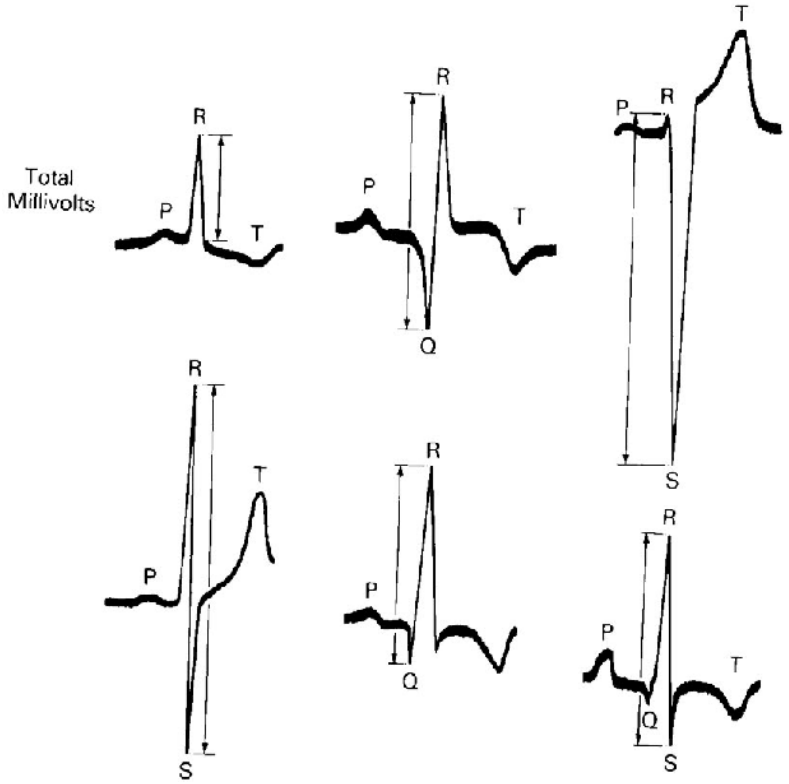

Figure 18 Various QRS complexes, and how each was measured. (Reproduced with permission from Siegel RJ, Roberts WC. Electrocardiographic observations in severe aortic valve stenosis: Correlative necropsy study to clinical, hemodynamic, and ECG variables demonstrating relation of 12-lead QRS amplitude to peak systolic transaortic pressure gradient. Am Heart J 1982; 103:210–221.)

reasonable to believe that mitral annular calcium in persons ≥80 years of age also is a manifestation of atherosclerosis. Calcium in a papillary muscle appears to be a consequence of aging and not a direct manifestation of atherosclerosis.

When the deposits of calcium on the aortic aspects of the aortic valve cusps are extensive, the cusps may become relatively or absolutely immobile, resulting in aortic valve stenosis. These valves usually lack commissural fusion (i.e., adherence of two cusps together near the lateral attachments) and, therefore, aortic regurgitation is usually absent. Although it is most often associated with some degree of mitral regurgitation, mitral annular calcium, if ''massive,'' and if the left ventricular cavity is also small and the wall quite thickened, may result in mitral stenosis (10).

Although the calcific deposits in the epicardial coronary arteries were located entirely in atherosclerotic plaques, which are located in the intima, the presence of calcific deposits in the coronary arteries in this older population did not necessarily indicate the

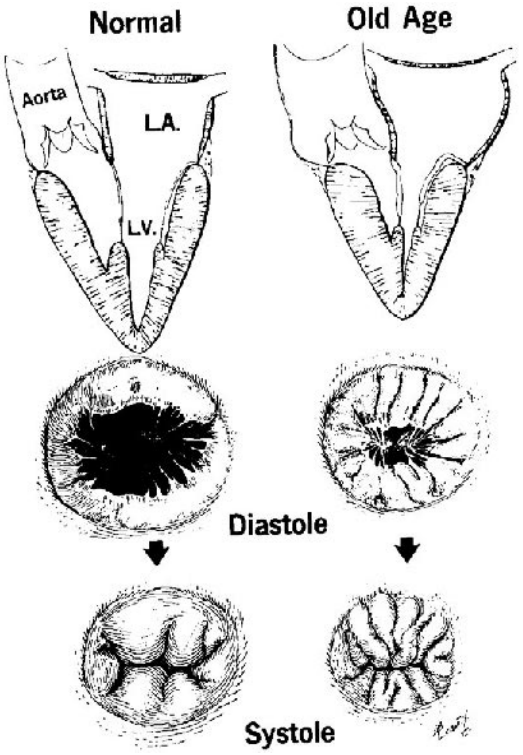

Figure 19 Cardiac changes in the very elderly. The left atrial (LA) cavity enlarges, and the left ventricular (LV) cavity becomes smaller. The amount of space available for the mitral leaflets decreases with aging, and consequently the number of scallops in the leaflets appears to increase. (Reproduced from Roberts WC, Perloff JK. Mitral valvular disease. A clinicopathologic survey of the conditions causing the mitral valve to function abnormally. Ann Intern Med 1972; 77:939–975.)

presence of significant (>75% cross-sectional area) luminal narrowing. In contrast, the presence of calcific deposits in epicardial coronary arteries in persons aged <65 years generally indicates the presence of significant luminal narrowing. The calcific deposits tended to occur in each of the four major (right, left main, left anterior descending, and left circumflex) epicardial arteries and were always larger in the proximal than in the distal halves of the right, left anterior descending, and left circumflex arteries or, if small, limited to their proximal halves. The plaques consisted mainly (87 ± 8%) of fibrous tissue with calcific deposits forming 7 ± 6% of the plaques (3).

The percent of patients with narrowing >75% in cross-sectional area by plaque of one or more major epicardial coronary arteries was similar in all three age groups, as was the percent of major coronary arteries narrowed significantly.

In 36 patients (all ≥90 years of age), each of the four major coronary arteries were divided into 5-mm-long segments and the degree of cross-sectional area narrowing by atherosclerotic plaque was determined for each segment. Of the 1789 5-mm segments in

Table 2 Causes of Death in the 490 Necropsy Patients Aged 80–103 Years

	Age group (Years)		
	80–89 (n = 391)	90–99 (n = 93)	≥100 (n = 6)
I. *Cardiac*	198(51%)	30(32%)	0
A. Coronary artery disease	129/198(65%)	12/30(40%)	0
1. Acute myocardial infarction	90	12	0
2. Chronic congestive heart failure	15	3	0
3. Sudden	19	3	0
4. Coronary bypass	7	0	0
B. Valvular heart disease	41/198(21%)	3/30(10%)	0
1. Aortic stenosis	33	3	0
2. Aortic regurgitation	2	0	0
3. Mitral regurgitation	5	0	0
4. Mitral stenosis	1	0	0
C. Primary cardiomyopathy	7/198(4%)	1/30(3%)	0
1. Hypertrophic	4	0	0
2. Idiopathic dilated	3	1	0
D. Secondary cardiomyopathy	16/198(8%)	8/30(27%)	0
1. Amyloidosis	14	8	0
2. Hemosiderosis	1	0	0
3. Myocarditis	1	0	0
E. Pericardial heart disease	3/198(2%)	0	0
II. *Vascular, noncardiac*	52(13%)	19(20%)	0
A. Stroke	17/52(33%)	6/19(32%)	0
B. Abdominal aortic aneurysm	14/52(33%)	5/19(26%)	0
C. Peripheral arterial disease	11/52(21%)	5/19(26%)	0
D. Aortic dissection	4/52(8%)	0/19(0)	0
E. Pulmonary embolism	6*/52(11%)	3/19*(16%)	0
III. *Noncardiac, nonvascular*	141(36%)	44(47%)	6(100%)
A. Cancer	52/141(37%)	13/44(29%)	0/6
B. Infection	37/141(26%)	17/44(39%)	0/6
C. Fall complication	10/141(7%)	3/44(7%)	3/6
D. Other	42/141(30%)	11/44(25%)	3/6

All had underlying chronic obstructive pulmonary disease.

the 36 patients, the average amount of cross-sectional area narrowing by atherosclerotic plaques per segment was 42% (range 19 to 69). Of the 467 5-mm segments in the 10 patients with clinical evidence of coronary artery disease, the average amount of cross-sectional area narrowing per segment was 55% (range 43 to 69); and, of 1322 5-mm segments in the 26 patients without clinical evidence of coronary artery disease, 38% (range 19 to 40; $p < 0.01$). Among 129 patients aged 22 to 85 years (mean 56), the amount of cross-sectional area narrowing by atherosclerotic plaques per segment averaged 67%; in the control subjects, that is, those without symptomatic coronary artery disease, cross-

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sectional area narrowing averaged 32%. The mean percentage of 5-mm coronary segments narrowed 76 to 100% in cross-sectional area in the 36 patients was 13% (range 2 to 89); of the 10 patients with symptomatic coronary artery disease, the mean was 19% (range 10 to 34); and of the 26 patients without symptomatic coronary artery disease, the mean was 7% (range 2 to 28) ($p < 0.05$). The mean of 19% in patients with symptomatic coronary artery disease aged ≥90 was half that observed in patients <85 years (mean 56) with fatal coronary artery disease, and the mean of 7% was nearly three times that observed in the younger patients without fatal coronary artery disease (11).

These detailed morphological studies of the coronary arteries in these very elderly persons suggest that the degree of severe coronary narrowing necessary to have a fatal or nearly fatal coronary event is considerably less than that necessary to have a coronary event in younger patients. Moreover, these studies indicate that these very elderly patients without symptoms of coronary artery disease have distinctly more coronary luminal narrowing by atherosclerotic plaques than control subjects who are younger (mean age 52 years) (11). The latter observation suggests that coronary artery disease may be underdiagnosed clinically in the very elderly.

Clinical diagnosis of cardiac and other conditions in patients aged 80 years and over, particularly those ≥90 years of age, appears more difficult than in younger persons. Historical information may be difficult to obtain because of impaired intellect on the part of the patient and an impaired diagnostic pursuit on the part of the physician. Physicians caring for these very elderly persons may focus primarily on the prevention of suffering and only secondarily on accurate diagnosis or longer term therapy. Patients aged 90 years and over generally have outlived their spouses and private physicians and are often ''inherited'' by nursing home physicians, who may have limited access to earlier medical records.

Angina pectoris appears particularly difficult to diagnose in the very elderly because they may not be able to describe this symptom. Acute myocardial infarction is also difficult to diagnose clinically, but it is often fatal in the very elderly. Furthermore, the electrocardiogram is not as useful in diagnosis of acute myocardial infarction in the very elderly because left bundle branch block is frequent and, of course, it prevents the appearance of typical changes. Serial recordings of electrocardiograms also appear to be quite infrequent in the very elderly.

Physical examination in the very elderly may be both difficult and misleading. The lack of mobility may prevent proper positioning of the elderly patient for proper examining. Precordial murmurs, although common, infrequently indicate significant functional abnormality. Although calcific deposits in the aortic valve are common, actual aortic valve stenosis is not nearly as frequent. Likewise, although mitral annular calcific deposits are common, these calcific deposits rarely narrow the mitral orifice or produce significant mitral regurgitation.

Electrocardiographic abnormalities are common in elderly persons. Of my patients for whom electrocardiograms were available, all had one or more abnormalities recorded, the most frequent being abnormal axis, atrial fibrillation, and complete bundle branch block. Although 15 of the 30 patients had cardiomegaly (>350 g in women; >400 g in men) at necropsy, only one had voltage criteria for left ventricular hypertrophy. Likewise, only one had low voltage. Measurement of the QRS amplitude in each of the 12 leads was performed in 24 patients. The total QRS voltage was similar in the eight patients with and in the 16 patients without clinical evidence of cardiac disease (mean 147 vs. 152 mm; 10 mm = 1 mV).

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SUMMARY

Certain clinical and necropsy cardiac findings are described and compared in 391 octogenarians (80%), 93 nonagenarians (19%), and 6 centenarians (1%). The numbers of men and women were similar (248[51%]) and 242[49%]). The cause of death was cardiac in 228 patients (47%), vascular but noncardiac in 71 (14%), and noncardiac and nonvascular in 191 (39%). The frequency of a cardiac condition causing death decreased with increasing age groups (51% vs. 32% vs. -0), and the frequency of a noncardiac, nonvascular condition causing death increased with increasing age groups (36% vs. 47% vs. 100%). Among the cardiac conditions causing death, coronary artery disease was the problem in 61% (141/228) followed by aortic valve stenosis in 16% (36/228) and cardiac amyloidosis in 10% (22/228). Calcific deposits were found at necropsy in the coronary arteries in 81% (398/490) of the patients, in the aortic valve in 47% (228/490), in the mitral annular area in 39% (190/490), and in one or both left ventricular papillary muscles in 25% (122/490). The calcific deposits tended to be less frequent in the octogenarians. Three hundred (61%) of the 490 patients had one or more major coronary arteries narrowed $>75\%$ in cross-sectional area by plaque and the percent of patients in each of the three age groups and the percent of coronary arteries significantly narrowed in each of the three age groups was similar.

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3

Electrocardiographic Findings in Older Persons Without Clinical Heart Disease

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Despite the introduction of numerous sophisticated cardiovascular techniques in the past 20 years, the resting electrocardiogram (ECG) remains our most widely applied diagnostic tool. The dramatic aging of the American population over the past several decades and the advent of Medicare have resulted in an increasing use of routine health screening for relatively healthy older individuals. It has therefore become important to recognize how age-associated alterations in cardiovascular anatomy and physiology affect the results of commonly used diagnostic procedures such as the ECG.

This chapter will therefore review the changes in the resting ECG that are thought to be secondary to age per se as well as those that appear more often in older subjects but may indicate undetected heart disease. The striking age-associated increase in cardiac arrhythmias on ambulatory electrocardiography and exercise testing will also be discussed. Whenever possible, the prognostic importance of these age-associated ECG changes will be addressed.

METHODOLOGICAL CONSIDERATIONS

The definition of what constitutes normative aging changes is strongly influenced by the criteria used to select the study population. In many early studies, the ECG findings in consecutive series of hospitalized elderly patients were tabulated. Although such studies provide prevalence data for specific ECG findings in the geriatric community, they do not provide insight regarding whether these findings are due to aging or disease. Thus ''aging'' changes delineated in a debilitated institutionalized geriatric population may differ greatly from aging changes in asymptomatic community-dwelling volunteers. Furthermore, even in apparently healthy populations, the use of additional screening procedures such as echocardiography, exercise ECG, and thallium scintigraphy may disclose covert heart disease that could warrant exclusion from a study of normative aging. Excessive screening, of course, will decrease the applicability of the results to the general population.

Several additional factors must be considered when interpreting investigations of

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the aging process. Cross-sectional studies, which dominate the aging literature, are influenced by the selective survival of the older cohorts; subjects in their 70s and above represent the ''survival of the fittest'' and may not be comparable to the younger individuals to whom they are being compared. In addition, secular trends such as the declines in smoking or cholesterol levels in the general population over time may influence study results. Finally, the limits chosen for body weight, blood pressure, exercise habits, and other constitutional or lifestyle variables will also influence the outcome of normative aging studies.

SPECIFIC ECG CHANGES

Sinus Node Function

Resting heart rate is unrelated to age in most studies (Table 1). However, the phasic variation in R-R interval known as respiratory sinus arrhythmia declines with age (1,2). Similarly, a reduced prevalence of sinus bradycardia on resting ECG is evident by the fourth decade (1). Because both sinus arrhythmia and sinus bradycardia are indices of cardiac parasympathetic activity, the age-associated reduction in parasympathetic function (2) may mediate both findings. Recently, spectral analysis of heart rate variability has confirmed an age-related reduction of high frequency (0.15–0.45 Hz) oscillations indicative of vagal efferent activity (Fig. 1) (3,4). Although physical conditioning status influences autonomic tone, a recent cross-sectional study demonstrated that the deconditioning which usually accompanies the aging process plays only a minor role in the age-associated blunting of these high-frequency oscillations (4). At any age, patients with organic heart disease demonstrate a reduced respiratory sinus arrhythmia compared to normal individuals. Such a blunting of sinus arrhythmia was also evident in apparently healthy volunteers approximately 2 years prior to experiencing a coronary event (5).

Sinus bradycardia below 50 bpm was found in 4.1% of 1172 healthy nonendurance-trained unmedicated participants aged 40 and older from the Baltimore Longitudinal Study of Aging (BLSA); the prevalence was similar in men (3.9%) and women (4.5%) (6). Although these 47 subjects (mean age 58 years) with unexplained sinus bradycardia had a significantly greater prevalence of associated conduction system abnormalities than non-bradycardic age-and sex-matched controls, there was no difference in the incidence of future coronary events (angina pectoris, myocardial infarction, or cardiac death) over a

Table 1 Normative Age-Associated Changes in Resting ECG Measurements

	Change with age
R-R interval	None
P-R interval	Increase
QRS duration	None
QRS axis	Leftward shift
QRS voltage	Decrease
Q-T interval	Small increase
T-wave voltage	Decrease

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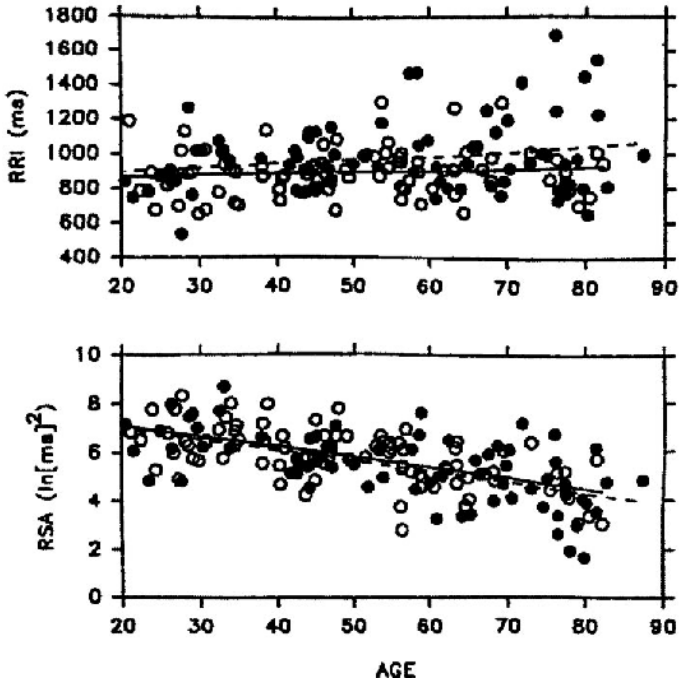


Figure 1 Scatter plot of mean R-R interval (RRI) and respiratory sinus arrhythmia (RSA) during 3 min of seated posture in 164 healthy men (closed circles and dashed line) and women (open circles and solid line). Although RRI (top panel) was not related to age in either sex, RSA declined substantially with age in both men ($r = -0.59$; $p < 0.001$) and women ($r = -0.61$; $p < 0.001$). (From Ref. 4, with permission.)

5.4-year mean follow-up period. Sinus bradycardia due to sick sinus syndrome is seen almost exclusively in old age and is probably due in part to the marked decline in the number of pacemaker cells in the SA node which begins by age 60. In the absence of organic heart disease, such bradycardia is not associated with increased cardiac mortality (7).

P Waves

Although age-specific rates have not been reported, the prevalence of left atrial abnormality, defined by a negative P terminal force in lead V_1 of at least 0.04 mm/s on the ECG, increases with age, paralleling the echocardiographic increase in left atrial size. Among 588 institutionalized elderly, such a P terminal force was only 32% sensitive, though 94% specific, for echocardiographic left atrial enlargement (8). A small increment in P-wave duration of about 8 ms from the third to seventh decades has been observed (9), presumably secondary to the modest increase in left atrial size. When subjects with significant chronic obstructive lung disease are excluded, there does not appear to be any increase in ECG evidence of right atrial enlargement with age.

P-R Interval

There is general agreement that the P-R interval undergoes a slight, but significant age-related prolongation, by approximately 0.01 s from the third to the sixth decades (10). An increase in P-R interval from 159 to 175 ms in men and from 156 to 165 ms in women was found between the ages of 30 and 72 years in BLSA volunteers (11). To ascertain whether this age-related slowing of A-V conduction was located proximal or distal to the His bundle, we performed high-resolution signal-averaged surface ECGs on these subjects. The prolongation of A-V conduction was found to reside completely proximal to the His bundle deflection, but within the P-R segment, presumably reflecting delay within the A-V junction (Fig. 2). In seven older men with first-degree A-V block, a similarly located but more pronounced delay was found. Given the age-associated slowing of A-V conduction, a value of 0.22 s has been proposed for the upper limit of normal P-R interval in persons over 50 years of age (10). Using the conventional upper limit of 0.20 s, the prevalence of first-degree A-V block in healthy older men is usually 3 to 4%, a prevalence severalfold greater than in young men (10). Cross-sectional studies have generally found no correlation between first-degree A-V block and cardiac disease (12). Similarly, longitudinal studies have reported no association of first-degree A-V block with cardiac mortality (13).

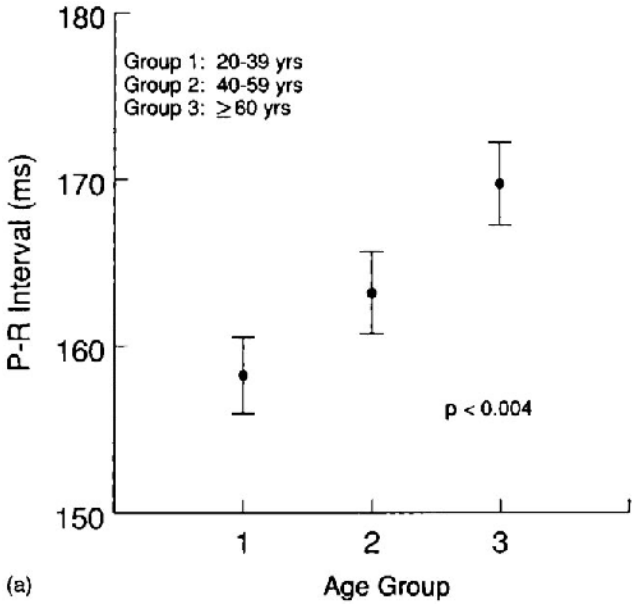
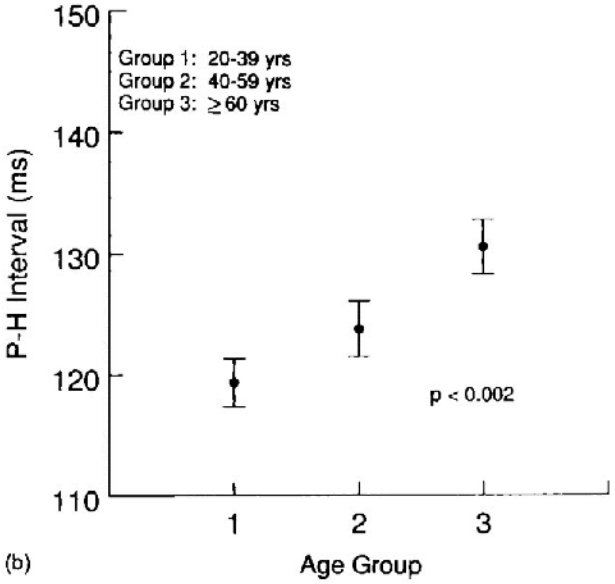


Figure 2 Age-associated changes in the P-R interval and its components, defined by noninvasive His bundle recording in 161 normal subjects without first degree A-V block (panel A). There is approximately a 12-ms prolongation of the P-R interval between group 1 and group 3, which is mirrored by a nearly identical increase in the interval from the P-wave onset to the His bundle deflection (P-H interval, middle panel). However, the interval from His bundle deflection to ventricular activation (H-V interval, bottom panel) is unrelated to age. (From Ref. 11, with permission.)



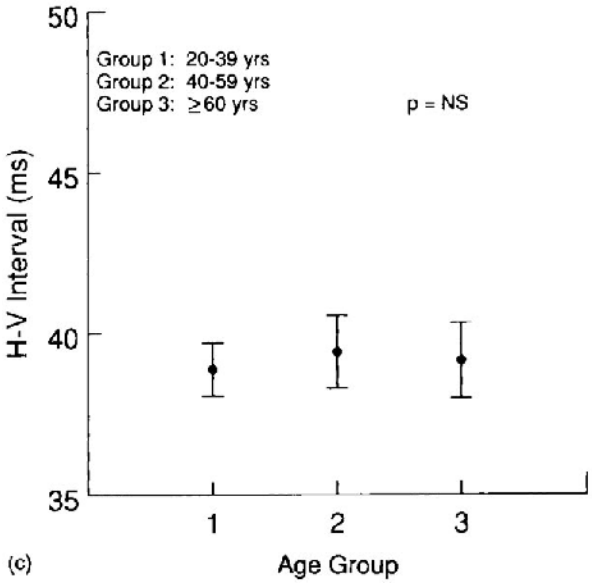


Figure 2 Continued

QRS Complex

Although the QRS duration shows no significant age relationship, the QRS axis shifts progressively leftward with age. In the extensive normative study of Simonson, the mean QRS axis shifted from 62.1 to 36.2 degrees from the third to the sixth decades, with no gender difference (10). The corresponding lower normal limits shifted from 2.9 to −28.4 degrees. The prevalence of left axis deviation <-30 degrees therefore increases dramatically with age, with prevalence figures of 20% reported by the 10th decade (14). The etiology of this leftward QRS axis shift may be the age-related increase in left ventricular mass (15). Longitudinal studies have failed to demonstrate any increase in cardiac morbidity or mortality associated with this isolated ECG finding (16,17). However, in patients with known organic heart disease, the presence of left axis deviation combined with left or right bundle branch block portends a worse cardiovascular prognosis (18).

A decrease in R- and S-wave amplitudes with advancing age, evident by the fourth decade, has been shown in both cross-sectional (19) and longitudinal (20) studies. At first glance, this decrease in QRS amplitude seems paradoxical, given the age-related increase in left ventricular mass. It must be remembered, however, that the surface ECG is influenced by extracardiac as well as cardiac factors. The increasing distance between the heart and the chest wall due to senile kyphosis and lung hyperinflation in older individuals may be largely responsible for the decrease of QRS voltage.

Notwithstanding the age-related decline in mean QRS amplitude, electrocardiographic left ventricular hypertrophy (LVH) increases in prevalence with age (21), probably secondary to the high prevalence of hypertension, coronary artery disease, and degenerative valvular disease in the elderly. Echocardiographic studies have demonstrated that the standard ECG is quite insensitive, though very specific, for anatomical LVH in older populations (22). Data from Framingham have shown convincingly that ECG evidence of LVH is strongly related to the presence of hypertension and is a potent independent risk factor for future cardiovascular morbidity and mortality (21–23). Thus, the presence of ECG criteria for LVH in an older individual should normally trigger further diagnostic assessment, particularly echocardiography.

Left and right bundle branch block (LBBB and RBBB) both increase in prevalence with age; nevertheless, these conduction defects should not be attributed to aging per se. In older populations LBBB occurs only about half as often as RBBB. In contrast to its right-sided counterpart, LBBB is uncommon in the absence of cardiovascular disease (24). The prognosis in LBBB therefore reflects that of the underlying heart disease. Although in men LBBB portends a more ominous prognosis than RBBB, the two conduction defects had similar prognostic significance in Framingham women (25,26). Among 310 predominantly middle-aged subjects with BBB and no apparent heart disease, both LBBB and RBBB increased in prevalence with age, but neither was associated with increased total mortality over a 9.5-year mean follow-up (27). A nonspecific intraventricular conduction defect exceeding 120 ms occurred in only 1.9% of Framingham subjects aged 70 and older and, like LBBB, was strongly associated with clinical heart disease (28).

Complete RBBB was found in 39 of 1142 men (3.4%) in the BLSA (29). Among the 24 individuals (mean age 64 years) without evidence of heart disease and for whom follow-up information was available, the incidence of angina, nonfatal MI, heart failure, advanced heart block, or cardiac death did not differ from those in age-matched controls over a mean observation period of 8.4 years. At latest follow-up, maximal exercise capac-

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ity and chronotropic response were similar to those of controls, although a higher prevalence of left axis deviation was found in the RBBB group (46% vs. 15%). These findings suggest that RBBB in the absence of clinical heart disease is not rare in older men and reflects a primary abnormality of the cardiac conduction system. In the Framingham study, women demonstrated a lower prevalence of RBBB than did men but had a higher association of this conduction defect with cardiomegaly and congestive heart failure than did their male counterparts (25).

The presence of Q waves in two or more contiguous ECG leads is generally considered evidence of prior myocardial infarction (MI). In older as in younger populations, such Q waves are usually associated with clinical heart disease and increased cardiac mortality. Pathological Q waves may in fact serve as the initial clue to the presence of coronary artery disease. Indeed, several studies have shown that 25 to 30% or more of acute infarctions are clinically silent (30–32). The incidence of these so-called ''silent'' MIs increases strikingly with age (Table 2). In geriatric chronic care facilities, rates of silent infarction as high as 68% have been reported (32). Despite the absence of symptoms, these silent infarctions portend a long-term risk of mortality similar to their symptomatic counterparts.

Q waves in the elderly not uncommonly occur in the absence of coronary artery disease. A QS complex in leads 3 and aVF may occasionally result from marked left axis deviation. A pattern of poor R-wave progression in leads V_1 to V_3 is a normal age trend, due to the decrease in the initial 20 ms anterior QRS vector with age (10). Such a pattern may also result from obesity, chronic obstructive lung disease, and LVH, all of which are common in older populations. Hypertrophic cardiomyopathy is also frequently associated with significant Q waves in the absence of coronary disease.

Repolarization

Abnormalities involving the ST segment and T wave are perhaps the most prevalent age-associated ECG finding. For example, nonspecific ST-T changes were the most common ECG abnormalities seen in 671 subjects aged 70 years and older in one study, occurring in 16% of subjects (24). In this series and others, repolarization abnormalities were generally associated with clinical heart disease. Such an association may stem in part from the

Table 2 Ten-Year Incidence (per 1000 subjects) of Unrecognized Myocardial Infarctions in the Framingham Study

	Men		Women	
Age	Unrecognized infarcts	All infarcts	Unrecognized infarcts	All infarcts
30–34	2.6	12.9	0.0	2.2
35–44	6.5	38.2	2.6	5.2
45–54	16.6	71.2	2.9	13.0
55–64	28.2	107.9	17.9	47.1
65–74	53.8	141.0	21.3	55.7
75–84	60.2	112.8	34.0	128.3

Source: Adapted from Ref. 30.

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frequent use of digitalis and various antiarrhythmic drugs by elderly cardiac patients. Thus, much of the reported increased risk attached to these nonspecific repolarization changes is undoubtedly due to the underlying heart disease that necessitated use of these cardiac medications. However, even among clinically healthy older subjects, minor ST-segment sagging or straightening is relatively common, though of questionable prognostic significance.

The T-wave amplitude begins to decrease with age by the fourth decade (10,19). The spatial T-wave vector shifts leftward with age in concert with the leftward shift in QRS axis. Obesity magnifies these changes in the T-wave direction and amplitude, particularly in men (10). The isolated presence of flattened T waves, especially in lead aVL, does not portend increased cardiovascular risk, at least in middle-aged subjects (33). Definite T-wave inversion, in contrast, usually occurs in patients with organic heart disease and therefore is associated with increased mortality. The heart-rate-corrected Q-T interval increases by about 10 ms from the third to the sixth decade (34). Table 1 summarizes those changes in resting ECG measurements thought to be secondary to normative aging.

Arrhythmias

Probably the most easily recognized ECG change associated with normative human aging is an increase in the prevalence and complexity of both supraventricular and ventricular arrhythmias, whether detected by resting ECG, ambulatory monitoring, or exercise testing. Isolated premature atrial ectopic beats (AEB) appear on resting ECG in 5 to 10% of subjects older than 60 years and are generally not associated with heart disease. Such isolated AEB were detected in 6% of healthy BLSA volunteers older than 60 years at rest, in 39% during exercise testing, and in 88% during ambulatory 24-h monitoring (35). Over a 10-year mean follow-up period, isolated AEB, even if frequent, were not predictive of increased cardiac risk in these individuals (36).

Atrial fibrillation (AF) is found in approximately 3 to 4% of subjects over age 60 years, a rate tenfold higher than the general adult population (37,38). Chronic AF is most commonly due to coronary and hypertensive heart disease, mitral valvular disorders, thyrotoxicosis, and sick sinus syndrome. The association between hyperthyroidism and AF occurs almost exclusively in the elderly (39); in fact, this arrhythmia may be the sole clinical manifestation of so-called ''apathetic'' hyperthyroidism in geriatric patients. In the Framingham population, atrial fibrillation without identifiable cause (so-called ''lone'' AF) represented 16.8% of men and 6.0% of women with AF, with mean ages of 70.6 and 68.1 years, respectively (40). During long-term follow-up, individuals with lone AF suffered over four times as many strokes as control subjects, although their rates of coronary events or congestive heart failure were similar to those of controls. Atrial flutter is a rare arrhythmia in any age group and is usually associated with organic heart disease. Short bursts of paroxysmal supraventricular tachycardia (PSVT) on resting ECG are found in 1 to 2% of normal individuals older than 65 years. Twenty-four-hour ambulatory monitoring studies have demonstrated short runs of this arrhythmia (usually 3 to 5 beats) in 13 to 50% of clinically healthy older subjects (Table 3) (35,38). Although the presence of nonsustained PSVT did not predict an increase in risk of a future coronary event in BLSA subjects (36), 2 of 13 with PSVT later developed de novo atrial fibrillation, compared with only 1 of the 85 subjects without PSVT.

Exercise-induced PSVT has been observed in 3.5% of over 3000 maximal treadmill tests on apparently healthy BLSA volunteers (41). The arrhythmia demonstrated a striking

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Table 3 Arrhythmia Prevalence on 24-h Ambulatory ECG in 1372 Subjects ≥ 65 Years Old

Arrhythmia	Women (%)	Men (%)	Gender difference[b]
Supraventricular			
Any	97	97	No
≥ 15 SVEB in any hour	18	28	Yes
PSVT (≥ 3 complexes)	50	48	No
Atrial fibrillation or flutter[a]	3	3	No
Ventricular			
Any	76	89	Yes
≥ 15 VEB in any hour	14	25	Yes
VT (≥ 3 complexes)	4	13	Yes
VT (> 5 complexes)	0.3	0.2	No

Abbreviations: PSVT = paroxysmal supraventricular tachycardia; SVEB = supraventricular ectopic beats; VEB = ventricular ectopic beats; VT = ventricular tachycardia.
[a] Sustained or intermittent.
[b] Defined by $p < 0.05$.
Source: Adapted from Ref. 38.

increase in incidence with age, from 0% in the 20s to approximately 10% in the 80s (Fig. 3); similar to PSVT on ambulatory ECG, the vast majority of these episodes were asymptomatic, 3- to 5-beat salvos. The prevalence of coronary risk factors and ECG or thallium scintigraphic evidence of ischemia in the 85 volunteers with exercise-induced PSVT resembled those of age- and sex-matched control subjects. Similarly, no increase in subsequent coronary events was observed over a 5.5-year mean follow-up period. How-

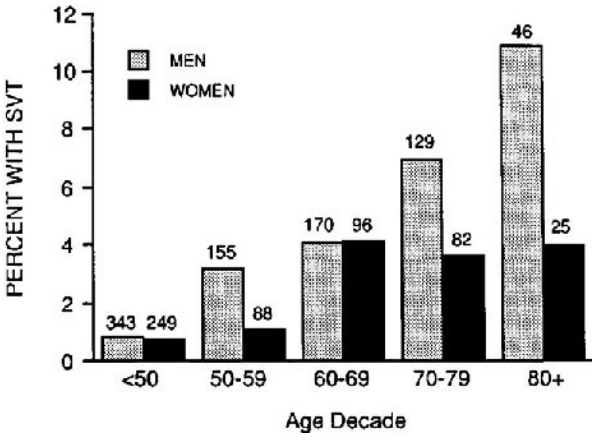

Figure 3 Prevalence of nonsustained supraventricular tachycardia (SVT) during a maximal treadmill exercise test in 1383 clinically healthy volunteers from the Baltimore Longitudinal Study stratified by age and sex. The numbers above each bar represent the sample size in each age decade. The prevalence of exercise-induced SVT increased strikingly with age in men ($p < 0.001$) but not in women ($p = 0.09$). (From Ref. 41, with permission.)

ever, 10% of the group with PSVT later developed a spontaneous atrial tachyarrhythmia compared with only 2% of the control group, analogous to the results of the ambulatory 24-h ECG (41).

An exponential increase in the prevalence of ventricular ectopic beats (VEB) with advancing age has been found both in unselected populations and in those clinically free of heart disease. Pooled data from nearly 2500 ECGs from hospitalized patients older than 70 years revealed VEB in 8% (42). Among apparently healthy BLSA volunteers with a normal ST segment response to treadmill exercise, isolated VEB occurred at rest in 8.6% of men over age 60 compared to only 0.5% in those 20 to 40 years old. In women, interestingly, the prevalence of resting VEB was not age-related.

The prognostic significance of VEB detected on the resting ECG in the general elderly population is controversial. Studies in Busselton (43) and Manitoba (44) detected significant increases in cardiac mortality in such populations, with risk ratios of 3.3 and 2.4, respectively, compared with arrhythmia-free cohorts. In the Framingham community, (45) however, no increase was found in the age-adjusted risk ratio for cardiac events. Data from the MRFIT study suggest that the prognostic significance of resting VEB may vary according to age; asymptomatic white men under 50 years with frequent or complex VEB on a 2-min resting rhythm strip suffered a 14-fold relative risk of sudden cardiac death, while in older men the risk was not significantly increased (46).

Twenty-four-hour ambulatory ECG recordings have demonstrated the presence of VEB in up to 69 to 96% of asymptomatic elderly subjects (35,38,47,48). Furthermore, not only the prevalence, but the density and complexity of VEB increase with age. Among 101 subjects aged 10 to 69 who were free of heart disease by rigorous screening, including coronary angiography, both the prevalence and absolute number of VEB in 24 h increased with age; however, only 12 individuals in this series were older than 60 years (47). In the Cardiovascular Health Study, VEB were found in 82% of 1372 subjects aged 65 and older, including 7% with short runs of nonsustained ventricular tachycardia. The prevalence of all VEB forms was higher in men than women (Table 3) (38). A study of 50 subjects, predominantly females, older than 80 years reported VEB in 96%, including multifocal VEB in 18%, couplets in 8% and nonsustained ventricular tachycardia (VT) in 2% (47). Among 106 predominantly healthy patients aged 75 and above, Camm et al. noted VEB in 69% of subjects (49). VEB were multiform in 22%, paired in 4%, and in short runs in 4%. Among 98 carefully screened asymptomatic BLSA participants older than 60 years, 35% had multiform VEB, 11% VEB couplets, and 4% short runs of ventricular tachycardia on 24-h monitoring (35). These figures are all much higher than in series of healthy younger subjects. Over a 10-year mean follow-up period, 14 of these 98 BLSA volunteers developed coronary events. The prevalence and complexity of VEB were virtually identical in the group who experienced an event and the group who did not (36). In contrast, horizontal or slowly upsloping ST-segment depression on the ambulatory ECG predicted an increased risk of such events (Fig. 4) (36). In the series of Camm et al., 92% of the 5-year survivors who were initially free of VEB remained without VEB on the 5-year follow-up recording (50). In contrast to the BLSA results, an almost doubled crude mortality was found among individuals with $\geq$10 VEB/h vs. those with fewer VEB. It should be pointed out, however, that 83% of the Camm et al. subjects were taking medications, including several patients with known heart disease.

Exercise testing, like the ambulatory ECG, elicits a striking increase in the prevalence and complexity of VEB with advancing age. In apparently healthy BLSA volunteers, isolated VEB during or after maximal treadmill exercise increased in prevalence fivefold, from 11% to 57% between the third and ninth decades. Although left ventricular mass

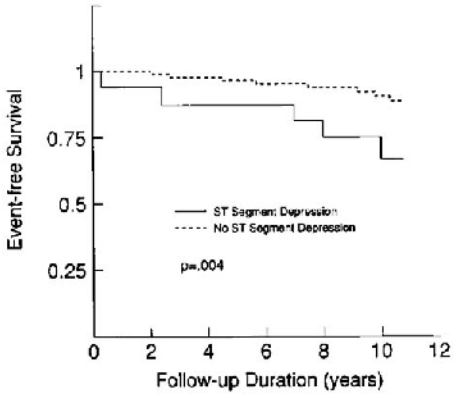

Figure 4 Survival free of angina pectoris, myocardial infarction, or coronary death in 98 apparently healthy subjects ≥ 60 years old stratified by the presence or absence of horizontal or slowly upsloping ST segment depression >1 mm during 24-h ambulatory ECG recording. The curves differ significantly ($p = 0.004$) by log-rank analysis. (From Ref. 36, with permission.)

index and peak exercise systolic blood pressure were higher in subjects who developed exercise-induced VEB than in those who did not, by multivariate analysis only older age independently predicted the appearance of VEB (51). Asymptomatic exercise-induced runs of VT, all ≤6 beats in duration, were found in 4% of apparently healthy individuals aged 65 and older, a rate 25 times that of younger subjects (52). Perhaps more significant, over a mean follow-up of about 2 years, none of these elderly subjects with nonsustained VT during exercise testing developed angina, myocardial infarction, syncope, or cardiac death.

In a later BLSA analysis, 80 of 1160 subjects developed frequent VEB (≥ 10% of beats in any minute) or nonsustained VT during maximal treadmill exercise testing (an average of 2.4 tests per individual were performed) (53). These 80 individuals were older than those free of such arrhythmia (64 vs. 50 years). Of note, the striking age-associated increase in the prevalence of these complex exercise-induced VEB was observed only in men. The prevalence of coronary risk factors and exercise-induced ischemia by ECG and thallium scanning did not differ between the 80 cases and a group of 80 age- and sex-matched controls. Furthermore, the incidence of cardiac events (angina pectoris, nonfatal infarction, cardiac syncope, or cardiac death) was nearly identical in cases and controls (10% vs. 12.5%, respectively) over a mean follow-up of 5.6 years without antiarrhythmic drug therapy (53). Thus, the limited data available in older subjects without apparent heart disease support a marked age-related increase in the prevalence and complexity of exercise-related VEB, at least in men; however, even frequent or repetitive VEB induced by exercise do not appear to increase cardiac morbidity or mortality in these older volunteers (Table 4) (54).

A critical factor in determining the prognostic significance of VEBs in the elderly is the milieu in which they occur. For example, among 467 patients aged 62–101 years in a long-term care facility, complex VEB occurred in 21% (55). In the subset without clinical heart disease, future coronary events developed in an identical 4% of those individuals with or without complex VEBs; among patients with coronary heart disease, however, such events developed in 46% with complex VEB vs. only 23% of those without them. A similar doubling of risk was seen in patients with hypertension, valvular disease, or

Table 4 Relationship of Arrhythmias to Age and Mortality

Arrhythmia	Effect of age on prevalence	Effect on mortality in otherwise healthy older subjects	Therapy
Supraventricular ectopic beats	Increased	None	None
Paroxysmal supraventricular tachycardia	Increased	Probably none	Digoxin, β-blocker, or calcium antagonist if frequent
Atrial fibrillation (chronic)	Increased	Increased	Cardioversion or rate control; Anticoagulation
Ventricular ectopic beats	Increased	Probably none	None
Ventrricular tachycardia	Increased	Probably none	β-blocker or antiarrhythmic drug in symptomatic healthy subject; AICD or endocardial resection if patient has coronary artery disease

Abbreviation: AICD = Automatic implantable cardioverter-defibrillator.
Source: Adapted from Ref. 54.

cardiomyopathy who demonstrated complex VEB. These data extend those of Hinkle et al., which documented increased coronary death rates in middle-aged men with suspected coronary heart disease and frequent VEB but not in their healthy age peers with similar VEB frequency (56).

CONCLUSION

Advancing age is accompanied by multiple electrocardiographic changes in apparently healthy subjects. Age-associated ECG changes with no known prognostic significance include a decrease in the prevalence of sinus bradycardia and sinus arrhythmia, an increase in the prevalence and density of supraventricular and ventricular ectopic beats, a mild P-R interval prolongation, and a leftward shift of the QRS axis. Although increased QRS voltage, Q waves, and ST-T-wave abnormalities may appear in older persons without evident heart disease, these findings are generally associated with increased cardiac risk. Certain abnormalities such as LBBB, definite LVH, or AF are uncommon in healthy older individuals and are strongly predictive of subsequent cardiac morbidity and mortality. Of greatest practical importance is the concept that the prognosis associated with a given ECG abnormality in the elderly is largely dependent on the presence and severity of any underlying heart disease.

ACKNOWLEDGMENT

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4

Echocardiographic Measurements in Elderly Patients Without Clinical Heart Disease

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INTRODUCTION

The ability to image cardiac structures and to evaluate left ventricular function noninvasively has made echocardiography extremely useful in the evaluation of individuals with known or suspected heart disease. The noninvasive character of the ultrasound technique has made it particularly applicable to an older population (1,2). The goals of this chapter are (1) to discuss the effect of aging on left ventricular systolic and diastolic function by M-mode and Doppler echocardiography, and (2) to present normative M-mode and Doppler echocardiographic measurement data that can serve as a basis for evaluating cardiac structure and function in elderly individuals.

In this chapter we present data derived from (1) Doppler measurements of aortic flow velocity, used to evaluate left ventricular systolic performance at rest and during exercise, and (2) transmitral flow velocity measurements, used to assess left ventricular diastolic function at rest.

RELATIONSHIP OF AGE TO NORMAL M-MODE ECHOCARDIOGRAPHIC MEASUREMENTS

To determine the relationship between age and M-mode echocardiographic measurements in normal subjects, we studied 136 adults (78 men and 58 women), 20–97 years of age, without evidence of cardiovascular disease (3). These subjects all underwent history taking and physical examination, chest roentgenography, electrocardiography, and M-mode echocardiography. In no subject did this evaluation reveal the presence of heart disease, hypertension, other serious illness, or obesity. Furthermore, all subjects had a normal electrocardiogram (ECG), normal chest film, and no evidence of mitral valve prolapse or pericardial effusion on M-mode echocardiogram. M-mode echocardiography was performed in the left lateral decubitus position, and the following measurements were made: left ventricular internal dimensions at end diastole ($LVID_d$) and end systole ($LVID_s$); ventricular septal (VS_d) and posterobasal left ventricular free-wall thickness ($LVPW_d$) at end diastole; aortic

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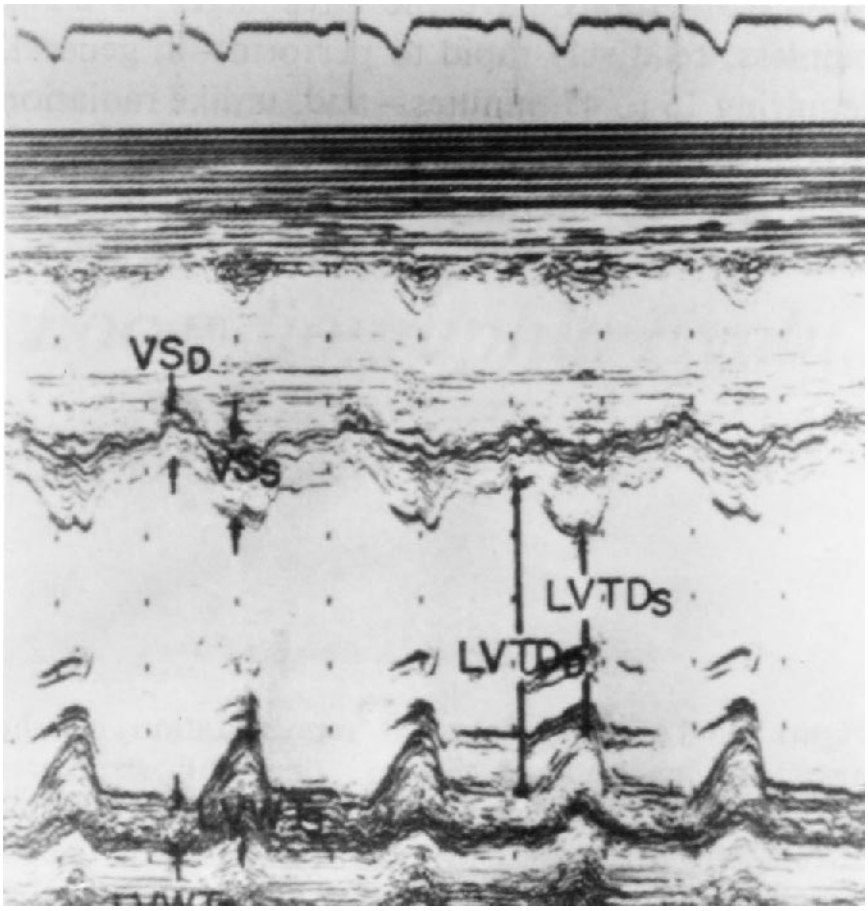

Figure 1 Echocardiographic recording of the left ventricle indicating measurements of parameters of left ventricular muscle mass and percentage fractional shortening. VS_D = interventricular septal thickness measured during diastole, VS_S = ventricular septal thickness measured during systole, $LVWT_D$ = left ventricle posterior wall thickness measured during diastole, $LVWT_S$ = left ventricular posterior wall thickness measured during systole, $LVTD_D$ = left ventricular transverse dimension measured during diastole, $LVTD_S$ = left ventricular transverse dimension measured during systole. (Reprinted from Drayer J, Gardin JM, Weber MA, Aronow WS. Changes in cardiac anatomy and function during therapy with alpha-methyldopa: An echocardiographic study. Curr Ther Res 1982; 32:856–865, with permission.)

root and left atrial dimensions; and mitral valve E-F slope, which corresponds to the rate of early diastolic closure of the anterior mitral valve leaflet (see Fig. 1). In addition, LV mass, ejection fraction, and fractional shortening were derived from the following formulas (4):

$$\text{LV mass} = (1.05)[(\text{LVID}_d + \text{VS}_d = \text{LVPW}_d)^3 - (\text{LVID}_d)^3] \quad (1)$$

$$\text{LV ejection fraction} = \frac{(\text{LVID}_d)^3 - (\text{LVID}_s)^3}{(\text{LVID}_d)^3} \times 100 \quad (2)$$

$$\text{LV \% fractional shortening} = \frac{(\text{LVID}_d - \text{LVID}_s)}{\text{LVID}_d} \times 100\% \quad (3)$$

In the absence of localized disorders of left ventricular function like those that may be present in coronary artery disease, M-mode echocardiographic estimates have been reported to correlate well with two-dimensional echocardiographic and angiographic measurements of left ventricular volume and ejection fraction (4). Also, under these conditions, LV percentage fractional shortening gives information similar to that obtained from LV ejection fraction. Although ejection fraction does not perfectly characterize the functional state of the left ventricle, this measurement is accepted as providing an overall assessment of pump performance. Furthermore, ejection fraction is thought to be a more sensitive measurement of myocardial contractile state than are either cardiac output or left ventricular end-diastolic pressure.

Echocardiographic measurements were analyzed for the influence of age, sex, and body surface area. When the data for each echocardiographic parameter were analyzed separately for men and women as a function of body surface area, statistically significant differences between men and women were found for three parameters: (1) ventricular septal thickness; (2) posterobasal free-wall thickness; and (3) estimated left ventricular mass. However, since the sex differences for these three parameters were relatively small (range 6.2 to 7.2%), we chose for the sake of simplicity to combine data for men and women in our calculation of regression equations and prediction intervals (3,5,6).

When patients were subdivided into six age groups, progressive changes were found in mean normal values for various M-mode echocardiographic parameters (Fig. 2). Specifically, when the oldest group (over 70 years) was compared with the youngest group (21–30 years), significant ($p < 0.01$) increases in aortic root (22%) and left atrial (16%)

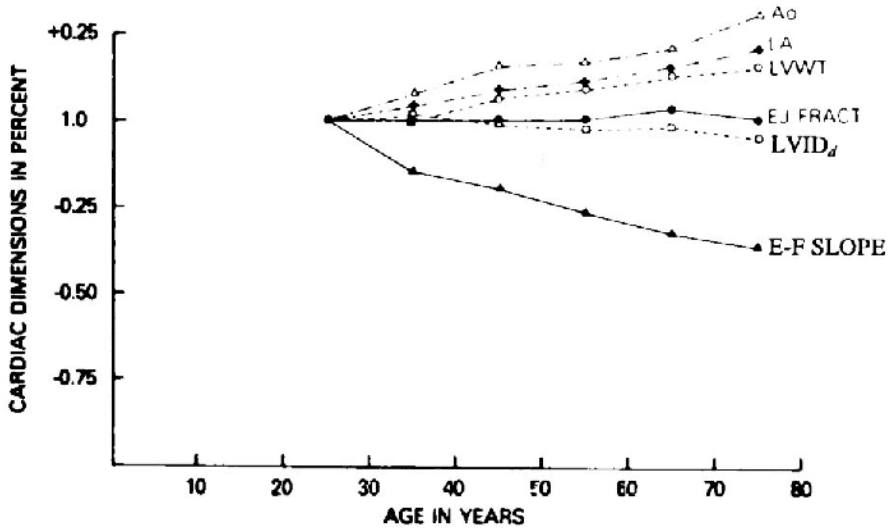

Figure 2 Percentage change in M-mode echocardiographic measurements in the five older age groups compared with the 21–30 year age group. Data are displayed for aortic root dimension (AO), left atrial dimension (LA), LV posterobasal free-wall thickness in diastole (LVWT), LV ejection fraction (EJ FRACT), left ventricle internal dimension in diastole (LVID_d), and mitral E-F SLOPE.

dimensions, in ventricular septal (20%) and left ventricular free-wall (18%) thicknesses, and in estimated left ventricular mass (15%) were noted (3,5,6). In addition, a significant ($p < 0.01$) decrease in mean mitral E-F slope (43%) and slight decreases in mean left ventricular systolic and diastolic internal dimensions (5 and 6%, respectively; $p < 0.05$) were noted. Left ventricular ejection fraction and percentage fractional shortening were found to be independent of age. These data were used to derive regression equations related to both age and body surface area (BSA). The regression equations can be used to calculate mean normal values and 95% prediction intervals for echocardiographic measurements in adults.

We analyzed our data according to the general regression equation,

$$\text{Echo parameter} = B(\text{BSA}) + A \pm C,$$

where A represents the intercept, B represents a slope unique for each parameter, and C represents the width of the 95% prediction interval; that is, the interval into which, with 95% confidence, a new normal observation would fall (3). When subjects were grouped into six age groups, the slope of the regression relationship was found to be independent of age for every parameter ($p > 0.05$), whereas the intercept showed significant variation with age for every parameter ($p < 0.05$). Therefore, we assumed that the intercept A, but not the slope B, was influenced by age and that the width of the 95% prediction interval C was constant and not appreciably influenced by age or BSA. The values of A derived from our data for each age group are given in Table 1, which also includes the values of B and C for each parameter (3).

Figures 3 through 7 depict the relationships between age and aortic root dimension, left atrial dimension, left ventricular diastolic and systolic dimension, left ventricular posterior wall thickness, and left ventricular mass. For each figure, the regression equations in Table 1 have been utilized to adjust the values to three common body surface area values (1.4, 1.8, and 2.2 m^2) (3).

Our echocardiographic findings are compatible with information derived from previous studies using other methods. Roberts and Perloff noted that hearts of older individuals studied at necropsy appear to have small ventricular chambers and thicker walls than those of their younger counterparts (7). Although the magnitude of the decrease was small, we also noted that the internal dimensions of the left ventricle decreased as age increased. We also noted progressive increases in the thicknesses of the ventricular septum and the left ventricular free wall with increasing age. The magnitudes and rates of increase were similar for septum and free wall, so that there was no change in the septum–free-wall ratio with increasing age. Estimated left ventricular mass showed a small, but progressive, increase from the 21 to 30 age group to the over-70 age group. This increase reflected an increase in wall thickness that was relatively greater than the decrease in left ventricular diastolic dimension. Since the mean systolic and diastolic blood pressures varied by less than 15 mmHg among the six age groups, we could not ascribe the increased wall thickness or mass observed in our subjects to a change in basal arterial blood pressure with aging.

Krovetz reviewed a number of published reports of measurements of aortic valve annulus size made at necropsy (8). When aortic annulus size was corrected for body surface area, progressive increases with age were noted in both men and women over 20 years of age. We noted similar increases in aortic root dimensions as measured by echocardiography. The progressive increase in left atrial dimension with increasing age noted in our normal adult subjects was noted by Roberts and Perloff at necropsy (7). It is important to take this age-related change into account when using echocardiographic measurements

Table 1 Regression Equations of Echocardiography Measurements Versus Age

Equation			Intercepts (age dependent)						
			21–30	31–40	41–50	51–60	61–70	≥70	Prediction interval
$LVID_d$	=	6.94 (BSA) +	35.5	36.2	34.4	34.1	34.8	32.7	±5.60
$LVID_s$	=	4.24 (BSA) +	22.4	22.6	21.5	21.1	21.7	20.8	±5.81
Septum	=	2.53 (BSA) +	5.27	5.47	6.27	6.53	6.84	7.20	±1.75
LVPW	=	2.18 (BSA) +	6.11	6.02	6.94	6.97	7.34	7.81	±1.43
LV mass	=	124 (BSA) +	9.87	−1.98	8.56	10.8	26.8	22.2	±57.6
Ao	=	8.31 (BSA) +	12.3	13.1	14.7	15.6	16.4	18.5	±5.76
LA	=	9.98 (BSA) +	16.3	16.7	17.6	18.0	19.3	21.7	±7.01
E-F slope	=	20.1 (BSA) +	99.9	90.2	78.3	66.6	62.2	43.5	±62.2

Abbreviations: Ao = aortic root dimension; BSA = body surface area; LA = left atrial dimension; LVID = left ventricular internal dimension; $_d$ = diastolic; $_s$ = systolic.
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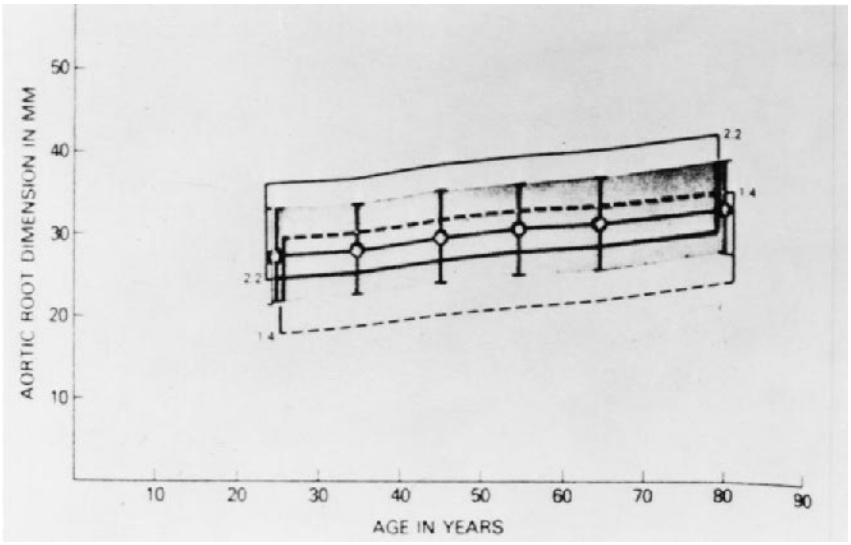

Figure 3 Aortic root dimension in late diastole is plotted in millimeters versus age in years. In Figures 3 through 7, the mean value for each age group is depicted by a circle plotted at the mean age in the age group. The bracketed and shaded area on either side of the circle represents the 95% prediction interval for normal values for a subject with a BSA of 1.8 m^2. The 95% prediction intervals are also shown for subjects with BSA values of 1.4 m^2 (dotted lines) and 2.2 m^2 (solid lines). (Reprinted from Ref. 3. Copyright 1979 John Wiley & Sons, Inc., with permission.)

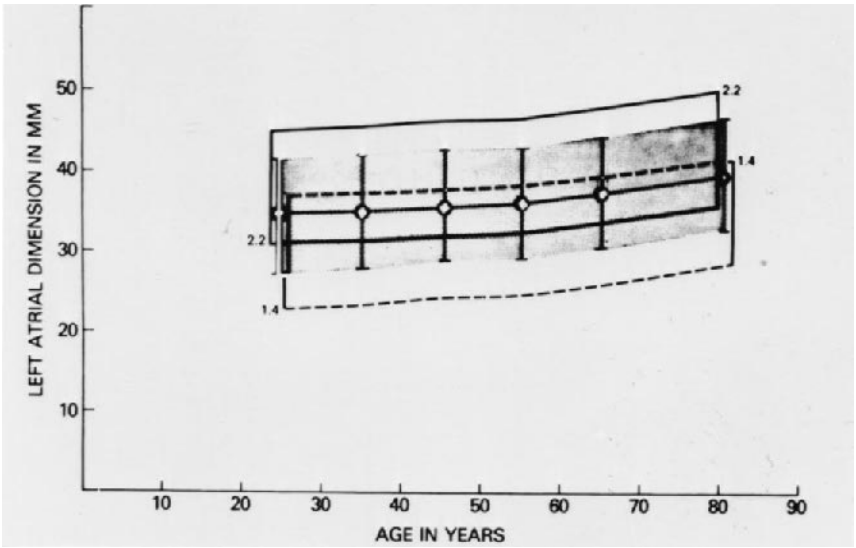

Figure 4 Left atrial dimensions in late diastole in millimeters versus age in years. For each age group, the mean and 95% prediction interval for normal values are depicted. (Reprinted from Ref. 3. Copyright 1979 John Wiley & Sons, Inc., with permission.)

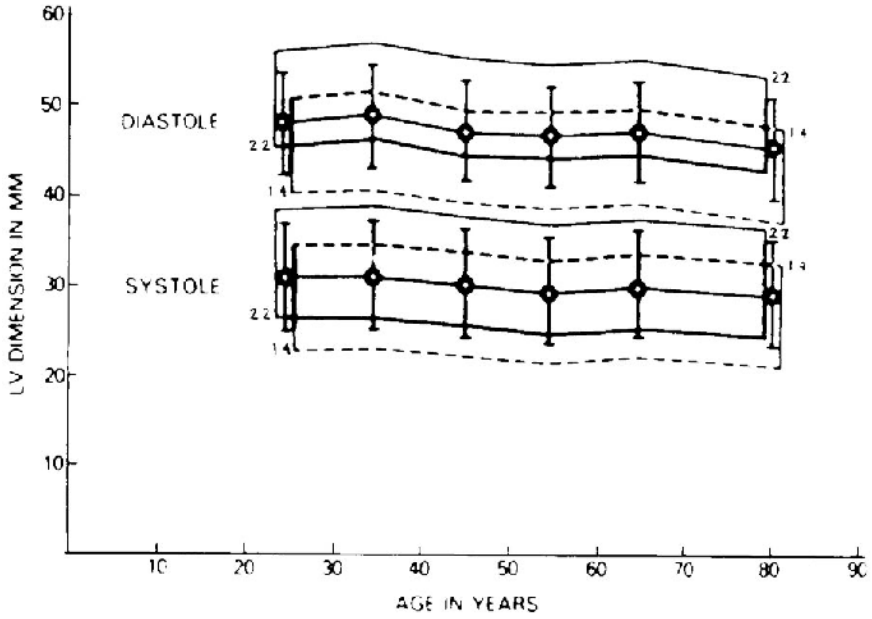

Figure 5 Left ventricular end-diastolic and end-systolic dimensions in millimeters versus age in years. For each age group, the mean and 95% prediction interval for normal values are depicted. (Reprinted from Ref. 3. Copyright 1979 John Wiley & Sons, Inc., with permission.)

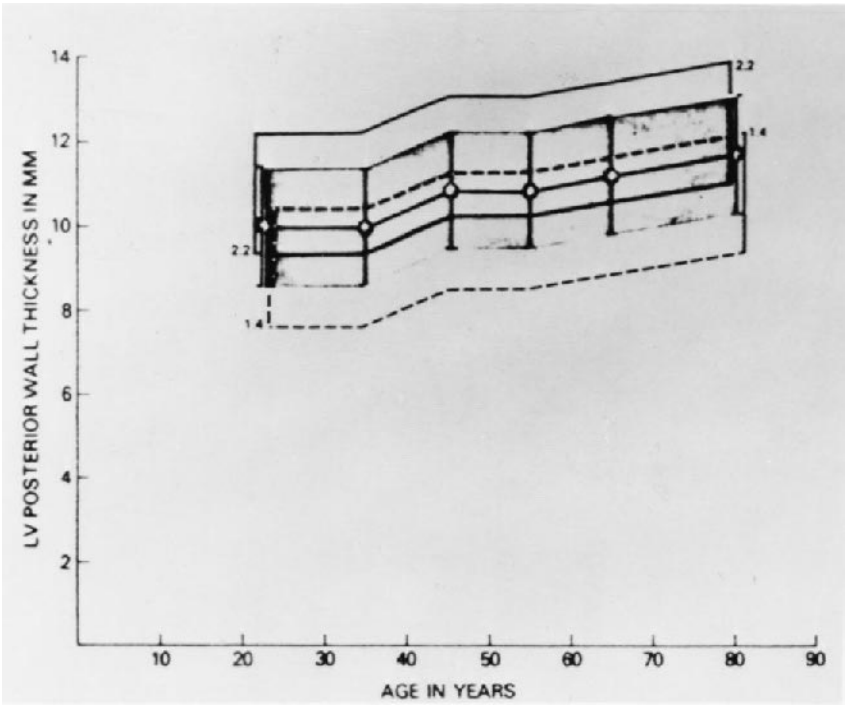

Figure 6 Left ventricular posterior wall thickness in late diastole in millimeters versus age in years. For each age group, the mean and 95% prediction interval for normal values are depicted. (Reprinted from Ref. 3. Copyright 1979 John Wiley & Sons, Inc., with permission.)

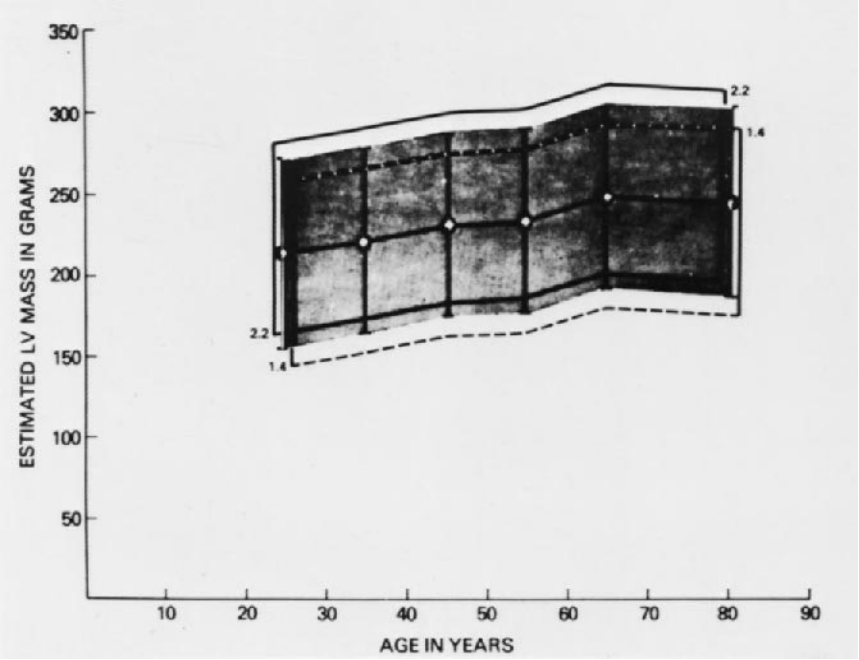

Figure 7 Estimated left ventricular mass in grams versus age in years. The mean and 95% prediction interval are depicted for each age group. (Reprinted from Ref. 6, with permission.)

of left atrial dimension to make quantitative statements about the effects of various disease states (e.g., hypertension or valvular or coronary disease).

Various investigators have reported functional changes with age in the mitral valve echocardiogram consistent with our findings of decreased E-F slope (9). Factors postulated to explain this decrease in the rate of early diastolic closure of the anterior mitral valve leaflet have included sclerosis of the mitral leaflets and/or decreased compliance of the left ventricle (9).

In our studies, left ventricular ejection fraction and percentage fractional shortening did not change appreciably as age increased from 20 to 97 years. These findings are consistent with several previous studies (10,11), including one in which left ventricular function was assessed with radionuclide cineangiography (10). If the left ventricular internal dimension at end diastole is mildly reduced in older subjects, while ejection fraction and heart rate are unchanged, stroke volume and cardiac output are expected to diminish slightly with advancing age. Data indicating that this is so have been reported using a dye-dilution technique (12,13).

Our findings relating changes in echocardiographic parameters to increasing age are generally in agreement with findings reported by Gerstenblith et al. (14). The major difference is that we found a slight, but significant, decrease in left ventricular systolic and diastolic internal dimensions with increasing age, whereas Gerstenblith and associates found no change. Furthermore, women were not included in their study population, nor did they report measurements of left atrial dimension or left ventricular mass.

Although it is highly likely that these echocardiographic changes reported in the

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different age groups are related to the aging process, one cannot be certain that this explanation is correct until these changes are documented during serial studies in the same patient. Nonetheless, this analysis makes it clear that it is important to use normal echocardiographic values corrected for both age and body surface area (or another measure of body size) when evaluating adult patients suspected of having heart disease.

RELATIONSHIP OF AGE TO LEFT VENTRICULAR SYSTOLIC PERFORMANCE AS MEASURED BY DOPPLER AORTIC FLOW VELOCITY PARAMETERS

Doppler flow velocity measurements in the aorta have been shown to be useful in differentiating normal subjects from those with left ventricular dysfunction (15,16). For example, patients with dilated cardiomyopathy demonstrate aortic peak flow velocity, flow velocity integral, and average acceleration that are markedly reduced compared to those in normal subjects (Fig. 8) (15). Furthermore, in patients with congestive heart failure undergoing vasodilator therapy, changes in Doppler aortic peak flow velocity and flow velocity

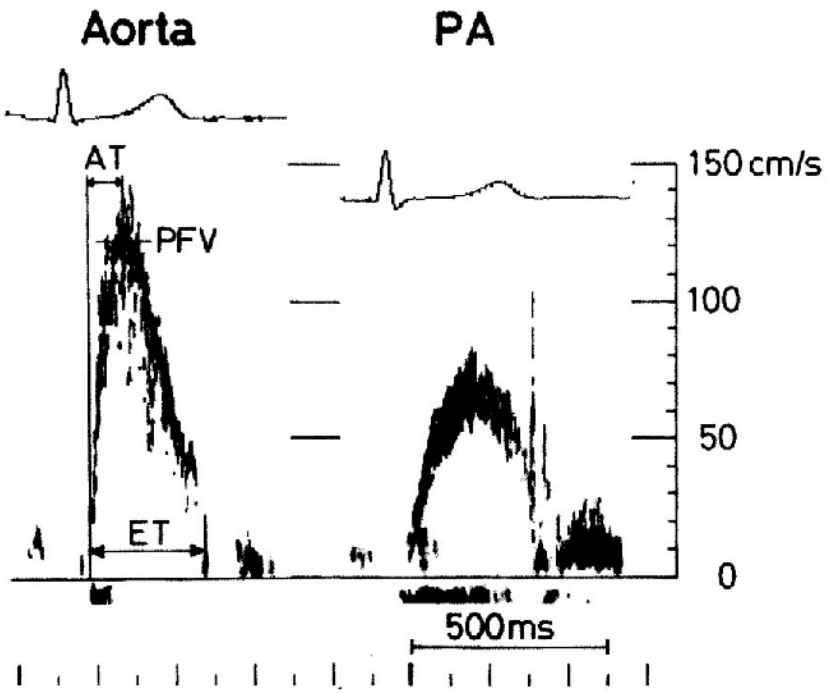

Figure 8 Doppler aortic and pulmonary flow velocity recording from a normal subject. Measurements made included peak flow velocity (PFV) in cm/s; ejection time (ET) in ms; acceleration time (AT), in ms; and average acceleration in cm/s^2 (calculated by dividing PFV by AT). In addition, the aortic flow velocity integral, or area under the flow velocity curve in cm, was estimated. (See text for details.) (Reprinted with permission from Ref. 17.)

integral have been shown to be useful in estimating changes in systemic vascular resistance and stroke volume, respectively (16).

We evaluated the relationship between age and Doppler aortic flow velocity measurements in 97 adults (45 men and 52 women, aged 21–78 years) without clinical evidence of cardiac disease (17). No subject had a history of hypertension or cardiovascular disease, and all had a normal cardiac examination, electrocardiogram, chest x-ray, and M-mode and two-dimensional echocardiogram.

Figure 8 demonstrates an aortic flow velocity recording from a normal subject (17,18). Peak flow velocity was measured in centimeters per second at the midpoint of the darkest area of the spectrum at the time of maximum flow velocity. Ejection time (ET) was measured in milliseconds from the onset of the systolic flow velocity curve to the time the curve crossed the zero-flow line at end systole. Aortic flow velocity integral (centimeters), which represents the area under the flow velocity curve, was estimated by the following formula: flow velocity integral $= 0.5 \times$ peak flow velocity $\times$ ET (16).

Multiple linear regression analysis revealed that age was significantly correlated with aortic peak flow velocity, average acceleration, and flow velocity integral (all $p < 0.001$) (18). Figure 9 depicts the relationship between aortic peak flow velocity and age. The two parameters were related by the following regression equation: aortic peak flow velocity $= -0.6$ (age) $+ 110$ ($r = -0.54$; $p = 0.001$). Aortic peak flow velocity was significantly lower in the 61- to 70-year age decade (mean $\pm$ SD $= 93 = \pm$ 11 cm/s) (18). The correlation of aortic peak flow velocity with age remained signif-

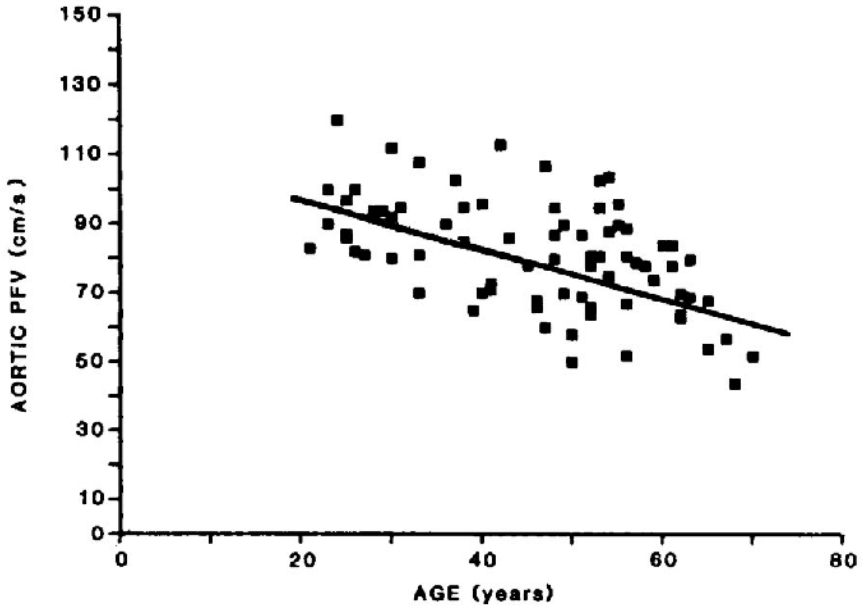

Figure 9 Relationship between aortic peak flow velocity (cm/s) and age (years) in 80 subjects. The solid line represents the line of regression. Note the negative slope of the relationship between the two parameters ($r = 0.54$). Aortic PFV is significantly lower in the 60- to 70-year age group than in the 21–30 year age group ($p < 0.001$). (Reprinted with permission from Ref. 18.)

icant ($p < 0.001$) after division of peak flow velocity by the square root of the R-R interval.

Figure 10 depicts the relationship between aortic flow velocity integral and age. Note the significantly lower ($p < 0.001$) aortic flow velocity integral in the 61- to 70-year age decade (mean ± SD = 9.5 ± 2.3 cm) compared with the 21- to 30-year age decade (13.8 ± 2.1 cm). Aortic flow velocity integral and age are related by the following regression equation: aortic flow velocity integral = −0.09 (age) + 16.5 ($r = -0.44$; $p < 0.001$) (18). This correlation with age remained significant ($p < 0.01$) after correction of aortic flow velocity integral for the square root of the R-R interval.

The decrease in aortic peak flow velocity and flow velocity integral noted with increasing age are probably due, at least in part, to the increases in aortic root diameter noted with aging (3,5,8,14). It was previously shown that resting stroke volume (3,5) and cardiac output (19) do not change significantly with aging. Since Doppler stroke volume can be estimated by multiplying the aortic flow velocity integral by the aortic root area, it follows that a decrease in flow velocity integral must be accompanied by an increase in aortic root area (and diameter) to maintain a constant stroke volume. Furthermore, since aortic flow velocity integral is approximately equal to 1/2 peak flow velocity × ejection time (16) and since we did not find any change in aortic ejection time with aging in this study, it follows that aortic peak flow velocity is expected to decrease with aging.

There were no significant differences in Doppler aortic flow velocity measurements between men and women of the same age. Furthermore, there was no significant relationship between body surface area or blood pressure and any of the aortic flow velocity parameters in this group of normal subjects (18).

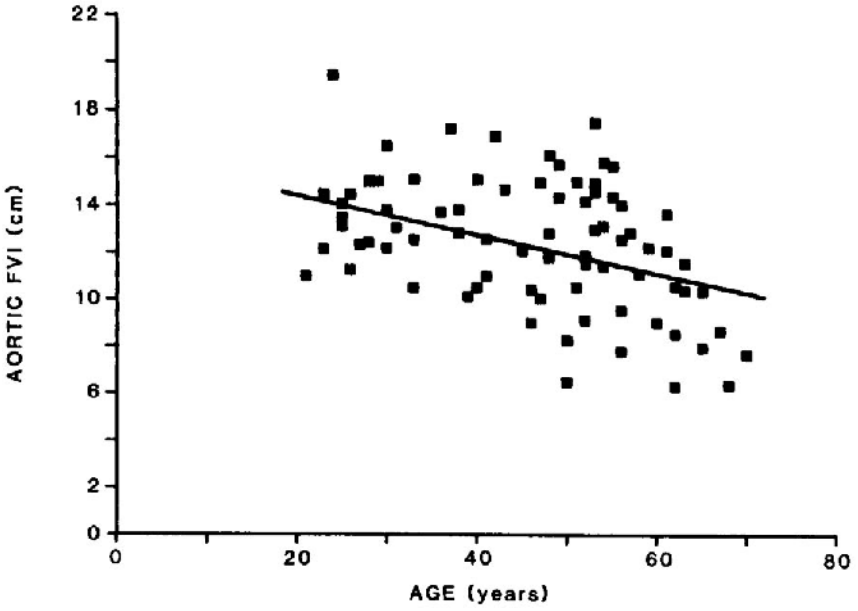

Figure 10 Relationship between aortic flow velocity integral (cm) and age (years). Note the significantly lower flow velocity integral in the 61- to 70-year age group than in the 21- to 30-year age group ($p < 0.001$). (Reprinted with permission from Ref. 18.)

RELATIONSHIP OF AGE TO LEFT VENTRICULAR SYSTOLIC PERFORMANCE WITH UPRIGHT EXERCISE AS MEASURED BY DOPPLER AORTIC FLOW VELOCITY RECORDING DURING TREADMILL TESTING

To evaluate the effect of upright exercise on aortic peak flow velocity and acceleration, 60 normal subjects, aged 15 to 74 years, were evaluated by continuous-wave Doppler during treadmill stress testing using the Bruce protocol (20). Subjects were divided into three age groups, each with 20 subjects: group I, 21 ± 4 years of age (mean ± standard deviation); group II, 36 ± 5 years; and group III, 58 ± 7 years. Periodic measurements of heart rate, blood pressure, and Doppler blood flow velocity and acceleration were made before, during, and after exercise. Continuous-wave Doppler measurements were recorded from the suprasternal notch. The relationship between Doppler aortic measurements and age, gender, heart rate, and blood pressure responses during exercise were evaluated.

Age alone was significantly related (inversely) to immediate postexercise Doppler aortic peak blood flow velocity (group I, 1.1 ± 0.2; group II, 1.0 ± 0.2; and group III, 0.8 ± 0.2 m/s, respectively; $p < 0.01$) and peak acceleration (group I, 55 ± 15; group II, 46 ± 11; and group III, 36 ± 9 m/s^2; $p < 0.05$) (Fig. 11 and 12). Gender, heart rate, and blood pressure changes during exercise, as well as exercise preconditioning, had no significant effect on these aortic flow characteristics.

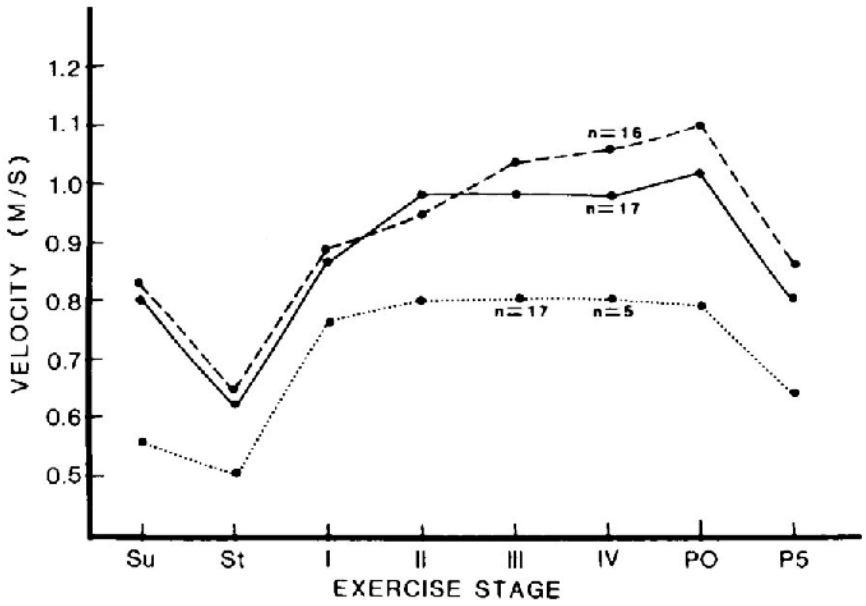

Figure 11 Doppler peak aortic bolld flow velocity measurements before, during, and immediately after exercise. Su = supine, St = standing, PO = immediate postexercise, P5 = 5 min after exercise. Data are shown as the mean for 20 subjects in each of the three groups, except as noted by *n* value in exercise stages III and IV. (Reprinted with permission from Ref. 20.)

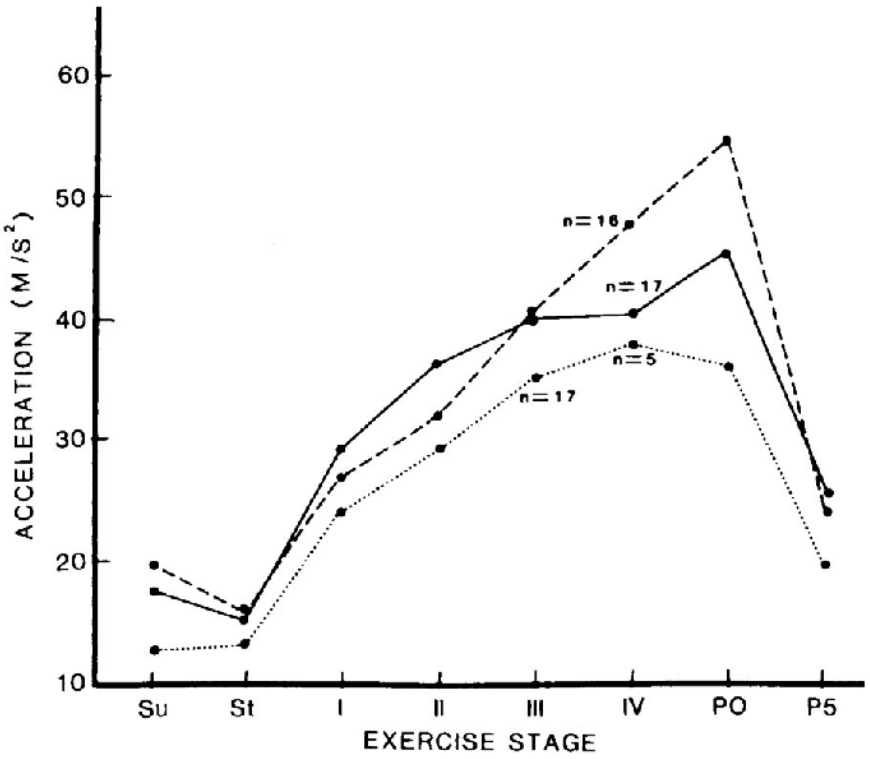

Figure 12 Doppler peak acceleration measurements before, during, and immediately after exercise. Abbreviations and data display are as in Figure 14. (Reprinted with permission from Ref. 20.)

These findings suggest that age is an important factor influencing aortic peak blood flow velocity and acceleration with exercise, as well as at rest. These changes in peak velocity and acceleration with exercise may reflect, in part, changes in exercise left ventricular function with age. Earlier studies (21–23) showed close correlations between these flow parameters and muscle contractility. However, alterations in aortic configuration, size, and compliance, as well as in impedance (afterload), probably affect these Doppler parameters to an important degree. Importantly, these age-dependent changes must be kept in mind when using Doppler-determined peak velocity and acceleration in evaluating left ventricular performance.

RELATIONSHIP OF AGE TO LEFT VENTRICULAR DIASTOLIC FUNCTION AT REST AS EVALUATED BY DOPPLER TRANSMITRAL FLOW VELOCITY MEASUREMENTS

Although left ventricular systolic function is generally maintained with aging in healthy subjects (19), alterations in diastolic function are known to occur with ''normal'' aging (24,25). We evaluated the relationship between age and pulsed Doppler transmitral flow

velocity measurements in 66 adult men and women, aged 21 to 78 years, without a history of hypertension or cardiovascular disease (25). Measurements of early and late diastolic transmitral peak flow (filling) velocities, flow times and flow velocity integrals, and early diastolic flow acceleration and deceleration were made at the level of the mitral leaflet tips. As shown in Figure 13, transmitral peak flow velocities in centimeters per second

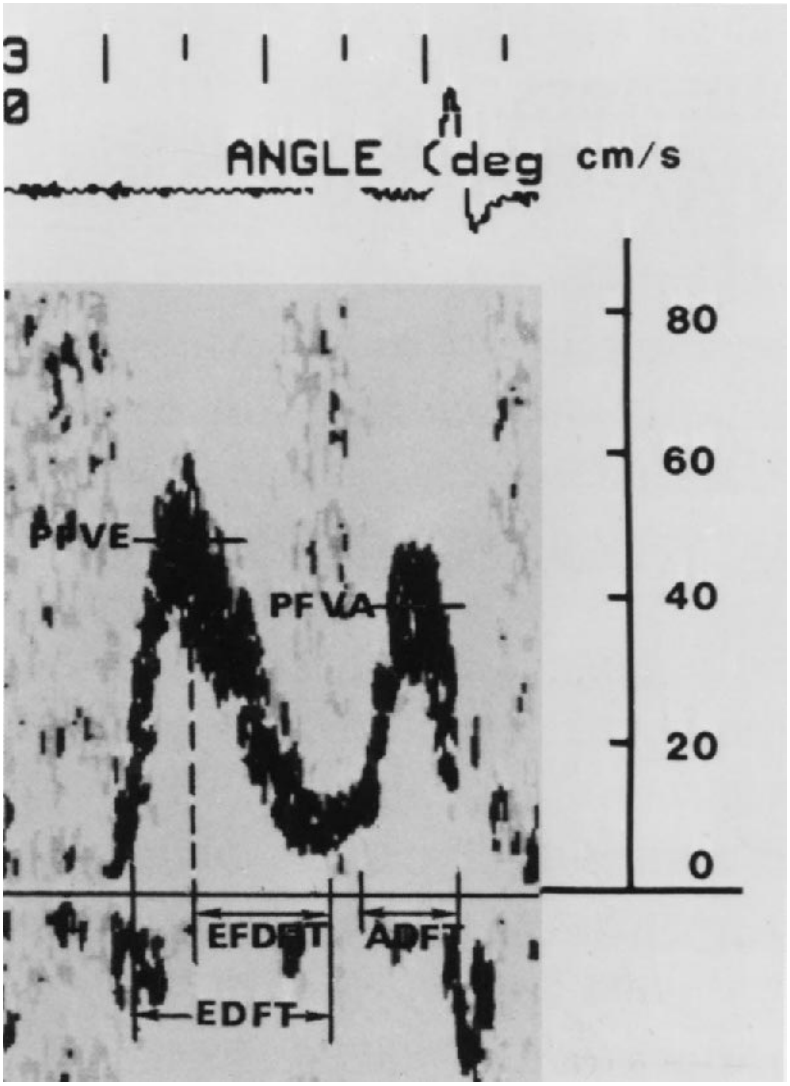

Figure 13 Normal flow velocity recording at the level of the mitral valve from the apical four-chamber view depicting the method for making Doppler measurements. Mitral peak flow velocity in early diastole (PFVE) and in late diastole (PFVA) were measured (cm/s) at the midpoint of the darkest portion of the spectrum at the time of the maximal flow velocity in early and late diastole, respectively. Early diastolic flow time (EDFT), late diastolic flow time (ADFT), and early diastolic deceleration time (EFDFT) were measured as noted. (Reprinted from Ref. 25, with permission.)

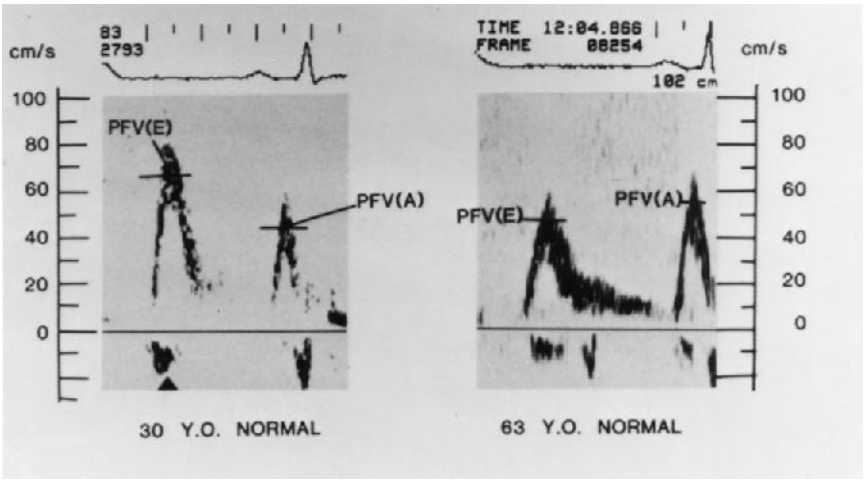

Figure 14 Doppler mitral valve flow velocity recordings from a younger normal subject, age 30 (left), and from an older normal subject, age 63 (right). Note that the peak flow velocity at early diastole in the older subject is lower and the late diastolic peak flow velocity is higher than in the younger normal subject. (Reprinted from Ref. 25, with permission.)

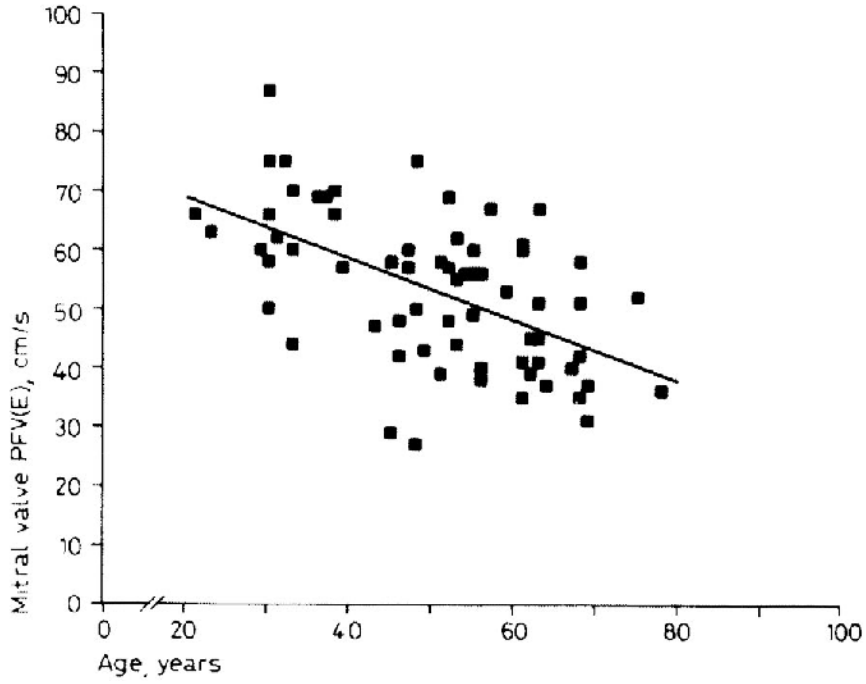

Figure 15 Data for mitral peak flow velocity in early diastole, PFV(E) (cm/s) is displayed on the vertical axis versus age in years on the horizontal axis ($n = 66$). Note the negative slope of the regression equation mitral, PFVE $= -0.52$ (age) $+ 79$. The correlation coefficient $r = -0.55$. (Reprinted from Ref. 25, with permission.)

were measured in early and late diastole (i.e., at the time of atrial systole) at the midpoint of the darkest portion of the spectrum at the time of peak flow velocity.

Differences in Doppler transmitral flow velocity patterns between 30-year-old and 63-year-old normal adults are depicted in Figure 14 (25). Mitral peak flow velocity in early diastole (PFVE) was significantly lower ($p < 0.01$) in the 61- to 70-year age decade (45 ± 10 cm/s) than in the 21- to 30-year age decade (66 ± 11 cm/s) (Fig. 15). Mitral peak flow velocity in late diastole (PFVA) was significantly higher ($p < 0.05$) in the 61- to 70-year age decade (55 ± 11 cm/s) than in the 21- to 30-year age group (41 ± 7 cm/s); (Fig. 16). Mitral A/E ratio (i.e., PFVA/PFVE) was significantly higher ($p < 0.01$) in the oldest (1.2 ± 0.3) compared to the youngest (0.6 ± 0.1) age group (Fig. 17). Early diastolic flow time increased with age ($r = 0.36$; $p < 0.001$), whereas early diastolic deceleration decreased with age ($r = -0.59$; $p < 0.001$). The combination of a diminished early diastolic peak flow velocity divided by a prolonged deceleration time resulted in a significant ($p < 0.001$) decrease in the rate of early diastolic deceleration with increasing age.

The results of this study demonstrated that aging is associated with progressive decreases in early diastolic transmitral peak flow velocity and early diastolic deceleration and progressive increases in late diastolic transmitral peak flow velocity and the ratio of

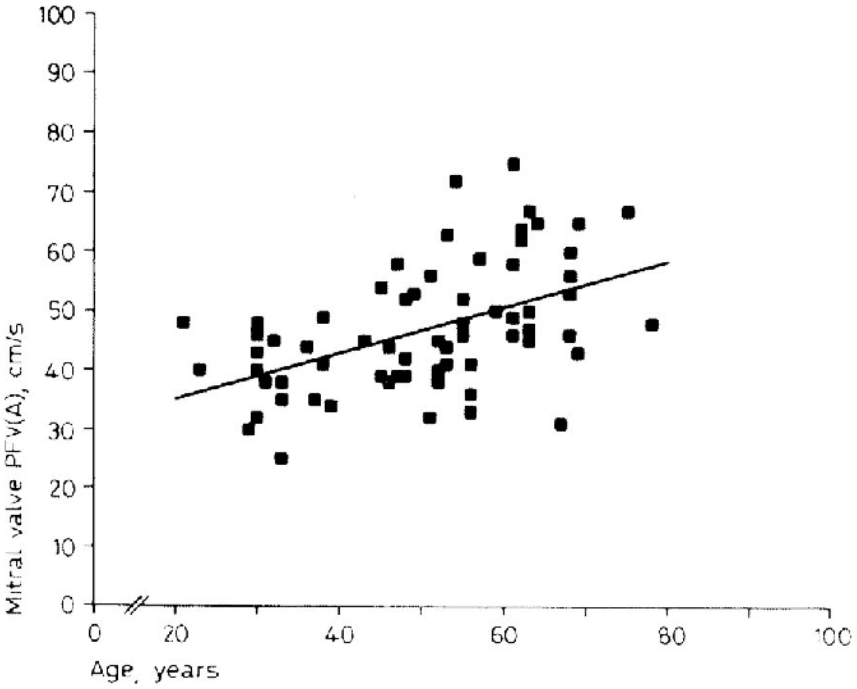

Figure 16 Data for mitral flow velocity in late diastole, PFV(A) (cm/s) is displayed versus age in years ($n = 66$). Note the positive slope of the relationship, mitral PFVA = 0.39 (age) + 27. (Reprinted from Ref. 25, with permission.)

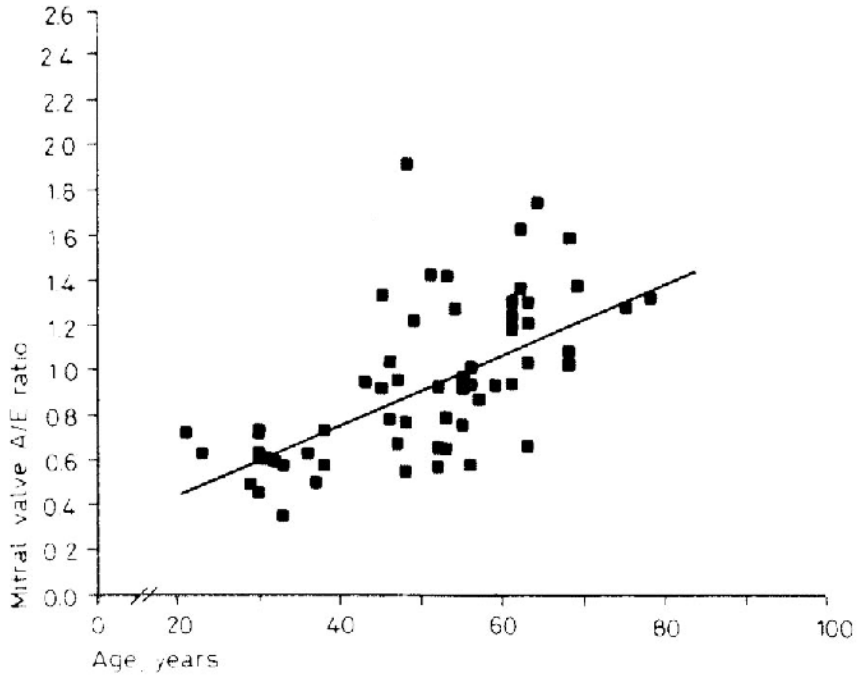

Figure 17 Data for mitral A/E ratio is depicted versus age in years. Note the positive slope of the relationship, mitral A/E ratio = 0.016 (age) + 0.13. (Reprinted from Ref. 25, with permission.)

late to early diastolic peak flow velocity. These findings are similar to those reported by Miyatake and associates (24).

Evidence that the decrease in early diastolic transmitral peak flow velocity is related to impaired early diastolic left ventricular filling has been provided by a number of workers. Dabestani et al. (26) showed in 10 patients who underwent both Doppler mitral flow velocity recording and videoensitometric analysis of left ventricular filling from digital subtraction left ventriculograms that the percentage of total filling completed by mid-diastole was directly related to the early diastolic peak flow velocity measured by Doppler. These findings suggest that Doppler measurements of peak flow velocity in early diastole are related to the rate of ventricular filling. Rokey et al. (27) also reported a significant correlation between early diastolic transmitral peak flow velocity and angiographic peak filling rate ($r = 64$). They noted even better correlations between Doppler echocardiographic and angiographic peak filling rates ($r = 0.87$).

Miyatake et al. (24) postulated that the increase in *late* diastolic peak transmitral flow velocity with aging reflects an augmentation of ventricular filling by atrial contraction that compensates for decreased early diastolic ventricular filling. Our study demonstrated not only age-related increases in late diastolic peak flow *velocity*, but also in late diastolic flow *time* and flow velocity *integral* (25). These findings are further evidence for an age-related increase in the contribution of atrial systole to ventricular filling.

EPIDEMIOLOGICAL STUDIES IN THE ELDERLY

The Framingham study has shown by M-mode echocardiography that (1) left ventricular hypertrophy is a powerful, independent predictor for mortality and morbidity from coronary heart disease, and (2) increased left atrial dimension is associated with an increased risk of stroke (28–30). However, no previous multicenter population-based study has evaluated specifically in the elderly predictive value for coronary heart disease and stroke of echocardiographic imaging and Doppler techniques.

The Cardiovascular Health Study (CHS) is a multiyear prospective epidemiological study of 5201 men and women older than 65 years recruited from four U.S. field centers: Davis, California; Hagerstown, Maryland; Winston-Salem, North Carolina; and Pittsburgh, Pennsylvania (31). The main objectives of incorporating echocardiography were to determine whether echocardiographic measurements, or changes in these measurements, are (1) correlated with traditional risk factors for coronary heart disease and stroke and (2) independent predictors of morbidity and mortality from coronary heart disease and stroke.

Echocardiographic measurements obtained include those related to global and segmental left ventricular systolic and diastolic structure and function and left atrial and aortic root dimension (32). For each subject, a baseline two-dimensional (2-D), M-mode (2-D directed), and Doppler echocardiogram was recorded on super-VHS tape using a standard protocol and equipment. All studies were sent to a reading center (University of California, Irvine), where images were digitized and measurements made using customized computer algorithms. M-mode measurements were made according to American Society of Echocardiography convention (33). LV mass was derived from the formula described by Devereux, et al:

$$\text{LV mass (g)} = 0.80 \times 1.04\,[(\text{VSTd} + \text{LVIDd} + \text{PWTd})^3 - (\text{LVIDd})^3] + 0.6,$$

where VSTd is ventricular septal thickness at end diastole, LVIDd is LV internal dimension at end diastole, and PWTd is LV posterior wall thickness at end diastole.

Calculated data and images were stored on optical disks to facilitate retrieval and future comparisons in longitudinal studies. Quality control measures included standardized training of echocardiography technicians and readers, technician observation by a trained echocardiographer, periodic blind duplicate readings with reader review sessions, phantom studies, and quality control audits (32).

Left Ventricular Mass. A number of initial cross-sectional associations with baseline echocardiographic data have been described in the Cardiovascular Health Study. M-mode measurements (2-D directed) of LV mass could not be made in 34% of CHS participants, and this was highly related to age (29% in the 65- to 69-year vs. 50% in the 85+ age group; $p < 0.001$), white race, male gender, and history of hypertension, diabetes, or CHD. LV mass was found to be significantly higher in men than women, even after multivariate adjustments, and modestly increased with aging (35,36). LV mass increased less than 1 g per year increase in age for both men and women. Of interest, across all CHS age subgroups, the difference in weight-adjusted LV mass by sex was greater in magnitude than the difference related to clinical CHD (Fig. 18). This may relate to the well-known relatively high prevalence of *subclinical* manifestations of cardiac disease (e.g., coronary disease) in elderly individuals without clinical disease.

Left Ventricular Wall Motion. In this regard, 4.3% of participants with hypertension but no clinical heart disease, and 1.9% of participants with neither clinical heart disease nor hypertension had LV segmental wall motion abnormalities, suggesting silent

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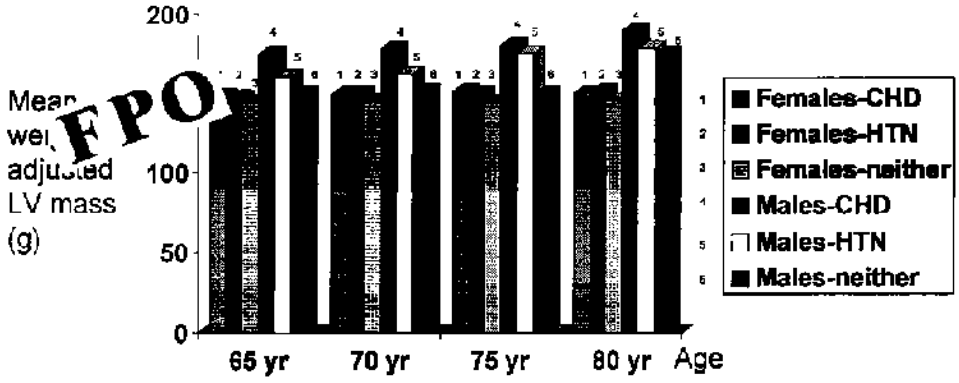

Figure 18 Cardiovascular Health Study data: Bar graph shows weight-adjusted mean left ventricular (LV) mass displayed by sex and disease status group across 5-year age intervals. Data are computed using the lower age end point and the mean weight for each age category (65 to 69, 70 to 74, 75 to 79, 80 to 84, 85+ years). Weight-adjusted LV mass was significantly associated with sex, disease status, and age. Of interest, within each age group, the magnitude of the sex effect exceeded that of the effect of the disease (e.g., clinical coronary heart disease [CHD]). HTN indicates hypertension.

coronary disease (36). Multivariate analyses revealed male sex and presence of clinical CHD (both $p < 0.001$) to be independent predictors of LV akinesis or dyskinesis.

Subclinical Disease. A new method of classifying subclinical disease at baseline examination in the Cardiovascular Health Study included measures of ankle-brachial blood pressure, carotid artery stenosis and wall thickness, ECG and echocardiographic abnormalities, and positive response to the Rose Angina and Claudication Questionnaire (see Table 2) (37). Participants were followed for an average of 2.4 years (maximum, 3 years). For

Table 2 Criteria for Clinical and Subclinical Disease in the Cardiovascular Health Study

Clinical disease criteria	Subclinical disease criteria
Atrial fibrillation or pacemaker	Ankle-arm index ∞ 0.9 mmHg
History of intermittent claudication or peripheral vascular surgery	Internal carotid wall thickness >80th percentile
	Common carotid wall thickness >80th percentile
History of congestive heart failure	Carotid stenosis >25%
History of stroke, transient ischemic attack, or carotid surgery	Major ECG abnormalities[a]
	Abnormal ejection fraction on echocardiogram
History of coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty	Abnormal wall motion on echocardiogram
	Rose questionnaire claudication positive
History of angina or use of nitroglycerin	Rose questionnaire angina positive
History of myocardial infarction	

[a] According to Minnesota Code, ventricular conduction defects (7-1, 7-2, 7-4); major Q/QS wave abnormalities (1-1, 1-2); left ventricular hypertrophy (high-amplitude R waves with major or minor ST-T abnormalities) (3-1, 3-3, and 4-1 to 4-3 or 5-1 to 5-3); isolated major ST/T wave abnormalities (4-1, 4-2, 5-1, 5-2).

Source: From Ref. 37, with permission of the author and the American Heart Association.

participants without evidence of clinical cardiovascular disease at baseline, the presence of subclinical disease compared with no subclinical disease was associated with a significant increased risk of incident total coronary heart disease including CHD deaths and nonfatal MI and angina pectoris for both men and women. For individuals with subclinical disease, the increased risk of total coronary heart disease was 2.0 for men and 2.5 for women, and the increased risk of total mortality was 2.9 for men and 1.7 for women. The increased risk changed little after adjustment for other risk factors, including lipoprotein levels, blood pressure, smoking, and diabetes. Consequently, the measurement of subclinical disease provides an approach for identifying high-risk older individuals who may be candidates for more active intervention to prevent clinical disease.

''Healthy'' Subgroup. By excluding CHS participants with either LV ejection fraction or wall motion abnormalities from the group of participants with neither clinical heart disease (including CHD) nor hypertension, a subgroup that was apparently free of clinical heart disease and hypertension was defined. The ''healthy'' subgroup consisted of 516 men and 773 women, with 339 and 569 having available echo measurements of LV mass, respectively. Preliminary analysis indicated that after adjustment for weight, no adjustment for height was necessary. Likewise, after adjustment for weight, age had only a modest effect on LV mass. Therefore, for simplicity, the reference equations were not expressed as a function of age. There was no evidence of an interaction between sex and weight. Since in the baseline CHS cohort race was not a significantly independent predictor of LV mass, the reference equations are not race-specific.

The expected LV mass (g) derived from the CHS healthy subgroup can be calculated from the following equations:

$$\text{Men:} \quad 16.6 \cdot [\text{Weight (kg)}]^{0.51}$$

$$\text{Women:} \quad 13.9 \cdot [\text{Weight (kg)}]^{0.51}$$

If the ratio of observed to expected LV mass is between 0.69 and 1.47, the patient's LV mass should not be considered larger than expected given his or her weight. This prediction procedure classified 28% of the men and 18% of the women with clinical CHD as outside the range of expected LV mass measurements. Exclusion of obese ($n = 220$) participants from this healthy group had a negligible effect on the reference equations.

Left Ventricular Diastolic Filling. Pulsed Doppler transmitral flow velocities were analyzed as part of the baseline examination in the Cardiovascular Health Study (32). Early diastolic LV Doppler (transmitral) peak filling velocity decreased, and peak late diastolic (atrial) velocity increased with increasing age in multivariate analyses (all $p < 0.001$) (38). Early and late diastolic peak filling velocities were both significantly higher in women than in men, even after adjustment for body surface area (or height and weight). In multivariate models in the entire cohort and a healthy subgroup ($n = 703$), gender, age, heart rate, and blood pressure were most strongly related to early and late diastolic transmitral peak velocities. Early and late diastolic peak velocities both increased with increases in systolic blood pressure, and decreased with increases in diastolic blood pressure ($p < 0.001$).

Doppler transmitral velocities were compared among health status subgroups. In multiple regression models adjusted for other covariates, and in analysis of variance models examining differences across subgroups adjusted only for age, the subgroup with CHF had the highest early diastolic peak velocities (38). All clinical disease subgroups had higher late diastolic peak velocities than did the healthy subgroup, with CHF and hyperten-

sive subgroups having the highest age-adjusted means. The hypertensive subgroup had the lowest ratio of early-to-late diastolic peak velocity, and men with CHF had the highest ratio. Borderline and definite isolated systolic hypertension were positively associated with LV mass ($p < 0.001$) and with increases in transmitral late peak flow velocity and decreases in the ratio of early-to-late diastolic peak flow velocity (39). These findings are consistent with previous reports that hypertensive subjects exhibit an abnormal relaxation pattern, whereas CHF patients develop a pattern suggestive of an increased early diastolic LA-LV pressure gradient.

In summary, echocardiographic imaging and Doppler flow recording have provided convincing evidence of structural and functional cardiac changes related to aging. These noninvasive ultrasound techniques have provided important insights into the cardiovascular epidemiology of aging, as well as the clinical evaluation of elderly patients with suspected cardiovascular disease.

ACKNOWLEDGMENT

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5

Cerebrovascular Disease in the Elderly

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INTRODUCTION

Stroke is primarily a disease of the elderly. The incidence of stroke under age 65 is less than 2 per 1000 per year, but rises to 4.6 per 1000 per year for men and 3.8 per 1000 per year for women aged 65 to 74, and to 9.4 per 1000 per year for men and 7.4 per 1000 per year for women aged 75 to 84 (1). Stroke is the third leading cause of death in the U.S. and is the leading cause of neurological disability. It is often felt to be a fate worse than death by elderly patients.

Stroke is caused by disruption of the circulation of blood to the brain, and can be ischemic due to occlusion of an artery or hemorrhagic due to rupture of an artery. Ischemia accounts for 80 to 85% of stroke while hemorrhage accounts for 15 to 20% (2,3). Ischemic stroke is caused primarily by atherosclerotic disease of large extracranial and intracranial vessels, occlusion of intracranial vessels by emboli from a cardiac source, and small vessel intracranial occlusive disease secondary to hypertension and diabetes (Figs. 1 and 2). Hemorrhage can be intraparenchymal in the brain itself, mainly from hypertension, or subarachnoid from rupture of an aneurysm arising from the vessels of the Circle of Willis.

The major risk factor for cerebrovascular disease in studies of patients matched for other cardiovascular risk factors is hypertension (4). Diabetes (5) and cigarette smoking also play a significant role (6), while elevation of serum lipids is less consequential for cerebrovascular disease than for coronary artery disease (7). Control of these risk factors at a young age has contributed to an impressive reduction in the incidence of stroke in recent years, but addressing these risk factors in the elderly patient still plays an important role (1). Cardiogenic embolization, particularly from nonvalvular atrial fibrillation, assumes greater importance as an etiology for stroke in the elderly patient and strategies have currently been developed to reduce the incidence of stroke in these patients (8).

While prevention of stroke is the principal goal in the treatment of patients with cerebrovascular disease, medical therapy for the elderly stroke patient can enhance outcome. New treatment modalities to restore cerebral circulation with thrombolytic therapy

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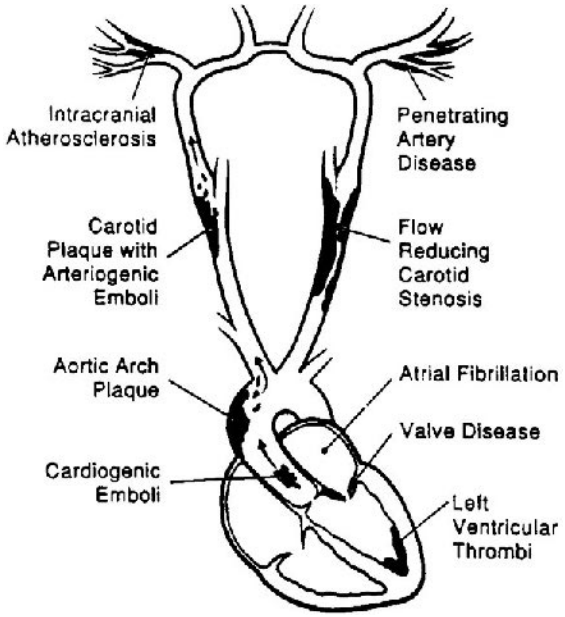

Figure 1 The anatomy of the cerebral circulation is diagrammed demonstrating the potential etiologies of ischemic stroke: cardioembolic, carotid atherothrombotic, intracranial atherosclerosis and small vessel intracranial vascular disease. (From Ref. 2.)

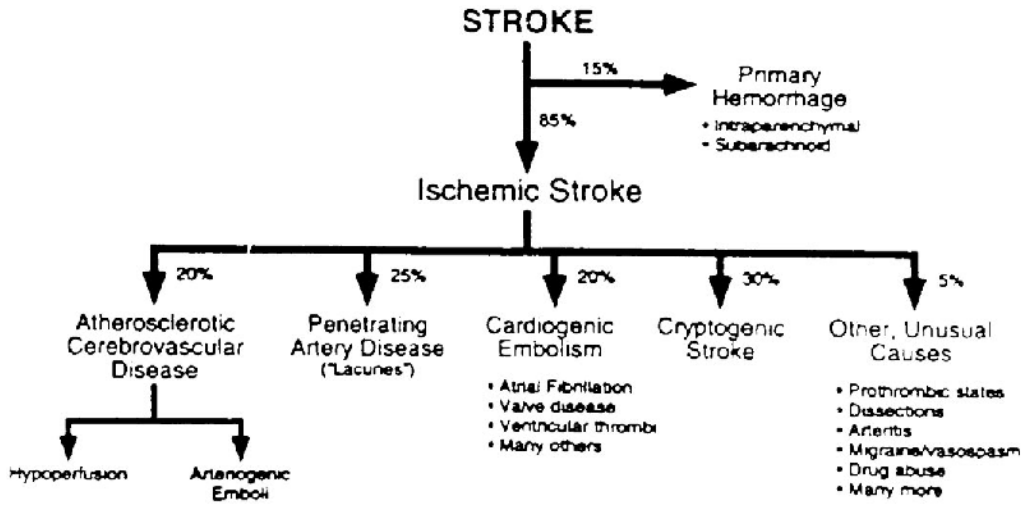

Figure 2 The incidence of the various etiologies of ischemic stroke. (From Ref. 2.)

have changed the outlook on treatment of stroke and therapeutic trials are underway to determine if neuroprotective agents can diminish the extent of irreversible brain damage in acute stroke.

ANATOMY AND PHYSIOLOGY OF THE CEREBRAL CIRCULATION

The brain is supplied by an extensive interconnected network of arterial circulation. Each cerebral hemisphere receives blood flow from the ipsilateral internal carotid artery, which branches into the middle cerebral artery over the lateral surface of the brain, and the anterior cerebral artery over the medial surface of the brain. The brainstem and cerebellum receive blood flow from the vertebral and basilar arteries, which terminate in the posterior cerebral arteries that feed the posterior portions of the cerebral hemisphere including the occipital and posterior parietal lobes and the thalamus.

Connections exist between the two carotid arteries through the anterior communicating artery and between the basilar artery and the two carotid arteries through the posterior communicating arteries. These collateral channels form a complete circuit of arterial supply known as the Circle of Willis. Collateral circulation also can be provided by the external carotid artery which branches from the internal carotid artery at the bifurcation of the cervical common carotid but can connect distally through the ophthalmic artery and through anastomoses between the meningeal branches of the external carotid artery and the surface branches of the cerebral arteries. Because of this collateral circulation, the brain can tolerate complete occlusion of a carotid artery without injury or symptoms and there are case reports of patients with bilateral carotid artery occlusion and unilateral vertebral artery occlusion whose only symptoms are nonspecific dizziness (9).

Another protective mechanism for circulation to the brain is autoregulation. Blood flow is maintained constantly at an average of 50 to 70 mL/100 g/min in the gray matter containing neuronal cell bodies and 10 to 20 mL/100 g/min in the white matter containing the neuronal axons at ranges of mean arterial blood pressure from 60 to 160 mmHg without fluctuations due to changes in pressure (10). Blood flow does fluctuate with the blood pCO_2 increasing or decreasing 4% per 1 torr of pCO_2. This insures that there will be increased blood supply to metabolically active regions of brain that are producing large amounts of carbon dioxide so that sufficient oxygen can be delivered.

PATHOPHYSIOLOGY OF ISCHEMIC STROKE

Ischemic stroke is caused by thrombotic or embolic occlusion of arteries supplying the brain. Atherosclerotic disease at the cervical carotid artery bifurcation accounts for about 20% of ischemic stroke (1,2). Because of the extensive collateral circulation of blood to the brain, it is unusual for ischemic stroke to occur on a hemodynamic basis because of occlusive disease in the carotid artery unless the channels through the Circle of Willis are incomplete. Therefore, the primary mechanism for stroke due to occlusive disease at the carotid artery bifurcation is embolization of thrombus or atherosclerotic debris from plaque at the bifurcation which occludes an intracerebral artery (11). With complete occlusion

of the internal carotid artery (Fig. 3), thrombus can propagate distally in the artery and obstruct collateral channels, causing infarction of a large portion of the cerebral hemisphere. Infarction can sometimes occur on a hemodynamic basis because of hypoperfusion in watershed areas that are supplied by the distal territories of two arterial trees, such as the parietal lobe, which receives terminal branches from both the middle and posterior cerebral arteries. Watershed infarcts can also sometimes occur when there is hypoperfusion due to cardiac arrhythmia, syncope, or cardiac arrest (12).

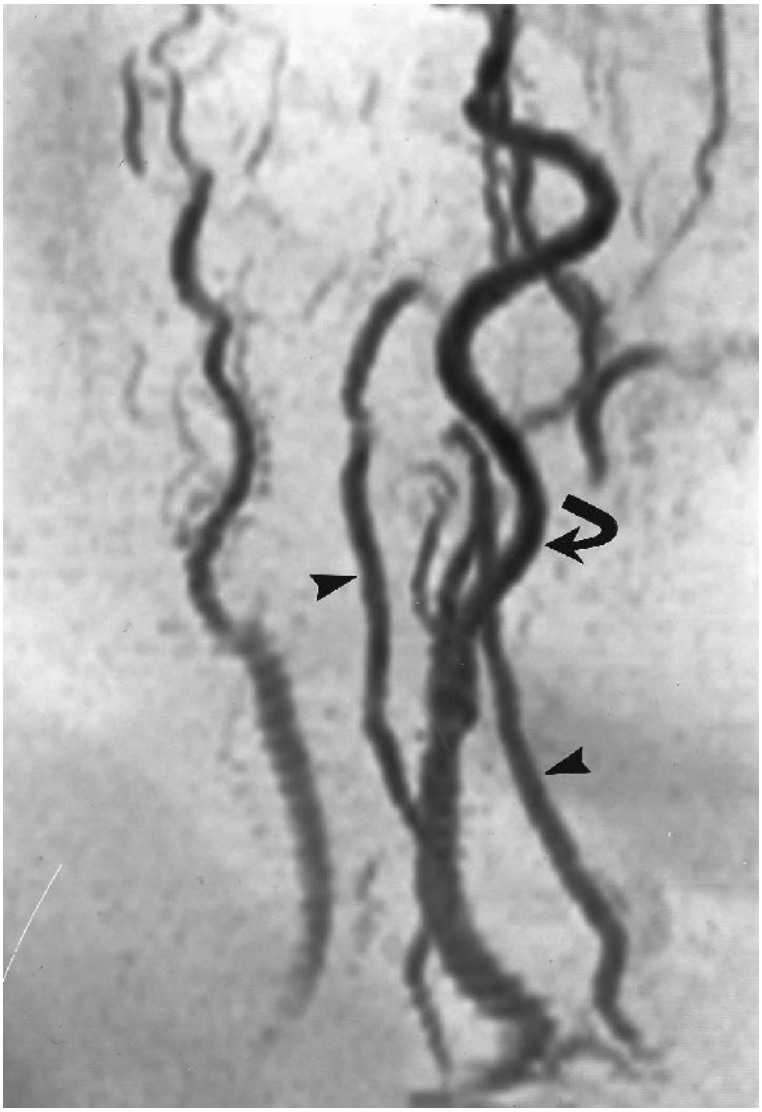

Figure 3 Internal carotid artery occlusion. Magnetic resonance angiography of the extracranial circulation performed using a 2-D time-of-flight sequence. This four-vessel view shows flow in the left internal carotid artery (curved arrow) and in the vertebral arteries (arrowheads) but no flow in the right internal carotid artery.

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Cardiogenic emboli to intracranial arteries accounts for 20 to 30% of ischemic strokes (1,2) (Fig. 4). The largest sources of these emboli are thrombus from the left atrium in patients with atrial fibrillation, particularly in patients over age 75 with a marked preponderance in women over age 80 (8). Valvular heart disease, thrombus from akinetic ventricular wall with myocardial infarction or cardiomyopathy, or right to left shunts through a patent foramen ovale or atrial septal defect also contribute to cardioembolic stroke (1,2,13). Artery to artery emboli can also arise from atheromatous plaque at the arch of the aorta and may account for up to 4% of strokes (14,15).

Atherosclerotic occlusive disease of the large intracranial arteries is an unusual cause of stroke in white patients, but is more common in African-American and Asian patients (11). Intracranial thrombosis of small penetrating arteries supplying the deep structures of the brain, such as the internal capsule and basal ganglia, account for about 25 to 50%

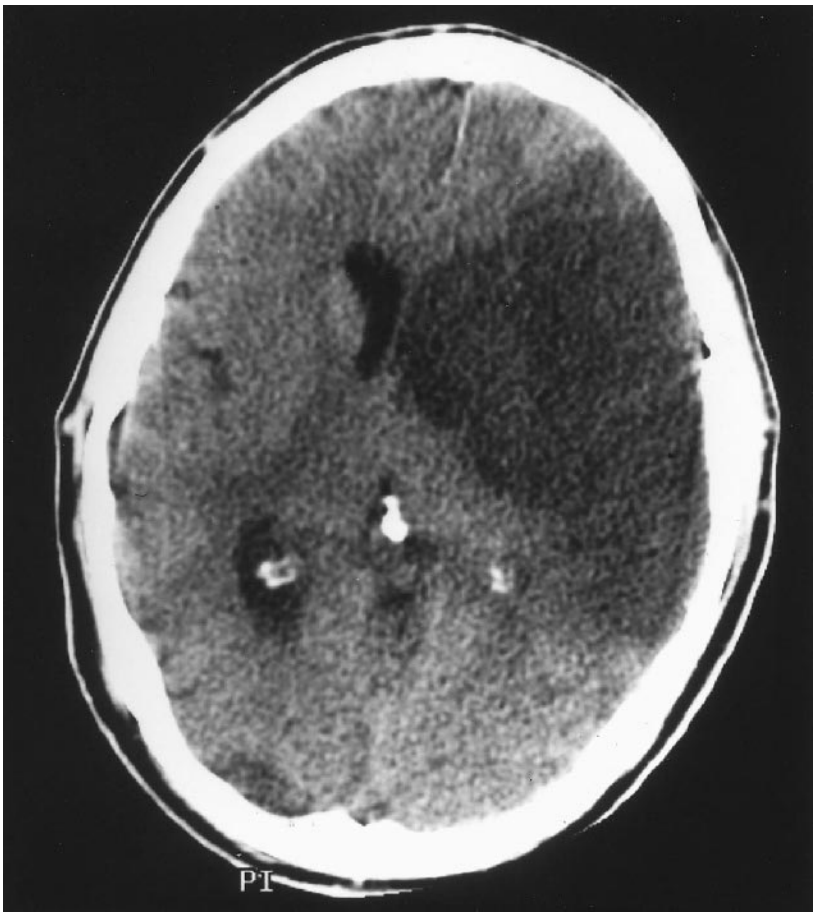

Figure 4 Middle cerebral artery occlusion. Computerized axial tomography at the level of the frontal horns of the lateral ventricles demonstrates a well-defined wedge-shaped area of low attenuation involving both gray and white matter of the left frontal lobe. There is mass effect demonstrated by shift of the midline to the right. This is consistent with a subacute (3- to 5-day-old) infarct in the middle cerebral artery territory secondary to suggesting middle cerebral artery occlusion.

of ischemic strokes (1,2). These vessels are endarteries that do not have collateral flow to the regions they supply. Thrombosis usually occurs because of proliferative thickening of the walls of these arteries due to fibrinoid necrosis or lipohyalinization and caused by diabetes and hypertension (16). When these arteries occlude, they produce small holes in the deep white matter, often referred to as lacunes (16) (Fig. 5). While the lesions may be small in size, if they are located in significant white matter tracts such as the internal capsule, which carries the main motor and sensory fibers from the cerebral hemispheres down to the spinal cord, a devastating neurological deficit such as complete paralysis of the contralateral arm and leg can result.

Unusual causes of stroke, such as vasculitis, hypercoaguable state from anticardiolipin antibody or protein C and protein S deficiency, arterial dissection, and hematological

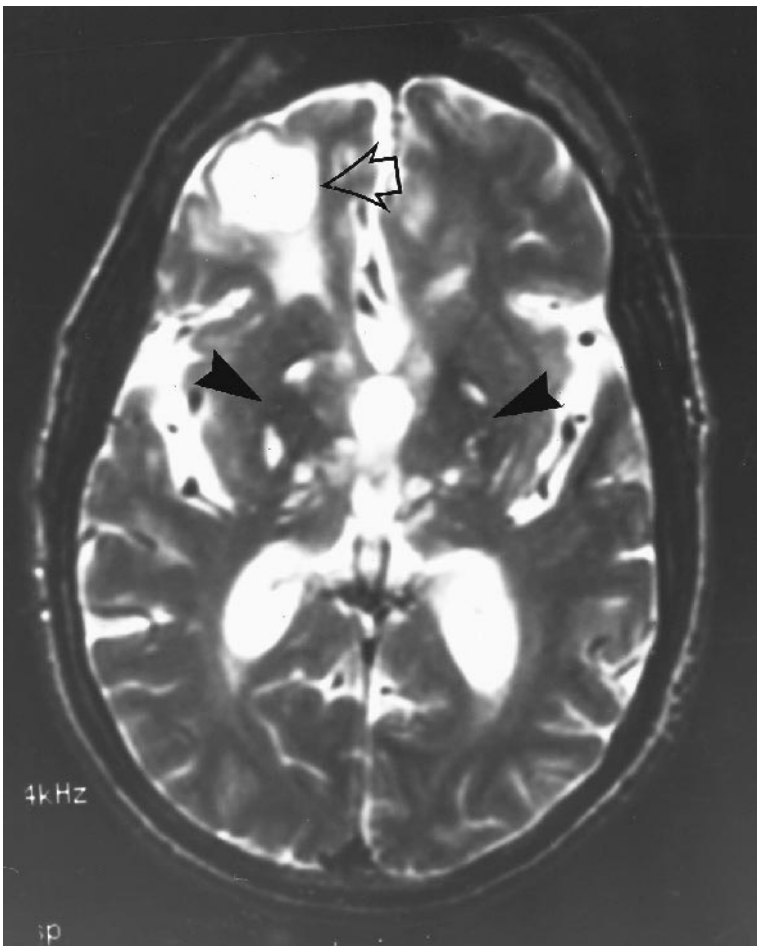

Figure 5 Multiple lacunar infarcts. Axial T_2 weighted magnetic resonance imaging sequence demonstrates multiple rounded areas of high signal intensity within the basal ganglia and thalamus (arrowheads). There is also an old infarct in the right frontal region (hollow arrow).

abnormalities such as sickle cell disease occur mainly in younger patients and are less likely to occur in the elderly (17–21). Even with the advent of noninvasive imaging techniques to identify the nature and causes of ischemic stroke, in 5 to 10% of strokes the etiology cannot be identified and these are classified as cryptogenic strokes (1,2).

Intracerebral hemorrhage usually involves rupture of a microaneurysm formed on the deep penetrating arteries and arterioles caused by hypertension, Charcot-Bouchard aneurysms (22). These hypertensive hemorrhages occur mainly in the deep structures of the brain in the region of the basal ganglia and external capsule (Fig. 6). In the elderly, more superficial hemorrhages into the lobes of the brain, lobar hemorrhages, become more frequent. Many of these lobar hemorrhages are still due to hypertension or can be hemorrhagic transformation of an embolic infarct (23). Another common cause of lobar hemorrhage in the elderly is amyloid angiopathy (Fig. 7), which can occur with or without coincident senile dementia of the Alzheimer's type (24).

Subarachnoid hemorrhage can also occur in the elderly, but a demonstrable berry aneurysm is less frequent than in younger patients (25). There are reports of newly diagnosed arteriovenous malformations in elderly patients (26), but these are also less common sources of bleeding in the elderly than in younger patients.

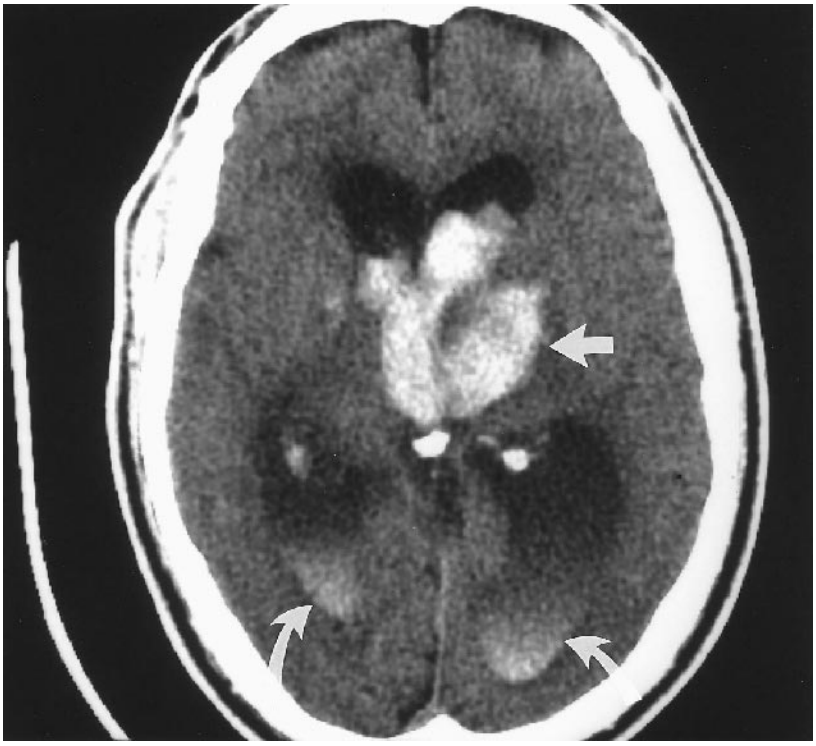

Figure 6 Hypertensive hemorrhage. Axial CT scan at the level of the third ventricle shows acute hypertensive hemorrhage in the left side of the thalamus (arrow), which has broken through into the third ventricle with blood seen layering in the occipital horns of the lateral ventricles (curved arrows).

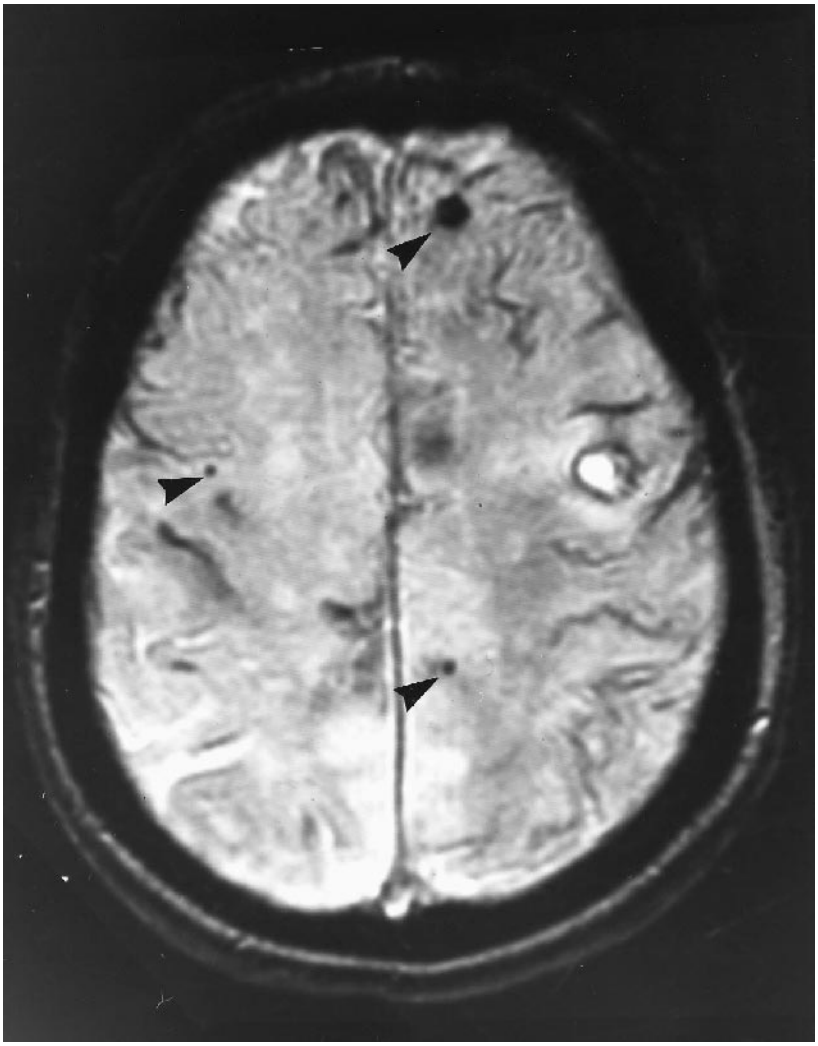

Figure 7 Amyloid angiopathy. Axial gradient echo sequence MRI shows an acute lobar hemorrhage in the posterior left frontal region with numerous areas of previous hemorrhage (arrows). The appearance of multiple areas of prior hemorrhage is not specific, but in an elderly patient is suggestive of cerebral amyloid angiopathy.

Diagnosis of Stroke

The symptoms and signs occurring with a stroke are determined by the anatomical location of the lesion. Most strokes involve the cerebral hemispheres, with contralateral hemiparesis or sensory loss, loss of vision in the contralateral visual field, and behavioral and speech disturbances. Strokes involving the brainstem present with ipsilateral deficits of cranial nerve function such as abnormality of eye movements and a contralateral hemiparesis. Dizziness is a common symptom in the elderly, but dizziness alone is rarely an indication

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of stroke unless it is accompanied by other signs of dysfunction in the region of the vestibular nuclei in the lateral medulla. Loss of sensation on the ipsilateral face and contralateral body, ipsilateral Horner's syndrome and loss of gag reflex and difficulty swallowing from involvement of the nucleus ambiguous supplying the vagus nerves are signs of lateral medullary infarction, known as Wallenberg's syndrome. Ataxia is found with strokes in the cerebellum as well as the brainstem.

It is important to establish the etiology of the stroke because treatment regimens vary with different subtypes of stroke. The clinical history and physical examination and laboratory analysis are obtained to identify risk factors that potentially could have caused the stroke. The neurological examination is helpful in determining if there is an extensive lesion caused by occlusion of a large vessel or a major hemorrhage by determining if there is alteration in level of consciousness along with the focal deficits involved. Lacunar strokes from occlusion of small vessels can also be diagnosed if the typical syndromes of pure motor stroke, pure sensory stroke, dysarthria clumsy hand syndrome, or ataxic hemiparesis are present in an alert patient (16).

The neck is auscultated with the stethoscope to detect a vascular bruit that could signify atherosclerosis at the carotid artery bifurcation as the cause of atheroembolic stroke. The blood pressure is taken to determine if there is hypertension and the blood glucose is measured to determine if diabetes is present. An electrocardiogram is essential to document if arrhythmias such as atrial fibrillation are present which could predispose to cardioembolic stroke.

Computerized axial tomography of the brain (CAT scan) is usually performed initially to differentiate between hemorrhagic and ischemic stroke. Signs of infarction often are not visualized on CAT scan within the first 4 to 12 h after ischemic stroke and the CAT scan may have to be repeated after 48 h to determine the location of the stroke. The initial CAT scan is important in order to help differentiate whether the stroke was atherothrombotic or cardioembolic. Thrombotic strokes more frequently occur in the deep structures of the brain. Cardioembolic strokes usually occur by occluding major branches of the internal carotid artery such as the middle cerebral artery (27), producing an infarct in the discrete territory of the artery involved or by occluding distal branches resulting in cortical infarctions (Fig. 4). Magnetic resonance imaging (MRI) is more sensitive than CAT scan for detecting early signs of infarction in the first 4 to 12 h, particularly when the technique of diffusion MRI is employed (Fig. 8) (28).

The presence of a small, deep, lacunar infarct in a patient with diabetes and/or hypertension usually indicates that the stroke was caused by small vessel occlusive disease. A cortical infarct in a patient with a known cardiogenic source such as atrial fibrillation usually is sufficient to diagnose a cardioembolic stroke. Carotid duplex ultrasonography is usually performed in all patients with ischemic stroke to determine if atherosclerotic disease at the carotid artery bifurcation is the cause, since carotid occlusive disease can produce both superficial or deep cerebral infarction (29). Magnetic resonance angiography (MRA) can also be performed (Fig. 3) (30). Transcranial Doppler can identify occlusive disease of large intracranial arteries (31).

Transthoracic echocardiography is employed to rule out a cardiogenic source for stroke. If the suspicion is high that the patient had a cardioembolic stroke and no obvious source is identified, transesophageal echocardiography is indicated to rule out thrombus in the atrium, right left shunts in the heart such as patent foramen ovale or atrial septal defect, and plaque in the arch of the aorta (32–34).

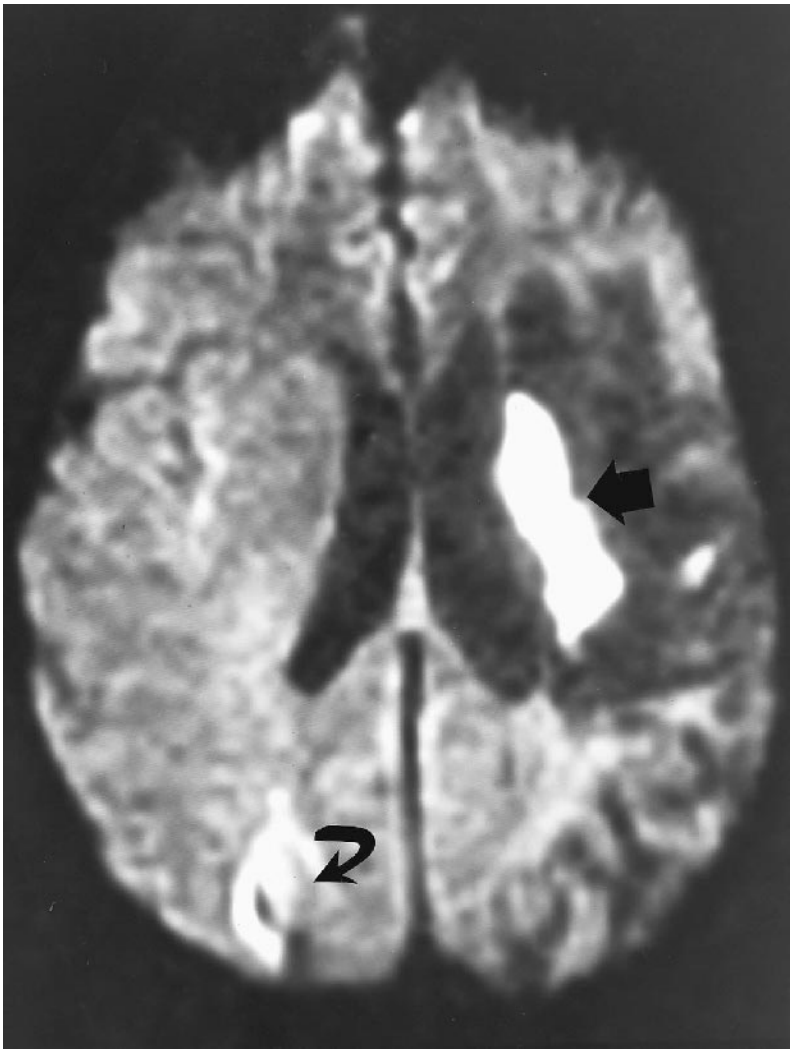

Figure 8 Diffusion weighted MRI. A diffusion weighted MRI sequence demonstrates an acute infarct in the region of a previous middle cerebral artery territory infarction (dark arrow) as well as an acute watershed type infarct in the right parietal region (curved arrow).

THERAPY OF ISCHEMIC STROKE

The management of ischemic stroke is summarized in Table 1.

Prevention of Ischemic Stroke

At the present time, therapy of ischemic stroke once it has already occurred is limited. The major goal for the management of cerebrovascular disease is prevention of stroke. Recent developments indicate that most strokes can be prevented, even if treatment is

Table 1 Management of Stroke

Stroke subtype	Etiology	Therapy
Ischemic		
1. Lacunar	Hypertension Diabetes	Control of hypertension and diabetes aspirin, ticlopidine, tPA
2. Cardioembolic	Atrial fibrillation Cardiac valve thrombi Cardiac valve replacement Occult (PFO, ASD)	heparin, warfarin, aspirin, tPA
3. Large vessel	Atherosclerotic	Extracranial—aspirin, ticlopidine, tPA, carotid endarterectomy Intracranial—aspirin, warfarin, tPA
Hemorrhagic		
1. Intracranial	Hypertension Amyloid angiopathy	Control of hypertension ?steroids, ?ventriculostomy ?removal
2. Subarachnoid	Aneurysm Arteriovenous malformation	Control of hypertension Nimodipine, malformation ?epsilonaminocaproic acid, aneurysm clipping, coils.

begun when the patient is already elderly, although early intervention is certainly preferable.

Control of Risk Factors

The modalities for prevention of occlusive cerebrovascular disease are similar to the strategies for prevention of coronary artery disease. Primary prevention is instituted in patients with the primary risk factors for cerebrovascular disease: hypertension, diabetes, atrial fibrillation, smoking, and elevated cholesterol. Secondary prevention is applied to patients who have had warning signs of occlusive cerebrovascular disease: auscultation of a cervical carotid artery bruit, transient ischemic attack lasting up to 24 h (TIA), transient monocular blindness (amaurosis fugax), reversible ischemic neurological deficits lasting over 24 h (RIND), or mild stroke from which the patient is not significantly disabled.

Hypertension is the most significant risk factor for stroke. While prevention of stroke is more effective if treatment is started when the patient is young, treatment of hypertension in the elderly, even isolated systolic hypertension, reduces the risk of stroke significantly (35). In coronary disease, some antihypertensive agents have been shown to have a greater protective effect than others, but in prevention of stroke all agents appear to be equally effective as long as there is an equivalent reduction in blood pressure (35).

Diabetes causes proliferation of the walls of small arteries in the deep structures of the brain, which can lead to thrombosis (36). Strict control of blood sugar can prevent similar vascular changes observed in the retina (37) and probably does so in the brain as well, although it has never been definitively documented that strict control of blood sugar prevents ischemic stroke. Control of blood sugar may lessen the severity when a stroke occurs, because hyperglycemia at the time of a stroke increases the extent of infarction from an equivalent vascular occlusion (38).

Serum lipids are not as significant a risk factor for stroke as they are for coronary heart disease, but reduction in serum cholesterol with the HMG coreductase inhibitors Simvistatin and Pravastatin for prevention of myocardial infarction also reduce the incidence of stroke in coronary patients by 33% (39,40). High dietary content of the antioxidants beta-carotene and vitamin E also have been shown to reduce the incidence of stroke, probably by prevention of the propagation of atherosclerosis (41,42).

MANAGEMENT OF PATIENTS WITH TRANSIENT ISCHEMIC ATTACK

Platelet Antiaggregant Therapy

Transient ischemic attacks are a warning sign of impending stroke. About 25 to 33% of patients with TIA go on to have a completed stroke (43) The incidence of stroke can be reduced by 50% in male patients with TIA treated with the platelet antiaggregant aspirin 650 mg twice a day (44). Significant reductions in stroke can also be achieved in women with TIA using aspirin therapy (45). Platelet antiaggregation can be achieved at lower doses of aspirin. Several studies have shown significant prevention of stroke with dosages ranging from 30 to 293 mg a day (46–48). However, a recent review of studies employing aspirin to prevent stroke in TIA patients determined that the risk of stroke was siginificantly lower with aspirin in dosages 975 mg to 1300 mg a day compared to dosages below 975 mg a day (49). Therefore, the current recommendation is to treat TIA patients with aspirin 975 mg a day, or the highest dosage that can be tolerated without gastrointestinal complaints at or above 325 mg a day (49).

Another platelet antiaggregant drug, ticlopidine, is available for patients who cannot tolerate aspirin because of gastrointestinal discomfort or prior history of ulcer disease. Ticlopidine is actually a stronger platelet antiaggregant than aspirin because it blocks the ADP receptor that is close to the final common pathway for platelet aggregation (50), while aspirin inhibits thromboxane synthesis by cyclooxygenase (51). Ticlopidine inhibits platelet aggregation from a greater number of stimuli in vitro than aspirin and prolongs the bleeding time in vivo to a greater extent (52).

In a trial comparing aspirin 650 mg twice a day to ticlopidine 250 mg twice a day in patients with TIA, ticlopidine conferred a 48% risk reduction of stroke after 1 year and 25% after 5 years compared to therapy with aspirin. Subgroup analysis revealed that both were equally effective in treating patients with carotid disease and TIA while ticlopidine had an advantage over aspirin in women, African Americans, and in prevention of lacunar type stroke from small vessel disease (52,53).

Ticlopidine bears a risk of hematological abnormalities. Significant neutropenia less than 800 cells/mm^3 occurs in 2% of patients treated with ticlopidine (52). Thrombocytopenia and hepatitis can occur in a smaller number of patients. Almost all complications occur within the first 3 months of therapy and are almost always reversible by stopping the drug. Patient monitoring must be performed every 2 weeks for the first 3 months and the drug discontinued if abnormalities develop. In general, aspirin is still used initially in the medical therapy of patients with TIA and ticlopidine is used in patients who continue to have TIA despite aspirin therapy or in patients who cannot tolerate the drug (52).

Dipyridamole prevents platelet aggregation by inhibiting the enzyme phosphodiesterase (54). In previous studies, dipyridamole has not been effective alone in preventing stroke in patients with TIA (55) and did not appear to have an additive protective effect

in combination with aspirin compared to aspirin alone (56). However, in the recent European Stroke Prevention Study, a time-release preparation of dipyridamole 400 mg was shown to have an equal effect to aspirin 50 mg a day in reducing the relative risk of stroke 18% compared to placebo, and had an additive effect when combined with aspirin 50 mg a day, reducing the relative risk of stroke 37% compared to placebo and 22% compared to aspirin 50 mg alone. Therefore, a combination of low-dose aspirin and high-dose dipyridamole may be adequate for TIA patients who cannot tolerate a higher dose of aspirin (57). Another new platelet antiaggregant agent, clopidegril, can also be used.

Maintenance aspirin therapy has been shown to be effective in prevention of myocardial infarction in asymptomatic elderly patients (58) and low-dose aspirin is commonly taken by the elderly on a daily basis. No definite similar reduction in the incidence of stroke in the well elderly patient has been documented with chronic maintenance aspirin therapy (59).

Carotid Artery Disease

Occlusive atherosclerotic disease at the carotid artery bifurcation is found in 50% of patients with TIA (43). In patients with TIA and less than 40% stenosis, carotid endarterectomy has been shown to be of no benefit compared to aspirin therapy 650 mg twice a day for prevention of stroke (60). A final resolution has not yet been determined for patients with 40 to 69% stenosis (60). For patients with 70% or greater stenosis of the internal carotid artery at the bifurcation ipsilateral to a TIA, surgical therapy has been shown to provide a 20% reduction in the incidence of subsequent stroke compared to medical therapy with aspirin in a center where the risk of the procedure itself is 2% or less (60).

Patients presenting with TIA are initially screened with ultrasonographic examination of the carotid bifurcation employing duplex sonography. The bifurcation is imaged with B-mode sonography to visualize atheroslcerotic plaque (61). The degree of stenosis is determined by Doppler sonography, which measures the velocity of the red cells flowing through the artery by the change in frequency shift of the ultrasound as it reflects back from the red cells as they go by (62). The velocity is increased as the lumen diameter narrows. Identification of stenosis greater than 70% can be obtained with about 95% accuracy compared to angiography (62).

If a stenosis of 70% or greater is established by duplex sonography, or if the results of the testing are not definitive, magnetic resonance angiography is performed to document the degree of stenosis (30). Magnetic resonance angiography also has an accuracy of 95% compared to angiography (30). When the results of the two studies agree, the accuracy is 99% (30). Performing these two noninvasive studies can avoid the risk of angiography, which can be as high as a 1% incidence of stroke, myocardial infarction, or death in patients with cerebrovascular disease (63). When the two studies do not agree, angiography is usually performed to determine if there is a greater than 70% stenosis or to be certain that there is not an inoperable complete occlusion of the internal carotid. Once the imaging procedures have documented a greater than 70% stenosis, the patient is usually treated with carotid endarterectomy unless there are outweighing medical contraindications to performing the surgery.

The management of asymptomatic carotid artery stenosis remains controversial. The Asymptomatic Carotid Atherosclerosis Study (ACAS) documented a significant benefit of carotid endarterectomy compared to medical therapy with aspirin 650 mg bid in patients with greater than 60% stenosis of the internal carotid artery (64). However, the difference

was small, with a 10% risk of stroke in the medical group compared to a 5% risk of stroke in the surgical group over a 5-year follow-up period. Furthermore, the results did not diverge until the fifth year of follow-up. This has implications for elderly patients, because an immediate risk of complication of carotid surgery may outweigh a risk of stroke 5 years in the future, if the life expectancy of the patient is diminished by other illnesses.

Several studies have indicated that acute proliferation of plaque with hemorrhagic changes and plaque growth are implicated in the etiology of thromboembolic events causing stroke from the carotid bifurcation (65–67). Since the overall incidence of stroke is low in asymptomatic patients, endarterectomy after the initial identification of asymptomatic carotid stenosis is usually reserved for patients with a very high-grade lesion or a plaque with large amounts of heterogeneous lucencies, suggestive of recent thrombus (66,67). The remaining patients can be followed with sequential duplex Doppler examinations every 6 months and endarterectomy performed if a progressive stenosis is identified (67,68) or if the patient becomes symptomatic with a TIA.

Prevention of Cardioembolic Stroke

The major risk factor for cardioembolic stroke in the elderly is nonvalvular atrial fibrillation (8). Patients under 70 years old with atrial fibrillation but no other associated heart disease can be managed with aspirin to effectively prevent stroke (69–72). In elderly patients over 70, all clinical trials for stroke prevention in patients with atrial fibrillation have shown that aspirin is ineffective in preventing embolic stroke due to atrial fibrillation and anticoagulation with warfarin had a significant protective effect (69,70,73–75). In the Stroke Prevention in Atrial Fibrillation Trial (SPAF), the risk of hemorrhagic stroke and other hemorrhagic complications in the elderly over 75 equaled the risk reduction of cardioembolic stroke induced by warfarin compared to aspirin (70). The degree of anticoagulation in the SPAF trial as measured by the INR was higher than in the other trials of warfarin to prevent stroke in atrial fibrillation, in which a significant reduction in the number of ischemic strokes and poor outcomes was demonstrated (73–75). Therefore, the current recommendation is to treat elderly patients over 75 who have atrial fibrillation with warfarin for stroke prophylaxis, keeping the INR between 2.0 and 2.9, with a target of 2.5.

Patients with mechanical cardiac valve replacements are generally treated with warfarin for prevention of embolic stroke with the INR maintained from 3.0 to 3.5 (76). Anticoagulation with warfarin has also been beneficial in preventing stroke during the first 3 months after myocardial infarction (77), although aspirin is usually used for long-term prophylaxis.

Atherosclerotic plaque in the ascending aorta and aortic arch has also been implicated as a potential source of cardioembolic stroke (33). When these plaques are identified as an incidental finding with transesophageal echocardiography performed for cardiac disease, stroke prophylaxis should be instituted, although it has not been documented whether aspirin therapy is sufficient or anticoagulation with warfarin is necessary.

Multi-Infarct Dementia

Elderly patients being evaluated for dementia are often found to have small infarcts or ischemic changes on images of the brain with MRI and CAT scan (Fig. 5) (78). Hypertensive patients have small lacunar infarcts in the deep structures, which may not be causing

any focal neurological deficits such as hemiparesis but may cause or contribute to cognitive decline. Patients with atrial fibrillation or other cardioembolic sources of stroke may have silent infarcts that cause cognitive deficits without focal signs. Patients with a history of stroke and mild focal neurological deficits may still have cognitive disturbances. When ischemia is identified as a contributor to the dementia, identification of stroke risk factors and vascular pathology is made and appropriate antithrombotic therapy is instituted.

Treatment of Acute Ischemic Stroke

There are four objectives in the treatment of the acute stroke patient: (1) diagnosis and prevention of medical complications that could be life threatening; (2) prevention of progression of the current stroke; (3) prevention of recurrent stroke; and (4) reversal of the symptoms of the current stroke.

Medical Complications

The major medical complications associated with stroke are myocardial infarction, pulmonary emboli, aspiration pneumonia, and airway obstruction or reduction in level of consciousness that compromises respiration. Electrocardiogram is imperative to rule out a concurrent myocardial infarction and if there is any suggestive history, serial enzymes are obtained. Stroke units with monitored beds are useful in detecting and preventing complications of arrhythmia that could occur with concomitant myocardial infarction or as the result of the stroke itself. While echocardiographic changes of ST segment depression, U waves, and ventricular fibrillation are more common with hemorrhagic strokes, they can occur with large infarctions severe enough to produce release of catecholamines that can injure the endocardium (79).

Patients who are immobilized from their strokes are treated with low-dose subcutaneous heparin 5000 U bid to prevent thrombophlebitis. If there is a substantial risk of bleeding, pressurized air boots can be used instead of low-dose anticoagulation. If there is airway obstruction or obtundation interfering with respiration, prophylactic endotracheal intubation is sometimes initiated, although observation of the oxygen saturation with a pulse oximeter may be sufficient to determine when a patient is becoming hypoxic and intubation is necessary. Patients are generally not fed when there is any obtundation or difficulty swallowing, usually for a period of 48 h. However, if there is prolonged inability to swallow, a nasogastric tube or percutaneous gastric tube must be inserted to maintain nutrition for better recovery of the stroke patient.

Prevention of Progression

Prevention of progression of stroke is attained by careful monitoring of the patient. The blood pressure must be maintained at a sufficient level to insure perfusion of the ischemic penumbra, the region of brain around the core area of infarction that is ischemic but not irreversibly damaged. Most stroke patients have an elevation of the blood pressure for the first 48 h—a response to the event—which resolves without treatment (80). If the blood pressure rises to a critical level over 200/120, moderate reduction with intravenous labetalol or oral but not sublingual calcium channel blockers such as nifedipine are employed to bring the pressure to the 180/100 range. Drastic reduction in blood pressure with agents such as nitroprusside can cause severe worsening of the stroke.

Progression of stroke can occur in both large vessel occlusive disease and in lacunar or small vessel occlusive disease. Acute intravenous anticoagulation with heparin or the

low-molecular-weigh heparanoid Orgaron has not been effective in improving outcome in controlled clinical trials (81,82) although subcutaneous administration of low-molecular-weight heparin has shown significant beneficial outcome for stroke patients in one trial (83). Therefore, it is generally not necessary to anticoagulate all stroke patients acutely.

Patients with large vessel occlusive disease who show signs of evolving stroke may benefit from anticoagulation with heparin (84,85), particularly when there is brainstem infarction (86). However, the evolution of infarction must be in the degree of extent of focal neurological findings, such as a worsening of limb weakness or new deficits such as a new abducens nerve paresis in a patient who already has other signs of brainstem stroke. Decline in the level of consciousness of the patient without new focal deficits is common, particularly in patients with middle cerebral artery occlusion from cardioembolic stroke, who develop cerebral edema associated with reprefusion. In this instance, anticoagulation can be associated with adverse outcome due to hemorrhagic transformation of the infarction and anticoagulation should not be administered. Anticoagulation should be employed judiciously in elderly patients over 80 who have a higher risk of hemorrhagic complications.

With mass lesions of the brain, corticosteroid medications such as Decadron and osmotic diuretics such as Mannitol are useful in reducing the amount of vasogenic edema surrounding the lesion. Administration of corticosteroids to all stroke patients acutely has been shown to be of no benefit and may actually be deleterious to the patient's outcome (87). In patients with reperfusion, vasogenic edema can develop, which responds to corticosteroids and osmotic agents (88). These agents can have adverse consequences for stroke patients, because the hyperglycemia associated with corticosteroids may cause exacerbation of infarction (37) and the dehydration associated with osmotic diuretics may cause reduced perfusion in the ischemic zone. When the patient is in danger of brain herniation, Decadron 10 mg i.v. acutely and 4 mg every 6 h can be administered for several days until the edema abates and the patient becomes less obtunded. Mannitol 1000 g i.v. over 1 h can be administered when herniation is imminent, particularly in cases of hyperperfusion with infarction following carotid endarterectomy (89).

In some instances, brainstem stroke that is likely to progress can be diagnosed clinically when a pontine infarct is located rostral to the facial nucleus, with ipsilateral face, arm, and leg weakness (90). This lesion usually involves the ventral anterior pons, where the pyramidal tracts carrying motor fibers from each cerebral hemisphere are located contiguously, and spread of infarction to both sides can result in the locked-in state, where there is quadraparesis and inability to speak, but the patient remains fully conscious. This type of stroke is often associated with basilar artery occlusion and identification and early heparinization of these types of patients may be beneficial in preventing worsening of the ischemic infarction. Carotid and transcranial ultrasound studies are performed on acute stroke patients to identify large-vessel occlusive disease in the carotid or vertebrobasilar circulation, because these patients may benefit from early anticoagulation with low-molecular-weight heparin, although this has not been definitively established (82).

Prevention of Recurrence

Prevention of recurrent stroke is particularly important in patients with a cardioembolic source of stroke such as atrial fibrillation or cardiac valve replacement to prevent further embolization from the heart (91). Cardioembolic stroke almost always causes red infarction, with petechial hemorrhage or hemorrhagic transformation of the infarct when reperfusion occurs with regression of the embolic clot, usually between 24 to 48 h after

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the acute event. Early anticoagulation with heparin can lead to increased size of the hemorrhagic transformation with associated worsening of the neurological condition as well as coma and death from brain herniation. This is particularly applicable to elderly patients, as the risk of major hemorrhagic transformation increases with age (92,93).

In several studies, it has been determined that the risk of reembolization in patients with atrial fibrillation is about 2%, while the risk of major hemorrhagic transformation resulting in clinical deterioration is about 8% in the first 48 h after stroke (91–93). Early anticoagulation of stroke patients with atrial fibrillation with heparin or the low-molecular-weight heparinoid Orgaron showed no benefit compared to placebo (82,94). Therefore, in patients with atrial fibrillation, anticoagulation is usually held for the first 48 h, a CAT scan of the brain is repeated, and anticoagulation is initiated if the infarct is not very large and there is no hemorrhagic transformation. In the patients who do have large infarction or hemorrhagic transformation, it is usually safe to anticoagulate from 96 h to 1 week following the acute stroke (95). A small area of infarction on the initial CAT scan does not indicate that it is safe to anticoagulate acutely because the full extent of the lesion may not be detected until up to 48 h after the initial event with CT. MRI, particularly with the diffusion technique, is more sensitive in identifying the full extent of early infarction, and when the region of ischemic brain on these studies is small, early anticoagulation can be instituted.

Early anticoagulation is also necessary in patients with prosthetic cardiac valves who break through with stroke because the risk of early reembolization is greater, particularly when noninfectious vegetations are seen on the prosthesis with echocardiography. However, bacterial endocarditis must be ruled out in these instances prior to anticoagulation because mycotic aneurysms can form from infected emboli and can cause hemorrhage when the patient is anticoagulated (96).

Long-term anticoagulation with warfarin can be started at the same time as acute anticoagulation with heparin to shorten the length of hospital stay. A loading dose of 10 mg per day for 2 days is started and subsequent doses are titrated to the prothrombin time. As in patients with progressive stroke, anticoagulation should be performed judiciously in elderly patients over 80 because of a higher risk of hemorrhagic complications.

The International Stroke Trial demonstrated a beneficial effect of aspirin 300 mg orally given at the time of onset of ischeimc stroke when outcome was analyzed after 3 months. A 10% reduction in poor outcomes was obtained, primarily from prevention of recurrent stroke. Subcutaneous heparin administration up to 12,500 U bid had an equal reduction in poor outcome from ischemic strokes, but this reduction in poor outcomes was equaled by adverse hemorrhagic events associated with anticoagulation (97).

Reversal of Stroke Symptoms

Administration of the thrombolysin tissue plasminogen activator (tPA) intravenously at a dosage of 0.9 mg/kg over 1 h with 10% given by bolus within 3 h after the onset of stroke increases the number of patients with a good outcome from stroke after 3 months, as measured by a functional scale from 21% in control patients to 31% in treated patients (98). There is an immediate improvement in 14% of the stroke patients administered tPA acutely, but there is a 3.6% rate of cerebral hemorrhage causing death, so that the overall difference within the first 24 h between control and treated patients was not significant. However, after 3 months, the overall mortality rate is equal in treated and untreated patients, suggesting that the patients with the most severe strokes are dying acutely with hemorrhagic complications of tPA, but are succumbing over the subsequent 3 months to

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the medical complications associated with severe stroke. Administration of tPA to patients more than 3 h after ischemic stroke or to patients who have early changes of infarction on CAT scan of the brain by the time they are ready for treatment leads to an unacceptable degree of hemorrhagic complications and should be avoided (99). Administration of streptokinase has been associated with an unacceptable risk of hemorrhage and is not employed in the treatment of ischemic stroke (100).

tPA or urokinase can also be administered directly by intra-arterial catheterization directly to the site of the occluded vessel under angiographic control (101–103). Studies are still underway to determine the efficacy and applicability of these techniques, but they may prove to be safer than systemic intravenous administration. The clinical improvement with administration of tPA to appropriate ischemic stroke patients is a major breakthrough in the medical management of stroke.

Another strategy for treatment of stroke is the use of neuroprotective agents. Ischemia induces release of excitotoxic neurotransmitters, particularly glutamic acid. In the setting of ischemia, glutamate causes neuronal death by stimulation of the N-methyl-d-aspartate receptor (NMDA), which allows lethal amounts of calcium to enter the neuron. In experimental animal models, administration of NMDA receptor antagonists protects neurons in the border zone of the infarct from ischemic necrosis, reducing the infarct volume and improving functional recovery of the animal from the ischemic insult (Fig. 9) (104). Several NMDA receptor antagonists are being examined in controlled treatment trials of ischemic stroke, but so far no significant improvement in outcome of stroke patients with these agents has been documented (105). Future studies may include reperfusion of the ischemic zone by administration of thrombolytic agents followed by administration of neuroprotective agents to prevent ischemic neuronal death.

The relative success of immediate treatment of stroke with tPA within 3 h after onset has altered the attitude about the management of stroke. Stroke now has to be considered an emergency just like heart attack and is now referred to as brain attack. Early recognition of stroke and emergency transport to a hospital facility capable of acute management of stroke has become imperative.

Management of Hemorrhagic Stroke

There are two types of hemorrhagic stroke, intracranial and subarachnoid. Intracranial hemorrhage usually commences with severe headache and progressive focal neurological deficit, often leading to obtundation. Most intracranial hemorrhage is due to hypertension and involves the deep structures of the brain around the basal ganglia and internal capsule (Fig. 6) (22). Hemorrhage into a more superficial lobe in the brain is more common in elderly patients than younger patients, in part due to amyloid angiopathy of the cerebral arteries (Fig. 7) (24). Medical therapy of hemorrhage consists primarily of reduction in blood pressure in hypertensive patients and supportive care. Endotracheal intubation may be necessary for airway protection and for impending brain herniation with respiratory failure. Hyperventilation may be helpful to reduce increased intracranial pressure. The osmotic diuretic Mannitol can be administered at a dosage of 100 g intravenously to reduce cerebral edema acutely in cases of impending herniation. There is no evidence that steroid medications are of any benefit in improving the outcome of patients with intracranial hemorrhage (106), but they are still commonly employed for the individual case where reduction of cerebral edema may be helpful. Decadron 10 mg i.v. acutely followed by 4

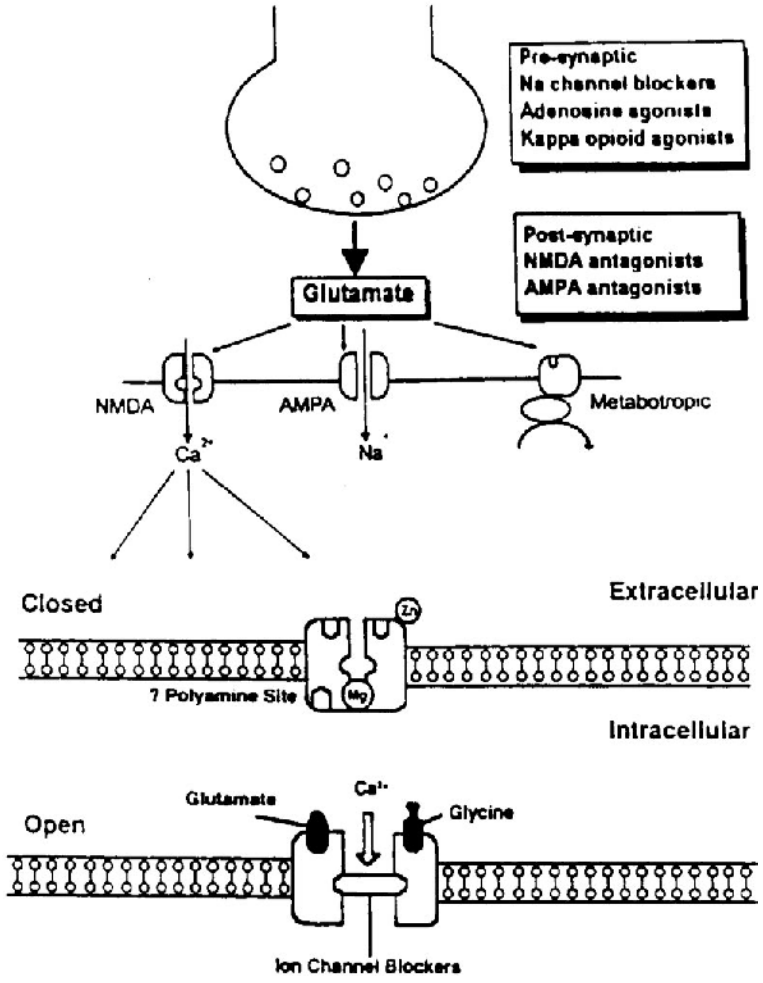

Figure 9 The ischemic cascade induced by release of the excitatory amino acids, glutamate, and aspartate which stimulate the NMDA and AMPA receptors is diagrammed. Experimental therapeutic strategies include inhibition of release of the excitatory neurotransmitters (lamotrigine, riluzole), inhibition of sodium influx from stimulation of the AMPA receptor (APV, NBQX), and inhibition of calcium influx from stimulation of the NMDA receptor (aptigenel, dextrorphan, memantine, selfatel, polyamines). (From Ref. 105.)

mg every 6 h is often used. Care must be taken to control blood sugar and prevent gastrointestinal hemorrhage when administering steroid medications.

Surgical management of intracranial hemorrhage is employed in certain instances. Shunting of fluid and removal of blood from the ventricular system can reduce intracranial pressure when there is hydrocephalus. Deep hemorrhages are usually not benefited by surgical intervention, but occasionally improvement can be obtained with removal of lobar hemorrhage. The one instance in which surgical management is generally utilized is cerebellar hemorrhage, where drainage of the hematoma can be performed without inordinate risk to prevent compression of the brainstem and death. Cerebellar hemorrhage usually

presents initially with dizziness and loss of balance along with headache, with progression of focal symptoms leading to somnolence and coma. Early recognition of this condition can improve the outcome considerably with surgery.

Subarachnoid Hemorrhage

The major intracranial vessels are located in the subarachnoid space between the pia mater and dura mater covering the brain. Aneurysms form primarily at branch points from the vessels of the Circle of Willis at the base of the brain. Rupture of these aneurysms produces severe headache, photophobia, and stiff neck. The patient may become somnolent or lapse into coma. A third nerve paralysis with ptosis, pupillary dilation, and ophthalmoplegia can result when hematoma forms on the oculomotor nerve running just below the Circle of Willis. Focal neurological disturbances such as hemiparesis can also result acutely. Patients with mild-to-moderate deficits have a better prognosis than patients with focal neurological deficit or stupor. The aneurysm is identified by cerebral angiography.

The optimum care is surgical clipping of the aneurysm within the first 24 h after hemorrhage in patients with mild-to-moderate deficits to prevent rebleeding. Surgical management after 24 h is dangerous because of increased ischemic complications because of vasospasm, and if surgery cannot be performed within the first 24 h, it is usually deferred for up to 14 days (107). The ischemic consequences of spasm can be reduced by administration of the calcium channel blocker Nimodipine 60 mg p.o. every 6 h (108,109). In some centers, the antifibrinolysin epsilon amino caproic acid is administered to prevent rebleeding when surgical therapy cannot be performed immediately, but is associated with an increase in ischemic complications (110). Spasm can be detected by measurement of increased flow velocities with transcranial Doppler techniques, which is often employed to monitor patients for the onset of spasm after subarachnoid hemorrhage. When spasm occurs postoperatively, the blood pressure can be elevated to increase cerebral perfusion. Angioplasty can also be performed to dilate vessels when spasm is severe and causing hemiparesis or stupor (111). When an aneurysm is inoperable, intravascular placement of coils under radiological guidance can be employed to thrombose the aneurysm. In the case of aneurysms located in areas not accessible to surgery, coils can be placed to occlude the lumen of the aneurysm (112).

Arteriovenous malformations (AVM) of the brain, in which arteries feed directly into the venous system without going through a capillary bed, can also be a cause of subarachnoid hemorrhage. Surgical extirpation can be performed to eliminate the source of the bleeding, but often the AVM can recur or too much brain parenchyma is at risk for resection to be feasible (113). Embolization of colloidal particles into the AVM to occlude it and/or radiosurgery with a gamma-knife can be performed to eliminate or reduce the volume of inoperable AVMs (114).

CONCLUSION

New developments in the understanding of the pathophysiology of stroke and imaging technology for identifying the cause of stroke have dramatically changed the management of cerebrovascular disease. While the main focus remains prevention, new treatments with thrombolysis have changed the concept of stroke from a hopeless condition to a treatable disease. Future developments with neuroprotective agents hold the promise for further

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advancements in the treatment of stroke. The treatment of stroke as an acute emergency, a brain attack, has introduced a new era in the management of stroke which can markedly alter the course of this disease in the elderly.

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6

Hypertension and Left Ventricular Hypertrophy in the Elderly

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Although arterial pressure is known to increase with age in westernized populations, it is a misconception to consider that an elevated pressure is a ''normal'' finding in the elderly and that it is a physiological compensatory response serving to restore or maintain adequate blood flow to aging vital organs. In addition, systolic hypertension, which predominates in the elderly, as well as diastolic hypertension, are harbingers of myocardial infarction (MI), cerebral vascular accident (CVA), and death in the elderly population.

Distinguishing between these two pathogenetic factors, age and hypertension, are important but difficult in the elderly population. On one side, progressive aging per se affects the cardiovascular system and can result in age-specific changes; on the other side, the cardiovascular system of an elderly patient with hypertension has been exposed to long-standing elevations in arterial pressure that by itself damages various organ systems, particularly the heart.

In this chapter, we try to distinguish between these two pathogenetic factors, age and hypertension, and we review the epidemiology and pathophysiology of hypertension in the elderly, including the effects of hemodynamics (including intravascular volume), the neuroendocrine system, renal adaptation, arterial compliance, and, particularly, cardiac adaptation and left ventricular hypertrophy (LVH). We also review the various agents available to treat hypertension in the elderly, including their proven and theoretical efficacy, effects on prevention and reduction of LVH, and effects on major cardiovascular morbid events.

EPIDEMIOLOGY

Since arterial pressure increases with age in most westernized populations, each year an increasing number of elderly patients fulfill arbitrarily set criteria for hypertension. In some studies in the U.S., the prevalence of hypertension may reach 50% in

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the elderly (1,2). Since life expectancy continues to increase, some statistics suggest that the prevalence of hypertension in the elderly may soon reach over 25 million individuals (3).

Although the prevalence of hypertension is extremely high in the elderly, numerous epidemiological studies have demonstrated that this condition is not benign, but is associated with an extremely high prevalence (63% over 5 years in one study) (4) of morbid cardiovascular events, including CVA, congestive heart failure (CHF), MI, and dissecting aneurysm, which have been noted in elderly with diastolic as well as pure systolic hypertension (5–9). Although some of the earlier treatment trials of hypertension in the elderly failed to provide clear evidence of protection from these major cardiovascular events, recent large trials, including the European Working Party for Hypertension in the Elderly (10), the Systolic Hypertension in the Elderly Programs (SHEP) (11), the Swedish Trial in Old Patients with Hypertension (STOP) study (12), and the Systolic Hypertension in Europe (SYST-EUR) Trial (13) have recently demonstrated distinct improvements in morbidity and mortality in elderly patients receiving antihypertensive therapy.

PATHOPHYSIOLOGY

Hemodynamics

In an attempt to untangle the two pathogenetic factors, age and hypertension, Messerli and colleagues 15 years ago matched 30 older patients with essential hypertension to an equal number of patients younger than age 42 with regard to mean arterial pressure, race, and gender, and they assessed cardiovascular hemodynamics, fluid volume, and endocrine aspects in these two groups, which had an average age difference of more than 40 years (14,15). At a similar level of mean arterial pressure, systolic pressure was considerably higher and diastolic pressure considerably lower in the elderly compared with the younger patients (Fig. 1), suggesting that the elderly have decreased arterial compliance. In contrast to the younger patients with borderline and early established essential hypertension, in whom cardiac output is often elevated, the elderly patient is characterized by a low cardiac output (Figs. 2, 3) (14–16) secondary to decreased stoke volume and relative bradycardia, and the elderly have considerably higher peripheral vascular resistance than do younger patients with similar mean arterial pressures (Fig. 4) (14–16).

Lund-Johansen performed a long-term follow-up study in mildly hypertensive patients who were left untreated for as long as 17 years, and he documented a distinct fall in cardiac output, mostly because of a reduction in stroke volume and an increase in total peripheral resistance, both during rest and after treadmill exercise (17). To a lesser extent, a fall in cardiac output with age has been observed in normotensive patients (18–20). However, a recent report from the Baltimore Longitudinal Study indicates that normotensive elderly who were free of both hypertension and coronary artery disease (CAD) demonstrated no decline in cardiac output with age either at rest or during exercise (21,22). However, whereas young patients tend to respond to exercise with a catecholamine-mediated increase in heart rate and a reduction in end-systolic volume, older patients compensated for their relatively blunted heart rate response to exercise with an increase in stroke volume (via the Frank-Starling mechanism) (22).

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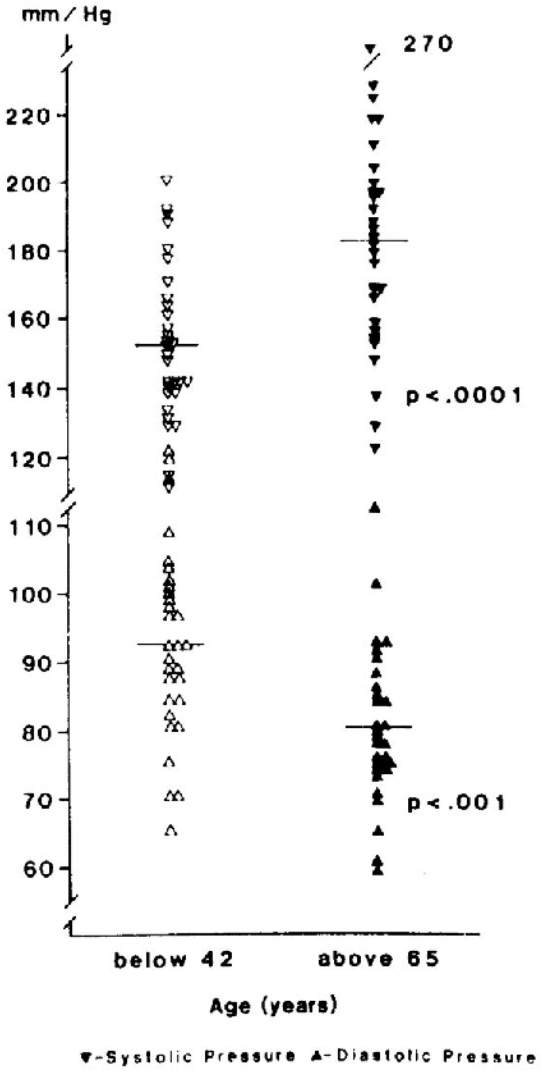

Figure 1 Systolic pressure was found to be higher and diastolic pressure to be lower in elderly hypertensive patients than in younger patients having similar levels of mean arterial pressure. Thus systolic hypertension merely reflects decreased arterial compliance. (Reproduced from Ref. 15.)

Autonomic Nervous System

Both reactivity of the baroreceptor reflex and chemoreceptor reflexes become blunted with progressive age, although the exact underlying mechanism remains unclear. Since hypertension impairs baroreceptor function, its presence will accelerate the deteriorating effects of aging. As a consequence, elderly hypertensive patients become predisposed to orthostatic hypotension and syncope, a propensity that can be unmasked by the leading antihypertensive therapy in the elderly—diuretics (23). In fact, Shannon et al. demon-

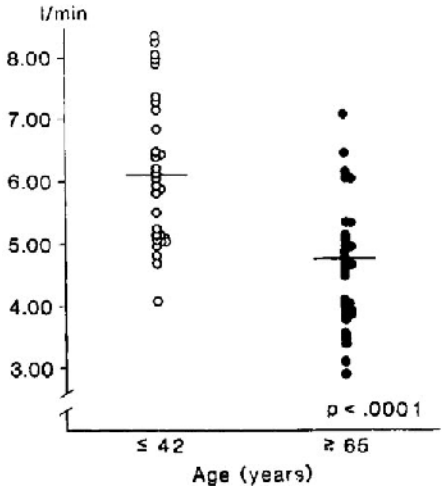

Figure 2 Cardiac output was found to be lower in elderly hypertensive patients when compared with younger patients having similar levels of arterial pressure. (Reproduced from Messerli FH. Hypertension Update II Symposium, Health Learning Systems, Washington, DC, 1985.)

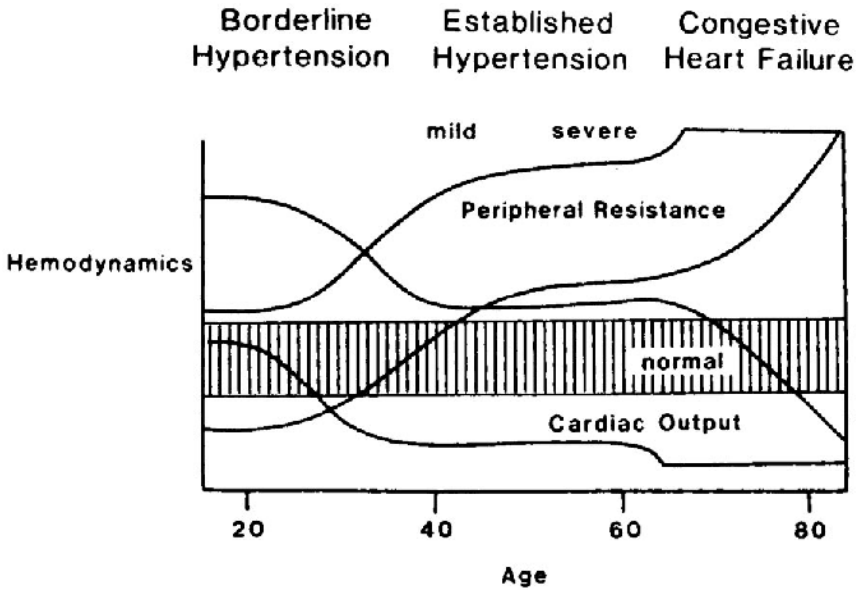

Figure 3 Hemodynamic change with age and as hypertension becomes more severe. The young patient is characterized by an elevated cardiac output and a normal total peripheral resistance. As hypertension becomes established, cardiac output reverts to normal and resistance becomes elevated. In the elderly and in the patient with congestive heart failure, cardiac output declines and total peripheral resistance becomes even more elevated. (Reproduced from Ref. 16.)

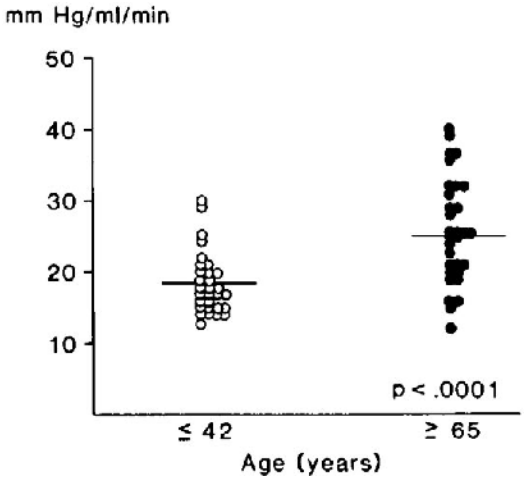

Figure 4 Total peripheral resistance was found to be elevated in elderly hypertensive patients when compared with younger patients having similar levels of mean arterial pressure. (Reproduced from Ref. 15.)

strated a >20-mmHg drop in systolic blood pressure during upright tilt testing associated with orthostatic hypotensive symptoms in elderly patients treated with diuretic therapy, whereas no change in orthostatic blood pressure was noted in younger subjects receiving the same doses of diuretic therapy.

Endocrine

Numerous studies have demonstrated that plasma renin activity decreases with advancing age, particularly in the hypertensive population (24). In younger and older patients matched for mean arterial pressure, we demonstrated that plasma renin activity was two to three times higher in the younger patients (Fig. 5) (14,15). This inverse relationship between plasma renin activity and age has been attributed to progressive sclerosis of the juxta glomerular apparatus, which would impair both basal renin secretion as well as the response to stimulation.

In contrast to plasma renin activity, circulating levels of catecholamines (e.g., norepinephrine) have been shown to increase progressively with advancing age, more so in normotensive than in hypertensive patients (19,24–27). Clinical and experimental evidence indicates that the responsiveness of the beta-adrenoreceptors diminishes with age in ways not associated with changes in beta-adrenoreceptor density (28). In asymptomatic, mildly hypertensive elderly patients, elevated norepinephrine values may reflect a mechanism to compensate for the relative insensitivity of the beta-adrenoreceptor. The effects of aging on sensitivity of alpha-adrenoreceptors is presently less clear.

Renal Adaptation

Although renal blood flow progressively declines with age in normotensive subjects, this decline is considerably more prominent in elderly with essential hypertension. Although

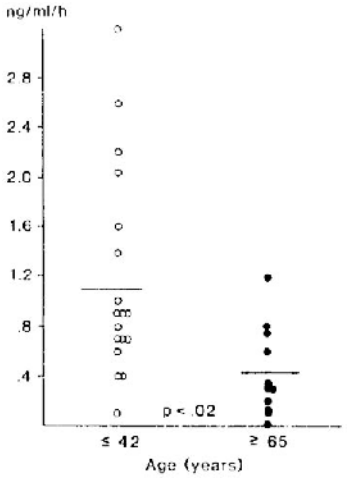

Figure 5 Plasma renin activity (ng/mL/h, after 1 h of recumbency and free sodium intake) was found to be lower in elderly hypertensive patients when compared with younger patients with similar levels of mean arterial pressure. (Reproduced from Ref. 15.)

cardiac output, as discussed above, also declines with age, the fall in renal blood flow is out of proportion (50% greater) to the fall in cardiac output. In our study of younger and older patients matched for mean arterial blood pressure, renal blood flow was 40% lower in the elderly patients (14,15,24). Not surprisingly, renal vascular resistance was distinctly elevated in elderly hypertensive patients, reflecting diffuse nephrosclerosis resulting from long-standing hypertension. Although glomerular filtration rate usually remains well preserved throughout life and only falls after age 65 years, a decline in renal blood flow has been shown to occur fairly early in mild essential hypertension (29,30), and this should be suspected when an otherwise unexplained increase in plasma uric acid occurs. Therefore, both renal vascular resistance and filtration fraction become elevated in the early phase of hypertensive renal involvement (30).

Obviously, long-standing hypertension contributes to significant renal dysfunction, characterized by marked reductions in glomerular filtration rate, creatinine clearance, and elevated levels of serum creatinine in elderly hypertensive patients. Studies have demonstrated that the major risk factors for progressive renal dysfunction are age, hypertension, diabetes, and black race (31). Therefore, diabetes and hypertension, which both increase dramatically with age, contribute to the high prevalence of renal failure in elderly hypertensives. Since the prevalence of hypertension and diabetes are increased in blacks compared to whites, renal failure is particularly a problem in elderly, diabetic, black hypertensives, although race seems to be an independent risk factor for renal dysfunction as well.

In addition, the higher prevalence of macrovascular atherosclerosis in elderly hypertensives makes renal arterial disease and renovascular hypertension more prevalent in this population. Renovascular hypertension should be strongly suspected in elderly patients who develop significantly high blood pressure de novo or marked worsening in previously controlled hypertension. In the past, evaluating elderly patients for renovascular hypertension was often unfulfilling since surgical correction was not always beneficial and was associated with considerable morbidity. In addition, although transluminal angioplasty

was helpful in selected patients, those with atherosclerotic lesions, which are extremely common in the elderly, usually were not as successfully treated as are those with fibromuscular dysplasia (uncommon in the elderly). However, recently my colleagues at Ochsner Clinic and elsewhere have published excellent short- and long-term results of renal arterial stenting for control of blood pressure as well as improving or stabilizing renal function in large cohorts of mostly elderly patients (32–34).

Intravascular Volume

In normotensive older subjects, intravascular volume remains relatively stable with aging (35). However, we have previously demonstrated that elderly hypertensives have considerably lower intravascular volume in comparison to younger hypertensives who were matched for mean arterial pressure (Fig. 6) (14,15,24). Despite the fact that plasma renin activity is often lower and relatively unresponsive in the elderly hypertensives, which normally would reflect a volume-dependent state, hypertension in the elderly does not appear to be volume dependent compared to younger patients. In both older and younger hypertensives, there is an inverse relationship between intravascular volume and total peripheral resistance. Elderly hypertensive patients with increased vascular resistance and low circulating intravascular volume are therefore susceptible to orthostatic hypotension.

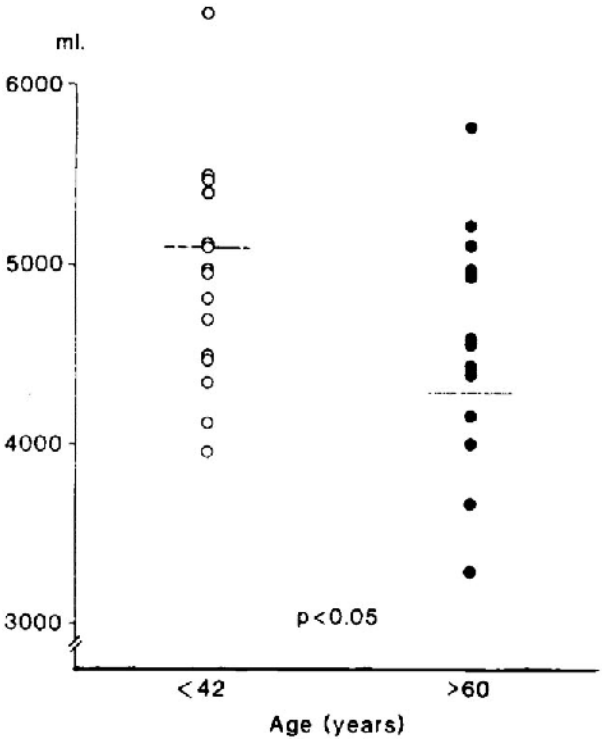

Figure 6 Total blood volume was found to be contracted in elderly hypertensive patients when compared with younger patients having similar levels of mean arterial pressure. (Reproduced from Ref. 15.)

As reviewed above, although diuretic therapy has been the mainstay for treating hypertension in the elderly, this therapy may further reduce intravascular volume, which is already relatively contracted in the elderly, thereby increasing the risk of symptomatic orthostatic presyncope and syncope (23).

Arterial Compliance

When a given stroke volume is ejected into an arterial system that has been stiffened by reduced elasticity, a higher systolic pressure and a lower diastolic pressure will result. As illustrated previously in Figure 1, this is the typical scenario in elderly hypertensive patients. With the decrease in arterial compliance with age, which is the result of progressive atherosclerotic process, medial hypertrophy, and reduced aortic elasticity, systolic hypertension becomes a particular problem in the elderly population. Although initially systolic hypertension was considered a relatively benign disorder, elevated systolic pressure clearly increases left ventricular wall stress and thus remains a potent determinant of hypertensive heart disease and other morbid cardiovascular sequelae in the elderly (11).

Because of reduced arterial compliance in the elderly, Spence et al. (36) reported that cuff pressure did not always accurately reflect intra-arterial pressure, particularly in elderly patients, and discrepancies of 50 to 100 mmHg can sometimes be found. ''Pseudohypertension'' should be suspected in elderly hypertensive patients in whom elevated cuff pressures seem out of proportion to the extent of target organ involvement in hypertension (e.g., absence of nephrosclerosis and LVH).

Sir William Osler first described such a phenomenon over 200 years ago saying, ''It may be difficult to estimate how much of the hardness and firmness is due to the blood within the vessel and how much to the thickening of the wall. If, when the radial is compressed with the index finger, the artery can be felt beyond the point of compression, its walls are sclerosed'' (37). We recently evaluated ''Osler's maneuver'' in elderly hypertensives and found an inverse relationship between pseudohypertension and arterial compliance (38). To perform this maneuver, the brachial artery is occluded by inflating the cuff above systolic pressure and then the brachial and radial arteries are palpated. In Osler-positive patients, the sclerotic walls of the pulseless artery were still palpable; in these patients, cuff pressures were found to exceed intra-arterial pressure by 10 to 55 mmHg in our laboratory. These elderly patients with pseudohypertension may by subjected needlessly to the inconveniences, costs, risks, and adverse effects of overzealous antihypertensive therapy. In fact, inappropriate antihypertensive therapy in the elderly could lead to orthostatic hypotension and syncope or transient ischemic attacks and even more serious neurological events (24).

Cardiac Adaptation and LVH

An important, but often overlooked, risk factor for CAD in the elderly is LVH (39–41). Although LVH is a target organ response to hypertension, substantial evidence indicates that it increases almost all morbid and fatal cardiovascular events, particularly major CAD events and CAD mortality.

Hypertension usually causes LVH of the concentric type, which results in increases in ventricular wall thickness without chamber dilatation. Obesity, on the other hand, as well as other conditions that increase preload (e.g., regurgitant valvular heart disease,

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volume overload states, and systolic ventricular failure) lead to eccentric LVH, consisting of chamber dilatation with only a minimal increase in wall thickness (Fig. 7) (42). According to Laplace's equation, this ventricular dilatation increases wall stress and leads to an increase in muscle mass. Since both hypertension and weight increases with age in most populations, LVH becomes a particular problem for the elderly, who have a prevalence of LVH as high as 50% in some studies (39–41,43). Therefore, advancing age is an important risk factor for the development of LVH. However, even in the elderly, other important risk factors are present (Table 1).

Although severe LVH can be determined by radiographic imaging of the chest, on physical examination, and particularly by electrocardiography (ECG), now the gold standard for the evaluation of LVH is echocardiography, which not only is sensitive and specific for detecting LVH, but also for new CAD events. Although some early studies, including many from our laboratory, defined LVH by wall thickness measurements, now the sensitivity and specificity for LVH are improved by LV mass calculations. Criteria for LVH using LV mass should be gender specific, and LV mass should be corrected for height (g/m) or body surface area (g/m_2) (43–49). Correction of LV mass by body mass indices is not as useful because it decreases the impact of obesity.

LVH may initially be considered a compensatory mechanism, for as indicated by Laplace's equation, an increase in wall thickness reduces ventricular wall stress. However,

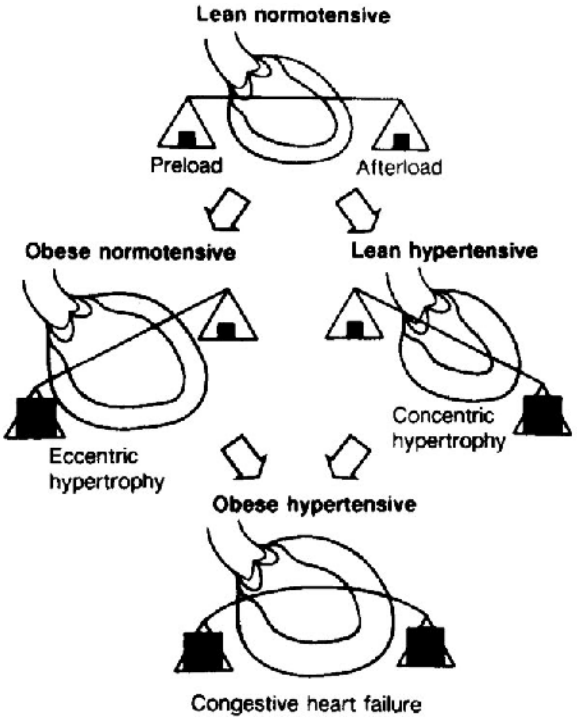

Figure 7 Cardiac structural adaptation to obesity, essential hypertension, and a combination of obesity and hypertension. (Reproduced from Ref. 42.)

Table 1 Risk Factors for Left Ventricular Hypertrophy

Age
Weight
Arterial pressure
Race (higher in blacks)
Increased sodium intake
Catecholamines
Renin-angiotensin aldosterone system
Various growth factors

as LVH progresses, it certainly is not benign, but rather increases almost all cardiovascular sequelae, including major cardiac morbidity and mortality (Fig. 8) (40).

Early studies demonstrated that LVH was associated with significant reductions in coronary flow reserve (39–41,50). In studies from the Ochsner Clinic, we have demonstrated that all types of LVH, including concentric LVH, eccentric LVH in obese hypertensives, and isolated septal hypertrophy are all associated with increases in the prevalence and complexity of ventricular dysrhythmias (39–41,51–55). Several other studies have confirmed this strong association between LVH and the prevalence and complexity of ventricular dysrhythmias (39–41,56).

In a study of 468 elderly nursing home patients, Aronow and colleagues (56) demonstrated that the risk of sudden cardiac death was increased by 3.3-fold in those with echo-

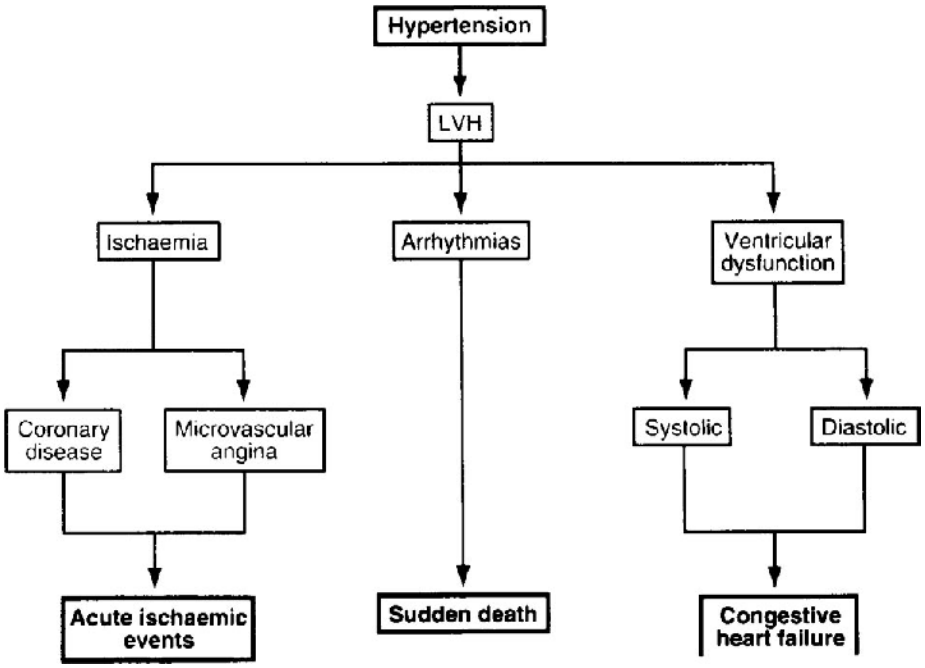

Figure 8 Consequences of left ventricular hypertrophy. (Reproduced from Ref. 40.)

cardiographic LVH; in those with nonsustained ventricular tachycardia on ambulatory ECG monitoring, sudden death was increased by twofold; in elderly with both echocardiographic LVH and nonsustained ventricular tachycardia, there was a marked tenfold increase in the risk of sudden death. These data support previous data from the Framingham Heart Study, demonstrating a tenfold increased risk of sudden death in subjects who demonstrated ECG evidence of LVH along with repolarization abnormalities (or LVH with ''strain'' pattern) (57).

As with increased ventricular ectopic activity, our studies from the Ochsner Clinic in New Orleans demonstrated that left ventricular diastolic dysfunction accompanies all types of LVH, including concentric, eccentric, and isolated septal hypertrophy (39–41,53,58,59). The most significant diastolic abnormality seems to occur in patients with both essential hypertension and obesity, two conditions (along with LVH) that increase with advancing age. Not surprisingly, these diastolic abnormalities are particularly problematic in the elderly.

In addition to diastolic ventricular abnormalities, some studies have demonstrated that ventricular functional reserve falls in hypertension (60). We have also demonstrated that with progression of obesity in hypertensive patients, as is frequently present in the elderly, contractility, as measured by a preload independent index, progressively falls (61). With these combinations of diastolic and systolic abnormalities, it is not surprising that CHF is quite prevalent in elderly hypertensives with LVH. In fact, data from the Framingham Heart Study indicate that LVH is even a stronger relative risk factor for CHF than it is for CAD events (43,57), although the absolute prevalence of CAD is considerably higher than is CHF.

Numerous studies have now documented the markedly increased risk of cardiac morbidity, cardiac mortality, and all-cause mortality associated with LVH, including several studies in elderly populations. In a study from the Framingham Heart Study of 1141 elderly patients followed for 4 years, echocardiographic-determined LV mass (corrected for height) was the strongest predictor of CAD events (62). In their study, for every 50 g/m increase in LV mass corrected for height, there was a 50% increase in the relative risk of new CAD events. In a prospective study of 557 elderly patients, Aronow and colleagues demonstrated that elderly subjects with known CAD and echocardiographic evidence of LVH had a 2.2 times greater risk of new CAD events compared to those without LVH (63). In the study of 410 elderly hypertensives, Aronow et al. demonstrated that those with echocardiographic LVH had a greater than threefold increased risk of major CAD events, which was independent of other factors (64).

In addition to the increase in the risk of major CAD events, data from Aronow and colleagues (63,64) and the Framingham Heart Study (65) both demonstrated that echocardiographic LVH is a strong predictor of stroke in the elderly. Recent evidence demonstrates that LVH is a risk factor for extracranial carotid artery disease in the elderly (66,67), and prior studies have demonstrated that extracranial carotid disease is also a risk factor for stroke in the elderly (67,68).

In addition to the considerable evidence discussed above, several recent studies have suggested that a reduction in LV mass during treatment is a favorable prognostic marker that predicts a lower risk of subsequent morbid cardiovascular events (69–72). Therefore, we strongly believe that efforts to prevent and reduce LVH, including both nonpharmacological and pharmacological strategies, are warranted (Table 2). In addition, some concern has been expressed that if treatment for hypertension is abruptly discontinued (as often seen in many elderly patients for various reasons) and blood pressure returns to pretreat-

Table 2 Measures Associated with Prevention and Reduction of Left Ventricular Hypertrophy

Weight reduction
Aerobic exercise
Pharmacological agents
ACE inhibitors
calcium antagonists
α-adrenergic blockers
β-adrenergic blockers
indapamide
chlorthalidone (in one major study)
centrally acting agents
serotonin uptake inhibition

ment levels or even higher after LVH is reduced, LV wall stress will be increased and this would theoretically predispose to severe CHF (73). However, we and others have demonstrated the efficacy and safety of reducing LVH (74–77). Even after LVH is reduced and the antihypertensive therapy is withdrawn, resulting in return of arterial pressure to pretreatment levels, both diastolic and systolic ventricular performance remain enhanced.

PHARMACOLOGICAL AGENTS

Diuretics

Recent recommendations from the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-V and VI) support the use of diuretics or β-adrenergic blocking agents as first-line treatment for hypertension even in the elderly population (78,79). There is no question that diuretic therapy has resulted in a marked (approximately 40%) reduction in stroke; however, most studies with diuretics indicate that major CAD events are reduced by only 10–15%, much less than the 35% reduction that is predicted based on control of arterial pressure. However, most recent trials in the elderly, mainly using low doses of diuretics and beta blockers, demonstrated a nearly 20% reduction in CAD events (10,12,80,81). Although some studies have demonstrated reductions in LVH with diuretics, we believe that optimal doses of other agents will reduce LVH more so than with diuretic therapy. In addition, diuretic therapy may worsen preexisting volume depletion, frequency and complexity of ventricular dysrhythmias, and lipid and glucose abnormalities, which are frequently present in the elderly hypertensive population.

β-Adrenergic Blocking Agents

Beta blockers have also been recommended as first-line therapy for hypertension. In general, beta blockers have inconsistent effects on LVH, but various studies, including some from our laboratory, have demonstrated modest reductions in LVH with beta blockers, but usually less of a reduction than that produced with angiotensin-converting enzyme (ACE) inhibitors and calcium channel blocking agents (39–41). Beta-blocker therapy may

be particularly effective in patients with known CAD, and there is some evidence that elderly patients with known heart disease may benefit from these agents. In a study of 245 elderly patients with prior MI or known hypertensive heart disease, complex ventricular ectopic activity, and relatively preserved global systolic function (ejection fraction measurements of 40% or greater), Aronow and colleagues demonstrated that the oldest beta blocker, propranolol, was associated with reductions in sudden cardiac death, total cardiac death, and total mortality by 47%, 37%, and 20%, respectively, compared with no specific antiarrhythmic therapy (82).

However, beta blockers have problems in elderly patients, particularly those with relative bradycardia and decreased baseline cardiac output, as well as those with lipid and glucose abnormalities. In fact, Messerli has recently reviewed all major studies of beta blockers as monotherapy in elderly hypertensives, demonstrating no benefits of this therapy. These data suggest that beta blockers as monotherapy should be abandoned as first-line therapy for uncomplicated elderly patients with hypertension (83).

Calcium Entry Blocking Agents

Calcium channel blockers have been demonstrated to reduce LVH in many studies with various medications in this class. In addition, calcium antagonists reduce several of the major consequences of LVH, including decreased coronary flow reserve, myocardial ischemia, abnormal diastolic relaxation, and prevalence and complexity of ventricular ectopic activity (39–41,84). Unlike ACE inhibitors and β-adrenergic blocking agents, which are not as effective in patients with low plasma renin activity (which is seen in most elderly hypertensives), calcium channel blockers are particularly effective in hypertensive patients with low plasma renin activity, making these agents particularly attractive for elderly hypertensives. In addition, calcium channel blocking agents seem to have no adverse metabolic effects, and they have direct antiatherosclerotic effects, particularly by reducing the formation of new coronary lesions in patients with CAD (85).

In a recent major study from the Systolic Hypertensive in Europe (SYST-EUR) Trial (13), a long-acting dihydropyridine calcium blocker (nitrendipine 10–40 mg/day) with the possible addition of low doses of diuretics, was studied in 4695 patients 60 years or older with isolated systolic hypertension. During a 2-year follow-up period, active treatment was associated with reductions in stoke (42%), sudden death (26%), nonfatal cardiac endpoints (33%), fatal and nonfatal cardiac endpoints (31%), cardiovascular mortality (27%; $p = 0.07$), and all-cause mortality (14%; $p = 0.22$). Treatment of 1000 elderly patients for 5 years may prevent nearly 30 strokes and over 50 major cardiovascular endpoints with this type of calcium blocker therapy.

In elderly with preserved systolic function, the rate slowing calcium blockers (verapamil or diltiazem) would be reasonable choices, although these agents (especially verapamil) may worsen constipation in the elderly. However, in elderly with relative bradycardia or those taking a beta blocker, a long-acting dihydropyridine drug may be more appropriate. In patients with systolic ventricular dysfunction who need a calcium blocker (usually in addition to ACE inhibitors, nitrates, diuretics, and digitalis) to treat myocardial ischemia or severe hypertension, a dihydropyridine drug with less negative inotropic effects (e.g., isradipine, felodipine, or, particularly, amlodipine) may be appropriate. Finally, in patients where rate-slowing effects are desired, but without negative inotropic effects, or in those effectively treated with calcium blockers but who have intolerable edema with

the other agents, a new T-channel calcium blocker, mibefradil, may be desirable, although substantial drug interactions markedly limit this drug's usefulness.

ACE Inhibitors

Most studies suggest that the ACE inhibitors are the most potent antihypertensives for the reduction in LVH, and recent evidence indicates that ACE inhibitors may reduce ventricular dysrhythmias in hypertensive patients (39–41,86). However, in the TOMHS Study, low doses of the ACE inhibitor enalapril (5 mg/day) did not reduce LVH as effectively as did diuretic therapy (87). In addition, although ACE inhibitors are usually efficacious in most hypertensive patients, they are generally not as effective in some groups with low plasma renin activity (e.g., obese, blacks, diabetics, and *elderly* hypertensives). Based on considerable evidence, however, ACE inhibitors should be considered the drugs of first choice for treatment of elderly with LVH and systolic dysfunction.

α-Adrenergic Blocking Agents

α-Adrenergic blockers reduce LVH in many studies, and these agents have beneficial lipid effects (e.g., increases in the cardioprotective levels of high-density lipoprotein cholesterol and reducing levels of triglycerides) and may improve insulin sensitivity (88). However, their major use today is for relieving the symptoms of prostatic hypertrophy in elderly men with significant urinary hesitancy and frequency. Therefore, α-adrenergic blockers should be considered in the elderly with hypertension, LVH, and, particularly, for those with significant prostatic hypertrophy.

Centrally Acting Agents

Finally, centrally acting agents may also reduce LVH; however, many elderly experience troublesome central side effects, particularly sedation. We have recently reported reductions in arterial pressure and LVH with sertraline, a serotonin uptake inhibitor, in obese patients with hypertension (89). Therefore, this therapy, which is frequently used for depression in the elderly, may be particularly effective for obese, elderly hypertensives with LVH and concomitant depression.

CONCLUSION

The data reviewed in this chapter suggest that emphasis needs to be placed not only on reducing arterial pressure, but also on the pathophysiology of hypertensive diseases in the elderly. Appropriate therapy should minimize adverse effects and prevent progression of target organ involvement, including renal disease and, particularly, heart disease (e.g., LVH, CAD, CHF, etc.). At present, the data appear most promising with low doses of diuretics and calcium antagonists for elderly with hypertension. Whereas low doses of beta blockers may be appropriate for elderly with known CAD, beta blockers as monotherapy, in our opinion, should not be first-line therapy for hypertension in the elderly. Data appear promising regarding the effect of ACE inhibitors on reducing and preventing LVH, as well as for treatment of hypertension and systolic dysfunction, although the effects of this therapy on major cardiovascular events remain unproven in patients with hypertension

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alone. Finally, further large-scale prospective studies are needed to determine the relative efficacies of various therapies in elderly hypertensives, as well as to determine whether a reduction in LVH and ventricular dysrhythmias are associated with major reductions in cardiovascular morbidity and mortality in elderly hypertensives, above and beyond that produced by adequate control of arterial pressure alone.

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7
Hyperlipidemia in the Elderly

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INTRODUCTION

Most of the gains in life span in western societies in the 20th century have been from the elimination of childhood diseases. The prevention of atherosclerotic disease and cancer in older individuals has contributed relatively little (1).

The notion of prevention of atherosclerosis in the elderly has been regarded as a non sequitur even though factors that predict atherosclerotic cardiovascular risk in younger individuals also predict risk in older people. Perhaps as a result, atherosclerosis is frequently viewed as an inevitable consequence of the aging process.

Although most individuals older than 65 years of age exhibit one or more cardiovascular risk factors (2), the prevalence of risk factors declines beyond age 75, probably as a result of selective survival (i.e., individuals with risk factors are likely to die at a younger age than those without).

Risk factors continue to predict cardiovascular disease (CVD) in older individuals (3–6) Most, however, including lipoprotein abnormalities, smoking, hypertension, and diabetes, lose some of their predictive potency, which may be due to the following:

1. The survivor effect already mentioned, leading to a surviving population with fewer risk factors.
2. The presence of other diseases that may alter either risk factor or mortality levels.
3. Death resulting from other causes but mistakenly attributed to atherosclerotic CVD.
4. Failure to take into account the total ''dose'' of a risk factor (i.e., the effects of lifelong exposure to less dramatically elevated levels of cholesterol, blood pressure, or smoking).

Moreover, although the relative risks of CVD associated with any given risk factor may decrease as individuals get older, the absolute risk of morbidity and mortality increases steeply with age. It is possible, then, that the number of heart attacks potentially prevented in a population with risk factor reductions may actually increase with age, even though the power of the risk factor to predict relative risk declines (7).

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LIPOPROTEIN DISORDERS AS PREDICTORS OF CVD RISK

Total cholesterol levels gradually increase with age. This effect is more prominent in women than in men. After the age of about 55 years, women consistently have higher total low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol levels than do men of the same age (5). The value of total cholesterol as a predictor of the relative risk of coronary disease decreases with increasing age in both men and women, undoubtedly because of some of the confounding factors mentioned in the previous section. Indeed, the value of total cholesterol as a predictor of risk can be restored by controlling for other risk factors and for indices of ''frailty,'' including low serum albumin and iron levels. In other words, depressed cholesterol levels in the chronically ill elderly are not reliable indicators of lifetime exposure to elevated cholesterol levels (8).

In addition, because HDL cholesterol makes up the greater share of the total cholesterol in women, total cholesterol may be an insufficiently precise predictor of risk. Even so, there is ample evidence that total cholesterol, LDL cholesterol, and HDL cholesterol levels are all univariant predictors of risk of coronary disease in both men and women over 65 years of age (3–6,9–11). HDL, in particular, is an important predictor of risk (5,12–15). Because HDL and triglyceride levels are strongly, and inversely, related, it would not be surprising that triglycerides continue to be predictors of coronary risk in older individuals. Although levels are higher in older men than in older women, they are better predictors of coronary risk in women than in men (16).

The concept of attributable risk is especially relevant to the issue of cholesterol and coronary risk in older individuals. As noted, the relative risk of coronary disease associated with increasing cholesterol levels decreases with age. As a result of the increased number of coronary events with increasing age, however, the risk attributable to increased cholesterol actually increases (Fig. 1) (10).

Lipoprotein(a) (LP[a]) is a newer, ''nontraditional'' risk factor that has attracted considerable interest among researchers. It is composed of a combination of an LDL molecule and a peptide that is a plasminogen analogue joined together by a disulfide bond. Lp(a) is highly predictive of coronary disease in both men and women (17). In two studies

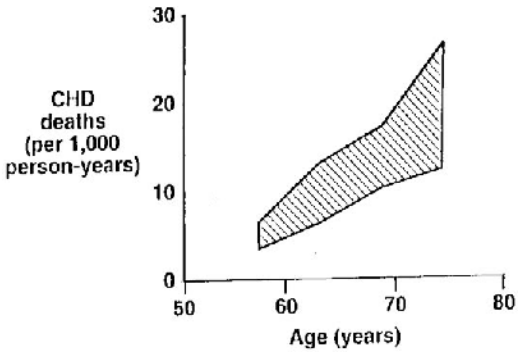

Figure 1 CHD mortality with increasing age. The upper line represents the risk of CHD death with age in those in the upper quartile of the cholesterol distribution. The lower line represents that risk in those in the lower three quartiles. The difference between the two lines, which increases with age, is the cholesterol-attributable risk. (From Ref. 10.)

in which Lp(a) was measured in men over 80 years of age, the percentage with high Lp(a) levels was considerably lower than in younger populations, indicating that those with higher Lp(a) levels may not survive as long (18,19). No data concerning Lp(a) in older women are as yet available.

The ''older'' elderly, those over 75 years of age, are often interested in health issues in general and cholesterol in particular. Whether lipoproteins continue to be potent predictors of risk in such individuals, however, is controversial. In the Bronx Aging Study, HDL levels <30 mg/dL (0.78 mmol/L) were significantly associated with an increased risk of myocardial infarction (MI) and death in men of 75 to 85 years of age, whereas LDL levels over 171 mg/dL (4.4 mmol/L) were associated with a higher risk of MI in women of the same age (14). In a recent study of a cohort of men and women, aged 65 to 90 years, low HDL and high LDL levels were correlated with increased risk for abdominal aortic aneurysm (20).

Patients over 65 years of age with established coronary disease represent a group of particular interest. Elevated cholesterol levels substantially increase the risk of recurrent MI or death in such men and women. In the Framingham Study, cholesterol levels over 275 mg/dL (7.1 mmol/L) were associated with a fourfold increase in risk of recurrent infarction or in coronary death, and almost a threefold increase in risk from all-cause mortality compared with cholesterol levels less than 200 mg/dL (5.1 mmol/L) (21). These observational data suggest that the secondary prevention of CVD through lipid lowering in older individuals is a worthwhile goal, a suggestion confirmed in recent clinical trials.

Dietary and drug interventions, which are effective in lowering LDL cholesterol in younger individuals, are generally effective in older people as well. In the Los Angeles-Veterans Administration (LA-VA) Dietary Study, for example, cholesterol lowering was achieved by a low cholesterol, low saturated fat diet in men both less than 65 and over 65 years of age (22). On the other hand, in a study of elderly men and women (average age of 70 years) observed over a 9-year period, from 1980 to 1989, the percentage of calories from fat consumed decreased from 37% to 31% in women, and from 37% to 33% in men. Saturated fat calorie consumption decreased from 11% to 9% in women, and from 11% to 10% in men. Nevertheless, for both men and women, total to HDL cholesterol and LDL to HDL cholesterol ratios increased (23). Thus the cholesterol-lowering effect of diet over a period of several years is probably counterbalanced by other, as yet ill-defined, effects of aging on lipoprotein metabolism. The metabolic effects of aging may, to some extent, counteract the effect of declines in total and saturated fat in the diet as individuals age.

Studies of cholesterol-lowering drugs in the elderly are also few. Such studies do not support concerns about increased adverse effects of drugs in the elderly. Side effects with one of the HMG-CoA reductase inhibitors or ''statins'' occur at the same rates as in younger patients (24). Although it is often stated, from clinical experience, that older patients are less tolerant of bile acid sequestrants or niacin, there are few published data that directly address this issue. Efficacy studies are also sparse, although the LDL cholesterol-lowering results of cholesterol-lowering drugs such as lovastatin are preserved in older subjects (25).

A barrier to aggressive lipid-lowering therapy in older individuals is physician concern that the patient's life span may be too limited, particularly if the patient has other potentially fatal diseases. This is a real issue. Nevertheless, it should not be invoked in the abstract, in the absence of specific evidence of such life-threatening disease. Too exclusive a focus on mortality, moreover, may be a misguided approach when dealing with

elderly patients. Prevention of morbidity and disability, as in the absence of life extension, is a worthwhile goal in the older populations with chronic illnesses.

CHOLESTEROL INTERVENTION AND CVD PREVENTION

Even if cholesterol can be successfully lowered, it remains uncertain whether that is of benefit in preventing CVD. No intervention studies directly address this issue. However, the LA-VA Study, (22) the Stockholm Secondary Prevention Study (26), the Scandinavian Simvastatin Survival Study (27), and the Cholesterol and Recurrent Events Trial (CARE) (28), studied large enough numbers of individuals over 60 years of age to provide some information.

The LA-VA Study (22) used diet to lower cholesterol. Both individuals with and without clinical CVD were included. The magnitude of the decline in MI or sudden death was associated with cholesterol lowering over the 8 years of the study in those over 65 as well as those under 65 years. The effect, however, only reached statistical significance in the younger age group.

Cholesterol and triglyceride lowering were achieved in the Stockholm Secondary Prevention Study (26) with a combination of niacin and clofibrate. In this study, both recurrent ischemic heart disease and total mortality were significantly decreased in those over as well as those under 60 years of age.

The Scandinavian Simvastatin Survival Study (4S) (27) utilized 20 mg simvastatin in 4444 men and women with elevated cholesterol and established coronary disease. An overall decline of 35% in total mortality and a 42% decline in coronary mortality was observed over 5 years. The effect was evident to about the same degree in those over 60 and those under 60 years of age.

The CARE trial examined the effect of cholesterol lowering in U.S. male and female CHD patients with average cholesterol of 209 mg/dL and LDL cholesterol of 140 mg/dL. In this group of CHD patients, with average cholesterol levels, cholesterol-lowering was effective in reducing recurrent event rates by almost 25%. The effect was roughly equivalent in those under and over 60 years of age (28).

An unexpected effect of cholesterol lowering made evident by recent trials has been the levels on stroke rates. In a review of 16 statin trials, an overall 29% reduction in stroke rates was demonstrated (29). Given the disability resulting from strokes in the elderly, these findings add to the rationale for cholesterol interventions in older individuals.

On the other hand, although these clinical trial data support the hypothesis that cholesterol lowering is of benefit in older individuals, they leave many uncertainties. It is unclear at what age (if any), cholesterol-lowering benefits are likely to stop accruing, and, therefore, at what age cholesterol-lowering intervention might no longer be considered. Although a range probably can be identified, it is unlikely that a precise chronological point will apply to all individuals. For the time being, cholesterol lowering in individuals without clinical vascular disease is difficult to justify unless other potent risk factors such as diabetes are also present. The elderly bear the greatest burden of atherosclerosis, however, and should not be excluded from cholesterol-lowering interventions simply because of chronological age. Clinical trials now in progress should provide more definitive data in a few years.

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SPECIAL CONSIDERATIONS FOR CHOLESTEROL INTERVENTIONS IN THE ELDERLY

The National Cholesterol Education Program (NCEP) guidelines note that consideration of the increased potential for adverse effect, limited life span, and the effect of other morbid conditions, including the need for other drugs, all limit the feasibility of cholesterol interventions for those over age 65 (30).

As with the younger patients, the most urgent candidates for intervention are those with established CVD. There is ample evidence of the benefit of cholesterol lowering in such individuals (16,31). Next are those with other risk factors, many of whom will have subclinical evidence of CVD (32). Least urgent are those with no evidence of clinical CVD and no other risk factors. Some would argue that the absence of CVD in individuals with hypercholesterolemia at this age demonstrates their ''resistance'' to elevated cholesterol.

Concern has been expressed about the potential adverse effects of dietary restrictions in older people, including the possibility of calcium deficiency secondary to dairy product restrictions, wasting secondary to caloric restriction, and constipation due to fiber overload. Documentation of such concerns, however, is scanty. Despite these concerns, if the decision is made to treat, the first intervention should be dietary (33). Proper dietary counseling can be the key to good dietary compliance. It is particularly important that attention be paid to individual food preferences because enjoyment of food may be particularly important in older individuals.

Drug interventions should be reserved for those at the highest risk, that is those with established CVD or multiple risk factors (34). A detailed description of individual drugs and their adverse effects is beyond the scope of this discussion. A summary of this information, however, is presented in Table 1.

Given their efficiency in lowering LDL-C, one of the statins is probably the best choice of drug to be added to a diet low in animal fat. As noted, such drug therapy has now been shown both to inhibit progression of coronary atherosclerosis and to reduce morbidity and mortality from coronary artery disease (CAD) (24–27). Alternative drug therapies such as bile acid sequestrants or niacin are likely to be less effective and associated with more side effects in patients of any age. Nevertheless, they may be useful in patients who, for whatever reason, do not tolerate statins.

The value of combination drug therapy in a case like this is more problematic. If sufficient LDL-C cannot be achieved with a statin alone, the addition of small amounts (1 to 3 doses per 5 day) of a bile acid sequestrant may be useful without increasing substantially the side-effect profile. An alternative is the addition of niacin; although in that case, the risk of drug-induced skeletal myopathy increases from 0.5% (or less) with a statin alone to about 2.5% (35).

In patients with CAD, it is important to obtain whatever LDL lowering can be achieved with single drug therapy. The evidence that cholesterol lowering in patients with CAD is useful in preventing progression of the disease is now too strong to be ignored.

The relative value of interventions on LDL, triglyceride, or HDL levels is not known. Most evidence in younger individuals has centered on the value of LDL lowering in preventing the onset and progression of atherosclerosis.

The NCEP guidelines are of particular note in the lipid management of older women. Two-thirds of individuals over 65 years of age are female, and CVD rates in older women approach those in men (36). Current evidence indicates that cholesterol lowering

Table 1 Lipid-Lowering Agents

Drug	Change in lipid fraction (%)			Effect on lowering CHD risk	Adverse effects	Toxicity
	LDL	TG	HDL			
Bile acid sequestrant (cholestyramine, colestipol)	↓ 15–30	0 or ↑[a]	↑ 3–5	Yes	Bloating nausea constipation	None
Nicotinic acid	↓ 15–25	↓ 20–50	↑ 15–30	Yes	Flushing	Hepatotoxicity hyperuricemia hyperglycemia
HMG-CoA reductase inhibitor[b] (statins)	↓ 20–40	↓ 10–15 (greater with atorvastatin)	↑ 5–10	Yes	Rare	Myopathy hepatotoxicity
Gemfibrozil	0–15 ↑[a]	↓ 20–50	↑ 10–15	Yes	Rare	Hepatotoxicity myopathy perhaps gallstones

[a] May increase in participants with high initial TG levels.
[b] Lovastatin, provastatin, simvastatin, fluvastatin, and atorvastatin LDL = low density lipoprotein cholesterol; HDL = high density lipoprotein cholesterol; TG = triglycerides; CHD = coronary heart disease; ↑ = increased levels; ↓ = decreased levels.
Source: Modified from Ref. 34.

in women with CHD may be even more effective in reducing recurrent events than in men (31).

Because estrogen both lowers LDL and increases HDL levels by about 15% (38), NCEP guidelines suggest that estrogen replacement therapy (ERT) be considered as an intermediate step between diet and drug therapy in women (30). (They are silent about the use of progestins, which are usually administered to women with an intact uterus in order to prevent uterine hyperplasia.) In cohort studies of women in the first 10 years after menopause, generally younger than 65 years old, ERT is associated with decreased death rates from CVD, both in those with and without apparent disease (37). No clinical trials of ERT with CVD endpoints, however, have been completed. No studies, even observational, have examined the protective value of ERT in women over 65.

Contrary to popular belief, blood sugar and body weight are probably not aggravated by ERT (36). Triglyceride levels may be increased, however, particularly in patients with a tendency to hypertriglyceridemia. Therefore, triglyceride levels must be closely monitored in women on ERT.

Estrogen appears to have numerous stabilizing effects on the vasculature, making it less susceptible to atherogenesis (36). Whether these effects are of clinical relevance is as yet unclear.

Finally, estrogen lowers levels of Lp(a), a CAD risk factor (38). There is no clinical trial evidence, however, that Lp(a) lowering is of benefit. Although these results are promising, no firm recommendations regarding ERT can be made for prevention of CVD in older women. Clinical trials now in progress should provide useful data in the next 5 to 10 years.

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CONCLUSION

Because the elderly carry the greatest burden of atherosclerosis, age should not be an automatic exclusion from cholesterol interventions with either diet or drugs. Elderly subgroups in such trials have demonstrated the same benefit as those found in younger age groups. Stroke rates, however, are also dramatically reduced. Even so, cholesterol-lowering interventions should be undertaken with special attention to their potential adverse effects in older people.

Two-thirds of all individuals over age 65 are female. Because postmenopausal women gradually increase their risk of coronary disease, the unique aspects of coronary risk in women are of particular relevance in the elderly.

In men and women in their 70s, CHD rates are almost equal. In addition to conventional lipid-lowering agents, ERT is a unique intervention for postmenopausal women at risk for CVD. Observational data demonstrating the benefit of ERT, however, have not yet been confirmed in clinical trials (39). In women over age 65, even observational data are lacking. Firm recommendations regarding such therapy for the prevention of CVD in older women cannot, therefore, be made at this time.

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8

Epidemiology of Coronary Heart Disease in the Elderly

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Coronary heart disease is the central component of a broad spectrum of disease conditions affecting the heart and circulation, collectively termed atherosclerotic cardiovascular disease, which progresses dramatically as age advances. Although coronary heart disease (CHD) in all its clinical manifestations contributes significantly to disability and death throughout life, its toll is heaviest in the elderly (1–7). Because there is a substantial paucity of epidemiological information regarding both the development and prevention of CHD in the elderly, a thorough evaluation of the role of risk factors for CHD in older persons and the potential benefits of their amelioration would represent an important contribution to the clinical and preventive management of this disease in a large segment of the U.S. and world population.

Considerations regarding the character of CHD and the role of risk factors for its development in older persons, which at the surface may appear straightforward, are in actuality quite complex because, of necessity, they involve interactions of the multiple and overlapping domains of aging, disease, and risk factors. This complexity is captured in the form of a Venn diagram proposed by Lakatta and his colleagues (8) (Fig. 1).

In this representation, aging denotes the constellation of processes that occur over time in the adult organism, and result in characteristic alterations of structure and function of body tissues and organs including the heart and blood vessels. CHD represents ''disease'' in this context, with underlying anatomical and pathophysiological features ultimately manifested as clinical symptoms and complications. Risk factors, in turn, index an array of atherogenic personal traits as well as lifestyle characteristics, including diet and exercise, that are associated with the development of CHD (9).

Separate perspectives for each interaction among these three domains will, therefore, constitute the framework for further discussion. First, we will examine the relation of CHD occurrence to advancing age and the character of CHD in older persons. Next, we will examine how established risk factors for CHD change with advancing age and their prevalence in the elderly. Finally, we will examine associations between specific risk factors and CHD in the elderly and comment on available information regarding the efficacy of treating such factors.

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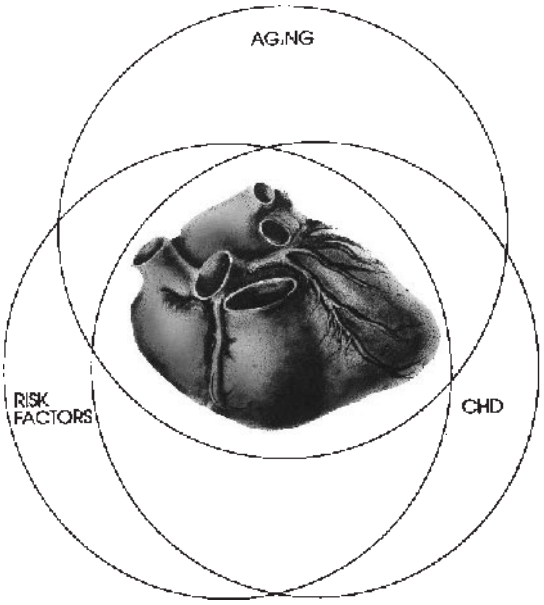

Figure 1 Conceptualized model of interactions between aging, coronary heart disease (CHD), and risk factors for CHD in older persons. (Modified from Ref. 8.)

Each of these perspectives is systematically examined in 30-year follow-up data from the Framingham Study, focusing on findings in subjects 65 to 94 years of age. Details of the examination and laboratory procedures, response rates, and criteria for disease outcomes in the Framingham Study have been previously described (10).

CORONARY HEART DISEASE IN THE ELDERLY

A fundamental observation of cardiovascular disease epidemiology is the distinct age-related rise in the incidence of nearly all manifestations of heart and circulatory disease across the lifespan. In addition to CHD, such cardiovascular disease conditions include stroke, peripheral arterial disease, and congestive heart failure. The increase in incidence of CHD with advancing age is clearly the most striking (Fig. 2) and illustrates the most important element of the first perspective (i.e., the relation between aging and CHD). Although calculated incidence rates in men and women at far-advanced age are based on relatively small numbers of CHD events, such rates clearly follow trends established earlier in life. Also, while incidence rates in men increase linearly with age, those in women tend to increase more steeply at advanced age, approximating an exponential function.

Similar trends of increasing incidence of disease events with age as noted in Figure 2 are observed in Framingham Study data for both men and women up to age 84 for nearly every major clinical manifestation of CHD including angina pectoris, myocardial infarction, sudden death, and death due to CHD (10).

Another important observation regarding the relation of CHD and advancing age is the progressive attenuation of male predominance of disease. This is illustrated in Figure

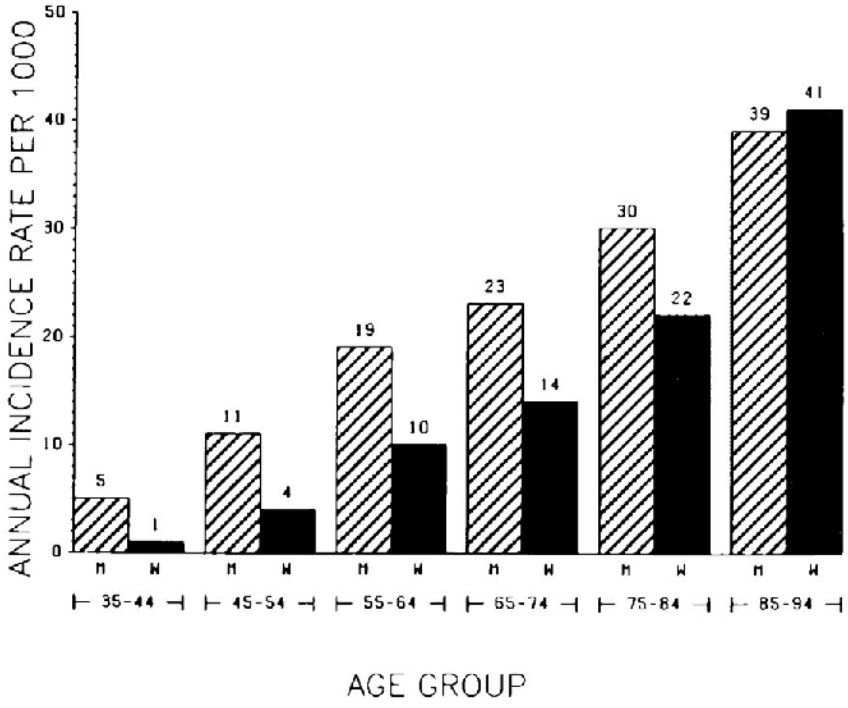

Figure 2 Age trends in total CHD incidence for men and women. Framingham Study, 30-year follow-up.

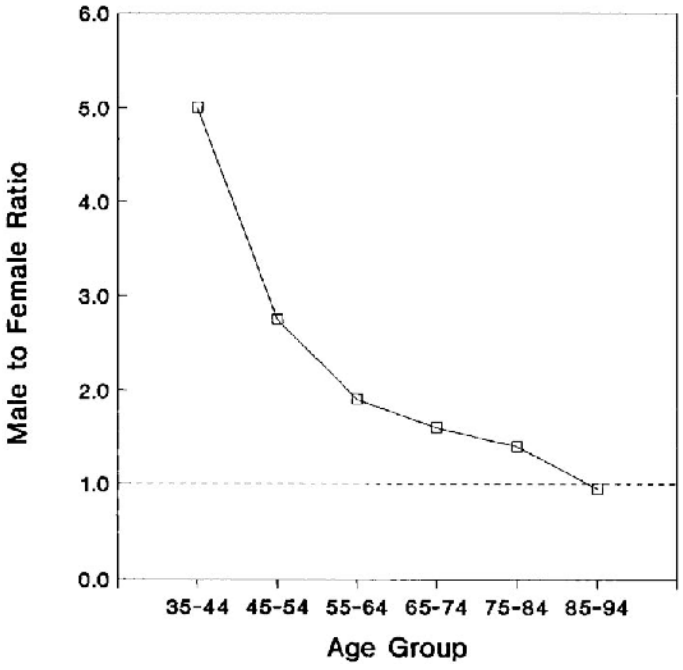

Figure 3 Age-related change in male-to-female ratios for total CHD incidence. Framingham Study, 30-year follow-up.

Table 1 Specified Clinical Manifestations of CHD: Men and Women; Aged 65–94, Framingham Study, 30-Year Follow-up

Manifestation	Men	Women
Myocardial infarction	135/244 (55%)	108/269 (40%)
Angina pectoris	73/244 (30%)	123/269 (45%)
Coronary insufficiency	16/244 (07%)	21/269 (08%)
Sudden death	37/244 (15%)	31/269 (12%)

3, which shows the marked decline in male-to-female ratio of incidence rates for CHD with the relation crossing the line of identity at far advanced age.

The character of CHD according to specified clinical manifestations for older men and women in the Framingham cohort is presented in Table 1. Data indicate the proportion of total coronary events represented by a specific manifestation. Symptomatic categories are not mutually exclusive and percentages exceed 100% because a given subject may have more than one clinical manifestation at the time of their initial presentation within a biennial period. Myocardial infarction represents the most common initial manifestation for CHD in older men, whereas angina pectoris appears to be the most common presenting feature in older women. Angina pectoris in older women frequently occurs as an isolated clinical entity. Angina pectoris in older men, however, is more often associated with acute myocardial infarction, either preceding or occurring after the acute event. Coronary insufficiency is the traditional term for unstable angina pectoris referring to the clinical situation of either prolonged chest pain or a progressive increase in the frequency and/or intensity of ischemic chest pain. This manifestation occurs at similar frequencies in older men and women. Sudden death, as an initial manifestation of CHD, occurs somewhat more frequently in older men than women.

Another characteristic of CHD in the elderly is the tendency for a larger proportion of myocardial infarction events to be clinically unrecognized (Table 2). The diagnosis of myocardial infarction in such instances is based on the occurrence of unequivocal electrocardiographic changes consistent with infarction between biennial examinations, where neither the subject nor his or her physician has suspected the diagnosis (11). Symptoms associated with such events are usually attributed to musculoskeletal chest discomfort,

Table 2 Proportion of Unrecognized Myocardial Infarctions by Age and Sex, Framingham Study, 30-Year Follow-up

Age (years)	Men	Women
30–44	29%	—
45–54	18%	41%
55–64	25%	31%
65–74	25%	35%
75–84	42%	36%
85–95	33%	46%
Average	28%	35%

upper gastrointestinal tract upset, gall bladder disease, or other conditions. Approximately one-half of such infarctions are completely silent. Unrecognized events represent a larger proportion of all infarctions in women and particularly older women.

CHANGES IN CHD RISK FACTORS WITH ADVANCING AGE

Nearly all of the established CHD risk factors change with advancing age. These include changes in blood pressure, serum lipids, cigarette smoking, glucose metabolism, body weight, and other factors. Several age-related trends in risk factors and their prevalence in older persons are described below. This constitutes the second perspective of our discussion (i.e., the interaction between aging and risk factors).

The most well-characterized change in an established CHD risk factor with age is elevation of blood pressure. In longitudinal data from the Framingham Study, systolic blood pressure is observed to rise nearly linearly with advancing age in both men and women (Fig. 4). Diastolic blood pressure, in contrast, tends to rise throughout middle age in both sexes and actually declines at advanced age. Diastolic blood pressures in women, however, usually remain 5 to 10 mmHg lower than those in men throughout the lifespan (1).

The consistent increase in systolic blood pressure is due to progressive vascular stiffening attributable, in turn, to alterations of the physicochemical properties of media of the arterial wall including overall thickening and changes in the nature and content of

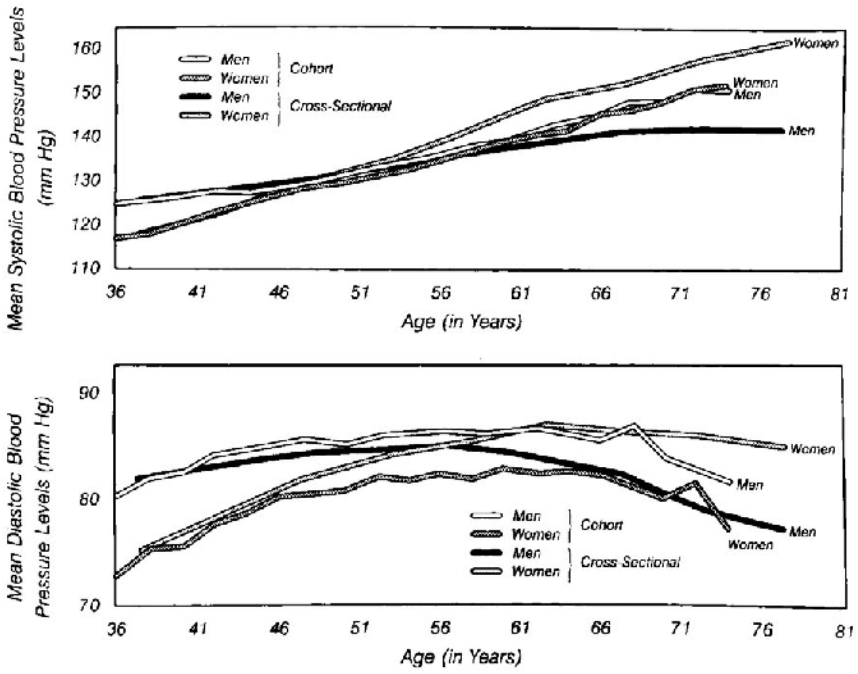

Figure 4 Average age trends in systolic and diastolic blood pressure levels for men and women based on cross-sectional and longitudinal (cohort) data. Framingham Study, biennial exams 3–10. (Modified from Ref. 1.)

collagen, elastin, and possibly other structural proteins that occur with advancing age (12). This process is dissimilar to that of atherosclerosis, which underlies the preponderance of cardiovascular disease observed in older people.

Although progressive elevation of systolic blood pressure with advancing age is consistently observed in nearly every western industrialized population studied, it does not appear to represent a universal feature of the aging process. Data from a number of isolated primitive populations suggest that this relation is markedly blunted (13). Possibilities accounting for differences in age-related change in blood pressure between populations likely include genetic factors as well as dietary influences, especially the higher intake of salt in industrialized nations (14).

Despite its ubiquity, however, progressive elevation of systolic blood pressure with advancing age should not be construed as an innocuous concomitant of the aging process since it clearly confers increased risk for stroke, CHD, and other cardiovascular disease events in both elderly men and women (15). Elevated diastolic blood pressure also occurs commonly in the elderly and remains an important risk factor for cardiovascular disease, particularly in older men.

As a consequence of the progressive age-related increase, primarily in systolic blood pressure (BP), approximately 40 to 50% of men and women in a typical westernized population such as Framingham meet one or more of the established criteria for hypertension after the age of 65. For persons categorized as being hypertensive, isolated systolic hypertension (defined as systolic BP $>$ 160 mmHg with diastolic BP $\leq$ 95 mmHg) accounts for nearly two-thirds of the total prevalence of hypertension in both older men and women (16). Combined hypertension characterized by abnormal elevations of both systolic and diastolic blood pressures accounts for less than one third of the total prevalence. Isolated diastolic hypertension is considerably less prevalent in older men and women, accounting for less than 15% of the prevalence.

Blood lipids, including serum total cholesterol, also vary with age across the lifespan and trends appear to be different in women as compared to men. Figure 5 shows longitudinal trends in average levels of serum cholesterol in the Framingham Study as a function of age. Note that levels in men tend to peak in early middle age and then slowly decline with advancing age. Levels in women peak later in middle age and remain relatively high until advanced age before a decline occurs. The practical implication of this trend is the relatively high prevalence of hypercholesterolemia likely to be encountered in comparable populations of older women.

Corresponding age trends for specific lipoprotein-cholesterol subfractions in the Framingham Study are illustrated in Figure 6. Trends for low-density lipoprotein (LDL) cholesterol, in general, are similar to those for serum total cholesterol. Mean levels of high-density lipoprotein (HDL) cholesterol are consistently higher in women than in men across the age span, but tend to decline slightly after menopause. Trends in men remain essentially unchanged throughout life. Mean values of very-low-density lipoproteins (VLDL) tend to be higher in men than women, but trends in both tend to rise throughout middle age and then remain relatively stable thereafter. Presumably, these trends reflect fluctuations in body weight occurring at corresponding ages in the sexes.

The prevalence of a number of cardiovascular risk factors in older subjects of the Framingham Study is presented in Table 3. Data are arrayed for each decade of age from 65 to 94 years and separately for men and women.

As would be expected from age trends observed earlier, hypercholesterolemia appears to be quite prevalent in older women. Glucose metabolism becomes progressively

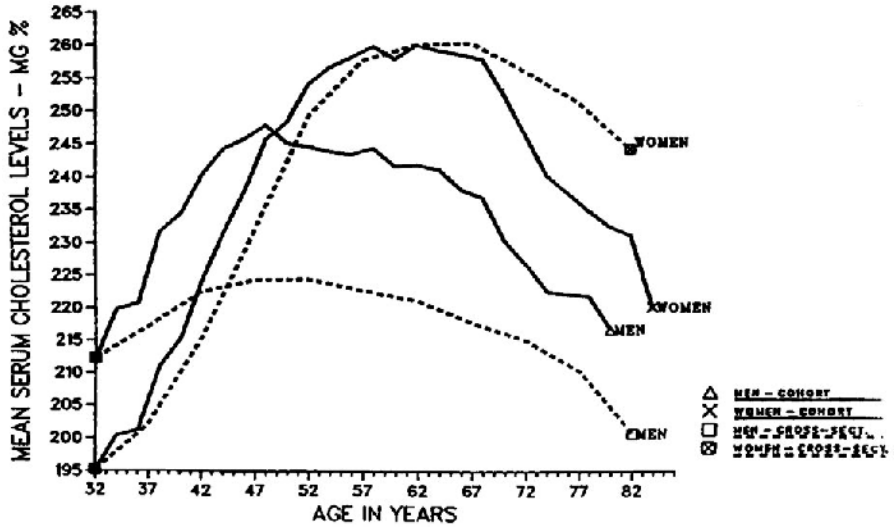

Figure 5 Average age trends in serum cholesterol levels in cross-sectional and longitudinal (cohort) data. Framingham Study, biennial exams 1–16.

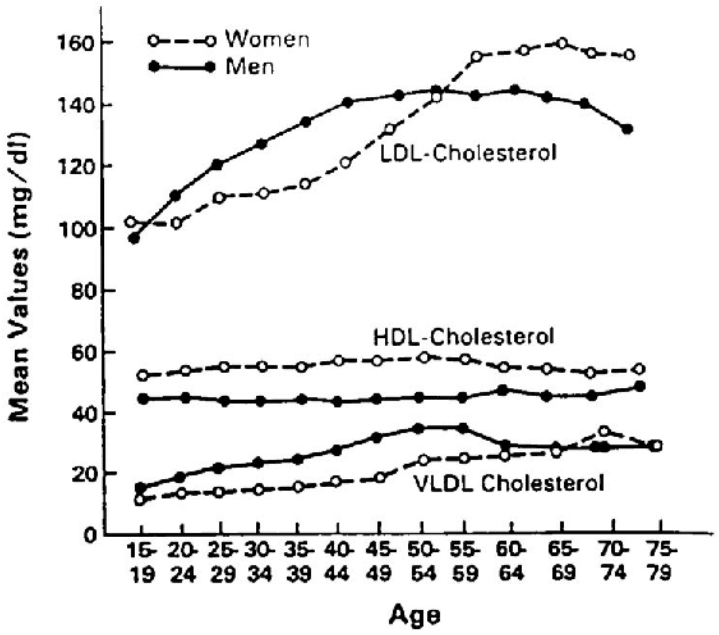

Figure 6 Average age trends in lipoprotein cholesterol subfractions. Framingham Study. (Reproduced with permission from Ref. 2.)

Table 3 Percentage Prevalence of Cardiovascular Risk Factors in the Elderly: Framingham Study, Exam 16

Age (years)	Definite hypertension		Hypercholesterol-emia		Glucose intolerance		Obesity		Cigarette smoking		ECG-LVH	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
65–74	42.1	48.9	16.6	39.7	29.5	17.5	52.2	47.8	21.9	23.0	5.5	4.2
75–84	45.5	61.1	9.7	36.3	30.9	26.0	35.4	39.3	13.9	8.5	6.0	7.8
85–94	20.7	64.8	9.4	18.4	33.3	29.0	7.7	30.0	9.4	3.2	10.4	13.0

Definite hypertension: BP >160/95 mmHg; hypercholesterolemia: serum cholesterol >250 mg/dL; glucose intolerance: blood glucose >120 mg/dL, glycosuria, or diabetes mellitus; obesity: relative weight >120%; cigarette smoking: any (exam 15); ECG-LVH: evidence of left ventricular hypertrophy on electrocardiogram.

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impaired with advancing age, resulting in increasing prevalence of glucose intolerance in both older men and women (17). Body weight tends to decrease at far advanced age. Weight loss, however, represents a reduction primarily in lean body mass (i.e., muscle and bone tissue) rather than adipose tissue. The result is an alteration of body composition in older persons, with higher proportional adiposity per unit of weight (18). Despite the tendency for lower body weights at advanced age, obesity appears to be well represented in both older men and women in this cohort. The prevalence of cigarette smoking appears to decrease with advancing age. This can be attributed not only to higher mortality rates in smokers but also to discontinuation of cigarettes because of health problems or concerns in older persons. The prevalence of left ventricular hypertrophy on electrocardiograms (ECG–LVH) increases with advancing age in both older men and women.

From the foregoing analysis, it is clear that the majority of established risk factors for CHD in middle-aged persons are prevalent in the elderly. What remains is the task of marshalling evidence to address the question of whether or not such risk factors continue to remain operative in the development of CHD in older persons. This constitutes the third and final perspective of interactions alluded to earlier (i.e., associations between specific risk factors and CHD in older persons, which will be reviewed next).

ASSOCIATIONS BETWEEN SPECIFIC RISK FACTORS AND CHD IN THE ELDERLY

Associations for a number of specific risk factors and CHD are summarized in Table 4. Putative risk factors are listed in the column on the left. Standardized, age-adjusted (bivariate) logistic regression coefficients are categorized for younger and older subjects of the Framingham cohort and also arrayed separately for men and women. Regression coefficients are derived using a logistic regression model to mathematically relate the level of a risk factor or its categorical value to the development of CHD events. The magnitude of the coefficient and also the level of statistical significance reflect the strength of the

Table 4 Impact of Risk Factors on Incidence of Coronary Heart Disease, Framingham Study, 30-Year Follow-up

	Bivariate standardized regression coefficients (age-adjusted)			
	Ages 35–64		Ages 65–94	
Risk factors	Men	Women	Men	Women
Systolic pressure	0.338[c]	0.418[c]	0.401[c]	0.286[c]
Diastolic pressure	0.321[c]	0.363[c]	0.296[c]	0.082
Serum cholesterol	0.322[c]	0.307[c]	0.121	0.213[c]
Cigarettes	0.259[c]	0.095	−0.017	−0.034
Blood glucose	0.043	0.206[c]	0.166[c]	0.209[c]
Vital capacity	−0.112[a]	−0.331[c]	−0.127	−0.253[c]
Relative weight	0.190[c]	0.264[c]	0.177[b]	0.124[a]

Significant at [a]$p < 0.05$; [b]$p < 0.01$; [c]$p < 0.001$.

association between the specific risk factor and CHD for the age group and sex under consideration.

A cursory inspection of the results indicates that the majority of significant associations between risk factors and CHD apparent in younger men and women remain significant in older age groups but not consistently in both sexes. Systolic blood pressure, for example, demonstrates strong risk associations for CHD in younger men and women and maintains strong associations in both older men and women. The risk association for diastolic blood pressure, in contrast, appears to lose significance in older women. Serum total cholesterol demonstrates strong risk associations for CHD in younger men and women; however, the strength of this risk association clearly weakens in older men but remains significant in older women. Cigarette smoking modeled using this methodology fails to show significant risk associations in either older men or women. Blood glucose levels, as well as other parameters reflecting impaired glucose metabolism including glucose intolerance and diabetes mellitus, show strong risk associations for CHD in both older men and women. Vital capacity demonstrates strong negative risk associations, particularly in older women. Of interest, significant risk associations between CHD and body weight expressed as Metropolitan Relative Weight are maintained in both older men and women. A number of these risk associations will be characterized in detail below.

Similar data for associations between specific risk factors and CHD incidence can be derived using an alternative regression methodology, the Cox proportional hazards model (19).

Blood Pressure and Hypertension

The relation between blood pressure and CHD, particularly in older persons, represents one of the most striking risk associations in data from the Framingham Study.

Risk relations between CHD incidence and systolic blood pressure in men and women are shown in Figure 7. CHD incidence, expressed as age-adjusted annual rate of CHD events per 1000, appears on the ordinates of left and right panels, respectively. Systolic blood pressure appears on the abscissas of both panels. Two risk relations are illustrated in each panel, one for younger men and women, aged 35–64, another for older men and women, aged 65–94. While overall incidence rates for CHD in women are substantially lower than those at corresponding blood pressures in men, the same underlying risk associations are observed. Note that CHD risk for systolic blood pressure rises with increasing pressure in all age groups and that this rise is even more striking in older than in younger persons. These trends are interpreted as marked increases in relative risk indicating that progressively higher levels of blood pressure confer additional risk for CHD. Although these trends do not establish causality, they serve to emphasize an important role for blood pressure in the extended sequence of pathophysiological events that result in manifest CHD. Also note that risk relations in older men and women are configured well above those of younger persons in each sex, indicating substantially higher incidence rates for CHD at similar blood pressures. This is interpreted as an increase in absolute risk for CHD in older men and women, suggesting a substantially higher burden of disease at all levels of blood pressure in older as compared to younger persons, even at normal or low blood pressures.

Risk relations between CHD incidence and diastolic blood pressure in men and women are shown in Figure 8. Again, risk appears to rise with increasing blood pressure in all age groups (i.e., increased relative risk) and incidence rates at the same level of

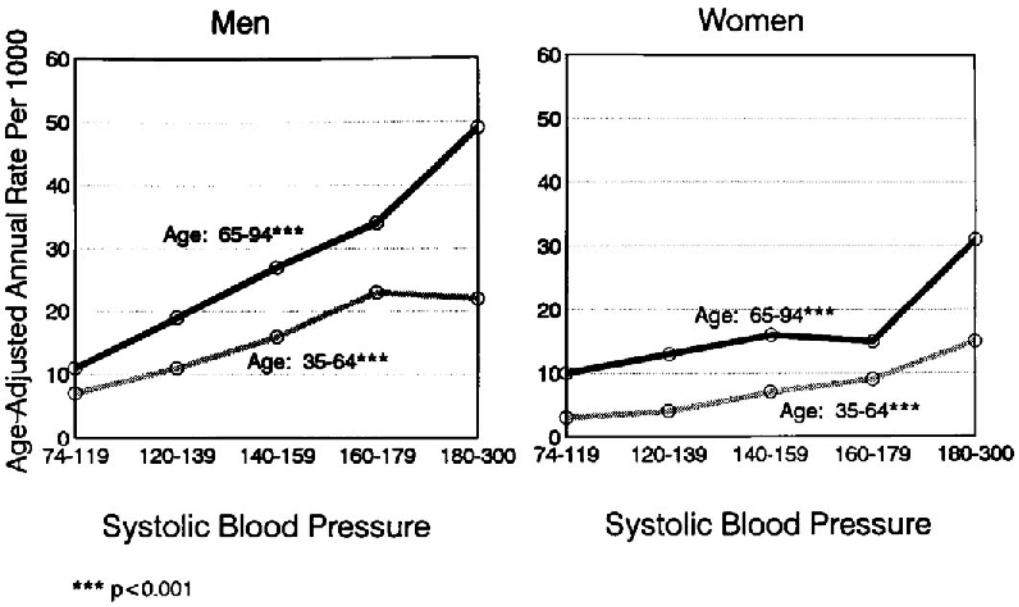

Figure 7 Risk of CHD by level of systolic blood pressure according to specified age groups in men and women. Framingham Study, 30-year follow-up.

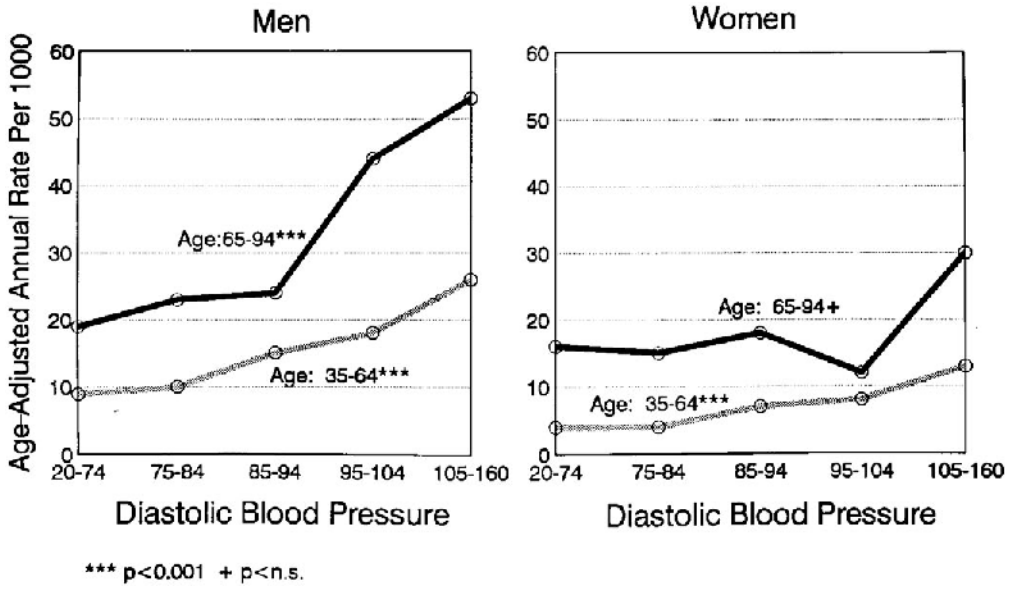

Figure 8 Risk of CHD by level of diastolic blood pressure according to specified age groups in men and women. Framingham Study, 30-year follow-up.

blood pressure are higher in older than in younger persons (i.e., increased absolute risk). Although there is a minor deviation from the nearly linear trend for the relation between diastolic blood pressure and CHD incidence in older men, the relation maintains strong statistical significance. In contrast, the deviation in the relation corresponding to the fourth level of diastolic blood pressure (95–104 mmHg) in older women yields a statistically insignificant result using the logistic regression model, despite an apparent upper curvilinear trend. Although the discontinuities in these curves remain unexplained, these findings suggest a more consistent and reliable role for systolic as compared to diastolic blood pressure as a predictor for CHD in both elderly men and women.

Risk gradients for CHD that, in general, are similar in direction and magnitude to those suggested earlier are observed when individuals are classified according to hypertensive status instead of absolute levels of blood pressure (Table 5). For all age and sex groups considered, the overall risk of CHD is two to three times higher in subjects with definite hypertension compared with normotensives, while risk is intermediate for those with mild hypertension. Absolute risk is two to three times higher in older subjects, both in men and women, and risk is nearly always higher in men than women, regardless of age. Similar patterns of risk attributable to hypertension have been observed specifically for cerebrovascular events, congestive heart failure, and peripheral vascular disease (15). When considered alone, isolated systolic hypertension also confers substantial risk for CHD and other cardiovascular disease outcomes.

Previous data from randomized clinical trials have established a strong case for the efficacy of treating combined elevations of systolic and diastolic blood pressure in older hypertensives (20,21), although considerable uncertainty remained regarding the treatment of isolated systolic hypertension. The findings of the Systolic Hypertension in the Elderly Program (SHEP) have served to dispel much of this uncertainty (22). This study documented impressive reductions in total numbers of fatal and nonfatal strokes in the active treatment group as compared to the placebo group. Statistically significant reductions in nonfatal myocardial infarctions plus coronary death, as well as combined CHD and total cardiovascular disease outcomes, were also noted in the group on active treatment. There appeared to be little or no evidence in this study that lowering of either systolic or diastolic blood pressure resulted in an increased risk of CHD events or mortality, particularly at the lower end of the distribution for blood pressure, the so-called J-shaped curve.

Three other recent clinical trials of drug therapy for hypertension in the elderly that included patients with isolated systolic hypertension also showed beneficial effects (23–

Table 5 Risk of CHD by Hypertensive Status According to Age and Sex, Framingham Study, 30-Year Follow-up

	Average annual age-adjusted rate per 1000, coronary heart disease			
	35–64 years[a]		65–94 years[a]	
Hypertensive status	Men	Women	Men	Women
Normal (<140/90 mmHg)	8	3	14	11
Mild (140–160/90–95 mmHg)	15	7	28	16
Definite (>160/95 mmHg)	21	10	41	22

[a] All trends significant at $p < 0.001$.

25). In addition to substantial reductions in cerebrovascular events and congestive heart failure, the majority of intervention studies of drug therapy for hypertension in older persons to date have consistently demonstrated either beneficial trends or significant reductions in CHD events and mortality. Such findings appear to be considerably less prominent in clinical trials experiences derived from predominantly middle-aged hypertensives (20,21,26).

Details regarding clinical evaluation and treatment of the elderly hypertensive patient appear in Chapter 6.

Blood Lipids

The risk of CHD in older persons attributable to serum lipids represents an area of considerable uncertainty and controversy.

Relations between CHD incidence and serum total cholesterol in the Framingham Study are shown in Figure 9. Separate trends are plotted in younger and older subjects for men and women, respectively. Note that absolute risk is substantially increased in older as compared to younger men. Note also that relative risk clearly rises over the entire distribution of serum total cholesterol in younger as well as older men. The break in continuity of the risk relation at the fourth level of the distribution in older men, however, yields results that narrowly miss statistical significance both in bivariate (age-adjusted) and multivariate estimates using the logistic regression model, whereas the association remains strongly predictive in younger men. Although incidence rates for CHD at corresponding levels of cholesterol are lower in women than in men, the same overall pattern

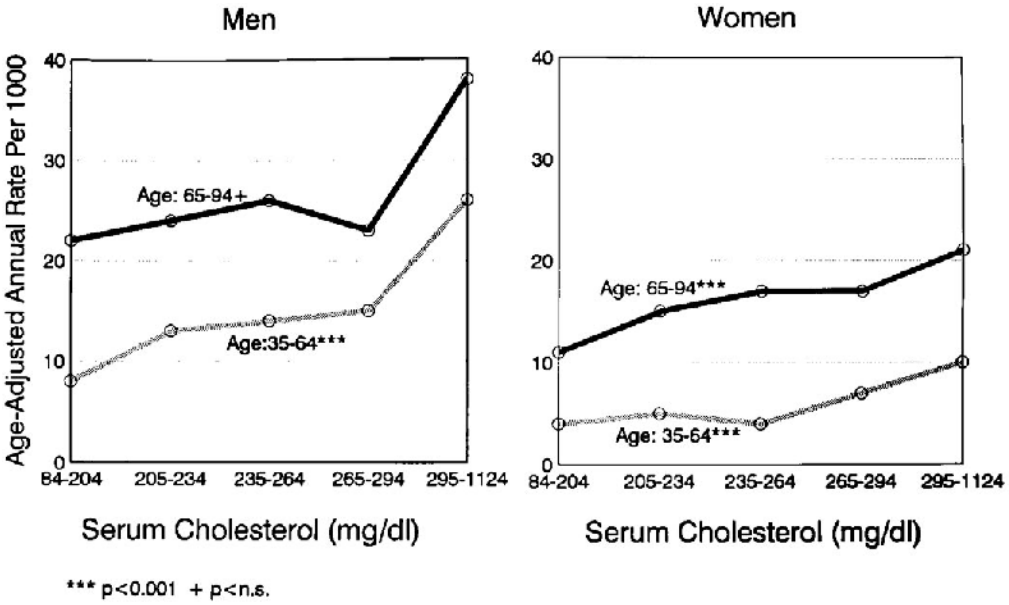

Figure 9 Risk of CHD by level of serum cholesterol according to specified age groups in men and women. Framingham Study, 30-year follow-up.

pertains (i.e., an increase in both absolute and relative risk). In this instance, however, statistical significance is maintained in both younger and older women.

The finding that serum total cholesterol loses strength as a risk factor for CHD, particularly in older men of the Framingham cohort, has resulted in serious misinterpretation by some authors who have used this information to argue that serum lipids do not represent important risk factors for CHD in the elderly and thus justify neither detection nor treatment (27,28). This view is both extreme and unreasonable, since several other studies have clearly validated the role of serum total cholesterol as a predictor of CHD events in older men (29–35) and also older women (29,31,35).

Despite these findings, however, a recent meta-analysis encompassing data from 22 U.S. and international cohort studies concluded that serum cholesterol did indeed lose strength as a risk predictor for CHD mortality in older men and also in older women (36), a finding consistent with original observations made in data from the Framingham Study. Cholesterol emerges as a significant predictor of CHD death when steps are taken to adjust for factors related to frailty or other comorbid conditions that serve to confound this risk association (37,38).

Focusing on serum cholesterol as the sole measure of risk for CHD attributable to serum lipids should now be considered obsolete based on our current understanding of lipoprotein subfractions and the availability of standardized laboratory methods to measure them in clinical practice. Substitution of either LDL or HDL cholesterol in the regression model fully restores statistical predictability for the risk relation between serum lipids and CHD (39). HDL cholesterol, in particular, has emerged as an important lipid moiety that adds substantial precision in assessing coronary risk at limited additional cost (40). Construction of a serum cholesterol/HDL ratio provides a highly accurate characterization of CHD risk in older men and women in the Framingham Study, which is illustrated in Figure 10. Indeed, data from Framingham as well as other studies confirm the overall reliability of the cholesterol/HDL ratio in assessing CHD risk in younger and older persons and in

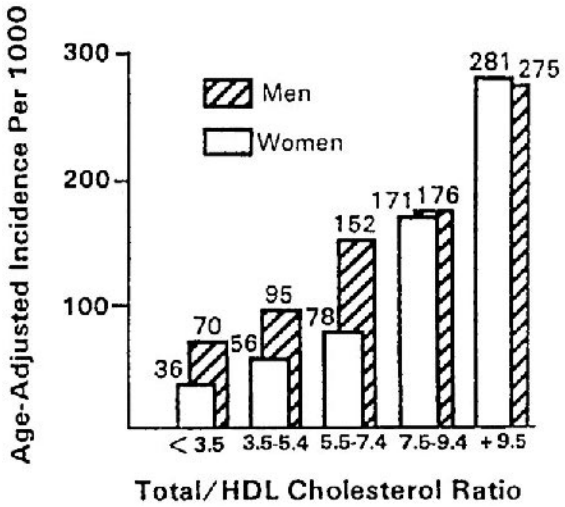

Figure 10 Risk of CHD by total/HDL cholesterol ratios among men and women aged 50 to 90 years. Framingham Study, 26-year follow-up.

men as well as women (31,39,41,42). The rationale for this approach is that the ratio reliably captures the effect of a dynamic equilibrium of lipid transport into and out of body tissues, possibly including the intima of blood vessels.

Several studies have suggested that serum triglycerides may be important predictors for CHD in either older men or older women, but not consistently in both sexes (31,39,41,43). Despite these observations, the present consensus holds that elevated levels of serum triglycerides represent a risk marker for obesity, glucose intolerance, and low HDL levels, all of which confer risk for CHD and, to the extent possible, deserve preventive attention.

Data from intervention studies using dietary measures or drug therapy demonstrate the benefit of lipid alteration in reducing risk of CHD events, particularly in middle-aged men (44,45). Systematic information from clinical trials regarding the efficacy and safety of treating lipid abnormalities in the elderly, despite their prevalence in this population, is not yet available. A strong case for the widespread application of drug therapy to reduce risk of CHD in older persons as an element of primary prevention is not warranted at the present time. Of considerable interest, information from two large clinical trials makes a compelling case for reducing elevated or even average levels of LDL cholesterol with drugs in patients with established CHD: angina pectoris or following myocardial infarction (46–48). These effects of drug therapy in the secondary prevention of CHD events (i.e., in persons with preexisting CHD) appear to be beneficial in both middle-aged and older patients of both sexes.

Current management of hypercholesterolemia for an older person considered to be at risk should consist of a highly individualized approach beginning with appropriate dietary measures and weight control before initiating a trial of specific drug therapy, preferably at lower doses, to achieve a carefully monitored lipid-lowering effect (49).

Details regarding treatment of dyslipidemias in elderly patients appear in Chapter 7.

Cigarette Smoking

Cigarette smoking fails to demonstrate strong risk associations for total CHD events in either older men or older women, using the logistic regression methodology indicated in Table 4. Significant risk associations, however, are discerned between cigarette smoking and death due to CHD (10). One explanation for this phenomenon is that smoking may be more closely related to lethal events than to outcomes comprised of combinations of morbid and lethal events (50). Another explanation is that the cross-sectional pooling approach used in the analysis may classify long-term smokers who have discontinued cigarettes for relatively brief periods as nonsmokers, in effect diluting the strength of the association between the risk factor and the outcome (51). Because of these difficulties, the most reliable approach in assessing risk associations between cigarette smoking and cardiovascular morbidity or mortality is to model these events prospectively for defined categories of smoking behaviors (e.g., current smoker, former smoker, and never smoker) and for longer time intervals. Such approaches yield strong risk associations between cigarette smoking and a broad array of cardiovascular outcomes including CHD, stroke, and peripheral arterial disease, even in older men and women. These observations have been documented using data from Framingham as well as other studies (31,52–54).

Reducing the risk of cardiovascular disease is not the only reason to encourage discontinuation of cigarettes in older persons. Cigarettes contribute to the development of chronic bronchitis and obstructive lung disease as well as lung cancer and other malig-

nancies. These conditions also exact a heavy toll in terms of disability and death in the elderly. Thus, the clinician can make a compelling case that it is never too late to stop smoking and extend appropriate advice and encouragement to assist patients in their effort to discontinue cigarettes.

Glucose Tolerance and Diabetes Mellitus

Impaired glucose metabolism is not only highly prevalent in the elderly but also confers substantial risk for CHD as well as other cardiovascular events in both older men and women. Various measures of glucose tolerance are employed and nearly all demonstrate significant risk associations with CHD in the Framingham Study (10). These measures include blood glucose levels, glycosuria, and the composite risk categories designated as glucose intolerance and diabetes mellitus. Although diabetes mellitus confers enhanced risk for both younger and older men, overall risk increases dramatically for both younger and older women (55) (Fig. 11). Similar patterns of risk are noted for coronary and cardiovascular mortality (10,55). Diabetes also emerges as an important risk factor in the development of congestive heart failure, particularly in older women with insulin-dependent diabetes mellitus (56). Presumably, the microvascular disease that is unique to diabetes,

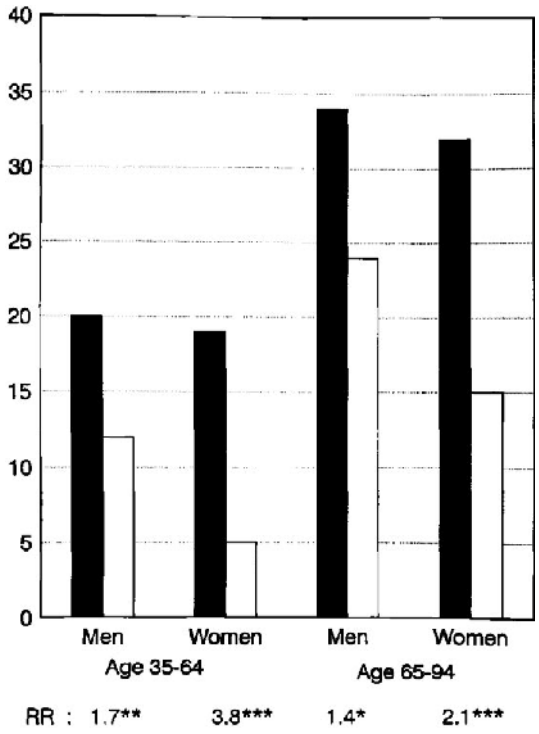

Figure 11 Age-adjusted incidence rates for CHD based on diabetic status classified according to age and sex. Framingham Study, 30-year follow-up. Solid bar = diabetic; open bar = nondiabetic; RR = risk ratio diabetic/nondiabetic. (Reproduced with permission from Ref. 55). (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.)

as well as other mechanisms, serves to produce progressive damage to heart muscle, ultimately resulting in compromised ventricular function and heart failure.

There is little evidence that control of hyperglycemia, either by oral hypoglycemic agents or insulin, effectively forestalls either the development or complications of cardiovascular disease (55,57), although encouraging trends in this regard were identified in the recently completed Diabetes Control and Complications Trial (58). Available evidence would, therefore, suggest that there is more to be gained in reducing risk by correcting associated cardiovascular risk factors in persons with diabetes than by attention confined to early detection and control of hyperglycemia.

Left Ventricular Hypertrophy

Left ventricular hypertrophy as determined by the electrocardiogram (ECG-LVH) emerges as strong risk factor for CHD in older men and women (Fig. 12). Marked increases in CHD incidence are noted for voltage criteria for LVH alone with additional risk conferred by definite LVH which, in addition to voltage criteria, includes repolarization (ST and T wave) abnormalities consistent with LVH. These electrocardiographic findings presumably reflect abnormalities of myocardial structure and function related to early compromise of the underlying coronary circulation that antedate the development of clinical manifestations of CHD (59–61).

In this context, left ventricular hypertrophy (LV mass) as determined by echocardiography has emerged as an extremely potent independent predictor of CHD as well as other cardiovascular disease events especially in older persons (62,63).

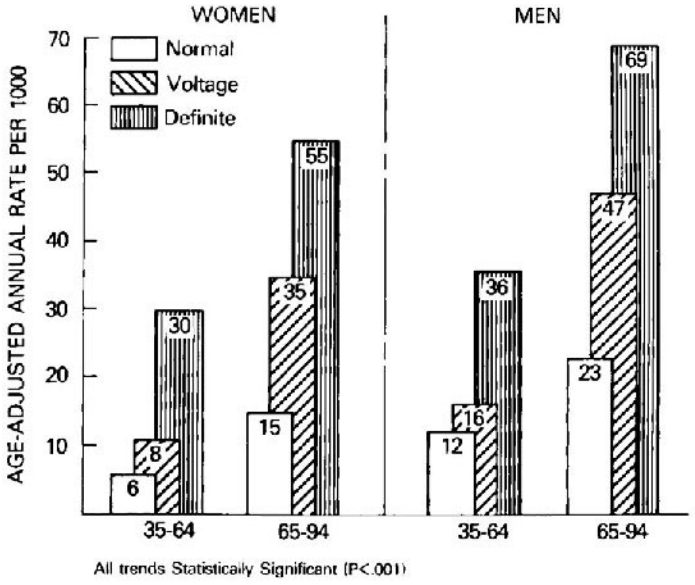

Figure 12 Risk of CHD according to ECG-LVH status. Framingham Study, 30-year follow-up.

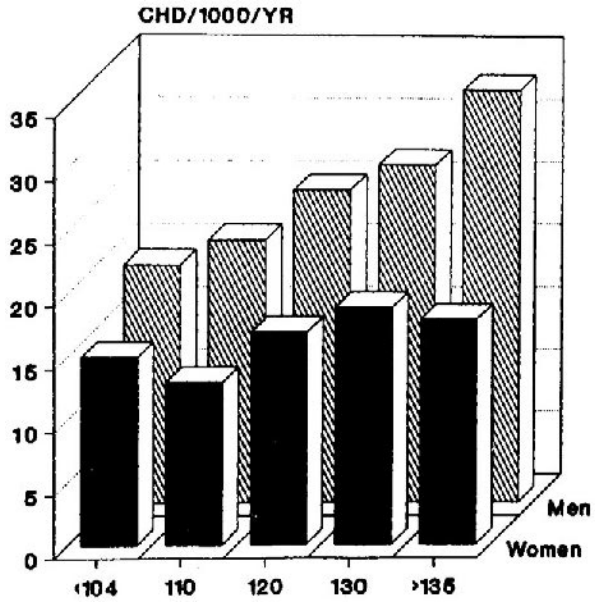

Figure 13 Risk of CHD according to body weight in men and women, aged 65 to 94 years. Framingham Study, 30-year follow-up.

Body Weight

Of considerable interest is the finding that increased body weight represents a significant risk marker for CHD even at advanced age.

The association between body weight and risk for CHD in older subjects of the Framingham Study is illustrated in Figure 13. Note that while CHD risk rises more strikingly with increasing body weight in older men, trends in older women clearly indicate enhanced risk at higher body weights. Progressive increases in body weight occurring earlier in life correlate closely with changes in the levels of several risk factors considered to be more directly related to pathogenesis of atherosclerosis (64). These include increases in blood pressure, serum cholesterol, triglycerides, and blood glucose with a reduction in HDL cholesterol. These findings serve to emphasize the need to incorporate measures ultimately designed either to control or, if necessary, to gradually reduce body weight as part of risk management even in older persons. When coupled with appropriate dietary measures, weight control would be particularly useful in the initial management of elderly patients with hypertension, dyslipidemia, and diabetes or combinations of these conditions.

Vital Capacity

Vital capacity is a simple and sensitive clinical technique for assessing compromise of pulmonary or cardiac function, or both, in individuals of all ages. In contrast to inconsistent risk associations with CHD found in younger subjects, vital capacity emerges as an important risk factor in the elderly, particularly with respect to risk for major coronary events (2,10). Vital capacity normally declines with advancing age, an effect that is strongly exacerbated by cigarette smoking and obesity (65). Diminished vital capacity in older

people is also correlated with loss of muscular strength as assessed by hand-grip, presumably reflecting overall neuromuscular debility (66). Low vital capacity remains a strong predictor of cardiovascular mortality, as well as mortality from all causes. Measurement of this parameter, therefore, should be considered as part of the standard risk assessment of all older patients.

Heart Rate

Recent data from the Framingham Study demonstrate that resting heart rate confers additional risk for CHD in men, both in younger as well as older men, although no similar risk association is observed in either younger or older women (2,10). An explanation for this finding is not readily apparent. Heart rate in men may be a more sensitive indicator of underlying cardiac dysfunction than in women or the net impact of sympathetic nervous system influences in precipitating CHD events is greater in men. High heart rates may also reflect physical deconditioning.

Physical Activity

Accumulating evidence now suggests that lifetime vigorous physical activity may forestall CHD in the elderly (67–69). Previously reported data from Framingham indicated that overall mortality, including coronary mortality, was inversely related to level of physical activity in middle-aged men (70). A benefit of exercise in older men was also suggested; however, the levels of exercise involved were quite modest. Although regular physical activity in the elderly is desirable and should be strongly encouraged, it would be unwise to place undue emphasis on this approach alone in attempting to reduce the risk for CHD.

Prevalent CHD

An important predictor of CHD events at all ages is the presence of antecedent CHD. It is therefore of interest that several of the risk factors associated with the initial development of CHD in the elderly not only continue to have strong correlations with prevalent disease but also maintain predictive associations for new CHD events in older persons with preexisting disease (31,33,71–73). Serum lipids, cigarette smoking, and diabetes appear to be more prominent in this context than hypertension. Blood pressure may fall substantially following myocardial infarction, especially extensive anterior myocardial infarction, which carries a poorer prognosis, thereby confounding the relation between hypertension and CHD morbidity and mortality (74). Blood pressure, however, reemerges as a significant predictor of recurrent CHD events in long-term survivors of myocardial infarction (75).

These findings serve to emphasize the critical role of controlling risk factors in older persons with established CHD. Effective treatment of hypertension, discontinuation of cigarettes, and adequate control of hyperglycemia are important measures in the preventive clinical management of such individuals. The potential benefit of lipid-lowering drugs in older persons with established CHD and hypercholesterolemia was alluded to earlier.

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Other Risk Factors

Several hematological or hemostatic factors have been described as risk variables in the Framingham Study. Hematocrit appeared to contribute to CHD in younger men and women in this analysis, but not in older persons (10). White blood cell count, which was strongly correlated with the number of cigarettes smoked per day, hematocrit, and vital capacity were also associated with enhanced risk for CHD and other cardiovascular endpoints in older men, both in smokers and nonsmokers, but only in women who smoked (76). These data were consistent with reports from other studies (77). Plasma fibrinogen showed strong risk associations for CHD and other cardiovascular disease outcomes in men, including older men (78), similar to findings from other studies (79). Significant risk associations, however, were not apparent in older women.

An extensive array of psychosocial, occupational, dietary, and other factors have been described as putative risk parameters for CHD in the Framingham Study (9,80); however, only limited information is available regarding specific associations of these factors with CHD in older persons. Although family history of CHD is strongly related to early development of CHD (before age 60) in both men and women, in the Framingham study, predictive associations also remained significant for the late onset of CHD (81).

CHD RISK PROFILES IN THE ELDERLY

Although associations between a specific risk factor and CHD can be considered in isolation as a single relation, in many instances combinations of several risk factors may constitute the observed risk profile, especially in older persons. Risk of CHD, in such instances, can be reliably estimated by synthesizing a number of risk factors into a composite score, based on a multiple logistic function (82,83). Risk factors are assessed by standard clinical procedures (smoking history, blood pressure, and electrocardiogram) and by routine laboratory studies (serum total cholesterol, HDL cholesterol, and blood glucose). This type of composite index permits detection of individuals at relatively high risk, either on the basis of marked elevation of a single factor or because of marginal abnormalities of several risk factors.

This multivariate risk scenario is illustrated in Figure 14, which characterizes the risk of CHD at two predefined levels of serum cholesterol and then considers changes in the levels or values of other risk factors toward worsening risk, as indicated in the table below the figure. Note that risk increases progressively with the additional impact of other risk factors for both categories of serum cholesterol, even in instances where a factor such as cigarette smoking has a relatively weak risk association with CHD when considered alone.

The major risk factors including age, when taken together, explain only a limited proportion of the variance of CHD incidence in younger as well as older persons (82,83). It is likely that other major risk attributes exist among both the young and the elderly, but are yet to be identified. It must be emphasized, however, that the factors that have already been delineated do identify high-risk subgroups of the elderly population that should be targeted for preventive management.

PERSPECTIVES FOR PRIMARY PREVENTION OF CHD IN THE ELDERLY

An important principle of prevention is the concept that measures limiting the effect of known risk factors should be initiated as early in life as possible to minimize the subse-

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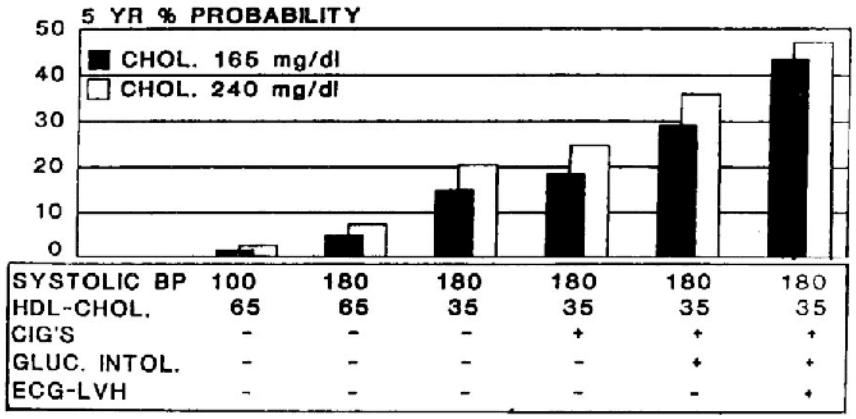

Figure 14 Risk of CHD of two levels of serum cholesterol according to specified levels or categories of other risk factors for 70-year-old women in the Framingham Study.

quent development of disease in both the young and the elderly. It is unreasonable to conclude, however, that modifications of risk factors initiated at advanced age are likely to be ineffective in reducing the toll of related disease in older persons. A simple, but important, observation in this context is that the incidence of CHD in the elderly varies widely within distributions of continuous risk factors such as blood pressure or serum cholesterol. Incidence also appears to differ markedly for values of categorical variables such as the presence or absence of left ventricular hypertrophy. In addition, data presented earlier indicate that the incidence of CHD, as well as other cardiovascular disease events, is not only substantially higher in populations of older persons but also continues to rise with advancing age across the life span. Because incidence is usually higher in older persons, the beneficial effect of a given intervention such as treatment of hypertension or hypercholesterolemia, as assessed by reduction in relative risk, may be similar to or lower than that observed in younger persons (2,20,49,84). In many such instances, however, the same effect measured as a difference in absolute risk, reflecting reduction in numerical toll of disease outcomes, actually remains higher in the elderly. A corollary of this effect is that a smaller number of older as compared to younger people must be treated to yield the same benefit in terms of numbers of disease events prevented.

These considerations are more relevant today than ever before. Recently, a marked and progressive decline in mortality due to coronary and cardiovascular disease has occurred in the U.S. and several other industrialized nations (85). Age-specific trends indicate decreasing mortality due to CHD and cardiovascular disease, both in the elderly and in younger adults of both sexes. Similar trends in cardiovascular mortality have been identified in the Framingham population (86). At the same time, the prevalence of several coronary risk factors, such as untreated hypertension, elevated serum cholesterol levels, and cigarette smoking, has diminished in the population at large, including the elderly, while impressive improvements have occurred in the diagnosis and treatment of CHD. Although the available information supports the contention that both of these potentially beneficial effects have contributed to the observed decline in mortality from CHD, the present consensus gives greater weight to the success of widespread primary preventive strategies, resulting in lowered levels of major risk factors that contribute to disease, rather than to improved diagnosis and treatment of established disease (87).

In this context, hypertension clearly emerges as the dominant, potentially remediable, risk factor for both CHD and cerebrovascular disease morbidity and mortality in the elderly. Hypertension is highly prevalent in the aged, easily detected, and can be corrected by the careful application of appropriate measures, including drug therapy. As mentioned earlier, direct evidence from clinical trials has already established the efficacy of antihypertensive measures in reducing the frequency of both stroke and CHD events in elderly hypertensives. Available information also makes a compelling case for discontinuation of cigarettes at all ages including the elderly. Information is needed, however, regarding the feasibility and effectiveness of nonpharmacological approaches such as diet and weight reduction in treating older persons with hypertension and lipid abnormalities both as initial therapy and as adjuncts to specific drug therapy. Also, as a matter of critical importance, the efficacy and safety of drug therapy for the treatment of lipid abnormalities in the elderly for the purpose of primary prevention should be established in large, well-designed clinical trials. Lack of such information severely limits our confidence in extending what may be a potentialy beneficial preventive measure to greater numbers of older persons.

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Pathophysiology of Coronary Artery Disease in the Elderly

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INTRODUCTION

Atherosclerotic involvement of coronary arteries with subsequent coronary heart disease is the leading cause of death and disability in the elderly. Approximately half of all deaths of persons older than 65 years of age are the result of coronary artery disease, and of all coronary deaths, 80% occur in patients 65 years of age or older (1,2). Although risk factor modification and advances in therapeutic modalities have resulted in a welcome decline in cardiovascular mortality during the past two decades, recent statistics indicate that this decline is less notable in the elderly, the fastest growing segment of society (3,4). In fact, with the aging of the population, the overall prevalence, mortality, and cost of coronary artery disease will increase (3,4). It has been projected that cardiovascular disease worldwide will climb from the second most common cause of death, with 29% of all deaths in 1990, to first place, with more than 36% of all deaths in 2020. This is more than twice the percentage of deaths from cancer (5). Thus, for the first time in human history, cardiovascular disease is likely to become the most common cause of death worldwide. Therefore, efforts to increase our knowledge in the pathophysiology of the atherosclerotic involvement of coronary arteries aimed to reduce the mortality, disability, and cost associated with coronary heart disease are an important public health priority. This chapter will provide pathophysiological explanation for the broad spectrum of ischemic coronary syndromes based on the most recent cell biology and molecular biology studies of the arterial wall.

INITIATION OF ATHEROSCLEROTIC LESIONS

Atherosclerosis is a primarily focal intimal disease of arteries ranging from the size of the aorta to the size of tertiary branches of coronary arteries (1 mm diameter). By definition,

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atherosclerosis is characterized by atherosis (soft, lipid) and sclerosis (hard, collagenous). In the prevalent view, atherosclerosis is considered a healing response of the arterial wall to various injurious stimuli (6). Chronic injury to the vessel wall in certain parts of the arterial tree may initially lead to endothelial dysfunction. Such dysfunction is characterized by an increased uptake of low-density lipoproteins (LDL) and enhanced monocyte recruitment into the vessel wall, both pivotal initiating events for atherosclerosis. Endothelial injurious stimuli to initiate atherosclerotic lesions may be classified into systemic and local risk factors (Table 1).

Systemic Atherogenic Risk Factors

There is actually general agreement to accept that hypercholesterolemia is an important causative factor in atherogenesis and that correction of it can strikingly reduce the risk of coronary heart disease. However, how cholesterol interacts with the cells of the arterial wall to initiate the atherogenic process has been only recently elucidated (7). Experimental studies have suggested a direct injurious effect of elevated levels of LDL cholesterol, in particular its oxidative derivative, on the endothelium (8,9). Two distinct mechanisms that link oxidative stress with impairment in endothelium-dependent vasodilatation have been described. First, lysolecithin, a product formed as a consequence of lipid peroxidation of LDL particles, may be involved in the development of abnormal arterial vasomotion (10). Second, hypercholesterolemia may be a stimulus to augmented generation of superoxide radicals by the endothelium (11) which directly inactivates nitric oxide and also increases the subsequent oxidation of LDL particles by the formation of peroxynitrate. More importantly, a randomized study has shown that coronary artery endothelial dysfunction in patients with hypercholesterolemia and atherosclerosis can be significantly improved by a combination of LDL-lowering and antioxidant therapy (12).

Chronic hyperglycemia may also damage the vascular endothelium, resulting in abnormal vasomotion (9,13). Extended exposure to hyperglycemia results in the glycation (i.e., the nonenzymatic conjugation of glucose) of extracellular matrix proteins, which leads to the formation of advanced glycosylation end products (13). Accumulation of nonenzymatic advance glycosylation end products in the vessel wall leads to increased vessel stiffness, lipoprotein binding, macrophage recruitment, secretion of platelet-derived growth factor, and proliferation of vascular smooth muscle cells (14). Other forms of endothelial injury such as those that can be induced by chemical irritants in tobacco smoke

Table 1 Endothelial Injurious Stimuli to Initiate Atherosclerotic Lesions

Systemic risk factors:	hypercholesterolemia
	chronic hyperglycemia
	tobacco smoke
	hypertension
	chronic infections (?)
Local risk factors:	low shear stress
	arterial bifurcations and trifurcations
	vascular bending points
	vascular curvatures

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or circulating vasoactive amines (9,15,16) may potentiate chronic endothelial injury favoring accumulation of lipids and monocytes into the intima.

Interestingly, conventional risk factors, such as lipids, diabetes, smoking, and hypertension, do not fully explain the diversity of this disease and why interventions have not reduced its incidence as much as epidemiologists have predicted. An infectious hypothesis for atherogenesis, proposed more than 20 years ago (17–19), could fit well into the currently accepted response-to-injury model of atherogenesis. Accordingly, chronic infections by inducing endothelial dysfunction and by increasing hypercoagulability, could contribute to initiate atherosclerotic lesion formation (20). Specifically, chlamydia pneumoniae, an intracellular organism, has been shown in case-controlled studies to be associated with coronary artery disease, atherosclerotic carotid disease, and stroke (21,22). However, proof that a risk factor is of causal importance and not merely statistically associated with disease requires the demonstration that its elimination or modification actually reduces the frequency of clinical manifestations. Whether chlamydia pneumoniae is an innocent bystander or whether it is a vicious assassin causing endothelial damage, hypercoagulability, and macrophage activation, remains uncertain. Large randomized, double-blind, placebo-controlled studies are underway to elucidate the precise value of antibiotic eradication therapy, at least in those patients with atherosclerotic disease who are seropositive for infection (23,24).

Local Atherogenic Risk Factors

Despite exposure of different areas of the endothelial surface to the same injurious stimuli concentration, spontaneous atherosclerotic lesions only develop in certain locations. Clearly, there must be local factors that modulate the impact of hypercholesterolemia and other risk factors on the vessel wall, determining the location and possibly the rate of atherosclerosis progression (25,26). Atherosclerotic plaques are located more frequently near bifurcations, near trifurcations, and in curvatures of vessels compared with other sites in the arterial tree (27–29). It is believed that disturbances in the pattern of blood flow in certain parts of the arterial tree, such as bending points and areas near branching vessels, might promote the development of atherosclerotic lesions. A recent study using a three-dimensional reconstruction technique to calculate shear stress on the endothelium has shown, for the first time in human vessels in vivo, evidence that low shear stress promotes atherosclerosis (30). Experimentally, it has been shown that endothelial cells undergo morphological alterations in response to change in the degree and orientation of shear forces. Whereas elongated endothelial cells are located in regions of high shear stress, polygonal endothelial cells are located in low shear stress regions (31,32). All these alterations may well explain changes in endothelial cell permeability for atherogenic lipoprotein particles (25,26,33).

PROGRESSION OF ATHEROSCLEROTIC LESIONS

In an effort to fit the morphological characteristics of the various atherosclerotic lesions (Fig. 1) into an overall framework that explains the pathogenesis and progression of the disease, the American Heart Association Committee on Vascular Lesions has outlined the morphological characteristics of the various lesions in five phases of progression of coronary atherosclerosis (33). In the first three decades of life, the composition of the lesions

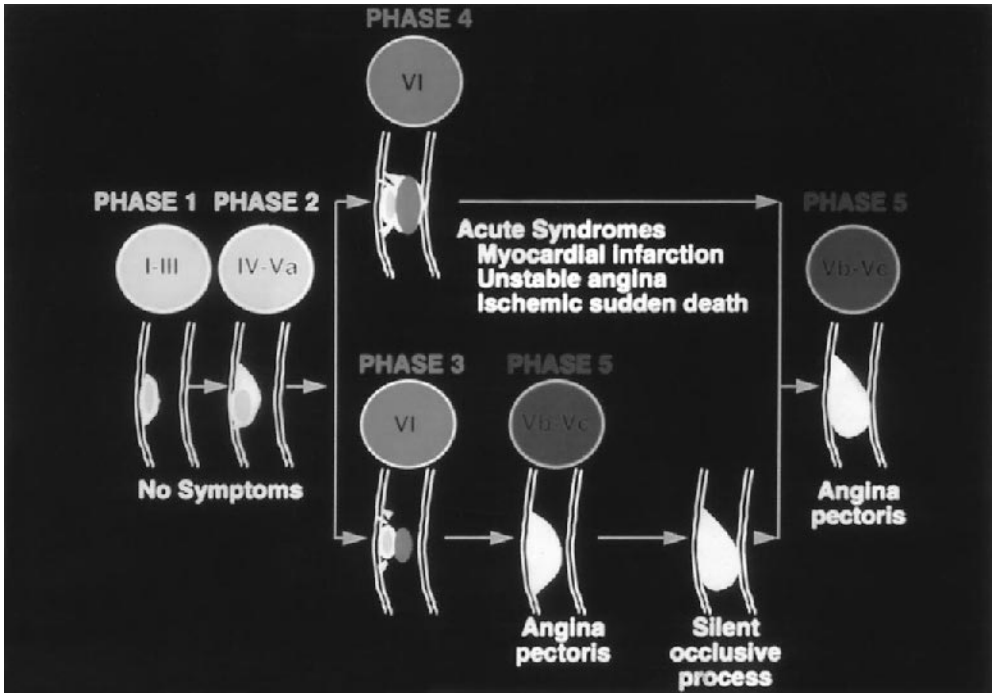

Figure 1 Schematic of staging (phases and lesion morphology of the progression of coronary atherosclerosis according to gross pathological and clinical findings. (Modified, with permission, from Ref. 37.)

are predominantly lipidic and relatively predictable (phases 1 and 2). However, from the fourth decade on, the composition of advanced plaques becomes unpredictable because some lesions continue to increase by mechanisms other than lipid deposition (phases 3 and 4), whereas other lesions grow by means of cellular proliferation and extracellular matrix formation (phase 5). Morphological studies by Stary (34) indicate that a plaque can take from 10 to 15 years to fully develop. Arteries may show all stages of plaque evolution, implying that new lesions are generated throughout life. Even in the same individual, there are major plaque-to-plaque variations in the relative proportions of extracellular lipid and collagen that are present (35).

Phase 1: Slow Progression of Atherosclerotic Lesions

Lipid accumulation, macrophage formation, and cell proliferation constitute the initial key events in atherosclerotic progression. Early stages of atherosclerotic plaque evolution are differentiated by their proportion of lipids, macrophages, and smooth muscle cells and by whether the lipid is intracellular or extracellular.

Lipid Accumulation into the Vessel Wall

Hypercholesterolemia is most commonly associated with an elevation of plasma LDL, and LDL is the ultimate source of the cholesterol that accumulates in atherosclerotic

plaques. The internalization and intravascular accumulation of cholesterol probably depend on two mechanisms: one is active and dependent on specific receptors located in the endothelial cells (and the other cells within the vessel wall) (36), and the other is passive and receptor-independent, presumably when endothelial damage is significant (15,37). The LDL membrane receptor, discovered by Goldstein and Brown (38), tightly regulates the cholesterol content of cells by increasing or decreasing the uptake of LDL according to needs for cholesterol. This applies perfectly to monocyte/macrophages and smooth muscle cells, which, under normal conditions, cannot increase their cholesterol content beyond a certain point even in the presence of a very high concentration of native LDL in the medium (39). Importantly, Goldstein et al. (40) showed that chemical acetylation of LDL modified it to a form that was taken up rapidly enough by macrophages to generate foam cells. They showed further that modified LDL uptake occurred via a specific, saturable receptor—the acetyl LDL receptor. Unlike the native LDL receptor, this receptor did not downregulate when the cholesterol content of the cell increased, so the cell continued to take up acetyl LDL until it became engorged with stored cholesterol esters.

However, because there is little or no evidence that acetylation of LDL occurs to any significant extent in vivo, the search for other biologically feasible modifications of LDL has continued. Experimental studies have shown that what the cells actually do is simply to oxidize the LDL (41–45). Such oxidation of LDL is an incredibly complex process involving oxidation of all classes of lipids and the protein moieties (46–48), resulting in a broad spectrum of ''oxidized LDLs'' that can differ not only structurally but functionally. Although, to this day, we cannot describe with great detail the conditions in which LDL undergoes oxidative modification in vivo, we are sure that oxidative modification of LDL particles plays a major role in the pathogenesis of lipid accumulation into atherosclerotic vessel wall (45,49). Several lines of evidence are available both in experimental animal models and in humans to indicate that oxidation of LDL does indeed occur in vivo. First, it has been demonstrated that LDL gently extracted from atherosclerotic lesions is in part oxidatively modified (50,51). Second, immunohistochemistry has shown that atherosclerotic lesions contain materials reactive with antibodies generated against oxidized LDL (52–54). Third, circulating antibodies react with oxidized LDL (53), implying the presence in vivo of oxidized LDL itself or a very similar antigen. Finally, and most important, evidence that intervention with antioxidants can slow the progression of the disease is provided by a large number of studies in experimental animals (55,56) and, recently, in a clinical study using vitamin E in patients with coronary artery disease demonstrated by angiography (57).

Monocyte Recruitment and Macrophage Formation

Monocytes/macrophages are involved in many aspects of the development of atherosclerotic plaques (6,33,37). It is likely that the focal accumulation of monocytes/macrophages in atherogenesis involves the local expression of specific adhesive glycoproteins on the endothelial surface and the generation of chemotactic factors by altered endothelium, its adherent leukocytes, and possibly underlying smooth muscle cells. Oxidized LDL may also play an initial role in monocyte recruitment by inducing the expression of adhesive cell-surface glycoproteins in the endothelium, the most important being E-selectin, VCAM-1 (athero-ELAM), ICAM-1, and a recently characterized leukocyte-binding molecule (58–62). Later on, several specific molecules may be relevant in attracting monocytes to the subendothelial space, such as specific chemotactic protein [monocyte chemotactic

protein-1, MCP-1] synthesized by vascular cells, colony stimulating factors (CSFs), and transforming growth factor-β (TGF-β) (63). In more advanced stages, during which there is significant connective tissue production and tissue necrosis, peptide fragments from fibrin, fibronectin, elastin, collagen degradation, and thrombin may be the predominant monocyte chemoattractants elaborated (64–66). A nice experimental study has recently demonstrated the inhibition of in vivo macrophage homing to atherosclerotic plaques by using specific inhibitors of adhesive molecules, such as antibodies against the α-subunit of the $\alpha_4\beta_1$ integrin and against ICAM-1 (67).

After entering the vessel wall, monocytes undergo a remarkable series of changes in their biological properties to become tissue macrophages. Among various receptors expressed by cultured macrophages, the acetyl-LDL or scavenger receptor increases dramatically, and is responsible for much of the uptake of lipoprotein that converts the macrophage into a foam cell. Such lipid-laden cells constitute the hallmark component of fatty streaks, the initial visible phase of atherosclerotic lesions (33,37). Recently, experimental studies have shown at least three additional different receptors involved in the binding and uptake of oxidized LDL by macrophages, namely, the CD36, Fc receptor, and microsilain (68–70), but how important each of them may be under in vivo conditions remains to be established. Additionally, it has been suggested that some of the lipid-laden cells in fatty streaks may be derived from smooth muscle cells, but the number of such cells is small compared to the number of macrophages-derived foam cells. Certainly, smooth muscle cells play their major role in the progression of atherosclerotic lesions by their replication and synthesis of connective tissue matrix as we will discuss below.

Smooth Muscle Cell Proliferation

Migration and proliferation of smooth muscle cells into the subendothelial space has been established as a key event in the evolution of atherosclerosis. The synthetic phenotype of smooth muscle cells is capable of expressing genes for a number of growth-regulatory molecule and cytokine receptors (6). They can respond to those mediators by proliferation and synthesis of extracelluar matrix. Smooth muscle cells isolated from atheroma can also secrete mitogenic proteins, some of which resemble platelet-derived growth factor (PDGF) (71). This capacity to produce endogenous, potentially self-stimulating growth factors may help to explain how replication of smooth muscle cells can begin in early phases of atherogenesis.

Vascular smooth muscle cells are the primary source for the extracelluar matrix accumulation characteristic of atherosclerosis and hypertensive arteries. Extracellular matrix primarily comprises collagen, elastin, proteoglycans, and microfibrillar proteins. Several cytokines, growth factors, and mechanical factors in the atheroma regulate the synthesis of matrix components; for example, TGF-β potentially stimulates collagen synthesis, whereas interferon-γ (IFN-γ) suppresses expression of collagen (63,72,73), and chronic pulsatile distention in the arterial wall also favors the synthesis of collagen by smooth muscle cells (72). Once cellular matrix constituents are secreted, they must organize into a functional three-dimensional structure. Smooth muscle cells, as well as fibroblasts and other cells, not only secrete collagen but also have β_1 integrins that serve as receptor for collagen participating in the process of matrix organization (74).

Phase 2: Unstable Lipid-Rich Plaque Formation

If excess influx of lipids predominates over its efflux and over the proliferative response, the atherosclerotic process progresses into the more clinically relevant phase 2 of plaque evolution, where the so-called unstable lipid-rich lesions develop (Figs. 2 and 3).

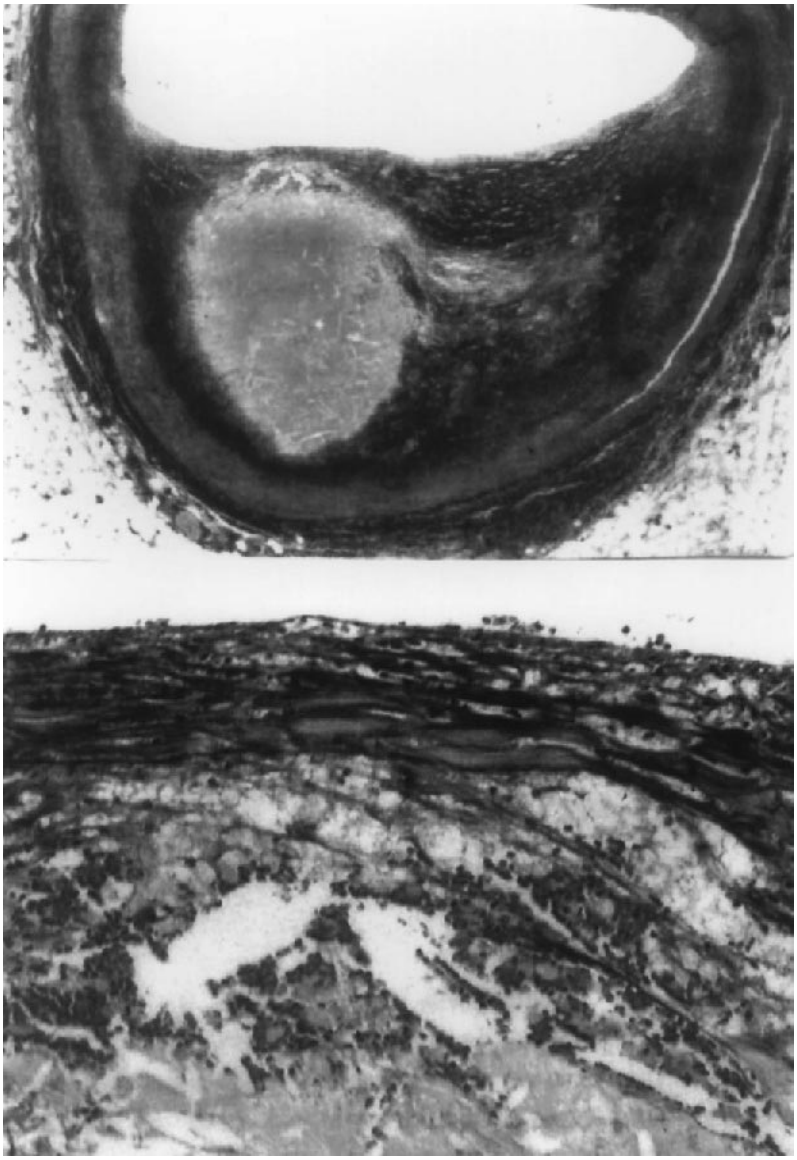

Figure 2 Photomicrographs illustrating composition and vulnerability of coronary plaques. A vulnerable plaque containing a core of soft atheromatous gruel (devoid of blue-stained collagen) that is separated from the vascular lumen by a thin cap of fibrous tissue. The fibrous cap is infiltrated by foam cells that can be clearly seen at high magnification, indicating ongoing disease activity. Such a thin and macrophage-infiltrated cap is probably weak and vulnerable, and it was indeed disrupted nearby, explaining why erythrocytes (red) can be seen in the gruel just beneath the macrophage-infiltrated cap. (From Ref. 74a, with permission.)

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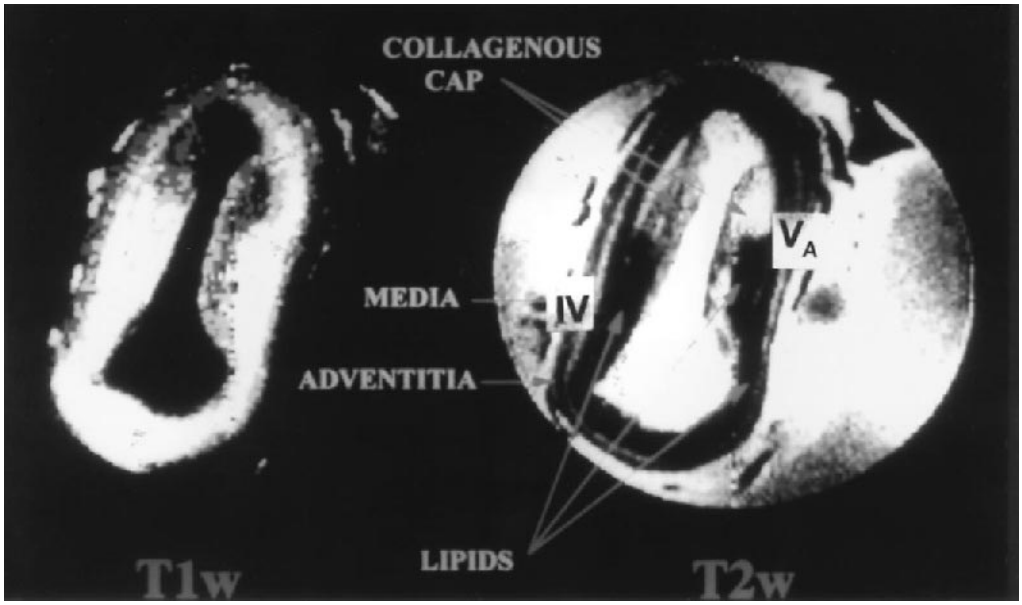

Figure 3 Nuclear magnetic resonance images of vulnerable or unstable lesions. T2w image identifies a collagenous cap on both plaques. In the type V lesions (right), the cap completely covers the lipid core. In the type IV lesions (left), the plaque is only partially covered, and infiltration of fat is more diffuse. (Modified, with permission, from Ref. 179.)

Lipid-Rich Core Formation

Atherosclerotic stage of evolution with a predominance of extracellular lipids occupying a defined region of the intima and separated from the vascular lumen by a thin fibrous cap constitutes advanced unstable lipid-rich lesions. This type of extracelluar lipid accumulation is known as the lipid core (75), and this is the most clinically relevant type of lesions since it is the pathogenic basis for plaque rupture and thrombus formation.

Little is known of what determines core size. Extracelluar accumulation of lipids appears to be mainly due to rupture of macrophages and to accumulated debris resulting from cell death (75). Since the macrophage receptor for modified LDL is not regulated, excessive intracellular accumulation of lipoproteins may lead to destruction of the cell with subsequent release of oxidized LDL and free radicals, which can cause cytotoxicity and further damage to the surrounded cells. Characteristically, the lipid core is relatively avascular and hypocellular, containing mainly cholesterol monohydrate, cholesterol esters, and phospholipids. Extracellular deposits of cholesterol esters are water insoluble and form an oil–lipid crystalline phase; however, as lesions progress, additional extracellular accumulation of free cholesterol results in the formation of cholesterol crystals into the lipid core (34). The lipid core is several orders of magnitude softer that the typical fibrous cap, with a semifluid consistency at body temperature (76). This mechanical property is likely to be a critical factor in determining plaque stability. The softer the lipid core, the more stress the overlying fibrous cap must bear and the higher the likelihood of plaque rupture.

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Plaque Vulnerability to Rupture

Plaque rupture is a mechanical event that depends on an imbalance between the stress imposed on the plaque cap in systole and the innate strength (resistance to fracture) of the cap tissue. In the coronary tree, marked oscillations in shear stress, acute change in coronary pressure or tone, and bending and twisting of an artery during each heart contraction could contribute to plaque rupture. Under some circumstances the collagenous extracelluar matrix of the fibrous cap cannot withstand these stresses, and the fibrous cap ruptures. Morphological features that characterize unstable atheroma include a thin, eccentric fibrous cap and a large necrotic core of lipids and cellular debris (77). This plaque configuration is particularly unstable because large mechanical stresses develop in the thinnest portion of the fibrous cap (78,79). In addition, a particular configuration of the plaque in which the lipid core is situated eccentrically is most often associated with fissuring (79). Computer modeling analysis of tensile stress across the vessel wall has shown high concentrations of stress at the ends of plaque caps overlaying an area of lipid pool, particularly when the extracellular lipid pool exceeds ~45% of the vessel wall circumference (76,79). In this area, the plaque cap lacks underlying collagen support and is more susceptible to rupture. The soft lipid core is unable to bear the mechanical forces, and excess stresses are thus concentrated in the fibrous cap, particularly at the junction with the normal vessel (the shoulder region).

Numerous recent observations tell us that other critical factors contribute to the ultimate fracture of the fibrous cap. Atheromas with similar geometric features rupture and others do not (80). A body of consistent evidence supports the view that the extracellular matrix of the fibrous cap is a dynamic, biologically active environment, and there is potential for modulating the biological activity of the fibrous cap. In fact, the fibrous cap matrix could be weakened by enzymatic degradation. It is now clear that some degree of ongoing matrix degradation is a highly controlled and essential component of normal tissue homeostasis. There are three major pathways of extracellular matrix degradation: the serine proteases, which include urokinase-type plasminogen activator and plasmin; the cysteine proteases; and the matrix metalloproteinases (MMPs). Experiments showing an increase in collagen breakdown when monocyte-derived macrophages are incubated with human aortic plaques (81) clearly indicate that macrophages could be responsible for plaque disruption. In addition, atherectomy specimens obtained from patients with unstable coronary syndromes have revealed significantly larger macrophage-rich areas compared with patients with stable angina (82), further supporting that macrophages play a crucial role in the inflammatory component of the acute coronary syndromes. Activated macrophages may synthesize and secrete MMPs into the extracellular space. Most MMPs are secreted as proenzymes and they must be activated into the extracellular space. The mechanism of in vivo MMP activation is unclear and may involve plasmin, urokinase-type plasminogen activator, membrane-type MMPs, or even autoactivation (83). Even after MMPs are activated, they may be inhibited. Specific endogenous inhibitors called tissue inhibitors of metalloproteinases (TIMPs) have an amino-terminal domain that binds to available MMP active sites on a 1:1 stoichiometric basis, thereby inhibiting these enzymes (84,85). Although several works have shown increased gene expression and presence of immunoreactive enzymes in the human atheroma (86–88), more interestingly, it has been demonstrated by technique of in situ zymography that excess matrix degrading activity is indeed present in the human atheroma, particularly in the shoulder region of

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the atheroma, where mechanical stresses are highest (89). In addition, in the presence of cytokines such as tumor necrosis factor-α (TNF-α) or interleukin (IL)-1β, smooth muscle cells by themselves may markedly increase synthesis of MMP-1 and MMP-3 (90). One additional sequence of events might be that infiltrating macrophages secrete cytokines that stimulate smooth muscle cells to produce MMPs.

A fascinating pathological observation is that fibrous caps that have ruptured have not only twice as many macrophages as unruptured fibrous caps but also half as many smooth muscle cells. Therefore, at the same time that inflammation and matrix degradation decrease plaque strength, inadequate numbers of smooth muscle cells may be present to repair the degradation. Recent findings suggest that smooth muscle cells of the atheroma undergo programmed cell death or apoptosis (91,92). The precise signals that regulate apoptosis in the atheroma are unknown, as multiple stimuli can provoke this process. Some proteins, including IL-1β-converting enzyme, TNF-α, interferon-γ, or the tumor suppressor p53 sometimes function as apoptosis on signals, while genes such as bcl-2 can function as apoptosis off genes (93,94). Lack of sufficient smooth muscle cells to secrete and organize the matrix in response to mechanical stress could render the fibrous cap even more vulnerable to weakening by extracellular matrix degradation.

Phase 3: Rapid Thrombus-Mediated Progression

Not every plaque disruption results in an acute coronary event. In fact, plaque rupture that culminates into an acute coronary syndrome is the ''exception rather than the rule'' (95,96). Plaque rupture with nonocclusive thrombus formation and activation of the inflammatory and reparative processes may be an important mechanism of plaque growth. Postmortem studies have reported that plaque ruptures can be found in 9% of subjects who died of noncardiac causes and in as many as 22% of patients with diabetes or hypertension (97). Fractured fibrous caps with intense inflammation are also a common finding in the abdominal aorta at necropsy, and asymptomatic carotid plaque rupture may be found in almost one-fifth of elderly persons at autopsy (98). Most plaque ruptures are probably asymptomatic; lack of symptoms may result from limited, nonocclusive mural or intramural thrombus or from maintained perfusion by collateral vessels.

Recently, a second mechanism of plaque disruption leading to coronary thrombosis has been described: superficial erosion of the endothelium (99). Small areas of endothelial denudation over established coronary plaques may lead to the adhesion of a monolayer of platelets, such microthrombi are too small either to be visible on angiography or to cause symptoms directly, but they may stimulate smooth muscle proliferation promoting plaque growth (6,15,90). Endothelial erosion and plaque rupture also differ in that after endothelial erosion the thrombus is laid down on the surface of the plaque, whereas in rupture there is an additional component of the thrombus deep within the lipid core of the ruptured plaque (100). At autopsy studies, erosions were less often associated with infiltration by macrophages and T cells and more often associated with proteoglycan-rich plaque and clusters of smooth muscle cells adjacent to the thrombi (99–102). Pathologists have suggested that plaque rupture is more common than erosion as a cause of major thrombi by a ratio of 3 to 1 (103).

The hypothesis that progression of atherosclerotic plaques may be brought about by thrombosis (104,105) has been for years overshadowed by a large body of literature on lipids and lipoproteins. However, recent angiographic studies have shown unequivo-

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cally that the progression of early atherosclerotic lesions to clinically manifest, enlarged atherosclerotic plaques, such as those which cause blood flow impairment, is frequently neither lineal nor predictable (106,107). While the process of lipid accumulation, cell proliferation, and extracellular matrix synthesis may be expected to be linear with time, new high-grade lesions often appear in segments of arteries that were normal at previous angiographic examination. Moreover, complex lesions in patients awaiting coronary angioplasty were more likely to progress in severity than smooth-shape lesions, even in the absence of acute coronary ischemic symptoms (108); analysis of the coronary tree in patients who died of ischemic heart disease has shown a morphological appearance consistent with previously healed fissures at different stages of thrombosis and thrombus organization (109), and fibrinogen and fibrin concentration in cholesterol-rich advanced plaques have been found to be 10 times higher than in normal vessels (110). It may well be that the healing organization process of intraplaque thrombi contributes to subclinical progression of the lesions through interactions between thrombotic elements and vascular cells. Besides platelets (6,111), thrombin has been shown to be a potent mitogen for mesenchymal-derived cells and it is chemotactic for monocytes (112,113); fibrinogen and its degradation products may also contribute to lesion progression by their ability to stimulate vascular cell proliferation (114). Therefore, thrombus formation in an artery may not only lead to occlusion of the vessel (115), but also contribute to the development of the atheromatous lesion itself. Therefore, it is likely that many lesions grow through small plaque rupture or superficial plaque erosion followed by wound repair of the breached lesion.

Importantly, although thrombus-mediated progression is clinically silent in most cases, it has important prognostic value. Clinically silent coronary atherosclerotic progression, assessed by angiography, was shown to be a strong and independent predictor of future coronary events, particularly cardiac death (116). Interestingly, this atherosclerotic progression is often more rapid in persons with coronary risk factors, and in lesions with certain topographic characteristics (37,117,118). In the Coronary Artery Surgery Study (CASS) (117), diabetes, proximal or midvessel coronary lesion location, elevated cholesterol, interval from myocardial infarction, and complex lesion morphology were identified as predictors of angiographic progression; and other angiographic study has found serum concentrations of Lp(a) clearly related to rapid progression of coronary artery disease (119).

Phase 4: Plaque Rupture and Occlusive Thrombus Formation

Although most ruptured plaques could be resealed by a small mural thrombus that becomes organized contributing to an episodic, clinically silent, growth of the lesion, occasionally large thrombi can impair coronary blood flow leading to acute syndromes of myocardial ischemia (37,96,118). It is likely that many variables determine whether a ruptured plaque proceeds rapidly to an occlusive thrombus with the potential for acute ischemic events or persists at an intermediate stage as a mural, nonocclusive, clinically silent thrombus. Local factors such as quantity (fissure size), quality of thrombogenic substrate (plaque composition), and rheology of blood flow at the site of plaque rupture, together with systemic factors inducing hypercoagulable or thrombogenic states (chatecolamines, lipoprotein(a), fibrinolytic system) may modulate thrombosis at the time of plaque rupture (Table 2) (120).

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Table 2 Determinants for Thrombotic Response Following Plaque Rupture

Local thrombogenic factors:	degree of plaque disruption
	tissue substrate
	degree of stenosis
	surface roughness
	residual thrombus
Systemic thrombogenic factors:	high levels of catecholamines
	cholesterol levels, lipoprotein(a), and other metabolic states
	fibrinolysis, platelets and coagulation activity
	Infections?

Local Thrombogenic Factors

Degree of plaque disruption. Experimentally, exposure of subendothelial superficial layers to flowing blood at high shear rate (mimicking a stenosed coronary artery) induces platelet adhesion and aggregation, but the thrombus is labile and may be partially dislodged from the substrate by the flowing blood leaving a small residual mural thrombus (121,122). However, exposure of deeper vascular layers to flowing blood produces a dense platelet thrombus that cannot be easily dislodged (121,122). As a clinical counterpart, probably when only the surface of a coronary plaque is eroded, the thrombogenic stimulus is relatively limited, resulting in small mural thrombosis with subsequent thrombus organization and asymptomatic growth of the lesion; however, a greater degree of plaque damage may be a marker of more extensive coronary thrombus formation leading to unstable angina, and an even more complex atherosclerotic plaque rupture may lead to persistent thrombotic coronary occlusion responsible for acute myocardial infarction.

Tissue substrate. Two retrospective clinical studies suggesting that myocardial infarction developed more frequently from previous nonsevere coronary lesions (106,107), and a recent angiographic study showing that the atheromatous plaque substrate may be different in Q-wave and non-Q-wave myocardial infarction (123), support the idea that plaque composition may be more important than plaque size for developing acute coronary syndromes. Moreover, differences in the incidence of total coronary occlusion among different acute coronary syndromes suggest possible differences in the pathological coronary substrate, being a more powerful triggering substrate responsible for a greater production of activated procoagulant factors, a larger thrombus formation, and hence a more severe coronary ischemic event (124).

Experimentally, the thrombotic response is influenced by the various components of the atherosclerotic plaque exposed following rupture. Exposure of macrophage-rich or collagen-rich matrix, which might be present in superficial plaque erosions or small plaque fissures, is associated with less platelet deposition than that seen after exposure of the lipid-rich core of the plaque (125). The lipid core is about sixfold more thrombogenic than the collagen-rich component of the plaque (125). Therefore, atheromatous plaques containing lipid-rich ''gruel'' are not only the most vulnerable plaques to rupture, but also they are the most thrombogenic when their content is exposed to flowing blood. Although, the component(s) responsible for such high thrombogenicity found in the gruel is unknown, tissue factor protein (derived from disintegrated macrophages?) has been proposed as a key factor initiating the thrombotic response. Tissue factor protein has been identified immunohistochemically in a scattered pattern within the atheromatous core of human carotid plaques (126), tissue factor expression has been more frequently found

on macrophages in the coronary atherosclerotic plaques of patients with unstable angina (127,128) and, more importantly, tissue factor has been recently demonstrated as a mediator of the increased thrombogenicity of atheromatous lesions by use of an in situ binding assay for factor VIIa (129). However, it is likely that other components of the gruel, such as lipids or collagen degradation products, might also contribute to induce platelet aggregation and activation of the coagulation system.

Degree of stenosis. Acute thrombotic response to plaque disruption depends also in part on the degree of stenosis and sudden geometric changes following the rupture (96). High shear rates at the site of a significant stenosis will predispose to increased platelet and fibrin(ogen) deposition by forcing both to the periphery where they may be deposited at the site of plaque damage (122,130,131). A small geometric change with only mild stenosis may result in a small mural thrombus, whereas a larger geometric change with severe stenosis may result in a transient or persistent thrombotic occlusion. Furthermore, the disruption of a plaque at the apex of a stenosis may result in a thrombus that is richer in platelets (121,122) and, therefore, less amenable to fibrinolytic agents than a thrombus formed in a zone distal to the apex (121,122,130).

Surface roughness. Besides degree of stenosis and the nature of the exposed thrombogenic material, fibrous cap disruption produces a rough surface within the arterial lumen that further stimulates the development of acute thrombosis. Recent data derived from ex vivo perfusion studies on human aortic atherosclerotic plaques have shown that the roughness of the exposed surface, measured by presence of microscopic flaps, dissections, fissures, and surface irregularities at the site of plaque rupture, also influence thrombogenicity (125). As roughness increases, thombogenicity increases probably due to the effect of local flow disturbances on the surface of the ruptured plaque.

Residual thrombus. After spontaneous lysis, residual mural thrombus predisposes to recurrent thrombotic vessel occlusion (132–134). Several factors that contribute to rethrombosis have been identified. The residual mural thrombus may encroach into the vessel lumen, resulting in increased stenosis and an increased shear rate, which facilitates the activation and deposition of platelets and fibrinogen (122,130,135). The thrombus itself, compared with a deeply injured arterial wall, is very thrombogenic (136) and continues to grow during heparin therapy, but is inhibited by direct antithrombins (136,137). After thrombolysis, thrombin bound to fibrin may become exposed to the circulating blood, leading to platelet and clotting activation and further thrombosis (138,139). Clinical studies have also suggested that the enhancement of platelet and thrombin activity by thrombolytic agents themselves may contribute to rethrombosis (140,141).

Systemic Thrombogenic Factors

Besides local factors, clinical and experimental evidence have suggested that systemic factors inducing a primary hypercoagulable or thrombogenic state may be responsible for formation of a large thrombus after plaque disruption.

High levels of catecholamines. Platelet activation and the generation of thrombin may be enhanced by high levels of sympathetic activity (142,143). Whereas much of the epinephrine-thrombogenic mechanism may be related to potentiation of other thrombogenic factors, such as serotonin, ADP, and thromboxane A_2 (144), the effect of norepinephrine on platelet function is controversial (145,146). A recent experimental study has shown opposing effects of plasma epinephrine and norepinephrine on coronary thrombosis (146). It is likely that activities and conditions such as smoking and mental stress, in

which a proportionally greater increase is observed in epinephrine, are associated with an elevated risk of thrombosis, whereas during exercise, where plasma norepinephrine tends to be proportionally greater, a diminished risk of thrombosis exists (146).

Cholesterol levels, lipoprotein(a), and other metabolic states. Hypercholesterolemia has been associated with hypercoagulability and enhanced platelet reactivity manifested at the site of induced experimentally acute vascular damage (147). Enhanced platelet reactivity has also been documented in young patients with a strong family history of coronary artery disease, regardless of whether the coronary disease is related to dyslipoproteinemia (148). However, mechanisms underlying the effect of high serum cholesterol level on acute thrombus formation need further investigation.

Lp(a) is an important risk factor for ischemic heart disease, particularly in persons with familial hypercholesterolemia or with a family history of premature coronary disease (149). Apo(a) is a glycoprotein present in Lp(a) that has close structural homology with plasminogen, with both genes being clearly linked on the long arm of chromosome 6 (150). There is evidence to suggest that the close homology of Lp(a) with plasminogen results in competitive inhibition of the fibrinolytic properties of plasminogen (151), thus predisposing patients to acute thrombotic complications. In a recent angiographic study, patients with rapid progression of coronary artery disease were found to have an increased level of Lp(a) when compared to those without progression, further supporting the role of Lp(a) in atherosclerotic disease (119). A decrease in HDL-associated Apo A-1 in patients with unstable angina and during the acute phase of myocardial infarction has suggested that HDL may also play a part in preventing intracoronary thrombus formation, in addition to the generally accepted biochemical property of HDL to prevent the accumulation of cholesterol by mobilizing free cholesterol from tissues or macrophages. It has been suggested that HDL stabilizes PGI_2 through the newly discovered function of Apo A-1, which is associated with the surface of HDL particles and identified as PGI_2 stabilizing factor (152). There is also a PGI_2 synthesis-stimulating factor in serum that has not yet been identified chemically.

Other metabolic abnormalities, such as diabetes mellitus, may enhance platelet reactivity and coagulation, perhaps through an increase in plasma von Willebrand factor (153), or other plasma factor, or through an alteration of the free cholesterol content of platelet membranes secondary to the changes of plasma lipoproteins (154). Consistent with the enhancement in thrombogenicity, a substantial increase in the incidence of myocardial infarction and microangiopathy has been observed in nonintensively treated diabetics (155,156). Other metabolic conditions, such as heterozygous homocystinuria or homocystinemia, are considered to be more atherogenic than thrombogenic risk factors.

Impaired fibrinolysis, enhanced platelet and coagulation activity, and high fibrinogen and factor VII levels. The above discussion on the effects of cathecholamines, cholesterol, and diabetes on enhancing platelet and coagulation activity and myocardial infarction opens the possibility that activated platelets and coagulation may be thrombogenic risk factors in patients with coronary disease. A recent study suggests that in patients with coronary disease, enhanced thrombin-induced platelet aggregation is a marker for subsequent acute coronary events and disease progression (157). It is also of interest that patients, long after clinical stabilization of an acute coronary syndrome, exhibit an increased basal level of thrombin generation as measured by serum fragments 1 and 2, and of thrombin activity as measured by serum fibrinopeptide A, suggesting that such increased activity may serve as a trigger of the primary or recurrent ischemic events (158).

Most important, other hemostatic proteins, specifically fibrinogen and factor VII,

have been implicated as major thrombogenic risk factors. Several prospective studies have shown a high plasma fibrinogen concentration to be a highly significant independent risk factor for coronary artery disease, specifically associated with myocardial infarction (159). High levels of factor VII coagulant activity are also associated with an increased risk of coronary events (159). Both proteins are elevated in relation to age, obesity, hyperlipidemia, diabetes, smoking, and emotional stress (160,161), and thus they may also explain partially the effect of other risk factors associated with the disease.

Phase 5: Stable Collagen-Rich Plaque Formation

Alternatively to plaque rupture and thrombus-mediated growth, if at early stages of atherosclerotic plaque evolution, smooth muscle cell proliferation and extracellular matrix synthesis predominates over lipid and macrophage entry and accumulation into the vessel wall, atherosclerotic lesions may grow by means of such fibrointimal response giving rise to an advanced sclerotic plaque. Such lesions consist entirely or almost entirely of scar collagen, and lipid may have regressed or it may never have been in the lesion (34,75). Collagen formation is the major contributor to the volume of such atherosclerotic plaques and, importantly, lesions that are primarily fibrotic, while they may cause very serious stenosis, are very seldom the site of thrombosis. Factors determining whether a lesion evolves as a primarily fibrotic lesion or as a primarily necrotic lesion with a large lipid core are actually under intensive investigation. It has been speculated that if the apoptotic cells are mostly cleared by phagocytosis before damage to the plasma membrane causes the cell contents to leak, a fibrotic lesion may develop. On the other hand, if a foam cell becomes necrotic (either because adjacent macrophages fail to engulf it or because its apoptotic program is defective), there will be a progressive accumulation of lipid in the extracellular space and the lesion may evolve to be an unstable thrombosis-prone type of lesion. Thus, the cell-scavenging function of macrophages may be playing a role both in the initiation of the fatty streak and in the evolution of the lesion that determines whether it will be stable or unstable. In addition, fibrinogen entering the vascular intima and being converted to fibrin by thrombin may contribute to stabilize the lesion by inducing smooth muscle cell proliferation (114,162).

CLINICAL CONSEQUENCES OF CORONARY PLAQUE EVOLUTION

Atherosclerotic lesions in the coronary tree may cause stable syndromes of ischemia by means of direct luminal arterial narrowing (*stable lesions*) or unstable ischemic syndromes by inducing acute intraluminal thrombus formation (*unstable lesions*). Clinical consequences of coronary lesions depend on many factors such as the degree and acuteness of blood flow obstruction, the duration of decreased perfusion, and the relative myocardial oxygen demand at the time of blood flow obstruction. In patients with chronic coronary artery disease, angina commonly results from increases in myocardial oxygen demand that outstrip the ability of stenosed coronary arteries to increased oxygen delivery. In contrast, acute coronary syndromes are usually characterized by an abrupt reduction in coronary blood flow due to atherosclerotic plaque rupture whereby thrombogenic material is exposed to blood flow and thrombosis develops.

Overall, the term ‘‘nonsignificant’’ when applied to atherosclerotic lesions with less than 50% luminal stenosis at coronary angiography may often be misleading and should

be revisited. It is now quite evident that a fissure may develop in an atherosclerotic plaque that occupies less than 50% of the diameter of a coronary artery, and such plaque may become a nidus for thrombosis. Overall, angiography may underestimate the extent and severity of atherosclerotic involvement of coronary arteries and it does not necessarily indicate the site at which coronary occlusion will occur. However, angiography is helpful as a determinant of the severity of coronary disease, and the number of diseased vessels are known markers of cardiac morbidity and mortality (163). The more severe the coronary disease is at angiography, the higher is the likelihood of the presence of small plaques prone to disruption. For instance, in the CASS (164) the subsequent coronary occlusion rate was 2% for diameter stenosis of 5% to 49% and 24% for stenosis of 81% to 95%, because nonobstructive lesions are common and obstructive lesions are rare, the ratio of occlusions at sites with $<$50% stenosis was 7.4 to 1 (2591 vs. 347). Consequently, most myocardial infarctions evolve from mild-to-moderate stenosis. Therefore, the risk of an acute event such as unstable angina or acute myocardial infarction to a patient with coronary artery disease ultimately depends on how many vulnerable plaques are present. It is the pathology of coronary atherosclerosis that provides the basis for understanding clinical outcomes of acute coronary syndromes. Plaque instability causes myocardial infarction, the unstable lesion that causes infarction is not necessarily severely stenotic, and the stenotic lesion is not necessarily unstable. Unfortunately, there are currently no sensitive and practical means of detecting vulnerable plaques in the coronary arteries in vivo (102).

Stable Coronary Syndromes

Pathological studies have found that, in patients with stable angina, severe atherosclerotic lesions (more than 75% cross-sectional area luminal narrowing equivalent to 50% diameter reduction) consist either of advanced fibrolipid plaques (60%) or predominantly pure fibrotic lesions (40%) (35). There is usually no plaque ulceration or thrombosis; however, intraplaque hemorrhage and rest from thrombus organization may be observed. Generally, the pattern of angina does not correlate with the extent or severity of the atherosclerotic disease. Mild or infrequent angina does not imply mild or insignificant disease. At the present time, it appears that prognosis in stable angina is most accurately predicted by the number and severity of individual obstructions of the three major coronary arteries and by left ventricular function (117). The threshold for pain in stable angina is usually fixed, but may be somewhat variable; that is, a stimulus that causes angina in one occasion may not in another, although a consistent pattern can usually be determined. This inconsistency in angina threshold in daily life is likely due to alterations in blood flow delivery, probably as a result of changes in vasomotor tone (165).

Unstable Coronary Syndromes

Rupture of the surface of an atherosclerotic plaque with subsequent exposure of thrombogenic plaque components to flowing blood is the key event to initiate thrombosis within coronary arteries. The amount and duration of intracoronary thrombus play a major pathophysiological role in acute ischemic syndromes. In general, acute myocardial infarction is associated with larger and more persistent thrombi than unstable angina.

In unstable angina, a relatively small fissuring or disruption of an atherosclerotic plaque may lead to an acute change in plaque structure and a reduction in coronary blood flow, resulting in exacerbation of angina. Transient episodes of thrombotic vessel occlusion at the site of plaque rupture may occur, leading to angina at rest. This thrombus is usually labile and results in temporary vascular occlusion, perhaps lasting only 10 to 20 min. In addition, vasoconstriction may contribute to a reduction in coronary flow.

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In non-Q-wave infarction, more severe plaque damage would result in more persistent thrombotic occlusion, perhaps lasting up to 1 h. About one-fourth of patients with non-Q-wave infarction may have an infarct-related vessel occluded for more than 1 h, but the distal myocardial territory is usually supplied by collaterals. Resolution of vasospasm may be also pathogenically important in non-Q-wave infarction. Therefore, spontaneous thrombolysis, spasm resolution, or presence of collateral circulation are important in preventing the formation of Q-wave infarction by limiting the duration of myocardial ischemia.

In Q-wave infarction, larger plaque fissures may result in the formation of a large, fixed, and persistent thrombus. This leads to an abrupt cessation of myocardial perfusion for more than 1 h, resulting in transmural necrosis of the involved myocardium. The coronary lesion responsible for the infarction is frequently only mildly to moderately stenotic, which supports the notion that plaque rupture with superimposed thrombi, rather than the severity of the lesion, is the primary determinant of acute occlusion. It is conceivable that in patients with severe coronary stenosis, well-developed collaterals prevent or reduce the extent of infarction. In perhaps one-fourth of patients, coronary thrombosis may result from superficial intimal erosion or blood stasis in areas of high-grade stenosis. Additionally, myocardial infarction may be promoted by alterations in hemostasis resulting in an increased activation of the coagulation system, or in an impairment of the fibrinolytic system.

In summary, the natural history of acute coronary syndromes probably mirrors that of the underlying plaque rupture and thrombus formation. Stabilization would correspond to resealing of a rupture, accentuation of symptoms to development of labile thrombosis, non-Q-wave infarction to development of transient occlusion, and transmural Q-wave infarction to establishment of a persistent occlusive thrombus. Furthermore, this natural history may be modified by vascular tone and presence of collateral circulation.

Role of Vasospasm and Collateral Circulation

Other mechanisms that may alter the balance between myocardial oxygen supply and demand in ischemic coronary syndromes include coronary vasoconstriction at the site of atherosclerotic involvement. Numerous studies have shown that atherosclerosis is associated with abnormal vasodilation or an exaggerated vasoconstriction response due to dysfunction in endothelial-dependent dilation mechanisms (9,166,167). Similarly, the presence of atherogenic risk factors, such as hypercholesterolemia, may increase the likelihood of vasoconstriction (166). This constrictor predominance of atherosclerotic disease may be enhanced further in the setting of acute coronary syndromes. A predisposition for platelet-dependent vasoconstriction mediated by serotonin and thromboxane A_2 (168,169) and thrombin-dependent vasoconstriction (170) at the site of plaque disruption suggest a direct interaction of these substances with smooth muscle cells. This information, along with recent data showing an increase in endothelin-1 immunostaining colocalized with plaque components indicative of inflammatory process (171), may provide a clue to the mechanism of increased reactivity of the culprit lesion in unstable coronary syndromes.

An important anatomical factor that may modify the hemodynamic effects of an atherosclerotic obstruction is the presence of collateral circulation. Collaterals are anatomical connections without an intervening capillary bed between portions of the same artery or between different arteries. In human hearts, the distribution and extent of collateral vessels are quite variable. Collaterals become angiographically visible only when coronary occlusion is complete or virtually so. Collaterals may equal perfusion through a vessel

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with 90% stenosis of the luminal diameter (172), providing perfusion just sufficient to maintain myocardial viability and prevent myocardial infarction (120) or even sudden ischemic death (173) when coronary occlusion takes place. There is evolving information regarding the ways in which opening and angiogenesis of the coronary collateral circulation can be stimulated. Exercise (174,175) and gradual rather than abrupt coronary occlusion appear to enhance the development of collaterals. New technologies aimed at the full understanding of collateral recruitment and angiogenesis, and the therapeutic impact of growth factors are being investigated in several animal models and even in the clinical setting with very promising preliminary results (176).

REGRESSION OF ATHEROSCLEROTIC LESIONS AND FUTURE APPROACHES

Old guidelines stated that the greater the stenosis, the greater the risk of cardiac events, and considered revascularization procedures the only effective approach to improve prognosis associated with coronary artery disease. In contrast, on the basis of the new knowledge, it is the nature of the plaque that determines the risk of acute cardiovascular events. Dangerous plaques have a large lipid-rich core with surrounding inflammation and a thin friable overlying fibrous cap, and these type of plaques may usually appear innocuous on angiography (Fig. 4).

In approaching the concept of reversibility or arrest of the coronary atherosclerotic process, it is essential to keep in mind that atherosclerosis disease starts at a young age and

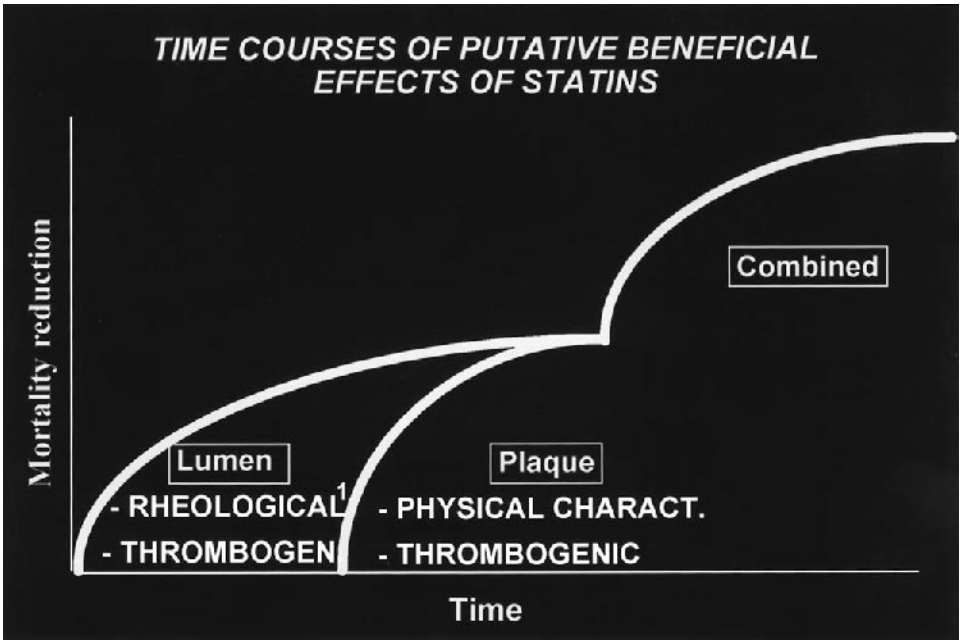

Figure 4 Time courses of putative beneficial effects of statins. (Modified, with permission, from Ref. 176a.)

takes many years to progress into the symptomatic stage. By the time the first symptoms of coronary atherosclerosis appear, the disease is usually advanced to two- or three-vessel involvement. This highlights the need for a practical method to identify vulnerable lesions before the first symptoms appear. In this field, noninvasive imaging of plaques with a high content of lipids is emerging as an important research tool, given the susceptibility of these plaques to rupture. In addition to intravascular ultrasound and coronary angioscopy (177,178), it may soon be possible to detect fatty plaques within the vascular system by high-resolution biochemical imaging techniques such as nuclear magnetic resonance (179–181). Once vulnerable plaque is identified, approaches may be taken toward retardation in the progression or even reversibility of plaque, reduction in the susceptibility of plaque rupture, and/or prevention of thrombosis after plaque rupture.

Approaches that have been taken toward retardation or even reversibility of atherosclerotic lesions include: better control of atherogenic risk factors; especially by reducing plasma cholesterol levels; enhancement of lipid-removal pathways from the vessel wall, particularly by increasing plasma HDL levels; and reduction of LDL oxidation by using antioxidant agents. Each of these approaches, by acting on the lipid-rich plaque more prone to rupture, might prevent progression and even induce removal of fat and regression of atherosclerotic plaques. After a number of suggestive studies that used diet and cholesterol-lowering agents of modest effectiveness, the favorable clinical effects of marked lowering of low-density lipoprotein cholesterol levels have now been demonstrated unequivocally in three large trials that used 3-hydroxy-methylglutaryl-coenzyme A reductase inhibitors (182–184). The clinical improvement seen with cholesterol-lowering therapy seems to be disproportionate to the small degree of anatomical regression of atherosclerotic stenoses that can be achieved by these therapies (182,185,186). It is likely that in plaques with large cholesterol pools, the resorption of cholesterol may diminish the propensity of the plaque to rupture (185), and an increase in the relative collagen content of the plaque may account for increasing plaque stability without significant reduction in plaque size (187). Additionally, antioxidant agents have shown regression of atherosclerosis in animal models (188) and stabilization in patients with coronary artery disease (57) to a greater degree than expected by its lipid-lowering action alone. Several other mechanisms may underlie the role of these therapies in preventing the clinical manifestations of coronary artery disease. For example cellular antioxidants inhibit monocyte adhesion, protect against the cytotoxic effects of oxidized LDL, inhibit platelet activation, and preserve endothelium-derived nitric oxide activity (189).

Other approaches, besides hypolipidemic and antioxidant therapy, that may possibly reduce the incidence of plaque rupture include angiotensin-converting enzyme inhibitors and beta-blockers. Recent evidence from three large placebo-controlled trials of angiotensin-converting enzyme inhibitors in patients with ischemic heart disease and/or mild left ventricular dysfunction points to a reduction of 14 to 28% in the incidence of myocardial infarction and other ischemic cardiac events (190–192). The mechanism of such reduction in infarction is uncertain. Experimentally, angiotensin-converting enzyme inhibitors have shown a reduction in intimal hyperplasia following endothelial injury (193,194). Although clinical data have shown angiotensin-converting enzyme inhibitors to reverse endothelial dysfunction in patients with coronary artery disease (195), there is no convincing clinical evidence that the prevention of infarction by these agents could be related to the prevention of preceding atherogenesis. Alternatively, enhanced fibrinolysis by angiotensin-converting enzyme inhibitors (196), as well as the microcirculatory vasodilating properties of these agents (197) may be the clue to the benefit of these agents in preventing myocardial

infarction. Meta-analysis of secondary prevention trials with beta-blockers has shown a 20% reduction in cardiac mortality, an additional 25% reduction in the incidence of reinfarction, and a 30% reduction in the incidence of sudden death (198). Beta-blockers reduce the circumferential plaque stress, and therefore the possibility of plaque rupture, by reducing blood pressure and blunting hypertensive pressure surges (199,200). By reducing heart rate, beta-blockers may also increase plaque tensile strength (200). Otherwise, the beneficial effect of beta-blockers in the prevention of reinfarction cannot be explained by a direct antithrombotic effect or by a direct atherosclerotic plaque growth effect since such effects have not been documented experimentally or clinically.

Because thrombus formation appears to be an important factor in the progression of atherosclerotic lesions and in the conversion of chronic to acute events after plaque rupture, a promising approach in the prevention of this process would be the use of antithrombotic therapy. The most beneficial effect of antiplatelet and anticoagulant agents has been observed in the prevention of acute coronary syndromes, although preliminary information indicates that antiplatelet agents may also offer some promise in preventing the progression of small coronary atherosclerotic plaques (120). Aspirin has shown to be effective in unstable angina and acute myocardial infarction, during and after coronary revascularization, in the secondary prevention of chronic coronary and cerebrovascular disease, and in primary prevention particularly in high-risk groups (201). Three recently performed randomized studies (202–204) have shown that low-molecular-weight heparins in unstable angina syndromes are at least as effective as unfractioned heparin, but with a lower risk of complications (205). Combination therapy with low doses of aspirin and anticoagulant agents may have additive effect. The rationale behind this combination is to block to some extent both platelet activation and the generation of thrombin by the intrinsic and extrinsic coagulation systems. The hope is to achieve this objective without enhancing bleeding. Thus far, such combination therapy is being considered only for the short term ($<$1 week to 3 months) in patients at high risk for thrombotic events, such as those with acute myocardial infarction or unstable angina (206), and although they are effective in diminishing acute coronary events, they cannot completely prevent them when used at pharmacological dosage.

Newer antithrombotic approaches that act directly by blocking the platelet membrane receptor glycoprotein IIb/IIIa, or by direct inhibition of thrombin, are under active clinical investigation. The monoclonal antibody 7E3 is currently the most advanced anti-glycoprotein IIb/IIIa agent in clinical development. It has been tested in patients with unstable angina (207,208), postfibrinolysis in acute myocardial infarction (209), and even primarily in acute myocardial infarction (210) with very promising results. Specific thrombin inhibitors, such as hirudin, a 65-residue polypeptide derived from the salivary gland of the medicinal leech, and now available by recombinant laboratory synthesis, have some advantages over heparin in patients with unstable angina and acute myocardial infarction (211). However, the increased risk of bleeding associated with these new antithrombotic strategies remains a concern.

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10

Recognition and Diagnosis of Coronary Artery Disease in the Elderly

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Coronary atherosclerosis is very common in the elderly population, with autopsy studies demonstrating a prevalence of at least 70% in persons over age 70 (1,2). These autopsy findings may be coincidental, with the disease clinically silent throughout the person's life; however, 20 to 30% of persons over age 65 show clinical manifestations of coronary heart disease (CHD). In most elderly persons, the disease will manifest itself much earlier in life, but in others the disease is entirely silent until the person's seventh or eighth decade. Unfortunately, even though CHD is so prevalent in elderly persons, the disease is often undiagnosed or misdiagnosed in this age group. Failure to correctly diagnose the disease in the elderly may be due to a difference in clinical manifestation in this age group compared to that of younger patients. Such differences may reflect a difference in the disease process between older and younger patients, or it may be related to the superimposition of normal aging changes with the presence of concomitant diseases that may mask the usual clinical manifestations.

MYOCARDIAL ISCHEMIA

Exertional angina pectoris caused by myocardial ischemia is commonly the first manifestation of CHD in young and middle-aged persons. It is usually easily recognized due to its typical features; however, in elderly persons this may not be the case. Due to limited physical activity, many elderly persons with CHD will not experience exertional angina. Even when angina does occur, the patient and physician may often attribute it to causes other than CHD. For example, myocardial ischemia, appearing as shoulder or back pain, may be misdiagnosed as degenerative joint disease, or, if the pain is located in the epigastric area, it may be ascribed to peptic ulcer disease. Nocturnal or postprandial epigastric discomfort that is burning in quality is often attributed to hiatus hernia or esophageal reflux instead of CAD. Furthermore, the presence of comorbid conditions, so frequent in

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the elderly patient, add to the confusion and may lead to a misdiagnosis of the patient's symptoms, which are actually due to myocardial ischemia.

Instead of typical angina, myocardial ischemia in elderly patients is commonly manifested as dyspnea, which is referred to as an ''angina equivalent.'' Usually the dyspnea is exertional and is thought to be related to a transient rise in left ventricular end-diastolic pressure caused by ischemia superimposed on reduced ventricular compliance. Reduction in ventricular compliance may reflect normal aging changes or, more likely, is caused by the presence of coexisting hypertension and left ventricular hypertrophy, disorders commonly present in elderly patients. Not infrequently, the dyspnea will occur in combination with angina, although the angina is frequently mild and of little concern to the patient.

In other elderly patients, myocardial ischemia is manifested as frank clinical heart failure with some patients presenting with acute pulmonary edema. Chest pain may not be present, although the myocardial ischemia is severe enough to produce a combination of diastolic and systolic left ventricular dysfunction. Siegel and associates (3) reported on a group of elderly patients (mean age 69 years) with CHD in whom the disease manifested as acute pulmonary edema. The majority of patients were without angina and many were without a prior history of CHD. Ninety percent, however, had a past history of hypertension and their electrocardiogram displayed left ventricular hypertrophy. Angiographically, the majority of patients had three-vessel CHD, though left ventricular systolic function was only moderately depressed with a mean ejection fraction of 43%. Over 60% of these patients were treated with interventional therapy (coronary bypass surgery or percutaneous transluminal angioplasty), and the long-term prognosis was excellent. Similar findings have been reported in other studies of acute pulmonary edema caused by CHD (4–8). Graham and Vetrovec (8) compared patients with CHD hospitalized with acute pulmonary edema to patients hospitalized with angina without heart failure. The patients with acute pulmonary edema were older and, as in Siegel's study, most of the patients had preexisting hypertension. Three-vessel CHD was common in both groups, although angina was infrequent in the patients with pulmonary edema. Left ventricular ejection fraction was more depressed in the patients with pulmonary edema, but the degree of systolic ventricular dysfunction was not severe (57% vs. 42%). In another study, Kunis (6) and associates reported findings of a small group of elderly patients with CHD who had recurrent pulmonary edema that could not be prevented with medical therapy. Angiographic studies demonstrated three-vessel coronary disease with preserved systolic function. Only after undergoing coronary bypass surgery was the recurrent pulmonary edema prevented in these very elderly patients.

Another subset of elderly patients with CHD who present with acute pulmonary edema will demonstrate mitral valvular regurgitation that may be secondary to papillary muscle ischemia. In a study of 40 patients with acute pulmonary edema who had CHD, Stone and associates (9) found 67% of the patients demonstrated moderate-to-severe mitral regurgitation on echocardiographic-Doppler examination. The mean age of the patients was 76 years. In the majority of patients (74%), a murmur of mitral regurgitation was not detected despite examination by multiple observers. The authors concluded that mitral valve regurgitation is not uncommon in patients with CHD who present with acute left ventricular failure and may contribute to the genesis of the pulmonary edema.

In another study of elderly patients with CAD, Tresch and associates (10) studied the initial manifestations of CHD in a group of elderly patients who underwent coronary angiography. The mean age of the group was 71 years, with some of the patients over the age of 80 before the onset of symptoms. The initial manifestation in the majority of

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patients was unstable ischemic chest pain; 34% of the patients presented with an acute myocardial infarction. In 8% of these elderly patients, the initial manifestation was acute heart failure unassociated with an acute myocardial infarction. Upon cardiac catheterization, multivessel disease was common, though left ventricular systolic function was good. Only 9% of the patients had an ejection fraction of less than 35%. Comparing these findings to those of patients younger than 65 years, younger patients more commonly sustained an acute myocardial infarction as the initial manifestation of CHD, were less likely to present with heart failure, and have less multivessel coronary disease.

Cardiac arrhythmia may be a manifestation of myocardial ischemia and is a common problem in elderly patients with CHD. Sudden death as an initial manifestation of CHD increases with age. In Tresch's study (10), 9 of 66 elderly patients had arrhythmias as the initial manifestation of CHD, and 2% of the patients experienced out-of-hospital cardiac arrest. (See Chap. 26 for further information.)

Silent or asymptomatic ischemia, as noted in younger patients, is a common problem in elderly patients with CHD. Approximately 15% of the elderly patients in Tresch's study (10) were asymptomatic and myocardial ischemia was detected by exercise stress testing during a preoperative evaluation. In a study of 185 very elderly (mean age 83 years) nursing-home residents, Aronow and associates (11) demonstrated silent myocardial ischemia by Holter monitoring in 34% of the residents and the prevalence was higher in patients with abnormal left ventricular dysfunction. Similar findings were reported by Hedblad and associates (12) in a study of 53 Swedish patients (mean age 68 years). Holter monitoring findings of silent ischemia were evident in 36% of patients.

MYOCARDIAL INFARCTION

As with myocardial ischemia, some patients with myocardial infarction may be completely asymptomatic or the symptoms may be so vague that they are unrecognized by the patient or physician as an acute myocardial infarction. The Framingham Heart Study (13,14) found that in the general population approximately 25% of myocardial infarctions diagnosed by pathological Q waves on electrocardiography were clinically unrecognized, and of these, 48% were truly silent. The incidence increased with age, with 42% of infarctions clinically silent in males aged 75 to 84 years. In women, the proportion of unrecognized myocardial infarctions was greater than in men, but the incidence was unaffected by increasing age. Other studies (15–21) have also reported a high prevalence of silent or unrecognized myocardial infarction in elderly persons, with some studies reporting as many as 60% of infarctions being unrecognized or silent in the very elderly (Table 1). Importantly, most studies (13,14,22) indicate that the incidence of new coronary events, including recurrent infarction, ventricular fibrillation, and sudden death, is similar in elderly patients with either recognized or unrecognized infarction.

The reason for the frequent absence of chest pain in elderly patients with CAD is unclear. Various speculations have included (1) mental deterioration with inability to verbalize a sensation of pain; (2) better myocardial collateral circulation related to gradual progressive coronary artery narrowing; and (3) a decreased sensitivity to pain because of aging changes. Ambepitiya and associates (23) recently investigated the issue of decreased pain perception and qualitatively demonstrated a higher anginal perceptual threshold (APT) in elderly patients by comparing the time between the onset of 1 mm of electrocardiographic ST depression and the onset of angina during exercise stress testing. The mean

Table 1 Prevalence of Incidence of Silent or Unrecognized Q-Wave Myocardial Infarction in Elderly Patients

Study (Ref.)	Number of patients	Age (years)	Unrecognized (number)	Painless MI (percent)
Rodstein (19)	52	>60	16	31
Aronow et al. (21)	115	>64	78	68
Aronow (16)	110	>62	23	21
Vokonas et al. (14)	199 (men)	>65	65	33
	162 (women)	>65	58	36
Muller et al. (17)	46 (men)	>65	14	30
	67 (women)	>65	34	51
Nadelmann et al. (18)	115	>75	50	43

MI = myocardial infarction.
Adapted from Ref. 20.

APT was 49 s in the older patients (age 70–82 years) compared to 30 s in the younger patients (age 42–59 years). The reason for this delay in perception of myocardial ischemia in the elderly is unexplained. The authors postulated that the impairment is most likely multifactorial in origin, involving peripheral mechanisms such as changes in the myocardial autonomic nerve endings with blunting of the perception of ischemic pain, as well as changes in central mechanisms. Another theory has suggested that the increase in silent myocardial ischemia and infarction in elderly patients with CAD is related to increased levels of, or receptor sensitivity to, endogenous opioids (24). This explanation does not appear likely, because studies have demonstrated a similar increase in response of β-endorphin levels to exercise in both elderly and younger subjects (25), and animal studies show a decrease in opiod receptor responsivity with advancing age (26).

Symptoms when present in elderly patients with an acute myocardial infarction may be extremely vague, and, as with myocardial ischemia, the diagnosis may be easily missed. Numerous studies (16,19,27–31) have demonstrated the atypical features and wide variability of symptoms in elderly patients with acute myocardial infarction (Table 2). In an early study, Rodstein (19) found that approximately 30% of elderly nursing home residents who sustained an acute myocardial infarction were without any symptoms referable to heart disease. In 40% of the patients, classic chest or neck pain was absent, but symptoms such as dyspnea, syncope, vertigo, or abdominal pain were common. In the 1960s, Pathy (29) reported similar findings. Patients older than 80 years who sustained an acute myocardial infarction commonly showed dyspnea or neurological symptoms such as acute confusion, stroke, or vertigo rather than typical chest pain (Fig. 1). Both Rodstein (19) and Pathy (29) emphasized the importance of suspecting an acute myocardial infarction in elderly persons who experience unexplained behavior changes, acute signs of cerebral insufficiency, or dyspnea. More recent studies (27,31,32) have also stressed the importance of atypical presentations in elderly patients with acute myocardial infarction, and some studies have suggested that dyspnea may be more common than chest pain as the presenting symptom. Bayer and associates, (27) in a study of 777 patients with documented acute myocardial infarction, reported a decline in chest pain with advancing age, whereas dyspnea increased (Fig. 2). In the Multicenter Chest Pain Study (32), the clinical presentation of acute myocardial infarction was compared in 1615 patients older than 65 years and 5109 patients younger than 65 years. Due to the decreased prevalence of some typical

Table 2 Prevalence of Chest Pain, Dyspnea, and Neurological Symptoms Associated with Acute Myocardial Infarction in Elderly Patients

Study (Ref.)	Number of patients	Age (years)	Chest pain		Dyspnea		Neurological symptoms	
			number	percent	number	percent	number	percent
Rodstein (19)	52	>60	15	29	*		*	
Pathy (29)	387	>65	75	19	77	20	126	33
Tinker (30)	87	74+	51	59	19	22	14	16
Bayer et al. (27)	777	76+	515	66	329	42	232	30
Aronow (16)	110	>62	24	22	38	35	20	18
Wroblewski (31)	96	84+	19	20	57	59	14	15

* = symptom present but number and percentage not stated; + = mean age.
Adapted from Ref. 20.

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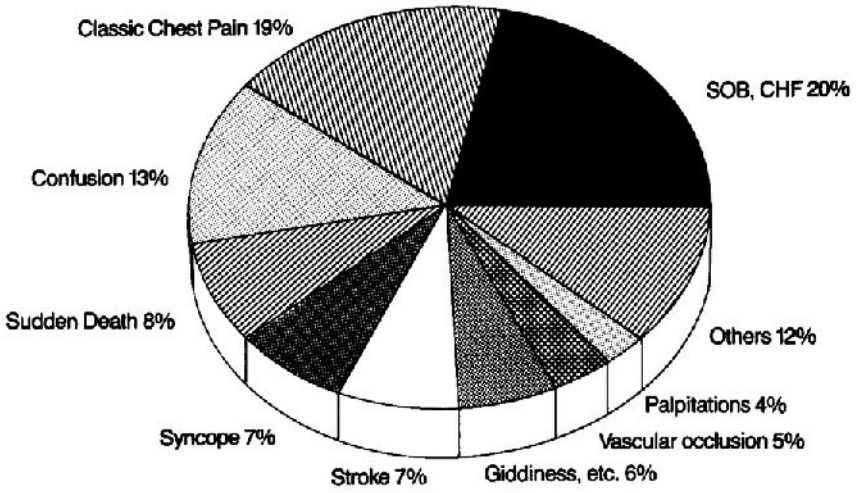

Figure 1 Prevalence of main symptom in elderly patients with acute myocardial infarction. (Adapted from Ref. 29.)

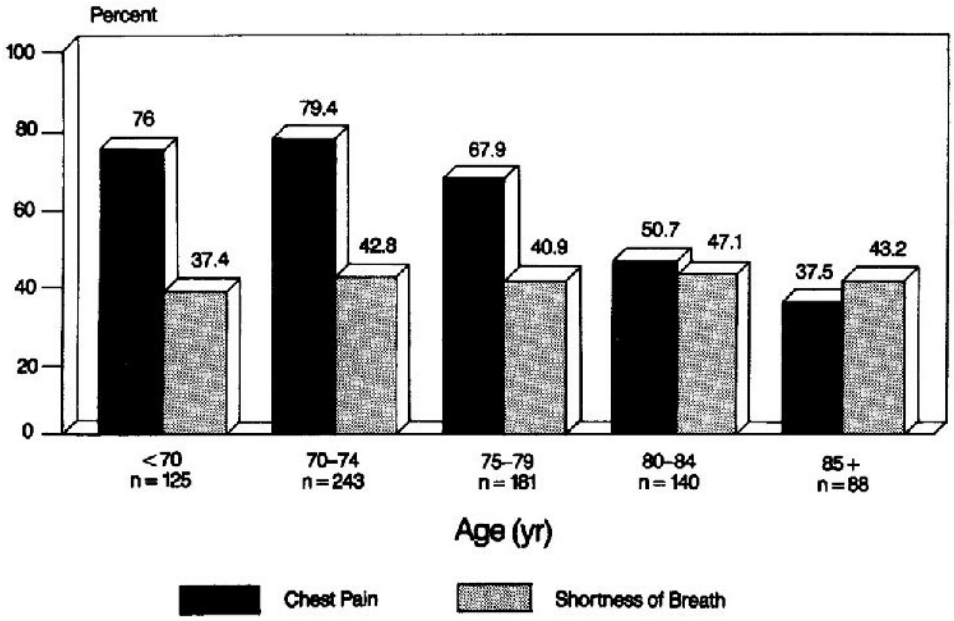

Figure 2 Presenting symptom of acute myocardial infarction in the elderly. (Adapted from Ref. 27.)

features (such as pressurelike pain), the initial symptoms and signs had a lower predictive value for diagnosing acute myocardial infarction in elderly patients compared to younger patients. In another recent prospective study, Wroblewski and associates (31) reported that only 20% of elderly patients in a Swedish geriatric hospital demonstrated chest pain at the onset of acute myocardial infarction, whereas 59% complained of dyspnea.

Other features that are different between elderly and younger patients with acute myocardial infarction, and which may modify therapy, need to be emphasized. An important difference is that elderly patients delay longer in seeking medical assistance after the onset of the chest pain (33,34). In a recent study of out-of-hospital chest pain, Tresch and associates (33) reported that elderly patients 80 years or older delayed greater than 6.5 h in calling paramedics, compared to 3.9-h delay in patients younger than 70 years. Interestingly, this prolonged delay occurred even though greater than 50% of the elderly patients had a past history of either a myocardial infarction or coronary bypass surgery. Such delay may be one of the reasons why elderly patients with acute myocardial infarction are less likely to receive thrombolytic therapy, compared to younger patients. Another important difference found in Tresch's study (33), and has been reported in other studies (35), was the greater incidence of non-Q-wave infarctions in elderly patients; 40% of the elderly patients with acute infarctions demonstrated non-Q-wave infarctions, compared to only 20% of the younger infarction patients. In younger patients, non-Q-wave myocardial infarctions are usually associated with a more benign acute hospital course than Q-wave infarctions, although this may not pertain to elderly patients with non-Q-wave MI. Chung and associates (36) reported a 10% hospital mortality and a 36% 1-year morality in a group of elderly patients sustaining acute non-Q-wave MI. In contrast, the acute hospital and 1-year mortality in younger patients was 3% and 16%, respectively. Moreover, 23% of the elderly patients with non-Q-wave developed atrial fibrillation and 53% had congestive heart failure. Regardless of the type of myocardial infarction, elderly patients with acute infarctions usually demonstrate more left ventricular dysfunction than younger patients upon hospital admission and have a more complicated hospital course (33). Complications are common in elderly patients (37), including heart failure, ventricular rupture, shock, and death; and, not infrequently, the elderly patient's initial complaints will reflect these complications, instead of chest pain.

DIAGNOSTIC TECHNIQUES

Resting Electrocardiogram

The resting electrocardiogram may be used in elderly patients to diagnose acute or old myocardial infarction, whether silent or symptomatic. Ischemic ST-T wave changes, as well as arrhythmias and conduction defects that may occur secondary to CHD, can be diagnosed with the resting electrocardiogram.

In addition to being beneficial in diagnosing CHD, electrocardiogram findings may be predictive of future coronary artery events, including death. In a study of elderly nursing home patients in whom resting electrocardiographic findings were assessed as predictors of mortality and new coronary events, Aronow and associates (38) found that at 37 months mean follow-up elderly patients (mean age 82 $\pm$ 8 years, range 62 to 103 years) with ischemic ST segment depression greater than 1.0 mm on the resting electrocardiogram were 3.1 times more likely to develop new coronary events (myocardial infarction, primary ventricular fibrillation, or sudden cardiac death) than were elderly patients with no signifi-

cant ST segment depression. Elderly patients with an ischemic ST segment depression of 0.5 to 0.9 mm on resting electrocardiography were 1.9 times more likely to develop new coronary events than were elderly patients with no significant ST segment depression. In another study of elderly nursing home patients (39), Aronow and associates found that resting electrocardiographic findings of electronic pacemaker rhythm, atrial fibrillation, premature ventricular complexes, left bundle-branch block, nonspecific intraventricular conduction defect, and type II second-degree atrioventricular block were also associated with a high incidence of new coronary events in elderly patients with CHD.

Numerous studies have documented that elderly patients with electrocardiographic left ventricular hypertrophy have an increased incidence of new cardiovascular events. Men and women 65 to 94 years of age participating in the Framingham Heart Study who showed electrocardiographic left ventricular hypertrophy had an increased incidence of coronary events, atherothrombotic brain infarction, congestive heart failure, and peripheral arterial disease compared to participants without left ventricular hypertrophy (40). Similar results were reported by Aronow and associates (41). Elderly nursing home patients with hypertension or CHD and electrocardiographic left ventricular hypertrophy had an increased incidence of new coronary events and atherothrombotic brain infarctions at 37 months mean follow-up. The increased incidence of cardiovascular morbidity was not different between black and white elderly nursing home patients who had hypertension and electrocardiographic signs of left ventricular hypertrophy.

Exercise and Pharmacological Stress Testing

Exercise stress testing using electrocardiography, isotope perfusion scintigraphy, radionuclide ventriculography, or echocardiography may be used to diagnose CHD in both asymptomatic and symptomatic elderly patients. Stress test findings may also be useful as prognostic markers of future coronary events. In elderly patients, who because of musculoskeletal disorders or general debilitation, are unable to perform exercise, intravenous dipyridamole-thallium has high sensitivity and specificity in diagnosing CHD in this subset of elderly patients (42). Recently, the pharmacological dobutamine-echocardiographic stress test has been shown to be an alternative to dipyridamole-thallium in diagnosing CHD in elderly patients who cannot exercise (43,44). The sensitivity and specificity of dobutamine echocardiography stress testing is similar to other types of stress testing and it is as safe in elderly patients as in younger patients. Recent studies have found dobutamine echocardiography stress testing to be useful in stratifying elderly patients into high- and low-risk groups after myocardial infarction. (For further details of stress testing in elderly patients, see Chap. 16.)

Ambulatory Electrocardiography (Holter Monitoring)

Ambulatory electrocardiography monitoring (AEM) is useful in the detection of transient cardiac arrhythmias and myocardial ischemia. Such applications are practically applicable in elderly patients in whom CHD is prevalent and for whom resultant arrhythmias and myocardial ischemia are major clinical problems.

The presence of underlying heart disease is the most important consideration of patient evaluation in reference to the significance of arrhythmias as a predictor of future cardiac events. Numerous studies (45–49) have shown ventricular arrhythmia to be an independent predictor of future cardiac events, including sudden death, in elderly patients

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with underlying heart disease. The risk of future cardiac events increases when ventricular arrhythmia occurs in combination with left ventricular dysfunction or left ventricular hypertrophy. In contrast, most studies have failed to show a correlation between arrhythmias and future cardiac events in healthy elderly patients without underlying heart disease (45–47,50,51) (Table 3). (For further information concerning ventricular arrhythmias, see Chap. 26.)

Ischemic electrocardiographic ST-T changes demonstrated on AEM correlate with transient abnormalities in myocardial perfusion and ventricular dysfunction. The changes may be associated with symptoms, or symptoms may be completely absent, which is referred to as silent ischemia. Silent ischemia is a frequent occurrence and is predictive of future cardiac events including mortality in patients with CHD. Such findings have been reported in both middle-aged and older patients (11,12,49,52–56) (Table 4). A 21% prevalence of silent ischemia as detected by AEM was reported by Aronow and Epstein (11) in a study of elderly nursing home patients (mean age 82 years) who had documented underlying heart disease; this compared with only a 5% prevalence in nursing home patients without heart disease. Nursing home patients with CHD had a prevalence of silent ischemia twice that found in patients with other forms of heart disease. Over a 26-month follow-up, 65% of patients with CHD and 33% of patients with other forms of heart disease who showed signs of silent ischemia on AEM had new cardiac events, compared with 32% and 18% patients, respectively, without silent ischemia. In another study of elderly nursing home patients (53), the prevalence of silent ischemia increased significantly in patients with a left ventricular ejection fraction of less than 50%, compared with patients with a normal ejection fraction ($>$50%); abnormal ejection fraction, as well as silent ischemia, was an independent predictor of new cardiac events. When both variables were present, the incidence of future coronary events markedly increased; 94% of nursing home patients with both silent ischemia and abnormal ejection fraction had new cardiac events during a 40-month mean follow-up period.

The combination of silent myocardial ischemia and ventricular arrhythmias as a predictor of future coronary events has also been studied by Aronow and associates in their elderly nursing home population (52). As expected, silent ischemia, ventricular tachycardia, and complex ventricular arrhythmias were all more prevalent in patients with CAD and ventricular arrhythmias were common in patients with silent ischemia. In regard to predicting cardiac events, 84% of patients with the combination of silent ischemia and complex ventricular arrhythmias had a cardiac event at a mean follow-up of 37 months, compared with 21% of the patients with neither silent ischemia nor complex ventricular arrhythmias.

As in Aronow's studies, Hedblad and associates (12) found ischemia detected on AEM to be highly predictive of cardiac events in older Scandinavian men, aged 68 years. A 4.4-fold increased risk of coronary events occurred in men without documented CAD who showed myocardial ischemia on AEM. The relative risk of coronary events increased 16-fold in the men with CAD. Fleg and associates (50,57), in studies of healthy elderly subjects who did not show a correlation between arrhythmias and future cardiac events, did find approximately a fourfold increase in cardiac events in elderly persons with signs of silent ischemia on AEM; two of the three patients in their study who died suddenly had signs of silent ischemia and ventricular tachycardia on AEM. Such findings suggest, as in Aronow's study (52), that the combination of silent ischemia and ventricular arrhythmias in elderly patients may be a potent indicator of increased cardiac risk.

Silent ischemia detected by AEM has been used in the assessment of patients under-

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Table 3 Relationship of Ventricular Arrhythmias to Future Cardiac Events in Older Patients

Study (Ref.)	Number of patients	Age (years)	Cardiac status	Variable	Mean follow-up period (months)	Incidence of cardiac events
Fleg (50)	98	69	Healthy*	VPCs, VT	120	No correlation
Kirkland (51)	30	79	Healthy*	VPCs	29	No correlation
Aronow (47)	843	82+	Heart disease	Complex VA	39	Approximately 2x incidence in patients with complex VA
	104		No heart disease	Complex VA	39	No correlation
Aronow (45)	391	82+	Heart disease	Complex VA, VT, & LVEF	24	Greater than 2x incidence in patients with complex VA or VT. 3x incidence in patients with abnormal LVEF. Greater than 7x incidence in patients with abnormal LVEF and complex VA or VT
	76		No heart disease	Complex VA, VT, & LVEF	24	No correlation
Aronow (46)	468	82+	Heart disease	Complex VA, VT, & LVH	27	3x incidence of SCD or VF in patients with complex VA, VT, or LVH. 7x incidence of SCD or VF in patients with LVH and complex VA or VT
	86		No heart disease	Complex VA	27	No correlation

* See text for definition of healthy; + age of total patients, including patients without heart disease; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; SCD = sudden cardiac death; VA = ventricular arrhythmias; VPC = ventricular premature beat; VT = ventricular tachycardia; VF = ventricular fibrillation.
Adapted from Ref. 49.

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Table 4 Relationship of Silent Ischemia to Future Cardiac Events in Older Patients

Study (Ref.)	Number of patients	Age (years)	Cardiac status	Variable	Mean follow-up period (months)	Incidence of cardiac events
Fleg (50)	98	69	No heart disease	SI*	120	Approximately 4x incidence in patients with SI
Aronow (11)	534	82+	Heart disease	SI	26	Greater than 2x incidence in patients with SI
	92		No heart disease	SI	26	No correlation
Aronow (53)	393	82	CAD or systemic hypertension	SI & LVEF	40	2x incidence in patients with SI. Greater than 2x incidence in patients with abnormal LVEF. Greater than 3x incidence in patients with SI and abnormal LVEF
Aronow (52)	404	82	CAD or systemic hypertension	SI, complex VA, & VT	37	2x incidence in patients with SI or complex VA. 4x incidence in patients with SI and complex VA. 1.7x incidence in patients with VT. 2.5x incidence in patients with SI and VT
Hedblad (12)	394	68	CAD or no CAD	SI	43	4.4x greater risk of MI in patients with SI. Risk increased 16x in patients with SI and CAD

* Included patients with ≥ 1 mm upsloping ST-segment depression; + age of total patients, including patients without heart disease; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SI = silent ischemia; VA = ventricular arrhythmias; VT = ventricular tachycardia.
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going noncardiac surgery. Such use of AEM may be especially beneficial in older patients, who frequently are at high surgical risk and may not be able to undergo preoperative exercise stress testing because of concomitant illness. No study, however, has shown silent ischemia detected by ACE to be more beneficial than pharmacological stress testing in stratifying preoperative elderly patients into high-and low-risk groups. Raby and associates (58) studied 176 patients who underwent 24-h AEM before noncardiac surgery. Eighteen percent of the patients had signs of ischemia on preoperative AEM, with the ischemia silent in the majority of patients; and the preoperative ischemia was highly predictive of postoperative cardiac events. The sensitivity of preoperative ischemia for postoperative cardiac events in these patients was 92%, the specificity 88%, the predictive value of a positive result 38%, and the predictive value of a negative result 99%. Multivariate analyses demonstrated preoperative ischemia to be the most significant correlative of postoperative cardiac events. The authors concluded that the absence of preoperative ischemia on AEM indicates a very low risk for postoperative cardiac events. Thirty-eight percent of the patients in this study were older than 69 years, and preoperative ischemia was more prevalent in these elderly patients compared with the younger patients.

In a follow-up study, Raby and associates (59) assessed the significance of intraoperative and postoperative silent ischemia, in addition to preoperative ischemia, detected on AEM in relationship to postoperative cardiac events in patients undergoing peripheral vascular surgery. The mean age of the patients was 67 years and 37% were 70 years or older. As in their previous study, the authors found preoperative silent ischemia to be the most important predictor of postoperative cardiac events. Preoperative ischemia also strongly correlated with intraoperative and postoperative ischemia, and perioperative ischemia commonly preceded clinical cardiac events.

Echocardiography

Echocardiography can be a useful procedure in the assessment of elderly patients with CHD. Detection of regional wall abnormalities, acute myocardial ischemia, left ventricular aneurysm, cardiac thrombus, left main coronary artery disease, left ventricular hypertrophy, left ventricular function, and cardiac chamber size is possible with echocardiography. Such findings are useful in diagnosing CHD, and may be particularly beneficial in diagnosing acute myocardial infarction or ischemia in elderly patients with atypical chest pain and a nondefinitive electrocardiogram. Echocardiographic findings are also useful in predicting future cardiac events and long-term prognosis in elderly patients (7,45,46,60). Aronow and associates (60), in studies of elderly nursing home patients, found left ventricular ejection fraction to be the most important prognostic variable for mortality in elderly patients with heart failure associated with CHD. Patients with heart failure and depressed systolic left ventricular ejection fraction had a worse prognosis than did patients with heart failure and normal systolic ejection fractions. Echocardiographic left ventricular hypertrophy is a predictor of future cardiac events in both middle-aged and elderly patients with CHD. The Framingham Heart Study (61) found echocardiographic left ventricular hypertrophy to be predictive of coronary events independently of standard risk factors in elderly patients with CHD. Echocardiographic left ventricular hypertrophy was 15.3 times more sensitive in predicting coronary events in elderly men and 4.3 times more sensitive in predicting coronary events in elderly women than was electrocardiographic ventricular hypertrophy. In studies of very elderly nursing home patients with CHD, Aronow and associates reported similar findings (46,62,63). Elderly nursing home patients with echo-

cardiographic left ventricular hypertrophy had at least a two times higher incidence of new coronary events at follow-up than did patients without echocardiographic left ventricular hypertrophy. The incidence of new atherothrombotic brain infarction, heart failure, and sudden death was also higher in elderly nursing home patients with CHD or hypertension and echocardiographic left ventricular hypertrophy than it was in patients without left ventricular hypertrophy regardless of whether CHD or hypertension was present.

Conclusions and Considerations

Even though CAD is prevalent in elderly persons, it is often undiagnosed or misdiagnosed, which may be related to its atypical presentation in this age group. Instead of typical chest pain, dyspnea or acute heart failure may be the initial manifestation of myocardial ischemia or infarction in elderly persons. In other elderly persons, myocardial ischemia or infarction will be silent, with the patient completely asymptomatic, even though electrocardiographic findings of ischemia or infarction are present. Some elderly patients with acute myocardial infarction will demonstrate neurological symptoms such as mental confusion or cerebral vascular accidents. Because of these atypical presentations and the wide variability of symptoms, physicians must be highly suspicious of the presence of myocardial ischemia or acute infarction in elderly patients who have an unexplained acute change in their physical condition. Diagnostic procedures such as resting electrocardiography, stress testing, ambulatory electrocardiographic monitoring, and echocardiography can be beneficial in diagnosing CAD in elderly patients as well as in predicting future coronary events in these patients. The use of these diagnostic techniques should be considered in the evaluation of elderly patients in whom CHD is suspected.

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11

Angina in the Elderly

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Coronary artery disease (CAD) is the number one cause of death in elderly patients and also the major cause of hospitalization and rehospitalizations in this age group. Clinically, CAD manifests as acute ischemic syndromes, and it is important that the practicing physician have an understanding of the pathophysiology of these syndromes, as well as be confident in managing these syndromes in elderly patients. This chapter will discuss the evaluation and management of elderly patients who demonstrate two of these ischemic syndromes—stable and unstable angina.

Recent advances in cellular and molecular biology have provided a better understanding of coronary atherosclerosis, the underlying disease process causing myocardial ischemia. Due to these advances and the development of new therapies, we are now not only able to relieve the patients' symptoms but are able to modify the underlying pathophysiology. (See Chap. 9.)

Evaluation and treatment of myocardial ischemia in elderly patients pose unique challenges to the physician. Although the pathophysiology of myocardial ischemia and the treatment options are similar in elderly and younger patients, there are significant differences in presentation and response to treatment between the age groups. Elderly CAD patients with myocardial ischemia often present with ''atypical'' symptoms, and have more comorbid illnesses, greater number of vessels involved, and worse left ventricular (LV) function (1–6). Pharmacokinetics of medications is altered in elderly patients and there is often a greater sensitivity to medication and greater potential for side effects and drug interactions. Since elderly patients often present with more advanced CAD and their prognosis is often worse, there is greater potential for gain from aggressive interventions, such as angioplasty (PTCA) and bypass surgery (CABG), although the risks are greater compared to younger patients. Finally, elderly patients and their families may place different values on risk, quality of life, and the importance of prognosis, all of which must be considered by the practicing physician.

EVALUATION AND MANAGEMENT

The most common symptom of myocardial ischemia in elderly patients as well as in younger patients is exertional chest pain (angina); however, in many older patients, instead

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of chest pain, exertional dyspnea may be the initial manifestation of ischemia. (See Chap. 10 for details concerning atypical presentation of CAD in elderly patients.) Other common symptoms experienced by elderly patients with myocardial ischemia are dizziness, mental confusion, or easy fatiguability. In some elderly patients with myocardial ischemia, the presentation will be the sudden onset of heart failure (''flash'' pulmonary edema) (7–9) or arrhythmias, including sudden death (10). Silent ischemia is particularly common in elderly patients with CAD, occurring in up to one-third of elderly nursing home patients, as documented by Holter monitoring (11,12).

The initial evaluation of the elderly patient with possible myocardial ischemia should begin with a thorough history and complete physical examination, and determination of coronary risk factors and comorbid illnesses. The assessment should determine if the patient is stable or unstable and the risk stratification of the patient. In addition to advanced age, morbidity and mortality in elderly patients with acute ischemia are directly related to left ventricular function, extent of CAD, and presence of comorbidity. During the evaluation, the physician caring for elderly patients with myocardial ischemia will need to consider the effects of the disease on the whole person (including physical, psychosocial, and economic aspects) and the impact of the disease on the patient's family.

Angina is a clinical syndrome reflecting inadequate oxygen supply for myocardial metabolic demands with resultant ischemia. Depending upon the underlying pathophysiology, the patient will present with stable or unstable angina. The goals of therapy in elderly patients with angina (ischemic syndromes) are (1) to relieve the acute symptoms and stabilize the acute pathophysiological process; (2) to minimize the frequency and severity of recurrent angina attacks; and (3) to prevent progression, plus produce regression of the underlying pathophysiological process. Therapeutic measures are directed at modifying the underlying pathophysiology with therapeutic agents and reducing myocardial ischemia by (1) reducing myocardial oxygen demands and (2) increasing coronary blood flow.

The main underlying pathological process in patients with angina is coronary atherosclerosis with plaque formation and narrowing of the vessel luminal diameter, plus intermittent rupture of the atherosclerotic plaque. Because thrombus formation is an important factor in the progression of atherosclerotic lesions and in the conversion of clinical to acute events after plaque rupture, antiplatelet and anticoagulant therapy is important in the management of elderly CAD patients. In addition, stabilization and regression of the atherosclerotic lesions are possible by vigorous control of the patient's serum lipids, particularly with HMG CoA-reductase inhibitors (statins), and treatment of other risk factors, such as hypertension, diabetes, and smoking.

The main determinants of myocardial oxygen demands are heart rate, myocardial contractility, and intramyocardial tension, which is a function of systemic pressure and ventricular volume. Reduction of the myocardial oxygen demands includes correction of potentially reversible factors, such as heart failure, hyperthyroidism, valvular heart disorders (particularly aortic stenosis), obesity, emotional stress, hypertension, and arrhythmias, such as atrial fibrillation. Drug therapy to decrease myocardial oxygen demands is directed at reducing myocardial contractility, slowing heart rate, and limiting myocardial tension by reducing systemic pressure (afterload) and preload.

Coronary blood flow is dependent upon duration of diastole, coronary arterial resistance, aortic diastolic pressure, and availability of coronary collateral vessels. Improvement in coronary blood flow can be accomplished by drugs that increase the duration of diastole, decrease coronary artery resistance by vasodilatation or by reduction of intramyocardial tension, and stimulate development of and flow through collateral vessels.

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SPECIFIC DRUG THERAPIES

The principles of drug therapy for treating angina in elderly patients are the same as that for younger patients. The physician treating elderly patients, however, must be aware that the pharmacokinetics of drugs may be different in this age group. Gastrointestinal disorders may potentially interfere with drug absorption, although drug bioavailability is usually unaffected by the aging process (13). The decrease in lean body mass and increase in adipose tissue associated with aging affects the volume of drug distribution. Hepatic blood flow and hepatic oxidation (phase I reactions) decrease with aging, whereas hepatic conjugation is unchanged. Not only is renal dysfunction common in elderly patients but aging is associated with a decline in glomerular filtration rate of 30% between the fifth and ninth decade in normal patients (13). The elderly often demonstrate increased sensitivity to drugs at any given dosage and may tolerate side effects less well. The presence of comorbid conditions greatly increases the potential for adverse drug reactions, although an actual increased rate of such reactions in the elderly population has been disputed (14). The axiom to remember when prescribing drugs in elderly patients is to start low and titrate up slowly.

Given the pharmacological considerations of drug therapy in elderly patients, the specific antianginal drugs can be very effective in controlling symptoms and modifying the underlying pathophysiological process in elderly patients with angina. The classes of drugs commonly used include (1) nitrates; (2) β-blockers; (3) calcium channel blockers; and (4) antiplatelet and/or anticoagulant agents.

Nitrates

Nitrates are safe, effective, and usually the first choice for treatment of angina. Denitration of the organic nitrate with the subsequent liberation of nitric oxide (NO) is necessary for the drug to have therapeutic effects. Nitric oxide stimulates guanylyl cyclase, which leads to the conversion of, guanosine triphosphate to cyclic guanosine monophosphate, which causes relaxation of vascular smooth muscle with vasodilatation (15,16). The exact mechanism by which the organic nitrates undergo denitration and thus liberate NO remains controversial (17,18).

The active metabolite, NO, is also known as the endothelium-derived relaxing factor (EDRF) (19) which, in addition to relaxing vascular smooth muscle, reduces platelet adhesion and aggregation (20). In vessels with atherosclerosis, it has been shown that the endothelium is dysfunctional with attenuation of EDRF activity (21). Such attenuation of EDRF has even been found in patients with hypercholesterolemia without overt coronary atherosclerosis (22). Due to this attenuated activity of EDRF, vascular vasoconstriction is predominant in patients with CAD. Therefore, nitrates as exogenous donors of NO would appear to be the ideal drug to use in elderly patients with angina (myocardial ischemia).

The mechanisms by which nitrates relieve and prevent myocardial ischemia include both (1) a reduction in myocardial oxygen demand and (2) an increase in myocardial oxygen supply due to the drug's potent vasodilator properties (Table 1). Dilatation of capacitance veins reduces ventricular volume and preload, thus lowering myocardial oxygen requirement and improving subendocardial blood flow. Dilatation of systemic conductive arteries decreases afterload, another determinant of oxygen consumption. Nitrates dilate epicardial coronary arteries with an increase in coronary flow and an improvement in subendocardial perfusion. Nitrates also dilate collateral vessels, which can improve

Table 1 Cardiovascular Effects of Nitrates and Mechanisms To Relieve Angina (Ischemia)

Decrease myocardial O_2 demands
*Venodilatation → ↓ preload → ↓ wall tension
*Arteriolar dilatation → ↓ afterload → ↓ wall tension
Increase myocardial blood flow (O_2)
*Coronary dilatation → ↑ coronary flow → ↑ regional myocardial perfusion (subendocardial)
*Increase collateral flow → ↑ myocardial perfusion (subendocardial)
*Decrease coronary resistance → ↑ coronary flow

blood flow to the areas of ischemia (23). In the doses used clinically, nitrates do not affect coronary resistance vessels (24). Thus the risk of myocardial ischemia due to coronary steal is minimal, which has been shown to occur with drugs such as dipyridamole and short-acting calcium channel blockers that cause arteriolar dilatation (25).

Nitrate Preparations (Table 2)

Short-acting nitrates: Nitroglycerin is the drug most frequently used for relief of the acute angina attack. It is given either as a sublingual tablet or a sublingual spray and is absorbed rapidly with hemodynamic effects occurring within 2 min after drug administration. The advantage of the spray is that that sublingual tablets deteriorate when exposed to light and will need to be renewed every 4 to 6 months to ensure complete bioavailability. The other advantage of nitroglycerin-spray is that it may be easier to administer in elderly patients who have difficulty with the fine motor skills necessary to administer sublingual tablets. Intravenous nitrates are also available to abort acute angina attacks that are not relieved with sublingual tablets or spray, and to prevent recurrent angina attacks.

Long-acting nitrates: Nitrates have been proven not only effective in relieving acute angina pain, but also beneficial in preventing recurrent angina attacks. The oral preparation is usually the nitrate of choice in the prevention of angina. Standard-formulation *isosorbide*

Table 2 Different Nitrate Preparations and Dosages

Medication	Usual dose (mg)	Onset of action (min)	Duration of action
Short-acting			
Sublingual nitroglycerin	0.3–0.6	2–5	10–30 min
Aerosol nitroglycerin	0.4	2–5	10–30 min
Sublingual and chewable isosorbide dinitrate	2.5–10	3–15	1–2 h
Intravenous	5 μg/mm; titrate to 30–80 μg/mm	1	Sustained during infusion
Long-acting			
Oral isosorbide dinitrate	5–40	15–30	3–6 h
Oral isosorbide dinitrate (SR)	40	30–60	6–10 h
Oral erythrityl tetranitrate	10	30	Variable
Oral isosorbide mononitrate	5–60	30	6–8 h
Transdermal nitroglycerin	5–15	30–60	8–14 h

SR = sustained release.
Adapted from Ref. 78.

dinitrate is rapidly absorbed and is typically administered 3 times a day with a 14-h tablet (nitrate)-free interval. Sustained-release isosorbide dinitrate has a slower rate of absorption and results in therapeutic plasma concentration for 12 h. The usual dosage schedule is twice daily in doses of 20 to 80 mg.

An *isosorbide mononitrate* is now available for the prevention of angina. The major advantage of the mononitrate preparation is that it is completely bioavailable, because it does not undergo first-pass hepatic metabolism. To avoid drug tolerance, it is recommended that the 20- to 40-mg tablets be given twice daily with 7 h between doses. A sustained-release formulation of isosorbide mononitrate is also available that provides therapeutic plasma drug concentrations for up to 12 h each day and low concentrations during the latter part of the 24-h period. The drug dose range is 30–240 mg given once daily.

Transdermal nitroglycerin is a topical nitroglycerin preparation that is effective in preventing angina, and may be particularly beneficial in elderly patients who are taking numerous pills and have difficulty in remembering drug schedules. Moreover, transdermal nitrate preparations will be more effective than oral preparations in elderly patients who have problems with gastrointestinal malabsorption. Transdermal nitroglycerin is available as an ointment or patch preparation. Both preparations are effective, although the patch obviates some of the inherent messiness of the ointment. As with the oral preparation, a 12- to 14-h nitrate-free interval is necessary to avoid tolerance when using nitroglycerin ointment or patches.

Adverse Effects

Elderly patients, in general, tolerate nitrates without significant adverse effects, although the two major side effects, hypotension and headaches, can be extremely bothersome in certain patients. Hypotension may occur within minutes after sublingual administration of a nitrate or 1 to 2 h after oral ingestion and is caused by the reduction in preload and afterload caused by the vasodilator effect of the drug. Symptoms may range from lightheadedness to syncope, and are commonly positional, precipitated by standing. The hypotension related to nitrates more commonly occurs following the initial use of the drug, when hypovolemia is present, or with concomitant vasodilator therapy use, such as calcium channel blockers or other antihypertensive drugs. The hypotension episode may also be potentiated by alcohol. The episodes can be alleviated by reduction of the dose of nitrate, correction of hypovolemia, and avoidance of immediately standing after sublingual use of the drug. In certain elderly patients, the hypotension will be associated with bradycardia, similar to a typical vasovagal reaction. The hypotension associated with nitrate use will usually be alleviated by the patients lying down; in certain patients with a severe hypotensive reaction, elevation of the legs, plus administration of fluid will be necessary.

The headache associated with nitrates can be a significant problem in certain elderly patients. It may be a mild, transient frontal headache, although in other patients the headache will be a diffuse, throbbing, and persistent head and neck pain associated with nausea or vomiting. Such severe headaches are more common with the use of intravenous or transdermal nitrates. Nitrates may also aggravate vascular headaches and even initiate episodes of ''cluster headaches.'' As in the management of hypotension related to nitrates, the best approach to alleviate or prevent headaches is to use the lowest doses of nitrates possible and titrate slowly upward if necessary. The use of an analgesic such as aspirin or acetaminophen in conjunction with the nitrate administration may prevent the associated

headache. Commonly, due to vascular adaptation, within 7 to 10 days after initiation of nitrate use, the headache will diminish and subside. However, while waiting for adaptation to occur, elderly patients will require much reassurance to continue using the drug; and in certain elderly patients, a different antianginal drug will have to be substituted for the nitrate because the patient will not be able to tolerate the recurrent headaches.

Nitrate tolerance, defined as the loss of hemodynamic and antianginal effects during sustained therapy (26), is another consideration when treating elderly CAD patients. Tolerance has been shown to occur, regardless of the nitrate preparation, if the patient is continuously exposed to nitrates throughout a 24-h period. The clinical impact of nitrate tolerance, however, is unknown, and the mechanism of nitrate tolerance remains unclear (26,27). Various possible hypothesis include (1) increased intravascular blood volume; (2) depletion of sulfhydryl groups, which are needed for conversion of nitrates to NO; (3) activation of vasoconstriction hormones; and (4) increase in free-radical production by endothelium during nitrate therapy (28–30). To prevent tolerance, it is recommended that a 12- to 14-h nitrate-free interval be established when using long-acting nitrate preparations. During the nitrate-free interval, the use of another antianginal drug will be necessary. In elderly patients with unstable angina who are receiving continuous intravenous nitrates, tolerance is not a consideration; if tolerance develops in this setting, the dose of the nitrate should be increased.

Studies have demonstrated that abrupt withdrawal of nitrate exposure may produce nonatherosclerotic ischemic cardiac events, including myocardial infarction (31,32). Such events are presumably due to coronary artery spasm. Therefore, caution should be exercised when high-dose nitrate therapy is discontinued in elderly patients; if possible, the nitrate dose should be slowly tapered downward before discontinuation.

β-Blockers

β-adrenergic blocking agents are effective in preventing angina and are considered by many authorities to be the drug of choice to prevent ischemic events. β-blockers prevent angina mainly by reduction in myocardial oxygen demands related to showing the heart rate, depressing myocardial contractility, and reducing blood pressure (Table 3). These effects are particularly impressive in the setting of increased emotional and physical stress, such as during exercise and high anxiety states. In addition to the reduction of myocardial oxygen demands, β-blockers will increase myocardial oxygen supply by slowing the heart rate and extending the period of diastole.

β-adrenergic blocking agents can be classified according to (1) cardioselectivity; (2)

Table 3 Cardiovascular Effects of β-Blockers and Mechanisms To Relieve Angina (Ischemia)

Decrease myocardial O_2 demand
*Decrease contractility → ↓ blood pressure and ↓ CO
*Decrease heart rate → ↓ blood pressure and ↓ CO
Increase myocardial blood flow (O_2)
*Decrease heart rate → ↑ diastolic perfusion time

CO = cardiac output.

Table 4 Pharmacology of β-Blockers and Dosage

General drug (brand)	Cardioselectivity (relative B_1 sensitivity)	Intrinsic sympathetic activity	Lipophilic properties	Usual maintenance dose
Propranolol (Inderal)	0	0	high	10–40 mg, q.i.d.
Propranolol LA (Inderal-LA)	0	0	high	40–240 mg, q.d.
Atenolol (Tenormin)	+	0	low	25–100 mg, q.d.
Metoprolol (Lopressor)	+	0	moderate	25–100 mg, b.i.d.
Metoprolol ER (Troprol XL)	+	0	moderate	50–200 mg, q.d.
Timolol (Blocadren)	0	0	low	10–20 mg, b.i.d.
Acebutolol (Sectral)	+	+	low	200–600 mg, b.i.d.
Pindolol (Visken)	0	+	moderate	5–20 mg, t.i.d.
Labetalol (Normadyne)	0	0	low	100–600 mg, b.i.d.
Nadolol (Corgard)	0	0	low	40–80 mg q.d.
Esmolol (Brevebloc injection)	+	0	low	0.10–0.15 μg/kg/min

ER = extended release; LA = long-acting.

intrinsic sympathomimetic activity; and (3) lipophilic activities (Table 4). Consideration of these specific properties is important when using the drug in elderly CAD patients. Cardioselectivity is determined by the extent the agent is capable of blocking B_1 receptors and not B_2 receptors (33). Certain agents, such as metoprolol and atenolol, are relatively more cardioselective than propranolol, which makes these drugs less prone to induce bronchospasm or peripheral arterial vasoconstriction, as compared to the nonselective agents. At higher doses, however, cardioselective β-blockers react like nonselective agents with full potential for bronchospasm and peripheral arterial constriction.

Some β-blockers, such as pindolol and acebutolol, in addition to blocking β-adrenergic receptors, possess partial agonist properties and, therefore, are capable of producing intrinsic sympathetic stimulation (ISA) (34). The degree to which sympathomimetic activity is clinically apparent depends upon the underlying sympathetic activity of the patient receiving the drugs. β-Blockers with ISA may prevent slowing of the heart rate, depression of atrioventricular conduction, and a decrease in myocardial contractility in the setting of a low sympathetic state, such as when the patient is resting. When the sympathetic state is high, however, the effect of β-blockers with ISA is similar to that of the usual β-blockers, with a slowing of heart rate and a decrease of blood pressure and ventricular contractility. It should be emphasized that β-blockers with ISA do not prevent sudden death in post-myocardial infarction patients, which has been demonstrated with the use of the usual β-blockers; therefore, these agents are not recommended in elderly patients who have had a myocardial infarction (35).

The various β-blockers differ in reference to their lipid selectability properties. Some β-blockers, such as propranolol and metoprolol, are highly lipophilic, which facilitates transfer of the drug across the blood-brain and, therefore, the lipophilic agents are more likely to produce central nervous system side effects, including mood changes, depression, and sleeping disturbances (36). In contrast, the hydrophilic β-blockers, such as atenolol and nadolol, are less likely to produce central nervous system side effects.

Some β-blockers, such as labetalol, bucindolol, and carvedilol, have vasodilator properties in addition to their β-blocker properties. This vasodilator property makes these agents especially useful in the management of elderly CAD patients with hypertension

and heart failure. The results of the recent studies assessing the benefits of carvedilol in treating patients with heart failure have been very impressive in prolonging survival in patients with heart failure (37).

In general, β-blockers are well tolerated in elderly patients and some studies have not shown any difference in prevalence of drug side effects between older and younger patients (38). However, significant drug side effects may occur in elderly patients and may be life-threatening. Bradycardia, secondary to the drug effects upon the sinus node and atrioventricular conduction may occur, and, due to attenuation of bronchodilatation, asthmatic attacks may be precipitated by the drugs. Therefore, β-blockers are contraindicated in patients with significant bradycardias, unless a pacemaker is inserted, and in persons with a history of bronchospasm. The drugs should also be avoided, or used with caution, in persons with hypotension, hypoglycemic reactions, severe peripheral vascular disease, mental depression, and severe heart failure secondary to severe systolic ventricular dysfunction. The possibility of withdrawal rebound phenomenon with activation of acute ischemic events should be considered when discontinuing β-blockers in elderly patients. Accordingly, if possible, the dose of β-blockers should slowly be tapered downward before discontinuation and another antianginal drug should be started; in addition, the patient should be advised to avoid strenuous activities during the tapering period.

β-Blockers do have effects on serum lipids, which need to be considered when managing elderly CAD patients. Some studies have shown β-blockers to increase triglycerides and to decrease HDL cholesterol, although no significant change was noted in total cholesterol or LDL cholesterol (39). Other studies have not demonstrated a significant effect of long-term propranolol use in serum lipids in elderly persons (40).

Calcium Channel Blockers

Calcium channel blockers are usually not considered as first-line drugs in elderly patients with acute coronary artery syndromes. Unlike β-blockers, their effects are less predictable and they have not been shown to reduce mortality, sudden death, or reinfarction in post-myocardial patients. The recent studies that have suggested possible increase of morbidity and mortality with the use of these drugs in treating hypertension are also disturbing (41,42). In turn, calcium blockers have cardiovascular effects that can be beneficial in preventing and controlling angina. In general, the calcium blockers exert their effect by inhibiting influx of calcium ions through calcium channels of cardiac and vascular smooth muscle cells. Due to this inhibition of calcium influx, myocardial contractility is decreased, dilatation of peripheral and coronary vasculature occurs, and sinus node and atrioventricular conduction function are suppressed. Therefore, myocardial oxygen demands are reduced by the decrease in preload and afterload and the decrease in myocardial contractility. Slowing of heart rate, which occurs with the use of nondihydropyridine calcium blockers, such as verapamil and diltiazem, is also effective in decreasing myocardial oxygen demands. In addition to reducing myocardial oxygen demands, calcium blockers can improve myocardial oxygen supply by relaxing the tone of coronary arteries and by promoting the development of coronary collaterals (Table 5). This property of relaxing coronary vasculature tone is particularly beneficial when Prinzmetal angina (vasospasm) is present.

Calcium channel blockers are usually divided into the dihydropyridine and nondihydropyridine groups, plus the agent, bepridil (Table 6). Nifedipine was the first dihydropyridine available for the treatment of angina, but newer generations of dihydropyridine agents

Table 5 Cardiovascular Effects of Calcium Blockers and Mechanisms To Relieve Angina

Decrease myocardial O_2 demands
*Arteriolar vasodilatation → ↓ afterload → ↓ wall tension
*Decrease contractility
*Decrease heart rate
Increase myocardial blood flow (O_2)
*Decrease heart rate → ↑ diastolic perfusion time
*Coronary vasodilatation → ↑ flow

are now available, including nicardipine, nisoldipine, nimodipine, felodipine, amlodipine, and isradipine. Nifedipine is a potent coronary and peripheral artery vasodilator with negative inotropic properties. Significant afterload reduction occurs due to the vasodilation. At therapeutic doses, nifedipine has only a minor effect on the sinus and atrioventricular nodes; thus due to the decrease in afterload, sympathetic reflex increase in heart rate commonly occurs when the drug is administered. The increased heart rate may ameliorate the negative inotropic effect and, clinically hemodynamic indices of contractility generally are unaffected. Due to intense vasodilation of the peripheral coronary circulation, however, the possibility of a coronary steal phenomenon has to be considered when using the drug (43). Such a phenomenon is more common when using a short-acting drug preparation and in patients with severe three-vessel coronary disease. Therefore, a β-blocker should be added if nifedipine is used to treat elderly patients with acute ischemic syndromes. A sustained-release preparation of nifedipine is now available, which results in less sympathetic activity and is considered to be a safer agent than the shorter-acting preparations. Nevertheless, the addition of a β-blocker with nifedipine, regardless of the type of preparation, is considered the best approach when managing elderly patients with acute ischemic syndromes. The second-generation dihydropyridines, amlodipine and felodipine, have greater vascular selectivity and less negative inotropy and have no clinical effect on the

Table 6 Calcium Channel Blocker Preparations and Dosage

Generic drug (brand)	Potential for SA node and AV node depression	Potential for depression of myocardial contractility	Usual adult oral dosage (mg)
Nifedipine (Procardia) (Adalat)	0	0 to +	10–30, t.i.d
Nifedipine GITS (Procardia XL)	0	0 to +	30–90, q.d.
Nicardipine (Cardene)	0	0 to +	20–30, t.i.d.
Amlodipine (Norvasc)	0	0	2.5–10, q.d.
Felodipine (Plendil)	0	0	2.5–20, q.d.
Diltiazem (Cardiazem)	++	+	30–90, t.i.d.
Diltiazem CD (Cardiazem CD)	++	+	120–300, q.d.
Verapamil (Isoptin) (Calan) (Verelan)	++	++	40–120, t.i.d.
Verapamil SR (Isoptin SR) (Calan SR)	++	++	120–240, q.d.

CD = controlled perfusion; GITS = gastrointestinal system; SR = sustained release.
Adapted from Ref. 78.

sinus or atrioventricular nodes. Therefore, coronary artery steal does not appear to be a major concern with these drugs, and the drugs can be used in elderly patients with heart failure. Amlodipine has been shown to be safe when used in patients with heart failure secondary to left ventricular systolic dysfunction, and may be beneficial in improving prognosis in patients whose heart failure is secondary to nonischemic cardiomyopathy (44).

Verapamil and diltiazem, two nondihydropyridine agents, are both potent inhibitors of sinus node activity and atrioventricular node conduction, in addition to being peripheral vasodilators (Table 6). Both drugs have significant negative inotropic effects. Due to these effects, the drugs are effective antianginal agents; however, caution is necessary when using the drugs in elderly patients with bradycardias and depressed systolic ventricular function. The drugs are contraindicated in patients with clinical heart failure secondary to systolic ventricular function and in patients with disorders of the sinus node and in patients with heart block. The Multicenter Diltiazem Post Infarction study (45) reported an increased mortality in postinfarction patients with heart failure who were randomized to diltiazem therapy. Therefore, if a calcium channel blocker is necessary to control angina in elderly postinfarction patients with depressed left ventricular function, the second-generation dihydropyridines, amlodipine or felodipine should be used instead of diltiazem or verapamil.

Extreme caution is required when using diltiazem or verapamil in combination with a β-blocker, particularly in elderly patients who demonstrate sinus node or atrioventricular conduction dysfunction, or in elderly patients who have depressed ventricular function. Some authorities recommend electrocardiographic monitoring when initiating these drugs, particularly verapamil, in combination with beta-blockers.

Bepridil is a calcium channel blocker structurally unrelated to the other calcium-blocker drugs. In addition to its beneficial antianginal effects of vasodilation and slowing heart rate, the drug has been shown to prolong the Qtc interval and to cause torsade de pointes (46,47). Sudden cardiac death has occurred in patients taking bepridel. Due to these unfavorable side effects, bepridil is not recommended as a first-line drug in elderly patients with angina, and, if used, continuous electrocardiographic monitoring is recommended when initiating the drug with measurement of Qtc intervals.

It should be emphasized that recent studies (41,42) have reported increased morbidity and mortality in CAD patients treated with calcium channel blockers, particularly short-acting nifedipine. The mechanisms for these adverse effects are unclear, and the results of the studies are controversial. Nevertheless, it is recommended that long-acting calcium channel preparations, such as diltiazem or verapamil, be used in elderly CAD patients instead of the short-acting dihydropyridine agents. If dihydropyridine agents are necessary, the addition of a β-blocker is recommended.

Aspirin

Recent knowledge of the importance of thrombus formation in acute coronary syndromes and the results of studies that demonstrate a decreased incidence of myocardial infarction in patients taking daily aspirin compared to patients receiving placebo (48), indicate that a daily aspirin should be prescribed for all elderly patients with angina. The specific dosage of oral aspirin is unclear, since the dosage in studies has varied; the usual dosage is considered to be 180 to 325 mg/day.

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Table 7 Unstable Angina Presentations

*Rest angina within 1 week of presentation
*New-onset angina of Canadian Cardiovascular Society Classification (CCSC) class III or IV within 2 months of presentation
*Angina increasing in CCSC class to at least CCSC III or IV
*Variant angina
*Non-Q-wave myocardial infarction
*Postmyocardial infarction angina (>24 hs)

AN APPROACH TO MANAGEMENT—SPECIFIC PRACTICE CONSIDERATIONS

Unstable Angina

Unstable angina is a transitory syndrome that results from disruption of a coronary atherosclerotic plaque with the subsequent cascade of pathological processes, including thrombosis formation that critically decreases coronary blood flow resulting in new onset or exacerbation of angina (ischemia) (49). Transient episodes of vessel occlusion or near occlusion by thrombus at the site of plaque injury may occur and lead to angina at rest. The thrombus may be labile and result in temporary obstruction to flow. Release of vasoconstriction substances by platelets and vasoconstriction secondary to endothelial vasodilator dysfunction contribute to further reduction in blood flow (50), and in some patients myocardial necrosis (non-Q-wave infarction) is documented. Table 7 lists the various clinical presentations that are classified as unstable angina.

In contrast to elderly patients with stable angina who do not require hospitalization, elderly patients with unstable angina are usually hospitalized, and depending upon their risk stratification, may require monitoring in an intensive care unit. Severe classification schemes of risk stratification have been developed. Table 8 lists a classification that subdivides patients into high-, intermediate-, and low-risk groups (51). As noted by this classification, clinical characteristics are readily identifiable on the initial patient evaluation that stratifies the patient into low-, intermediate-, or high-risk subgroups for hospital complications. For example, acute resting ECG abnormalities markedly worsen the prognosis. Other characteristics that identify the high-risk patient include prolonged ongoing rest pain longer than 20 min and signs of left ventricular dysfunction (S3, rales, new murmur of

Table 8 Risk Stratification Scheme of Unstable Angina Based on Presenting Clinical Characteristics

Risk class[a]	Clinical characteristics
IA	Acceleration of previous exertional angina without ECG changes
IB	Acceleration of previous exertional angina with ECG changes
II	New onset of exertional angina
III	New onset of rest angina
IV	Coronary insufficiency syndrome: protracted chest pain >20 min with persistent ECG changes

[a] IA = lowest risk for in-hospital complications; IV = highest risk for in-hospital complications.
Adapted from Ref. 51.

mitral regurgitation). Within each subgroup of unstable angina, it is important to recognize certain elderly patients who have specific characteristics that will influence therapy. Recurrent angina after PTCA is a common clinical event related to partial artery restenosis and occurs in as many as 40% of patients within the first 3 to 6 months post-PTCA, regardless of the patient's age. The prognosis is favorable and the elderly patient can usually be stabilized medically prior to a scheduled repeat angiogram and a possible repeat PTCA. Angina after intracoronary stent placement occurs less frequently than after isolated angioplasty and is often the result of subacute closure due to thrombus formation. These patients are at higher risk for MI and are usually managed as higher-risk patients (52). Patients with angina following CABG are another subgroup of elderly patients who require specific considerations; since the risk of reoperation is higher than that of the initial surgery, surgeons are often reluctant to reoperate in elderly patients, especially on those elderly patients who have had internal mammary grafting. Medical therapy is usually the first approach in this subgroup of elderly patients with unstable angina. Other clinical subgroups of elderly patients with unstable angina who require special considerations are the patient with a non-Q-wave infarct, the patient with variant angina, and the patient with cocaine intoxication.

Following risk stratification of the elderly patient with unstable angina, therapy should be initiated. The initial goals of therapy should be to alleviate symptoms by decreasing myocardial oxygen demands and increasing myocardial blood flow and to stabilize the atherosclerotic plaque. Furthermore, a plan to promote regression of the atherosclerotic lesion should be initiated during the patient's hospitalization.

Therapy, including drug therapy, should be started in the emergency department; it should not be delayed until hospital admission. Reversible factors causing angina should be identified and corrected. Electrocardiographic monitoring is important since arrhythmias can occur and ST-T changes are a marker of increased risk of complications. The aggressiveness of the drug dosage will depend upon the severity of symptoms and will need modification throughout the elderly patient's hospitalization. Oxygen should be given to patients with cyanosis, respiratory distress, heart failure, or high-risk factors. Oxygen therapy should be guided by arterial saturation; its use when the baseline saturation is more than 94% is questionable.

Aspirin should be given to all patients unless contraindicated. Ticlopidine, 250 mg twice a day, may be used as a substitution in patients unable to take aspirin because of a history of true hypersensitivity or recent significant gastrointestinal bleeding (53), although close monitoring of hematological parameters will be necessary when the drug is used. If electrocardiographic ST-T wave changes accompany rest pain, or if other factors are present that classify the patients as high risk, heparin infusion should be started in the absence of contraindications. The recommended initial dose is a bolus of 80 units/kg/h, titrated to an activated partial thromboplastin time of two to three times control. Risk factors for bleeding secondary to heparin therapy include advanced age, female sex, hypertension with systolic blood pressure greater than 180, and patients with lower body weight. The increased use of aspirin in combination with heparin appear modest, although some investigators advocate combination therapy and have reported less ''rebound'' angina when stopping heparin if aspirin is given concomitantly. It should be emphasized that thrombolytic therapy has not been shown to be beneficial in patients with unstable angina.

As with the use of aspirin, nitrates should be instituted quickly in the emergency department. Patients whose symptoms are not fully relieved with three sublingual nitroglycerin tablets should receive continuous intravenous nitroglycerin. The initial dose is 5

to 10 mg/min and the dose should be titrated every 3 to 5 min to relieve symptoms or hypertension. If angina is relieved, then an oral or transdermal preparation can be started after 24 h of intravenous therapy. β-Blockers (in addition to aspirin, heparin, and nitrates) should also be started in the emergency room unless there are contraindications. Intravenous loading (e.g., metoprolol 5 mg for 5 min, repeated every 15 min for a total of 15 mg) followed by oral therapy is recommended. A continuous β-blocker intravenous infusion may be used (esmolol, starting maintenance dose of 0.1 μg/kg/min intravenously with titration upward in increments of 0.5 μg/kg/min every 10 to 15 min as tolerated by blood pressure until the desired response has been obtained, limiting symptoms develop, or a dose of 0.20 mg/min is reached).

Interventional Therapy

The majority of elderly patients with stable and unstable angina can be stabilized with medical management. Patients who continue to have unstable angina 30 min after initiation of therapy or have recurrent unstable angina during the hospitalization are at increased risk for myocardial infarction or cardiac death. In addition, patients who demonstrate major ischemic complications, such as pulmonary edema, ventricular arrhythmias, or cardiogenic shock associated with unstable angina also have a poor prognosis. In these patients, emergency cardiac catheterization should be performed with the consideration of interventional therapy (CABG or PTCA). Insertion of an intraaortic balloon pump may be necessary in some of these elderly patients.

For the majority of elderly patients whose angina is stabilized, two alternate strategies for definitive treatment of angina need to be considered:''early invasive'' and ''early conservative'' (54). The ''early invasive strategy'' approach is to perform cardiac catheterization in all patients after 48 h of presentation, unless interventional therapy is contraindicated due to extensive comorbidities. In contrast, the ''early conservative'' strategy is to perform cardiac catheterization only in patients who have one or more of the following high-risk indicators: prior revascularization, associated congestive heart failure, or depressed left ventricular function (ejection fraction <0.50) by noninvasive study, malignant ventricular arrhythmia, persistent or recurrent pain/ischemia, and/or a functional study (stress test) indicating high risk.

A stress test can be performed 48 to 72 h after the patient has stabilized; the choice of the type of stress testing (exercise, exercise with imaging, or pharmacological) will depend upon the resting electrocardiographic findings and the patient's ability to exercise.

Myocardial revascularization is indicated in patients who at catheterization are found to have significant left main CAD ($\geq$50%) or significant ($\geq$70%) three-vessel disease with depressed left ventricular function (ejection fraction <0.50); patients with two-vessel disease with proximal severe subtotal stenosis ($\geq$95%) of the left anterior descending artery and depressed left ventricular function for revascularization; and patients with significant CAD, if they fail to stabilize with medical treatment, have recurrent angina/ischemia at rest or with low-level activities, and/or if ischemia is accompanied by congestive heart failure symptoms, an S_3 gallop, new or worsening mitral regurgitation, or definite ECG changes (54).

For some patients without these high-risk features, revascularization may still be an option, depending on recurrent symptoms, test results, and patient preferences.

The health care team should educate the patient and his or her family or advocate

about the expected risks and benefits of revascularization and determine individual patient preferences and fears that may affect the selection of therapy.

Interventional therapy with PTCA, atherectomy, and/or some combination of PTCA and coronary artery stenting has increased in usage in patients with CAD, diminishing the frequency of CABG. Studies comparing PTCA and CABG have been performed, and, generally, the results of PTCA and CABG are similar in reference to mortality, although an increased incidence of recurrent angina and need for revascularization procedure occurs with PTCA (55–57). Further studies are necessary to determine if coronary stenting in conjunction with PTCA will decrease the incidence of recurrent angina and the need for revascularization (see Chaps. 14 and 15 for further details concerning roles of CABG and PTCA in elderly CAD patients).

STABLE ANGINA

Elderly patients with stable angina who are at ''low risk'' (preserved left ventricular function and no left main CAD) can be treated as effectively with medical therapy as with interventional therapy. In patients with stable angina the atherosclerotic lesions are predominantly advanced fibrolipoid plaques or fibrotic lesions (58). Usually no plaque ulceration or thrombosis is present, and the main cause of angina is the reduction of luminal diameter of the coronary vessel due to chronic atherosclerosis. Therefore, therapy is directed at decreasing myocardial oxygen demand and increasing coronary blood flow. In addition, prevention of plaque instability and initiation of therapy to cause regression of the atherosclerotic lesion are necessary.

Studies have not demonstrated any significant benefit of a specific class of antianginal drugs compared to other classes in treatment of stable angina. Therefore, the choice of a single antianginal drug will depend upon the clinical situation, contraindications, and the physician's preference. Surely, a β-blocker should be the first choice in elderly patients who have a history of a myocardial infarction or demonstrate electrocardiographic evidence of silent infarction.

Combination drug therapy, in which a β-blocker and a vasodilator are used, is highly advantageous in treating elderly patients with angina. Theoretically, combination drug therapy would appear more advantageous than use of a single drug; although combination drug therapy has not been shown more effective in the clinical control of angina, compared to monotherapy. Studies have shown that combination therapy with a nitrate and β-blocker decreases the number of angina attacks and increases the duration of time of treadmill stress testing, as compared to either nitrates or β-blockers alone (59). The combination of a β-blocker and a calcium blocker has also been shown to be more effective in reducing angina and extending exercise time than monotherapy (60). Such a combination can be very beneficial when attempting to control both hypertension and angina in elderly patients. In turn, caution is necessary when using β-blockers in combination with diltiazem or verapamil, due to the potential risk of provoking serious bradycardia, or precipitating heart failure. This is particularly a concern when verapamil and a β-blocker are used in combination, and when underlying sinus or atrioventricular nodal disease or left ventricular systolic dysfunction is present. In elderly patients whose angina is refractory to double drug combination, triple drug therapy may be necessary. Such therapy would include a β-blocker, a long-acting nitrate, and calcium blocker. Such therapy may be beneficial in

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preventing angina attacks, although elderly patients taking these multiple drugs will need to be monitored closely for side effects; and the drugs should be started at low doses.

Aspirin therapy should be used in all elderly patients with CAD, whether symptomatic or asymptomatic, unless contraindicated. The specific dosage of oral aspirin is unclear and doses of 180 to 325 mg have been found to be beneficial.

A preventive program in elderly patients with angina is mandatory, including abstinence from smoking, an exercise program, and control of lipids and weight. The recent studies (61–63) that have demonstrated the efficacy of statin therapy in lowering serum lipids and preventing future coronary artery events in patients with CAD compel physicians to screen elderly angina patients for elevated lipids, and to be aggressive in their treatment of lipid abnormalities. In addition, elderly patients will require counseling in reference to lifestyle, with avoidance of activities that ''trigger'' ischemic attacks (64). The physician will need to be aware of the potential for the development of mental depression in elderly CAD patients. The symptoms of depression may be subtle in these elderly patients, although symptoms will be progressive unless the disease is treated. Furthermore, depression has been shown to be a risk factor for future coronary events in patients with CAD (65).

The role of exercise should be emphasized when managing elderly patients with angina. Exercise programs that progressively increase physical endurance and reduce the heart rate and cardiac work at any given level of activity lead to improvement in cardiac performance and prolong exercise time before onset of angina (66). In addition, some studies have shown stress-induced myocardial ischemia (as assessed by thallium 201 scintigraphy) to be significantly decreased after a 1-year program of supervised exercise and low cholesterol diet in patients with stable angina (67). Caution is necessary, however, when initiating an exercise program in elderly CAD patients. Elderly patients should be screened for high-risk characteristics, including results of a stress test, before starting an exercise program, since exercise can provoke serious arrhythmia in high-risk patients, and especially in underconditioned patients. It has been recommended to start an exercise training program with a walking program, which is both easy and inexpensive for elderly patients. Other exercise programs can be advised according to the patient's needs and preference, such as swimming or stationary cycling.

New Approaches to Management of Angina

Over the years the management of patients with angina constantly changes and new approaches are developed. Some of these changes are due to the increased knowledge of the underlying pathophysiology of myocardial ischemia with the development of new drugs. Other changes are related to the development of innovative mechanical devices and techniques that theoretically should relieve angina.

New drugs that appear promising in modifying the underlying pathophysiological process are more aggressive antithrombotic and antiplatelet agents and agents that block platelet receptors. Results of studies investigating these agents are still preliminary; however, available data suggest that coronary artery thrombus dissolution or prevention of thrombus accumulation can be favorably affected by those drugs, and clinical trials have demonstrated improvement in outcome in patients with unstable angina treated with these agents (68,69).

The role of antioxidants has recently received renewed interest in the treatment of CAD. In the Cambridge Heart Antioxidant Study (70), vitamin E therapy was evaluated

for its ability to prevent coronary events among patients with CAD. At follow up, patients taking 400 or 800 mg of vitamin E daily had a lower incidence of nonfatal myocardial infarction than patients on placebo.

Two recent mechanical techniques for the treatment of angina include transmyocardial laser revascularization (TMLR) and enhanced external counter pulsation (EECP). Both of these approaches have been used in patients with severe angina who are not candidates for PTCA or CABG, usually due to diffuse CAD or extreme comorbidities. Such approaches would appear to be suitable for many elderly CAD patients who may have inoperative coronary artery disease and multiple comorbidities, plus, not infrequently, angina that is difficult to control with medical therapy.

TMLR employs a high-energy laser beam to create channels in the myocardium from the epicardial to the endocardial surface (71). The channels allow oxygenated left ventricular blood to profuse ischemic myocardial zones (72). The human myocardium contains an extensive network of sinusoids and TMLR, theoretically, delivers oxygenated blood to these sinusoids with improving myocardial delivery to the ischemic region. Some studies (71,73,74), which investigated TMLR in patients with inoperable CAD and severe angina, reported favorable results in that the patients' number of episodes of angina were significantly decreased, as were the thallium perfusion defects.

EECP is a noninvasive outpatient treatment designed to increase coronary flow in the treatment of angina (75). This treatment involves wrapping the calves, thighs, and buttocks with pneumatic cuffs. Synchronized pulsatory pressure is applied sequentially from calves to thighs during diastole, returning arterial blood to the heart to increase diastolic pressure in the coronary vessels. Pressure is relieved during systole, reducing afterload and cardiac work, thus decreasing myocardial oxygen requirements. The typical course of treatment is 35 1-h sessions over a period of 7 weeks. EECP has been shown to improve ischemia in patients who have thallium reperfusion evidence of ischemia. In one study of patients who received EECP, 75% of subjects had resolution of ischemia, demonstrated by improved thallium scintigraphy with normal thallium stress tests, except for areas scarred by previous myocardial infarctions (76). In addition, the subjects showed exercise improvement. Other studies of EECP have demonstrated similar subjective improvement in angina and resolution of ischemia demonstrated by improved thallium scintigraphy and electrocardiography in patients with severe angina (77).

Upon the results of the preliminary studies, these new drugs and techniques may have a role in the management of certain elderly CAD patients with angina. Further studies are necessary, however, before these new approaches can be recommended as therapy for managing elderly CAD patients.

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12

Therapy of Acute Myocardial Infarction

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In 1995, there were 771,000 hospital admissions in the U.S. with a first-listed diagnosis of acute myocardial infarction (MI) (1). Of these, 471,000 (61.1%) occurred in patients 65 years of age or older, and approximately one-third occurred in patients over the age of 75 years (1,2). Moreover, 80% of all deaths attributable to acute MI occurred in patients over age 65, and 60% occurred in patients over age 75 (2,3). It is thus clear that acute MI is exceedingly common in older adults, and the case-fatality rate in this population is particularly high.

In this chapter, the treatment of elderly patients with acute MI, including the management of selected complications, will be reviewed.

GENERAL PRINCIPLES

Numerous studies have demonstrated that elderly patients with acute MI are at increased risk for a variety of complications, including atrial fibrillation, congestive heart failure, myocardial rupture, cardiogenic shock, and death (4–9). The risk of each of these complications is two- to fourfold higher in patients over age 65 than in younger patients (10). Older age thus defines a high-risk subgroup of MI patients who could potentially derive substantial benefit from aggressive therapeutic interventions. On the other hand, elderly patients are at increased risk for serious adverse consequences arising from aggressive treatments, such as thrombolytic therapy or early catheterization and angioplasty. In addition, the risk–benefit ratio may be modulated by the presence of comorbid conditions (e.g., diabetes, renal insufficiency, dementia), as well as social considerations and patient preferences. It is thus evident that the potential benefits and risks of each intervention must be carefully considered on an individualized basis.

While elderly MI patients clearly represent a high-risk subgroup, it is important to recognize that they also comprise an extremely heterogeneous subgroup, and this heterogeneity has important therapeutic implications. For example, an 80-year-old patient presenting with a large anterior MI complicated by heart failure and hypotension has an expected mortality of over 50%. As a result, the potential benefit to be derived from maximally aggressive therapy (e.g., immediate catheterization and angioplasty) is large, thereby justifying a moderate increase in procedural risk. In contrast, an 80-year-old individual present-

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ing with a small inferior MI of more than 12 h duration who is hemodynamically stable and free of chest pain has a relatively favorable prognosis, and the risks associated with thrombolysis and direct angioplasty may not be justified. Thus, in considering the interventions described below, the clinician should keep in mind that the ''sickest'' patients have the most to gain from aggressive treatment, while those with a more favorable prognosis often respond satisfactorily to conservative management.

GENERAL MEASURES

As in younger patients, the early management of older patients with acute MI should include measures designed to relieve the patient's discomfort and treat any hemodynamic disturbances, such as heart failure or hypotension (Table 1). Morphine sulfate in doses of 2 to 4 mg intravenously is the recommended agent for treating chest pain in patients with acute MI (11). Empiric administration of supplemental oxygen is appropriate, but it is unlikely to improve tissue oxygen delivery if the baseline arterial saturation exceeds 94%. Nitroglycerin is safe in the majority of patients with acute MI, and it is effective in reducing

Table 1 General Measures for the Early Management of Elderly Patients with Acute Myocardial Infarction

Symptom or sign	Agent	Dose	Comment
Chest pain	Oxygen	2–5 L/min	Probably not helpful if O_2 saturation $\geq$ 94%
	Morphine	2–4 mg i.v., q 5–10 min	Watch for respiratory depression
	Nitroglycerin	0.4 mg sublingually 2% ointment, 1/2–2″ transdermally 10–200 μg/min i.v.	Watch for hypotension, esp. in inferior MI
	Metoprolol Atenolol	2.5–5 mg i.v., up to 15 mg 2.5–5 mg i.v., up to 10 mg	Watch for bradycardia, hypotension heart block, bronchospasm, worsening CHF
Congestive heart failure	Oxygen	As needed to maintain arterial saturation $\geq$ 92%	
	Furosemide	20–80 mg i.v.	Watch for hypotension
	Bumetanide	0.5–2 mg i.v.	Watch for hypotension
	Nitroglycerin	2% ointment, 1/2–2″ transdermally 10–200 μg/min i.v.	Avoid hypotension
Hypotension	IV fluids	As needed to maintain adequate perfusion	Watch for worsening heart failure
	Dobutamine	2.5–10 μg/kg/min	Watch for worsening hypotension; may aggravate ischemia
	Dopamine	2–40 μg/kg/min	May worsen ischemia
	Norepinephrine	1–4 μg/min	May worsen ischemia

CHF = congestive heart failure; i.v. = intravenously; MI = myocardial infarction.

myocardial oxygen demand when administered sublingually, transdermally, or intravenously. Nitrates can occasionally result in a precipitous fall in blood pressure, especially when given sublingually to patients with inferior MI associated with right ventricular involvement (12). Intravenous beta-blockers are also highly effective in relieving chest pain, and both metoprolol and atenolol have been approved for use in patients with acute MI (13,14). As discussed below, contraindications to beta-blockers include marked bradycardia, hypotension, moderate or severe heart failure, advanced atrioventricular block, and significant bronchospastic lung disease.

Congestive heart failure (CHF) and hypotension are common complications of acute MI in the elderly, and each is discussed in more detail later in this chapter. They are mentioned briefly here because they are often present when the patient arrives in the emergency room, and empiric therapy may be necessary in order to stabilize the patient and reduce the risk of other interventions. In most cases, CHF occurring in the early stages of acute MI can be effectively treated with a combination of diuretics, nitrates, and supplemental oxygen. In patients who do not respond to these measures, further investigation into the etiology of CHF is appropriate. Urgent echocardiography with Doppler is the most useful noninvasive test in this setting, since it allows assessment of left and right ventricular function, valvular structures, and the pericardium. Sympathomimetic agents such as dobutamine and dopamine are best avoided in the early hours of acute MI because they increase myocardial oxygen demand and may worsen ischemia, but patients with severe heart failure, particularly when accompanied by hypotension, may require inotropic therapy. In the absence of supraventricular tachyarrhythmias, digitalis has little value in the management of CHF associated with acute MI.

Hypotension, particularly when accompanied by CHF or impaired tissue perfusion, is a grave prognostic sign warranting prompt attention. Hypotension without CHF should be treated with intravenous fluids (0.45–0.9% saline) at a rate of 75–250 cc/h until an adequate blood pressure has been restored or until signs of CHF develop. In patients with inferior MI, hypotension associated with bradycardia may be due to heightened vagal tone, and may respond to subcutaneous or intravenous atropine, 0.5–1.0 mg. Further investigation is required if the blood pressure fails to respond to fluid resuscitation, and both noncardiac (e.g., sepsis, medications) and cardiac causes of hypotension should be considered. In patients with persistent unexplained hypotension, the use of an inotropic or vasopressor agent may be necessary, but the precautions discussed above should be borne in mind.

Aspirin

Aspirin is of proven benefit in patients with either unstable angina (15,16) or acute MI (17), and it should be considered standard therapy in all patients presenting with acute ischemic heart disease in the absence of major contraindications. Evidence supporting the use of aspirin for acute MI derives from the Second International Study of Infarct Survival (ISIS-2), in which 17,187 patients with suspected MI were randomized to receive either 162.5 mg aspirin or placebo, and either 1.5 million units streptokinase or placebo (17). Overall, patients receiving aspirin experienced a 23% reduction in the risk of vascular death within 35 days of hospitalization, and this effect was independent of whether or not the patient received streptokinase. In 3411 patients over 70 years of age, aspirin was associated with a 21% reduction in vascular deaths (17.6% vs. 22.3%, $p < .01$) (17). These data clearly demonstrate that aspirin is beneficial in all patients with acute MI, regardless of age. With respect to aspirin dosage, available evidence suggests that the

minimum effective dose in patients with acute MI is 162.5 mg, and that doses in excess of 325 mg provide no additional benefit (18). Importantly, the initial dose of aspirin should be administered as soon as possible after presentation, and the nonenteric-coated form should be used to ensure rapid absorption. When possible, the first dose should be chewed rather than swallowed. Following MI, aspirin should be continued indefinitely at a dose of 75–325 mg daily or every other day (19,20).

Beta-Blockade

Most of the major trials evaluating beta-blockers in the early hours after acute MI were conducted prior to the thrombolytic era. However, since most elderly patients with acute MI do not receive a thrombolytic agent (21,22), the results of these earlier trials remain applicable.

Table 2 summarizes data from three large randomized trials of early intravenous β-blockade in patients with suspected MI (13,14,23). In the ISIS-1 study, administration of intravenous atenolol followed by oral therapy was associated with a 15% reduction in vascular deaths within the first 7 days (13). Among 5222 patients 65 years of age or older, there was a 23% mortality reduction ($p = 0.001$) (13). Similarly, in two trials using intravenous metoprolol, older patients benefited more than younger patients (14,23). In pooling the results of these three trials, mortality was reduced by 23% in older patients ($p = 0.005$), but by only 5% in younger patients (p = NS). These data clearly indicate that older patients, who are at higher risk for adverse outcomes if left untreated, derive proportionately greater benefit from early beta-blocker therapy than younger patients. As a result, intravenous beta-blockers should not be withheld on the basis of age.

The value of intravenous β-blockade in combination with thrombolytic therapy was

Table 2 Mortality in Three Large Trials of Intravenous Beta-Blockade

		Mortality (%)				
	No.	Active	Control	Difference	% Change	*p* value
Atenolol						
ISIS-1 (13)	16,027					
<65 yrs	10,805	2.5	2.6	−0.1	−4.0	NS
≥65 yrs	5,222	6.8	8.8	−2.0	−22.7	0.001
Metoprolol						
Goteborg (23)	1,395					
<65 yrs	917	4.5	5.7	−1.2	−21.1	NS
65–74 yrs	478	8.1	14.8	−6.6	−45.0	0.03
MIAMI (14)	5,778					
<60 yrs	2,965	1.9	1.8	+0.1	+3.1	NS
61–74 yrs	2,813	6.8	8.2	−1.5	−17.8	NS
Pooled totals	23,200					
Younger	14,687	2.5	2.6	−0.1	−5.0	NS
Older	8,513	6.9	8.9	−2.1	−23.2	0.0005

ISIS-1 = First International Study of Infarct Survival; MIAMI = Metoprolol in Acute Myocardial Infarction; NS = not significant.
From Ref. 23a, with permission.

assessed in the second Thrombolysis in Myocardial Infarction trial (TIMI-II) (24,25). In this study, 1434 patients with acute MI were treated with rt-PA and then randomized to receive intravenous metoprolol or placebo. Although there was no difference in hospital or 6-week mortality, patients receiving metoprolol experienced significantly fewer nonfatal ischemic events during follow-up. These findings provide support for the use of early intravenous β-blockade as an adjunct to thrombolysis in patients with acute MI (26).

The long-term use of β-blockers for secondary prevention following acute MI has been extensively investigated, and Table 3 summarizes data from three of the largest and most frequently cited trials (23,27–31). As with early β-blockade, reductions in mortality and reinfarction during long-term therapy were at least as great in the elderly as in younger patients. In addition, the survival benefits of beta-blockers following MI appear to extend to patients over 75 years of age (32), and beta-blockers are highly cost-effective in all age groups (33). Thus, β-blockers should be administered without respect to age to all patients following acute MI in the absence of contraindications.

At the present time, only atenolol and metoprolol have been approved for intravenous (i.v.) use in the acute MI setting. The recommended dose for atenolol is 10 mg given in two divided doses at 10-min intervals. In patients tolerating the i.v. infusion, oral atenolol 50 mg every 12 h should be initiated 10 min after the second i.v. dose. For metoprolol, the recommended i.v. dose is 15 mg (three 5-mg doses at 2-min intervals). Oral metoprolol 50 mg every 6 h should be started 15 min after the third i.v. dose, progressing to 100 mg twice daily after 24 to 48 h. In very elderly patients, it may be advisable to reduce the dosages of both agents.

Contraindications to the use of intravenous β-blockers include marked sinus bradycardia (heart rate < 45/min), systolic blood pressure < 100 mm Hg, marked first-degree AV block (PR interval ≥ 0.24 s) or higher levels of block, moderate or severe congestive

Table 3 Mortality in Three Large Trials of Long-Term Beta-Blockade

		Mortality (%)				
	No.	Active	Control	Difference	% Change	*p* value
Propranolol						
BHAT (27)	3,837					
30–59 yrs	2,588	6.0	7.4	−1.4	−18.7	NS
60–69 yrs	1,249	9.7	14.7	−5.0	−33.7	0.01
Timolol						
Norwegian (29,30)	1,884					
<65 yrs	1,149	5.0	9.7	−4.7	−48.3	0.003
65–75 yrs	735	8.0	15.3	−7.3	−47.8	0.003
Metoprolol						
Goteborg (23)	1,395					
<65 yrs	917	4.5	5.7	−1.2	−21.1	NS
65–74 yrs	478	8.1	14.8	−6.6	−45.0	0.03
Pooled totals	7,116					
Younger	4,654	5.5	7.6	−2.2	−28.3	0.004
Older	2,462	8.9	14.9	−6.0	−40.1	0.0001

BHAT = Beta Blocker Heart Attack Trial; NS = not significant.
From Ref. 23a, with permission.

heart failure, active wheezing, or a history of significant bronchospastic pulmonary disease. Mild CHF and chronic lung disease without bronchospasm are not contraindications to β-blocker therapy.

Propranolol, metoprolol, and timolol have all been approved for long-term use following MI. Recommended daily dosages of these agents are as follows: propranolol 180–240 mg, metoprolol 200 mg, and timolol 20 mg. Elderly patients may require lower doses to avoid adverse effects, but the efficacy of lower doses has not been established. Contraindications to oral beta-blockers are similar to those listed for the i.v. drugs.

Thrombolytic Therapy

Thrombolytic therapy administered within 6 to 12 h after onset of acute transmural MI reduces infarct size and mortality in all patient subgroups, including the elderly (34). Table 4 summarizes early mortality data from five major placebo-controlled trials involving the

Table 4 Early Mortality by Age in Five Large Thrombolytic Trials

		Mortality (%)				
	No.	Active	Control	Difference	% Change	*p* value
Streptokinase						
GISSI-1 (36)	11,709					
≤65 yrs	7,608	5.7	7.7	−2.0	−26.0	0.0005
66–75 yrs	2,886	16.6	18.1	−1.5	−8.3	NS
>75 yrs	1,215	28.9	33.1	−4.2	−12.7	NS
ISAM (37)	1,741					
<70 yrs	1,454	5.1	6.6	−1.5	−22.7	NS
70–75 yrs	287	13.0	9.6	+3.4	+35.4	NS
ISIS-2 (17)	17,187					
<60 yrs	7,720	4.2	5.8	−1.6	−27.6	0.001
60–69 yrs	6,056	10.6	14.4	−3.8	−26.4	<0.0001
≥70 yrs	3,411	18.2	21.6	−3.4	−15.7	0.02
≥80 yrs	401	20.1	34.2	−14.1	−41.2	0.002
rt-PA						
ASSET (38)	5,031					
≤65 yrs	3,352	5.4	6.3	−0.9	−14.3	NS
66–75 yrs	1,679	10.9	16.4	−5.5	−33.5	0.001
APSAC						
AIMS (35)	1,257					
<60 yrs	751	4.0	6.1	−2.1	−34.4	NS
60–70 yrs	506	9.9	21.3	−11.4	−53.5	0.0007
Pooled totals	36,925					
Younger	26,941	6.2	8.4	−2.2	−25.7	<0.0001
Older	9,984	17.2	20.7	−3.5	−16.9	<0.0001

AIMS = APSAC Intervention Mortality Study; APSAC = anisoylated plasminogen streptokinase activator complex; ASSET = Anglo-Scandinavian Study of Early Thrombolysis; GISSI-1 = Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico; ISAM = Intravenous Streptokinase in Acute Myocardial Infarction; ISIS-2 = Second International Study of Infarct Survival; NS = not significant; rt-PA = recombinant tissue plasminogen activator.
From Ref. 23a, with permission.

three most commonly used thrombolytic agents in the U.S.: streptokinase, rt-PA, and anistreplase (APSAC) (17,35–38). Of note is that in each of these studies, mortality increased as a function of age in both the control group and the active treatment group. However, with the exception of the smallest study (ISAM) (37), the absolute benefit of thrombolysis was greatest in the oldest age group, with statistical significance being reached in three of the five trials (17,35,38). Of particular note is that among 401 patients 80 years of age or older randomized in ISIS-2, mortality was reduced from 34.2% to 20.1% with streptokinase ($p = 0.002$) (17). Moreover, compared to control group patients, there was no increase in the incidence of stroke or major bleeding in these very elderly subjects.

Pooling data from these five trials demonstrates an absolute mortality reduction of 3.5% in older patients, as compared to 2.2% in younger patients ($p < 0.0001$ for both age groups). Similarly, long-term results following thrombolysis are at least as favorable in older as in younger patients, with absolute mortality reductions of 3% and 2%, respectively (Table 5) (39–41). Therefore, rather than excluding older patients from thrombolytic treatment, advanced age should be considered as an indication for active therapy.

Despite these considerations, numerous studies have shown that older patients are much less likely to receive thrombolytic treatment (7,9,21,22,42–45). Factors contributing to lower treatment rates in the elderly include delayed presentation, atypical symptomatology, nondiagnostic electrocardiograms, greater frequency of non-Q-wave infarctions, increased likelihood of contraindications to thrombolysis, and concerns about serious adverse effects such as stroke and bleeding (46,47). To date, most trials have not shown higher overall stroke rates in patients receiving thrombolytic therapy. However, in a recent overview of nine large thrombolytic trials, strokes occurred in 1.2% of patients receiving a thrombolytic agent, compared to 0.8% in control group patients (absolute difference 0.4%, $p < 0.0001$) (34). Moreover, the excess in strokes attributable to thrombolysis

Table 5 Late Mortality by Age in Three Large Thrombolytic Trials

		Mortality (%)				
	No.	Active	Control	Difference	% Change	*p* value
Streptokinase						
GISSI-1 (12-mo F/U) (40)	1,696					
≤65 yrs	7,603	9.8	12.1	−2.3	−19.0	0.002
66–75 yrs	2,881	26.0	25.6	+0.4	+1.6	NS
>75 yrs	1,212	43.1	46.1	−3.0	−6.5	NS
rt-PA						
ASSET (6-mo F/U) (41)	5,031					
≤65 yrs	3,352	7.9	9.1	−1.2	−13.6	NS
66–75 yrs	1,679	15.4	20.9	−5.5	−26.3	0.004
APSAC						
AIMS (12-mo F/U) (39)	1,257					
<60 yrs	751	7.5	11.1	−3.6	−32.4	NS
60–70 yrs	506	16.3	28.0	−11.7	−41.8	0.002
Pooled totals	17,984					
Younger	11,706	9.1	11.2	−2.0	−18.1	0.0003
Older	6,278	25.6	28.6	−3.0	−10.3	0.009

F/U = follow-up; other abbreviations as in Table 4. From Ref. 23a, with permission.

increased with age. Thus, in patients over 75 years of age, the stroke rate was 2.0% in patients receiving thrombolytic therapy, as compared to 1.2% in controls (34). On the other hand, earlier reports of an age-related increase in major bleeding episodes was not confirmed by the nine-trial overview (34,48). Serious bleeding episodes, defined as either life-threatening or requiring transfusion (but excluding hemorrhagic strokes), occurred in 1.1% of patients over 75 years of age receiving thrombolytic treatment, as compared to 0.5% in control group patients (34). The modest excess in major bleeding complications attributable to thrombolysis was similar to that seen in younger patients (34). Thus, the risk of stroke is increased in elderly patients receiving thrombolytic therapy, but the absolute excess for both strokes and major bleeding is less than 1%. Thus, caution is advised when using thrombolytic agents in elderly patients at increased risk for stroke (e.g., those with prior cerebrovascular disease, severe uncontrolled hypertension, or a markedly increased arterial pulse pressure), as well as in patients at increased risk for serious bleeding (49–51).

Although the choice of thrombolytic drug remains controversial, there is general agreement that minimizing treatment delays is more important than agent selection. There have now been three large trials comparing various thrombolytic regimens in over 100,000 patients (52–56). In two of these trials, there were no differences in mortality between streptokinase, rt-PA, and anistreplase (52–54). However, rt-PA and anistreplase were associated with small, but statistically significant, increases in stroke relative to streptokinase (52–54). More recently, the GUSTO investigators (Global Utilization of Streptokinase and tPA for Occluded Arteries) reported that front-loaded rt-PA was associated with a modest reduction in mortality compared to streptokinase (absolute difference 1%; $p = 0.001$) (55). In GUSTO, the absolute mortality difference between rt-PA and streptokinase was similar in patients under and over age 75, but statistical significance was achieved only in the younger subgroup (55). In addition, hemorrhagic strokes occurred more frequently with rt-PA than with streptokinase (0.7% vs. 0.5%; $p = 0.03$), and this excess was most pronounced in the elderly (2.1% vs. 1.2%; $p < 0.05$) (55). Thus, rt-PA is associated with slightly lower mortality and higher stroke rates in older patients. Therefore, the choice of thrombolytic agent remains largely a matter of clinical judgment and physician preference.

The streptokinase dosage in all of the above trials was 1.5 million units administered intravenously over 1 h, and there was no dosage adjustment for elderly patients. Based on the GUSTO trial, rt-PA should be administered using an accelerated, weight-adjusted regimen, consisting of an initial bolus of 15 mg, followed by 0.75 mg/kg over 30 min (not to exceed 50 mg), and 0.5 mg/kg over the next 60 min (not to exceed 35 mg) (55). As discussed previously, aspirin should be given in conjunction with thrombolytic therapy (17). Patients treated with rt-PA should also receive intravenous heparin to maintain the activated partial thromboplastin time (aPTT) in the range of 50–70s for the first 24 to 48 h (57,58). For patients treated with streptokinase, data from the GUSTO study indicate that intravenous heparin increases bleeding complications but does not improve survival relative to high-dose subcutaneous heparin (12,500 U every 12 h) (55).

Other Pharmacological Agents

Anticoagulants

Subcutaneous heparin in a dose of 7500 U every 12 h reduces the risk of venous thromboembolic complications in patients hospitalized with acute MI (11,59). Since older patients

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are at increased risk for deep vein thrombosis and pulmonary embolism, prophylaxis against these events is particularly appropriate in this age group (11,59).

At present, the value of routine intravenous heparin for all patients with acute MI remains unproven, but several subgroups do appear to benefit (11,60). Patients with large anterior MIs, acute or chronic atrial fibrillation, or severe left ventricular dysfunction with congestive heart failure are at increased risk for mural thrombus formation and embolization. Intravenous heparin at doses adjusted to maintain the aPTT at 1.5 to 2 times the control value appears to reduce arterial thromboembolism in patients with large anterior MIs (56–61), and routine heparinization is appropriate (11). Patients with atrial fibrillation should be anticoagulated with heparin or warfarin, but the value of systemic anticoagulation in patients with severe left ventricular dysfunction is unproven, and its use in this situation should be individualized (11). Patients who experience recurrent ischemia during the first few days after MI are at increased risk for infarct extension, and i.v. heparin is recommended (11,59).

Recently, two new classes of antithrombotic agents, the low-molecular-weight heparins (LMWHs) and glycoprotein (GP) IIb/IIIa inhibitors, have been shown to exert salutary effects in selected patients with coronary heart disease (62–65). Compared to unfractionated intravenous heparin, LMWHs offers several advantages: once or twice daily subcutaneous dosing, no need to monitor aPTTs, and fewer side effects (especially thrombocytopenia). Moreover, in a recent, randomized trial involving 3171 patients with unstable angina or non-Q-wave MI, the LMWH enoxaparin was associated with a 15% reduction in the composite endpoint of death or recurrent ischemia at 30 days compared to conventional heparin therapy (64). The use of LMWHs in patients with acute MI is being evaluated in several ongoing trials. In the meantime, available data suggest that this class of agents may prove to be an important adjunct to aspirin therapy in selected high-risk patients, including the elderly.

The GP IIb/IIIa inhibitors are potent antiplatelet agents that block the final common pathway leading to platelet aggregation. As such, they are substantially more effective than aspirin, which inhibits only one of the major pathways. Several GP IIb/IIIa inhibitors are currently undergoing testing in clinical trials involving diverse populations of patients with coronary heart disease, including individuals with acute MI. However, most of the published trials have involved patients undergoing percutaneous coronary interventions. In one study, 1265 patients with refractory unstable angina referred for coronary intervention were randomized to receive abciximab (the Fab fragment of an antibody to the GP IIb/IIIa receptor) or placebo (65). At 30 days follow-up, the combined endpoint of death or MI was reduced 47% in patients receiving abciximab (4.8% vs. 9.0%; $p = 0.003$) (65). Although no age-specific data were reported, the findings were consistent across all subgroups and were independent of age, gender, and comorbid illnesses (65). Abciximab is available only for intravenous administration and it is quite expensive, but orally active GP IIb/IIIa inhibitors could become available in the U.S. in the near future. Although their role in treating older MI patients requires further study, these agents have the potential for substantially improving both short- and long-term outcomes in this population.

Long-term anticoagulation with warfarin has been shown to reduce the risk of reinfarction and cardiac death in post-MI patients, including the elderly (66–68). However, the magnitude of risk reduction is similar to that seen with aspirin alone, and the latter agent is not only safer and more convenient to use, but it is considerably less expensive (11,59). Moreover, the addition of low-dose warfarin to aspirin increases the risk of bleeding but does not improve clinical outcomes compared to aspirin alone (69). The use of

warfarin in the post-MI setting should therefore be restricted to those situations for which there is a clear indication for its use, such as chronic atrial fibrillation, the presence of a mechanical prosthetic heart valve, or active thromboembolic disease. In patients with a left ventricular mural thrombus following acute MI, anticoagulation for at least 3 months is recommended (11).

Nitrates

Nitrates have been widely used in the treatment of acute MI, and a pooled analysis of several small studies suggested that nitrates may exert a favorable effect on survival (70). However, two recently completed megatrials (GISSI-3 and ISIS-4) failed to confirm a beneficial effect when nitrates were initiated within 24 h of MI onset (71,72). However, among 5234 patients 70 years of age or older enrolled in GISSI-3, the combined endpoint of death or severe left ventricular dysfunction at 6 months follow-up was significantly reduced by nitroglycerin (odds ratio 0.88; $p = 0.04$) (73). This finding, coupled with the fact that both GISSI-3 and ISIS-4 demonstrated that nitrates can be administered safely to the majority of older patients suggests that the continued use of nitrates for treating ischemic pain and peri-infarctional heart failure is appropriate. Routine use of nitrates in elderly patients without pain or pulmonary congestion is of unproven value.

Calcium Antagonists

Calcium channel blockers have been widely studied in both the acute MI and post-MI settings, and the results of these trials have been reviewed (74–76). At present, there is no evidence that treatment with calcium antagonists initiated within the first 24 h after MI onset is beneficial, and the use of dihydropyridine calcium antagonists (e.g., nifedipine) may be harmful (74,76). One relatively small study showed that diltiazem 60 to 90 mg q.i.d. initiated 24 to 72 h after admission for non-Q-wave MI reduced the rate of reinfarction during short-term follow-up, but there was no effect on mortality (77). In another study, long-term diltiazem administration following MI did not affect overall mortality, but a modest benefit was seen in the subgroup of patients with preserved left ventricular function and no heart failure (78). Similar results have been reported with long-term verapamil use in post-MI patients (79), but a more recent study failed to confirm these findings (80). Subgroup analysis in these trials did not demonstrate a differential effect of age (78,79). Thus, calcium antagonists cannot be recommended for routine use in acute MI patients, but short-term administration of diltiazem may be of value in patients with non-Q-wave infarction, and the long-term use of either diltiazem or verapamil may be appropriate in patients with good ventricular function who are not candidates for β-blockade (11).

Angiotensin Converting Enzyme (ACE) Inhibitors

Early administration of an ACE inhibitor to acute MI patients has been evaluated in several large trials. The first of these, CONSENSUS-2 (Cooperative New Scandinavian Enalapril Survival Study), was discontinued after 6000 patients were enrolled due to a higher frequency of adverse outcomes in patients receiving enalapril (81). Moreover, patients over 70 years of age experienced an increased incidence of serious hypotension (81). In contrast, the GISSI-3 and ISIS-4 trials reported small, but statistically significant, reductions in mortality in patients receiving captopril or lisinopril within 24 h of MI onset (71,72). In addition, patients 70 years or older treated with lisinopril in GISSI-3 experienced a 14% reduction in the combined endpoint of death or severe left ventricular function at 6 months followup ($p = 0.01$) (73). More recently, the Survival of Myocardial Infarction

Long-Term Evaluation (SMILE) investigators randomized 1556 patients with anterior MI who were not candidates for thrombolytic therapy to either the ACE inhibitor zofenopril or to placebo within the first 24 h after symptom onset (82). The incidence of death or severe heart failure at 6 weeks follow-up was reduced 34% by zofenopril, and this benefit was maintained for 1 year (82). Moreover, the absolute benefit was threefold greater in individuals over 65 years of age compared to younger patients (82).

The applicability of the above findings to the general MI population is unclear, since the small benefit seen in the largest trials (absolute mortality reduction 0.5%) (72) may reflect a larger benefit in some patients (e.g., those with anterior MI or significant left ventricular dysfunction), but no benefit or even harm in other subgroups. At the present time, early administration of an ACE inhibitor is recommended in hemodynamically stable patients with large anterior MIs, as well as in patients with heart failure or a left ventricular ejection fraction of less than 40% (11). In other cases, early ACE inhibitor therapy is optional (11).

The value of ACE inhibitors in post-MI patients with significant left ventricular dysfunction (ejection fraction $< 40\%$) or clinical heart failure has been well established by the Salvage and Ventricular Enlargement (SAVE) (83) and Acute Infarction Ramipril Efficacy (AIRE) trials (84,85). In SAVE, captopril reduced mortality and the occurrence of other cardiac events during an average follow-up of 42 months in asymptomatic or minimally symptomatic patients with left ventricular dysfunction after MI (ejection fraction $\leq 40\%$) (83). In AIRE, ramipril produced similar effects in post-MI patients with clinical heart failure (84,85). Therapy was initiated 3 to 16 days after MI in SAVE (mean 11 days), and 2 to 10 days after MI in AIRE (mean 5 days). The maximum dose of captopril in SAVE was 50 mg tid, while the target dose of ramipril in AIRE was 5 mg bid. Importantly, in both SAVE and AIRE, the beneficial effects of therapy were most pronounced in elderly patients (83,84). In 783 patients over 65 years of age enrolled in SAVE, mortality was reduced 23% with captopril (27.9% vs. 36.1%; $p = 0.017$), whereas patients under age 65 experienced a statistically insignificant 9% mortality reduction (16.6% vs. 18.3%) (83). Similarly, ramipril significantly decreased mortality in patients over age 65 enrolled in AIRE, but not in younger patients (84).

An additional consideration in using ACE inhibitors in post-MI patients is the potential for interactions with other medications, particularly aspirin and beta-blockers which, as discussed above, are the only other agents that are of proven benefit. As with nonsteroidal anti-inflammatory drugs, the effects of aspirin on prostaglandins may antagonize the effects of ACE inhibitors, and there is evidence to suggest that this interaction is clinically important. In a recent analysis of data from CONSENSUS-2, enalapril was significantly less efficacious among patients taking aspirin (86). The clinical implication of these findings is unclear, however, since a more recent analysis suggested that aspirin does not inhibit the long-term beneficial effects of ACE inhibitors in post-MI patients (87).

With regard to beta-blockers, a retrospective, analysis of data from the SAVE trial indicated that patients receiving a beta-blocker had 30% lower mortality and 21% less heart failure than patients not receiving a beta-blocker (88). Moreover, this effect was independent of age and captopril therapy (88). Although these data are limited by the fact that beta-blocker treatment was prescribed nonrandomly, long-term outcomes appear to be superior in patients receiving both an ACE inhibitor and a beta-blocker.

To summarize, ACE inhibitors are appropriate for all patients, including the elderly, who have heart failure or significant left ventricular dysfunction following MI (i.e., ejec-

tion fraction ≤ 40%). Therapy should be initiated within the first several days in hemodynamically stable patients, but may be deferred in other cases. The use of beta-blockers in combination with ACE inhibitors is encouraged, but the combination of aspirin with an ACE inhibitor requires further study. The role of ACE inhibitors in MI patients without left ventricular systolic dysfunction remains to be defined.

Magnesium

Several small trials of intravenous magnesium in acute MI suggested that this agent may have salutary effects on mortality and other endpoints (89), and these findings were apparently confirmed by the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) (90,91). In addition, a small trial involving MI patients not treated with a thrombolytic agent suggested that elderly patients in particular may benefit from intravenous magnesium (92). Unfortunately, the ISIS-4 study failed to replicate these results (72). ISIS-4 has been criticized because treatment was initiated relatively late (approximately 8 h after symptom onset) and the dose of magnesium was somewhat higher than in LIMIT-2 (90). Nonetheless, the routine use of intravenous magnesium in elderly patients with acute MI is not currently recommended (11).

Antiarrhythmic Agents

The administration of prophylactic lidocaine to patients with acute MI was once common practice. However, a meta-analysis suggested that lidocaine does not improve survival and may increase the incidence of asystolic cardiac arrest (93). Moreover, elderly patients hospitalized with acute MI appear to be at lower risk for primary ventricular fibrillation than younger patients, and toxicity from lidocaine is more common in the elderly (10). Thus, although lidocaine remains an effective agent for treating life-threatening ventricular arrhythmias, its routine use in elderly patients with acute MI is no longer recommended (11).

Frequent ventricular premature beats and nonsustained ventricular tachycardia are each associated with an increased risk of sudden cardiac death during the first 2 years after MI (94), but to date only beta-blockers have been shown to significantly reduce this risk (95). In particular, the class IC agents flecainide, encainide, and moricizine were associated with increased mortality in the Cardiac Arrhythmia Suppression Trial (CAST), and these agents are therefore contraindicated in the post-MI setting (96,97). Similarly, a study evaluating d-sotalol in post-MI patients was discontinued due to excess mortality in the d-sotalol group (98).

Two recent trials addressed the role of amiodarone in the treatment of high-risk post-MI patients (99,100). In these studies, which involved a total of 2688 patients, amiodarone reduced the incidence of arrhythmic death by 35–38%, but there was no difference in total mortality (99,100). In one study, the absolute reduction in arrhythmic deaths was greatest in patients over 70 years of age (100). A recent meta-analysis, based on data from 13 amiodarone trials, found that amiodarone was associated with a 13% reduction in total mortality ($p = 0.03$) and a 29% reduction in arrhythmic deaths ($p = 0.0003$) (101). In patients over 65 years of age, amiodarone reduced arrhythmic deaths by 32%, but total mortality was reduced by only 8% (not significant) (101). Thus, the use of amiodarone in elderly patients following MI requires further investigation. Similarly, although a growing body of evidence suggests that implantable defibrillators reduce mortality in selected high-risk patient populations (102,103), their role in managing older post-MI patients remains undefined.

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Coronary Angioplasty

Percutaneous transluminal coronary angioplasty (PTCA) has several potential applications in the acute MI setting: as a primary reperfusion strategy; as an adjunct to thrombolysis; as a ''rescue'' procedure for failed thrombolysis; and in the management of recurrent ischemia (104,105).

In several studies, PTCA has been shown to be more effective than thrombolytic therapy in recanalizing the infarct-related coronary artery, with reperfusion rates of over 90% in some series (105). In addition, an overview of seven randomized trials comparing PTCA with thrombolysis found that PTCA was associated with lower mortality, better left ventricular function, and fewer intracranial bleeds (104). Moreover, high-risk subgroups, including the elderly and patients with large infarcts, appeared to derive the most benefit from primary PTCA (106). Consequently, it has been suggested that PTCA may be the preferred treatment for elderly patients who are suitable candidates for reperfusion (107).

Unfortunately, most of the studies comparing PTCA and thrombolytic therapy have been relatively small and have included very few elderly patients. Thus, there are limited data on the use of primary PTCA in the elderly, particularly in patients over 75 years of age. In an early series of 35 patients 70 years or older undergoing PTCA for acute MI, Holland reported a 34% hospital mortality rate (108). In another series of 105 patients 70 years or older undergoing primary PTCA, Lee reported a 91% angiographic success rate and an 18% hospital mortality rate, which compares favorably with thrombolytic therapy in this age group (109). However, in a subsequent overview of direct PTCA for acute MI, Eckman concluded that patients over 70 years of age undergoing PTCA faired ''no better than the placebo arms of the thrombolytic trials'' (110).

More recently, Stone et al. analyzed age- and gender-specific data from the Primary Angioplasty in Myocardial Infarction (PAMI) trial (106,111,112). Among 150 MI patients 65 years of age or older randomized to PTCA or rt-PA, hospital mortality was 15% in the rt-PA arm vs. 5.7% with PTCA ($p = 0.066$) (111). PTCA was also associated with fewer intracranial hemorrhages and recurrent ischemic events than rt-PA (111), and the benefits of PTCA were greater in women than in men (112). Although these data suggest that primary PTCA may be the best reperfusion strategy in older patients, particularly women, the study is small and very few patients over the age of 75 were enrolled.

The largest study to date comparing angioplasty and thrombolysis for acute MI was the GUSTO-IIB trial (Global Use of Strategies to Open Occluded Coronary Arteries) (113). In this study, which involved 1138 patients, the composite outcome of death, non-fatal reinfarction, and disabling stroke at 30 days follow-up was reduced 33% with PTCA as compared with rt-PA ($p = 0.033$), but mortality did not differ between groups (113). Among 300 patients over 70 years of age, mortality tended to be lower with PTCA, but again the difference was not significant (113). With respect to the composite endpoint, patients 70 to 79 years of age appeared to benefit from PTCA, but too few patients over the age of 80 were enrolled to analyze outcomes in this age group.

To assess the safety and short-term efficacy of primary PTCA in the very elderly, Laster et al. retrospectively analyzed data on 55 octogenarians with acute MI referred for direct PTCA (114). The initial angiographic success rate was 96%, and no patients required emergency bypass surgery. Four patients (7%) required a transfusion for bleeding, but there were no strokes. Hospital mortality was 16% and 1-year actuarial survival was 67% (114).

In summary, current data suggest that PTCA can be performed safely in elderly

patients with acute MI, and that it is associated with fewer hemorrhagic strokes than thrombolysis. While present data are insufficient to allow definitive conclusions on the relative merits of primary PTCA compared to thrombolysis in the elderly, PTCA is an effective alternative in appropriately selected patients, and should be strongly considered when thrombolytic therapy is contraindicated. Very high-risk elderly patients, such as those with large anterior MIs or severe hemodynamic disturbances, may also benefit from this approach. In addition, two recent reports indicate that elderly patients with cardiogenic shock may benefit from prompt revascularization by PTCA or bypass surgery (115,116).

The routine use of PTCA following thrombolysis has been evaluated in several trials, none of which have demonstrated improved outcomes relative to conservative management (25,117–122). Patients who experience recurrent ischemic pain or marked ST segment changes on a predischarge stress test are at high risk for recurrent ischemic events following hospital discharge. Coronary angiography and revascularization with either PTCA or coronary bypass surgery is appropriate in these patients (123), and age per se is not a contraindication to these procedures (104,105). Patients with persistent ischemic pain following administration of a thrombolytic agent, particularly when accompanied by hemodynamic instability (e.g., hypotension or marked CHF), are also at high risk for adverse outcomes, and ''rescue'' PTCA may improve prognosis in this subgroup (104,105,124). In summary, cardiac catheterization and revascularization are not recommended as routine procedures for all patients with acute MI, but they should be strongly considered in patients with persistent chest pain, marked hemodynamic instability, or recurrent ischemia in the early post-MI period (11).

MANAGEMENT OF COMPLICATIONS

As previously noted, elderly patients are at increased risk for several complications of acute MI, including CHF, hypotension, supraventricular arrhythmias, conduction disturbances, myocardial rupture, and cardiogenic shock. In general, the management of these complications is similar in older and younger patients. In the following sections, the treatment of each of these complications is briefly reviewed, with special attention to the elderly. For a more comprehensive discussion of these disorders, the reader is referred to standard texts (125,126).

Congestive Heart Failure

Several factors predispose the elderly patient with acute MI to the development of CHF, including an increased incidence of prior MI, higher prevalence of multivessel disease, impaired diastolic relaxation, reduced contractile reserve, and an increased prevalence of comorbid illnesses, both cardiac (e.g., aortic stenosis) and noncardiac (e.g., renal insufficiency) (127). As a result, CHF occurs in approximately 50% of older patients with acute MI (7,10), and CHF is often the presenting manifestation of MI in the elderly (128).

As discussed above, the initial treatment of CHF includes supplemental oxygen, diuretics, and nitrates. In more severe cases, morphine should also be given. In patients who fail to respond to these measures, additional information must be obtained in order to determine the etiology of CHF, which is frequently multifactorial. Commonly occurring factors that may contribute to CHF in the elderly include persistent or recurrent ischemia, extensive myocardial damage, aortic or mitral valve disease (especially aortic stenosis or

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mitral regurgitation), arrhythmias (especially atrial fibrillation), uncontrolled hypertension, diastolic dysfunction due to left ventricular hypertrophy, inappropriate bradycardia, mechanical complications (e.g., papillary muscle rupture or ventricular septal perforation), severe renal insufficiency, and medications (e.g., β-blockers, calcium antagonists, and antiarrhythmic agents) (127). In most cases, an echocardiogram with Doppler studies, in conjunction with a careful review of the patient's medications and laboratory data, will be sufficient for determining the pathogenesis of CHF (11). Occasionally, supplemental studies, such as pulmonary artery catheterization or left ventricular angiography, may be necessary (11).

Once the etiology has been established, an effort should be made to correct any treatable disturbances and remove any offending medications. If CHF persists despite aggressive diuresis, placement of a pulmonary artery catheter should be considered as an aid to diagnosis and therapy. When indicated, treatment with an inotropic agent and/or an intravenous vasodilator should be instituted. Dobutamine is the most frequently used intravenous inotrope for treating severe left ventricular dysfunction, but dobutamine may be less effective in the elderly due to an age-related decline in β-adrenergic responsiveness (129,130). Phosphodiesterase inhibitors such as amrinone and milrinone have theoretical advantages over sympathomimetic agents in coronary patients because they augment cardiac output without increasing myocardial oxygen demand (131). In addition, the effects of phosphodiesterase inhibitors are independent of adrenergic activation. Nonetheless, in elderly patients with severe CHF without recent MI, dobutamine appears to be at least as effective as amrinone (132). In refractory cases, however, combination therapy with dobutamine and amrinone is more effective than either agent alone (133).

Nitroglycerin and nitroprusside are the most commonly used intravenous vasodilators. Both have very short half-lives, which permit rapid drug titration. Hypotension can occur with either agent, but is more common with nitroprusside. Nitroprusside can also result in thiocyanate toxicity during prolonged administration, particularly in elderly patients with impaired renal function. As a result, thiocyanate levels should be monitored closely. Clinical manifestations of thiocyanate toxicity include nausea, vomiting, mental status changes, and metabolic acidosis. Intravenous enalaprilat is an alternative to nitrovasodilators, and may be useful in patients who are likely to require long-term ACE inhibition. However, enalaprilat may also induce hypotension and renal dysfunction, and it offers no clear advantage over conventional agents in the acute MI setting (134).

Patients who fail to respond to the above measures have refractory CHF, and the prognosis is grave unless a correctable problem, such as a ventricular aneurysm, can be identified. Additional interventions that may help stabilize patients with refractory CHF include endotracheal intubation with assisted ventilation and placement of an intra-aortic balloon pump. Such therapies are usually appropriate only in patients with potentially reversible pathology.

Hypotension

Hypotension in the setting of acute MI usually reflects a low cardiac output state arising from extensive myocardial damage, intravascular volume depletion, right ventricular infarction, valvular dysfunction (especially mitral regurgitation), pericardial effusion, or arrhythmias (both tachycardias and bradycardias). Other factors that may contribute to hypotension in elderly patients include preexisting cardiac conditions, such as aortic stenosis or cardiomyopathy; ventricular septal perforation; aortic dissection; sepsis; bleeding (e.g.,

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from thrombolytic therapy or catheterization); and medications. The cause of hypotension is frequently multifactorial, and it is incumbent upon the physician to consider all potential etiologies and to perform appropriate diagnostic investigations as indicated. If the history, physical examination, and laboratory data fail to provide an explanation, echocardiography should be performed promptly (11). If hypotension persists or if the etiology remains unexplained, pulmonary artery catheterization is indicated (11).

In the absence of CHF, intravascular volume expansion is the appropriate initial treatment for hypotension. Subsequent therapy will depend on the response to fluid administration and the underlying etiology. Patients who fail to respond to i.v. fluids or who have coexistent CHF may require pulmonary artery catheterization (11). Based on the hemodynamic findings and the severity of hypotension, treatment with sympathomimetic agents such as dobutamine, dopamine, or norepinephrine may be necessary to maintain organ perfusion. Other supportive measures include assisted ventilation and intraaortic balloon counterpulsation (11). It is important to emphasize that all of these interventions are palliative, and unless the underlying etiology of hypotension can be corrected, the prognosis is grave.

Arrhythmias and Conduction Disturbances

Elderly patients with acute MI are at increased risk for supraventricular arrhythmias, particularly atrial fibrillation, and for conduction disturbances, including bundle branch block and high-degree atrioventricular block (10). The incidence of ventricular tachycardia is similar in older and younger patients, but primary ventricular fibrillation appears to occur less frequently in the elderly (10), possibly reflecting reduced β-adrenergic responsiveness in this age group.

New-onset atrial fibrillation following acute MI usually results from atrial distension due to an increase in ventricular diastolic pressure. Contributing factors may include mitral or tricuspid regurgitation, atrial infarction, pericarditis, electrolyte abnormalities (particularly hypokalemia), and medications (e.g., inotropic agents, theophylline). Because elderly patients frequently have preexisting diastolic dysfunction and an increased reliance on atrial contraction to augment ventricular filling (the ''atrial kick'') (135), atrial fibrillation often precipitates congestive heart failure or a low cardiac output state.

Treatment of atrial fibrillation includes correcting any reversible abnormalities (e.g., hypokalemia), controlling the ventricular rate, and restoring sinus rhythm. In patients who are hemodynamically stable, rate control with digoxin, intravenous β-blockade (e.g., metoprolol or esmolol), or intravenous diltiazem is appropriate. Effective rate control often results in spontaneous conversion to sinus rhythm. However, if atrial fibrillation persists longer than 24 h heparinization followed by pharmacological or electrical cardioversion should be strongly considered. Antiarrhythmic agents commonly used in the cardioversion of atrial fibrillation include quinidine, procainamide, propafenone, ibutilide, sotalol, and amiodarone. All of these agents are negatively inotropic, and they should be used with caution in the presence of significant left ventricular dysfunction. In patients who exhibit hypotension, severe heart failure, or organ hypoperfusion attributable to atrial fibrillation, immediate direct current (DC) cardioversion is the treatment of choice (11). Patients should be sedated before cardioversion is attempted, and an initial energy level of 50 to 100 J is appropriate (11). Patients with persistent or chronic atrial fibrillation should receive long-term antithrombotic therapy (136). Warfarin remains the preferred agent in this

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setting, but aspirin is a suitable alternative in patients with contraindications to warfarin (137,138).

The treatment of peri-infarctional ventricular tachyarrhythmias is similar in older and younger patients and will not be reviewed here. In general, initial therapy should follow the Advanced Cardiac Life Support (ACLS) guidelines (139), and subsequent therapy should be individualized, based on symptoms, severity of the arrhythmia, and other factors, such as left ventricular function. Similarly, the treatment of bradyarrhythmias and conduction disturbances does not differ in younger and older patients. In general, temporary pacing (transthoracic or transvenous) should be considered in patients with symptomatic or hemodynamically compromising bradyarrhythmias unresponsive to atropine, in patients with new bundle branch block, and in patients with 2° or 3° infranodal block complicating anterior MI. The ACLS guidelines should be followed in treating life-threatening bradyarrhythmias such as asystole (139).

Right Ventricular Infarction

Right ventricular infarction occurs in up to 50% of patients with inferior MI, with similar frequencies in younger and older patients. The pathophysiology, clinical features, and treatment of right ventricular infarction have recently been reviewed and will not be discussed in detail here (12). However, it is worth noting that in patients with inferior MI associated with right ventricular infarction, as evidenced by ST segment elevation in the right precordial electrocardiographic leads, hospital mortality is increased fivefold in both younger and older patients compared to those without right ventricular involvement (140,141).

Myocardial Rupture

Myocardial rupture is an infrequent complication of acute MI, occurring in less than 5% of patients (142). However, when rupture does occur, the course is frequently catastrophic, with death ensuing in over 50% to almost 100% of cases, depending on rupture location (143,144). There are three principal types of rupture: ventricular free wall rupture, papillary muscle rupture (PMR), and ventricular septal perforation (acute VSD). Papillary muscle rupture almost always occurs following an inferoposterior or posterolateral MI, whereas septal rupture occurs with approximately equal frequency following inferior and anterior infarcts. Free wall rupture can complicate an infarct of any location.

Although precise figures are unavailable, all forms of rupture appear to occur more frequently in patients over 65 years of age (10,145). Other risk factors for myocardial rupture include female gender and persistent peri-infarctional hypertension (10,142). Thrombolytic therapy may also increase the risk of myocardial rupture within the first 24 to 48 h after treatment, particularly in older patients undergoing delayed thrombolysis (i.e., more than 6 h after symptom onset) (142,146). However, this association should not dissuade physicians from using thrombolytics in appropriate situations, since total mortality is clearly reduced.

Impending myocardial rupture is occasionally heralded by persistent vague chest discomfort or unexplained hypotension, but sudden hemodynamic deterioration, new or worsening congestive heart failure, or asystolic cardiac arrest may be the first indication that rupture has occurred (145,147,148). The presence of a new systolic murmur, particularly in association with hemodynamic deterioration, strongly suggests the possibility of

papillary muscle dysfunction or ventricular septal perforation, and further investigation is warranted in all cases (149,150). Urgent bedside echocardiography with Doppler should be performed, since this will enable accurate diagnosis in the majority of cases (149,150). Pulmonary artery catheterization can provide definitive confirmation of a septal perforation by demonstrating an oxygen saturation step-up of greater than 10% at the level of the shunt (usually the right ventricle). Similarly, the presence of an abnormally elevated V-wave in the pulmonary capillary wedge pressure waveform strongly suggests significant mitral regurgitation. Cardiac catheterization is usually necessary to define coronary anatomy in elderly patients with cardiac rupture, and left ventriculography can provide diagnostic information on the severity of mitral regurgitation and on the presence and location of an acute VSD.

Once a diagnosis of acute VSD or PMR has been confirmed, supportive measures should be rapidly instituted, and urgent surgical consultation should be obtained. Diuretics, an intravenous inotropic agent, and afterload reduction with intravenous nitroprusside (blood pressure permitting) are appropriate therapy in most cases. Intra-aortic balloon counterpulsation is often effective in stabilizing the patient, and should be strongly considered in all surgical candidates (11). Mechanical ventilation is indicated in patients with severe heart failure or persistent hemodynamic instability.

Surgery is recommended in almost all cases of acute VSD or PMR, since medical therapy is associated with mortality rates in excess of 75% (143,144). The timing of surgical intervention remains controversial, but many surgeons favor early operation, since the natural history is often one of progressive hemodynamic deterioration and death (151,152). Perioperative mortality rates range from 10% to 70%, with preoperative left ventricular function and the presence of cardiogenic shock being the most important factors influencing survival (143,144,151–155). The long-term prognosis following successful surgical repair of acute VSD or PMR is favorable (151–155).

In contrast to acute VSD and PMR, which often allow the physician time to intervene, ventricular free wall rupture usually progresses rapidly to pericardial tamponade, asystole, and death. Occasionally, however, the rupture will be locally contained as a result of pericardial adhesions or other factors, resulting in the formation of a pseudoaneurysm. Differentiation of a pseudoaneurysm from a true left ventricular aneurysm may be difficult, but echocardiography, magnetic resonance imaging, and left ventriculography are all useful in making this distinction. The hemodynamic effects of a pseudoaneurysm are variable, depending on its size and location, but there is a tendency for pseudoaneurysms to undergo further rupture, resulting in pericardial tamponade (156). Although conservative management may be associated with a favorable outcome in some cases (157), prompt surgical attention is usually recommended once a pseudoaneurysm has been identified (158,159).

Cardiogenic Shock

Cardiogenic shock is defined as the combination of markedly reduced cardiac output (cardiac index < 1.8 L/min/m^2), increased left ventricular diastolic pressure or pulmonary wedge pressure (≥ 22 mm Hg), hypotension (systolic blood pressure < 80 mm Hg), and tissue hypoperfusion (e.g., prerenal azotemia, impaired sensorium) (160). This syndrome occurs twice as frequently in elderly patients with acute MI as in younger subjects, and it accounts for most of the excess mortality associated with acute MI in the elderly (10,161). Moreover, despite dramatic advances in the treatment of acute MI in the last 30 years, the case fatality rate from cardiogenic shock remains at approximately 80% (161,162).

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While recent studies suggest that early revascularization may improve prognosis in patients with cardiogenic shock, the applicability of these findings to the elderly is unknown (115,163–167).

The causes of cardiogenic shock complicating acute MI are similar to the causes of CHF and hypotension. Since few patients survive cardiogenic shock in the absence of a treatable underlying disorder, immediate evaluation for a potentially correctable problem is critical. Emergent echocardiography with Doppler should be performed to assess overall left ventricular function and to rule out valvular lesions, pericardial disease, and septal perforation (11). Pulmonary artery catheterization is indicated, both to facilitate diagnosis and as an aid to therapy (11). Cardiac catheterization may be necessary in some cases if the diagnosis remains in doubt, or as a prelude to angioplasty or corrective surgery (115,163–167).

In patients for whom a treatable cause of shock has been identified, maximally aggressive therapy is indicated to stabilize the patient. In most cases, this will include assisted ventilation, an intra-aortic balloon pump (168), and intravenous vasoactive therapy. However, when shock is due to irreversible myocardial damage or other untreatable disorder, invasive interventions are unlikely to influence survival and should generally be avoided.

NON-Q-WAVE MYOCARDIAL INFARCTION

Non-Q-wave MI increases in frequency with advancing age, and accounts for over 50% of all MIs in patients over the age of 70 (7,169). While acute transmural MI is almost always caused by total thrombotic occlusion of the infarct-related vessel (170), the pathogenesis of non-Q-wave MI is more variable. In the elderly, non-Q-wave MI may be precipitated by a sustained imbalance between myocardial oxygen supply and demand resulting from such diverse influences as severe hypertension, marked hypoxemia due to congestive heart failure or pulmonary embolus, atrial fibrillation with rapid ventricular response, or acute hypotension due to sepsis or other factors. Diffuse, multivessel coronary disease is often present, but total occlusion of the infarct artery is the exception rather than the rule (171,172).

The short-term prognosis following non-Q-wave MI tends to be better than that following Q-wave MI, since non-Q-wave MIs are usually smaller and associated with greater preservation of ventricular function (173–175). However, patients with non-Q-wave MI are at increased risk for ischemia and reinfarction during the subsequent 1- to 2-year period, and long-term survival is similar to that of patients with Q-wave MI (173–175). In one recent series, for example, over 60% of all deaths within the first year after hospitalization for acute MI occurred in patients over the age of 70 presenting with non-Q-wave infarctions (176).

Because the clinical course following non-Q-wave MI is distinct from that following Q-wave MI, several studies have focused specifically on the management of this disorder. As noted previously, diltiazem has been shown to reduce early reinfarction in patients with non-Q-wave MI (77), and diltiazem may also improve long-term prognosis in the subgroup of patients with normal left ventricular function (78,177). Beta-blockers have not been evaluated specifically in non-Q-wave MI patients, but it is likely that these agents are efficacious (178). Similarly, aspirin is of value in post-MI patients in general, and it is likely to be beneficial in patients with non-Q-wave MI as well (19,179). Recently, several studies have evaluated the use of low-molecular-weight heparin (LMWH) in pa-

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tients with unstable coronary syndromes, including non-Q-wave MI (62–64). As discussed previously, LMWH appears to reduce the risk of recurrent ischemic events in patients with unstable angina or non-Q-wave MI, and the benefit appears to be most pronounced in the elderly (64). The results of ongoing trials will further clarify the role of LMWHs in the management of patients with acute coronary ischemia.

In the third Thrombolysis in Myocardial Infarction trial (TIMI-III), the value of thrombolytic therapy and of early catheterization and revascularization were evaluated in 1473 patients with non-Q-wave MI or unstable angina (180). Consistent with earlier reports, thrombolytic treatment with rt-PA did not reduce the incidence of death or reinfarction in non-Q-wave MI patients (180). Therefore, thrombolytic therapy is not recommended for patients with non-Q-wave MI. Similarly, although routine catheterization following non-Q-wave MI has been recommended in the past, TIMI-III failed to demonstrate an improvement in 6-week outcomes using this approach (180). Interestingly, in the subgroup of 472 patients 65 years or older with non-Q-wave MI or unstable angina, the strategy of early catheterization and revascularization was associated with a significant reduction in the 6-week event rate (7.9% vs. 14.8%; $p = 0.02$), whereas no benefit was seen in patients under 65 years of age (181). Moreover, the advantage of early catheterization was maintained at 1 year follow-up in the older cohort (181). Although future studies are required to confirm these findings, the data again suggest that older, higher risk patients are at least as likely to benefit from aggressive interventions as younger patients.

To summarize, elderly patients with non-Q-wave MI are at increased risk for recurrent ischemic events and death during the first 2 years following hospitalization. Aspirin and beta-blockers are appropriate therapies in this population, primarily based on their known beneficial effects in other cohorts of MI patients. Diltiazem is recommended during hospitalization for non-Q-wave MI in the absence of heart failure, and it may be beneficial in the long-term treatment of patients with preserved left ventricular function. Finally, although the role of early catheterization and angioplasty in non-Q-wave MI patients requires further study, the TIMI-III data suggest that older age should not be construed as a contraindication to invasive treatment in appropriately selected patients.

RISK STRATIFICATION

In the past 20 years, the concept of risk stratification has been developed as a means for selecting subgroups of post-MI patients who are most likely to benefit from further diagnostic and therapeutic measures, and, conversely, to identify those with a favorable prognosis who are unlikely to benefit from high-cost interventions (94). Factors associated with an increased risk for adverse outcomes include older age, anterior MI location, ischemia occurring either spontaneously or during a post-MI stress test (94), reduced left ventricular systolic function (especially an ejection fraction less than 40%) (94), frequent premature ventricular contractions or higher grades of ventricular ectopy (94), and reduced heart rate variability (182). Although none of the major risk stratification studies have specifically targeted older patients, key factors identified in younger individuals, particularly ventricular function and residual myocardial ischemia, almost certainly retain their prognostic significance in the elderly. In older patients who are suitable candidates for invasive treatment, predischarge risk stratification seems appropriate and should include an echocardiogram or radionuclide ventriculogram to assess left ventricular function, and an exercise or pharmacological stress test (e.g., dipyridamole-thallium or dobutamine-echocardio-

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gram) to determine the extent of residual ischemia (183–185). Based on the results of these investigations, additional intervention may be appropriate, but further study is needed to define the optimal approach to managing high-risk elderly patients (186).

ETHICAL ISSUES

In general, the foregoing discussion has been predicated on the notion that a given patient is an ''appropriate'' or ''suitable'' candidate for each intervention under consideration. These terms, while vague, imply that not all patients should receive every intervention, and that multiple factors must be taken into consideration during the decision-making process. Among these are the wishes of the patient, as expressed either directly or through a prior communication such as a living will; the anticipated impact of the intervention on quality of life and long-term prognosis; the potential for the intervention itself to add to the patient's suffering; and the concerns of the patient's family and friends.

The physician's role in guiding these decisions is critically important, and a high level of compassion, honesty, and respect for the patient's autonomy is required. Thus, the physician must provide a balanced view of the available therapeutic options, including a realistic discussion of the likelihood of various outcomes and adverse events. The physician should avoid creating an overly grim picture, but at the same time must avoid fostering unrealistic hopes. Finally, when the patient's condition is such that death seems inevitable, the physician must be able to provide appropriate counsel to forego or withdraw interventions that are unlikely to be helpful, and that will only serve to prolong the dying process. In addition, the physician must provide comfort and emotional support for the patient and family. In this regard, the importance of the nursing staff, members of the clergy, and other health professionals in helping the patient and family deal with emotional issues and other concerns cannot be overemphasized.

SUMMARY

Acute myocardial infarction occurs at increasing frequency with advancing age, and older patients with acute MI are at increased risk for a variety of complications, including congestive heart failure, arrhythmias and conduction disturbances, myocardial rupture, cardiogenic shock, and death. Older patients thus comprise a large high-risk subgroup of the MI population who may derive substantial benefits from appropriately selected therapeutic interventions. At the same time, many interventions are associated with increased risk in the elderly, so that *individualization* of treatment is essential. Optimal therapy is thus based on a careful risk-benefit assessment of the available treatment options, in conjunction with appropriate consideration of patient preferences and other relevant factors.

Although many therapeutic trials in acute MI patients have either excluded elderly patients or enrolled too few older subjects to permit definitive conclusions, sufficient data are available to make specific recommendations in several areas. As shown in Table 6, aspirin and thrombolysis are of proven value during the acute phase of MI in elderly patients. Intravenous β-blockers are likely to be of benefit as well, and long-term oral β-blockade following MI is clearly beneficial. ACE inhibitors are of proven value in the long-term management of patients with impaired left ventricular systolic function (ejection fraction $< 40\%$), and early initiation of an ACE inhibitor is probably beneficial in selected

Table 6 Efficacy of Selected Treatments for Acute Myocardial Infarction in Elderly Patients

Effective	Probably effective	Uncertain efficacy	Ineffective
	Acute phase		
Aspirin	Intravenous β-blockade	Magnesium	Calcium antagonists
Thrombolysis[a]	ACE inhibitors	Nitrates	Antiarrhythmic agents
Direct angioplasty[a]	Heparin[a]		
	LMWH[a]		
	Chronic phase		
Aspirin	Lipid-lowering agents	Amiodarone	Other antiarrhythmics
β-blockers	Diltiazem[a]	Newer calcium antagonists	Nifedipine
ACE inhibitors[a]	Verapamil[a]		
	Coumadin[a]		
	Angioplasty[a]		
	Coronary bypass surgery[a]		

[a] Selected subgroups; see text.
ACE: angiotensin converting enzyme; LMWH: low-molecular-weight heparin.

subgroups. The role of other agents, including nitrates, magnesium, diltiazem, and verapamil, requires further study, but antiarrhythmic drugs and first-generation dihydropyridine calcium antagonists should be avoided in the absence of specific indications for their use. Finally, although the role of catheterization and revascularization in elderly patients with acute MI requires clarification, advanced age per se should not be considered a contraindication to these procedures.

As the age of the population continues to increase, the number of older patients at risk for acute MI will rise commensurately. Although progressively more sophisticated interventions may result in sizable reductions in post-MI morbidity and mortality, it is apparent, given the high risk of adverse outcomes in the elderly population, that the best treatment is prevention. Thus, the greatest potential for the future, as well as the greatest challenge, will be to develop more effective strategies for preventing atherosclerosis and for conquering the epidemic of coronary heart disease in our aging population.

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13

Management of the Older Patient After Myocardial Infarction

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INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death in older persons. Although persons older than 65 years comprise 12% of the population (1), approximately 60% of hospital admissions for acute myocardial infarction (MI) occur in persons older than 65 years of age, and persons older than 75 years of age account for nearly half of these admissions of patients with MI older than 65 years (2). Not only is the in-hospital mortality higher in older patients with MI than in younger patients with MI, but the postdischarge mortality rate is higher in older persons, with the 1-year cardiac mortality rate 12% for patients aged 65 to 75 years and 17.6% for patients older than 75 years (3). Approximately two-thirds of these 1-year deaths were sudden or related to a new MI (3). This chapter discusses the management of the older patient after MI.

CONTROL OF CORONARY RISK FACTORS

Cigarette Smoking

The Chicago Stroke Study demonstrated that current cigarette smokers 65 to 74 years of age had a 52% higher mortality from CAD than nonsmokers, ex-smokers, and pipe and cigar smokers (4). Ex-smokers who had stopped smoking for 1 to 5 years had a similar mortality from CAD as did nonsmokers (4). The Systolic Hypertension in the Elderly Program pilot project showed that smoking was a predictor of first cardiovascular event and MI/sudden death (5). At 30-year follow-up of persons 65 years of age and older in the Framingham Study, cigarette smoking was not associated with the incidence of CAD in older men and women but was associated with mortality from CAD in older men and women (6).

At 12-year follow-up of men aged 65 to 74 years in the Honolulu Heart Program, cigarette smoking was an independent risk factor for nonfatal MI and fatal CAD (7). The

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Table 1 Risk Factors for New Coronary Events in 664 Older Men and in 1488 Older Women

Risk factor	Relative risk of new coronary events	
	Men	Women
Age	1.04	1.03
Prior coronary artery disease	1.7	1.9
Cigarette smoking	2.2	2.0
Hypertension	2.0	1.6
Diabetes mellitus	1.9	1.8
Obesity	NS	NS
Serum total cholesterol	1.12[a]	1.12[a]
Serum HDL cholesterol	1.70[b]	1.95[c]
Serum triglycerides	NS	1.002

Adapted from Ref. 10.
NS = not significant by multivariate analysis; HDL = high-density lipoprotein.
[a] 1.12 times higher probability of developing new coronary events for an increment of 10 mg/dL of serum total cholesterol.
[b] 1.70 times higher probability of developing new coronary events for a decrement of 10 mg/dL of serum HDL cholesterol.
[c] 1.95 times higher probability of developing new coronary events for a decrement of 10 mg/dL of serum HDL cholesterol.

absolute excess risk associated with cigarette smoking was 1.9 times higher in older men than in middle-aged men. At 5-year follow-up of 7178 persons 65 years of age or older in three communities, current cigarette smokers had a higher incidence of cardiovascular mortality than nonsmokers (relative risk = 2.0 for men and 1.6 for women) (8). The incidence of cardiovascular death in former smokers was similar to those who had never smoked (8). At 6-year follow-up of older men and women in the Coronary Artery Surgery Study registry, the relative risk of MI or death was 1.5 for persons aged 65 to 69 years and 2.9 for persons 70 years of age or older who continued smoking compared with quitters during the year before study enrollment (9).

At 40-month follow-up of 664 older men, mean age 80 years, and at 48-month follow-up of 1488 older women, mean age 82 years, current cigarette smoking increased the relative risk of new coronary events (nonfatal or fatal MI or sudden cardiac death) 2.2 times in older men and 2.0 times in older women (Table 1) (10). We have also observed that cigarette smoking aggravates angina pectoris and precipitates silent myocardial ischemia in older persons with CAD.

On the basis of the available data, older men and women who smoke cigarettes should be strongly encouraged to stop smoking because it will reduce cardiovascular mortality and all-cause mortality after MI.

Hypertension

Increased peripheral vascular resistance is the cause of systolic and diastolic hypertension in older persons. Systolic hypertension in older persons is diagnosed if the systolic blood pressure is 160 mm Hg or higher on three occasions (11). Diastolic hypertension in older persons is diagnosed if the diastolic blood pressure is 90 mmHg or higher on three occa-

Table 2 Decrease in New Coronary Events in Older Persons with Hypertension Treated with Antihypertensive Drugs vs. Placebo

Study	Follow-up	Result
European Working Party on High Blood Pressure in the Elderly (13) (age 60–97 years)	4.7 years	Drug therapy caused a 60% reduction in fatal MI and a 47% reduction in cardiac deaths
Swedish Trial in Old Patients with Hypertension (14) (age 70–84 years)	25 months	Drug therapy caused a 25% decrease in fatal MI and a 67% decrease in sudden deaths
Medical Research Council (15) (age 65–74 years)	5.8 years	Drug therapy caused a 19% reduction in coronary events
Systolic Hypertension in the Elderly Program (16) (mean age 72 years)	4.5 years	Drug therapy caused a 27% decrease in nonfatal MI plus coronary deaths

MI = myocardial infarction.

sions (11). Isolated systolic hypertension in older persons is diagnosed if the systolic blood pressure is 160 mm Hg or higher on three occasions, and the diastolic blood pressure is normal (11). Isolated systolic hypertension occurred in 51% of 499 older persons with hypertension (11).

Isolated systolic hypertension and diastolic hypertension are both associated with increased cardiovascular morbidity and mortality in older persons (12). Increased systolic blood pressure is a greater risk factor for cardiovascular morbidity and mortality than is increased diastolic blood pressure (12). The higher the systolic or diastolic blood pressure, the greater the morbidity and mortality from CAD in older men and women.

At 30-year follow-up of persons aged 65 years and older in the Framingham Study, systolic hypertension correlated with the incidence of CAD in older men and women (6). Diastolic hypertension correlated with CAD in older men but not in older women (6). At 40-month follow-up of older men and 48-month follow-up of older women, systolic or diastolic hypertension increased the relative risk of new coronary events 2.0 times in men and 1.6 times in women (Table 1) (10).

Older persons with hypertension should be treated initially with salt restriction, weight reduction if necessary, cessation of drugs that increase blood pressure, avoidance of alcohol and tobacco, increase in physical activity, reduction of dietary saturated fat and cholesterol, and maintenance of adequate dietary potassium, calcium, and magnesium intake.

Antihypertensive drugs have been demonstrated to decrease new coronary events in older men and women with hypertension (Table 2) (13–16). The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommends as initial drug therapy diuretics or beta-blockers because these drugs have been shown to reduce cardiovascular morbidity and mortality in controlled clinical trials (17).

The authors recommend that the drug selected as monotherapy for hypertension should depend on associated medical conditions. Older persons with hypertension who have had a MI should be treated initially with a beta-blocker.

Dyslipidemia

Serum Total Cholesterol

In the Framingham Study, serum total cholesterol was an independent risk factor for CAD in older men and women (18). Among patients aged 65 years or older with prior MI in

the Framingham Study, serum total cholesterol was most strongly related to death from CAD and to all-cause mortality (19). Many other studies have documented that a high serum total cholesterol is a risk factor for new coronary events in older men and women (5,10,20–22).

During 9-year follow-up of 350 men and women, mean age 79 years, in the Bronx Aging Study, a consistently increased serum low-density lipoprotein (LDL) cholesterol was associated with the development of MI in older women (23). In the Established Populations for Epidemiologic Studies of the Elderly study, serum total cholesterol was a risk factor for mortality from CAD in older women but not in older men (24). At 40-month follow-up of older men and 48-month follow-up of older women, an increment of 10 mg/dL of serum total cholesterol increased the relative risk of new coronary events 1.12 times in men and 1.12 times in women (Table 1) (10).

Serum High-Density Lipoprotein Cholesterol

A low serum high-density lipoprotein (HDL) cholesterol is a risk factor for new coronary events in older men and women (5,10,18,23–26). In the Framingham Study (18), in the Established Populations for Epidemiologic Studies of the Elderly Study (24), and in our study (10), a low-serum HDL cholesterol was a more powerful predictor of new coronary events than was serum total cholesterol.

During 9-year follow-up of 350 men and women in the Bronx Aging Study, a consistently low-serum HDL cholesterol level was independently associated with the development of MI, cardiovascular disease, or death in men (23). At 40-month follow-up of 664 older men and 48-month follow-up of 1488 older women, multivariate analysis showed that there was a 1.70 times higher probability of developing new coronary events in men and a 1.95 times higher probability of developing new coronary events in women for a decrement of 10 mg/dL of serum HDL cholesterol (Table 1) (10).

Serum Triglycerides

Hypertriglyceridemia has been reported to be a risk factor for new coronary events in older women but not in older men (10,18). At 40-month follow-up of older men and at 48-month follow-up of older women, multivariate analysis demonstrated that serum triglycerides was not a risk factor for new coronary events in older men and was a very weak risk factor for new coronary events in older women (Table 1) (10).

Drug Therapy of Hypercholesterolemia

At 5.4-year median follow-up of 4444 men and women with CAD and hypercholesterolemia in the Scandinavian Simvastatin Survival Study, compared with placebo, simvastatin decreased major coronary events 34%, coronary death 42%, and total mortality 30% (Table 3) (27). The reductions in coronary events and in total mortality in patients treated with simvastatin were similar in men and in women between 60 to 70 years of age at study entry (65 to 75 years of age at follow-up) and those younger in age (27).

At 5-year follow-up of 4159 men and women with MI and serum total cholesterol levels below 240 mg/dL but serum LDL cholesterol levels $\geq$ 115 mg/dL in the Cholesterol and Recurrent Events (CARE) trial, compared with placebo, pravastatin reduced major coronary events 27% in persons 60 to 75 years of age at study entry (65 to 80 years of age at follow-up) and 20% in persons younger than 60 years of age at study entry (Table

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Table 3 Effects of Lowering Increased Serum Total Cholesterol and Low-Density Lipoprotein Cholesterol Levels by Simvastatin and Pravastatin vs. Placebo in Older Patients with Coronary Artery Disease

Study	Follow-up	Results
Scandinavian Simvastatin Survival Study (27) (4444 men and women with CAD and hypercholesterolemia)	5.4 years	Compared with placebo, simvastatin decreased serum total cholesterol 25% and serum LDL cholesterol 35%, increased serum HDL cholesterol 8%, and reduced major coronary events 34%, coronary death 42%, and total mortality 30%. The reductions in coronary events and total mortality were similar in men and in women 60 to 70 years of age at study entry and those younger.
Cholesterol and Recurrent Events (CARE) trial (28) (4159 men and women with MI and serum total cholesterol <240 mg/dL but serum LDL cholesterol ≥ 115 mg/dL)	5.0 years	Compared with placebo, pravastatin decreased serum total cholesterol 20%, serum LDL cholesterol 28%, and serum triglycerides 14%, increased serum HDL cholesterol 5%, and decreased major coronary events 27% in persons 60 to 75 years of age at study entry and 20% in persons younger than 60 years. The decrease in major coronary events was 46% in women and 20% in men.

CAD = coronary artery disease; MI = myocardial infarction; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

3) (28). The decrease in coronary events was greater in women (46%) than in men (20%) treated with pravastatin.

On the basis of the above data, older patients after MI who have elevated serum LDL cholesterol levels despite dietary therapy should be treated with a statin drug such as simvastatin, pravastatin, lovastatin, fluvastatin, or atorvastatin. The serum LDL cholesterol level should be reduced to 100 mg/dL or lower (29).

Diabetes Mellitus

Diabetes mellitus is a risk factor for new coronary events in older men and in older women (10,30). At 40-month follow-up of older men and 48-month follow-up of older women, diabetes mellitus was found by multivariate analysis to increase the relative risk of new coronary events 1.9 times in men and 1.8 times in women (Table 1) (10).

Diabetic patients are more often obese and have higher serum LDL cholesterol and triglyceride levels and lower serum HDL cholesterol levels than do nondiabetics. Diabetics also have a higher prevalence of hypertension and left ventricular hypertrophy than do nondiabetics. These risk factors contribute to the higher incidence of new coronary events in diabetics than in nondiabetics.

Older persons after MI who have diabetes mellitus should be treated with dietary therapy, weight reduction if necessary, and appropriate drugs if needed to control hyper-

glycemia. Other coronary risk factors such as smoking, systolic or diastolic hypertension, dyslipidemia, obesity, and physical inactivity should be controlled.

Obesity

In the Framingham Study, obesity was an independent risk factor for new coronary events in older men and in older women (30). Disproportionate distribution of fat to the abdomen assessed by the waist-to-hip circumference ratio has also found to be a risk factor for cardiovascular disease, mortality from CAD, and total mortality in older men and women (31,32). At 40-month follow-up of older men and 48-month follow-up of older women, obesity was a risk factor for new coronary events in men and in women by univariate analysis but not by multivariate analysis (Table 1) (10).

Obese patients who have had a MI must undergo weight reduction. Weight reduction is also a first approach to controlling hyperglycemia, mild hypertension, and dyslipidemia before placing persons on long-term drug therapy. Regular aerobic exercise should be added to diet in treating obesity.

Physical Inactivity

Physical inactivity is associated with obesity, dyslipidemia, hyperglycemia, and hypertension. At 12-year follow-up in the Honolulu Heart Program, physically active men aged 65 years or older had a relative risk of 0.43 for CAD compared with inactive men (33). Exercise training programs are not only beneficial in preventing CAD (34), but also have been shown to improve endurance and functional capacity in older persons after MI (35). Moderate exercise programs suitable for older persons after MI include walking, climbing stairs, bicycling, or swimming.

ASPIRIN

Aspirin decreases the aggregation of platelets exposed to thrombogenic stimuli by inhibiting the cyclooxygenase enzyme reaction within the platelet and thereby blocking synthesis of thromboxane A_2, a powerful stimulus to platelet aggregation and vasoconstriction (36).

Randomized trials involving 19,791 patients showed that aspirin and other antiplatelet drugs administered to patients after MI decreased the incidence of recurrent MI, stroke, or vascular death by 25% at 27-month follow-up (37). The benefit of aspirin in decreasing MI, stroke, or vascular death in patients after MI was irrespective of age, sex, blood pressure, and diabetes mellitus (37).

Data from the Multicenter Study of Myocardial Ischemia in 936 patients enrolled 1 to 6 months after an acute MI (70% of patients) or unstable angina pectoris (30% of patients) showed at 23-month follow-up that the cardiac mortality rate was 1.6% for aspirin users and 5.4% for nonusers of aspirin (38). Cardiac mortality was reduced 90% in aspirin users who underwent thrombolytic therapy compared with nonusers of aspirin who underwent thrombolytic therapy (38).

The Coumadin Aspirin Reinfarction Study (CARS) randomized 8803 low-risk patients after MI to aspirin 160 mg daily, aspirin 80 mg plus warfarin 1 mg daily, or to aspirin 80 mg plus warfarin 3 mg daily (39). At follow-up, the combined incidence of

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cardiovascular death, recurrent MI, and stroke was similar in the three treatment groups (39). The incidence of mortality was similar in the three treatment groups. However, the incidence of nonfatal stroke was reduced by aspirin 160 mg daily (39).

On the basis of the available data, all patients should receive aspirin in a dose of 160 mg to 325 mg daily on day 1 of an acute MI and continue this dose of aspirin for an indefinite period unless there is a specific contraindication to its use (40).

ANTICOAGULANTS

The routine use of warfarin after MI is controversial (41). However, three well-controlled studies have shown a reduction in mortality and/or morbidity in patients receiving long-term oral anticoagulation therapy after MI (42–44). The Sixty Plus Reinfarction Study Group reported at 2-year follow-up after MI of patients, mean age 68 years, that compared with placebo, acenocoumarin or phenprocoumon caused a 26% nonsignificant decrease in mortality, a 55% significant reduction in recurrent MI, and a 40% nonsignificant decrease in stroke (42). The Warfarin Reinfarction Study Group showed at 37-month follow-up after MI of patients 75 years of age or younger that compared with placebo, warfarin caused significant reductions in mortality (24%), recurrent MI (34%), and stroke (55%) (43). The Anticoagulation in the Secondary Prevention of Events in Coronary Thrombosis Research Group reported at 37-month follow-up after MI of patients, mean age 61 years, that compared with placebo, nicoumalone or phenprocoumon caused a 10% nonsignificant decrease in mortality, a 53% significant reduction in recurrent MI, and a 42% significant decrease in stroke (44).

The CARS trial showed in 8803 low-risk patients after MI that the combined incidence of cardiovascular death, recurrent MI, and stroke and the incidence of mortality were similar in patients treated with aspirin 160 mg daily, aspirin 80 mg plus warfarin 1 mg daily, or aspirin 80 mg plus warfarin 3 mg daily (39). The incidence of nonfatal stroke was lower in patients treated with aspirin 160 mg daily than in patients treated with aspirin 80 mg plus warfarin 1 mg daily or aspirin 80 mg plus warfarin 3 mg daily (39). On the basis of the available data, older patients treated with oral warfarin after MI should achieve an INR of 2.0 to 3.0.

The American College of Chest Physicians Consensus Conference on Antithrombotic Therapy recommended long-term aspirin after MI in preference to warfarin because of its simplicity, safety, and low cost (36). Warfarin was recommended for 1 to 3 months after MI in patients with previous emboli, severe left ventricular dysfunction, congestive heart failure (CHF), or two-dimensional echocardiographic evidence of mural thrombosis (36). Long-term warfarin was recommended indefinitely in patients after MI with atrial fibrillation (36).

The American College of Cardiology/American Heart Association guidelines recommend as class I indications for long-term oral anticoagulant therapy after MI (1) secondary prevention of MI in post-MI patients unable to tolerate daily aspirin; (2) post-MI patients with persistent atrial fibrillation; and (3) post-MI patients with left ventricular thrombus (40).

BETA-BLOCKERS

Beta-blockers are very effective antianginal and anti-ischemic agents and should be administered to all patients with angina pectoris or silent myocardial ischemia due to CAD

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Table 4 Effect of Beta-Blockers on Mortality After Myocardial Infarction

Study	Follow-up	Results
Goteborg Trial (47)	90 days	Compared with placebo, metoprolol caused a 21% nonsignificant decrease in mortality in patients <65 years and a 45% significant decrease in mortality in patients 64–74 years.
Norwegian Multicenter Study (48)	17 months (up to 33 months)	Compared with placebo, timolol caused a 31% significant reduction in mortality in persons <65 years and a 43% significant reduction in mortality in persons 65 to 74 years.
Norwegian Multicenter Study (49)	61 months (up to 72 months)	Compared with placebo, timolol caused a 13% nonsignificant decrease in mortality in persons <65 years and a 19% significant decrease in mortality in persons 65–74 years.
Beta Blocker Heart Attack Trial (50)	25 months (up to 36 months)	Compared with placebo, propranolol caused a 19% nonsignificant reduction in mortality in persons <60 years and a 33% significant reduction in mortality in persons 60–69 years.

unless there are specific contraindications to their use. Teo et al. (45) analyzed 55 randomized controlled trials comprising 53,268 patients that investigated the use of beta-blockers after MI. Beta-blockers significantly decreased mortality by 19% in these studies (45). A randomized, double-blind, placebo-controlled study of propranolol in high-risk survivors of acute MI at 12 Norwegian hospitals showed a 52% reduction in sudden cardiac death in persons treated with propranolol for 1 year (46).

Table 4 shows that metoprolol (47), timolol (48,49), and propranolol (50) caused a greater decrease in mortality after MI in older persons than in younger persons. The reduction in mortality after MI in patients treated with beta-blockers was due both to a reduction in sudden cardiac death and recurrent MI (48–50). A retrospective cohort study also showed that MI patients aged 60 to 89 years treated with metoprolol had an age-adjusted mortality decrease of 76% (51).

In the Beta-Blocker Heart Attack Trial, propranolol caused a 27% decrease in mortality in patients with a history of CHF and a 25% decrease in mortality in patients without CHF (52). In this study, propranolol caused a 47% reduction in sudden cardiac death in patients with a history of CHF and a 13% reduction in sudden cardiac death in patients without CHF (52).

In the Beta-Blocker Pooling Project, results from nine studies involving 3519 patients with CHF at the time of acute MI demonstrated that beta-blockers caused a 25% decrease in mortality (53). In the Multicenter Diltiazem Post-Infarction Trial, the 2.5-year risk of total mortality in patients with a left ventricular ejection fraction (LVEF) $< 30\%$ was 24% for patients receiving beta-blockers (relative risk $= 0.53$) vs. 45% for patients not receiving beta-blockers (54). Beta-blockers have also been found to reduce mortality in patients with CAD and CHF associated with a LVEF $\leq 35\%$ (55) or $\geq 40\%$ (56).

A retrospective analysis of the use of beta-blockers after MI in a New Jersey Medicare population from 1987 to 1992 showed that only 21% of older persons after MI without contraindications to beta-blockers were treated with beta-blockers (57). Older patients who were treated with beta-blockers after MI had a 43% decrease in 2-year mortality and a

22% decrease in 2-year cardiac hospital readmissions than older patients who were not treated with beta-blockers (57). Use of a calcium channel blocker instead of a beta-blocker after MI doubled the risk of mortality (57).

Beta-blockers have also been demonstrated to reduce mortality in older patients with complex ventricular arrhythmias after MI and a LVEF $\geq$ 40% (58) or $\leq$40% (59). The decrease in mortality in older patients with heart disease and complex ventricular arrhythmias caused by propranolol is due more to an anti-ischemic effect than to an antiarrhythmic effect (60). In these patients, propranolol also markedly decreased the circadian variation of ventricular arrhythmias (61), abolished the circadian variation of myocardial ischemia (62), and abolished the circadian variation of sudden cardiac death or fatal MI (63).

A meta-analysis of trials also showed that the use of beta-blockers after non-Q-wave MI is likely to reduce mortality and recurrent MI by 25% (64). Therefore, older patients with Q-wave MI or non-Q-wave MI without contraindications to beta-blockers should be treated with beta-blockers for at least 6 years after MI. Beta-blockers with intrinsic sympathomimetic activity should not be used. The American College of Cardiology/American Heart Association guidelines recommend that patients without a clear contraindication to beta-blocker therapy should receive beta-blockers within a few days of MI (if not initiated acutely) and continue them indefinitely (40).

NITRATES

Long-acting nitrates are effective antianginal and anti-ischemic drugs (65). These drugs should be administered along with beta-blockers to patients after MI who have angina pectoris. The dose of oral isosorbide dinitrate prescribed should be gradually increased to a dose of 30 to 40 mg administered three times daily if tolerated. Isosorbide-5-mononitrate in a dose of 60 mg may also be administered once daily. To avoid nitrate tolerance, there should be a nitrate-free interval of 12 h each day (66). Beta-blockers should be used to prevent angina pectoris and rebound myocardial ischemia during the nitrate-free interval.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Angiotensin converting enzyme (ACE) inhibitors improve symptoms, quality of life, and exercise tolerance in patients with CHF and an abnormal LVEF (67) or a normal LVEF (68). An overview of 32 randomized trials comprising 7105 patients with CHF showed that ACE inhibitors reduced mortality by 23% and mortality or hospitalization for CHF by 35% (69). Patients who develop CHF after MI should be treated with ACE inhibitors unless there are specific contraindications to their use.

Table 5 shows that ACE inhibitors reduce mortality in patients after MI (70–73). In the Survival and Ventricular Enlargement Trial, asymptomatic patients with a LVEF $\leq$ 40% treated with captopril 3 to 16 days after MI had at 42-month follow-up compared with placebo, a 19% reduction in mortality, a 21% decrease in death from cardiovascular causes, a 37% reduction in development of severe CHF, a 22% decrease in development of CHF requiring hospitalization, and a 25% reduction in recurrent MI (70). Captopril decreased mortality independent of age, sex, blood pressure, LVEF, and use of thrombolytic therapy, aspirin, or beta-blockers (70).

Table 5 Effect of Angiotensin-Converting-Enzyme Inhibitors on Mortality in Patients After Myocardial Infarction

Study	Follow-up	Results
Survival and Ventricular Enlargement Trial (70)	42 months (up to 60 months)	In patients with MI and LVEF ≤ 40%, compared with placebo, captopril reduced mortality 8% in patients aged ≤55 years, 13% in patients aged 56 to 64 years, and 25% in patients aged ≥65 years
Acute Infarction Ramipril Efficacy Study (71)	15 months	In patients with MI and clinical evidence of CHF, compared with placebo, ramipril decreased mortality 2% in patients aged <65 years and 36% in patients aged ≥65 years
Survival of Myocardial Infarction Long-Term Evaluation Trial (72)	1 year	In patients with anterior MI, compared with placebo, zofenopril reduced mortality or severe CHF 32% in patients aged <65 years and 39% in patients aged ≥65 years
Trandolapril Cardiac Evaluation Study (73)	24 to 50 months	In patients, mean age 68 years, with LVEF ≤ 35%, compared with placebo, trandolapril reduced mortality 33% in patients with anterior MI and 14% in patients without anterior MI

MI = myocardial infarction; LVEF = left ventricular ejection fraction; CHF = congestive heart failure.

On the basis of the available data, ACE inhibitors should be administered after MI to older patients who have CHF, an anterior MI, or a LVEF ≤ 40% unless there are specific contraindications to their use.

CALCIUM CHANNEL BLOCKERS

Teo et al. (45) analyzed randomized controlled trials comprising 20,342 patients that investigated the use of calcium channel blockers after MI. Mortality was insignificantly higher (relative risk = 1.04) in patients treated with calcium channel blockers (45). A meta-analysis of randomized, clinical trials of the use of calcium channel blockers in patients with MI, unstable angina pectoris, and stable angina pectoris showed that the relative risk for mortality in the trials using dihydropyridines such as nifedipine that increase heart rate was 1.16 (74). The calcium channel blockers diltiazem and verapamil which reduce heart rate had no effect on survival (74).

Furberg et al. (75) performed a meta-analysis of the effect of nifedipine on mortality in 16 randomized secondary prevention clinical trials in patients with CAD. In this study, the relative risk for mortality was 1.06 for patients treated with nifedipine 30 mg to 50 mg daily, 1.18 for patients treated with nifedipine 60 mg daily, and 2.83 for patients treated with nifedipine 80 mg daily (75).

The Multicenter Diltiazem Postinfarction Trial demonstrated at 25-month follow-up in patients after MI that compared with placebo, diltiazem caused no significant effect

on mortality or recurrent MI (76). However, in patients with pulmonary congestion at baseline or a LVEF $< 40\%$, diltiazem caused a significant increase in new cardiac events (hazard ratios $= 1.41$ and 1.31, respectively) (76). In this study, diltiazem also increased the incidence of late-onset CHF in patients with a LVEF $< 40\%$ (77). Use of a calcium channel blocker instead of a beta blocker after MI in a New Jersey Medicare population also doubled the risk of mortality (57).

Since no calcium channel blocker has been shown to improve survival after MI except for the subgroup of patients with normal LVEF treated with verapamil in the Danish Verapamil Infarction Trial II (78), calcium channel blockers should not be used in the treatment of patients after MI. However, if patients after MI have persistent angina pectoris despite treatment with beta-blockers and nitrates, a nondihydropyridine calcium channel blocker such as verapamil or diltiazem should be added to the therapeutic regimen if the LVEF is normal. If the LVEF is abnormal, amlodipine or felodipine should be added to the therapeutic regimen. The American College of Cardiology/American Heart Association guidelines state that there are no class I indications for the use of calcium channel blockers after MI (40).

ANTIARRHYTHMIC THERAPY

Class I Drugs

A meta-analysis of 59 randomized controlled trials comprising 23,229 patients that investigated the use of quinidine, procainamide, disopyramide, imipramine, moricizine, lidocaine, tocainide, phenytoin, mexiletine, aprindine, encainide, and flecainide after MI demonstrated that mortality was significantly higher in patients receiving class I antiarrhythmic drugs than in patients receiving no antiarrhythmic drugs (odds ratio $= 1.14$) (45). None of the 59 studies showed a decrease in mortality by class I antiarrhythmic drugs (45).

In the Cardiac Arrhythmia Suppression Trials I and II, older age also increased the likelihood of adverse effects including death in patients after MI receiving encainide, flecainide, or moricizine (79). Compared with no antiarrhythmic drug, quinidine or procainamide did not decrease mortality in older patients with CAD, normal or abnormal LVEF, and presence versus absence of ventricular tachycardia (80). On the basis of the available data, patients after MI should not receive class I antiarrhythmic drugs.

d,L-Sotalol and d-Sotalol

Studies comparing the effect of d,l-sotalol with placebo on mortality in patients with complex ventricular arrhythmias have not been performed. Compared with placebo, d,l-sotalol did not reduce mortality in post-MI patients followed for 1 year (81). In the Survival with Oral d-Sotalol (SWORD) trial, 3121 survivors of MI with a LVEF $\leq 40\%$ were randomized to d-sotalol or placebo. Mortality was significantly higher at 148-day follow-up in patients treated with d-sotalol (5.0%) than in patients treated with placebo (3.1%) (82). On the basis of the available data, d,l-sotalol and d-sotalol should not be used to treat patients after MI.

Amiodarone

In the European Myocardial Infarction Amiodarone Trial, 1486 survivors of MI with a LVEF $\leq 40\%$ were randomized to amiodarone (743 patients) or to placebo (743 patients)

(83). At 2-year follow-up, 103 patients treated with amiodarone and 102 patients treated with placebo had died (83). In the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial, 1202 survivors of MI with nonsustained ventricular tachycardia or complex ventricular arrhythmias were randomized to amiodarone or to placebo (84). Amiodarone was very effective in suppressing ventricular tachycardia and complex ventricular arrhythmias. However, the mortality rate at 1.8-year follow-up was not significantly different in the patients treated with amiodarone or placebo (84). In addition, early permanent discontinuation of drug for reasons other than outcome events occurred in 36% of patients taking amiodarone (84).

In the Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation Study, the incidence of pulmonary toxicity was 10% at 2 years in patients receiving amiodarone in a mean dose of 158 mg daily (85). The incidence of adverse effects for amiodarone also approaches 90% after 5 years of therapy (86). On the basis of the available data, amiodarone should not be used in the treatment of patients after MI.

Beta-Blockers

However, beta-blockers have been demonstrated to reduce mortality in patients with nonsustained ventricular tachycardia or complex ventricular arrhythmias after MI in patients with normal or abnormal LVEF (58,59,87,88). On the basis of the available data, beta-blockers should be used in the treatment of older patients after MI, especially if nonsustained ventricular tachycardia or complex ventricular arrhythmias are present, unless there are specific contraindications to their use.

Automatic Implantable Cardioverter-Defibrillator

In the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial, 1016 patients, mean age 65 years, with a history of ventricular fibrillation or serious sustained ventricular tachycardia were randomized to an automatic implantable cardioverter defibrillator (AICD) or to drug therapy with amiodarone or d,l-sotalol (89). Patients treated with an AICD had a 39% reduction in mortality at 1 year, a 27% decrease in mortality at 2 years, and a 31% reduction in mortality at 3 years (89). If patients after MI have life-threatening ventricular tachycardia or ventricular fibrillation, an AICD should be inserted. The efficacy of the AICD implanted for ventricular fibrillation or recurrent sustained ventricular tachycardia on survival is similar in older and younger patients (90).

The Multicenter Automatic Defibrillator Implantation Trial randomized 196 patients with prior MI, a LVEF $\leq$ 35%, a documented episode of asymptomatic nonsustained ventricular tachycardia, and inducible ventricular tachycardia or ventricular fibrillation not suppressed by intravenous procainamide or an equivalent drug at electrophysiological study to conventional medical therapy or implantation of an AICD (91). At 27-month follow-up, patients treated with an AICD had a 54% reduction in mortality (91). These data favor considering the prophylactic implantation of an AICD in post-MI patients at very high risk for sudden cardiac death.

HORMONE REPLACEMENT THERAPY

Observational studies suggest that postmenopausal women who use estrogen are at lower risk for developing CAD than those who do not use estrogen (92). Progestins added to

estrogen therapy prevent the excess risk of endometrial carcinoma due to the unopposed effect of estrogen. Observational studies also suggest that estrogen/progestin regimens have a cardioprotective effect similar to that of estrogen alone (93,94).

Studies suggest that the most important mechanism for the cardioprotective effect of estrogen is raising serum HDL cholesterol levels (95,96). In the Postmenopausal Estrogen/Progestin Interventions trial, conjugated equine estrogens 0.625 mg daily plus cyclic micronized progesterone 200 mg/day for 12 days per month had the most favorable effect on serum HDL cholesterol with no excess risk of endometrial hyperplasia (97). In 58 postmenopausal women with serum total cholesterol levels >250 mg/dL treated for 8 weeks with simvastatin and for 8 weeks with estrogen plus progestin, there was a 14% decrease in serum total cholesterol with hormone therapy and a 26% decrease in serum total cholesterol with simvastatin, a 24% decrease in serum LDL cholesterol with hormone therapy and a 36% decrease in serum LDL cholesterol with simvastatin, a 7% increase in serum HDL cholesterol with hormone therapy and with simvastatin, and a 29% increase in serum triglycerides with hormone therapy versus a 14% decrease in serum triglycerides with simvastatin (98).

Estrogen-associated changes in coagulation factors may also contribute to a reduction in coronary events. In the Postmenopausal Estrogen/Progestin Interventions trial, placebo was associated with a greater increase in mean fibrinogen than any of the hormone regimens (97). In addition, enhancement of endothelium-dependent vasodilatation by estrogen may contribute to a reduction in coronary events (99).

However, the Heart Estrogen/Progestin Replacement Study (HERS) investigated in 2763 women with documented CAD the effect of hormonal therapy versus double-blind placebo on coronary events (100). At 4.1-year follow-up, there were no significant differences between hormonal therapy and placebo in the primary outcome (nonfatal MI or CAD death) or in any of the secondary cardiovascular outcomes. Women on hormonal therapy had a higher incidence of venous thromboembolic events (relative hazard = 2.89, 95% CI 1.50–5.58) and a higher incidence of gallbladder disease (relative hazard = 1.38, 95% CI 1.00–1.92) than women on placebo. On the basis of these data, the author cannot recommend the use of hormonal therapy in the treatment of postmenopausal women with MI.

REVASCULARIZATION

Medical therapy alone is the preferred treatment in older patients after MI. The two indications for revascularization in older patients after MI are prolongation of life and relief of unacceptable symptoms despite optimal medical management. In patients older than 80 years of age, the goal is less to prolong life than it is to improve the quality of life. Revascularization by percutaneous transluminal coronary angioplasty (Chap. 15) or by coronary artery bypass graft surgery (Chap. 14) is extensively discussed elsewhere. If revascularization is performed, aggressive medical therapy must be continued.

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14

Surgical Treatment of Coronary Artery Disease in the Elderly

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Since 1900, the U.S. population over the age of 65 years has been growing rapidly in both absolute and relative numbers. Currently, 33.5 million individuals are over age 65. By 2010, when the first of the baby boomers (those born between 1946 and 1964) reach 65, there will be 40 million people aged 65 years or older. By 2030, when the last of the baby boomers reach 65, the number of individuals aged 65 years or older is projected to reach 70 million. Moreover, the elderly are living longer. In 1900, at age 65, 13% of men and 16% of women could expect to live to age 85 years. By 1992, these percentages were 30 and 50%, respectively. As the baby boomers age, the percentage of the population age 85 years or older will grow from the current level of 1.4 to 2.4% in 2030 and to 4.6% in the year 2050. Octogenarians are, in fact, the fastest growing segment of the population in the U.S. (Table 1) (1,2).

While arthritis is the most common chronic disease borne by the elderly, heart disease is the most common cause of major disability in the elderly as well as the most common reason for hospitalization and death. Clinically evident heart disease affects 30% of those aged 65 years or older (1,3). Approximately 12% of the elderly population suffer from major limitations of activities because of heart disease (4). Forty percent of deaths in the over-65 population are due to heart disease (5). Clinically recognized ischemic heart disease (and its complications) are responsible for 70% of the deaths due to heart disease (6,7).

In 1993, 7 to 8% of men and women aged 65 years or older were hospitalized for ''diseases of the heart,'' with an average hospital stay of 6 to 7 days (1,8). Congestive heart failure was the most common reason for hospitalization (9), but from 6 to 9% of the elderly discharged with a diagnosis of ''diseases of the heart'' underwent coronary arterial bypass (CABG) at an estimated cost of 6 to 7 billion dollars per year (8,10–14).

As modern medical treatment is being employed for increasing numbers of progressively older patients, dire predictions about the solvency of Social Security and Medicare abound. By 2030, the number of individuals over the age of 65 will more than double

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Table 1 Demographics of Current and Projected Resident Population of the U.S.: 1900–2050

Year	Resident population (1000s)	Number of persons (in 1000s)		Percentage of resident population		Life expectancy (yrs)	
		≥65	≥85	≥65	≥85	at birth	at age 65
1900	75,995	3116	125	4.1	0.2	49.2	11.9
1995	263,434	33,648	3598	12.8	1.4	76.3	17.7
2010	297,716	40,104	5671	13.2	1.9	77.9	18.6
2030	346,899	70,175	8455	20.0	2.4	78.8	20.0
2040	369,980	80,109	13,552	20.3	3.7	79.3	20.7
2050	393,931	77,014	18,223	20.0	4.6	79.8	21.6

(2). It has been suggested that by 2050 outflow of funds from Social Security and Medicare will exceed inflow by 75% (16). Rationing (in one form or another) of healthcare coverage for the elderly is being discussed openly. Healthcare planners question whether the rapidly increasing expenditure of funds, particularly for highly technical procedures, is justified in a population that is nearing the end of life or, at least, the end of active life (17).

It is against this background that the merits of performing CABG in the elderly must be discussed. Before deciding whether or not the benefits that the elderly reap from sophisticated surgical procedures are worth the risks and the costs, however, it is important to appreciate the characteristics of the population commonly referred to as elderly. How sick, impaired, and disabled are the elderly? How prevalent is coronary artery disease (CAD) in the elderly? Does the nature and presentation of CAD in the elderly differ from that in a younger population? Can current medical and surgical treatments of ischemic heart disease prevent disabilities, restore function, prolong life, and increase the quality of life in the elderly with CAD?

CHARACTERISTICS OF THE POPULATION OVER 65

Most discussions about the elderly center on prevalence of disease, degrees of physical or mental impairment, need for hospitalization or institutionalization and end-of-life expenses. Indeed, 80% of the elderly population do suffer from one or more chronic conditions. Overall, however, the elderly population is surprisingly healthy. Only 20% of those in the 65- to 74-year-old group have major or severe limitations of activities due to their chronic diseases (Table 2) (18). Only 5% reside in institutions (many temporarily) (19).

Table 2 Percentage of Noninstitutionalized Population Whose Activities Are Limited by One or More Chronic Conditions

Age group (yrs)	Degree of limitation			
	None	Minor	Major	Severe
65 or older	61.2	15.6	12.5	10.6
65 to 74	65.6	13.6	10.4	10.4
75 or older	54.7	18.6	15.7	11.1

Table 3 Percentage of Population Age 65 or Older with Major Limitations of Activities Because of Specific Conditions

	Major limitations (%)	
Disease/condition	Men	Women
Heart	12	10
Arthritis	8	13
Visual impairment	4	5
Emphysema	4	XX
Hypertension	3	5
Cerebrovascular disease	3	3
Mental/nervous	2	2
Diabetes mellitus	3	3
Other circulatory	3	3

In 1994, 77% of those older than 65 years of age were living in their own households. Of these, 55% were living with their spouses; 30% lived alone but independently; 12% lived with other relatives; only 2% resided with nonrelatives (20). Even among those aged 85 or older, half still live alone or with their spouses (21). In the community, about 5% of the elderly have some clinically detectable impairment of cognitive function, but only 2% of the elderly have major limitations of activity because of mental or nervous disease (22). Seventy percent of the elderly rate their health as good, very good, or excellent (23). Whatever the nature, degree, and permanence of their disabilities might be, it is apparent that the chronic diseases that do cause severe disability and death in the elderly can be treated very successfully by currently available methods (Tables 3, 4). It is also apparent that heart disease stands out as the most common chronic disease that results in major limitations of activity and death in the elderly (4,18,24).

Table 4 Selected Causes of Death in 65-Year-Old or Older Population, 1992

	Men		Women	
Cause	Number	Percent of total	Number	Percent of total
All causes	735,298	100.0	839,916	100.0
Heart disease	271,214	36.9	324,100	38.5
Cancer	191,204	26.0	170,856	20.3
Stroke	46,722	6.4	78,670	9.4
Obstructive pulmonary disease	42,961	5.8	35,221	4.2
Pneumonia/influenza	30,374	4.1	37,115	4.4
Diabetes mellitus	14,865	2.0	22,463	2.7
Accidents	13,335	1.8	13,298	1.6

PREVALENCE OF CAD IN THE ELDERLY

While there is general agreement that prevalence of CAD increases markedly with increasing age, the true prevalence of CAD in the elderly is difficult to determine. About 28% of those over 65 die from ischemic heart disease (6,7). Epidemiological studies, relying on history and resting electrocardiographs, have found symptomatic coronary disease in 20 to 22% of the general population over 70 (25,26). When rest and stress criteria are combined, at least half of those over 70 were found to have CAD (27). Autopsy studies indicate the prevalence of significant CAD (stenosis $\geq$ 60% of at least one coronary artery) to be as high as 60 to 70% in the elderly (28).

EVOLUTION OF THE TREATMENT OF CAD

Evolution of the treatment of CAD took place over a period of 200 years. During the eighteenth century, angina pectoris was recognized as a common and lethal illness that frequently attacked without warning and was associated with sudden death. Its relationship to arterial disease was recognized. During the nineteenth century, the basic instruments necessary for detecting CAD were developed as were the basic medications for treating its symptoms. Myocardial infarction was recognized as a pathological entity. The early and midportion of the twentieth century saw the development of sophisticated diagnostic techniques that made modern treatment of coronary arterial disease and its complications a reality during the last half of the twentieth century.

Recognition of Angina Pectoris

Twenty-four hundred years ago, Hippocrates noted that frequent attacks of pain in the heart in an old person often predicted sudden death. Treatises describing the pulse and its abnormalities date far back in history as do descriptions of the anatomy of the heart. Nevertheless, appreciation and understanding of the role of the coronary arteries in the production of cardiac disease did not begin to develop until the late eighteenth century when Heberden introduced the term angina pectoris (Greek for strangling or choking, breastbone or breast) during a lecture before the Royal College of Physicians of London in July, 1768. He described symptoms he had observed in ''at least 20 men almost all above 50 years old, most with a short neck, and inclining to be fat.'' Heberden commented that angina pectoris was ''not extremely rare''; that it was associated with walking, particularly after eating, and that the uneasiness vanished the moment the patient stood still. He noted the symptoms worsened with time and could occur while lying down. He reported that though the natural tendency of the illness was to kill the patient suddenly, the disorder could last ''near 20 years.'' Because the patient's pulse was not usually disturbed by the pain, Heberden concluded that ''the heart is not disturbed by it.'' He ascribed the illness to ''a strong spasm sometimes accompanied by an ulcer,'' but commented that he had never had it in his power to ''see anyone opened who had died of it.'' Heberden published his report in 1772 (29–31).

In 1775, Edward Jenner helped his close friend, John Hunter, perform an autopsy on one of Heberden's patients who had died suddenly following an anginal attack associated with a sense of impending death. Ossified coronary vessels were found, but the arteries were not examined carefully. In 1785, Jenner made the connection between angina pectoris

and coronary arterial disease but did not publish his conclusions until 1799 (in a letter to Parry who included it his text, Syncope Anginosa). John Hunter, who had developed angina pectoris in 1773, finally died of the disease in 1793 at age 65 years. His death occurred suddenly during a dispute with the board of St. George's hospital. Jenner's delay in reporting his conclusions about the basis of angina pectoris until after Hunter's death has been attributed to his desire not to alarm his life-long friend (32–34).

Defining the Pathophysiology of CAD

Although the frightening and disabling nature of angina pectoris was clearly recognized as a major clinical problem during the nineteenth century, little that was new was added to the basic understanding of coronary arterial disease during that time. Burns, in Scotland, in his 1809 textbook on diseases of the heart attributed angina pectoris to myocardial ischemia. In 1819, Laennec introduced the stethoscope. In 1840, Williams, in Edinburgh, suggested that obstruction of a coronary artery was the cause of the pallid, yellowish appearance of a segment of myocardium discovered at autopsy. The term myocardial infarction was not then in use (as late as 1884, what is now known as a myocardial infarction was referred to as ''fibrinoid degeneration''). In 1867, Brunton, in England, introduced amyl nitrite for the treatment of angina pectoris. Nitroglycerin, the mainstay of the treatment of angina pectoris even today, was introduced in 1879 by Murrell, in England. Riva-Rocci in Italy developed the first practical sphygmomanometer in 1891. In 1896, the year following the serendipitous discovery of x-rays by Roentgen in 1895, roentgen studies of the heart were being performed by Williams, in the U.S. That same year, Pierre Marie, in France, writing his thesis on complications of cardiac disease, used the term myocardial infarction. Dock, in 1896, was the first physician in the U.S. to make a diagnosis of coronary thrombosis during life (32,35,36). Widespread appreciation of the relationship between CAD, angina pectoris and myocardial infarction did not occur until the second quarter of the twentieth century. Sir Clifford Allbutt, in 1900, attributed angina pectoris to disease of the aorta, an understandable conclusion in view of the likelihood of coronary ostial occlusion secondary to the syphilitic aortitis that was so common at the time (36). A major contribution to establishing the pathophysiology of coronary arterial disease was made in 1903 by Einthoven, in Holland, when he developed a practical method for performing electrocardiography. Sir William Osler commented in 1910 that he did not see a case of coronary thrombosis until he became a Fellow of the Royal College of Physicians (37). Coronary artery disease remained virtually unrecognized as a cause of death until 1912, when Herrick in Chicago described (in six patients) the clinical features of sudden obstruction of the coronary arteries including the gross changes that occurred in the myocardium in the region of the infarct. He noted that, while previous attacks of angina had generally been experienced by the patient, fatal coronary arterial thrombosis might be the first evidence of coronary disease (38). In 1918, he republished his data and reported electrocardiographic studies conducted in patients with coronary artery thrombosis (39). White comments that, in the mid 1920s in Massachusetts General Hospital, diagnoses of coronary artery thrombosis and myocardial infarction were rare among the autopsies performed (31). He stated that he did not see his first patient with a myocardial infarction until he was in his second year of practice in 1921. Wearn, in 1923, wrote that ''coronary thrombosis with infarction of the heart as a clinical entity is a condition which is generally classed among the rarities of medicine'' (37). In the U.S., the most famous instance of failure to recognize the signs and symptoms of fatal coronary arterial disease

occurred in San Francisco on August 2, 1923, when Warren Harding, the twenty-ninth president of the U.S. died following an acute myocardial infarction. His death was attributed to acute indigestion or (by *The New York Times*) to a ''stroke of apoplexy.'' By the late 1920s, however, coronary thrombosis, alias myocardial infarction, was a well-established diagnosis.

Development of Modern Diagnostic Techniques

In 1929, a German intern, Werner Forssmann, having heard of an experiment by Claude Bernard, threaded a catheter through his antecubital vein into his right atrium. His goal was to devise a technique to speed delivery of drugs to a patient and, in addition, understand the mysteries of the heart and circulatory system (40,41). Discouraged from pursuing his experiments by Sauerbruch, the Professor of Surgery, Forssmann became a urologist. Cournand, in New York, became aware of Forssmann's work and, by 1941, had developed a technique for catheterizing the right heart in humans (42). Zimmerman, in 1950, and Seldinger, in 1953, developed the techniques of left heart catheterization. In 1958, in Cleveland, Ohio, F. Mason Sones, Jr., accidentally injected the right coronary artery with contrast material producing the first selective coronary angiogram. Louis Pasteur is credited with the statement ''chance favors the prepared mind.'' Sones not only recognized the potential value of his serendipitous observation, but pursued development of the technique of selective coronary arteriography to make it a practical diagnostic technique. The presentation of his results during the 1959 meeting of the American Heart Association introduced the modern era of medical and surgical treatment of coronary artery disease (43).

NATURAL HISTORY OF PATIENTS WITH ANGINA PECTORIS

Only 30 to 40% of 70-year-old individuals with anatomically significant disease of one or more coronary arteries will be overtly symptomatic (classical angina pectoris or evidence of a myocardial infarction on a resting electrocardiogram) (25,27). Of those who have symptomatic CAD, about 37% of men and 65% of women will have angina pectoris as the initial manifestation of the disease. If death as an initial manifestation of symptomatic CAD is excluded, then about 40% of men and 70% of women with CAD will present with angina pectoris as their initial symptom (Table 5) (44,45). Since severe and/or intrac-

Table 5 Distribution and Frequency of Initial Manifestations of Coronary Heart Disease in 492 Individuals from the Framingham Study

	Men		Women		Total	
Manifestation	(No.)	(%)	(No.)	(%)	(No.)	(%)
Angina pectoris	119	37	110	65	229	47
Coronary insufficiency	23	7	12	7	35	7
Myocardial infarction	139	43	30	18	169	34
Death	42	13	17	10	59	12
Total	323	100	169	100	492	100

table angina pectoris is the major indication for 75 to 95% of the CABGs performed in the U.S., particularly in the elderly, an understanding of the natural history of those with angina pectoris must be the foundation for evaluating the effectiveness of medical or surgical therapy of CAD.

Unfortunately, the natural history of angina pectoris is difficult to document. Early studies by Herrick (1918) and by White (1926, 1931, 1943) were handicapped because investigators lacked technology to determine the extent of disease in the coronary arteries during life (39,46–48). In addition, patients with angina pectoris complicated by associated diseases such as hypertension, valvular heart disease, myocardial infarction, and congestive heart failure were often included with those who suffered from uncomplicated angina pectoris. In these early series, the annual mortality of patients with angina pectoris ranged from 2.5 to 9.0% (49).

In 1952, Block et al. (50) described 5- and 10-year survivals by age group for 6882 patients in whom a diagnosis of angina pectoris had been made. The study population included patients with cardiac enlargement, congestive heart failure, and myocardial infarction. Table 6 summarizes their results. Annual mortality (averaged over 10 years) for the entire group was 6.0%. Annual mortality was greatest during the first year (15.3%), then decreased in subsequent years. Overall, 5-year survival for the group was 58%; 10-year survival was 37%. Expected survivals in a general population of like ages would have been 87% at 5 years and 70% at 10 years.

In 1971, Gordon and Kannel (44) reported the frequency with which coronary events occurred during a 14-year follow-up of 5209 people randomly sampled from a general population. One hundred and ninety-seven persons developed angina pectoris as their initial manifestation of coronary artery disease. The risks of dying in this group of individuals varied with the severity of their symptoms. Annual mortality for those free of heart disease was 1/1000. For those in New York Heart Association (NYHA) class I, the risk of dying was 4/1000/year; for those in NYHA class II, the risk was 19/1000/year, and for those in classes III or IV, 43/1000/year. In 1972, Kannel and Feinleib (45) reported presentations and outcomes in 492 persons who first developed coronary artery disease during the 14-year follow-up of a general population of 5127 individuals from the Framingham study (Table 5). Coronary angiography was not performed in these patients. Of the 492 people, 229 presented with angina pectoris; 200 of these manifested ''uncomplicated'' angina pectoris (i.e., angina not complicated by myocardial infarction, coronary insufficiency, or coronary death). Forty percent of the men with uncomplicated angina and 40% of women

Table 6 Prognosis of Angina Pectoris: Its Natural History Survival Rates of Patients with Angina Pectoris According to Ages at Time of Diagnosis

Age group (yrs)	Number of patients	Percentage alive at	
		5 yrs	10 yrs
<40	112	66.1	46.5
40–49	935	65.2	43.1
50–59	2067	61.0	37.2
60–69	2046	55.4	29.0
70–79	572	42.8	16.4
>80	34	26.5	13.0

≥ 60 years of age with uncomplicated angina died within 8 years. Only 15% of women under age 60 with uncomplicated angina died during the 8 years. Annual mortality was 4% for men with uncomplicated angina pectoris. Over a period of 5 years, myocardial infarction was relatively uncommon in women with angina pectoris (7%) but occurred in 24% of men. Half of the men over age 45 years with angina suffered a myocardial infarction within 8 years.

While studies conducted in the 1950s and 1960s could relate the effects of age, severity of symptoms, and presence of associated cardiac diseases with outcome in patients with angina pectoris, it was not until coronary arteriography became widely available that it was possible to correlate the natural history of these patients with the extent of their coronary disease. In 1972, Oberman (51) analyzed the course of 246 patients with angina but without associated cardiovascular disease or serious noncardiovascular disease. All had undergone coronary arteriography between 1965 and 1970, a time period prior to the advent of aortocoronary bypass grafting in their institution. At 22 months, there were no deaths in patients with one-vessel disease and small hearts or in those with one-vessel disease and no electrocardiographic evidence of an old transmural infarction. The annual mortality for all patients with one-vessel disease was 2.0%. Annual mortality for patients with two-vessel disease was 13.0%, and for three-vessel disease, 15.0%. The presence of an old myocardial infarction, a history of congestive heart failure, or an enlarged heart markedly increased the annual mortality in patients with angina pectoris. In 1974, Reeves et al. (49) analyzed the course of 705 patients who had undergone coronary arteriography prior to 1970. The annual mortality for the entire group was 6.5%. For one-vessel disease, annual mortality was 2.2%; for two-vessel disease, 6.8%; and for three-vessel disease, 11.4%. In 1983, Proudfit et al. (52) presented 15-year survivals for 598 patients with chest pain treated medically following angiography. All but 64 were male. Annual mortality averaged over 10 years was 5.4%, with a 31% 15-year survival.

Overall, the natural history of most patients with angina pectoris is poor, with annual mortality rates for uncomplicated disease of 4 to 6%. However, angina pectoris taken by itself is a poor predictor of survival (53). Individuals with single-vessel disease and angina pectoris uncomplicated by a history of transmural myocardial infarction, congestive heart failure, cardiomegaly, associated cardiovascular disease, or serious noncardiovascular disease appear to have annual mortality rates of 1% or less (49). In Oberman et al.'s study, in the order of their importance, the independent predictors of increased annual mortality in patients with angina pectoris followed for 22 months were: heart size, stenosis of the left anterior descending artery, dyspnea on effort with either paroxysmal nocturnal dyspnea or orthopnea, heart rate, stenosis of the left main coronary artery, stenosis of the left circumflex artery, and stenosis of the right coronary artery (51). The need to identify subsets of patients with coronary artery disease was to assume greater importance as the outcomes of CABG and percutaneous transluminal coronary angioplasty (PTCA) began to be evaluated.

EVOLUTION OF SURGICAL TREATMENT

At about the time of Herrick's report that sudden occlusion of a major coronary artery was not ''almost universally fatal,'' surgeons began their attempts to relieve the pain of angina pectoris. François-Franck, in 1899, proposed removal of the cervical and first thoracic ganglia. His intent was to accomplish a complete cure of certain cases of Graves

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disease, which were complicated by aortitis and angina (54). Bilateral extirpation of the cervical sympathetic chain together with removal of both thoracic ganglia for the treatment of angina pectoris was first performed by a Bucharest surgeon, Jonnesco, in 1916 (55).

From 1916 through 1982, no less than 59 different varieties of surgical procedures were performed for the treatment of coronary artery disease. The procedures ranged from those designed to interrupt the afferent nerve pathways from the heart to those developed to replace the heart. These surgical approaches to coronary arterial disease can be divided into four broad categories: extrapericardial procedures; techniques for indirect myocardial revascularization; direct revascularization of the coronary arteries; and cardiac replacement (Table 7) (41,56–58). A few of these procedures were performed only in experimental animals; some represented variations of a more basic concept; many were devised by more than one individual; most were performed in humans at one time or another often over a period of many years. Eventually, all but a few were found to be ineffective or minimally effective.

A major share of the credit for the development of modern coronary arterial surgery belongs to Claude Beck of Western Reserve University and to his persistent efforts to prevent sudden death in patients with a heart ''too good to die.'' Beginning in 1935, he devised and applied numerous variations of his Beck I and Beck II operations. He noted that increases of arterial flow of as little as 5 mL/min into anoxic areas of the myocardium could relieve the pain of angina pectoris and could afford protection against a fatal heart attack (59,60). About 10 years later, Arthur Vineberg of Montreal began advocating implantation of systemic arteries into the myocardium, thus beginning the era of indirect myocardial revascularization (61).

Two sentinel events in the 1950s made possible the modern era of myocardial revascularization. On May 6, 1953, the ability to operate on a quiet heart free of blood became a reality when John Gibbon successfully closed an atrial septal defect using a heart lung

Table 7 Classification of Surgical Procedures Designed to Treat Coronary Arterial Disease

1. Extrapericardial procedures
   - A. denervation procedures
   - B. procedures to decrease metabolic demand of myocardium
   - C. procedures to redirect blood flow to coronary arteries
2. Indirect myocardial revascularization procedures
   - A. cardio-pericardiopexy procedures
   - B. epicardial grafting procedures
   - C. procedures to increase retrograde flow into native vessels
   - D. procedures to increase oxygen extraction
   - E. procedures to stimulate collateral development
   - F. myocardial channelization procedures
   - G. myocardial implant procedures
3. Procedures for direct revascularization of the coronary arteries
   - A. angioplastic (endarterectomy) procedures
   - B. replacement grafting
   - C. bypass grafting
4. Cardiac replacement
   - A. transplantation
   - B. mechanical heart

machine he and his wife had developed (62,63). In 1958, F. Mason Sones, Jr., provided the means to accurately identify, localize, and quantify coronary arterial lesions (43,64). Widespread application of the current techniques of direct myocardial revascularization began after the reports of Favoloro, Johnson, Urschel, and Kerth, in 1969 (64–67). The first transplantation of a human heart was performed in 1967 by Christiaan Barnard, in South Africa (68). On September 16, 1977, Andreas Gruentzig, in Zurich, performed the first balloon dilatation of a coronary artery in a human. The technique was referred to as PTCA and was quickly adopted as an alternative to CABG (41). In the mid-1970s, 70,000 CABGs were performed annually in the U.S. (64). By 1994, the number had grown to 318,000 per year (69).

As early as 1971, however, there were those who questioned the efficacy of aorto-coronary bypass grafting and the justification for its widespread application. The objections and criticisms were based in part on the past history of failures and marginal results of surgical procedures intended to treat coronary arterial disease; in part on what were considered to be the high risks inherent in coronary arterial surgery; and in part on the availability of techniques of medical management that presumably could yield results comparable or superior to those achieved by surgery. These concerns led to performance of numerous controlled studies that compared the outcomes of medical and surgical therapy. The advent of PTCA led to additional randomized studies comparing PTCA with CABG and with medical treatment.

OUTCOME OF RANDOMIZED STUDIES

Since 1972, five large randomized studies have compared the results of coronary arterial bypass plus medical therapy with intensive medical therapy of angina pectoris. Stable angina pectoris was the subject of three studies; unstable angina was the subject of two studies. More recently, two more randomized studies have compared outcomes in patients treated by PTCA and CABG. While various criticisms can be made of the design and conduct of these studies, it is important to summarize their findings, since the conclusions drawn from them have shaped the indications for CABG in patients of all ages.

Early VA Studies

In the mid-1960s, cardiologists and thoracic surgeons in the Veterans Administration developed a keen interest in evaluating current surgical procedures to revascularize the ischemic heart. Three operations were studied, each in increasing detail, employing randomization techniques: the Beck ''poudrage'' procedure; the Vineberg implant procedure; and direct revascularization procedures. Analyses of the Beck procedures did not reach the literature. In the study of the Vineberg procedure, a total of 146 patients (75 medical and 71 surgical) were randomized between 1966 and 1972. Thirty-day operative mortality was 12.3%. Visualization of the implant 1 year after operation was accomplished in half of the eligible patients. Fifty percent of the patients with single implants and 69% of those with double implants were found to have patent grafts. At 12 years, 41% of the medical group and 42% of the surgical group were alive. Eighty-one percent of the deaths in both the medical and surgical groups were due to cardiac disease. The degree of revascularization achieved by the implants did not improve survival. The study ended partly because

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of these findings and partly because of the shift to direct revascularization of the coronary arteries (70).

VA Stable Angina Study

Six hundred and eighty-six patients were entered into the stable angina study between 1972 and 1974. Three hundred and fifty-four individuals were randomized to medical therapy; 332 were randomized to medical plus surgical therapy. Ninety-one patients had greater than 50% stenosis of the left main coronary artery (43 medical, 48 surgical). Five hundred and ninety-five patients were ''non-left main'' (311 medical and 284 surgical). All patients were men. There were no age restrictions. The age range of those in the study was 27 to 68 years, with a mean age of 50.5 years. Forty-four percent of the patients were less than 50 years old. Patients with all degrees of angina were accepted. There was no minimum ejection fraction set for selection. During 11 years of follow-up, 38% of the 354 patients assigned to medical treatment underwent bypass surgery. Twenty-two of those crossing over had left main coronary arterial disease.

At 11 years, survival for patients without significant left main disease was 58% in both treatment groups. Survival between treatment groups of patients with one-vessel or three-vessel disease was not significantly different at either 7 or 11 years. At 11 years, survival for patients with two-vessel disease treated surgically was marginally worse than for their counterparts treated medically (55% vs. 69%; $p = 0.045$). Patients treated surgically for left main disease clearly did better than those treated medically (88% vs. 65%; $p = 0.016$). Patients who were categorized as high risk by angiographical and/or clinical criteria had significantly better survival with surgical treatment. Patients were classified as angiographically high risk if they had three-vessel disease and impaired left ventricular function. They were classified as clinically high risk if they had at least two of the following: resting ST depression, a history of myocardial infarction, or a history of hypertension. Survival at 11 years in the high-clinical-risk group was 49% for the surgical group and 36% for the medical group ($p = 0.015$). In the low-clinical-risk group, survival at 11 years was 63% for the surgical group and 73% for the medical group ($p = 0.066$). In the high-angiographical-risk group, survival at 11 years was 50% for surgical patients and 38% for medical patients ($p = 0.026$). In the low-angiographical-risk group, the corresponding survival data were 61% and 68% ($p = 0.105$). In the combined high-angiographical and clinical risk group, survival at 11 years was 54% in the surgical group and 24% in the medical group ($p = 0.005$). Corresponding survivals in the combined low-angiographical and clinical risk group were 66% and 76% ($p = 0.092$). The average annual mortality rates during the first 7 years of the study were 3.3% for all surgically treated patients without left main disease and 4.0% for all medically treated patients without left main disease. During the next 4 years the corresponding annual mortality rates were 4.8% and 3.5%. Thus, three groups of patients benefited from surgical treatment: those with significant left main disease; those with extensive coronary arterial disease associated with reduced ventricular function; and those who fell into clinical- or angiographical-high-risk categories.

Quality of life was better in those patients treated surgically. At 5 years, 41% of surgical patients and 17% of medical patients reported marked improvement in symptoms. Twenty percent of the surgical patients and 42% of the medical patients described worsening symptoms. Over the 5-year period, the benefits of surgery deceased but at 5 years were still significantly better than medically treated patients ($p = 0.0014$). The incidence

of nonfatal myocardial infarction was not significantly different between the two treatment groups. At 5-year follow-up, left ventricular function remained unchanged in both treatment groups (71–74).

VA Unstable Angina Study

Four hundred and sixty-eight patients were entered into the unstable angina study between 1976 and 1982 (237 medical, 231 medical plus surgical). Three hundred and seventy-four patients were identified as type I (accelerated angina, rest angina, and recent-onset angina); 94 were identified as type II (prolonged angina unrelieved by nitrates and accompanied by ST segment changes on electrocardiogram). All patients were men. There were no age restrictions. The age range in the study was 32 to 73 years, with a mean age of 56 years. Patients with all degrees of angina were accepted. Patients with ejection fractions below 30% and those with left main lesions greater than 50%, recent myocardial infarction, or prior coronary artery surgery were excluded. At the end of 10 years, 50% of patients randomized to medical treatment had crossed over to surgery.

At 10 years, survival was 61% for surgical patients and 62% for medical patients. At 5 years and 8 years, there was significantly better survival for patients with three-vessel disease treated surgically (89% vs. 77% and 77% vs. 65%, respectively). At 10 years, however, the surgical advantage was no longer significant (63% vs. 57%; $p = 0.190$). At 8 years, survival of patients with three-vessel disease and an ejection fraction of 58% or less was significantly better in the surgical group (79.5% vs. 57.1%; $p = 0.018$). In contrast, survival at 8 years in those with one- or two-vessel disease and an ejection fraction greater than 58% was significantly better with medical treatment (83.2% vs. 67.8%; $p = 0.022$).

A major finding in this study was the effect of surgical treatment on survival of patients with an ejection fraction between 30% and 58% if the crossovers from medicine to surgery were censored (counted as lost to follow-up at the time of crossover). When this was done, there was a strong advantage to surgical treatment throughout the 10 years of follow-up (59% vs. 43%; $p = 0.007$) (75).

Continued smoking was an independent predictor of death in the surgical group at 2, 5, and 10 years. At 10 years, New York Heart Association class III or IV, age, and diabetes mellitus were additional independent predictors of mortality in the surgical group. In the medically treated group, decreased ejection fraction and the number of vessels diseased were consistent, independent predictors of mortality.

As in the stable angina study, quality of life was better in the surgically treated group with superior pain control, reduced medication requirements, and significantly fewer new cardiovascular hospitalizations over the 10-year observation period ($p = 0.0001$). At the end of 10 years, the number of nonfatal myocardial infarctions were not significantly different between treatment groups (76–79).

European Coronary Surgery Study Group

Seven hundred and sixty-eight patients were entered into the study between 1973 and 1976 (373 medical, 395 surgical). One patient was lost to follow-up before operation, leaving 394 surgical patients. All were men under the age of 65 years (mean age 50 years). Those with severe angina pectoris as well as those with ejection fractions below 50% or single-vessel disease were excluded from the study. Patients with left main lesions of 50%

or more were included on a discretionary basis (31 medical, 28 surgical patients). Those assigned to medical treatment could cross over to the surgical group if they had unacceptable symptoms despite adequate medical therapy (24% did cross over within 5 years). All patients were followed for 5 years; 60% were followed for 6 years; 25% for 7 years; and 10% for 8 years.

At 5 years, 92.4% of the surgical patients and 83.6% of the medical patients were alive ($p = 0.00025$). In those patients with left main disease, there was a markedly increased 5-year survival with surgery, but because of the small numbers, the difference was not significant (81.7% vs. 67.9%; $p = 0.11$). Survival was markedly improved in the surgical group with three-vessel disease and also in the group with two- or three-vessel disease when it was associated with stenosis of 50% or greater in the proximal left anterior descending artery. An abnormal electrocardiogram, ST segment depression of 1.5 mm or more during exercise, and the presence of peripheral vascular disease were each independent predictors of better survival with operation. Survival at 10 years in patients over the age of 53 years was significantly better in the surgical group (72% vs. 57%; $p = 0.007$). Below age 53 years, age was not a significant factor affecting outcome between the two treatment groups. A conclusion drawn from the study was that the greatest benefits of surgery occurred in the high-risk group of patients. Surgery was unlikely to improve 5-year survivals in patients with good left ventricular function, ST segment depression less than 1.5 mm on exercise, a normal resting electrocardiogram, and absence of peripheral vascular disease. These conclusions closely resemble those reached in both the stable and unstable VA randomized studies (79–82).

Operation markedly improved the quality of life as measured by the percentage of patients free of angina or by the degree of increased exercise tolerance. As in other studies, these effects diminished with time, although the advantage over medical treatment remained statistically significant at 4 years for exercise performance ($p = 0.001$) and throughout the study for relief of angina ($p = 0.001$) (80).

Coronary Artery Surgery Study (CASS)

In 1973, the National Heart, Lung, and Blood Institute organized a randomized trial designed to compare results of medical and surgical therapy in patients with coronary artery disease. The goal of the randomized trial was to test the hypothesis that coronary artery bypass surgery significantly reduced the mortality rate and the incidence of myocardial infarction in patients with mild angina or in those who were asymptomatic after a myocardial infarction (but who had CAD documented by angiography) (82,83).

Between 1975 and 1979, 780 patients were entered into the study (390 medical, 390 surgical). Ninety percent of the patients were men. All enrollees were 65 years of age or less; the mean age was 51.2 years. Patients with angina more severe than Canadian class II were excluded, as were those with unstable angina, progressive angina, congestive heart failure, previous coronary bypass surgery, or serious coexisting illness. Patients with an ejection fraction less than 35% and those with left main lesions greater than 70% were also excluded. Patients with a well-documented myocardial infarction more than 3 weeks before randomization were accepted into the study. Analyses were performed on the basis of treatment assigned (79,83).

At 8 years, 87% of the surgical patients and 84% of the medical patients were alive ($p = 0.14$). However, in the subset of patients with ejection fractions below 50%, 84% of the surgical patients and 70% of the medical patients were alive at 7 years ($p = 0.012$).

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When this subset of patients was analyzed by the number of diseased vessels, a significant difference in survival was found only in those patients with three-vessel disease (88% in the surgical group, 65% in the medical group; $p = 0.0094$). There was no significant difference between the medical and surgical treatment groups in the occurrence of nonfatal myocardial infarction. At 5 years, the crossover rate from medicine to surgery was 24% (82).

From the standpoint of quality of life at 5 years, the surgical group had significantly less chest pain ($p < 0.0001$), fewer limitations of activity ($p < 0.0001$), and a lower requirement for beta blockade ($p < 0.0001$). In the surgical group, treadmill exercise tests documented less exercise-induced angina, less ST segment depression, and longer treadmill times (84).

National Cooperative Study Group: Unstable Angina

Under the auspices of the National Heart, Lung, and Blood Institute, a prospective, randomized study was initiated comparing intensive medical therapy with urgent coronary arterial bypass for the management of patients with unstable angina. Between 1972 and 1976, 288 patients were entered into the study (147 medical, 141 surgical). Eighty-two percent were men. All enrollees were under the age of 70 years. The patients had to have angina associated with transient ST segment or T-wave changes on electrocardiogram. Ninety percent of the patients had rest pain while in the hospital. Although the patients had to have greater than 70% occlusion of at least one coronary artery to be eligible for randomization, 76% had multivessel coronary arterial disease. Thirty percent of the individuals in the study had proximal left anterior descending arterial disease. Thus, the group corresponded to patients with type II symptoms in the VA unstable angina study. Ejection fractions of 30% or less and greater than 50% narrowing of the left main coronary artery were reasons for exclusion, as were a myocardial infarction within 3 months or serious illnesses other than coronary arterial disease.

At 65 months, there was no significant difference in survival between surgical and medical patients (85% surgery vs. 84% medical). Forty-three percent of patients crossed over from medicine to surgery (34% of those in NYHA classes I and II and 60% of those in NYHA classes III and IV). Crossover occurred sooner in patients with more severe angina (85).

As was the case in the other randomized studies, quality of life was better in the surgical group. At the end of the first year, severe angina was significantly more common in the medical group in patients with one-vessel disease ($p < 0.05$), two-vessel disease ($p < 0.01$), and three-vessel disease ($p < 0.01$). There was no significant difference in the incidence of nonfatal myocardial infarction between the two treatment groups (86).

Emory Angioplasty Versus Surgery Trial (EAST)

The EAST study was designed to determine whether initial revascularization with angioplasty in patients with multivessel coronary disease is a viable alternative to bypass surgery, on the basis of outcome at 3 years. Between 1987 and 1990, 5118 patients were screened. Exclusion criteria included left main disease, two or more total occlusions of the coronary vessels, an ejection fraction $\leq 25\%$, recent myocardial infarction (within 5 days), insufficient symptoms, and life-threatening noncardiac illnesses. Advanced age was not a criterion. Three hundred and ninety-two patients were randomized, 198 to PTCA

and 194 to CABG. All had two- or three-vessel disease. The mean age of the PTCA patients was 61.8 years. The mean age of the CABG patients was 61.4 years. 74.7% of the PTCA patients and 72.7% of the CABG patients were men. Data were analyzed according to intention to treat.

Operative mortality was 1% in both groups. In-hospital Q-wave myocardial infarctions were suffered by 10.3% of CABG patients and 3.0% of PTCA patients. Ten percent of the PTCA patients required CABG at the time of initial revascularization.

Within 3 years, 6.2% of the CABG group had died compared with 7.1% of the PTCA group ($p = 0.72$). 19.6% of the CABG patients had suffered a Q-wave myocardial infarction compared with 14.6% of those treated by PTCA ($p = 0.21$). During the 3-year follow-up, 1% of the CABG group and 22% of the PTCA group required CABG. Thirteen percent of the CABG group and 41% of the PTCA group required PTCA. In terms of quality of life, the CABG group had a better outcome than the PTCA patients. Twenty percent of those treated by PTCA were in Canadian Cardiovascular Society (CCS) classes II, III, or IV compared with 12% of those treated by CABG ($p = 0.039$). Sixty-six percent of the PTCA group and 51% of the CABG group required antianginal medication ($p = 0.005$).

Median initial procedure costs (in 1987 dollars) for PTCA were $14,166 compared with $22,894 for CABG. At 3 years, the median costs for treating a PTCA patient totaled $19,059; those for a CABG patient totaled $23,572. Procedure costs included physician and hospital costs (87,88).

The Bypass Angioplasty Revascularization Investigation (BARI)

In 1987, the National Heart, Lung, and Blood Institute initiated the BARI study to test the hypothesis that, during a 5-year follow-up period, PTCA does not result in a poorer clinical outcome than does CABG in patients with multivessel coronary disease and severe angina or myocardial ischemia. Between 1988 and 1991, 1829 patients were randomized: 914 to CABG and 915 to PTCA. Mean age of the CABG patients was 61.1 years. That of the PTCA patients was 61.8 years. Seventy-three percent of the PTCA patients and 74% of the CABG patients were men. Data were analyzed according to the intention-to-treat principle.

Operative mortality was 1.3% in the CABG group and 1.1% in the PTCA group. 4.6% of the CABG group and 2.1% of the PTCA group suffered a Q-wave myocardial infarction ($p = 0.004$). 12.8% of those assigned to PTCA had additional revascularization procedures during the initial hospitalization; 6.3% of the PTCA patients required emergency CABG.

Cumulative survival rates at 5 years were 89.3% for CABG patients and 86.3% for PTCA patients ($p = 0.19$). Rates of survival free of Q-wave infarction at 5 years were 80.4% for those treated by CABG and 78.7% for those treated by PTCA ($p = 0.84$). Cumulative rates of Q-wave infarction at 5 years were 11.7% for CABG and 10.9% for PTCA ($p = 0.45$). During the 5-year follow-up, 54.5% of the PTCA patients required revascularization procedures compared with 8.0% of the CABG patients. Nineteen percent of the PTCA group required multiple revascularization procedures compared with 3.0% of the CABG group. Improvement in functional status (as measured by the Duke Activity Scale) was better in the CABG patients (5.6 units vs. 3.2 units; $p = 0.04$).

Mean initial procedure cost for PTCA was $21,113 compared with $32,347 for

CABG. At 5 years, the total mean costs for PTCA were $56,225 compared with $58,889 for CABG.

A major finding in this study was the difference in survival at 5 years between treated diabetics assigned to PTCA and treated diabetics assigned to CABG (65.5% for PTCA patients vs. 80.6% for CABG patients; $p = 0.003$). The term treated diabetics referred to those requiring insulin or oral hypoglycemic agents. As is true in most studies, the overall survival at 5 years for diabetics was less than that of nondiabetics (73.1% vs. 91.3%) (12,88,89).

Overview

While the general goal of each of the randomized trials summarized above was to compare the results of medical and surgical treatment of coronary arterial disease, it is clear that the individual studies differed substantially in mortality data, study design, patient selection, and patient recruitment. It is nevertheless striking that there are a number of major conclusions for which there is substantial agreement among the studies:

1. Angina pectoris is of itself not an indication for CABG except for the quality of life. Surgical treatment for this purpose had a significant advantage in each of the trials.
2. CABG does not increase survival over that obtained by medical therapy for one- or two-vessel disease unless the patient falls into a high-risk category.
3. CABG has a clear advantage over medical management in the treatment of significant left main disease.
4. CABG results in a significantly increased survival when compared with medical management in patients with three-vessel disease and abnormal left ventricular function.
5. CABG results in better survival than medical management in patients who are high risk by clinical or angiographical criteria or a combination of both.
6. Quality of life is uniformly better in the group treated by CABG. Exercise tolerance and freedom from angina are better in the surgical group. Requirements for medication and new hospitalizations for cardiovascular events are less in the surgical group.
7. In those groups that benefited from CABG, the benefits, particularly as they concern quality of life, tend to decrease with time. Even so, the advantages of CABG continue for 5 to 10 years.
8. When analyzed on the basis of decision to treat, there is no difference in 3- to 5-year survival of patients randomized to PTCA or CABG as the initial treatment for multivessel disease.
9. Over a 3- to 5-year period, there is no difference in the rate of Q-wave infarctions in patients initially randomized to PTCA or CABG.
10. Patients undergoing PTCA as the initial treatment of multivessel disease require additional revascularization procedures much more frequently than those initially treated by CABG.
11. Initial costs of PTCA are lower than those of CABG, but at 5 years, the total costs are about equal.
12. Diabetics requiring insulin or oral hypoglycemic agents fare better with CABG than PTCA for multivessel coronary artery disease.

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THE ELDERLY AS CANDIDATES FOR CABG

The five randomized studies comparing CABG with medical treatment were conducted in the 1970s in a younger, primarily male population. Mean ages in the five studies varied from 50 to 56 years. Patient outcomes in that group were used to determine indications for surgery. The current population undergoing CABG, however, has a different composition. It is older (mean age 65 years) and has a larger percentage of women (30%). The patients present for surgery with more advanced coronary disease, more complications from their heart disease, and a greater number of coexisting diseases. Although reports of outcomes following CABG in 70, 80, and even 90-year-olds are easily found in the literature, determining the benefits of CABG in this group and establishing indications for operation in the elderly necessarily involves an appreciation of the nature and extent of CAD in the patient population at risk.

The prevalence of angina pectoris in the general population in the U.S. is approximately 1%. Prevalence increases with increasing age, afflicting 9.2% of a general population 55 to 69 years old and 14.7% of a general population 70 to 88 years old ($p = 0.0002$) (53). Even so, the prevalence of ischemic heart disease increases more rapidly with age than does angina (3), indicating that CAD in the elderly is more likely to present with manifestations other than uncomplicated angina.

Silent ischemia affects about 30% of the population over 70 years of age in contrast to 10% of a population in its 50s (25,26,90–93). Silent ischemia is not a benign event even in the middle aged, but it is much more dangerous in the elderly. In Erikssen and Thaulow's study of younger patients (90), there was a 0.5% incidence of sudden death. Cardiac events occurred in 21 to 46% of younger patients with silent ischemia (91). In a study by Aronow (94), the prevalence of sudden death and coronary events in octogenarians was 38% and 69%, respectively, during 43 months of follow-up.

Myocardial infarction is not only more common in the elderly, it often goes unrecognized (39% of those over 65 vs. 27% of those under 65) (95,96). Dyspnea rather than chest pain becomes the predominant symptom of an acute myocardial infarction in those over the age of 80 (97,98). Compared with a younger population, the elderly also have a higher mortality after infarction (12 to 39% vs. 2.0 to 8.0%) and a higher incidence of complications secondary to the infarction (98,99).

Congestive heart failure (CHF) is more common in older individuals with an annual incidence rising from 2/1000 in men 45 to 64 years old to 8/1000 in those 65 to 74 years old; 14/1000 in those 75 to 84, and 54/1000 in those 85 to 94. Women over the age of 75 years have a similar or greater incidence. Mortality from CHF in those between the ages of 65 and 94 is 88% within 6 years (100).

The incidence of sudden death from CAD in a general population rises from 1.1/1000 in men 45 to 54 years old to 2.6/1000 in men 65 to 74 years old. In women, the respective incidences are 0.3/1000 and 1.2/1000. The percentage of coronary attacks (death and/or myocardial infarction) whose initial manifestation is sudden death increases from 13.6% in men 35 to 44 years old to 20% in men over 65. The probability of sudden death also increases with the duration of uncomplicated angina (2.6% at 2 years; 9.7% at 7 years). Males who have heart disease and are hypertensive, diabetic, and cigarette smokers represent an identifiable group who are at high risk for sudden death. The risk of sudden death over the age of 65 years is three to four times higher in men with CAD and two to seven times higher in women with CAD than it is in those without CAD (101,102). Table 8 represents a composite of 34 nonrandomized studies reported between 1982 and

Table 8 Characteristics of Patients Undergoing Coronary Bypass Grafting Comparison of Those <70 with Those >70 Years Old

	Prevalence (in percentage)			
	Under 70 yrs old		70 yrs old or older	
Factor	Range	Mean	Range	Mean
Female gender	13.0–38.7	28.3	24.6–46.0	27.8
NYHA IV	23.0–56.0	44.8	20.0–63.0	36.7
Left main disease	7.0–20.9	13.1	3.4–35.0	16.4
3-vessel disease	40.8–78.0	49.0	27.0–90.0	61.9
EF >30%, <50%	19.7–42.0	24.6	22.0–66.0	33.3
Prior myocardial infarct	35.0–62.0	57.4	22.8–68.5	53.6
Hx congestive heart failure	3.0–33.6	9.7	7.0–67.0	17.1
Diabetes mellitus	4.0–28.0	16.1	3.0–60.0	12.6
Cerebrovascular disease	XXX	6.0	6.4–21.0	9.0
Peripheral vascular disease	4.4–13.0	4.4	4.2–26.0	5.4
Urgent or emergent surgery	6.0–41.0	9.5	7.0–56.8	17.3

NYHA = New York Heart Association; EF = ejection fraction; Hx = History.

1997 of patients who had undergone CABG. It compares the characteristics of a population under age 70 years with those of a population over 70. While there is considerable overlapping of data, it is apparent that those over 70 are more likely to have a history of CHF and a higher prevalence of left main disease, three-vessel disease, and impaired left ventricular function. In addition, more of the elderly are operated upon urgently or emergently, a circumstance that in itself will double or triple their operative mortality (103).

OUTCOME

Effectiveness of CABG in the elderly must be measured against the results of alternative treatments such as PTCA, maximal medical management, or routine symptomatic treatment. When costs are being compared, expenses of treatment over a period of years must be considered rather than just those of the initial episode. Mortality and morbidity are the obvious short-term measurements to be made. The critical long-term measurements are survival and quality of life. Survival must not only be measured against that of the general population of similar age but against the projected survival of a population in which CAD was allowed to pursue its natural course. Quality of life includes measurements such as relief of symptoms, freedom from further coronary events, and improvement in functional capacity. Costs are of concern to patients, their families, and society as both a practical matter and a philosophical issue.

Baseline Data

Table 9 depicts both expected survivals for a general population aged 60 years in 1940 and for individuals in a general population of selected ages in 1992. The same table also depicts the expected survivals of patients with angina pectoris prior to the advent of modern medical and surgical treatment. The data reported by White (48) and Block (50) ex-

Table 9 Survival Data: General Population, Natural History of Population with Angina Pectoris, Diabetic Population with CAD

Source	Reference yr	Age of population	Nature of population	Percentage survival at specified intervals (yrs)				
				1	5	10	15	20
Life Tables US	1940	60	General Population	98.2	87.6	72.0	53.3	33.2
"	1992	50	"	99.5	97.2	92.9	86.6	77.9
"	"	60	"	98.8	93.2	83.8	71.5	56.4
"	"	70	"	97.3	85.3	67.2	46.1	—
"	"	80	"	94.0	68.5	—	—	—
"	"	80–89	"	92.0	62.0	—	—	—
White, Bland	1931	56.5	Nat Hx Angina Pectoris	89.3	64.2	39.8	19.5	12.7
Block	1927–1944	58.8	"	84.7	58.4	37.1	22.1	14.1
Kannel	1949–1952	≥50, men	Nat Hx Uncomplicated AP	100	84.0	58.0	—	—
Barzilay	1944	68	ND + CAD	—	75.0	55.0	34.0	—
"	"	"	DM + CAD	—	63.0	39.0	21.0	—

CAD = Coronary artery disease; ND + CAD = nondiabetic patient with CAD treated either medically or surgically; DM + CAD = diabetic patient with CAD treated either medically or surgically; uncomplicated AP = angina pectoris uncomplicated by myocardial infarction, coronary insufficiency, or coronary death.

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Table 10 Summary of Reported Operative Mortality Following Coronary Artery Bypass by Age Groups

	30-Day operative mortality (%)			
Priority of operation	≤50	<70	≥70	≥80
Overall	0.6–3.0	1.0–5.2	1.8–12.0	2.0–24.0
Elective	0.4–0.7	0.6–1.6	1.0–4.2	0.0–8.0
Urgent or emergent	2.2–4.8	4.9–5.1	4.1–22.2	8.8–28.6

clude patients with valvular disease, but includes some patients with a history of myocardial infarction, congestive heart failure, hypertension, and diabetes. The data reported by Kannel (45) represent survivals of patients with uncomplicated angina pectoris; that is, patients without valvular disease, myocardial infarction, or the coronary insufficiency syndrome. While the data from White and Block are older (1930s and 1940s) than those from Kannel, the composition of their patient populations more closely approximates that of current populations undergoing CABG. The two sets of data represent the extremes of outcome against which the results of medical and surgical treatment can be evaluated.

Operative Mortality

Reported operative mortality following CABG in the elderly varies widely as a result of differences in patient selection. Advanced cardiac disease, high prevalence of associated diseases, and the need for urgent or emergency surgery are the major factors that increase mortality in the elderly. Table 10 (103–109) is a composite of operative mortalities reported in various age groups undergoing elective or emergency operation. It is apparent that operative mortality increases with advancing age and the priority of the procedure. Performing CABG urgently or emergently in the elderly is associated with a very high operative mortality. Table 11, a compilation of data from Curtis et al. (105), Peterson et al. (106), and He et al. (110), lists the effects of selected factors on operative mortality

Table 11 Relative Effects of Selected Factors on 30-Day and 3-Year Mortality

	Relative mortality	
Factor	30 days	3 yrs
Urgent or emergent operation	4.50	
Cigarette smoking	2.69	
Chronic renal failure	2.42	2.38
History of myocardial infarct	2.33	
Cerebrovascular disease	2.22	1.70
Congestive heart failure	1.77	1.73
Peripheral vascular disease	1.42	1.33
Age	1.37–3.50	1.33
Female gender	1.19–2.90	1.33
Pulmonary disease	0.96	1.11
Diabetes mellitus	0.93	1.17

following CABG in the elderly. Again, performing CABG as an urgent or emergency procedure clearly has the greatest adverse effect on operative mortality. Dziuban (111), describing his group's experience with 460 patients, found an operative mortality of 1.2% following elective CABG; 3.2% after urgent CABG, and 26% if the operation was performed as an emergency. In series in which the adverse factors listed in Table 11 were not significantly higher in elderly patients, operative mortalities of 1.0 to 1.3% were reported in groups of patients with a mean age of 61 and 1.0 to 4.2% in those ≥70 years of age (13,89,107,112).

Morbidity After CABG

Overall postoperative morbidity in the elderly can be as high as 65%. Nineteen percent of the complications are life threatening, while 30% of the patients have two or more complications (113). Table 12 summarizes morbidity following CABG (107–109, 114,115–122). It is apparent that the overall frequency of complications increases with age over 70 years. The most common minor complications over age 70 were cardiac arrhythmias. Atrial fibrillation occurred in from 10 to 40% of patients (108,112,123). Major complications were suffered by 22 to 24% of those older than 70 years (118,123). The most common major complications were myocardial infarction, pneumonia, and stroke.

Survival

Table 13 summarizes survival data from several authors (112–116,119,122,124–126). Again, there is some variation as a result of patient selection, but it is clear that long-term survival of those 70 years of age or older, as well as those in their 80s closely approximates that of a general population of like age (Table 9). It is also clear that survival of patients after CABG is markedly better than would have been the case if the angina had been allowed to pursue its natural course (Table 9). Although most authors have reported a higher operative mortality in women, long-term survival of women following CABG is at least as good as that of men in all age groups (Table 13) (114).

Table 12 Summary of Reported Morbidity Following Coronary Artery Bypass by Age Groups

	Prevalence (%)			
Complication	≤50	<70	>70	≥80
Overall	0.6–26.0	16.0–20.0	20.0–58.0	54.0–73.0
Cardiac				
atrial arrhythmia	—	4.0–8.0	11.0	19.0–42.0
ventricular arrhythmia	6.0	—	—	6.0–8.0
perioperative MI	1.8–6.0	0.9–7.0	0.0–9.9	1.4–13.0
Pulmonary	3.7	41.0	—	20.0–36.0
Stroke	0.0–2.4	0.7–2.0	1.3–6.5	1.3–5.6
Renal failure	1.2	0.3–3.5	0.9–3.5	6.3–19.0
GI bleeding	—	0.9–1.6	1.8–4.3	—
Sepsis	—	0.0–1.2	1.2–1.4	7.0
Pneumonia	—	3.4	4.4–6.5	14.0
Wound infection	2.5	2.5	5.4	3.9–5.0

Table 13 Reported Survivals Following Coronary Artery Bypass by Author, by Year, and by Duration

Ref. (yr)	Age (yrs)	Survival in percent					
		1 yr	3 yrs	5 yrs	6–7 yrs	10 yrs	15 yrs
112 (94)	36			86		77	
124 (95)	36	98	93	90	85	74	
125 (85)	69	93	90	83	80		
119 (88)	>70	91	88	86	85		
115 (94)	>80	89	77	66		42	
116 (90)	>80	90	76	60			
126 (97)	>80	87	78	66	47		
109 (92)	82		77.4				
114 (93)	≤45			92 (96)		82 (85)	64 (81)
men (women)	46–54			94 (98)		86 (81)	72 (67)
	55–64			90 (87)		75 (71)	55 (55)
	65–74			83 (84)		60 (70)	35 (32)
	≥75			69 (77)		40 (38)	(28)

Increasing age, ejection fraction below 35%, severe wall motion abnormalities, end-systolic volume greater than 80 mL, and the presence of two or more associated medical conditions are predictors of decreased long-term survival (124,127). Over age 65 years, 45% of late deaths are due to noncardiac causes. Below age 65 years, 29% of late deaths are due to noncardiac causes. Diabetics with CAD, particularly those requiring insulin or oral hypoglycemic agents, have a decreased long-term survival regardless of the method of treatment of their CAD. However, their survival is better with CABG than it is with either PTCA or medical management (Table 14) (89,128–132).

Table 14 Reported Survivals of Diabetics with CAD by Author, by Year, and by Duration Various Modes of Therapy

Ref. (yr)	Mean age (yrs)	Study	Survival in percent					
			1 yr	3 yrs	5 yrs	7 yrs	10 yrs	15 yrs
128 (94)	68	DM + CABG			72		48	24
		DM + MED			50		24	18
130 (91)	82	ND + CABG	88	83	64			
		DM + CABG	65	—	—			
131 (93)	59	ND + CABG		98	96	94		
		DM + CABG		96	89	81		
132 (91)	55	ND + CABG	95	93	91	86	76	64
		DM + CABG	92	88	85	74	63	41
89 (97)	62	TDM + CABG			81			
		TDM + PTCA			66			
129 (96)	57	ND + PTCA	97	95	92	87		
	60	DM + PTCA	93	90	82	74		

ND = nondiabetic; DM = diabetic; TDM = diabetic patients requiring insulin or oral hypoglycemic agents; +CABG = treated by coronary artery bypass; +PTCA = treated by balloon angioplasty.

Table 15 Reported Survivals Following PTCA or CABG by Author, by Year, by Duration and by Treatment

Ref. (yr)	Mean age (yrs)	Study	Survival in Percent				
			1 yr	3 yrs	5 yrs	7 yrs	9–10 yrs
129 (96)	57	ND + PTCA	97.9	95.0	91.6	86.6	82.3
	60	DM + PTCA	92.8	89.5	81.5	74.1	64.1
87 (94)	62	PTCA	96.5	92.9			
	61	CABG	97.9	93.8			
88 (96)	62	PTCA	96.5	91.8	86.3		
	61	CABG	96.5	93.8	89.3		
89 (97)	62	ND* + PTCA			90.5		
		ND* + CABG			89.7		
133 (94)	75	PTCA	87.5	77.5	63.0		
	75	CABG	85.0	72.5	65.0		
115 (94)	84	PTCA	88.0	83.0	55.0		21.0
	82		89.0	77.0	66.0		42.0

ND = nondiabetic; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass; ND* = includes nondiabetics and diabetics not requiring insulin or oral hypoglycemic agents.

Table 15 summarizes survival data following PTCA (115,119,87,88,133). Immediate mortality following PTCA in the elderly is consistently lower than that following CABG. In controlled studies, 5-year survival following PTCA closely approximates that following CABG (except for TDM) (88,89,133).

Table 16 lists long-term survival following medical treatment of CAD in the elderly (109,125). Although it is probable that, in these nonrandomized studies, patients treated medically were sicker than those treated surgically, the data that are available strongly suggest that elderly patients who undergo CABG fare better than their medical counterparts in terms of prolonged survival, relief of symptoms, and restoration of an active lifestyle. Cumulative 6-year survivals of 1491 patients 65 years old or older in the Coro-

Table 16 Reported Survivals Following CABG or Medical Management by Author, by Year, by Duration, and by Treatment

Ref. (yr)	Age (yrs)	Study	Survival in percent			
			1 yr	3 yrs	5 yrs	6 yrs
125 (85)	≥65	CABG	93	90	83	80
	65–69					81
	70–74					77
	≥75					75
	≥65	Med manag	89	78	68	63
	65–69					67
	70–74					51
	≥75					56
109 (92)	81	CABG		77		
	83	Med manag		55		

CABG = coronary artery bypass; Med manag = medical management.

nary Artery Surgery Study (CASS) were 80% in the surgical group and 63% in the medical group (125) Ko et al. (109) reported in 1992 that octogenarians treated by CABG had a better 3-year survival than those treated medically (77.2% vs. 55.2%). Peterson (106), describing Medicare data, noted that 1-year survival was 92.1% after CABG in 147,822 individuals 65 to 70 years old. Three-year survival was 86.9%. One- and 3-year survivals were 80.9% and 71.2% in 24,461 patients $\geq$ 80 years old.

Quality of Life

Freedom from Events

At 5 years 59 to 78% of elderly patients surviving CABG, 40 to 70% of those surviving PTCA, and 67% of those treated medically for CAD were free of recurrent cardiac events (126,133–135). The term ''cardiac events'' usually includes death or new Q-wave infarction but in some publications can also include reoperation, arrhythmia, and stroke.

Freedom from Angina

Severe intractable angina is the most frequent indication for CABG in the elderly. After CABG, 62 to 94% of patients were free of angina with follow-up ranging from 3 months to 8 years (12,109,116,120,125,133,135,136). Fifty-five to 82% of elderly patients treated by PTCA and 29 to 51% of those treated medically were free of angina (12,87,116, 125,133,135,137). Vogt et al. (137) reported that 85% of elderly patients treated by CABG were free of angina 6 to 12 months later, compared with 55% of those treated by PTCA and 51% of those managed medically. In general, PTCA and medically treated patients were more likely to be taking antianginal medications than were the CABG patients. The advantages of surgical treatment over medical treatment seem to decrease slowly over time, but are sustained for at least 10 years (136).

Post-Treatment Myocardial Infarction

The frequency of recurrent or late myocardial infarction 1 to 5 years after CABG in the elderly ranges from zero to 2%. Following PTCA, the frequency is 2 to 6%. After medical management, the frequency of a new myocardial infarction is as high as 28% (120,133,138).

Functional Status

In terms of mobility and ability to care for themselves or live independently, the elderly clearly benefit more from CABG than from medical management. When the high frequency of CABG following PTCA is considered, patients treated only by CABG probably have a better quality of life than do those treated only by PTCA.

Ko et al. (109) reported that CABG produced a significant improvement in functional capacity, lowering the NYHA classification from an average of 3.4 preoperatively to 1.2 postoperatively. Medical management did not (2.8 to 2.5). Similarly, Mullany et al. (116) found that 89% of the elderly undergoing CABG were returned to NYHA 1 or 2. Preoperatively 97% of the patients were NYHA class 3 or 4. Krumholz et al. (138), evaluating 93 octogenarians following hospitalization for an acute myocardial infarction, found that 1 year later 89% of those treated by CABG, 86% of those treated by PTCA, and 44% of those treated medically rated their quality of life as good or excellent. King et al. (87) reported that 44.5% of patients treated by CABG and 47% of those treated by PTCA were able to engage in moderate or strenuous activity.

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Akins et al. (126) commented that 86% of octogenarians who had undergone CABG were living at home or with their families. Krumholz et al. (138) found that 89% of octogenarians treated by CABG, 89% of those undergoing PTCA, and 55% of those treated medically for CAD were living independently. For comparison, earlier in this chapter, the comment was made that half of the general population 85 years old or older still lived alone or with their spouses (21).

Several authors have attempted to measure quality of life objectively. Vogt et al. (137), measuring outcomes in 98 individuals older than 70, found that patients undergoing CABG were significantly more able to engage in the basic and intermediate activities of daily living (ADL) than were those who underwent PTCA or medical therapy. Hlatky et al. (12) measured functional status following CABG or PTCA in a group of 934 patients with a mean age of 62 years. Employing the Duke Activity Status Index, he reported that improvement was significantly better after CABG than after PTCA (7.0 vs. 4.4). Chocron et al. (136), using the Nottingham Health Profile, found that 3 months after CABG 92% of elderly patients reported improvement in their social activities; 89% in their energy; 80% in their physical mobility; and 79% in their pain. Speziale et al. (139), using a questionnaire that evaluated five areas of activity, reported the results at 3 years from 203 patients treated by CABG, 107 patients treated medically, and 107 normal patients. Mean age was 60 years. The surgical patients scored significantly better than the medical patients, but both treatment groups scored significantly worse than the normals.

INDICATIONS FOR CABG IN THE ELDERLY

Compared with cardiac disease in the younger population, CAD in the elderly is more likely to be associated with severe complications of the disease and a higher mortality from those complications. Age, in itself, has been shown repeatedly to be an independent predictor of an increased operative mortality. Thus, the elderly face greater risks in the perioperative period while at the same time the durability of long-term benefits is necessarily limited. Nevertheless, conclusions drawn from the randomized studies together with data from multiple nonrandomized studies of coronary revascularization in the elderly have led to generally accepted indications for CABG in older patients. As summarized by Aronow (140), they are:

1. Significant left main disease.
2. Significant three-vessel disease, especially in the presence of a decreased left ventricular ejection fraction and ischemia.
3. Significant two- or three-vessel disease, a decreased left ventricular ejection, and significant stenosis of the proximal left anterior descending coronary artery.
4. ST-segment depression on resting ECG plus at least two of the following: New York Heart Association (NYHA) functional class III or IV, history of MI, history of hypertension, or all three without ECG changes.
5. Significant two- or three-vessel disease and exercise-induced ischemic ST-segment depression of 1.5 mm or greater.
6. Clinical evidence of CHF during ischemic episodes with ischemic but viable myocardium.
7. Unacceptable symptoms despite optimal medical management.

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COSTS

From the data presented, it is apparent that CABG and/or PTCA can not only extend the life of elderly patients with CAD, but also prevent further myocardial injury, restore function, and increase the quality of life. Costs, however, are a valid consideration as these procedures are performed in increasing numbers of the elderly. Peterson et al. (106) noted that the rate of CABGs performed in those aged 65 to 70 grew from 38.1/10,000/year in 1987 to 42.1/10,000/year in 1990. The rate in octogenarians grew from 7.2/10,000/year in 1987 to 12.0/10,000/year in 1990. The total number of bypass operations performed in octogenarians is expected to increase from 8000 in 1990 to more than 30,000 by 2050 at an in-hospital cost that will exceed $ 1.2 billion in 1990 dollars. In 1990 dollars, the mean hospital cost for a CABG performed in patients 65 to 70 years old was $21,700; for those in their 80s the mean cost was $27,200 (106).

The increased costs for CABG in the elderly result primarily from longer hospital stays and more intensive treatment rather than from the procedure itself. In turn, the prolonged stays are due to the presence and severity of coexistent disease, the generally more advanced stage of CAD at the time of surgery, and the increased frequency of postoperative complications in the elderly.

Smith et al. (141), reviewing economic outcomes in 1114 patients undergoing CABG, found that lower ejection fractions, higher age, congestive heart failure, presence of unstable angina, cardiomegaly, stroke, renal disease, and diabetes requiring insulin were significant patient factors that predicted higher costs. Lower age, higher ejection fractions, absence of diabetes, no prior PTCA, and male sex predicted earlier hospital discharge.

Comparative costs of PTCA and CABG are also valid considerations. It is generally accepted that the initial costs for PTCA are significantly less than the costs of CABG (35 to 84% less) (12). Over a period of time, however, the total cost of PTCA approaches that of CABG because of more frequent hospitalizations, more frequent revascularization procedures, and a greater cost for medications. Hlatky (12) concluded that over a 3- to 5-year period, balloon angioplasty has a significant cost advantage over CABG in patients with two-vessel disease. In patients with three-vessel disease, the costs were similar. In diabetics with CAD, bypass surgery was more cost effective than angioplasty.

SUMMARY

Coronary angioplasty or bypass is being performed for increasing numbers of patients in their seventh, eighth, ninth, and even tenth decade of life. Both silent and overt CAD are more common in the population over 65. Because CAD in the elderly presents more often in an atypical manner, diagnosis of the disease is frequently delayed. As a result, the elderly typically face the operation with a higher prevalence of complications of their CAD. Myocardial infarction, impaired myocardial function, and congestive heart failure are more frequent in the elderly. CABG's are performed more frequently as emergencies in older individuals, particularly those $\geq$80.

Nevertheless, it is clear from recent reports that elective CABG can be performed with operative mortalities in the 1.0 to 4.0% range even in 70- and 80-year-olds. Survival of the elderly treated by CABG approximates that of a general population of like age and is markedly superior to that achieved by medical management. It is also true that CABG

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in older individuals improves the quality of life over and above that observed following alternative methods of treatment, particularly medical management.

While the costs of performing CABG in the elderly are higher than they would be for a younger population, it is not clear that these costs are higher in the long run than they would be for nonoperative treatment with its associated costs of repeated interventions and hospitalizations.

Greater efforts directed toward detection of ischemic heart disease in the older population and performance of earlier, elective surgery could significantly reduce both the mortality and disability associated with CAD in the elderly. Delay in operation until the patient has a complication of CAD, particularly a myocardial infarction, has a markedly adverse outcome in both the short term and the long term.

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15

Percutaneous Transluminal Coronary Angioplasty in the Elderly

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The number of elderly patients in our society who have symptomatic coronary artery disease is steadily increasing. As this trend continues, 20 to 25% of the population in most western countries will be elderly by the middle of the next century (1). The number of patients in the category of ''very old'' is also increasing steadily; currently more than 7 million people older than 80 years of age live in the U.S. (2). Coronary artery disease is a disease of aging and up to 60% of patients over age 60 have significant atherosclerotic disease in at least one coronary artery (3). The relative number of older patients being treated for coronary artery disease is thus increasing steadily. For example, at some medical centers in the U.S., more than 50% of patients undergoing either angioplasty or bypass surgery are over the age of 65 years (4–6).

Despite the large number of elderly patients being treated for coronary artery disease, prospective randomized trials of medical versus bypass surgery have excluded older patients, and more recent randomized trials of angioplasty versus bypass surgery have not included large numbers of older subjects. Nevertheless, a careful analysis of the rapidly expanding experience of angioplasty as well as other treatments for coronary artery disease in the elderly allows the clinician to draw informed conclusions and make intelligent decisions regarding treatment options.

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY FOR CHRONIC CORONARY ARTERY DISEASE

An increased morbidity and mortality for elderly patients undergoing coronary bypass surgery is well established (4,7–13). However, symptomatic coronary artery disease, especially angina pectoris, may be more refractory in the elderly (14), and older patients do not tolerate medical therapy as well as younger patients; older patients have a higher incidence of intolerable side effects (15–17). Thus, the attraction of angioplasty as a less invasive alternative for myocardial revascularization is obvious. However, because of the

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higher incidence of comorbid medical conditions and other factors related to aging, the results of percutaneous transluminal coronary angioplasty (PTCA) will be less desirable than in younger patients.

Characteristics of the Elderly Angioplasty Population

Elderly subjects undergoing PTCA are sicker than younger patients undergoing PTCA. They have a higher incidence of multivessel coronary artery disease, prior myocardial infarction, and lower left ventricular ejection fraction (6,18–22,23). For example, one series found that multivessel disease was present in more than 50% of patients older than age 75 undergoing PTCA, versus 33% of younger patients (24). Another study of octogenarians undergoing angiography found that only 31% were suitable candidates for PTCA, primarily because of diffuse occlusive coronary artery disease; 13% of patients older than age 80 had left main coronary artery disease (24). Patients undergoing angioplasty also have more complex target stenoses, and a greater frequency of type C lesions occurs in the elderly (25). The older angioplasty population also has more severe symptoms with a greater frequency of class III and IV angina and more frequent unstable angina (6,19,20,23,26–30). Unstable angina is present in 70 to 80% of patients who are older than 65 and are undergoing PTCA. (6,18–20,26–30). The frequency is even higher in those over 80 (19,27,31–33), whereas the incidence of unstable angina is approximately 50% in younger patients (21,29).

Elderly patients undergoing angioplasty also have a higher incidence of comorbid medical conditions. Hypertension and diabetes are more frequent (6,21,29) and a history of congestive heart failure is more than twice as common in older patients as in younger ones. In one multicenter registry study, the incidence of previous congestive heart failure was 9% in those older than 65 years, but 4% in younger subjects (20). In patients over 75, the incidence of previous heart failure is 17 to 24% (6,20). The older angioplasty population also has a higher proportion of women. Female patients account for only 8 to 21% of patients aged less than 65 years (20,23,29), but this increases with the age of the patient group. In populations over age 75, 40 to 50% of those undergoing angioplasty are women (6,20,27).

Procedural Outcome

Although initial reports of angioplasty in the elderly described a lower acute success rate, the technical rate of success for PTCA in the elderly is now high and is essentially equivalent to that achieved in younger patients (6,18,25–27,30,31,33,34–44). Series of angioplasty cases from more recent years show striking improvement in technical success rate, which is now consistently in the range of 88 to 93%, even in very elderly patients (12,13,18,23,27,34,37–39,45). Despite this high technical success rate, elderly patients, especially the ''old old'' have a higher rate of complications, especially procedure-related mortality (6,20,26,27,41). For example, in our series of elderly patients undergoing angioplasty at the Mayo Clinic from 1980 to 1989, mortality was increased significantly in the oldest age group. The mortality associated with PTCA was 1.2% in patients aged 65 to 74 years, but 6.2% in those older than 75 years (6). Bedotto and colleagues (18) reported a similar mortality rate in comparable patients having procedures during a similar time frame. Series of PTCA in octogenarians have reported procedural mortality rates of 2 to 19%, with an average of 8 to 10% (19,31–33,46–49). A study of over 20,000 patients

from the Medicare provider data file reported a hospital mortality rate of 7.0% in patients over 80 years (50). At our institution, the rates of major procedural complications after angioplasty in the elderly are much lower in all age subgroups since 1990 than in previous years (45). However, the relative mortality is still highest in the oldest patients. For angioplasties performed from 1990 to 1992, the hospital mortality rate was 0.8% in patients 65 to 74 years old and 3% in those over age 75. Compared with the era prior to 1990, the rate of procedure-related myocardial infarction in patients over age 65 has fallen from 3.9 to 2.2%, and, even more strikingly, the rate of emergency bypass surgery has fallen from 5.5 to 0.65% (45). Numerous technical advances account for this improvement in procedural outcome such as lower profile balloons, use of stents and other bailout devices, perfusion balloons, in-laboratory monitoring of anticoagulation status, and increasing operator experience. However, the magnitude of the improvement in hospital outcome is quite striking.

Age appears to be an independent predictor of procedure-related mortality of PTCA in the elderly (6,38). No increased incidence of abrupt vessel closure in older patients occurs; the increased procedural mortality appears to be related to lower reserve in frail, older patients who tolerate ischemic complications poorly (25).

Nonfatal morbid complications are also more common in older patients. For example, Maiello and colleagues (38) described a 1.1% rate of renal insufficiency and a 5.4% rate of requirement for blood transfusion in a group of patients over 70 years of age undergoing PTCA. Very old patients also have longer average hospital stays after PTCA (27). However, unlike the experience with cardiac surgery, the incidence of major strokes after PTCA is extremely low, even in very elderly patients.

Many elderly patients who undergo angioplasty are poor surgical candidates and some undergo PTCA as a ''salvage'' procedure. In other words, they are referred for PTCA with the understanding that complications will be treated medically. The rate of emergency bypass surgery in the very old is less than that in younger patients (6,18,26), indicating that physicians are sometimes less inclined to refer very old patients for emergency bypass surgery.

Thus, though the rate of procedure-related mortality and other complications is increased in elderly patients undergoing PTCA, especially the very elderly, the rate of complications is improving and is very acceptable, especially when compared with the rates of morbidity and mortality of bypass surgery in the aged.

Predictors of Poor Early Outcome

The strongest predictor of hospital death or myocardial infarction after angioplasty in the elderly is multiple diseased coronary segments (51). Elderly patients with multivessel coronary artery disease likewise do less well than do those with less extensive disease. Maiello (39) described a clinical success rate of 100% for angioplasty patients older than 75 years with single-vessel disease, but in the subgroup with three-vessel coronary artery disease the success rate was only 52%, and mortality rate was 14% (39). Calcified coronary lesions were reported to predict unsuccessful PTCA in one study (26) of elderly patients, but not in another (51).

Long-Term Outcome After PTCA in the Elderly

Overall intermediate-term survival after PTCA is good, even in very old patients (6,19,23,26,34,36,42). For example, in patients older than 75 years undergoing angio-

plasty, Regnen (42) reported 87% survival at 3 years and Buffet (26) and Thompson (6) reported 4-year survivals of 83% and 86%, respectively. The rates of overall survival are almost as good for patients older than 75 years as they are for those 65 to 75 years. (6) However, event-free survival is not as good as in younger patients undergoing angioplasty and a higher rate of recurrent angina exists in the oldest patients undergoing angioplasty (6,28). The higher recurrence of angina is in contrast to the results with coronary bypass surgery, in which angina relief in older patients who survived surgery is at least as good as in younger surgical patients (7,8,10,12,52,53). This less durable angina relief in the oldest patients does not appear to be related to an increased rate of restenosis. For example, Jackman and colleagues (31) reported a restenosis rate of 31% in patients older than 80 years and Macaya (29) reported a restenosis rate of 44% in patients older than 65 and undergoing angioplasty. These results are similar to restenosis rates in other age groups (54–59).

The extent of coronary artery disease is an important determinant of overall survival as well as event-free survival. For example, de Jaegere (34) reported an 81% event-free survival postangioplasty in patients over 70 years who had single-vessel disease vs. 45% in patients with multivessel disease. Using multivariate analysis, the extent of coronary artery disease was the strongest predictor of long-term event-free survival after PTCA in our analysis of the Mayo Clinic experience (51). Other baseline variables found to be predictors of long-term event-free survival are left ventricular systolic function, unstable angina, and the number of concomitant medical diseases (51,60).

The heterogeneity of the elderly population is emphasized by high- and low-risk subgroups that can be identified. For example, in the Mayo Clinic series we found that an elderly patient undergoing angioplasty with a single significant coronary stenosis, no recent congestive heart failure, and no other important medical illnesses had only a 4% event rate of death or myocardial infarction after 3 years. On the other hand, the event rate was 33% in the high-risk group, such as one with three significant coronary segment stenoses, recent congestive heart failure, and two other concurrent medical illnesses (51) (Fig. 1).

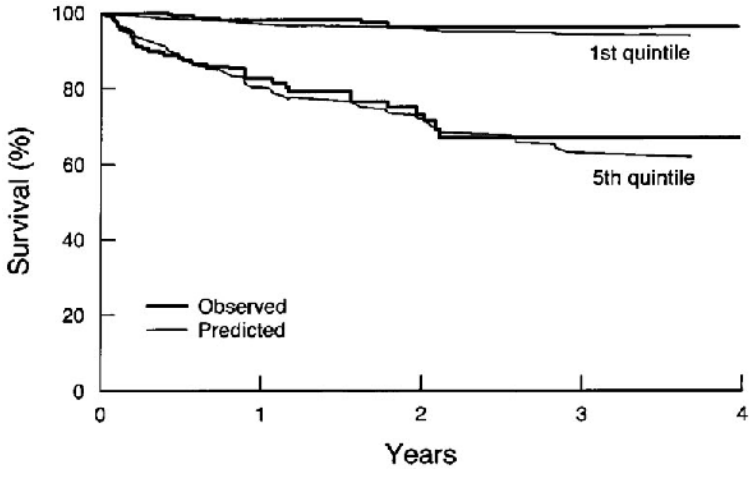

Figure 1 Survival free of myocardial infarction (MI).

O'Keefe et al. (60) reported that incomplete revascularization is a predictor of late mortality after angioplasty in elderly patients; but incomplete revascularization is highly correlated with extensive coronary artery disease, and completeness of revascularization was not an independent predictor of event-free survival in an analysis performed by de Jaegere (34) or in our series (51).

More recent data from Mayo Clinic compared the outcome of older patients undergoing nonemergent coronary angioplasty from 1980 to 1989 with 1990 to 1992 (61). In the former there were 982 patients $\geq$ 65 years of age (group A) and in the latter 768 patients $\geq$ 65 years (group B). Patients in group B were older (73.5 $\pm$ 5.7 years vs. 72.4 $\pm$ 5.4 years; $p < 0.001$); had a higher incidence of prior CABG (21.4% vs. 14.6%; $p < 0.001$); and had more diabetes (19.8% vs. 15.7%; $p < 0.05$) and more concomitant disease. Despite the increased complexity of these patients, the angiographic outcome was improved. The success rate per patient in the early cohort was 86.4% compared with 92.0% in the later cohort ($p < 0.001$) (Table 1). In the cohort from 1990 to 1992, the procedural success rate did not vary whether the patient was 65 to 69 years, 70 to 74 years, or $\geq$75 years, and was >91% in each.

The mean follow-up period was 58 $\pm$ 25 months for the initial group and 17 $\pm$ 1 months for the latter group. A risk stratification model was developed based upon quintiles of risk in the initial group and was applied to the patients treated from 1990 to 1992 (group B). For each risk quintile, the event-free survival in the latter group was lower than expected. The authors (61) concluded that the technical success rate is substantially higher and acute complication rates are substantially lower for coronary angioplasty in elderly patients treated from 1990 to 1992 despite an increase in patient age and extent of coronary artery disease compared with patients treated from 1980 to 1989. Despite improved initial success rate, these findings have not translated into improved intermediate event-free survival. Whether this relates to changes in patient characteristics or other issues remains uncertain.

Table 1 Outcome

	Group A (1980–1989) $n = 982$	Group B (1990–1992) $n = 768$	p value
No. of segments	1421	1097	
No. of vessels dilated (%)			
1	80.7	83.1	
2	18.1	16.4	0.19
3	1.2	0.52	
Success rate/segment (%)	86.4	92.0	<0.001
Success rate/patient (%)	88.1	93.5	<0.001
No. of grafts attempted	69	87	0.007
MI	38 (3.9)	17 (2.2)	0.049
Ventricular arrhythmia	38 (3.9)	20 (2.6)	0.14
Abrupt coronary artery occlusion	67 (6.8)	25 (3.3)	0.001
CABG within 24 h	54 (5.5)	5 (0.65)	<0.001
Death	32 (3.2)	11 (1.4)	0.014
Death or MI	62 (6.3)	26 (3.4)	0.005

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Completeness of Revascularization

Complete revascularization is logical and desirable when feasible. However, many elderly patients are treated conservatively in an attempt to limit procedure-related complications. For example, a strategy of ''culprit vessel angioplasty'' is often applied in frail, elderly patients. Thirty-three to 53% of elderly patients having PTCA receive complete revascularization at the time of the procedure (23,27,39,60,62); complete revascularization is obtained in only 16 to 25% of patients with three-vessel disease (62,63). In patients undergoing cardiac surgery, the importance of complete revascularization is well documented (64–66). With angioplasty, incomplete revascularization is associated with a high rate of subsequent bypass surgery and recurrent angina (18,41,62). However, incomplete revascularization after angioplasty does not independently influence survival of patients with multivessel disease, which is instead influenced by baseline clinical variables (34,62,67). Though achieving as complete a revascularization as possible with angioplasty is desirable and logical, whether more aggressive procedures are beneficial in elderly patients is not clear. More extensive PTCA could increase the complication rate and instance of restenosis. Also, unlike bypass surgery, PTCA is easier to repeat. One logical approach is to attempt to dilate all functionally significant stenoses rather than plan the procedure based on purely angiographic anatomy. Elderly patients have a higher instance of silent ischemia and more events occur in elderly patients who have silent ischemia (68), but no data exist on whether angioplasty would alter the prognosis in these patients.

COMPARISON OF PTCA WITH BYPASS SURGERY IN THE ELDERLY

Randomized trials of bypass surgery versus multivessel angioplasty have not included large numbers of elderly patients, but conclusions can be drawn from the large reported clinical experience of revascularization in older patients. In the Emory Angioplasty Surgery Trial (EAST), the average patient age was 61.6 years (69). The hospital mortality rate (1%) was identical for patients receiving surgery or PTCA and, at the end of 3 years, survival was 94 and 93%, respectively. The main difference observed was the need for repeat revascularization. At the end of 3 years of follow-up, only 13% of the patients in the bypass group required additional revascularization, compared to over half the patients in the PTCA group. Other randomized trials have roughly similar patient populations and have so far reported roughly similar results (70–72).

The Bypass Angioplasty Revascularization Investigation (BARI) (73) is the largest randomized trial comparing PTCA and CABG. Seven hundred and nine patients were 65 to 80 years at baseline. These older patients were more likely to have unstable angina, congestive heart failure, peripheral vascular disease, and hypertension. The in-hospital and 30-day mortality was higher in older patients; however, in the older patients, the percentage was identical, at 1.7%, for both PTCA and CABG. During follow-up, the older patients had less recurrent angina than younger patients. In patients over age 65, patients treated with CABG had better relief of angina and less repeat procedures similar to that seen in the trial as a whole. In nondiabetics, there was no difference in mortality at 5 years.

Mortality Rate

For elderly subgroups, indirect comparison of PTCA and bypass surgery is available. In a nonrandomized retrospective study of angioplasty versus bypass surgery in patients over the age of 70, O'Keefe and colleagues (60) found that short-term mortality was lower in patients receiving PTCA, but mortality crossover occurred after 1 year. Mortality curves were essentially parallel between the first and the fifth years. As in the EAST trial, this retrospective study found that after angioplasty, more patients required repeat procedures. At the end of 5 years, 50% of patients undergoing angioplasty had had repeat revascularization procedures versus only 10% of the surgical group (60). This study's findings of a higher hospital mortality rate for the surgical group are consistent with generally higher operative mortality rates in the elderly surgical population versus the elderly angioplasty population (46,47,49,69,74,75). Also, in a nonrandomized retrospective study by Vacek (76), of patients having angioplasty or bypass surgery, the average patient age was 65 years of age. The results were similar to those of O'Keefe in that long-term survival was similar, but a greater incidence of subsequent need for repeat revascularization occurred in the angioplasty group. Very elderly patients who survive bypass surgery have good angina relief (52,77). Recurrent angina appears to be more frequent in very old patients who undergo angioplasty, but this may be related to difficulty in achieving full revascularization in many of the oldest patients (6,28). Thus, in the elderly patients, bypass surgery can be considered more definitive and durable, but also riskier, than PTCA.

Stroke and Cognitive Dysfunction

Important differences also exist in the frequency of nonfatal complications. Stroke after bypass surgery becomes more frequent with advancing age. The largest surgical series to report stroke rates found an incidence of 2.5% in patients over 65 years, compared with 1% of the younger patients (10). Though this risk of stroke is relatively low, the increased risk strongly favors consideration of PTCA as an alternative. Also favoring PTCA are disturbances in cognitive function, which frequently occur in older patients after bypass (53,78). Reversible postoperative confusional states are fairly common in the elderly. Also, neuropsychological testing indicates that as many as 60% of patients undergoing cardiac surgery with cardiopulmonary bypass have some postoperative neuropsychological disturbance (79,80). Elderly patients are more likely to develop these deficits (81). Most patients return to baseline by 6 months, but the decline in function is permanent in 20 to 30%. A decline in cognitive function is frankly symptomatic in about 10% of the total patient population (82,83). Cost is also a consideration, and length of stay is understandably longer in older patients, especially those having bypass surgery (59,84).

Predictors of Outcome

Factors shown to predict poor outcome with bypass surgery in the elderly include: depressed left ventricular systolic function, previous myocardial infarction, class IV symptoms, cigarette smoking, hypertension, previous bypass surgery, cachexia, female sex, and emergency surgery (8,10,11,13,75,85–90). Of these factors, several have not been shown to be important in angioplasty procedural success, including emergency procedure, cachexia, and previous myocardial infarction. For long-term success, measures of poor

Table 2 Factors Predicting Adverse Outcome After Revascularization

In-hospital outcome	
Bypass surgery	PTCA
Age	Age
Cachexia	Extent of coronary artery disease
Emergency surgery	Calcified coronary lesion[a]
Depressed LV ejection fraction	
Cigarette smoking	
Hypertension	
Previous bypass surgery	
Prior MI	
Renal insufficiency	
Female sex[a]	
Other medical illness	
Late outcome	
Bypass surgery	PTCA
Number of associated medical illnesses	Extent of coronary artery diseases
Left ventricular function	Left ventricular dysfunction
Peripheral vascular disease	Unstable angina
	Number of associated medical illnesses

[a] Found to be predictive in some studies but not others.

left ventricular systolic function predict lower event-free survival after both angioplasty and surgery in the elderly. For acute success for PTCA, this factor seems to be a relatively less important predictor (10,11,51,91). Left ventricular systolic function is also an important determinant of long-term outcome. The number of associated medical diseases is an important predictor of long-term survival in both the elderly surgical population (10,91) and the elderly angioplasty population (51). Factors that predict adverse outcome after revascularization in the elderly are listed in Table 2.

PTCA FOR ACUTE MYOCARDIAL INFARCTION IN THE ELDERLY

Prompt and complete restoration of coronary blood flow in the infarct-related artery (IRA) is the principal mechanism by which reperfusion therapy improves survival after acute myocardial infarction (AMI). Primary PTCA has several advantages over lytic therapy, including the fact that there are fewer contraindications to it. In elderly patients, thrombolytic therapy often is not used. It does improve mortality; however, the decrease in the mortality in the elderly in second International Study of Infarct Survival and Gruppo Italiano per lo Studie della Streptochinasi nell' Infarto Miocardio (GISSI) study was modest in comparison to the placebo arm. There is also a higher incidence of hemorrhagic strokes in elderly patients. In elderly patients treated with rtPA, the incidence of hemorrhagic stroke may be higher than with SK treatment.

The use of primary angioplasty in the elderly has been reported in various small

series. The procedural success rates vary from 61 to 92%. In-hospital mortality in these patients is significantly higher as compared to the younger population and varies from 11 to 35%. This high mortality is due to a number of factors, including a higher prevalence of comorbidities, higher prevalence of triple-vessel disease, poor left ventricular function, and higher complication rates during the procedure, in particular bleeding complications. In a recently published abstract (92), the overall in-hospital mortality after primary angioplasty in patients over 80 years of age was 11.6% and was significantly higher in comparison to the group aged between 60 to 69 years, where it was 4.2%. Successful reperfusion was achieved in 92% and was comparable to the younger group.

The effect of age on outcome in patients treated with primary angioplasty compared with thrombolysis was assessed in the GUSTO IIb trial. For each 10-year patient group, the outcome with PTCA was improved compared with tPA. However, regardless of the treatment given, the risk increased with age. Each increment of 10 years of age increased the risk of death or myocardial infarction by 1.32 (CI 1.04–1.76; $p = 0.022$).

Primary angioplasty is an excellent alternative to lytic therapy in elderly patients with AMI. This includes patients with a contraindication to the lytic therapy such as patients with stroke, trauma, recent major surgery, or severe hypertension. Given the available literature, it would be appropriate to conclude that primary angioplasty may well be the treatment of choice in elderly patients, provided it can be accomplished safely and rapidly in an experienced center. Even with PTCA, the risks in elderly patients are increased.

USE OF INTRACORONARY STENTS IN THE ELDERLY

Intravascular stents have become the most widely used procedure in interventional cardiology replacing conventional PTCA. These have been found to be effective in treating abrupt or threatened closure as well as prevention of restenosis. There is relatively limited published experience with stenting in older patients.

For elective placement of the Palmaz-Schatz intracoronary stent, the technical success rate has been reported to be lower in very elderly patients. Yokoi et al. (93) reported a technical success rate of 86% in patients over 75 years vs. a 95% success rate in those aged 65 to 74 years. The oldest patients had a higher incidence of calcified vessels and other unfavorable lesion characteristics. The hospital mortality rate was 4.1% in the over-75-year group vs. 1.2% in the 65- to 74-year-old group (93).

Chevalier et al. (94) evaluated the results of therapy in 142 patients $\geq$ 80 years compared with 3484 patients $<$80 years. Older patients had more unstable angina, multivessel disease, and type C lesions. The majority of patients in each group were treated with stents (77.5 and 80.5%, respectively). Clinical success was lower in older patients, at 90.8% vs. 95.5% in younger patients ($p < 0.05$), but there was no difference in subacute closure, Q-wave infarction, coronary surgery, or death. Batchelor et al. (95) studied 3740 octogenarians in the National Cardiovascular Network database. Similar to that seen by Chevalier et al. (94) the procedural success rate without major complications was achieved in 90.2% of cases. In-hospital death occurred in 3.5% and death/infarction/stroke in 5.17%. After risk adjustment, stents were associated with higher procedural success and lower need for repeat revascularization, but with higher vascular complications.

These preliminary reports appear promising. The longer term outcome may continue to be problematic. De Gregorio et al., in a study of 137 consecutive patients $\geq$ 75 years,

Table 3 Bypass Surgery vs. PTCA in the Elderly

Characteristics favoring bypass surgery	Characteristics favoring PTCA
Left main coronary disease	Limited coronary disease
Poor LV function	Multiple medical problems
Extensive coronary disease	Frail physical condition
Few other medical problems	Good LV function
Younger physiological age	Patient attitude
Patient attitude and ability to convalesce	

found that restenosis and need for repeat revascularization were more common in older patients.

WHO SHOULD HAVE CORONARY BYPASS SURGERY RATHER THAN ANGIOPLASTY?

As with younger patients, bypass surgery improves survival in elderly patients with left main stenoses and those with three-vessel coronary artery disease and poor left ventricular systolic function (7,91,96,97). Patients with decreased left ventricular contractile function do not do as well with angioplasty compared to bypass surgery (6,98,99). Thus, in elderly patients who have multivessel coronary disease with poor left ventricular systolic function, bypass surgery may be more appropriate than PTCA, especially if complete revascularization can be achieved surgically but not with PTCA.

Elderly patients in whom angioplasty may be more appropriate than bypass surgery include those who are frail or who have multiple medical problems and would probably have morbid surgical complications. Also, elderly patients who are at increased risk of stroke with surgery because of preexisting cerebral vascular or diffuse aortic disease should be considered for angioplasty, as should patients who would appear to be at increased risk of postoperative cognitive dysfunction. Older surgical patients should be prepared for a 3- to 4-month convalescence. Characteristics favoring bypass surgery vs. PTCA in elderly patients are shown on the following page in Table 3.

GOALS OF THERAPY

In the ''young old,'' the goals of revascularization therapy are similar to those in younger patients. Symptom relief, maintenance of an active lifestyle, and (to a slightly lesser extent) improvement in long-term survival are the focuses of treatment. However, in the ''old old,'' for example, those over 80 years of age, the objectives are different. Given the increased risk of intervention, relief of disabling symptoms and maintenance of independence are the primary goals. The key is patient selection. Many patients, despite advanced age, are not willing to accept significant limiting symptoms of angina pectoris. For them, PTCA, when feasible, is appropriate therapy with very acceptable limitations and risk given the caveats discussed above.

Our society is faced with an aging population and a large fraction of health care expenditure is devoted to the care of older patients with coronary artery disease. The

efficacy and feasibility of aggressive cardiovascular intervention are not in dispute, but the cost and resources to be devoted to the elderly are a societal issue that should be addressed in the current era. To this end, prospective databases that encompass the socioeconomic diversity of our society should be developed.

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16

Exercise Training of the Elderly Cardiac Patient

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MAGNITUDE OF THE PROBLEM

Coronary heart disease affects 13.5 million Americans, many of whom are elderly. More than half of the 1.5 million episodes of myocardial infarction that occur annually involve patients older than 65 years of age. In the mid-1990s, 55% of the more than 300,000 patients who underwent coronary artery bypass graft (CABG) surgery each year were 65 years of age and older, as were 45% of the patients who had percutaneous transluminal coronary angioplasty (PTCA) and other transcatheter interventional procedures. Approximately one-fifth of the U.S. population older than age 80 has clinical evidence of coronary heart disease. Although coronary events are more frequent among men than among women at middle age, these events occur with equal frequency in both sexes at elderly age (1). Heart failure is the most common discharge diagnosis for hospitalized Medicare patients. Importantly, elderly patients are at high risk for physical disability following a coronary event (2), such that exercise training has substantial potential to improve their functional outcome.

Physical activity, and particularly vigorous physical activity, decreases progressively with increasing age (3–5). Elderly individuals constitute an increasing proportion of the U.S. population; by the year 2000 an estimated 35 million people will be older than 65 years of age. The subset older than 85 years of age is the fastest-growing segment.

CHANGES IN THE CARDIOVASCULAR RESPONSES TO EXERCISE AND TO EXERCISE TRAINING AT ELDERLY AGE

Cardiovascular Responses to Exercise

Because of the decreased compliance of the aged ventricle, there is an increased dependence on late diastolic filling to maintain the exercise cardiac output. Because the cardiac filling pressures increase more with exercise at elderly age in response to the left ventricular diastolic dysfunction and increased left ventricular mass, there is a mechanical disadvantage of the aged heart. Nonetheless, these increased exercise-related filling pressures

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permit an increase in stroke volume that compensates for the decrease in cardiac compliance. The large end-diastolic volume and resultant increase in stroke volume is the major contributor to the increase in cardiac output needed for the exercising elderly individual (6).

There is decreased responsiveness to beta-adrenergic stimulation with aging; as a result, the needed increase in exercise cardiac output is dependent on the Frank Starling mechanism noted above rather than on the increase in heart rate and decrease in end-systolic volume seen at younger age.

Exercise recommendations at elderly age must address these cardiovascular changes of aging, as well as those related to physical inactivity, and those reflecting the cardiac dysfunction related to coronary heart disease (7).

Cardiovascular Responses to Exercise Training

As is the case at younger age, the hemodynamic benefits of exercise training reflect predominantly peripheral adaptations. There is improved extraction of oxygen by trained skeletal muscle from the perfusing blood, resulting in a decrease in cardiac work. As well, owing to the decrease in systemic vascular resistance, the adaptations of the skeletal muscle, and the autonomic nervous system, there is a resultant decrease in rate-pressure product, limiting the myocardial aerobic requirements for any submaximal task. The decrease in myocardial oxygen demand, particularly in coronary patients with residual myocardial ischemia, limits the activity-induced angina that often is a barrier to the performance of activities of daily living. Stated otherwise, after exercise training, coronary patients function farther from their ischemic threshold in the performance of daily tasks, because these tasks require a lesser percentage of their improved physical work capacity. This is the physiological basis for the improvement in stamina and endurance that is described in the trained elderly coronary patient who now accomplishes routine activities with less fatigue.

HABITUAL PHYSICAL ACTIVITY AT ELDERLY AGE

Physiological Variables That Limit Habitual Physical Activity at Elderly Age

The three major physiological variables that limit the habitual preillness physical activity level of elderly individuals are decreased aerobic capacity, ventricular diastolic dysfunction, and increased work of breathing.

There is a progressive age-related decrease in aerobic capacity, although this is not as pronounced as previously described, once the maximal oxygen uptake is corrected for the decrease in lean body mass that is characteristic of aging (8). As a result, the performance of any submaximal task entails a greater percentage of the lowered functional capacity, and therefore is perceived by the elderly individual as requiring a higher intensity of work. Although there is limited information as to the extent of the decrease in muscle mass that is primarily an aging phenomenon and that related to habitual physical inactivity, the adoption of a physical activity regimen even in very elderly populations can increase muscle mass, maximal oxygen uptake, and improve functional status (9–11). Among women, who comprise a large proportion of the elderly patients with a coronary event, the decrease in habitual physical activity and resultant deconditioning is far greater than that of their age-matched male counterparts.

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Diastolic dysfunction, a characteristic of the aged ventricle, limits early diastolic filling; the resultant exercise-related dyspnea, even at low intensities of exercise, causes elderly individuals to overestimate the intensity of their physical activity (12). Resistance to atrial emptying may produce symptoms of dyspnea, even at very low intensities of exercise, increasing the perception of increased work when indeed this is not the case. Continued physical activity does not increase the dyspnea, and recent studies suggest an improvement in the diastolic dysfunction of aging with habitual physical activity (13).

The increased work of breathing characteristic of the decreased compliance of the aged lung further enhances the perception of greater work intensity for any submaximal task. However, although pulmonary function declines with aging, the decline is not sufficient to limit physical work capacity unless underlying pulmonary disease is present.

Thus many elderly individuals perceive that they have not reduced their activities of daily living and exercise since younger age, when in fact they perform at substantially lower levels (7).

Influence of Comorbidity and Societal Features

The habitual physical activity level at elderly age is often also unintentionally limited, owing to combinations of musculoskeletal instability, decreased muscle mass and muscular contractile strength, other concomitant illnesses, peripheral vascular disease, anxiety, depression, and/or loss of motivation, as well as cardiovascular symptoms. Important concomitant illnesses include arthritis and other orthopedic problems, neurological problems, nutritional deficiencies, decrease in pulmonary function, psychological problems; and a distorted perception of exertion, as previously discussed. Family, friends, and medical personnel may also inappropriately recommend restriction of levels of physical activity.

About half of individuals older than 60 years of age in the U.S. describe themselves as sedentary; it is likely that a substantial component of the decreased functional capacity of elderly age reflects this sedentary lifestyle. The decrease in habitual physical activity is more prominent for elderly women than for elderly men, possibly related to their prior lack of physical activity or to the comorbidities of arthritis, osteoporosis, and other musculoskeletal complications.

As well, many physicians often underestimate the habitual activity level of their elderly patients and fail to recommend initiation of activity as would be the case for patients of younger age with a comparable cardiac problem. The deconditioned elderly patient, with limitation of ability to perform daily tasks and maintain independence, becomes anxious, depressed, involved in a vicious circle of lessening activity.

Little of the habitual decrease in physical activity characteristic at elderly age reflects the precipitation of cardiovascular symptoms. More frequently, it relates to anxiety, depression, loss of motivation, with musculoskeletal instability and fear of falling also contributory. Although some reduction in physical activity relates to lessened muscular strength owing to the gradual decrease in lean body mass and muscle with aging, this component can be substantially limited, and even reversed, with the reinstitution of physical activity. Patients often fail to appreciate their decrease in activity with aging, because even a lesser work intensity represents a greater percentage of their lowered functional capacity.

With aging of the population, and predominance of women in this aged population, the appropriate institution of a physical activity regimen has the potential to substantially improve functional status and reverse the habitual physical inactivity of elderly age.

Recommendations for Physical Activity in the Absence of Cardiovascular Illness at Elderly Age (Primary Prevention) (14)

The U.S. National Council on Fitness and Aging classifies physical activities for elderly persons as follows:

1. Activities with little energy expenditure that occur too intermittently to promote endurance: light housework, walking at 1 to 2 mph on level ground, playing golf using a powered cart, or bowling.
2. Activities that build moderate endurance if carried out continuously for 15 to 30 min: cleaning windows, mopping floors, walking 3 mph on level ground, cycling at 6 mph, and playing golf pulling a cart.
3. Activities that promote good endurance if carried out for 15 to 30 min: walking at 3.5 to 4 mph, cycling at 8 to 10 mph, playing golf carrying clubs, skating (ice or roller), aerobic dancing, and swimming at less than 20 yards/min.

Enjoyable recreational activities are more likely to be undertaken at elderly age (15). Very low-level physical activities, appropriate for previously very sedentary elderly individuals, entail a 1- to 2-MET energy cost. Such activities include sewing, knitting, or painting while seated, as well as walking slowly (1 mph). In the 2- to 3-MET range are activities such as riding a lawn mower, driving a car, light woodworking, and playing the piano and other musical instruments. Progressing to the 3- to 4-MET range involves physical activities that include golfing using a golf cart, bowling, horseshoe pitching, and pushing a light lawn mower. The 4- to 5-MET range involves cycling at 8 mph on level ground, swimming, slow dancing, gardening, and raking leaves. The 5- to 6-MET range activities recommended by the U.S. National Council on Physical Fitness and Aging for elderly patients with a well-preserved exercise capacity include walking at 4 mph, ice- or roller-erskating, and swimming, with the latter characterized by less musculoskeletal discomfort owing to the buoyancy of the water.

In one study, exercising older subjects developed disability at a rate only one-fourth of that of sedentary controls; mortality was reduced; and medical care costs of exercisers were 25% less than controls (16).

EARLY AMBULATION AFTER MYOCARDIAL INFARCTION AND MYOCARDIAL REVASCULARIZATION PROCEDURES: IN-HOSPITAL PHYSICAL ACTIVITY

Elderly patients with both myocardial infarction and myocardial revascularization procedures have more complications than are characteristic at a younger age, with increased requirements for ventilatory support, cardiovascular support, etc. These result in longer periods of immobilization and bed rest during the hospital stay, longer hospital stays, and longer stays in an intensive care setting.

This increased likelihood of immobilization at bed rest results in deconditioning. Bed rest, even for as little as several days, often results in orthostatic intolerance and reflex tachycardia, impairing functional status when physical activity is resumed; this is secondary to the hypovolemia, to which elderly individuals are particularly susceptible, as a result of the protracted bed rest.

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Sitting in bed or in a bedside chair for 15 to 30 min several times daily provides adequate orthostatic stimulus to induce neurohumoral adaptive responses that limit the hypovolemia. This level of activity is well tolerated even by most elderly patients with complications of their coronary event. In one study (17), walking following a meal reversed the hypotensive effect of digestion even in a population of elderly nursing home residents, with the potential of this intervention to limit postprandial hypotension and resultant falls.

During the hospital stay, gradual progression of activity, beginning with stretching and range-of-motion exercise, can be followed by gradually progressive increases in the pace and distance of walking. Maintenance of this activity at home requires appropriate reinforcement both by family and by health professionals. Even for elderly patients who undergo a progressive ambulation regimen, their decreased functional capacity at return home must be anticipated by the physician and related to their prolonged bed rest, lest the patient assume that the disease and disability are more severe than that described or that the myocardial revascularization has been unsuccessful. Even elderly patients who have previously had a moderate to high level of physical activity often experience limitation of exercise tolerance upon returning home following a coronary event. These clinical characteristics of coronary events at elderly age underscore the importance of exercise rehabilitation. Following hospitalization, patients should be encouraged to enter an ambulatory exercise program or be prescribed a program of independent unsupervised exercise.

GUIDELINES FOR AMBULATORY EXERCISE TRAINING AT ELDERLY AGE

Informal Physical Activity Recommendations

Independent exercise is currently frequently recommended by physicians to aid in the recovery of elderly patients following a coronary event. Recommendations for physical activity must encompass attention to the cardiovascular changes of aging, those related to the physical inactivity of the acute illness, and those reflecting the cardiac dysfunction attendant on the acute coronary episode.

Individualized exercise prescription based on exercise testing is necessary for elderly as well as for younger coronary patients (18). It is important that the absence of angina not be assumed to indicate that exercise-induced myocardial ischemia is not present, in that asymptomatic ischemia is more common at elderly age (19). Often dyspnea is an anginal equivalent. Painless ischemia is typically detected at the pre-exercise training exercise test, with such ischemia determining the level of physical activity that should not be undertaken during exercise training.

Although the ideal exercise regimen for an elderly population is not yet clear, the components recommended should include both aerobic and (to be discussed) strength training, the exercise setting should be easily accessible, and exercise should occur without adverse sequelae. Because elderly patients often have substantial deconditioning and may have musculoskeletal limitations as well, low-level, modest-duration physical activity is initially recommended and may be undertaken several times daily, with progressive increases in exercise intensity (20). As such, brisk walking is an excellent prototype for achieving aerobic fitness, with gradual increases in the pace and distance of walking (21). Importantly, walking requires no exercise skills, training, or special equipment or facilities and allows for socialization during exercise as well. Although at younger age this activity

entails an inadequate percentage of the maximal oxygen uptake to stimulate a training effect, brisk walking entails an adequate percentage of the lower maximal oxygen uptake of the aged individual to provide an effective and safe physical conditioning stimulus (Fig. 1) (22).

Ideal sites for walking for elderly coronary patients are enclosed shopping malls, which provide a level surface for exercise, as well as a temperature- and humidity-controlled environment. Because skin blood flow decreases with aging and there is lessened efficiency of sweating and of temperature regulation with exercise, exercise intensity should be reduced in hot and humid environments (20). Although elderly patients can control the intensity of unsupervised exercise by pulse counting or by the use of the Rating of Perceived Exertion (Borg) scale (23), an easier and often better accepted control of exercise at elderly age is achieved by the ''talk test,'' wherein patients limit their exercise to an intensity that permits them to continue to talk with an exercising companion. As the anaerobic threshold is reached, respiratory rate increases, making talking difficult, such that the ''talk test'' is a good control mechanism.

The current recommendations of lower intensity and longer duration exercise for individuals of all ages is particularly valuable for elderly patients in that lower intensity exercise is associated with less injury and discomfort and thus encourages exercise adherence when the intervention is comfortable and enjoyable. In a number of studies, elderly individuals in exercise rehabilitation regimens following a coronary event had an excess of musculoskeletal complications when their exercise intensity exceeded 70 to 80% of the maximal heart rate or when high-impact activity such as jogging or jumping were undertaken. Jogging injuries were more common among elderly women than among elderly men (24).

Formal Exercise Training Regimens

Although referral to formal exercise rehabilitation is less prominent for elderly individuals, and particularly for elderly women, than is characteristic at younger age, an increasing

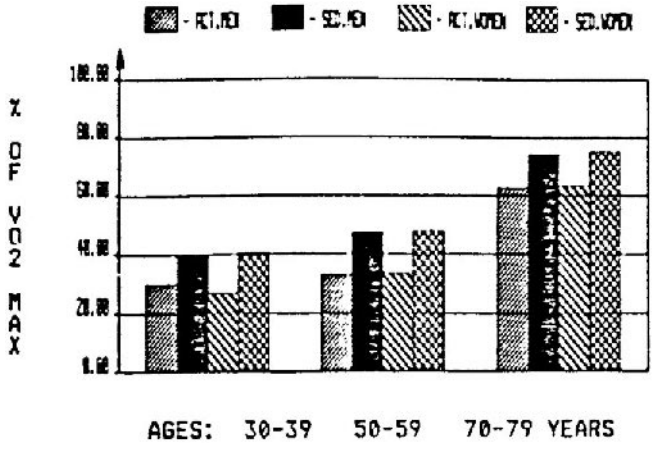

Figure 1 Changes in relative aerobic costs of walking on a level surface at the same pace by 12 healthy men and women of three different age groups.

proportion of elderly patients currently participate in structured exercise rehabilitation following a coronary event. There is substantial documentation that comparable improvement in aerobic capacity results from similar exercise training in elderly and younger patients (7,18,20,25,26).

Several distinctive features of the exercise response at elderly age must be incorporated in the design of the physical activity regimen. Greater time should be allotted for both warm-up and cool-down activities (27). Warm-up activities characteristically involve flexibility and range-of-motion exercise and facilitate both musculoskeletal and cardiorespiratory readiness for exercise. Because exercising elderly individuals are at greater risk from venous pooling because of the slower baroreceptor responsiveness with aging, cool-down activities must allow gradual dissipation of the heat load of exercise and of the exercise-induced peripheral vasodilation. Also because of the more gradual return to resting values of the exercise heart rate at elderly age, longer rest periods are required between components of exercise, or longer periods of low-intensity activity when such is alternated with higher-intensity exercise training.

Initiating aerobic exercise at the 2- to 3-MET level, with gradual increases in both the intensity and duration of training, limits discomfort and injury. Because of the lower intensity and shorter duration of initial exercise training sessions at elderly age, longer-term exercise programs may be beneficial (28). Because of the increased likelihood of musculoskeletal complications with running, jumping, and other high-impact aerobic activities, the ideal physical activity regimen is one of moderate-intensity, low-impact physical activity. Treadmill or bicycle exercise, walking, rowing machine and arm/leg cycles are commonly used modalities.

Recommendations for exercise training of the elderly individual show that an exercise intensity of 60 to 75% of the highest heart rate safely achieved at exercise testing compensated for by an increase in exercise duration, provide both greater safety and improved adherence to exercise because of the lack of exercise-related symptoms, yet entails an effective stimulus for aerobic metabolism and improved endurance. Because training of arm muscles is required to improve the exercise response to arm work, arm exercise should be added to the training regimen. Flexibility exercises should be incorporated, as flexibility is an important determinant of the ability to exercise. As well, resistance training (see below) improves muscle function and increases muscle mass, with resultant improvement in aerobic capacity; thus strength training is a valuable component of the exercise rehabilitation of the elderly coronary patient (27).

Musculoskeletal and neurological disabilities, common at elderly age, may require specific adaptations of exercise regimens and intensities.

Resistance/Strength Training

High-intensity resistance exercise substantially increased both muscle mass and strength, as well as functional mobility, even in a frail population of nonagenarians in a nursing home (29,30); nonetheless, continued resistance training was required to preserve these improvements in functional status.

Resistance/strength training improves muscle function and increases muscle mass, thereby also improving aerobic capacity and endurance (31). It appears feasible and safe for coronary patients who have successfully accomplished aerobic exercise training. Detailed instructions for the performance of specific activities, including proper breathing

techniques, are required. Resistance training protocols are available (32) and may also have to be adapted for musculoskeletal comorbidities.

BENEFICIAL RESULTS OF EXERCISE TRAINING AT ELDERLY AGE

Physiological adaptations to exercise training decrease the myocardial oxygen demand for any submaximal task, such that angina often does not limit activities of daily living. The improvement in endurance and physical work capacity can prolong the duration of an active lifestyle (21), and retard disability and dependency and the need for costly custodial care. Elderly coronary patients, following exercise training after a coronary event, can often resume levels of activity undertaken 10 or 15 years earlier, once the physical deconditioning and loss of muscle mass have been reversed by involvement in a dynamic and resistance exercise training regimen.

In addition, enhancement of flexibility, joint mobility, balance, stability, muscle strength and tone, and neuromuscular coordination decreases the likelihood of falls and thereby reduces morbidity. Moderate exercise can retard bone demineralization and resultant osteoporotic fractures. Physical fitness has been shown to be a major determinant of bone mass and bone density (33); this is particularly important in elderly women among whom osteoporosis predominates (34).

Physical activity favorably affects a number of coronary risk factors as well (35–37): increase in HDL cholesterol, decrease in triglycerides, blood pressure control, improved glucose tolerance, insulin sensitivity, body fat distribution, enhanced fibrinolysis, and more favorable platelet function, among others (14).

The increased energy expenditure of exercise can aid in weight control. Also described is an improvement in self-confidence and self-image, a sense of well-being, with lessening of anxiety, depression, and loss of motivation (38). Although some studies describe an association between exercise training and improved cognitive and motor speed function at elderly age, a more likely explanation is that elderly patients who are less depressed test better in that they are more likely to complete the test; thus this appears more prominently to reflect a favorable effect of exercise on depression than on cognitive and motor function.

Because of its proven benefits, individually prescribed exercise should be included in the coronary recovery program for all elderly patients.

RECOMMENDATIONS OF THE AHCPR CLINICAL PRACTICE GUIDELINE: CARDIAC REHABILITATION

The rehabilitative goals for exercise training at elderly age are to improve the physical function (mobility and self-sufficiency) needed for an active lifestyle. In addition, there is maintenance of mental function, limitation of sick role behavior, improved maintenance of functional independence, and facilitation in resumption of prior community and societal roles (39).

The Clinical Practice Guideline, *Cardiac Rehabilitation*, recently released by the Agency for Health Care Policy and Research and cosponsored by the National Heart, Lung, and Blood Institute, highlights that cardiac rehabilitation services are widely under-

utilized, despite their proven benefits (40). It specifically addressed the application of cardiac rehabilitation to elderly patients, highlighting that rates of entry into cardiac rehabilitation were substantially lower for elderly than for younger patients (35,41), and that elderly women were even less likely than elderly men to be referred for exercise rehabilitation. Although few studies and no randomized controlled trials cited in the Guideline involved patients of elderly age, owing to the specific exclusion of patients 70 years of age and older from randomized trials of exercise training after myocardial infarction, the available studies provide important new information for contemporary clinical practice. Elderly coronary patients have exercise trainability comparable to that of younger patients participating in similar exercise rehabilitation, with comparable statistically significant improvement in exercise tolerance documented in elderly male and female patients (18,35,41–45). Also, in one study (42), exercise tolerance improved comparably in patients 60 to 70 years of age and in patients older than 70 years of age.

The Guideline further highlighted that elderly patients were less fit following a coronary event, in part owing to their lesser fitness prior to the event. Although elderly patients had a lower peak exercise capacity both at study entry and at the completion of rehabilitative exercise training, a comparable percentage increase in maximal oxygen uptake was documented in elderly and younger patients. Further, adherence to exercise training at elderly age was high, 90% (45), with no complications or adverse outcomes of exercise training at elderly age described in any study reviewed in the guideline. Significant reduction in coronary risk factors also occurred in elderly patients who participated in multifactorial cardiac rehabilitation (35).

The Clinical Practice Guideline also highlighted approaches to the delivery of cardiac rehabilitation services other than the traditional supervised group interventions for carefully selected clinically stable coronary patients. Although all seven randomized controlled trials of this alternate approach included patients older than 65 years of age and patients up to 75 years of age (46–49), no study compared outcomes in older and younger patients. Nonetheless, transtelephonic and other monitoring and surveillance of patients participating in independent, home-based rehabilitation can safely and effectively extend cardiac rehabilitation services beyond the setting of supervised, structured, group-based rehabilitation.

SUMMARY

Prescribed physical exercise of moderate intensity, tailored to the capacity of the individual elderly coronary patient, can improve physical work capacity and endurance, prolong an active lifestyle, and retard disability and dependency, with resultant enhancement of quality of life.

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17

Aortic Valve Disease in the Elderly

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AORTIC STENOSIS

Etiology and Prevalence

Valvular aortic stenosis in the elderly is usually due to stiffening, scarring, and calcification of the valve leaflets. The commissures are not fused as in rheumatic aortic stenosis. Calcific deposits in the aortic valve are common in elderly persons and may lead to valvular aortic stenosis (1–5). Calcific deposits in the aortic valve were present in 22 of 40 necropsy patients (55%) aged 90–103 years (2). Calcium of the aortic valve and mitral annulus may coexist (1–3,6,7).

In a prospective study in a long-term health care facility of unselected persons older than 62 years, mean age 82 years, with technically adequate M-mode and two-dimensional echocardiograms of the aortic and mitral valves, a calcified aortic valve occurred in 28 of 119 men (24%) and in 67 of 354 women (19%) (3). Calcified or thickened aortic cusps or root occurred in 65 of 119 men (55%) and in 176 of 354 women (50%) (3). Mitral annular calcium was present in 84% of 95 patients with calcified aortic cusps, in 70% of 146 patients with thickened aortic cusps or root, and in 33% of 232 patients with normal aortic cusps and root (3).

In the Helsinki Aging Study, calcification of the aortic valve was diagnosed by Doppler echocardiography in 28% of 76 persons aged 55 to 71 years, in 48% of 197 persons aged 75 to 76 years, in 55% of 155 persons aged 80 to 81 years, and in 75% of 124 persons aged 85 to 86 years (5). Aortic valve calcification, aortic sclerosis, and mitral annular calcium are degenerative processes (1,2,8–10), accounting for their high prevalence in an elderly population.

Otto et al. (9) demonstrated that the early lesion of degenerative aortic stenosis is an active inflammatory process with some similarities to atherosclerosis, including lipid deposition, macrophage and T-cell infiltration, and basement membrane disruption. In a

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prospective study in a long-term health care facility of 571 unselected persons older than 62 years, mean age 82 years, with technically adequate M-mode and two-dimensional echocardiograms of the aortic valve, 292 persons (51%) had calcified or thickened aortic cusps or root (11). A serum total cholesterol ≥200 mg/dL, a history of hypertension, diabetes mellitus, and a serum high-density lipoprotein cholesterol <35 mg/dL were more prevalent in elderly persons with calcified or thickened aortic cusps or root than in elderly persons with normal aortic cusps and root (11).

In the Helsinki Aging Study, age, hypertension, and a low body mass index were independent predictors of aortic valve calcification (12). In 5201 persons older than 65 years of age in the Cardiovascular Health Study, independent clinical factors associated with degenerative aortic valve disease included age, male gender, smoking, history of hypertension, height, and high lipoprotein (a) and low-density lipoprotein cholesterol levels (10). In 1275 older persons in a long-term health care facility, mean age 81 years, valvular aortic stenosis was present in 52 of 202 persons (26%) with 40 to 100% extracranial carotid arterial disease and in 162 of 1073 persons (15%) with 0 to 39% extracranial carotid arterial disease (13). These and other data suggest that aortic valve calcium, mitral annular calcium, and coronary atherosclerosis in the elderly have similar predisposing factors (9–15).

The frequency of aortic stenosis increases with age. In a prospective study in a long-term health care facility of unselected persons older than 60 years, mean age 82 years, with technically adequate M-mode and two-dimensional echocardiograms and continuous-wave Doppler recordings for determining the prevalence and severity of valvular aortic stenosis, valvular aortic stenosis was diagnosed in 301 of 1797 older persons (17%) (16). Severe aortic stenosis (peak gradient across the aortic valve ≥50 mm Hg) occurred in 40 of 1797 older persons (2%). Moderate aortic stenosis (peak gradient across the aortic valve 26 to 49 mm Hg) was present in 96 of 1797 older persons (5%). Mild aortic stenosis (peak gradient across the aortic valve 10 to 25 mm Hg) occurred in 165 of 1797 older persons (9%). In 501 unselected persons aged 75 to 86 years in the Helsinki Aging Study, critical aortic stenosis was present in 3% and moderate-to-severe aortic stenosis in 5% of the 501 older persons (5).

Pathophysiology

In valvular aortic stenosis, there is resistance to ejection of blood from the left ventricle into the aorta, with a pressure gradient across the aortic valve during systole and an increase in left ventricular systolic pressure. The pressure overload on the left ventricle leads to concentric left ventricular hypertrophy, with an increase in left ventricular wall thickness and mass, normalizing systolic wall stress, and maintenance of normal left ventricular ejection fraction and cardiac output (17,18). A compensated hyperdynamic response is common in elderly women (19). Older patients with a comparable degree of aortic valve stenosis have more impairment of left ventricular diastolic function than do younger patients (20).

The compensatory concentric left ventricular hypertrophy leads to abnormal left ventricular compliance, left ventricular diastolic dysfunction with reduced left ventricular diastolic filling, and increased left ventricular end-diastolic pressure, further increased by left atrial systole. Left atrial enlargement develops. Atrial systole plays an important role in diastolic filling of the left ventricle in patients with aortic stenosis (21). Loss of effective

atrial contraction may cause immediate clinical deterioration in patients with severe aortic stenosis.

Sustained left ventricular hypertrophy eventually leads to left ventricular chamber dilatation with decreased left ventricular ejection fraction and, ultimately, congestive heart failure. The stroke volume and cardiac output decrease, the mean left atrial and pulmonary capillary pressures increase, and pulmonary hypertension develops. Elderly patients with both obstructive and nonobstructive coronary artery disease have an increased incidence of left ventricular enlargement and left ventricular systolic dysfunction (22). In a percentage of elderly patients with valvular aortic stenosis, the left ventricular ejection fraction will remain normal and left ventricular diastolic dysfunction will be the main problem.

In 48 older patients with congestive heart failure associated with unoperated severe valvular aortic stenosis, the left ventricular ejection fraction was normal in 30 patients (63%) (23). The prognosis of patients with aortic stenosis and left ventricular diastolic dysfunction is usually better than that of patients with aortic stenosis and left ventricular systolic dysfunction, but is worse than that of patients without left ventricular diastolic dysfunction (23,24).

Symptoms

Angina pectoris, syncope or near syncope, and congestive heart failure are the three classic manifestations of severe aortic stenosis. Angina pectoris is the most common symptom associated with aortic stenosis in elderly persons. Coexistent coronary artery disease is frequently present in these patients. However, angina pectoris may occur in the absence of coronary artery disease as a result of an increase in myocardial oxygen demand with a reduction in myocardial oxygen supply at the subendocardial level. Myocardial ischemia in patients with severe aortic stenosis and normal coronary arteries is due to inadequate left ventricular hypertrophy with increased left ventricular systolic and diastolic wall stresses causing decreased coronary flow reserve (25).

Syncope in patients with aortic stenosis may be due to reduced cerebral perfusion following exertion when arterial pressure drops because of systemic vasodilatation in the presence of a fixed cardiac output. Left ventricular failure with a decrease in cardiac output may also cause syncope. In addition, syncope at rest may be caused by a marked reduction in cardiac output secondary to transient ventricular fibrillation or transient atrial fibrillation or transient atrioventricular block related to extension of the valve calcification into the conduction system. Coexistent cerebrovascular disease with transient cerebral ischemia may contribute to syncope in older persons with aortic stenosis.

Exertional dyspnea, paroxysmal nocturnal dyspnea, orthopnea, and pulmonary edema may be caused by pulmonary venous hypertension associated with aortic stenosis. Coexistent coronary artery disease and hypertension may contribute to congestive heart failure in older persons with aortic stenosis. Atrial fibrillation may also precipitate congestive heart failure in these patients.

Congestive heart failure, syncope, or angina pectoris was present in 36 of 40 older patients (90%) with severe valvular aortic stenosis, in 66 of 96 older patients (69%) with moderate valvular aortic stenosis, and in 45 of 165 older patients (27%) with mild valvular aortic stenosis (26).

Sudden death occurs mainly in symptomatic valvular aortic stenosis patients (23,26–29). It may also occur in 3 to 5% of asymptomatic patients with aortic stenosis (27,29). Marked fatigue and peripheral cyanosis in patients with aortic stenosis may be caused by

a low cardiac output. Cerebral emboli causing stroke or transient cerebral ischemic attack, bacterial endocarditis, and gastrointestinal bleeding may also occur in older patients with aortic stenosis.

Signs

A systolic ejection murmur heard in the second right intercostal space, down the left sternal border toward the apex, or at the apex is classified as an aortic systolic ejection murmur (ASEM) (3,4,30,31). An ASEM is commonly heard in elderly patients (1,3,30), occurring in 265 of 565 unselected elderly patients (47%) in a long-term health care facility (3). Of 220 elderly patients with an ASEM and technically adequate M-mode and two-dimensional echocardiograms of the aortic valve, 207 (94%) had aortic cuspal or root calcification or thickening (3). Of 75 elderly patients with an ASEM, valvular aortic stenosis was diagnosed by continuous-wave Doppler echocardiography in 42 patients (56%) (31).

Table 1 shows that an ASEM was heard in 100% of 19 elderly patients with severe aortic stenosis, in 100% of 49 elderly patients with moderate aortic stenosis, and in 95% of 74 elderly patients with mild aortic stenosis (4). However, the ASEM may become softer or absent in patients with congestive heart failure associated with severe aortic stenosis because of a low cardiac output. The intensity and maximal location of the ASEM and transmission of the ASEM to the right carotid artery do not differentiate among mild, moderate, and severe aortic stenosis (3,4,31). The ASEM may be heard only at the apex in some elderly patients with aortic stenosis. The apical systolic ejection murmur may also be louder and more musical than the basal systolic ejection murmur in some elderly patients with aortic stenosis. The intensity of the ASEM in valvular aortic stenosis increases with squatting and by inhalation of amyl nitrite and decreases during the Valsalva maneuver.

Prolonged duration of the ASEM and late peaking of the ASEM best differentiate severe aortic stenosis from mild aortic stenosis (3,4,31). However, the physical signs do not distinguish between severe and moderate aortic stenosis (Table 1) (4,31).

A prolonged carotid upstroke time does not differentiate between severe and moderate valvular aortic stenosis in elderly patients (4,31). A prolonged carotid upstroke time

Table 1 Correlation of Physical Signs of Valvular Aortic Stenosis with the Severity of Aortic Stenosis in Elderly Patients

	Severity of aortic stenosis		
Physical sign	Mild (n = 74)	Moderate (n = 49)	Severe (n = 19)
ASEM	95%	100%	100%
Prolonged duration ASEM	3%	63%	84%
Late-peaking ASEM	3%	63%	84%
Prolonged carotid upstroke time	3%	33%	53%
A_2 absent	0%	10%	16%
A_2 decreased or absent	5%	49%	74%

ASEM = aortic systolic ejection murmur; A_2 = aortic second sound.
Source: Adapted from Ref. 4.

was palpable in 3% of elderly patients with mild aortic stenosis, in 33% of elderly patients with moderate aortic stenosis, and in 53% of elderly patients with severe aortic stenosis (Table 1) (4). Stiff noncompliant arteries may mask a prolonged carotid upstroke time in elderly patients with severe aortic stenosis. The pulse pressure may also be normal or wide rather than narrow in elderly patients with severe aortic stenosis because of loss of vascular elasticity. An aortic ejection click is rare in elderly patients with aortic stenosis because the valve cusps are immobile (4,31).

An absent or decreased A_2 occurs more frequently in elderly patients with severe or moderate aortic stenosis than in patients with mild aortic stenosis (Table 1) (4,31). However, an absent or reduced A_2 does not differentiate between severe and moderate aortic stenosis (4,31). The presence of atrial fibrillation, reversed splitting of S_2, or an audible fourth heart sound at the apex also does not differentiate between severe and moderate aortic stenosis in elderly patients (31). The presence of a third heart sound in elderly patients with aortic stenosis usually indicates the presence of left ventricular systolic dysfunction and elevated left ventricular filling pressure (32).

Table 2 compares clinical manifestations and pathological changes of valvular aortic stenosis in elderly and younger patients (33). The rigid calcified valve with commissural fusion usually found in younger patients is responsible for the ejection sound so commonly audible in younger patients with valvular aortic stenosis. Moreover, such a valve is a suitable mechanism to produce the classic harsh, rough, grunting murmur, which is usually loudest at the right base and with radiation upward to the right carotid. In certain elderly patients, by contrast, a calcified stenotic trileaflet aortic valve without commissural fusion may produce a ''spray'' of the blood flow instead of a ''jet'' into the ascending aorta. Thus, the harsh murmur at the right base may be appreciably less intense and comparatively inconspicuous. Because of the lack of commissural fusion, an ejection sound is usually

Table 2 Clinical Manifestations of Elderly and Younger Patients with Valvular Aortic Stenosis

	Elderly	Younger
Sex	M = F	3M, 1F
Etiology	Degenerative	Congenital, rheumatic
Valve deformity	Tricuspid	Bicuspid
	No commissural fusion	Commissural fusion
Systemic blood pressure	Elevated or normal	Usually low
Pulse pressure	Frequently wide	Narrow
Carotid upstroke	Normal	Diminished, slow
Left ventricular hypertrophy by palpation	Uncommon	Common
Thrill by palpation	Uncommon	Common
Ejection sound	Uncommon	Common
S_4	Common	Common
Systolic murmur	Musical, apical	Harsh, rough, upper sternum
Atrial fibrillation	25%	Rare
Aortic valve calcium	Common	Variable
Mitral annular calcium	Common	Uncommon

Source: Modified from Ref. 33.

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not present. Since the cusps are not fused, the murmur may be a higher frequency, musical systolic murmur that is heard all over the precordium. In some elderly patients, the murmur may be heard well at or near the cardiac apex and may be confused with mitral regurgitation.

Electrocardiography and Chest Roentgenography

Table 3 shows that echocardiography is more sensitive than electrocardiography in detecting left ventricular hypertrophy in elderly patients with valvular aortic stenosis (4). The heart size is usually normal on the chest x-ray in patients with aortic stenosis. Rounding of the left ventricular border and apex may occur as a result of concentric left ventricular hypertrophy. Poststenotic dilatation of the ascending aorta is commonly seen. Calcification of the aortic valve is best seen by echocardiography or fluoroscopy.

Involvement of the conduction system by calcific deposits may occur in elderly patients with valvular aortic stenosis. In a study of 51 elderly patients with aortic stenosis who underwent aortic valve replacement, conduction defects occurred in 58% of 31 patients with mitral annular calcium and in 25% of 20 patients without mitral annular calcium (7). In another study of 77 elderly patients with aortic stenosis, first-degree atrioventricular block occurred in 18% of patients, left bundle branch block in 10% of patients, intraventricular conduction defect in 6% of patients, right bundle branch block in 4% of patients, and left axis deviation in 17% of patients (34).

Complex ventricular arrhythmias may be detected by 24-h ambulatory electrocardiography in patients with aortic stenosis. Elderly patients with complex ventricular arrhythmias associated with valvular aortic stenosis have a higher incidence of new coronary events than elderly patients with aortic stenosis and no complex ventricular arrhythmias (35).

Echocardiography and Doppler Echocardiography

M-mode and two-dimensional echocardiography and Doppler echocardiography are very useful in the diagnosis of aortic stenosis. Of 83 patients with congestive heart failure or angina pectoris and a systolic precordial murmur in whom severe valvular aortic stenosis was diagnosed by Doppler echocardiography, aortic stenosis was not clinically diagnosed in 28 patients (34%) (36). Echocardiography can detect thickening, calcification, and de-

Table 3 Prevalence of Electrocardiographic and Echocardiographic Left Ventricular Hypertrophy (LVH) in Elderly Patients with Mild, Moderate, and Severe Valvular Aortic Stenosis

	Severity of aortic stenosis		
	Mild (n = 74)	Moderate (n = 49)	Severe (n = 19)
Electrocardiographic LVH	11%	31%	58%
Echocardiographic LVH	74%	96%	100%

Source: Adapted from Ref. 4.

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creased excursion of aortic valve leaflets (3). Left ventricular hypertrophy is best diagnosed by echocardiography (4). Chamber dimensions and measurements of left ventricular end-systolic and end-diastolic volumes, left ventricular ejection fraction, and assessment of global and regional left ventricular wall motion give important information on left ventricular systolic function.

Doppler echocardiography is used to measure peak and mean transvalvular gradients across the aortic valve and to identify associated valve lesions. Aortic valve area can be calculated by the continuity equation using pulsed Doppler echocardiography to measure left ventricular outflow tract velocity, continuous-wave Doppler echocardiography to measure transvalvular flow velocity, and two-dimensional long-axis view to measure left ventricular outflow tract area (37,38). Aortic valve area can be detected reliably by the continuity equation in elderly persons with valvular aortic stenosis (38). Figures 1 through 5 illustrate two-dimensional echocardiographic findings (Figs. 1 and 3), continuous-wave Doppler echocardiographic findings (Figs. 2 and 4), and simultaneous left ventricular and femoral arterial pressure tracings (Fig. 5) in elderly patients with severe valvular aortic stenosis.

Shah and Graham (39) found that the agreement in quantitation of the severity of aortic stenosis between Doppler echocardiography and cardiac catheterization was greater

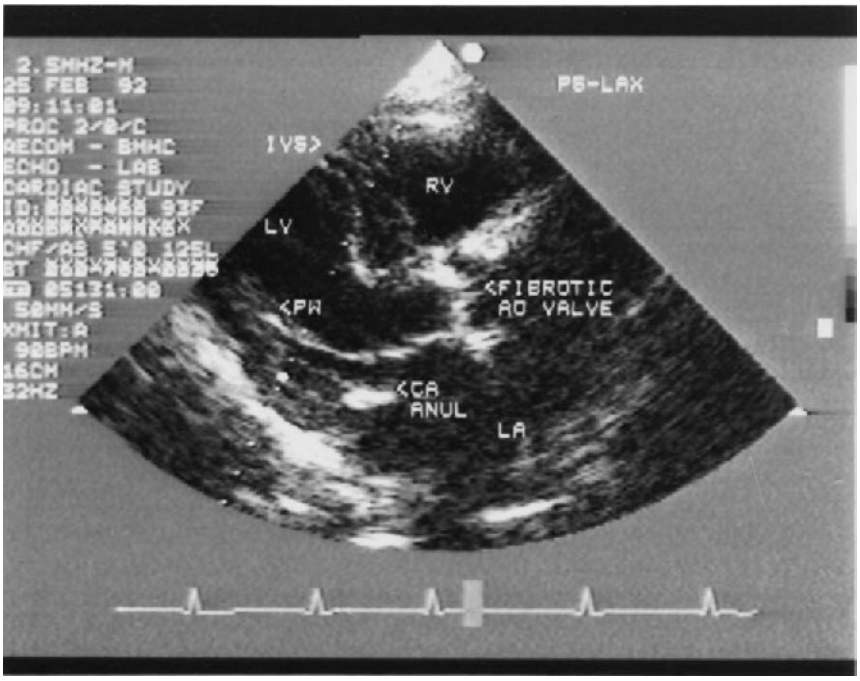

Figure 1 Two-dimensional echocardiographic image from a parasternal long-axis view of a 93-year-old female with aortic stenosis and moderately depressed left ventricular function showing a fibrotic aortic valve and mitral annular calcification. PS-LAX =parasternal long-axis view; RV = right ventricular cavity; LV = left ventricular cavity; IVS = interventricular septum; PW = posterior wall; CA ANUL = mitral annulus calcification; LA = left atrium; AO = aorta.

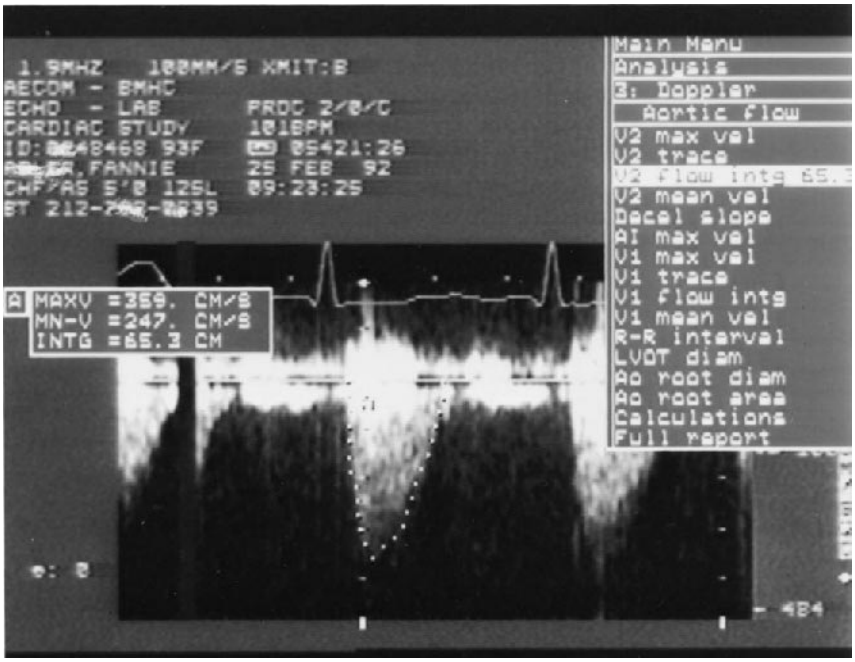

Figure 2 Continuous-wave Doppler recording of the velocity profile across the aortic valve in the same patient shown in Figure 1. A 52-mmHg gradient across the aortic valve is measured using the Bernoulli equation. Indexed aortic valve area measured by the continuity equation using Doppler data = 0.5 cm^2/m^2.

than 95%. Patients with a peak jet velocity ≥4.5 m/s had critical aortic stenosis, and those with a peak jet velocity <3.0 m/s had noncritical aortic stenosis. Slater et al. (40) demonstrated a concordance between Doppler echocardiography and cardiac catheterization in the decision to operate or not to operate in 61 of 73 patients (84%) with valvular aortic stenosis.

Cardiac catheterization was performed in 105 patients in whom Doppler echocardiography demonstrated an aortic valve area ≤0.75 cm^2 or a peak jet velocity ≥4.5 m/s, consistent with critical aortic stenosis (41). Doppler echocardiography was 97% accurate in this subgroup. Cardiac catheterization was performed in this study in 133 patients with noncritical aortic stenosis. Doppler echocardiography was 95% accurate in this subgroup. Although most elderly persons do not require cardiac catheterization before aortic valve surgery, they require selective coronary arteriography before aortic valve surgery. Patients in whom Doppler echocardiography shows a peak jet velocity between 3.6 and 4.4 m/s and an aortic valve area >0.8 cm^2 should undergo cardiac catheterization if they have cardiac symptoms attributable to aortic stenosis (39). Patients with a peak jet velocity between 3.0 and 3.5 m/s and a left ventricular ejection fraction <50% may have severe aortic stenosis, requiring aortic valve replacement, and should undergo cardiac catheterization (39). Patients with a peak jet velocity between 3.0 and 3.5 m/s and a left ventricular ejection fraction >50% probably do not need aortic valve replacement but should undergo cardiac catheterization if they have symptoms of severe aortic stenosis (39).

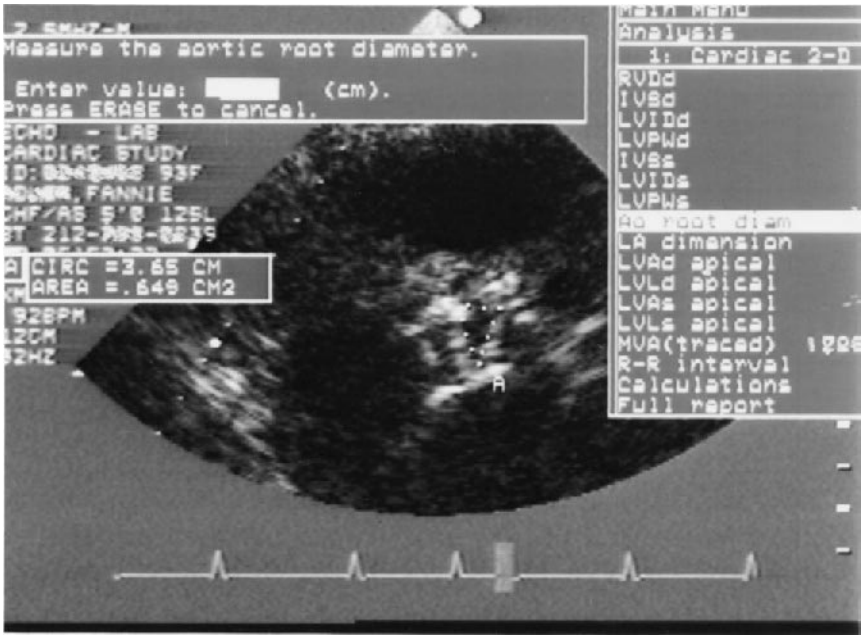

Figure 3 Two-dimensional echocardiographic image obtained in the same patient in Figures 1 and 2 from a short-axis parasternal view in which the aortic valve orifice is mapped, yielding an indexed area of 0.4 cm^2/m^2.

Natural History

Ross and Braunwald (27) found that the average survival rate was 3 years after the onset of angina pectoris in patients with severe aortic stenosis. Ross and Braunwald (27) reported that the average survival rate after the onset of syncope in patients with severe aortic stenosis was 3 years. Ross and Braunwald (27) found that the average survival rate after the onset of congestive heart failure in patients with severe aortic stenosis was 1.5 to 2 years.

Patients with symptomatic severe valvular aortic stenosis have a poor prognosis (26–29,42). At the National Institutes of Health, 52% of patients with symptomatic severe valvular aortic stenosis not operated on were dead at 5 years (28,29). At 10-year follow-up, 90% of these patients were dead.

At 4-year follow-up of persons aged 75 to 86 years in the Helsinki Aging Study, the incidence of cardiovascular mortality was 62% in persons with severe aortic stenosis and 35% in persons with moderate aortic stenosis (43). At 4-year follow-up, the incidence of total mortality was 76% in persons with severe aortic stenosis and 50% in persons with moderate aortic stenosis (43).

In a prospective study, at 19-month follow-up (range 2 to 36 months), 90% of 30 patients with congestive heart failure associated with unoperated severe valvular aortic stenosis and a normal left ventricular ejection fraction were dead (23). At 13-month follow-up (range 2 to 24 months), 100% of 18 patients with congestive heart failure associated with unoperated severe valvular aortic stenosis and an abnormal left ventricular ejection fraction were dead (23).

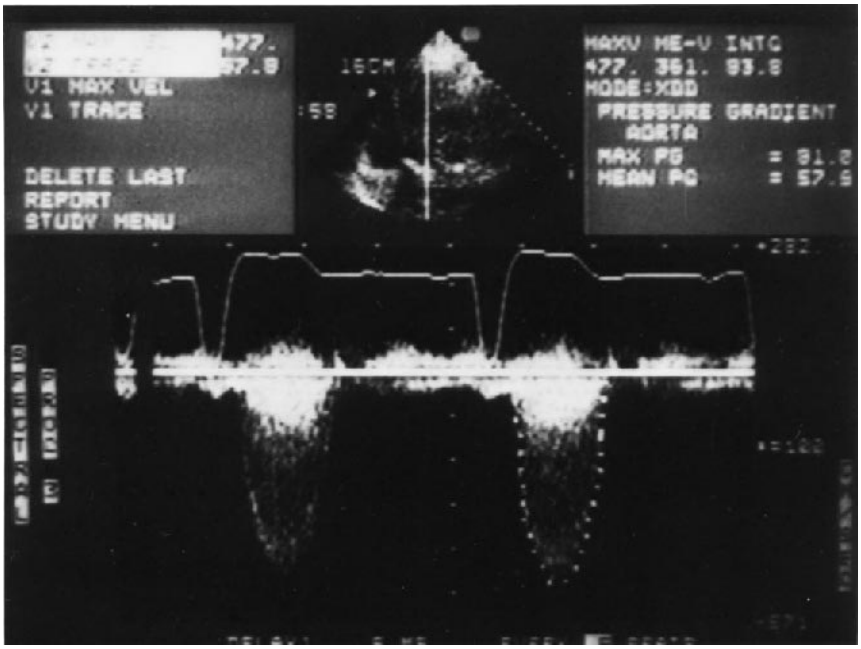

Figure 4 Continuous-wave Doppler recording of the velocity profile across the aortic valve in an elderly patient with aortic stenosis and normal left ventricular systolic function. The indexed aortic valve area is 0.5 cm^2/m^2 by both Gorlin's formula and the Doppler continuity equation. The peak gradient across the aortic valve by Bernouilli's equation is 81 mmHg, a value higher than that recorded in Figure 2 for the same indexed aortic valve area.

Table 4 shows the incidence of new coronary events in older persons with no, mild, moderate, and severe valvular aortic stenosis. Independent risk factors for new coronary events in this study were prior myocardial infarction, valvular aortic stenosis, male gender, and increasing age (26). In this prospective study, at 20-month follow-up of 40 older patients with severe valvular aortic stenosis, congestive heart failure, syncope, or angina pectoris was present in 36 of 37 patients (97%) who developed new coronary events and in none of 3 patients (0%) without new coronary events (26). At 32-month follow-up of 96 older patients with moderate valvular aortic stenosis, congestive heart failure, syncope, or angina pectoris was present in 65 of 77 patients (84%) who developed new coronary events and in 1 of 19 patients (5%) without new coronary events (26). At 52-month follow-up of 165 older patients with mild valvular aortic stenosis, congestive heart failure, syncope, or angina pectoris was present in 40 of 103 patients (39%) who developed new coronary events and in 5 of 62 patients (8%) without new coronary events (26).

Kennedy et al. (44) followed 66 patients with moderate valvular aortic stenosis diagnosed by cardiac catheterization (aortic valve area 0.7 to 1.2 cm^2). In 38 patients with symptomatic moderate valvular aortic stenosis and 28 patients with minimally symptomatic moderate valvular aortic stenosis, the probabilities of avoiding death from aortic stenosis were 0.86 for patients with symptomatic aortic stenosis and 1.0 for patients with minimally symptomatic aortic stenosis at 1-year follow-up, 0.77 for patients with symptomatic aortic stenosis and 1.0 for patients with minimally symptomatic aortic stenosis at 2 years,

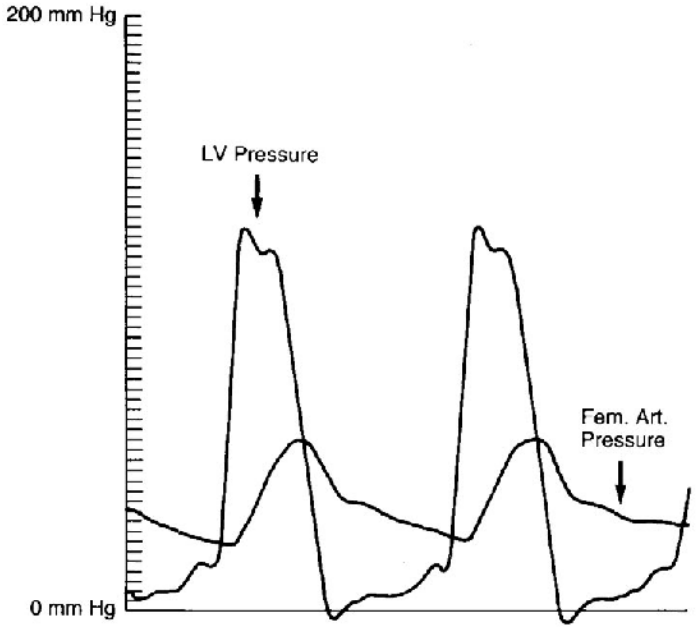

Figure 5 Simultaneous left ventricular and femoral artery pressure recordings obtained in the same patient in Figure 4 confirming a large gradient across the aortic valve with a maximum value of 81 mm Hg (instantaneous pressure). Fem. Art. = femoral artery pressure tracing; LV = left ventricular pressure tracing.

0.77 for patients with symptomatic aortic stenosis and 0.96 for patients with minimally symptomatic aortic stenosis at 3 years, and 0.70 for patients with symptomatic aortic stenosis and 0.90 for patients with minimally symptomatic aortic stenosis at 4 years (44). During 35-month mean follow-up in this study, 21 patients underwent aortic valve replacement.

Hammermeister et al. (45) followed 106 patients with unoperated valvular aortic stenosis in the Veterans Administration Cooperative Study on Valvular Heart Disease for a mean duration of 5 years. During follow-up, 60 of 106 patients (57%) died. Multivariate analysis demonstrated that measures of the severity of the valvular aortic stenosis, the presence of coronary artery disease, and the presence of congestive heart failure were the important predictors of survival in unoperated patients.

Table 4 Incidence of New Coronary Events in Older Persons with No, Mild, Moderate, and Severe Valvular Aortic Stenosis (AS)

	No AS (n = 1496)	Mild AS (n = 165)	Moderate AS (n = 96)	Severe AS (n = 40)
Age (years)	81	84	85	85
Follow-up (months)	49	52	32	20
New coronary events	41%	62%	80%	93%

Source: Adapted from Ref. 26.

Three studies have demonstrated that patients with asymptomatic severe valvular aortic stenosis are at low risk for death and can be followed until symptoms develop (46–48). Turina et al. (46) followed 17 patients with asymptomatic or mildly symptomatic aortic stenosis. During the first 2 years, none died or had aortic valve surgery. At 5-year follow-up, 94% were alive and 75% were free of cardiac events. Kelly et al. (47) followed 51 asymptomatic patients with severe valvular aortic stenosis. During 17-month mean follow-up, 21 (41%) of the patients became symptomatic. Only 2 of the 51 patients (4%) died of cardiac causes. In both patients, death was preceded by the development of angina pectoris or congestive heart failure. Pellikka et al. (48) observed that 113 of 143 patients (79%), mean age 72 years, with asymptomatic severe aortic stenosis were not initially referred for aortic valve replacement or percutaneous aortic balloon valvuloplasty. During 20-month mean follow-up, 37 of 113 patients (33%) became symptomatic. The actuarial probability of remaining free of cardiac events associated with aortic stenosis, including cardiac death and aortic valve surgery, was 95% at 6 months, 93% at 1 year, and 74% at 2 years. No asymptomatic patient with severe aortic stenosis developed sudden cardiac death while asymptomatic.

Medical Management

Prophylactic antibiotics should be used to prevent bacterial endocarditis in patients with valvular aortic stenosis regardless of severity, according to American Heart Association guidelines (49). Patients with congestive heart failure, exertional syncope, or angina pectoris associated with moderate or severe valvular aortic stenosis should undergo aortic valve replacement promptly. Valvular surgery is the only definitive therapy in these elderly patients (50). Medical therapy does not relieve the mechanical obstruction to left ventricular outflow and does not relieve symptoms or progression of the disorder. Patients with asymptomatic aortic stenosis should report the development of symptoms possibly related to aortic stenosis immediately to the physician. If significant valvular aortic stenosis is present in asymptomatic older patients, clinical examination and an electrocardiogram and Doppler echocardiogram should be performed at 6-month intervals. Nitrates should be used with caution in patients with angina pectoris and aortic stenosis to prevent the occurrence of orthostatic hypotension and syncope. Diuretics should be used with caution in patients with congestive heart failure to prevent a decrease in cardiac output and hypotension. Vasodilators should be avoided. Digitalis should not be used in patients with congestive heart failure and a normal left ventricular ejection fraction unless needed to control a rapid ventricular rate associated with atrial fibrillation.

Aortic Valve Replacement

Aortic valve replacement is the procedure of choice for symptomatic elderly patients with severe aortic stenosis. The bioprosthesis has less structural failure in elderly patients than in younger patients and may be preferable to the mechanical prosthetic valve for aortic valve replacement in the elderly due to the anticoagulation issue (51). Patients with mechanical prostheses need anticoagulant therapy indefinitely. Patients with porcine bioprostheses require anticoagulant therapy for 3 months after hospital discharge and then may be treated with antiplatelet therapy alone (52).

Arom et al. (53) performed aortic valve replacement in 273 patients aged 70 to 89 years (mean age 75 years), 162 with aortic valve replacement alone, and 111 with aortic

valve replacement plus coronary artery bypass. Operative mortality was 5%. Late mortality at 33-month mean follow-up was 18%. Actuarial analysis showed at 5-year follow-up that overall survival was 66% for patients with aortic valve replacement alone, 76% for patients with aortic valve replacement plus coronary artery bypass, and 74% for a similar age group in the general population.

Culliford et al. (52) performed aortic valve replacement in 71 patients aged ≥80 years, 35 with aortic valve replacement alone, and 36 with aortic valve replacement plus coronary artery bypass. Hospital mortality was 6% for patients with aortic valve replacement alone and 19% for patients with both aortic valve replacement plus coronary artery bypass. At 1-year follow-up, survival from late cardiac death was 100% for patients who had aortic valve replacement alone and 96% for patients who had aortic valve replacement plus coronary artery bypass. At 3-year follow-up, survival from late cardiac death was 100% for patients who had aortic valve replacement alone and 91% for patients who had aortic valve replacement plus coronary artery bypass. Freedom from all valve-related complications (thromboembolism, anticoagulant-related complications, endocarditis, and reoperation or prosthetic failure) was 93% at 1-year follow-up and 80% at 3-year follow-up. At follow-up, 65% of survivors were in New York Heart Association functional class I or II, 31% in New York Heart Association functional class III, and 4% in New York Heart Association functional class IV.

Levinson et al. (54) performed aortic valve replacement in 71 octogenarians, mean age 82 years. The operative mortality was 9% in these elderly patients. At 28-month mean follow-up, 100% of the survivors were in New York Heart Association functional class I or II. Actuarial 1-, 5-, and 10-year survival rates were 83%, 67%, and 49%, respectively.

Aortic valve replacement is associated with a reduction in left ventricular mass and in improvement of left ventricular diastolic filling (55,56). Hoffmann and Burckhardt (57) performed a prospective study in 100 patients who had aortic valve replacement. At 41-month mean follow-up, the yearly cardiac mortality rate was 8% in patients with electrocardiographic left ventricular hypertrophy and repetitive ventricular premature complexes ≥2 couplets per 24 h during 24-h ambulatory electrocardiographic monitoring and 0.6% in patients without either of these findings.

If left ventricular systolic dysfunction in patients with severe valvular aortic stenosis is associated with critical narrowing of the aortic valve rather than myocardial fibrosis, it often improves after successful aortic valve replacement (58). In 154 patients, mean age 73 ± 10 years, with aortic stenosis and a left ventricular ejection fraction ≤35% who underwent aortic valve replacement, the 30-day mortality was 9%. The 5-year survival was 69% in patients without significant coronary artery disease and 39% in patients with significant coronary artery disease. New York Heart Association functional class III or IV was present in 58% of patients before surgery vs. 7% of patients after surgery. Postoperative left ventricular ejection fraction was measured in 76% of survivors at a mean of 14 months after surgery. Improvement in left ventricular ejection fraction was found in 76% of patients (58).

Balloon Aortic Valvuloplasty

Aortic valve replacement is the procedure of choice for symptomatic elderly patients with severe valvular aortic stenosis. In a Mayo Clinic study, the actuarial survival of 50 elderly patients, mean age 77 years, with symptomatic severe aortic stenosis in whom aortic valve replacement was refused (45 patients) or deferred (5 patients) was 57% at 1 year, 37%

at 2 years, and 25% at 3 years (59). Because of the poor survival in this group of patients, balloon aortic valvuloplasty should be considered when operative intervention is refused or deferred.

Balloon aortic valvuloplasty is effective palliative therapy for some elderly patients with symptomatic valvular aortic stenosis, although restenosis with recurrence of symptoms is common (60–69). Rodriguez et al. (66) demonstrated in 42 elderly patients, mean age 78 years, undergoing aortic valvuloplasty that the 2-year survival was 36% in patients with left ventricular ejection fractions $<40\%$, and 80% in patients with left ventricular ejection fractions $\geq 40\%$. The 2-year event-free survival (freedom from aortic valve surgery or severe congestive heart failure) was 0% in patients with left ventricular ejection fractions $<40\%$ and 34% in patients with left ventricular ejection fractions $\geq 40\%$ (66). Block and Palacios (61) observed recurrence of symptoms, death, or hemodynamic evidence of restenosis in 56% of 90 elderly patients, mean age 79 years, an average of 5.5 months after aortic valvuloplasty. Kuntz et al. (67) observed immediate clinical improvement after successful aortic valvuloplasty in the majority of 205 elderly patients, mean age 78 years, but restenosis in more than 50% of the patients within 1 to 2 years. On the basis of the available data, balloon aortic valvuloplasty should be considered for elderly patients with symptomatic severe valvular aortic stenosis who are not candidates for aortic valve surgery and possibly for patients with severe left ventricular dysfunction as a bridge to subsequent valve surgery (67–69).

AORTIC REGURGITATION

Etiology and Prevalence

Acute aortic regurgitation in elderly persons may be due to infective endocarditis, rheumatic fever, aortic dissection, trauma following prosthetic valve surgery, or rupture of the sinus of Valsalva, and causes sudden severe left ventricular failure. Chronic aortic regurgitation in elderly persons may be caused by valve leaflet disease (secondary to any cause of aortic stenosis, infective endocarditis, rheumatic fever, congenital heart disease, rheumatoid arthritis, ankylosing spondylitis, following prosthetic valve surgery, or myxomatous degeneration of the valve) or by aortic root disease. Examples of aortic root disease causing chronic aortic regurgitation in the elderly include association with systemic hypertension, syphilitic aortitis, cystic medial necrosis of the aorta, ankylosing spondylitis, rheumatoid arthritis, Reiter's disease, systemic lupus erythematosus, Ehlers-Danlos syndrome, and pseudoxanthoma elasticum. Mild or moderate aortic regurgitation was also diagnosed by Doppler echocardiography in 9 of 29 patients (31%) with hypertrophic cardiomyopathy (70). Margonato et al. (71) linked the increased prevalence of aortic regurgitation with age to aortic valve thickening.

The prevalence of aortic regurgitation increases with age (71–73). In a prospective study in a long-term health care facility of 450 unselected persons older than 62 years, mean age 82 years, with technically adequate M-mode and two-dimensional echocardiograms and pulsed Doppler recordings of the aortic valve, aortic regurgitation was diagnosed in 39 of 114 men (34%) and in 92 of 336 women (27%) (73). Severe or moderate aortic regurgitation was diagnosed in 74 of 450 elderly persons (16%). Mild aortic regurgitation was diagnosed in 57 of 450 elderly persons (13%). In a prospective study of 554 men, mean age 80 years, and 1243 women, mean age 82 years, in a long-term health care

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facility, aortic regurgitation was diagnosed by pulsed Doppler echocardiography in 174 of 554 men (31%) and in 352 of 1243 women (28%) (16).

Pathophysiology

The primary determinants of aortic regurgitant volume are the regurgitant orifice area, the transvalvular pressure gradient, and the duration of diastole (74). Chronic aortic regurgitation increases left ventricular end-diastolic volume. The largest left ventricular end-diastolic volumes are seen in patients with chronic severe aortic regurgitation. Left ventricular stroke volume increases to maintain the forward stroke volume. The increased preload causes an increase in left ventricular diastolic stress and the addition of sarcomeres in series. This results in an increase in the ratio of the left ventricular chamber size to wall thickness. This pattern of left ventricular hypertrophy is called eccentric left ventricular hypertrophy.

Primary myocardial abnormalities or ischemia due to coexistent coronary artery disease depress the contractile state. Left ventricular diastolic compliance decreases, left ventricular end-systolic volume increases, left ventricular end-diastolic pressure rises, left atrial pressure increases, and pulmonary venous hypertension results. When the left ventricular end-diastolic radius-to-wall thickness ratio rises, left ventricular systolic wall stress increases abnormally because of the preload and afterload mismatch (18,75). Additional stress then reduces the left ventricular ejection fraction response to exercise (76). Eventually, the left ventricular ejection fraction, forward stroke volume, and effective cardiac output are reduced at rest. We observed that an abnormal resting left ventricular ejection fraction occurred in 8 of 25 elderly patients (32%) with congestive heart failure associated with chronic severe aortic regurgitation (77).

In patients with acute severe aortic regurgitation, the left ventricle cannot adapt to the increased volume overload. Forward stroke volume falls, left ventricular end-diastolic pressure increases rapidly to high levels (78), and pulmonary hypertension and pulmonary edema result. The rapid rise of the left ventricular end-diastolic pressure to exceed the left atrial pressure in early diastole causes premature closure of the mitral valve (79). This prevents backward transmission of the elevated left ventricular end-diastolic pressure to the pulmonary venous bed.

Symptoms

Patients with acute aortic regurgitation develop symptoms due to the sudden onset of congestive heart failure, with marked dyspnea and weakness. Patients with chronic aortic regurgitation may remain asymptomatic for many years. Mild dyspnea on exertion and palpitations, especially on lying down, may occur. Exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and edema are common clinical symptoms when left ventricular failure develops. Syncope is rare. Angina pectoris occurs less often in patients with aortic regurgitation than in patients with aortic stenosis and may be due to coexistent coronary artery disease. However, nocturnal angina pectoris, often accompanied by flushing, diaphoresis, and palpitations, may occur when the heart rate slows and the arterial diastolic pressure falls to very low levels. Most patients with severe aortic regurgitation who do not have surgery die within 2 years after congestive heart failure develops (80).

Signs

The aortic regurgitation murmur is typically a high-pitched blowing diastolic murmur that begins immediately after A_2. The diastolic murmur is best heard along the left sternal border in the third and fourth intercostal spaces when aortic regurgitation is due to valvular disease. The murmur is best heard along the right sternal border when aortic regurgitation is due to dilatation of the ascending aorta. The diastolic murmur is best heard with the diaphragm of the stethoscope with the patient sitting up, leaning forward, and holding the breath in deep expiration. The severity of aortic regurgitation correlates with the duration of the diastolic murmur, not with the intensity of the murmur.

Grayburn et al. (81) heard an aortic regurgitation murmur in 73% of 82 patients with aortic regurgitation and in 8% of 24 patients without aortic regurgitation. Saal et al. (82) heard an aortic regurgitation murmur in 80% of 35 patients with aortic regurgitation and in 10% of 10 patients without aortic regurgitation. Meyers et al. (83) heard an aortic regurgitation murmur in 73% of 66 patients with aortic regurgitation and in 22% of 9 patients without aortic regurgitation. Table 5 shows that an aortic regurgitation murmur was heard in 95% of 74 elderly patients with severe or moderate aortic regurgitation diagnosed by pulsed Doppler echocardiography, in 61% of 57 elderly patients with mild aortic regurgitation, and in 3% of 319 elderly patients with no aortic regurgitation (73).

In patients with chronic severe aortic regurgitation, the left ventricular apical impulse is diffuse, hyperdynamic, and displaced laterally and inferiorly. A rumbling diastolic murmur (Austin Flint) may be heard at the apex, with its intensity reduced by inhalation of amyl nitrite. A short basal systolic ejection murmur is heard. A palpable left ventricular rapid filling wave and an audible S_3 at the apex are usually found. Physical findings due to a large left ventricular stroke volume and a rapid diastolic runoff in patients with severe aortic regurgitation include a wide pulse pressure with an increased systolic arterial pressure and an abnormally low diastolic arterial pressure, an arterial pulse that abruptly rises and collapses, a bisferiens pulse, bobbing of the head with each heart beat, booming systolic and diastolic sounds heard over the femoral artery, capillary pulsations, and systolic and diastolic murmurs over the femoral artery when compressing it proximally and distally.

Electrocardiography and Chest Roentgenography

The electrocardiogram may initially be normal in patients with acute severe aortic regurgitation. Roberts and Day (84) showed in 30 necropsy patients with chronic severe aortic regurgitation that the electrocardiogram did not accurately predict the severity of aortic

Table 5 Correlation of Aortic Regurgitation Murmur with Severity of Aortic Regurgitation (AR) in Elderly Patients with Chronic Aortic Regurgitation

	AR murmur
Severe or moderate AR ($n = 74$)	95%
Mild AR ($n = 57$)	61%
No AR ($n = 319$)	3%

Source: Adapted from Ref. 73.

regurgitation or cardiac weight. Using various electrocardiographic criteria, the prevalence of left ventricular hypertrophy varied from 30% ($RV_6 > RV_5$) to 90% (total 12-lead QRS voltage $>$ 175 mm). The P-R interval was prolonged in 28% of patients, and the QRS duration was $\geq$0.12 s in 20% of patients (84).

The chest x-ray in patients with acute severe aortic regurgitation may show a normal heart size and pulmonary edema. The chest x-ray in patients with chronic severe aortic regurgitation usually shows a dilated left ventricle, with elongation of the apex inferiorly and posteriorly and a dilated aorta. Aneurysmal dilatation of the aorta suggests that aortic root disease is causing the aortic regurgitation. Linear calcifications in the wall of the ascending aorta are observed in syphilitic aortic regurgitation and in degenerative disease.

Echocardiography and Doppler Echocardiography

M-mode and two-dimensional echocardiography and Doppler echocardiography are very useful in the diagnosis of aortic regurgitation. Two-dimensional echocardiography can provide information establishing the etiology of the aortic regurgitation and measurements of left ventricular function. Eccentric left ventricular hypertrophy is diagnosed by echocardiography if the left ventricular mass index is increased with a relative wall thickness $<$0.45 (85–87). Echocardiographic measurements reported to predict an unfavorable response to aortic valve replacement in patients with chronic aortic regurgitation include a left ventricular end-systolic dimension $>$55 mm (88), a left ventricular shortening fraction $<$25% (88), a left ventricular diastolic radius-to-wall thickness ratio $>$3.8 (89), a left ventricular end-diastolic dimension index $>$38 mm/m^2 (89), and a left ventricular end-systolic dimension index $>$26 mm/m^2 (89).

Grayburn et al. (81) showed that pulsed Doppler echocardiogaphy correctly identified the presence of aortic regurgitation in 57 of 57 patients (100%) with $\geq$2+ aortic regurgitation and in 22 of 25 patients (88%) with 1+ aortic regurgitation. Saal et al. (82) demonstrated that pulsed Doppler echocardiography identified the presence of aortic regurgitation in 34 of 35 patients (97%) with documented aortic regurgitation. Continuous-wave Doppler echocardiography has also been shown to be very useful in diagnosing and quantitating aortic regurgitation (90,91). Aortic regurgitation is best assessed by color flow Doppler imaging (92). Figure 6 illustrates two-dimensional echocardiographic and color Doppler findings in an elderly patient with chronic severe aortic regurgitation. Figure 7 illustrates continuous-wave Doppler findings in the elderly patient with chronic severe aortic regurgitation shown in Figure 6.

Natural History

The natural history of chronic aortic regurgitation is significantly different than the natural history of acute aortic regurgitation. Patients with acute aortic regurgitation should have immediate aortic valve replacement because death may occur within hours to days. In one study of patients with hemodynamically significant chronic aortic regurgitation treated medically, 75% were alive at 5 years after diagnosis (42,93). Of patients with moderate-to-severe chronic aortic regurgitation, 50% were alive at 10 years after diagnosis (42,93). The 10-year survival rate for patients with mild-to-moderate chronic aortic regurgitation was 85 to 95% (42,94).

In another study of 14 patients with chronic severe aortic regurgitation who did not

have surgery, 13 (93%) died within 2 years of developing congestive heart failure (80). The mean survival time after the onset of angina pectoris is 5 years (93).

During 8-year mean follow-up of 104 asymptomatic patients with chronic severe aortic regurgitation and normal left ventricular ejection fraction, 2 patients (2%) died suddenly, and 23 patients (22%) had aortic valve replacement (95). Of the 104 patients, 19 (18%) had aortic valve replacement because of cardiac symptoms and 4 patients (4%) had aortic valve replacement because of the development of left ventricular systolic dysfunction in the absence of cardiac symptoms. Multivariate analysis showed that age, initial end-systolic dimension, and rate of change in end-systolic dimension and resting left ventricular ejection fraction during serial studies predicted the outcome.

In a prospective study, at 24-month follow-up (range 7 to 55 months) of 17 patients, mean age 83 years, with congestive heart failure associated with unoperated severe chronic aortic regurgitation and a normal left ventricular ejection fraction, 15 patients (88%) were dead (77). At 15-month follow-up (range 8 to 21 months) of 8 patients, mean age 85 years, with congestive heart failure associated with unoperated severe chronic aortic regurgitation and an abnormal left ventricular ejection fraction, 8 patients (100%) were dead (77).

Medical and Surgical Management

Asymptomatic patients with mild or moderate aortic regurgitation do not require therapy. However, prophylactic antibiotics should be used to prevent bacterial endocarditis in patients with aortic regurgitation, according to American Heart Association guidelines (49). Echocardiographic evaluation of left ventricular end-systolic dimension should be performed yearly if the measurement is less than 50 mm but every 3 to 6 months if the left ventricular end-systolic dimension is 50 to 54 mm. Aortic valve replacement should be considered when the left ventricular end-systolic dimension exceeds 55 mm, even in the absence of cardiac symptoms (88). Aortic valve replacement should also be considered when the left ventricular ejection fraction approaches 50% before the decompensated state (74).

Patients with asymptomatic, chronic severe aortic regurgitation should be treated with hydralazine (96), nifedipine (97), or preferably angiotensin-converting-enzyme therapy (98) to reduce the left ventricular volume overload. Infections should be treated promptly. Systemic hypertension increases the regurgitant flow and should be treated. Drugs that depress left ventricular function such as beta-adrenergic blockers should not be used. Arrhythmias should be treated. Patients with aortic regurgitation due to syphilitic aortitis should receive a course of penicillin therapy. Prophylactic resection should be considered in patients with Marfan's syndrome when the aortic root diameter exceeds 55 mm (99).

Bacterial endocarditis should be treated with intravenous antibiotics. Indications for aortic valve replacement in patients with aortic regurgitation due to bacterial endocarditis are congestive heart failure, uncontrolled infection, myocardial or valvular ring abscess, prosthetic valve dysfunction or dehiscence, and multiple embolic episodes (100–102).

Congestive heart failure should be treated with sodium restriction, diuretics, digoxin if the left ventricular ejection fraction is abnormal, vasodilator therapy, and aortic valve replacement. Angina pectoris should be treated with nitrates.

Patients with acute severe aortic regurgitation should undergo aortic valve replacement immediately. Patients with chronic severe aortic regurgitation should have aortic

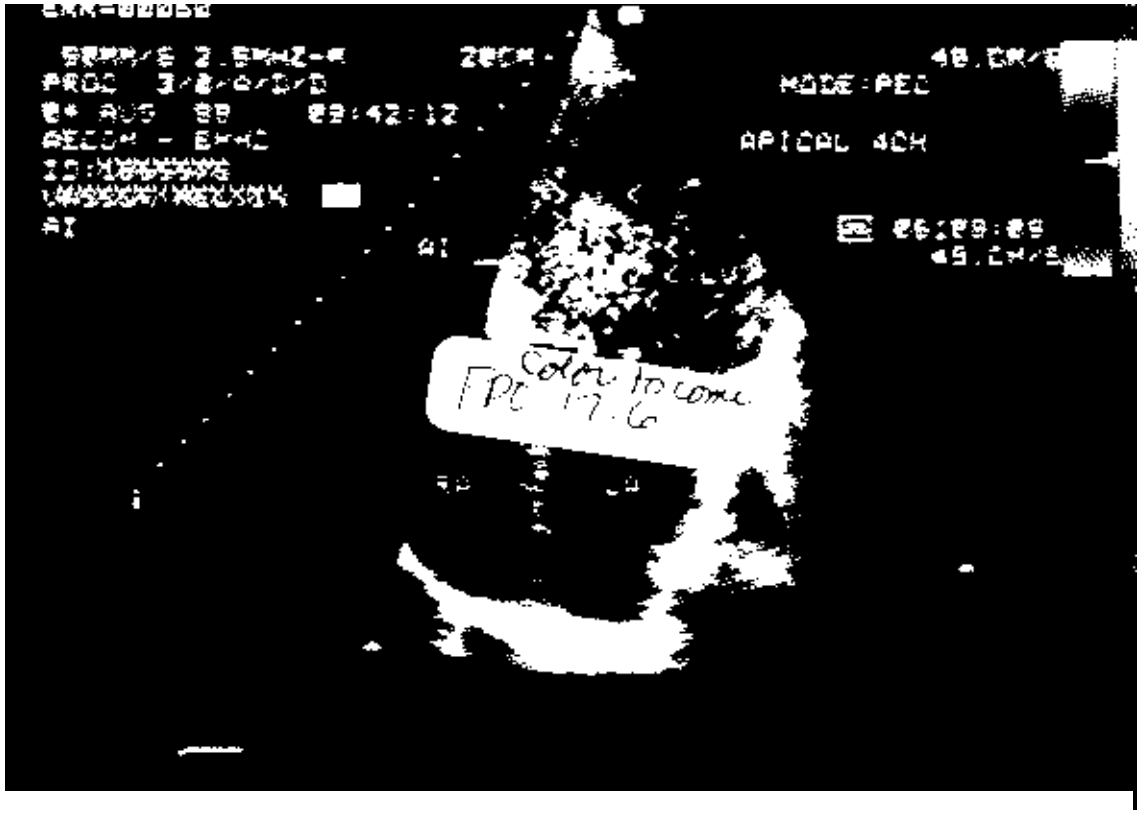

Figure 6 Two-dimensional echocardiographic image from an apical four-chamber view in an elderly patient with severe aortic insufficiency, showing a large diastolic aliasing color Doppler jet in the left ventricular outflow tract. AI = aortic insufficiency; LV = left ventricular cavity; MV = mitral valve leaflets; LA = left atrium; RA = right atrium.

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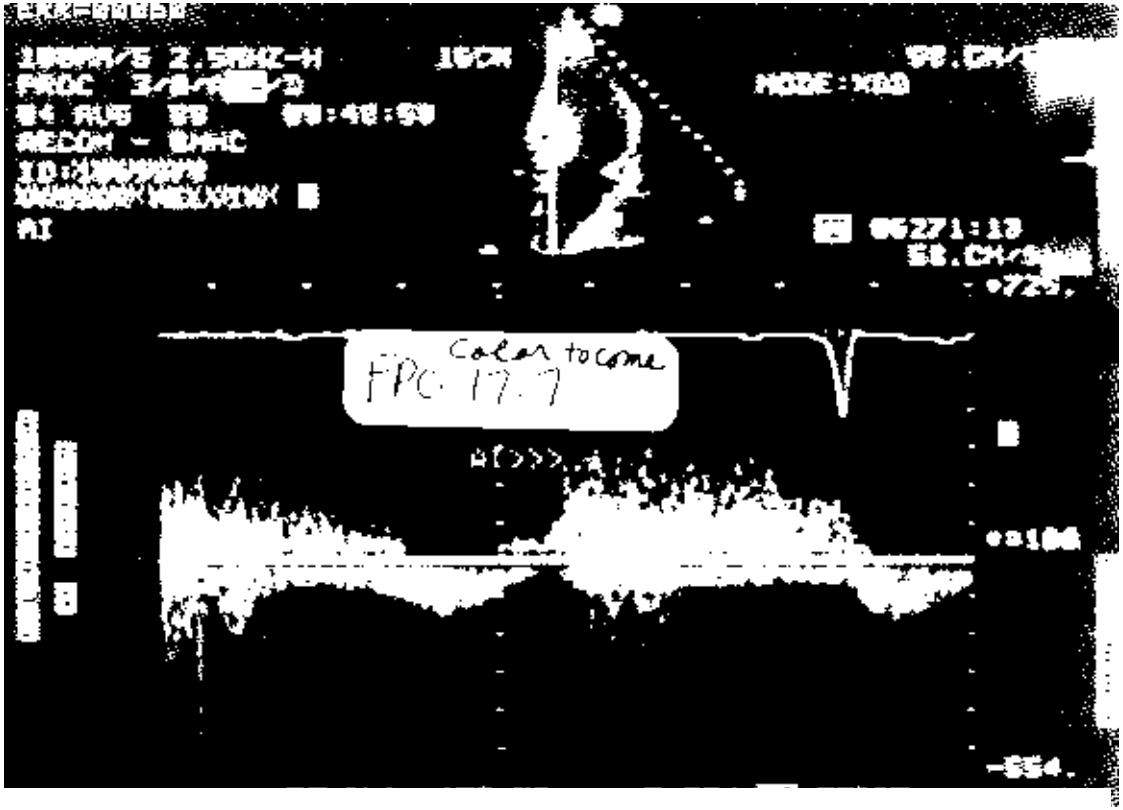

Figure 7 Continuous-wave Doppler recording of the velocity profile across the aortic valve in the same patient shown in Figure 6. A holosystolic decrescendo high-velocity profile is recorded from the left ventricular outflow tract, characteristic of aortic insufficiency. AI = aortic insufficiency.

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valve replacement if they develop symptoms of congestive heart failure, angina pectoris, or syncope (95). Aortic valve replacement should also be performed in asymptomatic patients with chronic severe aortic regurgitation if they develop left ventricular systolic dysfunction (95).

Elderly patients undergoing aortic valve replacement for severe aortic regurgitation have an excellent postoperative survival if the preoperative left ventricular ejection fraction is normal (103,104). If left ventricular systolic dysfunction was present for less than 1 year, patients also did well postoperatively. However, if the patient with severe aortic regurgitation has an abnormal left ventricular ejection fraction and impaired exercise tolerance and/or the presence of left ventricular systolic dysfunction for longer than 1 year, the postoperative survival is poor (103,104). After aortic valve replacement, women exhibit an excess late mortality, suggesting that surgical correction of severe chronic aortic regurgitation should be considered at an earlier stage in women (105).

The operative mortality for aortic valve replacement in elderly patients with severe aortic regurgitation is similar to that in elderly patients with aortic valve replacement for valvular aortic stenosis. The mortality rate is slightly increased in patients with infective endocarditis and in those patients requiring replacement of the ascending aorta plus aortic valve replacement. The bioprosthesis is preferable to the mechanical prosthetic valve for aortic valve replacement in the elderly as in elderly patients with valvular aortic stenosis (51). Patients with porcine bioprostheses require anticoagulant therapy for 3 months after hospital discharge and then may be treated with antiplatelet therapy alone (51).

In a prospective study, aortic valve replacement in 38 patients with severe aortic regurgitation normalized left ventricular chamber size and mass in two-thirds of patients undergoing surgery (106). At 9-month follow-up after aortic valve replacement, 58% of patients had a normal left ventricular end-diastolic dimension and 50% of patients had a normal left ventricular mass. During further follow-up (18 to 56 months postoperatively), 66% of patients had a normal left ventricular end-diastolic dimension and 68% of patients had a normal left ventricular mass. The left ventricular end-diastolic dimension normalized in 86% of patients with a preoperative left ventricular end-systolic dimension $\leq$55 mm. A preoperative left ventricular end-systolic dimension $>$55 mm occurred in 81% of patients with postoperative persistent left ventricular dilatation.

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18

Mitral Valvular Disease in the Elderly

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INTRODUCTION

The mitral valve undergoes structural changes related to aging (1–3). The anterior leaflet demonstrates lipid disposition, nodular thickening at the free edges, and atheromatosis of the ventricular surface. This atheromatosis differs from vascular atheromatosis in that thrombosis, hemorrhage, and calcification are not present. The posterior leaflet demonstrates small puckered scars and diffuse opacification of the leaflet. Microscopically, collagen fibers become disorganized, the posterior leaflet demonstrates fibroelastic hyperplasia, and there is microscopic calcification of both valve leaflets.

Most of these changes are thought to be secondary to years of stress and adaptive processes secondary to the stress. Usually such changes do not produce significant valvular dysfunction, and clinically the process is silent. Two degenerative aging processes, mitral annulus calcification and mucoid (or myxomatous) degeneration of the valve leaflets and chordae tendineae, however, can produce significant valvular dysfunction (4,5).

In certain elderly patients, the degenerative aging changes are severe enough to cause significant valvular dysfunction with clinical manifestations. In other elderly patients, the aging changes may be superimposed on inherited or acquired valvular disorders with resultant significant valvular dysfunction secondary to the combination of disorders. Some primary cardiac disorders such as rheumatic mitral valve disease, even though acquired early in life, may become clinically symptomatic only when the patient reaches his or her seventh or eighth decade, at which time the heart decompensates secondary to the years of accumulated stress from the valvular dysfunction. Another disease with possible mitral valvular involvement is coronary artery disease, which may not cause any mitral valvular dysfunction until the patient is elderly when the disease is first manifested as an acute infarction with mitral regurgitation. Some elderly persons will have an insignificant silent mitral valvular disorder until a systemic illness, such as an infection, affects the abnormal valve with the development of clinical symptoms (endocarditis).

Specific mitral valvular disorders in the elderly may produce clinical symptoms, which are similar to those in younger patients who have the same valvular disorders. In some elderly persons, however, the clinical manifestations are different from those usually seen in younger patients with the disease. Because of this different presentation, the valvular disorder may be clinically missed or the patient's symptoms are misdiagnosed as related

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to another abnormality. Furthermore, valvular disorders in the elderly can have more severe clinical manifestations than are usually seen in younger patients with the disorder and management will have to be modified.

MITRAL VALVULAR REGURGITATION

Mitral Valve Prolapse

Mitral valve prolapse (MVP) is a common valvular abnormality with distinct anatomical findings. The disorder occurs in all ages, with reported prevalence varying from 5 to 21% depending on the diagnostic technique and the population tested (6–9). Gross pathology typically reveals the mitral leaflets, both anterior and posterior, to be enlarged, redundant, and voluminous; they appear deformed, giving the appearance of a parachute, or what has been referred to as ''ballooning'' (Fig. 1). The posterior leaflet is more commonly involved or may be more severely affected than the anterior leaflet. Because of this involvement, the posterior leaflet may be twice the depth of the anterior leaflet, instead of the normal one-third to one-half. The annular circumference of the valve is increased, and the chordae tendineae are often elongated and generally thin. The commissures of

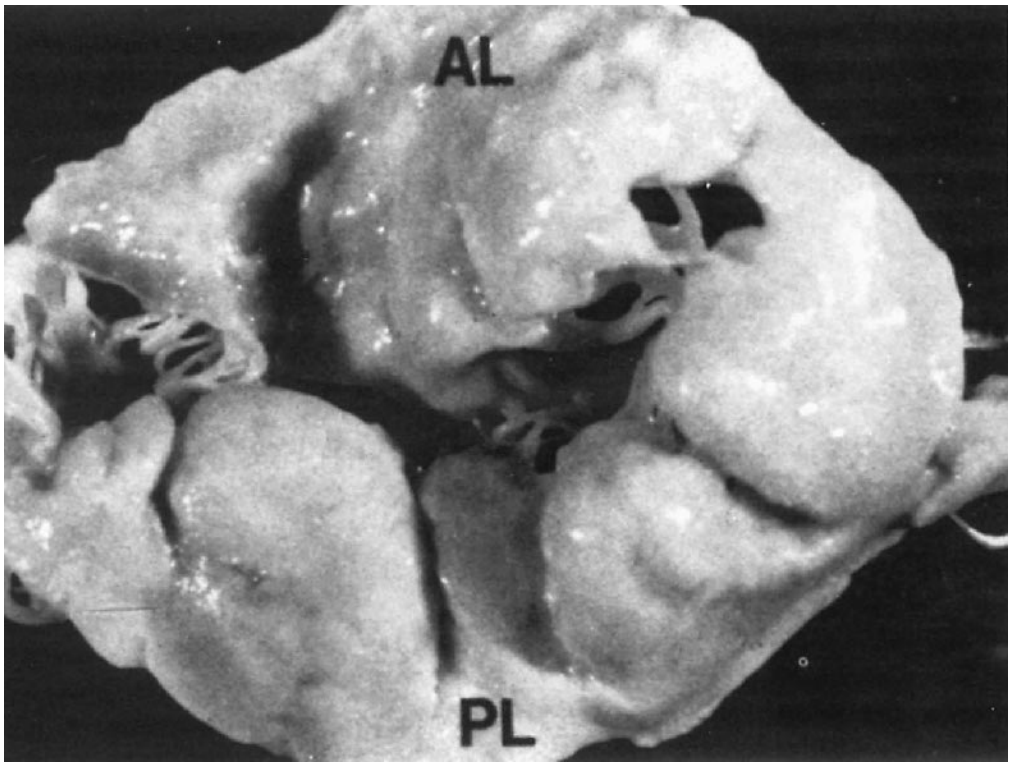

Figure 1 Excised mitral valve displaying gross changes of mitral valve prolapse. Leaflets are enlarged and redundant, giving the appearance of a parachute—''ballooning.'' AL = anterior leaflet; PL = posterior leaflet. (Reprinted with permission from Ref. 31.)

the leaflets do not demonstrate fusion, a finding that distinguishes MVP from a rheumatic valve.

Microscopically, abnormal collagen tissue replaces the normal homogeneous collagen of the fibrosa of the leaflets; the abnormal tissue demonstrates thinning, fragmentation, and loss of fiber orientation. The increase in the abnormal collagen tissue is mainly due to excessive mucopolysaccharides, which may be secondary to a fundamental abnormality in collagen metabolism (myxomatous degeneration) (10). This myxomatous degeneration leads to softening of the fibrosa with stretching of the affected leaflet, which causes prolapse of the leaflet into the left atrium. The annulus and chordae tendineae are also usually affected with degenerative changes similar to those in the fibrosa of the valve leaflets, and the elongated redundant chordae tendineae may also be responsible for producing prolapse of the leaflets.

Anatomically, the final structural abnormality of mitral valve prolapse is disproportion between the left ventricular volume and the mitral valve (Fig. 2). The valve is ''too big'' for the ventricle, or the ventricle is ''too small'' for the valve. In many cases this disproportion between the ventricle and the valve may not be present at the beginning of systole and only becomes evident during midsystole, as the ventricular volume dynamically decreases, at which time the valve becomes incompetent with regurgitation.

Numerous conditions, including Marfan's syndrome (11), Ehlers-Danlos syndrome (11,12), muscular dystrophy (13), congenital abnormalities, particularly atrial septal defect (14), and rheumatic heart disease (15), have all been associated with MVP. The specific pathogenesis of mucoid degeneration that results in MVP, however, remains unknown. Most likely, it is a nonspecific change that results from a number of factors, with a genetic etiology playing a major role in the majority of patients, particularly in the young and middle-aged persons with the disorder. Some studies (16,17) have shown as high as 50% of first-degree relatives of families of probands to demonstrate echocardiographic and

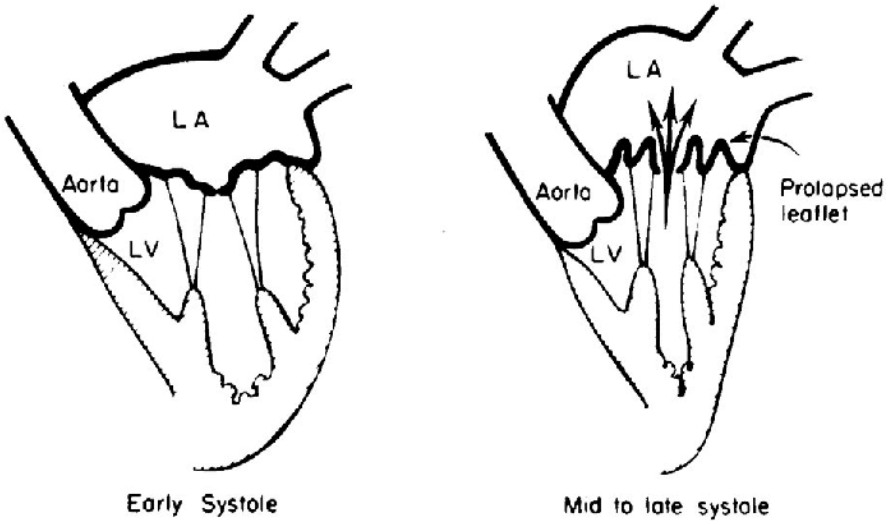

Figure 2 The mitral valve is noted to be large and redundant, but competent, at the beginning of systole. In mid-to-late systole, with changes in left ventricular volume, the valve is ''too large,'' and prolapse occurs with mitral insufficiency. (Reprinted with permission from Ref. 117.)

auscultatory findings of the disorder. The inheritance appears to be autosomal dominant. Studies (17,18) have found one parent to be affected in the majority of the patients studied and in studies of identical twins, the auscultatory and/or echocardiographic findings of MVP have been concordant.

In addition to a genetic basis for the pathological findings associated with MVP, some investigators speculate that the underlying mechanism is a continuing process of repeated minor injury and repair occurring during the cardiac cycle, superimposed on a mitral valve with minor congenital anatomical variations of the valve apparatus (19). This explanation would be compatible with the finding that MVP is uncommon in young children. After the growth spurt, a considerable increase in MVP is seen in late adolescence in both the general population and in first-degree relatives of persons with MVP. Also, a continuous wear-and-tear mechanism would possibly explain the difference in the clinical manifestations between older and younger persons with MVP. This may provide some answers to the questions of why the clinical presentation is different between older males and females with the disorder.

Pomerance (5) reported findings of severe mucoid degeneration of the mitral valve in approximately 1% of autopsies in patients over 50 years of age. Whether this mucoid degeneration related to aging is the major cause of the clinical entity, mitral valve prolapse syndrome, seen in elderly patients remains unclear.

Diagnosis of Mitral Valve Prolapse

The diagnosis of MVP is usually made from the physical examination and confirmed by the echocardiographic findings. On occasion, however, the physical examination, including the cardiac auscultatory findings, is completely normal, and the echocardiogram demonstrates findings of MVP (20). The general appearance of the person with MVP may be entirely normal, although one may be struck by the asthenic body habitus and thoracic bony abnormalities. Pectus excavatum, ''straight back,'' and scoliosis are so common that they may in some cases be considered part of the syndrome. Ansari (21) found in a series of 50 patients with straight back syndrome that 64% had MVP, whereas only 17.5% of age- and sex-matched controls demonstrated echocardiographic findings of MVP.

The typical auscultatory findings produced by MVP are a midsystolic click followed by a mid-to-late systolic murmur. These findings, however, can be quite variable in location and intensity. The click is thought to originate from the prolapsing redundant valve leaflets or the tensing of the chordae. A single systolic click may be heard, or multiple clicks may be present. The click may vary in timing and also be transient, disappearing from one examination to the next.

As with the click, the murmur is also variable in timing and intensity. The typical murmur occurs in mid-to-late systole and is ''blowing'' in quality. In some persons the murmur may be holosystolic, with radiation into the axilla, displaying all the qualities of a murmur of typical mitral regurgitation. In contrast, occasionally the murmur may have an ''ejection'' quality and be heard extremely well at the base. The ''honking'' and ''whooping'' murmurs associated with mitral incompetence have also been reported.

Variability of the systolic click and murmur is the hallmark of the auscultatory findings in MVP. This variability may be modified by bedside maneuvers (both physical and pharmacological), and it should be emphasized that the findings may be completely missed unless a specific effort is made to bring them out.

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Maneuvers that decrease left ventricular volume result in a smaller chamber size and accentuate leaflet or chordae redundancy. Therefore, earlier and more pronounced systolic prolapse of the mitral leaflet occurs and the murmur and click are audible earlier in systole, and the murmur is louder (Fig. 3). In contrast, maneuvers that increase left ventricular size delay the onset of the click and murmur in systole, and in most cases, the murmur is softer or may even disappear.

These maneuvers are quite helpful and are mandatory in attempting to elicit the typical auscultatory findings of MVP. Nevertheless, some investigators (19,20) have reported that 10 to 20% of persons with MVP remain ''silent'' to auscultation, even when maneuvers are performed.

The chest x-ray may confirm the thoracic bony abnormalities of a straight back, pectus excavatum, and scoliosis or may be entirely normal. In uncomplicated MVP, the cardiac silhouette is rarely enlarged. The electrocardiographic abnormalities seen in patients with MVP are usually nonspecific ST-T–wave changes with partial or total T-wave inversions, particularly localized to leads II, III, and aVF and occasionally involving left precordial leads (22,23). Almost all types of arrhythmias have been reported in patients with MVP, although the most common are supraventricular and ventricular premature contractions and ventricular tachycardia. Prolonged Q-T interval has been reported, as have bradyarrhythmias and Wolfe-Parkinson-White syndrome.

The echocardiogram is considered the most definitive laboratory test for confirming the diagnosis of MVP (24,25). Two distinctive M-mode echocardiographic patterns have been reported: the classic and most definitive is the abrupt late posterior displacement

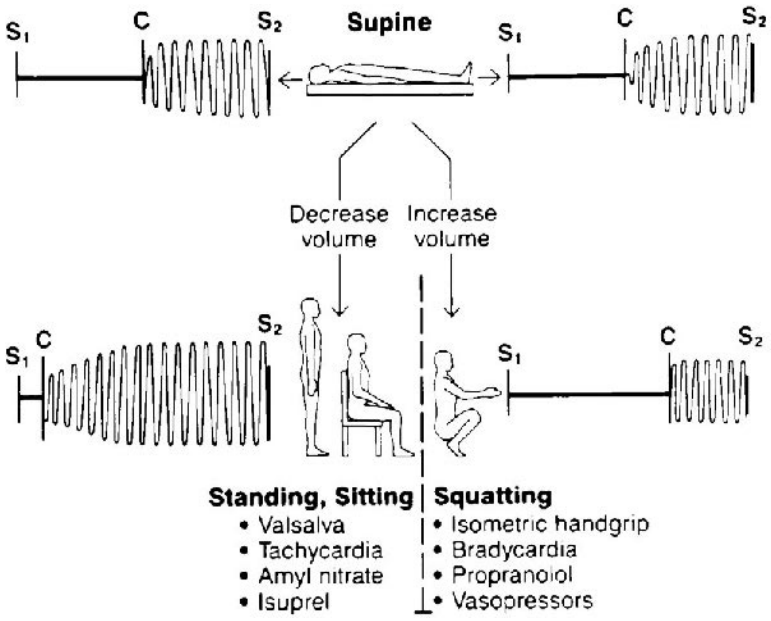

Figure 3 Typical auscultatory findings in mitral valve prolapse and change in intensity and timing of murmur and click with maneuvers. The variability of the timing and intensity of the murmurs depends on the position of the patient. (Reprinted with permission from Ref. 118.)

(prolapse) of either or both leaflets in mid and late systole, and the other finding is the ''hammocklike'' parasystolic displacement of the leaflets (Fig. 4). Two-dimensional echocardiography has been beneficial in determining echocardiographic criteria for diagnosing MVP. With two-dimensional echocardiography, the mitral annulus is clearly visible as a reference point, and systolic displacement of either the anterior or posterior leaflets into the left atrium can be readily appreciated (Fig. 5). Other two-dimensional echocardiographic findings of MVP are thickening of the mitral valve leaflets as a result of redundancy, dilatation of the mitral annulus, and coexistence of prolapse of other cardiac valves. Transesophageal echocardiography will provide better visualization of mitral valve and added details.

Left ventricular angiography is usually not necessary to make the diagnosis of MVP but can confirm the abnormality. In the right anterior oblique projection, the bulging of the leaflets (one or both) into the left atrium is considered diagnostic of MVP (Fig. 6). Care should be taken not to overdiagnose MVP in the presence of normal radiographic variants, since normal ''pouches'' or fornices of the normal valve may be misinterpreted as abnormal prolapse.

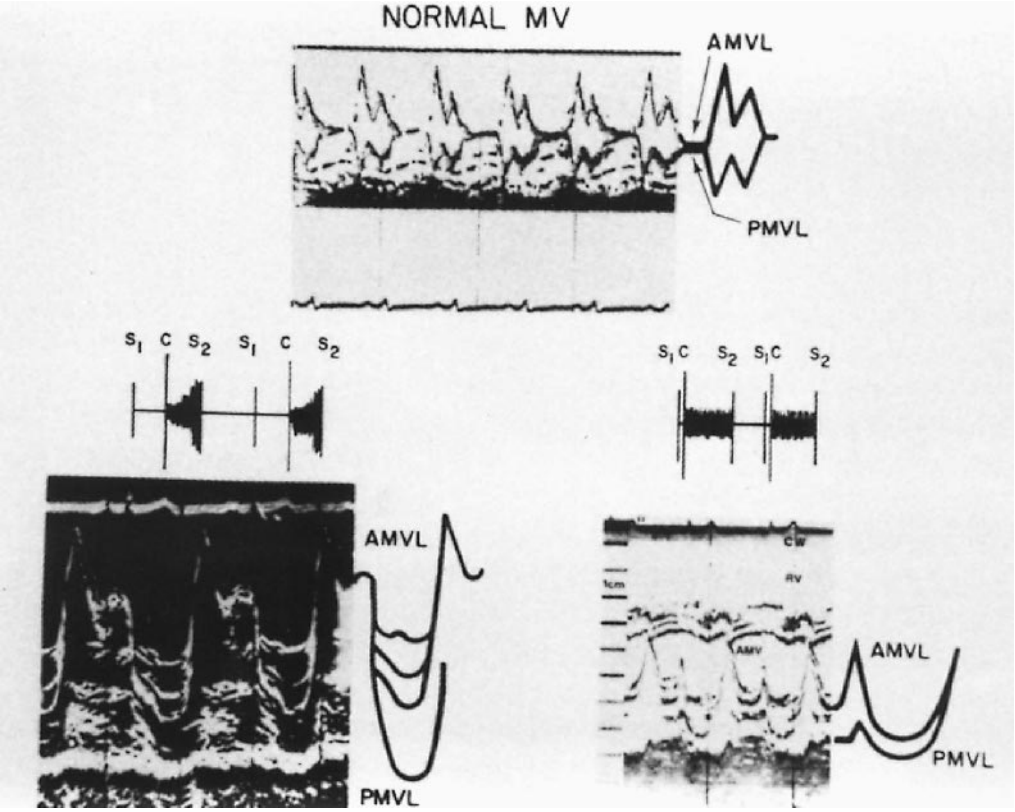

Figure 4 Normal M-mode echocardiogram; echocardiograms showing two types of mitral valve prolapse and simultaneous echocardiograms and phonocardiograms. AMVL = anterior mitral valve leaflet; PMVL = posterior mitral valve leaflet; MV = mitral valve. (Reprinted with permission from Ref. 117.)

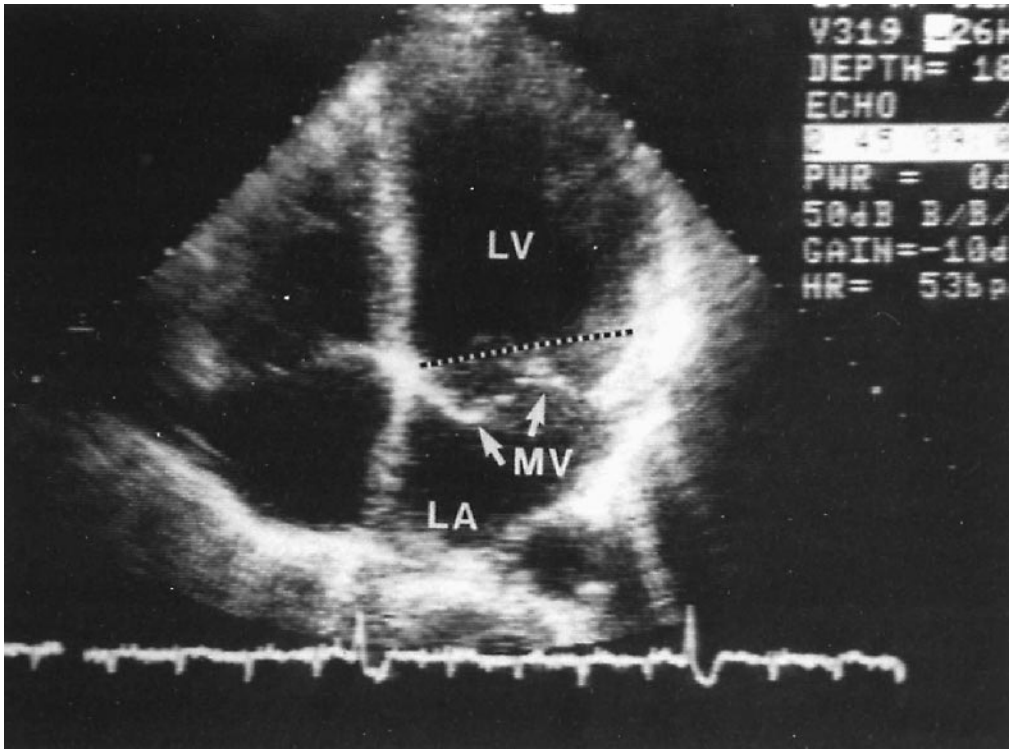

Figure 5 Two-dimensional echocardiogram (apical four-chamber view) demonstrating thickening and prolapse of leaflets above annulus plane. LA = left atrium; LV = left ventricle; MV = mitral valve. (Reprinted with permission from Ref. 119.)

Mitral Valve Prolapse Syndrome

Mitral valve prolapse syndrome (MVPS) is the presence of anatomical MVP accompanied by a set of clinical symptoms and features. The syndrome is considered the most common cardiac disorder seen by the practicing physician (26), and MVP is the most common etiology of mitral valvular incompetence for which mitral valve surgery is necessary (27,29).

Patients with MVP may be asymptomatic, although the majority will have symptoms (30,31). Symptoms are often nonspecific and include chest pain, palpitations, dyspnea, dizziness, easy fatigability, and anxiety attacks. On occasion, patients with MVP present with supraventricular tachycardia and, infrequently, ventricular tachycardia or ventricular fibrillation. There is a good deal of controversy concerning the actual prevalence of symptoms in persons with MVP compared to a matched control population. Deveraux et al. (32) found no difference in prevalence of chest pain, dyspnea, or anxiety between persons with MVP and a matched control group of subjects without MVP, whereas palpitations were more common in persons with MVP. The Framingham Heart Study (33) reported that chest pain, dyspnea, or syncope was not specifically associated with MVP.

Heart failure may develop in persons with MVP when mitral incompetence is severe. The heart failure can be insidious and progressive or may be abrupt, with development

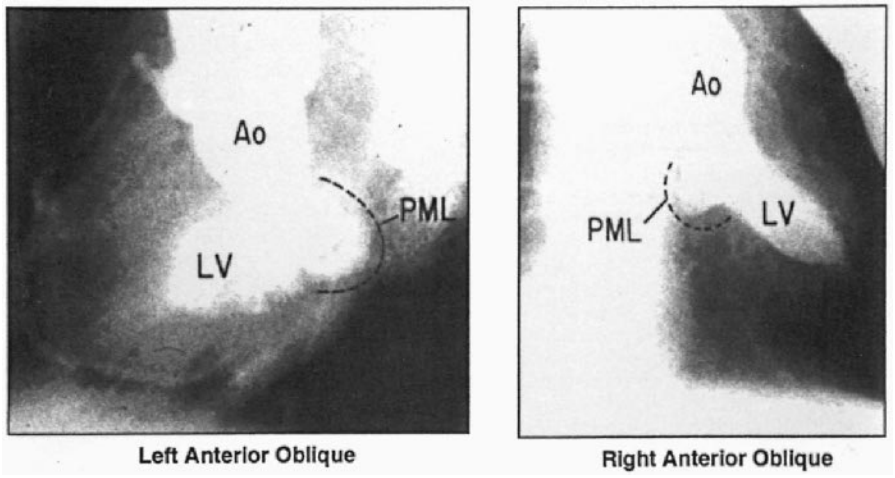

Figure 6 Left ventriculogram, end-systole, in the left anterior oblique and right anterior oblique projections in a patient with a flail posterior mitral leaflet (PML) secondary to a ruptured chordal structure. The dotted lines outline the extent of the posterior displacement of the leaflet at the end of ejection. Ao, aorta; LV, left ventricle. (Reprinted with permission from Ref. 120.)

of acute pulmonary edema when the severe mitral incompetence is related to an acute spontaneous rupture of the chordae tendineae.

Comparison of Elderly Patients and Younger Patients with MVP and MVPS

Mitral valve prolapse syndrome usually becomes clinically manifested in the third through the fifth decades and is more common in women than men in this age group (34,35). This gender difference has been reported by some investigators to decrease with age, although other studies have found approximately 2:1 female-to-male ratio, regardless of the patient's age (36).

Recently, MVP has become increasingly recognized in the population 60 years of age or older. The natural history of the disorder remains unclear, and it is not known if the condition in the elderly represents a sudden onset of the entity, or the disease has progressed to the point at which it becomes clinically recognizable.

Auscultatory and echocardiographic findings may be different between older and younger patients with MVP, and the difference most likely reflects the severity of the valvular regurgitation (Table 1). The frequency of an isolated systolic click or late systolic murmur declines with age, whereas holosystolic murmurs are more common in older patients. Differences in echocardiographic findings between age groups include a higher prevalence of pansystolic prolapse and flail valves in patients over 50 years of age. Furthermore, increased cardiac chamber dimensions are more common in older patients.

The majority of older patients with MVPS have symptoms similar to those of younger patients with the disorder (Table 2). In separate studies by Tresch (37) and Higgins (38), one-third to one-fourth of older patients (mean age 67 years) with MVP were asymptomatic, and the echocardiogram was obtained because of a heart murmur or click.

Table 1 Mitral Valve Prolapse in the Older Patient

1.	Holosystolic murmurs are common.
2.	Isolated systolic clicks are rare.
3.	Atrial fibrillation is not uncommon.
4.	Mitral regurgitation is more severe, compared to younger patients.
5.	LAE and LVE may be present, despite absence of symptoms.
6.	Echo findings of pansystolic prolapse and flail leaflet are common.
7.	Heart failure is a major complication, especially in males.
8.	Onset of heart failure may be abrupt or chronic.
9.	Mitral valve surgery is usually necessary.
10.	Results of valve surgery are excellent with relief of symptoms and improved survival.

Echo = echocardiography; LAE = left atrial enlargement; LVE = left ventricular enlargement.

When present, symptoms are usually nonspecific with palpitations and atypical chest pain not unusual. Even though studies have demonstrated approximately one-third of patients with MVPS will have symptoms thought to be related to arrhythmias, cardiac arrest did not occur in any of the older patients in Tresch (37) or Higgins' (38) studies. Thirteen percent to 35% of the patients in these two studies did demonstrate atrial fibrillation. Endocarditis was diagnosed in 10% and 8% of the patients, respectively.

In another study of older patients with MVPS, Kolibash and associates (39) found many older patients with MVPS to be significantly disabled (Table 2). Approximately 30% of the 62 patients over 60 years of age in their study presented with severe chest pain that had characteristics suggestive of ischemic pain in most cases; 26% had symptoms related to arrhythmias (syncope and palpitations); and two patients were successfully resuscitated following out-of-hospital cardiac arrest.

The main clinical feature that is different between older and younger patients with MVPS is the presence of severe mitral regurgitation with resultant heart failure (40). In younger patients, severe mitral regurgitation with resultant heart is rare, whereas with aging the risk of developing severe mitral regurgitation that necessitates valvular surgery significantly increases in patients with MVP. In 1976, Collins and associates (41) reported four patients, all over 65 years of age, who presented with heart failure. In two of the four patients the heart failure was of acute onset, 1 week or less. All four patients died, and at autopsy all four patients demonstrated severe myxomatous changes of the mitral valve and findings consistent with MVP; in two of the four patients, ruptured chordae were noted. Tresch (37) and Kolibash (39) in their studies also found heart failure to be present in a percentage of the older patients with MVPS.

In Tresch's study, 25% of patients over age 60 (mean 67) with MVP demonstrated heart failure and approximately 50% of these patients required valvular surgery (37). Kolibash and associates (39) found the percentage of older patients with heart failure secondary to MVP to be even higher than in Tresch's study: 42% of patients 60 years or older with MVP demonstrated heart failure and 80% of these patients required valvular surgery. Other studies (42–45) have confirmed the influence of age upon the development of severe mitral valve regurgitation and heart failure in patients with MVP. In a study of residents of South Wales, Australia, Wilcken and associates (45) found the risk of severe mitral regurgitation and valve replacement to be minimal below the age of 50 years in persons with MVP, but approached 4% by age 70 years. The authors hypothesized that the progressive severity of mitral regurgitation in older patients with MVP is due to progressive myxomatous

Table 2 Clinical Findings in Elderly Patients with Mitral Valve Prolapse

Study (Ref.)	Number of patients	Ages (years)	Asymptomatic	Absence of murmur	AF	Chest pain	Palpitations	Syncope	Endocarditis	CHF
37	62	60–81 (67)[a]	0	1 (2%)	3 (5%)	20 (32%)	11 (18%)	5 (8%)	—	26 (42%)
38	40	50–90 (66)[a]	15 (38%)	11 (28%)	14 (35%)	6 (15%)	15 (38%)	—[b]	3 (8%)	—[b]
39	40	61–86 (67)[a]	11 (28%)	5 (13%)	4 (10%)	9 (22%)	20 (25%)	4 (10%)	4 (10%)	10 (25%)

AF = atrial fibrillation; CHF = congestive heart failure.
[a] Mean age in parentheses.
[b] Not mentioned.

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changes in the valve related to response to injury (wear-and-tear theory) occurring over time.

Besides age, numerous studies (42–46) have found an association between male gender and severity of mitral regurgitation, plus complications in patients with MVP. Wilcken and associates (45) found the calculated annual risk of mitral valve replacement for severe regurgitation was 1.8% in men at 60 years of age, compared to 0.7% for women and 3.5% vs. 1.2%, respectively, at age 70 years. Tresch and associates (46), in a study of 30 patients with MVP who required mitral valve surgery for severe mitral regurgitation, found 20 of the patients to be males. The explanation for this gender difference is unclear. Some investigators have related this gender difference to an increase of blood pressure and physical activity in males. Both factors would be compatible with the wear-and-tear theory, with increased force on the mitral valve apparatus causing further valvular changes and more severe regurgitation.

The recognition of the progression from mild or moderate regurgitation to severe mitral regurgitation with or without clinical heart failure in older patients with MVP has important clinical implications. In many older patients with MVP, the development of severe mitral regurgitation will be abrupt with the sudden development of pulmonary edema, whereas in other older patients the presentation will be more chronic. In Tresch's study (46) of patients with MVP who required valve surgery, the mean age of the patients was 59.2 years, range 25 to 72, and the majority (20) were male. Patients were usually aware of having a heart murmur for many years (mean duration 15.3 years), although symptoms of heart failure were of recent onset; 24 of the 30 patients had symptoms less than 6 months, and in some patients the initial manifestation of the disorder was acute pulmonary edema. At the onset of heart failure, the majority of patients demonstrated a loud holosystolic murmur characteristic of severe mitral regurgitation. In 2 of the 30 patients, instead of the typical blowing murmur of severe mitral regurgitation, an ejection-type murmur was heard best at the upper sternal border, mimicking the murmur of aortic stenosis. A systolic click was not detected in any of the patients, even though auscultatory findings before the onset of heart failure were commonly the typical mid-to-late systolic murmur preceded by a nonejection systolic click. However, prior to the onset of heart failure, some patients were unaware of ever having a heart murmur. Forty-three percent of the patients demonstrated atrial fibrillation and all had chest x-ray findings of pulmonary congestion, although only moderate cardiomegaly was usually noted. At the time of surgery, all patients demonstrated a myxomatous mitral valve with a dilated mitral annulus and redundant leaflets. Of the 30 patients, 17 demonstrated rupture chordae tendinae. In a follow-up study, Kolibash and associates reported on 86 older patients with MVP and significant mitral regurgitation. (47) Fifty-three were males and 73 (85%) of the 86 patients presented with heart failure. Seventy-six (88%) required mitral valve surgery. In the majority of patients (72%), a heart murmur was detected before age 50; however, only 11 patients (13%) became symptomatic and underwent heart surgery before age 50. As in the Tresch study (46), the majority of patients were asymptomatic for a prolonged period (average 24 years) after detection of a murmur, but once they became symptomatic mitral valve surgery was necessary in a relatively short period. At surgery, all valves were described as enlarged and floppy; ruptured chordae were noted in 51% of the patients. Other investigators (48,49) have reported similar findings in patients with MVP who demonstrate chordae tendinae rupture; in this subset of MVP patients, the onset of heart failure is often compatible with acute severe mitral valvular regurgitation superimposed on mild chronic regurgitation.

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In certain patients with MVPS, the clinical deterioration will not be so abrupt, and there will be a slow development of mild or moderate valvular regurgitation progressing to severe regurgitation. Many of these patients will remain asymptomatic or have only mild symptoms for many years even though the clinical findings of regurgitation are severe and cardiac chamber dimension is increased.

Endocarditis and Cerebral Ischemic Events

Other complications that must be considered in elderly patients with MVP are infectious endocarditis and cerebral thromboembolism. Clement and associates (50), in a case-controlled study of hospitalized patients who had echocardiographic findings of MVP and who lacked any other known cardiovascular risk factors for endocarditis, found a significantly higher risk for endocarditis in patients with MVP than for those without MVP. Similar conclusions have been reached in other studies (51–53). McMahon and associates (53), in a review of the literature, reported that the risk of endocarditis in patients with MVPS is two to three times greater in men than women, with the risk most marked in patients over age 45 when the MVP is associated with mitral incompetence. The absolute risk of endocarditis in MVP patients without clinical or Doppler findings of mitral valvular incompetence is considered to be so low that prophylactic antibiotics are not considered necessary in this subset of patients with MVP (53–55).

Patients with MVP have been found to be at increased risk for cerebral ischemic events (56–61). Sandok and Guiliani (56), in a study of 1138 persons with MVP (mean age 48 years), found a 3.5% incidence of cerebral ischemic events and suggested that the prevalence of such events in persons with MVP was four times greater than the rate expected in the normal population. Interestingly, as in patients with MVPS who require valvular surgery and in MVP patients who develop endocarditis, the association of MVP with ischemic cerebral events has been found to be more common in men than women (57,58). When comparing younger (mean age 34 years) and older (mean age 65 years) persons with MVP, Barnett and associates (58) concluded that MVP was associated with cerebral ischemia and/or cerebral infarction events in younger persons with the disorder but not in older persons. Other studies (57,59,60) have reported similar findings, although in the Sandok and Guiliani study (56) the incidence of MVP-associated cerebral ischemia did not vary with patient age.

Despite the increased prevalence of cerebral ischemic events in patients with MVP, most authorities (56,58,59) do not recommend prophylactic anticoagulation or antiplatelet therapy in patients with MVP who have not had a cerebral ischemic event. In elderly patients with MVP who experience a cerebral ischemic event, a thorough evaluation should be performed to rule out other potentially responsible etiologies before attributing the event to MVP. When no other mechanism is recognized, MVP may be presumed to be the etiology and antiplatelet drugs are recommended. In patients with recurrent cerebral events thought to be related to MVP, anticoagulation is suggested.

Rheumatic and Other Etiologies of Valve Incompetence in the Elderly

In addition to MVP, the other disorders producing mitral valvular incompetence in elderly patients include rheumatic heart disease, coronary artery disease, and calcified mitral annulus. The disorders of coronary artery disease and calcified mitral annulus with resul-

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tant mitral incompetence (acute and chronic) are discussed in Chapters 12 and 19, respectively.

Residual rheumatic heart disease is found in the elderly. Although the disorder is less common than in the general population, the incidence of rheumatic mitral valvular disease in the elderly is higher than commonly realized. Hargreaves (62), in an autopsy study, found rheumatic mitral incompetence or stenosis or both in 3.1% of autopsies in patients over the age of 50. Most investigators have reported mitral incompetence to be the predominant valvular lesion in elderly patients with rheumatic mitral valve disease. As in MVP, echocardiography with Doppler examination is very useful in diagnosing and assessing the severity of rheumatic mitral valvular incompetence.

Mitral Valve Surgery in Elderly Patients with Mitral Regurgitation

Mitral valve surgery for severe regurgitation is followed by marked improvement in cardiac symptoms; however, in the past, mitral valve surgery has been associated with a relatively high hospital mortality, particularly in older patients (63,64). Age is considered to be an independent predictor of survival in patients having mitral valve surgery (65). Some studies have reported an operative mortality as high as 15% in patients 70 years or older, compared to 4.5% mortality in patients <70 years of age (66). Other studies have noted even higher operative mortality in this age group and in octogenarians the operative mortality has been reported to be as high as 60% when emergency mitral valve replacement with coronary bypass grafting was necessary (67,68). Besides age, most studies have found urgent surgery, presence of coronary artery disease, functional class, and depressed left ventricular function to be significant predictors of increased mortality (69,70).

In the last decade, with newer operative techniques, better myocardial protection, and the increasing percentage of patients undergoing valve repair rather than replacement, results of surgery for mitral regurgitation in elderly patients has become more encouraging. Cohn and associates (71) reported a 2.3% operative mortality in patients who had mitral valve surgery for severe regurgitation at Brigham and Women's Hospital in Boston from 1988 to 1990. The mean age of the patients was 62 years with 26% of the patients >70 years. Age was not correlated with operative mortality in this study; one death (3%) occurred in the 33 patients >70 years compared to two deaths (2%) in 94 patients <70 years. Sixty-three percent of the total patients demonstrated myxomatous valves at the time of surgery and over 50% of the total patients had their valve repaired. Patients >70 years were more likely to have their valve repaired than younger patients. The investigators attributed their improved operative success, compared to earlier reported results, to newer operative and postoperative management techniques, especially valve repair. Other studies have reported similar results with an improved success with repair, instead of replacement of the mitral valve in patients with severe regurgitation (72–74). Moreover, the increased number of valves repaired, instead of replaced, has significantly increased in the last decade, which most likely reflects the improvement of surgical techniques, plus the increased prevalence of myxomatous valves as the etiology of severe mitral regurgitation in patients undergoing valve surgery.

In a recent study, Shapira and associates reported on the success of valve surgery performed in 147 patients >75 years between 1992 and 1995 at the Boston Medical Center (75). Thirty of the 147 patients had mitral valve surgery and 12 patients had both mitral and aortic valve surgery. The 30-day mortality was 7.5%, and actual survival at 55 months

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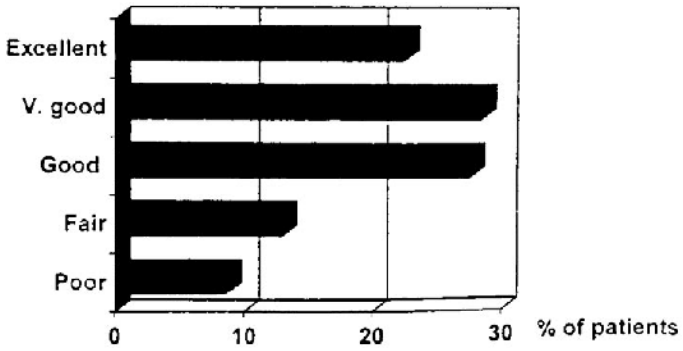

Figure 7 Health self-perception. Summary of the patients' responses to the first question being asked to define their overall health status at the time of follow-up. (Reprinted with permission from Ref. 75.)

was equivalent to a general age-, race-, and gender-matched population. Quality-of-life assessment demonstrated 78% of the patients defined their health status between good and excellent (Figs. 7 and 8) and 81% stated that the operation improved their health status.

The Mayo Clinic compared their results with mitral valve surgery in 409 patients with severe regurgitation between the periods of 1980–1984 to 1985–1989, with specific assessment of the success of surgery in different age groups (76). In patients <75 years, operative mortality decreased from 7% in 1980–1984 to 1.1% in 1985–1989. The operative mortality also improved between the two periods in the patients ≥ 75 years, although the improvement was not as impressive as in younger patients (31% to 12%, respectively). In this study, 76% of the patients demonstrated degenerative MVP and a ruptured chordae was present in 65% of patients. The surgical procedure was valve repair in 48% of the patients and coronary bypass grafting was performed in 24%. Independent predictors of operative mortality included age, urgency of operation, and functional class. When assessing predictors of late mortality, the most powerful predictor was left ventricular ejection

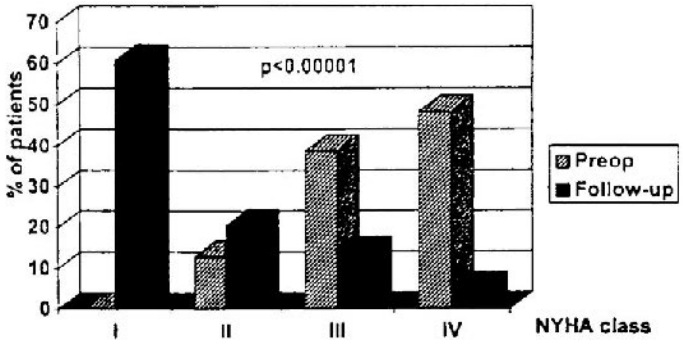

Figure 8 Functional capacity. Summary of the patients' responses to the third question evaluating their own functional capacity. Preoperative vs. follow-up NYHA functional class. (Reprinted with permission from Ref. 75.)

fraction, followed by patient's age. Multivariate analysis of age-adjusted survival showed that, overall, age was not associated with long-term excessive mortality compared to expected survival curves (Fig. 9).

More recently, Mayo Clinic reported on their surgical experience with mitral valve regurgitation in 825 patients operated on between 1980 and 1991 (77). Three hundred and twenty-seven patients were <65 years, 497 were ≥65 years, and 167 patients were ≥75 years. Patients ≥65 years compared to patients <65 years had more ischemic mitral regurgitation (25% vs. 18%), class III–IV symptoms (69% vs. 53%), coronary artery disease (54% vs. 33%), and associated coronary surgery (46% vs. 29%). The two groups, however, had similar left ventricular ejection fractions and valve repair was equally feasible (57% vs. 59%). As in their earlier studies, operative mortality was higher in the older patients (11.5% vs. 4.9%), although surgical mortality significantly improved in all age groups throughout the study period: operative mortality in the period 1988 to 1991 was 3.8% in patients <65 years, 3.8% in patients ≥65 to <75 years, and 7.7% in patients ≥75 years, compared to a mortality of 6.8, 21, and 29%, respectively in 1980 to 1983. Postoperative survival was worse in the elderly patients but observed to expected survival ratios were similar in the three age groups.

Based upon the findings of the recent studies of mitral valve surgery it appears that despite the higher operation mortality in elderly patients, mitral surgery for severe regurgitation is beneficial in this age group with a marked improvement in symptoms and quality of life plus the observed to expected survival ratio is similar to younger patients. Furthermore, operative success has continually improved in the last decade in both elderly and younger patients, which most likely reflects the increase in successful valve repair and the increased prevalence of degenerative myxomatous valve disorders. It should be emphasized that the difference in operative mortality between elderly and younger patients with severe mitral regurgitation is primarily related to the worse outcome in the patients 75 years or older. Patients aged 65 to 75 years, in general, have surgical outcomes similar

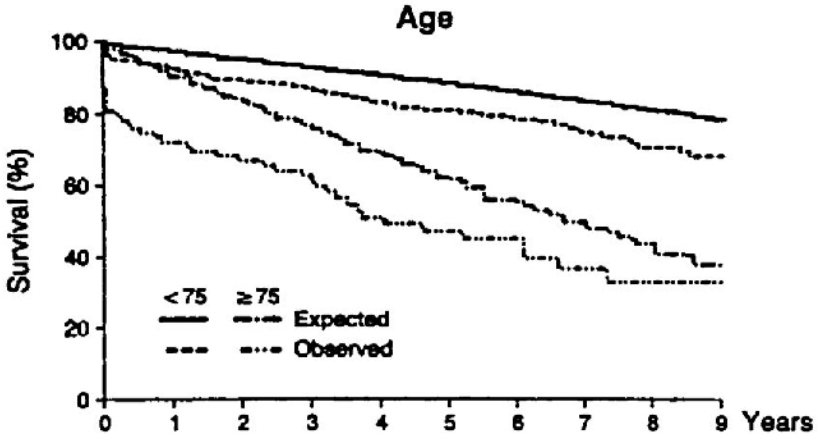

Figure 9 Graph of postoperative survival according to age in patients ≥75 years or <75 years. For each group, the expected survival curve is indicated. Survival was significantly different between the two groups, but at 9 years survival represented 87% of the expected survival in each group. (Reprinted with permission from Ref. 76.)

to younger patients. Therefore, mitral valve surgery should be considered as a reasonable option in selective elderly patients with severe regurgitation.

Timing of Valve Surgery in Elderly Patients with Mitral Regurgitation

One of the most difficult problems when managing patients with severe mitral regurgitation is the proper timing of surgical intervention (medical management of heart failure, arrhythmias, and endocarditis are discussed in Chaps. 23, 24, 26, and 28, respectively). When to recommend valve surgery in patients with mitral regurgitation is a difficult decision regardless of patient's age, but the decision is particularly difficult in elderly patients in whom the risk of cardiac surgery is higher than in younger patients.

The natural history of mitral regurgitation is poorly defined, with some studies reporting survival roles of 70% at 10 years, whereas survival rates of 50% at 5 years have been noted in other studies (78,79). Also, morbidity associated with mitral regurgitation has been inconsistently reported. However, it is well established that some patients with mitral regurgitation will have a long clinical course free of symptomatic heart failure. Despite this lack of symptoms, significant left ventricular dysfunction occurs, and when symptoms of heart failure do appear irreversible myocardial damage is present (80,81). Such ventricular dysfunction is a major source of poor outcome following valvular surgery. Waiting for symptoms to indicate surgical correction of mitral regurgitation is associated with excessive mortality (82) and morbidity with increased incidence of significant postoperative left ventricular dysfunction and heart failure (83,84). Studies have demonstrated clinical heart failure is common postoperatively in patients undergoing mitral valve surgery, usually related to left ventricular dysfunction, and is associated with a fivefold increase in mortality (84).

Preoperative markers of left ventricular dysfunction are not precise in patients with mitral regurgitation, although increasing left ventricular dimensions and decreased ejection fraction are considered important predictors. It is now generally accepted that left ventricular dimension in the range of 45–50 mm or a resting left ventricular ejection of $<50\%$ are two markers that are accepted as indicators for valve surgery in asymptomatic patients with chronic mitral regurgitation (85–87). Such markers may be determined by periodic echocardiography or radionuclide angiography. Some authors recommend obtaining the examinations every 6 to 12 months in patients with severe chronic mitral regurgitation.

Recently, the Mayo Clinic investigated the issue of the proper timing of surgical intervention in patients with severe mitral regurgitation (88–90). They initially reported the clinical outcome of 229 patients with mitral regurgitation due to flail leaflets (88). Baseline clinical characteristics included a mean age of 66 years; 70% were male, left ventricular ejection fraction was 66%, and 3+ or 4+ mitral regurgitation by Doppler echocardiography was present in 87% of the patients. The 86 patients who were treated medically had a mortality rate significantly higher than expected, based on U.S. population. At 10 years, follow-up rates of heart failure, atrial fibrillation, and death or surgery were 63, 30, and 90%, respectively. All patients who had valve surgery demonstrated flail leaflets and all but two patients had ruptured chordae. Mitral valve repair was performed in 66% of the patients who had surgery and the operative mortality was 4%. In multivariate analysis, surgical correction of mitral regurgitation was associated with a reduced mortality rate. The investigators concluded that mitral regurgitation is not a benign disorder and is associated with significant morbidity and mortality. Moreover, surgery is almost unavoid-

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able within 10 years after diagnosis of severe mitral regurgitation secondary to flail leaflets and valve surgery is associated with an improved prognosis. Therefore, valve surgery should be considered early in the course of the disease.

In a follow-up study (90), the Mayo Clinic group compared outcomes of a group of 63 patients with severe mitral regurgitation secondary to flail leaflets who had early valve surgery (within 1 month after diagnosis) to a group of 158 patients with mitral regurgitations initially treated medically (80% whom were operated on later). The mean age of the groups was 61 and 67 years, respectively. At follow-up, the early surgery group had an improved survival rate and lower incidence of cardiovascular deaths, heart failure, and new chronic atrial fibrillation. As in their early study, over 65% of the surgical patients had valve repair. Operative mortality was 1.6% in patients who had early surgery and 6.3% in patients in whom surgery was delayed. Age of patient was an independent determinant of surgery.

Based upon the results of their studies, the Mayo Clinic investigators advocate early surgical intervention in certain asymptomatic patients with severe mitral regurgitation, even when ejection fraction is $\geq$60% and left ventricular end systolic dimensions are less than 45 min. The investigators, however, emphasize the importance of having a low operative mortality (1 to 2%) verified by post performance, and further stress the significance of patient's age when deciding upon early surgery in asymptomatic patients. In elderly patients $\geq$75 years (a group that has been shown to have increased operative mortality), conservative management may be appropriate until symptoms occur, or evidence of significant left ventricular dysfunction is present.

In summary, valvular surgery should be considered in elderly patients with mitral valvular regurgitation who have significant symptoms and are not functionally incapacitated from comorbidities. In addition, mitral valve surgery should be considered when indicators of significant left ventricular dysfunction are present even in the absence of severe or limiting symptoms. In some patients $<$75 years with severe mitral regurgitation who are without significant comorbidities and have a mitral valve disorder that is preoperatively considered suitable for repair, early surgery may be considered, regardless of ventricular size or ejection fraction. In asymptomatic patients $>$75 years, due to the high mortality associated with surgery, a conservative approach is recommended.

MITRAL VALVULAR STENOSIS

Mitral valvular stenosis in the adult is usually always rheumatic in origin. Mitral ''stenosis'' has been reported to occur secondary to severe annular calcification in patients with small hypertrophied ventricles (91) (for details concerning annular calcification see Chap. 19). Mitral valvular stenosis commonly manifests clinically in the third or fourth decade, and studies have reported that the average age of death in patients with mitral stenosis is between 40 and 45 years (92). However, certain patients with mitral stenosis survive into their seventh and eighth decades, with the patient unaware of having the valvular disorder. Limas (93), in an autopsy study, found the incidence of mitral valvular stenosis to be 2.5% in patients older than 65 years; the mean age of the patients was 77 years, and the oldest patient was aged 86 years. Only 35% of the 39 patients with mitral stenosis had a history rheumatic fever. In 65% of the cases, mitral stenosis was the only valvular abnormality. Review of the patients' clinical findings revealed that the typical diastolic murmur of mitral stenosis was detected in only 40% of the patients, although

50% had atrial fibrillation and heart failure was the major clinical manifestation. The average duration of atrial fibrillation before death in these patients was 8 years. Clinical evidence of embolization was noted in 35% of the patients with embolization resulting in a cerebral event in the majority of patients.

Sherrid and associates (94) reported 18 patients with mitral stenosis in whom the diagnosis was unsuspected until an echocardiogram was performed. The median age of these patients was 72 years; only one patient was less than 50 years of age. Of the 18 patients, 8 were referred for echocardiogram because of evaluation of heart failure, 3 patients were referred because of cerebral vascular accidents and atrial fibrillation, and 5 patients were referred for aortic valve disease. Before the echocardiogram, a diastolic murmur was not noted in any of the 18 patients. The authors speculated that seven patients had coexisting conditions besides mitral stenosis that may have obscured the auscultation findings of mitral stenosis, although after the echocardiogram was performed, a diastolic murmur was detected in 8 of the 13 patients examined. The degree of stenosis varied from mild to severe, with a valve area less than or equal to 1.5 cm^2 in 8 patients. After evaluation, two patients underwent mitral valve surgery, with improvement of heart failure, and three patients were begun on anticoagulation therapy. An additional two patients were offered surgery and balloon valvuloplasty, respectively, but declined.

As noted in these two studies, the diagnosis of mitral stenosis in elderly patients is frequently missed. Occasionally, truly silent mitral stenosis occurs; that is, mitral stenosis without an appreciative apical murmur (95,96). More often, the murmur may be overlooked on examination, especially if there is a low index of suspicion or if other medical conditions are present that complicate the physical examination. If the suspicion is high, even if a diastolic murmur is not detected, echocardiography should be performed, which makes the definitive diagnosis. In addition, echocardiography and Doppler echocardiography should be able to assess the severity of the stenosis. The elderly patient, especially if the patient is a woman, who presents with atrial fibrillation and demonstrates findings of embolization should arouse suspicions that underlying mitral stenosis may be the etiology of the patient's symptoms. Also, the clinical picture of an elderly patient presenting with pulmonary congestion with radiographic findings of an isolated enlarged left atrium and pulmonary hypertension should alert the physician that mitral stenosis may be present.

Management of Elderly Patients with Mitral Stenosis

As in the younger patient with mitral stenosis, many elderly patients with this valvular disorder can be treated medically. Digitalization and/or verapamil, diltiazem, or a β-blocker will slow the ventricular heart rate if atrial fibrillation is present, and diuretics will control the congestive symptoms. ''Unloading therapy'' with vasodilators is not considered beneficial in patients with mitral stenosis and may result in a significant decrease in cardiac output (97). Anticoagulation to prevent embolization is considered beneficial in patients with mitral stenosis who demonstrate atrial fibrillation, and some authorities consider anticoagulation mandatory in all patients with mitral stenosis regardless of the patient's heart rhythm. The role of interventional therapy to prevent recurrent embolization in patients with mitral stenosis is controversial. Some authorities recommend valvular surgery or valvuloplasty in all patients with mitral stenosis who have experienced embolization regardless of the severity of the stenosis (98). Other authorities favor medical ther-

apy with anticoagulation unless the stenosis is significant or the patient has recurrent embolization while taking anticoagulation (99,100).

In elderly patients with pure mitral stenosis and a critical valve area of 1.0 cm^2, interventional therapy is necessary. Rather than mitral valve replacement, open mitral commissurotomy may be an option in certain elderly patients with mitral stenosis. Open commissurotomy in this age, however, is usually quite low. Unfortunately, the majority of stenotic valves in this age group are usually calcified and severely deformed, with associated significant mitral incompetence, and successful commissurotomy is not possible.

Percutaneous Balloon Mitral Valvuloplasty

In the last decade following the report of the first successful balloon dilatation for mitral stenosis in 1984 by Inone and associates (101), the use of percutaneous balloon valvuloplasty has markedly increased (Fig. 10). Comparative studies have shown that mitral balloon valvuloplasty is as effective and safe as surgical commissurotomy and is as cost-effective (102,103). Procedure mortality is $<1.0\%$ and associated morbidity is unusual; long-term follow-up has demonstrated 80% of patients to be in New York Heart Association functional class I, and mitral restenosis is uncommon (104,105). The most common complication associated with mitral balloon valvuloplasty has been mitral regurgitation, reported to occur in 1 to 6% of cases (102,105,106). Success of the procedure is directly related to preprocedure echocardiographic valve assessment (107,108).

As expected with an intervention that does not require general anesthesia or thoracotomy and may be performed in patients with general debilitating conditions, percutaneous

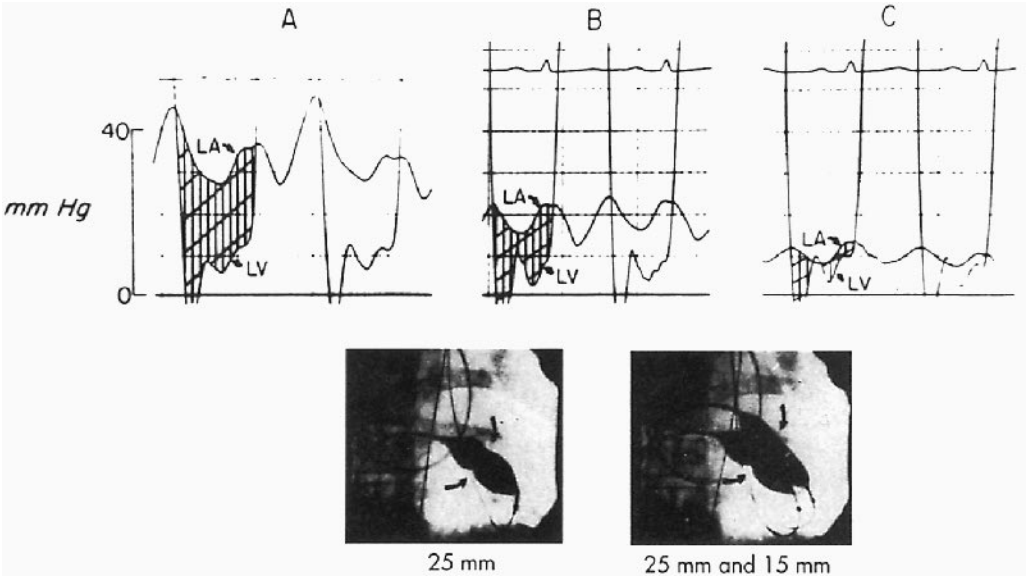

Figure 10 Hemodynamics of balloon mitral valvuloplasty: baseline (A), and after single (B) and double (C) balloon techniques. Note the near complete abolition of gradient when simultaneous inflation of two balloons is performed. (Reprinted with permission from Ref. 121.)

mitral balloon valvuloplasty has been used in elderly patients with critical mitral stenosis. Most of the early studies of mitral balloon valvuloplasty in elderly patients demonstrated that despite being more functionally impaired and having more severe valve deformity, the majority of elderly patients had significant improvement in cardiac functional level following balloon valvuloplasty and no difference in procedural complications was noted, compared to younger patients (109–112).

In one of the largest series of elderly patients (65 years or older, mean age 72) who have had mitral valvuloplasty, Tuzcu and associates (112) found that a successful outcome (defined as mitral valve area of 1.5 cm^2 or greater without a two-grade increase in mitral regurgitation and without significant left-to-right shunt) was achieved in 46 (46%) of 99 patients. As in the other studies, before the valvotomy the majority of elderly patients were severely functionally impaired with approximately 85% of the patients in NYHA functional class III or IV, and 37 patients had at least two or more comorbidities. In the majority of patients the mitral valve was severely deformed, with significant valvular calcification, before the valvuloplasty. Of the 99 patients, 3 died of causes related to the procedure; all deaths occurred early in the authors' experience with percutaneous valvuloplasty. The majority of patients at follow-up were functionally improved compared to their prevalvuloplasty state with freedom from mitral valve replacement and with freedom from NYHA functional class III or IV at 1, 2, and 3 years 72, 53, and 46%, respectively. More recent studies have reported similar findings: significant functional improvement occurs after balloon valvotomy in the majority of elderly patients with significant mitral stenosis and procedure risk is low; favorable acute and long-term results are more dependent upon preprocedure echocardiographic characteristics than patient's age (113–116).

Most authorities conclude that because of the severely deformed mitral valve morphology commonly seen in elderly patients with mitral stenosis, balloon valvuloplasty may be less anatomically successful in elderly patients than in younger patients undergoing valvotomy. The majority of elderly patients, however, will be clinically improved following the intervention; therefore, mitral balloon valvuloplasty is an excellent therapy for certain elderly patients with symptomatic mitral stenosis. Selection of therapy must be made on an individual basis.

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19

Mitral Annular Calcium in the Elderly

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INTRODUCTION

Mitral annular calcium (MAC) is a chronic degenerative process that is common in older persons, especially women. The amount of calcium may vary from a few spicules to a large mass behind the posterior cusp, often extending to form a ridge or ring encircling the mitral leaflets, occasionally lifting the leaflets toward the left atrium. Sphincter function loss of the mitral annulus and mechanical stretching of the mitral leaflets can cause improper coaptation of the leaflets during systole, resulting in mitral regurgitation (1). Although the calcific mass may immobilize the mitral valve, actual calcification of the leaflets is rare. In persons with severe MAC, the calcification may extend inward to involve the underside of the leaflets. Mitral stenosis may result from severe calcific deposits within the mitral annulus protruding into the orifice (2,3). Calcific deposits may extend from the mitral annulus into the membranous portions of the ventricular septum, involving the conduction system and causing rhythm and conduction disturbances (4–6). Although the annular calcium is covered with a layer of endothelium, ulceration of this lining can expose the underlying calcific deposits, which may serve as a nidus for platelet-fibrin aggregation and subsequent thromboembolic episodes (7–9). In patients with endocarditis associated with MAC, the avascular nature of the mitral annulus predisposes to periannular and myocardial abscesses (10–13).

PREVALENCE

MAC is a degenerative process that increases with age and occurs more frequently in women than in men (7,14–24). In a prospective study of 1797 unselected elderly persons in a long-term health care facility, mean age 81 $\pm$ 8 years (range 60 to 103 years), with technically adequate M-mode and two-dimensional echocardiograms of the mitral valve, MAC was present in 665 of 1243 women (53%) and in 194 of 554 men (35%) (24).

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Table 1 Prevalence of Mitral Annular Calcium with Increasing Age in Elderly Men and in Elderly Women

Age (years)	Mitral annular calcium			
	Men		Women	
	n	(%)	*n*	(%)
62–70	4/22	(18)	7/35	(20)
71–80	13/42	(31)	40/116	(34)
81–90	44/75	(59)	146/226	(65)
91–100	19/22	(86)	56/63	(89)
101–103	—	—	3/3	(100)

Source: Adapted from Ref. 21.

Table 1 shows the prevalence of MAC with increasing age in elderly men and elderly women (21).

PREDISPOSING FACTORS

Because calcific deposits in the mitral annulus, in the aortic valve cusps, and in the epicardial coronary arteries are commonly associated in elderly persons and have similar predisposing factors, Roberts (17) suggested that MAC and aortic cuspal calcium are a form of atherosclerosis. MAC and aortic cuspal calcium may coexist (1,7,17–19,25–27). Breakdown of lipid deposits on the ventricular surface of the posterior mitral leaflet at or below the mitral annulus and on the aortic surfaces of the aortic valve cusps is probably responsible for the calcification (1). Increased left ventricular systolic pressure due to aortic valve stenosis increases stress on the mitral apparatus and may accelerate development of MAC (1,7,19,20,27). Tricuspid annular calcium and MAC may also coexist and have similar predisposing factors (28).

Systemic hypertension increases with age and predisposes to MAC (1,7,18,19, 25,26,29). Persons with diabetes mellitus also have a higher prevalence of MAC than nondiabetic persons (1,19,25,26). MAC occurs in the teens in persons with serum total cholesterol levels >500 mg/dL (30). Waller and Roberts (19) suggested that hypercholesterolemia predisposes to MAC. The prevalence of hypercholesterolemia with a serum total cholesterol ≥ 200 mg/dL was higher in elderly persons with MAC than in elderly persons without MAC (26). Roberts (8) also stated that MAC is rare in older persons residing in areas of the world where serum total cholesterol levels are <150 mg/dL. However, Nair et al. (25) found no significant difference in mean serum total cholesterol levels between persons younger than 60 years with MAC and a control group.

Roberts and Waller (31) found that chronic hypercalcemia predisposes to MAC. Patients undergoing dialysis for chronic renal insufficiency have an increased prevalence of MAC (31–37). MAC has also been found to be a marker of left ventricular dilatation and decreased left ventricular systolic function in patients with end-stage renal disease on peritoneal dialysis (37). Cardiac calcium in patients with chronic renal failure has been attributed to secondary hyperparathyroidism (33,36). Nair et al. (25) demonstrated a similar mean serum calcium, a higher mean serum phosphorus, and a higher mean product of

serum calcium and phosphorus in patients younger than 60 years with MAC than in a control group. However, Aronow et al. (26) observed no significant differences in mean serum calcium, serum phosphorus, or product of serum calcium and phosphorus between elderly persons with and without MAC.

By accelerating left ventricular systolic pressure, hypertrophic cardiomyopathy predisposes to MAC (1). Kronzon and Glassman (38) diagnosed MAC in 12 of 18 patients (67%) older than 55 years with hypertrophic cardiomyopathy and in 4 of 28 patients (14%) younger than 55 years with hypertrophic cardiomyopathy. Nair et al. (39) found MAC in 12 of 42 patients (27%) with hypertrophic cardiomyopathy. Their patients with both MAC and hypertrophic cardiomyopathy were older than their patients with hypertrophic cardiomyopathy and no MAC. Motamed and Roberts (40) demonstrated MAC in 30 of 100 autopsy patients (30%) with hypertrophic cardiomyopathy older than 40 years and in none of 100 autopsy patients (0%) younger than 40 years with hypertrophic cardiomyopathy. Aronow and Kronzon (41) diagnosed MAC in 13 of 17 older persons (76%) with hypertrophic cardiomyopathy and in 176 of 362 older persons (49%) without hypertrophic cardiomyopathy.

DIAGNOSIS

Calcific deposits in the mitral annulus are J-, C-, U-, or O-shaped and are visualized in the posterior third of the heart shadow (7,16,32,42–48). MAC may be diagnosed by chest x-ray films or by fluoroscopy (48). However, the procedures of choice for diagnosing MAC are M-mode and two-dimensional echocardiography.

Posterior MAC (Fig. 1) is diagnosed by M-mode echocardiography when a band

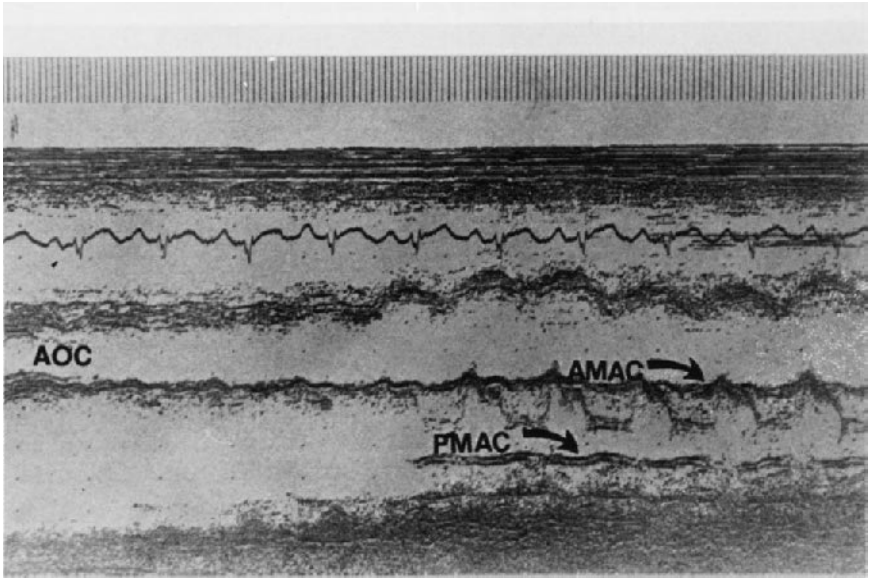

Figure 1 M-mode echocardiogram with scan from the aortic root to the left ventricular apex in a patient with both anterior and posterior mitral annular calcium. AOC = aortic calcium; AMAC = anterior mitral annular calcium; PMAC = posterior mitral annular calcium.

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of dense echoes is recorded anterior to the left ventricular posterior wall and moving parallel with it (49). These echoes end at the atrioventricular junction and merge with the left ventricular posterior wall on echocardiographic sweep from the aortic root to the left ventricular apex.

Anterior MAC (Fig. 1) is diagnosed by M-mode echocardiography when a continuous band of dense echoes is observed at the level of the anterior mitral leaflet in both systole and diastole (49). These echoes are contiguous with the posterior wall of the aortic root. Calcification may extend from the mitral annulus throughout the base of the heart and into the mitral and aortic valves.

Figures 2 and 3 are two-dimensional echocardiograms showing increased echogenicity and brightness of the mitral annulus characteristic of MAC. Using multiple echocardiographic views, MAC may be classified as mild, moderate, or severe (50). The echo densities in mild MAC involve less than one-third of the annular circumference (<3 mm in width) and are usually restricted to the angle between the posterior leaflet of the mitral valve and the left ventricular posterior wall. The echo densities in moderate MAC involve less than two-thirds of the annular circumference (3 to 5 mm in width). The echo densities in severe MAC involve more than two-thirds of the annular circumference (>5 mm in width), usually extending beneath the entire posterior mitral leaflet with or without making a complete circle.

MAC was mentioned in the original radiological report in 3 of 8 patients (38%) with MAC diagnosed at autopsy (16). Schott et al. (32) detected MAC by chest x-ray films in 2 of 41 patients (5%) with MAC diagnosed by echocardiography. Dashkoff et

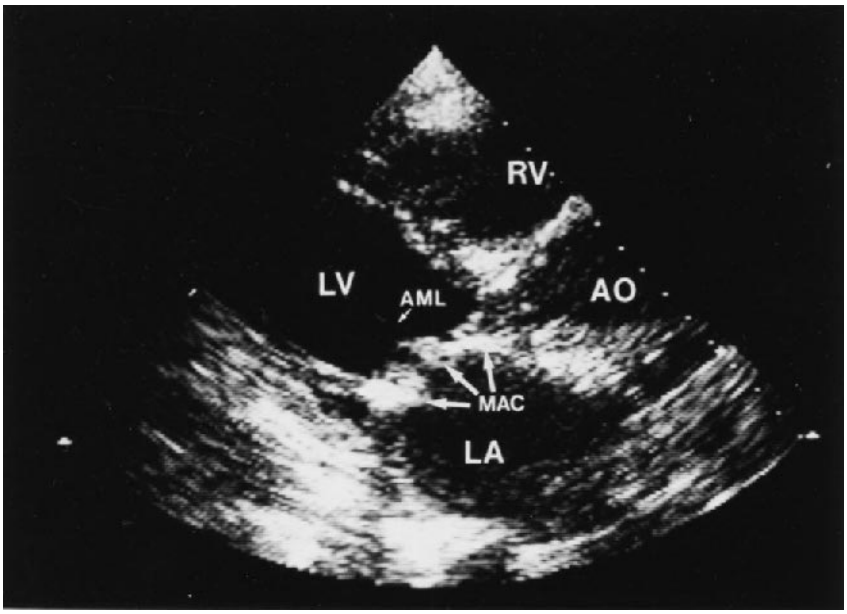

Figure 2 Two-dimensional echocardiogram long-axis view depicting mitral annular calcium (MAC). LA = left atrium; LV = left ventricle; RV = right ventricle; AO = aorta; AML = anterior mitral leaflet.

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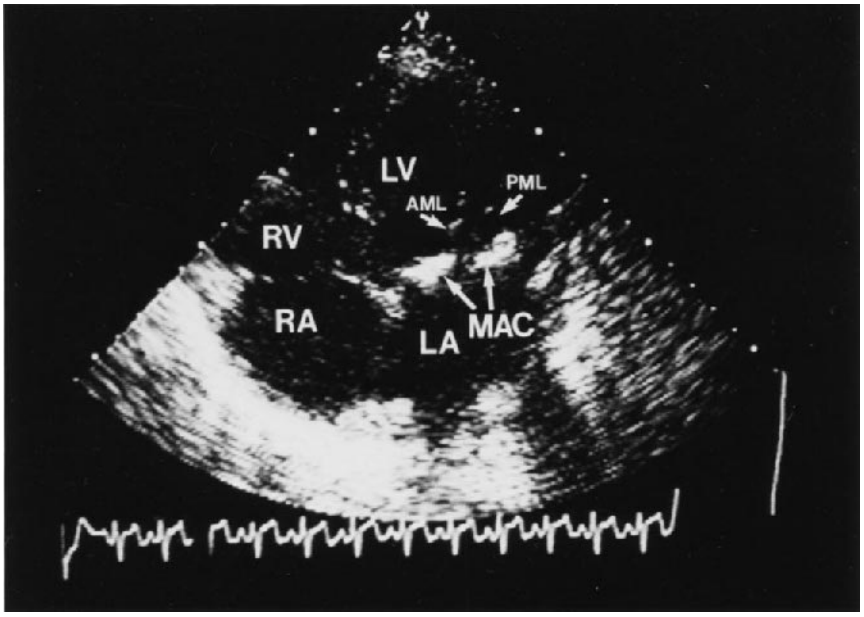

Figure 3 Two-dimensional echocardiogram four-chamber view of a patient with mitral annular calcium (MAC). LA = left atrium; RA = right atrium; RV = right ventricle; LV = left ventricle; AML = anterior mitral leaflet; PML = posterior mitral leaflet.

al. (51) detected MAC by chest x-ray films in 5 of 8 patients (63%) with MAC diagnosed by echocardiography.

In a blinded prospective study, MAC was diagnosed by M-mode and two-dimensional echocardiography in 55% of 604 unselected elderly patients in a long-term health care facility (48). Table 2 shows that the diagnosis of MAC by chest x-ray films using a lateral chest x-ray in addition to the posterior-anterior or anterior-posterior chest x-ray had a sensitivity of 12%, a specificity of 99%, a positive predictive value of 95%, and a negative predictive value of 47%. Patients with radiographic MAC were more likely than patients without radiographic MAC to have a more severe form of the disease, with sig-

Table 2 Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value of Chest X-Ray Films in Detecting Mitral Annular Calcium Diagnosed by Echocardiography in Elderly Patients

	n	(%)
Sensitivity	39/332	(12)
Specificity	270/272	(99)
Positive predictive value	39/41	(95)
Negative predictive value	270/563	(47)

Source: Adapted from Ref. 48.

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nificant mitral regurgitation, functional mitral stenosis, or conduction defects. However, patients with echocardiographically severe MAC and significant mitral regurgitation, functional mitral stenosis, or conduction defects may have no evidence of MAC on chest x-ray films. Figure 4 shows C-shaped calcification of the mitral annulus. Figure 5 illustrates J-shaped calcification of the mitral annulus.

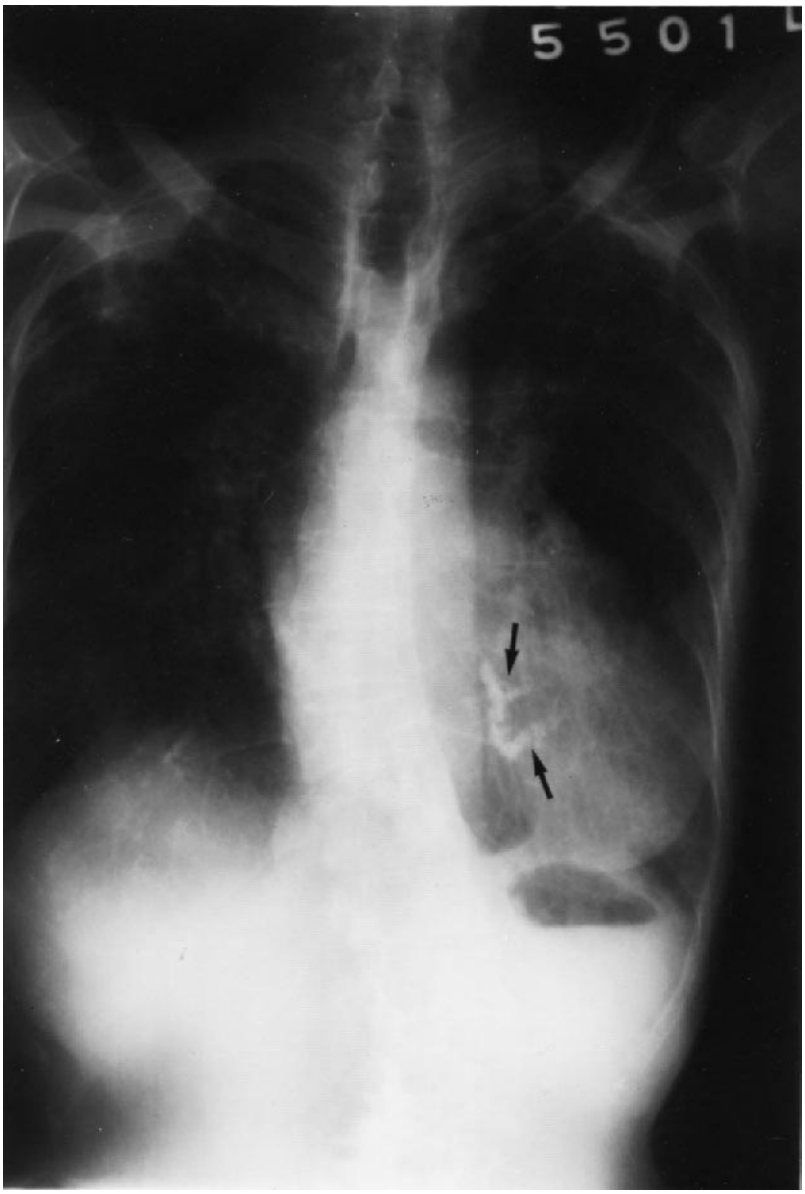

Figure 4 Posterior-anterior chest x-ray in a patient with C-shaped calcification of the mitral annulus (arrows).

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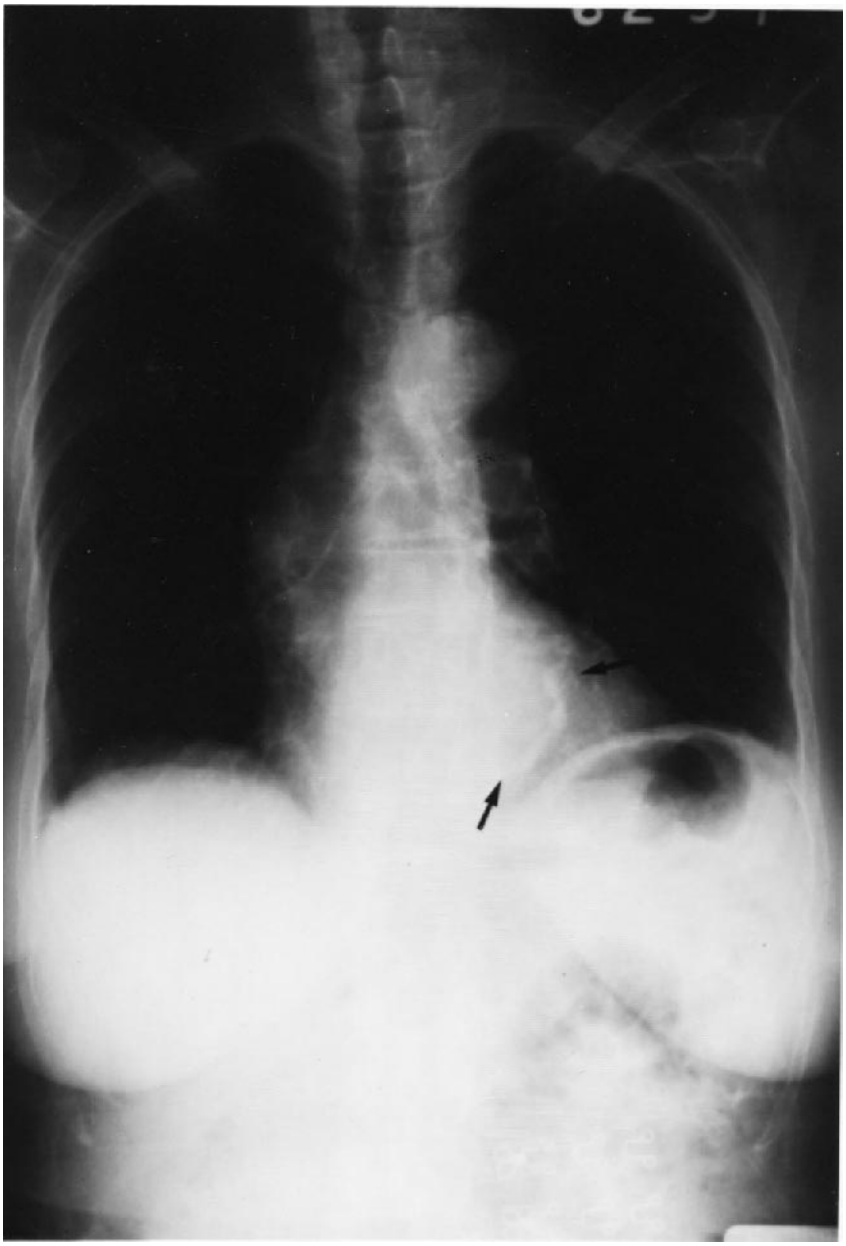

Figure 5 Posterior-anterior chest x-ray in a patient with J-shaped calcification of the mitral annulus (arrow).

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CHAMBER SIZE

Patients with MAC have a higher prevalence of left atrial enlargement (7,16,18,21, 23,25,50,52) and left ventricular enlargement (16,18,25,50,52) than patients without MAC. In a prospective study of 976 elderly patients (526 with MAC and 450 without MAC), left atrial enlargement was 2.4 times more prevalent in patients with MAC than in the group without MAC (23).

ATRIAL FIBRILLATION

Patients with MAC also have a higher prevalence of atrial fibrillation than patients without MAC (7,16,18,21,23,50,53,54). Table 3 shows that the prevalence of atrial fibrillation was increased 12, 5, and 2.8 times in patients with MAC than in patients without MAC (18,50,54).

CONDUCTION DEFECTS

Because of the close proximity of the mitral annulus to the atrioventricular node and the bundle of His, patients with MAC have a higher prevalence of conduction defects, such as sinoatrial disease, atrioventricular block, bundle branch block, left anterior fascicular block, and intraventricular conduction defect, than patients without MAC (4–7,27,50). The calcific deposits may also extend into the membranous portions of the interventricular septum involving the conduction system, or may even extend to the left atrium, interrupting interatrial and intraatrial conduction. In addition, MAC may be associated with a sclerodegenerative process in the conduction system. Nair et al. (50) demonstrated in their prospective study that patients with MAC had a higher incidence of permanent pacemaker implantation because of both atrioventricular block and sinoatrial disease than patients without MAC.

Table 3 Prevalence of Atrial Fibrillation in Patients With and Without Mitral Annular Calcium (MAC)

	Atrial fibrillation				
	MAC		No MAC		Relative risk
	n	(%)	*n*	(%)	
Framingham Study (18)	20/162	(12)	53/5532	(1)	12
Patients younger than 61 years (50)	11/107	(10)	2/107	(2)	5
Patients older than 60 years (mean age 81 ± 8) (54)	225/1028	(22)	85/1120	(8)	2.8

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Table 4 Prevalence of Apical Systolic Murmurs of Mitral Regurgitation (MR) in Patients with Mitral Annular Calcium

	Prevalence of MR murmur	
	n	(%)
Korn et al. (16)	14/14	(100)
Schott et al. (32)	10/14	(71)[a]
Hammer et al. (2)	2/4	(50)
Fulkerson et al. (7)	72/80	(90)
Savage et al. (18)	26/132	(12)
Nair et al. (49)	17/104	(16)
Aronow et al. (22)	129/293	(44)
Aronow et al. (55)	43/100	(43)

[a] MAC due to noninflammatory calcific disease.

MITRAL REGURGITATION

MAC is thought to generate systolic murmurs by the sphincter action loss of the annulus and the mechanical stretching of the mitral leaflets causing mitral regurgitation and from vibration of the calcified ring or vortex formation around the annulus. Table 4 shows that the prevalence of apical systolic murmurs of mitral regurgitation in patients with MAC ranged from 12 to 100% in different studies (2,7,16,18,22,32,49,55). Table 5 states the prevalence of mitral regurgitation diagnosed by Doppler echocardiography in patients with MAC (52,54–56). The prevalence of mitral regurgitation associated with MAC ranged from 54 to 97% in the Doppler echocardiographic studies (52,55,56). Figure 6 illustrates severe mitral regurgitation due to MAC diagnosed by color Doppler echocardiography.

The greater the severity of MAC, the greater the severity of mitral regurgitation associated with MAC. Moderate-to-severe mitral regurgitation was diagnosed by Doppler echocardiography in 33% of 51 patients with MAC by Labovitz et al. (56) and in 22% of 1028 patients with MAC by Aronow et al. (54). Kaul et al. (52) diagnosed severe mitral regurgitation in 7% of their 29 patients with MAC. Kaul et al. (52) also concluded from

Table 5 Prevalence of Mitral Regurgitation (MR) Diagnosed by Doppler Echocardiography in Patients with Mitral Annular Calcium

	MR		Moderate to severe MR	
	n	(%)	*n*	(%)
Labovitz et al. (56)	28/51	(55)	17/51	(33)
Aronow et al. (55)	54/100	(54)	18/100	(18)
Kaul et al. (52)	28/29	(97)[a]	—	—
Aronow et al. (54)	—	—	224/1028	(22)

[a] Severe mitral regurgitation in 2 of 29 patients (7%).
Ref. 54.

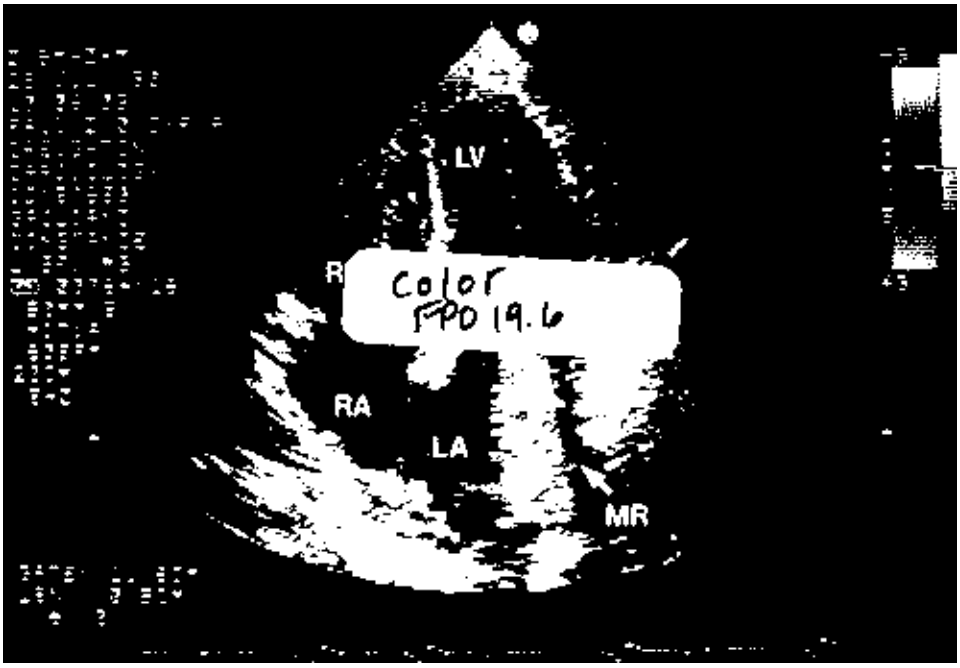

Figure 6 Color Doppler echocardiographic findings in a patient with mitral annular calcium and severe mitral regurgitation (MR). LA = left atrium; RA = right atrium; RV = right ventricle; LV = left ventricle.

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Table 6 Prevalence of Apical Diastolic Murmurs of Mitral Stenosis (MS) and of Mitral Stenosis in Patients with Mitral Annular Calcium

	Prevalence of MS murmur		Prevalence of MS by Doppler echocardiography	
	n	(%)	*n*	(%)
Simon and Liu (44)	5/59	(8)	—	—
Korn et al. (16)	3/14	(21)	—	—
Schott et al. (32)	2/14	(14)[a]	—	—
Hammer et al. (2)	1/4	(25)	—	—
Savage et al. (18)	2/132	(2)	—	—
Nair et al. (49)	7/104	(7)	—	—
Aronow et al. (22)	28/293	(10)	—	—
Labovitz et al. (56)	0/51	(0)	4/51	(8)
Aronow et al. (55)	6/100	(6)	6/100	(6)
Aronow et al. (54)	—	—	83/1028	(8)

[a] MAC due to noninflammatory calcific disease.

their study that mitral regurgitation in patients with MAC is caused by a reduced sphincteric action of the mitral annulus, with MAC preventing the posterior annulus from contracting and assuming a flatter shape during systole.

MITRAL STENOSIS

An apical diastolic murmur may be heard in patients with MAC as a result of turbulent flow across the calcified and narrowed annulus (annular stenosis). Table 6 shows that the prevalence of apical diastolic murmurs of mitral stenosis in patients with MAC ranged from 0 to 25% in different studies (2,16,18,22,32,44,49,55,56). Table 6 also indicates that mitral stenosis associated with MAC was diagnosed by Doppler echocardiography in 8% of 51 patients by Labovitz et al. (56), in 6% of 100 patients by Aronow and Kronzon (55), and in 8% of 1028 patients by Aronow et al. (54). Figure 7 illustrates mitral stenosis due to MAC diagnosed by Doppler echocardiography.

The reduction of mitral valve orifice in patients with MAC is due to the annular calcium and to reduced mitral excursion and mobility secondary to calcium at the base of the leaflets (55). The commissures are fused in rheumatic mitral stenosis but are not fused in mitral stenosis associated with MAC. The mitral leaflet margins in MAC may be thin and mobile, and the posterior mitral leaflet may move normally during diastole. However, Doppler echocardiographic recordings show increased transvalvular flow velocity and prolonged pressure halftime and, therefore, smaller mitral valve orifice in patients with mitral stenosis, regardless of the etiology.

BACTERIAL ENDOCARDITIS

Bacterial endocarditis, with a high incidence of *Staphylococcus aureus* endocarditis, may complicate MAC (7,10–13,23). Patients with MAC associated with chronic renal failure are especially at increased risk for developing bacterial endocarditis (32). The calcific

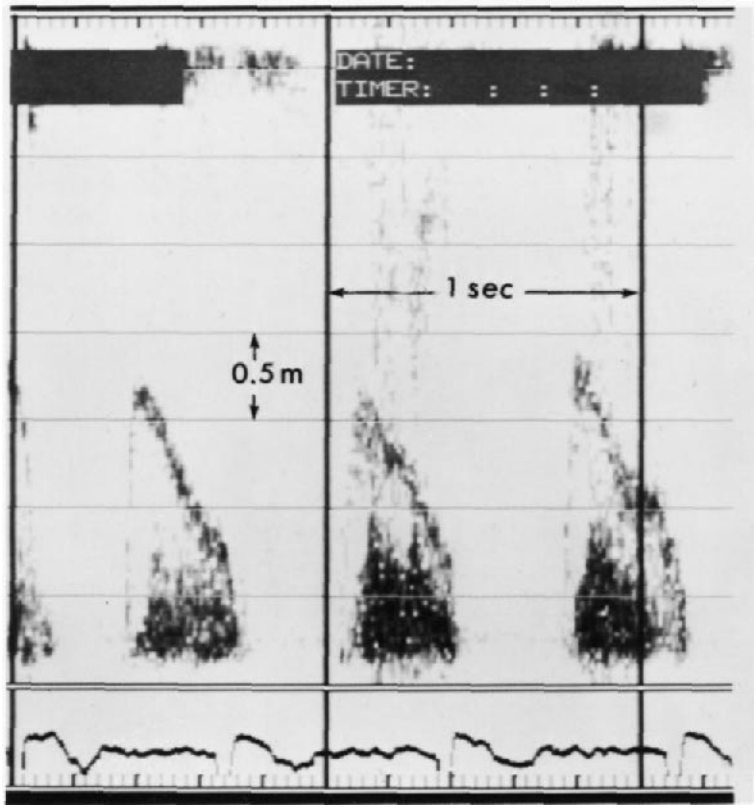

Figure 7 Continuous-wave Doppler tracing across a stenotic mitral valve orifice due to mitral annular calcium. Peak diastolic gradient = 12 mm Hg. Pressure halftime = 200 ms. Mitral valve area = 1.1 cm^2.

mass erodes the endothelium under the mitral valve, which is exposed to transient bacteremia. The avascular nature of the mitral annulus interferes with antibiotics reaching a nidus of bacteria, predisposing to periannular and myocardial abscesses and, consequently, to a poor prognosis (10–13). Burnside and DeSanctis (10) therefore recommended prophylactic antibiotics to prevent bacterial endocarditis in patients with MAC.

Nair et al. (18) observed at 4.4 years mean follow-up no significant difference in incidence of bacterial endocarditis in 99 patients younger than 61 years with MAC compared to a control group of 101 patients. However, Aronow et al. (23) demonstrated at 39 months mean follow-up a 3% incidence of bacterial endocarditis in 526 elderly patients with MAC and a 1% incidence of bacterial endocarditis in 450 elderly patients without MAC. On the basis of these data, we recommend using prophylactic antibiotics to prevent bacterial endocarditis in patients with MAC according to American Heart Association guidelines (57).

CARDIAC EVENTS

In a prospective study of 107 patients (8 lost to follow-up) younger than 61 years with MAC and 107 (6 lost to follow-up) age- and sex-matched control subjects, Nair et al. (50)

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Table 7 Incidence of New Cardiac Events in Patients With and Without Mitral Annular Calcium (MAC)

		Cardiac events				
		MAC		No MAC		Relative
	Follow-up	*n*	(%)	*n*	(%)	risk
Nair et al. (50)	4.4 years					
Total cardiac death		31/99	(31)	2/101	(2)	15.5
Sudden cardiac death		12/99	(12)	1/101	(1)	12.0
Congestive heart failure		41/99	(41)	6/101	(6)	6.8
Mitral or aortic valve replacement		9/99	(9)	0/101	(0)	—
Aronow et al. (23) cardiac events,[a] if	39 months					
Atrial fibrillation		62/90	(69)	22/41	(54)	1.3
Sinus rhythm		157/436	(36)	106/409	(26)	1.4
All patients		219/526	(42)	128/450	(28)	1.5

[a] Myocardial infarction, primary ventricular fibrillation, or sudden cardiac death.

demonstrated at 4.4 years mean follow-up that patients with MAC had a higher incidence of new cardiac events than control subjects (Table 7). In a prospective study of 526 elderly patients with MAC and 450 elderly patients without MAC, Aronow et al. (23) found at 39 months mean follow-up that the incidence of new cardiac events (myocardial infarction, primary ventricular fibrillation, or sudden cardiac death) was also higher in elderly patients with MAC than in elderly patients without MAC.

MITRAL VALVE REPLACEMENT

Nair et al. (58) reported that mitral valve replacement can be accomplished in patients with MAC with morbidity and mortality similar to those in patients without MAC. Following mitral valve replacement, subsequent morbidity and mortality during 4.4 years mean follow-up were also similar in patients with and without MAC.

CEREBROVASCULAR EVENTS

Although the increased prevalence of atrial fibrillation, mitral stenosis, mitral regurgitation, left atrial enlargement, and congestive heart failure predisposes patients with MAC to thromboembolic stroke, some investigators consider MAC a marker of other vascular disease causing stroke rather than the primary embolic source (59). In a retrospective study of 110 elderly patients with chronic atrial fibrillation, 44 (40%) had documented thromboembolic stroke (60). In this study, the prevalence of MAC was not significantly different in elderly patients with thromboembolic stroke (80%) or without thromboembolic stroke (65%) (relative risk = 1.2). However, six prospective studies have demonstrated an increased incidence of new cerebrovascular events in patients with MAC than in patients without MAC (Tables 8–10) (23,50,54,61–63).

Nair et al. (50) observed at 4.4 years mean follow-up in 107 patients (8 lost to

Table 8 Incidence of New Cerebrovascular Events in Patients With and Without Mitral Annular Calcium (MAC)

		Cerebrovascular events				
		MAC		No MAC		Relative
	Follow-up	*n*	(%)	*n*	(%)	risk
Nair et al. (50) TE cardiovascular events	4.4 years	10/99	(10)	2/101	(2)	5.0
Benjamin et al. (61), stroke	8 years	22/160	(14)	51/999	(5)	2.7
Aronow et al. (23), TE stroke if	39 months					
Atrial fibrillation		45/90	(50)	14/41	(34)	1.5
Sinus rhythm		59/436	(14)	38/409	(9)	1.6
All patients		104/526	(20)	52/450	(12)	1.7
Boston Area Anticoagulation Trial for Atrial Fibrillation (62), ischemic stroke	2.2 years	10/129	(8)	5/291	(2)	4.0
Aronow et al. (63), TE stroke if	45 months					
40–100% ECD		52/101	(51)	16/49	(33)	1.5
0–39% ECD		88/365	(24)	47/413	(11)	2.2
TIA if						
40–100% ECD		8/101	(8)	3/49	(6)	1.3
0–39% ECD		11/365	(3)	3/413	(1)	3.0

TE = thromboembolic; ECD = extracranial carotid arterial disease; TIA = cerebral transient ischemic attack.

follow-up) younger than 61 years with MAC and 107 (6 lost to follow-up) age- and sex-matched control subjects that patients with MAC had a 5 times higher incidence of new thromboembolic cerebrovascular events than patients without MAC (Table 8). The Framingham Study demonstrated at 8 years follow-up in 160 persons with MAC and 999 persons without MAC that the incidence of stroke was increased 2.7 times in patients with MAC than in patients without MAC (Table 8) (61). At 39 months mean follow-up of 526 elderly patients with MAC and 450 elderly patients without MAC, Aronow et al. (23) found a 1.5 times higher incidence of new thromboembolic stroke in patients with MAC than in patients without MAC if atrial fibrillation was present, a 1.6 times higher incidence of new thromboembolic stroke in patients with MAC than in patients without MAC if sinus rhythm was present, and a 1.7 times higher incidence of new thromboembolic stroke in all patients with MAC than in all patients without MAC (Table 8). The Boston Area Anticoagulation Trial for Atrial Fibrillation study documented at 2.2 years mean follow-up in 129 patients with atrial fibrillation and MAC and 291 patients with atrial fibrillation without MAC a 4 times higher incidence of ischemic stroke in patients with MAC than in patients without MAC (Table 8) (62). At 45 months mean follow-up, Aronow et al. (63) observed that the incidence of thromboembolic stroke was 1.5 times higher in 101 patients with 40 to 100% extracranial carotid arterial disease and MAC than in 49 patients with 40 to 100% extracranial carotid arterial disease and no MAC and 2.2 times higher in 365 patients with MAC and 0 to 39% extracranial carotid arterial disease than in 413 patients with no MAC and 0 to 39% extracranial carotid arterial disease.

Table 9 Incidence of New Thromboembolic Stroke at 44 Months Mean Follow-Up in Elderly Patients With Chronic Atrial Fibrillation

	Thromboembolic Stroke (%)
Atrial fibrillation, no MAC ($n = 85$)	(35)
Atrial fibrillation with mitral stenosis due to MAC ($n = 42$)	(74)
Atrial fibrillation with MAC and 2–4+ mitral regurgitation ($n = 90$)	(59)
Atrial fibrillation with MAC and 0–1+ mitral regurgitation ($n = 93$)	(48)

MAC = mitral annular calcium.
Source: Adapted from Ref. 54.

Table 9 shows the incidence of new thromboembolic stroke at 44 months mean follow-up in 310 unselected elderly patients in a long-term health care facility with chronic atrial fibrillation (54). Mitral stenosis and the severity of mitral regurgitation were diagnosed by Doppler echocardiography in this study (54). In elderly persons with chronic atrial fibrillation, MAC increased the incidence of new thromboembolic stroke 2.1 times if mitral stenosis was associated with MAC, 1.7 times if 2–4+ mitral regurgitation was associated with MAC, and 1.4 times if 0–1+ mitral regurgitation was present.

Table 10 shows the incidence of new thromboembolic stroke at 44 months mean follow-up in 1838 unselected older persons, mean age 81 years, in a long-term health care facility with sinus rhythm (54). In elderly persons with sinus rhythm, MAC increased the incidence of new thromboembolic stroke 3.6 times if mitral stenosis was associated with MAC, 3.1 times if 2–4+ mitral regurgitation was associated with MAC, and 2.7 times if 0–1+ mitral regurgitation was present. Using the multivariate Cox regression model, independent risk factors for new thromboembolic stroke in this study were prior stroke (risk ratio = 2.4), MAC (risk ratio = 2.6), atrial fibrillation (risk ratio = 3.0), and male gender (risk ratio = 1.6).

There was a higher prevalence of MAC in elderly patients with 40 to 100% extracranial carotid arterial disease (67% of 150 patients) than in elderly patients with 0 to 39%

Table 10 Incidence of New Thromboembolic Stroke at 44 Months Mean Follow-Up in Elderly Patients With Sinus Rhythm

	Thromboembolic stroke (%)
Sinus rhythm, no MAC ($n = 1035$)	(9)
Sinus rhythm with mitral stenosis due to MAC ($n = 41$)	(32)
Sinus rhythm with MAC and 2–4+ mitral regurgitation ($n = 134$)	(28)
Sinus rhythm with MAC and 0–1+ mitral regurgitation ($n = 625$)	(24)

MAC = mitral annular calcium.
Source: Adapted from Ref. 54.

extracranial carotid arterial disease (47% of 778 patients) (63). The increased prevalence of significant extracranial carotid arterial disease contributes to a higher incidence of thromboembolic stroke in elderly patients with MAC. Thrombi of the mitral annulus also contribute to thromboembolic stroke in elderly patients with MAC (64–66). In addition, MAC is associated with complex intraaortic debris, which could contribute to thromboembolic stroke (67).

Since patients with MAC and atrial fibrillation or sinus rhythm have a higher incidence of thromboembolic stroke than patients without MAC, antithrombotic therapy should be considered in patients with MAC and no contraindications to antithrombotic therapy. In the Boston Area Anticoagulation Trial for Atrial Fibrillation study, warfarin decreased the incidence of thromboembolic stroke in patients with MAC by about 90% (68,69).

Until data from prospective, randomized studies evaluating the efficacy and risk of antithrombotic therapy in patients with MAC are available, we recommend treating patients with MAC associated with either atrial fibrillation, mitral stenosis, or moderate-to-severe mitral regurgitation with warfarin if they have no contraindications to anticoagulant therapy. The INR should be maintained between 2.0 and 3.0. The efficacy of antiplatelet therapy in patients with MAC is unknown.

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20

Endocarditis in the Elderly

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Encocarditis is a disease with variable manifestations. In the preantibiotic era, endocarditis predominately occurred in the third and fourth decades (1), but numerous publications have now provided an increasing awareness of the growing proportion of older individuals afflicted with this disease.

The first comprehensive account of endocarditis in the English literature was provided by William Osler (2). Generally thought to be a result of the infections of platelet fibrin deposition on the endocardial surface (3,4) of previously damaged heart valves, the manifestations of endocarditis are many and the consequences great; however, it is acknowledged that certain organisms may infect normal heart valves. A number of recent reviews have crystallized the nature of this disease for the clinician. King and Harkness (5) have provided one such survey of the general nature of this disease process.

The overall incidence of endocarditis worldwide has been estimated to be 60 per million per year (6), with the majority of cases typically seen in males (5). The changing age incidence of this process is reviewed here.

Classically, the most common predisposing factor for infection of the endocardium has been rheumatic heart disease. Of all cases, 25 to 60% occur on valves damaged by the consequences of rheumatic fever (5). Less common predisposing factors include congenital heart disease (10–20% of cases), mitral valve prolapse, prosthetic valves, and degenerative processes occurring on the valves. Traditionally the viridans streptococci, other strains of streptococci, and the staphylococci have accounted for the majority of cases of bacterial endocarditis (7) occurring over all age groups (8).

According to King and Harkness, endocarditis can lead to clinical manifestations in four ways: (1) constant bacteremia, (2) local invasion, (3) peripheral embolization, and (4) circulating immune complexes. These lead to the classic signs and symptoms associated with endocarditis, including changing murmurs, skin manifestations, embolic episodes, and splenomegaly. Treatment depends on identification of the appropriate organism, generally by culture of the blood, and selection of an antibiotic to which the organism is susceptible. In some cases surgery is indicated.

In past years, a number of overviews of endocarditis have appeared that have defined the character of endocarditis in the postantibiotic era. Rabinovich et al. (9) reviewed the cases of bacterial endocarditis occurring over a 40-year period at the university hospitals in Iowa. They confirmed the male predominance of the disease and that rheumatic heart disease was the major predisposing factor over the years, accounting for 68.2% of all

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cases. Congenital heart disease was the second most common identifiable predisposing factor, accounting for 13.1% of the cases; however, no identifiable heart disease was found in 16.3% of the cases. α-Hemolytic streptococci accounted for 61.4% of the cases. Fever was present in every case, skin manifestations (petechiae) in 48% of the cases, clubbing in only 15%, and splenomegaly in 43%. As regards laboratory values, hematuria was present in 28% of the patients and anemia in 78%. Complications reported included embolic episodes in 55 of the 337 individuals and congestive heart failure in 25. The immediate fatality rate since 1950 was 30% for the total group, and the authors significantly noted that ''age by itself did not seem to have any effect on the fatality rate.''

A year later Lerner and Weinstein (10) published one of the best-known endocarditis series reported in the modern era. They described 100 patients seen at the New England Medical Center in Boston. They clearly documented the rising age of patients with endocarditis occurring after the studies of Kelson and White (1) and appreciated that 60% of these individuals were over the age of 50. They again noted 56% of the patients were infected with streptococci (27% viridans streptococci) and 23% with staphylococci (20% with *Staphylococcus aureus*). In reviewing the underlying heart disease predisposing to endocarditis, these authors noted no antecedent cardiac disorder could be ascertained in 39% of the cases. Of those in whom an underlying cardiac diagnosis seemed apparent, Lerner and Weinstein reported that rheumatic heart disease was most common (40%), followed by congenital heart disease (10%) and arteriosclerotic disease (3%). They emphasized that many elderly patients with endocarditis had no knowledge of antecedent cardiac disease. In reviewing the clinical features of the disease, these authors reported 97% of the patients were febrile, 85% had murmur, 29% had petechiae, 44% had splenomegaly, and 30% had at least one episode of major embolic phenomenon. Hematuria was found in 26% of the cases, anemia in 50%, and elevated erythrocyte sedimentation rates (ESR) in 90%. These authors pointed out that mortality rate did not seem affected much by age until the eighth decade of life. Of the eight patients who were 70 or older, seven succumbed to illness.

In 1971, Cherubin and Neu (11) reported a 30-year experience with endocarditis at Presbyterian Hospital in New York City. They reviewed the records of 656 cases of infective endocarditis seen between 1938 and 1967. They again appreciated the increasing mean age of the patients, from 31 years in 1938 to 52 years of age in 1966, and described the impact of social change on the epidemiological characteristics of endocarditis. Thus, they reported an increase in staphylococcal and fungal valvular infections secondary to increasing narcotic usage. Similarly, they appreciated a rising incidence of enterococcal disease despite the fact that *Streptococcus viridans* remained the most common causative organism for bacterial endocarditis. Rheumatic fever was the most common predisposing factor for bacterial endocarditis (38.5% of cases) in this study, followed by congenital heart disease (5.8% of the cases). They commented that ''the older the patient the less frequent is an antecedent history of valvular heart disease.'' These authors noted an increase in aortic valve disease, a slight decrease in mitral valve disease, and a marked decline in combined aortic-mitral disease.

In 1978, Garvey and Neu (12) reported the occurrence of endocarditis at Columbia-Presbyterian Hospital for the years 1968 to 1973. Those years saw 154 patients admitted to that institution, with a total of 165 episodes of endocarditis. In this series, the mean age of the patients rose a further 3 years, to 55 years. Infection on prosthetic valves accounted for 20.6% of the cases, but in the cases of natural valve endocarditis, aortic involvement exceeded mitral involvement (39–35%). Rheumatic fever was again the most

common predisposing factor, followed by congenital heart disease, although 65% of the cases for whom information was available had no known underlying cardiac process. Streptococci were the most common organisms producing natural valve endocarditis; however, enterococci accounted for 6.5% of the cases and *S. aureus* for 16%. Negative blood cultures were found in 11% of the patients. In 84% of the cases of natural valve endocarditis, fever was appreciated and murmurs were found in 96%. Elevated ESR were noted in 86% of the cases. Major emboli occurred in 55 of the 107 cases of natural valve bacterial endocarditis, and congestive heart failure was seen in half the patients in this series. One-quarter of the cases died, but half of these were lost because the true diagnosis was not appreciated.

In 1980, Lowes et al. (13) published their experience at St. Bartholomew's Hospital, London, during the years 1966 to 1975. These authors followed 60 patients. As found by authors before them, the age of the patients increased over reports from the preantibiotic era; thus, 45% of the cases occurred in patients over the age of 50. The male–female ratio was 1:5 to 1:0. The predominant underlying heart disease was rheumatic in nature (35%), followed by congenital lesions (22%); however, no underlying disease was found in 30%. Clinically only two-thirds of the patients reported fever, but congestive heart failure, cutaneous manifestations, and splenomegaly occurred in almost half the individuals. In this period, echocardiography was introduced, and six patients were described in whom this procedure localized the process. Blood cultures were positive in 86% of the patients from whom samples were taken, and streptococci accounted for nearly two-thirds of the isolates. Enterococci were reported in seven instances (13%). The overall mortality in this series was 20%, but these authors suggested mortality was much higher in patients over 40 (25% vs. 10% in younger patients).

Von Reyn et al. (14) in 1981 surveyed endocarditis at the Beth Israel Hospital in Boston between the years 1970 and 1977. They reported 104 instances in 94 patients and noted the advanced age of the patients (57 years mean age), the short duration of symptoms (27 days mean), and the high incidence of underlying valvular heart disease (66%). The highest percentage of cases occurred on the mitral valve (40%). Most of the cases were due to viridans streptococci, and only 5% were culture negative. Additionally, 13% of the patients had nosocomial endocarditis, 12% had prosthetic valve infections, and 18% required surgery. A total of 86% of the cases were febrile, 86% had murmurs, and 32% had splenomegaly. The overall mortality was 15% in this series. M-mode echocardiography was done in 32 patients, 6 of whom were demonstrated to have vegetations.

In 1993, Watanakunakorn and Burkert (15) reported on 210 cases of endocarditis from a large community teaching hospital. They noted that the largest percentage of their patients were in the age group between 60 and 70 years of age. Almost 46% of their non-IVDU patients had no underlying valve disease. Thirty of the 210 cases of endocarditis in their series were nosocomial and the most frequently encountered organism responsible for the endocarditis was *S. aureus* (48.6% of nonprosthetic valve infection in patients who were not intravenous drug users). Fever (66.2%), chills (42.6%), and malaise (39.9%) were the most common symptoms in this group and 81.1% had murmurs. Twenty eight percent of their cases occurred in individuals with atherosclerotic valves and only 7% in patients with valves damaged by rheumatic fever. Twenty-seven of their cases occurred in individuals with prosthetic valves.

In 1995, Hogevik et al. (16) described the epidemiological aspects of endocarditis in a Swedish population. They pointed out the incidence of endocarditis was more than six times greater in the age group over 70 than in the age group under 70, and the median

age of their patients was 69 years. Forty-four percent of their patients had no previous history of valvular disease, but rheumatic fever was the predisposing factor in 186 of the episodes and 15% of the cases occurred in patients with prosthetic valves. Fever and fatigue were again the most common symptoms. Most importantly, they noted that the risk of embolization was less in the group greater than 70 years of age as compared to the group below age 70. In this series, streptococci were encountered slightly more commonly than staphylococci.

Thus, a summary of some of the major reviews of endocarditis occurring over the last 65 years shows several changing trends. Perhaps most striking has been the advancing age of the patients, which was an almost universal finding. In addition, most of these extensive reviews found fever and murmurs to be very frequent in endocarditis patients and anemia and elevated ESR to be common. Other manifestations, including cutaneous findings, splenomegaly, and neurological findings, occurred in half or less of the cases. Rheumatic heart disease remained a common predisposing factor but many of the more recent cases occurred in individuals with no known valvular problems. Streptococci, especially viridans streptococci, were the most frequent etiological agents identified.

Since the early descriptions of Osler, various authors have focused on age-related differences in the disease process. Kerr (17), in his classic monograph, noted that in 1896 Gibson remarked on the modified character of the disease in old age. Kerr himself suggested that as the population aged, arteriosclerotic valvular heart disease would become a significant antecedent cardiac lesion for bacterial endocarditis. Later in this chapter we focus on the surveys of endocarditis reported in the English literature that have examined the specifics of endocarditis in the elderly. This provides a basis for determining differences between the disease in the general population, as described earlier, and older individuals.

In 1940, Bayles and Lewis (18) reported 28 cases of endocarditis diagnosed at autopsy in people over the age of 40. The authors noted the majority of cases occurred on valves damaged by rheumatic fever but that 25% of the cases occurred on arteriosclerotic valves. They commented on the similarity of the clinical features between younger and older patients but noted the greater subtlety of the disease in the older group.

In the same year, Willis (19) described the occurrence of endocarditis in an 82-year-old. In 1945, Zeman and Siegal (20) reported 27 cases of bacterial endocarditis in patients over the age of 60. They emphasized that the features of endocarditis in the older population were more likely classified as acute. The features of acute disease have generally implied a more aggressive course with a shorter duration of symptoms. To some authors, acute disease has suggested the occurrence of infection on presumably normal valves, generally caused by *S. aureus*, *Streptococcus pneumoniae*, or group A β-hemolytic streptococci. In recent years the utilization of the terms ''acute'' and ''subacute'' endocarditis have not been as popular. Zeman and Siegal also stressed the diagnostic difficulties encountered in older patients with bacterial endocarditis because of the frequent occurrence of other underlying disease processes.

In 1949, Traut et al. (21) reported 94 cases of bacterial endocarditis in patients over 45 years of age diagnosed at Cook County Hospital during the years 1935 to 1946. The vast majority of these (61%) occurred on valves damaged by rheumatic fever, but five occurred on atherosclerotic valves. They emphasized the infrequency of the disease in older people.

In an autopsy series, Wallach et al. (22) described 13 cases of bacterial endocarditis superimposed on rheumatic valves and 17 cases imposed on valves without rheumatic

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disease, all of which occurred in patients over the age of 50. These authors noted that the disease in the older patients was more often incidental, not directly related to the cause of death. They further noted that the older patients more frequently had underlying genitourinary infections or other diseases (diabetes mellitus) and more often had sclerotic changes in the valves.

A year later Anderson et al. (23) emphasized the occurrence of endocarditis in older patients from St. Thomas Hospital, London. They reviewed 14 cases (18.4% of the total cases) seen from 1946 to 1954 occurring in people older than 60 years. In this group, mortality was higher (50%) versus the entire group of patients with endocarditis seen at their hospital (31%). The patients included 10 with *S. viridans* infection and 4 with either negative cultures or no cultures. Virtually all patients had evening temperatures of 100°F or higher, and all had murmurs; 43% of the patients had splenomegaly, and the same number had cutaneous manifestations. They commented that endocarditis was ofter missed in the elderly because it was not generally realized that the disease could occur in this age group, that the disease in the aged was less severe, and that several criteria usually associated with endocarditis were not necessarily found in the aged.

Somewhat later, Gleck (24) described 10 cases of endocarditis occurring in patients over age 55. He noted that in addition to dental extractions and skin infections, genitourinary tract manipulations were precipitating events in the elderly. The subjects of this report were six men and four women. Although three patients had typical features of endocarditis, another three patients presented with changes in mental status or depression; one patient presented with liver disease; one with uremia, one with anorexia and weight loss; and one with stroke. At least two patients had maximum daily temperatures below 100°F. Of the atypical patients, four died.

In the same year, Hartman and Myers (25) noted 7 of 20 patients with endocarditis to be over the age of 60. Of the seven, four were female, five were infected by *S. viridans*, one by staphylococcus, and one by enterococcus. Of these patients, four had rheumatic heart disease and three had arteriosclerotic disease; two patients died. These authors suggested enterococcal endocarditis was common in the older patient.

In 1960, Cummings et al. (26) noted that 18 of 55 patients with endocarditis were over age 50. Of these patients, 13 died (72%), as opposed to 10 of 37 below this age (27%). Of these patients, 10 were females and, in all but 3, murmurs were described. Of all patients, 27% had splenomegaly, but only half were reported to have fever. Streptococcal infections were seen in six patients, and in one *Proteus vulgaris* was isolated from the blood. The rest either had negative cultures or no cultures were drawn.

Uwaydah and Weinberg (27), in 1965, noted the changing pattern of endocarditis. They reviewed 100 total patients seen at the Massachusetts General Hospital in Boston. In their series, 38% of the cases were over the age of 60, and half of these had infection superimposed on arteriosclerotic or calcified valves. They commented on the declining incidence of rheumatic fever as a predisposition for endocarditis in the older patient. In this series, 37% of the young patients died, but 68% of the older group expired.

In 1973, Habte-Gabr et al. (28) reported 57 patients over the age of 60 with endocarditis seen at the University of Iowa Hospital between 1940 and 1971. They noted endocarditis in the elderly had gradually increased. The male–female incidence was 4:1. They commented that although all the patients were febrile, half complained of weight loss, confusion, or other symptoms. These authors noted that the signs and symptoms were similar between younger and older patients. Of all patients, 27% had negative cultures; however, the most common organisms isolated from the older age group included α-

hemolytic streptococcus (40%), other streptococci (23%), and staphylococci (23%). Of the patients who were treated, 56% survived. These authors stressed the varied presentation of endocarditis in the elderly, especially the prevalence of central nervous system complaints and uremia as presenting symptoms in the elderly. They emphasized the difficulty of making the true diagnosis in the elderly.

Watanakunakorn and Tan (29) reported 19 of 33 cases of staphylococcal endocarditis occurring in people over the age of 60. Presenting complaints were often nonspecific, such as anorexia and mental deterioration. Highlighting a modern risk factor for endocarditis, two patients were infected from indwelling intravenous catheters. In 10 patients, the diagnosis was established antemortem from blood cultures, but in the others it was established at autopsy or by direct culture of surgically removed valves. All but four patients were febrile. Only 2 of the 10 in whom the diagnosis was made antemortem survived. At autopsy, the mitral valve was the source of the infection in 13 of the 16 cases and atherosclerosis was the predisposing cardiac condition in 8 of 16 cases.

This same group of authors also reported 20 patients, over age 60, with *S. viridans* endocarditis, who were seen at the University of Cincinnati Medical Center (30). The presenting complaints of these patients were generally weakness, fatigue, and weight loss. All patients had fever, all had cardiac murmurs (40% had splenomegaly, and 60% had cutaneous lesions). In 55% of the patients, the disease involved the mitral valve, in 30% the aortic valve, and in 15% both valves. Of these patients, 85% were alive 2 years after treatment and it appeared survival was similar to that in a younger group of patients with the same disease.

Later, Applefield and Hornick (31) conducted a retrospective analysis of patients admitted to the University of Maryland Hospital between the years 1950 and 1970 with a diagnosis of endocarditis. Of 29 patients, 21% fulfilled the criteria for endocarditis and were 60 years of age or older. Among these older individuals, pyrexia of unknown origin was the presenting complaint in 48% of the cases; however, 45% presented with neurological findings, including delirium. In 10 patients, no murmur was detected. In 18 individuals, aortic valve disease predisposed to infection, and in 10, mitral valve disease was a preexisting condition. Staphylococci accounted for 24% of the cases and streptococci for 41% (including three cases of enterococcal disease), but in 29% of the cases (eight cases in all) no organism was isolated. Of this group, 72% died, but 48% had received antimicrobial therapy judged to be inappropriate.

Thell et al. (32) presented data on 42 cases of endocarditis occurring in subjects over 60 years and confirmed by autopsy or surgery. In this series, five cases of right-sided endocarditis were reported. The most common organisms isolated were staphylococci (33% of the cases), followed by streptococci (24% of the cases). In 37% of the cases, no underlying heart disease was found, but aortic valve disease was most common in those in whom an underlying process could be identified. This included calcific aortic disease. These authors stressed that the diagnosis of endocarditis was suspected in only 38% of the cases despite the fact that fever was present in 94% of the cases in whom it was recorded and murmurs in 68% of the patients.

Robbins et al. (33) also contributed to our understanding of endocarditis in the elderly. They reviewed 56 cases of infective endocarditis in patients 65 years of age and older. In this group, 93% were febrile, 86% had murmurs, and 36% had peripheral stigmata. They appropriately divided the cases into community-acquired and nosocomially acquired cases. Of a total of 41 community-acquired cases of endocarditis, 71% were found to be due to streptococci, including six cases of *Streptococcus faecalis*; eight cases

(20%) were due to staphylococci. Among 15 nosocomially acquired cases, three were due to *S. faecalis*, seven to staphylococci (six attributed to *S. aureus*), and three to fungi. Of the total cases, five were caused by undetermined bacteria. Underlying diseases found to predispose to natural valve endocarditis in this series included six cases of rheumatic heart disease, three cases of calcific aortic valve disease, and 16 cases of atherosclerotic disease. Complications occurred in 34 individuals (64% of the patients) who developed congestive heart failure and in 20 patients (35%) who had neurological abnormalities. All patients tested had an elevated ESR, and two-thirds were anemic. The overall mortality in this series was 45%.

Terpenning et al. (34) compared infective endocarditis in patients over the age of 60 (53 episodes) to the disease in patients 40 to 60 years of age and to patients under 40 years of age (55 episodes). The percentages of cases caused by streptococci and staphylococci were approximately equal, but infection due to enterococci, *Streptococcus bovis*, and coagulase-negative staphylococci were more common in the older age group. Strikingly, 23% of the cases in the older patients were nosocomially acquired. The proportion of cases associated with various types of underlying heart disease was similar in all three groups, but the highest percentage of cases in all age groups was associated with no known underlying disease. A slightly greater percentage of the elderly group had prosthetic valves. Clinical manifestations were also similar in the various age groups, with fever present in over 80% of all individuals included regardless of age. Confusion was slightly more common in the older age group, and new or changing murmurs were present more often in the younger groups. Errors in diagnosis were significantly more common in the older age group. Echocardiograms were read as showing vegetations in 56.8% of the group under 40, 47.8% of the group 40 to 60 years of age, and 43.7% of the group over 65 years of age. The aortic valve was the most common valve infected overall, but the mitral was more often the site of infection in the elderly (54.7%). In the youngest age group, the tricuspid was most often infected because of the higher incidence of intravenous drug use as a predisposing factor in the process. Major neurological events were slightly more common in the elderly, and pulmonary embolic events were more frequent in the younger group. Overall mortality was significantly more common with increasing age, reaching 45% in the oldest group.

In 1994, Durack et al. (35) described new criteria for the diagnosis of endocarditis incorporating the findings of echocardiography. This refined the method of establishing the diagnosis of endocarditis. Using these new criteria, Weiner et al. (36) reported on endocarditis in the elderly and compared the findings with those in younger patients. The utilization of transesophageal echocardiography by these authors provided an interesting tool for the comparison between the older and younger age groups. They reported on 106 episodes of endocarditis and divided them into three groups; those under age 50, those between 50 and 70, and those over 70 years of age. The median age of all the cases was 59 years. *S. viridans* and staphylococci were the most common causative organisms in all age groups. While no significant differences were found between the age groups with respect to the source of the infection or the type of organism responsible, elderly patients more often had degenerative and calcified lesions or prosthetic valves. Vegetations were smaller in the two older groups. Fever (55%) and leukocytosis (25%) were less common in those over 70 as opposed to those under 50. The outcome in the older patients, however, was no worse than in the younger group. Embolic events were again more common in the younger group.

Selton-Suty et al. (37) also described the clinical and bacteriological characteristics

of endocarditis in the elderly. They reported on a total of 114 patients with endocarditis. They divided the patients into two groups; those over 70 years of age and those under 70. These authors also utilized the newer echocardiographic criteria. While streptococci were again the most common causative organism in both age groups, these authors thought older patients had a greater number of infections related to organisms normally inhabiting the gastrointestinal tract. Fever was common in both age groups (>80%). Again, these authors noted that elderly patients had a higher percentage of infections occurring on prosthetic valves (52% vs. 25%) and less often experienced embolic complications (8% vs. 28%). The mortality in the older age group was higher, however, than in the younger age group (28% vs. 13%).

In summary, endocarditis is an evolving process that is becoming increasingly a disease of older patients. This is in part related to a declining incidence of rheumatic fever as a predisposing factor in younger patients, leaving degenerative disease as a relatively more common underlying factor. Thus older individuals constitute a greater percentage of cases. Similarly, older patients, because of more frequent underlying disease processes and a greater number of hospitalizations, are more likely to develop nosocomial infections of the sclerotic valves. Furthermore, the greater frequency of genitourinary procedures in the older patient means the older patient may more often be infected with enterococci. The major clinical manifestations in the older patient are likely to be similar. Thus the older patients still commonly have fever and some form of murmur. Peripheral manifestations (petechiae, splinter hemorrhages, Osler nodes, Janeway lesions, an so on) should be found in frequency about equal to that generally observed in other age groups and observed in the past. It is of interest that more recent studies have suggested the older patients are less prone to embolic complications. Common laboratory features of the disease, that is, anemia, elevated ESR, and hematuria, appear to be observed in the elderly with equal frequency. Confusion should be more likely in the older patient, since this is often a nonspecific response in the elderly to any physiological stress and should always force a search for infections, including endocarditis. With regard to mortality, it appears that the older patient with more frequent underlying disease and less ability to adapt to new stresses experiences a higher overall mortality from endocarditis (38). This must be extrapolated to the individual situation, however. An otherwise healthy older person with viridans streptococci on a prolapsed mitral valve may be at no greater risk of death than a younger person. In contrast, a more mature individual with underlying disease and a more difficult organism to eradicate (enterococci and methicillin-resistant coagulase-negative staphylococci) may indeed experience a higher risk of death from endocarditis. Finally, in the older patient, it is clear the diagnosis is more difficult because clinicians are less apt to consider it until greater damage is done.

The diagnosis of endocarditis in the older adult is probably no less difficult to establish if it is considered. Blood cultures taken before empirical antibiotics, especially if endocarditis is a consideration, are certainly helpful. Echocardiography (38) in the older patient is clearly a useful diagnostic maneuver and transesophageal echocardiography may be especially valuable. The treatment of endocarditis in the older patient is similar to that in the younger individual (9). Care must be exerted in the older individual when using potentially toxic agents (aminoglycosides), and greater attention must be paid to renal function, toxicity monitoring, drug levels, and so on. In treating any case of endocarditis, serum cidal levels should be monitored and attempts made to keep serum levels, especially peak levels, at 1:8 or greater.

Suggested regimens for the treatment of endocarditis are listed in Table 1 and are

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Table 1 Regimens for the Treatment of Endocarditis

Etiology	Treatment	Duration (weeks)
Natural valve endocarditis		
S. viridans	Penicillin G, 12 million U/day (divided dose)	4
Enterococci	Ampicillin, 12 g/day or Vancomycin[a] (500–1000 mg b.i.d., and gentamicin, 3 mg/kg/day (divided dose)	6
Staphylococci		
Coagulase positive (methicillin-sensitive)	Nafcillin, 12 g/day (divided dose)	6
Coagulase negative (methicillin-resistant)	Vancomycin[a], 500–1000 mg b.i.d.	6
Fastidious Gram-negative rods (e.g., Hemophilus)	Ampicillin, 12 g/day, and gentamicin, 3 mg/kg/day (divided dose)	6
Prosthetic valve endocarditis		
Coagulase-negative or positive (methicillin-resistant)	Vancomycin[a], 500–1000 mg b.i.d. + gentamicin, 3 mg/kg/day, + rifampin, 300 mg every day (orally)	6 (first 5 days only)

All doses are intravenous unless otherwise indicated.

[a] Vancomycin 30 mg/kg per 24 h in two divided doses not to exceed 2 g in 24 h unless serum levels are monitored.

derived from Wilson et al. (39). Prophylaxis for bacterial endocarditis in the older patients is identical to that recommended for the younger patient (40).

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21

Cardiomyopathies in the Elderly

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The true prevalence of cardiomyopathies in the elderly may be underestimated because of the low sensitivity of the clinical criteria, particularly in milder cases. The prevalence of congestive heart failure and the clinical manifestation of various myocardial diseases increase with advancing age and have been estimated at 9.1% of the population 80 years and older. Postmortem evaluations have revealed prevalence rates as high as 18 to 25% in the elderly. This chapter focuses on common cardiomyopathies encountered in the elderly.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is a primary myocardial disorder characterized by a hypertrophied and nondilated left ventricle (LV) not directly caused by other concomitant cardiovascular conditions (1). When occurring in the elderly population, it is often characterized by the presence of a localized hypertrophy of the basal portion of the interventricular septum (''sigmoid septum'' or ''septal bulge'').

Incidence

Whiting et al. (2) showed that 32% of patients with hypertrophic cardiomyopathy were older than 60 years of age. Petrin and Tavel (3) reported that 83% of patients with hypertrophic cardiomyopathy were older than 50 years of age. Lever et al. (4) found that hypertrophic cardiomyopathy was more commonly diagnosed in patients 65 years or older than in patients younger than 40 years. Aronow and Kronzon (5) demonstrated that hypertrophic cardiomyopathy was present in 17 of 379 unselected elderly patients (4%), mean age 82 $\pm$ 8 years, in a long-term health care facility. Hypertrophic cardiomyopathy was present in 3% of elderly men and in 5% of elderly women. Of 17 elderly patients with hypertrophic cardiomyopathy, 10 (59%) had asymmetric septal hypertrophy without obstructive physiology and 7 (41%) had idiopathic hypertrophic subaortic stenosis (obstructive hypertrophic cardiomyopathy), with LV outflow tract obstruction at rest and gradients across the LV

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outflow tract ranging from 20 to 110 mmHg (5). The prevalence of hypertrophic cardiomyopathy was 3% of 554 men and 4% of 1243 women studied by the same investigators in a subsequent larger series of individuals aged >60 years in a long-term health care facility (6).

Diagnostic Criteria

The diagnostic criteria used in the elderly population are not dissimilar from those used in the younger group. In one study (5), asymmetric septal hypertrophy was diagnosed when the ratio of the interventricular septum to posterior wall thickness was greater than 1.3 and the septal thickness exceeded 15 mm in the absence of other acquired or congenital heart disease likely to cause asymmetric septal hypertrophy (5). Obstructive physiology, at rest or following amyl nitrate stimulation, was diagnosed when asymmetric septal hypertrophy coexisted with systolic anterior motion of the mitral leaflet and Doppler evidence of left ventricular outflow tract (LVOT) gradient (5). The Doppler spectral characteristics of dynamic LV outflow tract obstruction included increased LV outflow tract velocity (>200 mm/s) and late systolic peaking of flow velocity with ''ski slope'' appearance (5). Some authors distinguish ''hypertrophic cardiomyopathy'' from ''hypertensive hypertrophic cardiomyopathy of the elderly'' (see later).

Lever et al. (4) compared 28 patients 65 years or older with hypertrophic cardiomyopathy with 28 patients younger than 40 years of age affected by the same condition. Clinical findings were similar in the two groups, except for a higher prevalence of female sex, systemic hypertension, and atrial fibrillation in the elderly group. Echocardiographic findings including asymmetric hypertrophy, systolic anterior motion of the mitral valve, and a LVOT gradient >20 mmHg were similar in both groups. However, the elderly group had a predominantly ovoid cavity contour with normal septal curvature. The younger group had a predominantly crescent-shaped LV cavity and a reversed curvature of the interventricular septum. The right ventricular free wall was also more prominent in the younger group.

LV hypertrophy is more severe in younger than in older patients with hypertrophic cardiomyopathy (7). Lewis and Maron (8) reported a group of 52 elderly patients (45 women) with obstructive cardiomyopathy. Echocardiographic examination showed a relatively small LV cavity with modest LV septal hypertrophy and marked distortion of LV outflow tract morphology. LV outflow tract size at end diastole was greatly reduced and anterior displacement of the mitral valve within the LV cavity was marked. In most patients, anterior excursion of the mitral valve leaflets was restricted, and systolic apposition between the mitral valve and the LV septum resulted from a combination of anterior mitral valve excursion toward the LV septum and posterior excursion of the LV septum toward the mitral valve.

Subaortic Septal Bulge

More recently, the existence of a separate entity characterized by subaortic septal bulge, independent of focal hypertrophy, and caused by an increased angulation of the septum, has been recognized in the elderly population (9). In these cases, an abnormally angulated septum is thought responsible for increased outflow tract narrowing and increased velocity. In senescent hearts, the ascending aorta moves to a more rightward position with the septum aligned below the aortic valve (10). Previous studies had indicated that protrusion

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of the septum is a function of age not correlated with LV hypertrophy (11). Patients with septal protrusion (sigmoid septum) have been found to present with a more acute angle between midseptum and aorta compared with controls or patients with asymmetric septal hypertrophy (ASH) (12,13). The resulting changes in convective acceleration simulate the dynamics of hypertrophic cardiomyopathy (9). The author concluded that, in elderly patients, basal focal septal hypertrophy should be considered secondary and contributory to the enhanced ventricular dynamics, but distinct from a primary cardiomyopathy (9). Although subaortic septal bulge may not be associated with hypertrophy, a focal septal hypertrophy, in association with systolic anterior motion of the mitral valve leaflets, can develop (Figs. 1,2). This can be explained by the effect of high-velocity stream in the narrowed outflow tract with development of impact pressure on the basal septum (Fig. 3) (14). The focal increase in impact pressure stimulates local angiotensin II receptors (15) or other stretch-sensitive factors (16) capable of inducing hypertrophy. Furthermore, distortion of flow stream across the outflow tract may cause an increase in shearing stress in the basal septum region, which may stimulate focal hypertrophy (17–19).

Hypertensive Hypertrophic Cardiomyopathy of the Elderly

Topol et al. (20) reported 21 elderly patients (16 female) with a syndrome the authors defined as hypertensive hypertrophic cardiomyopathy of the elderly. Patients had severe

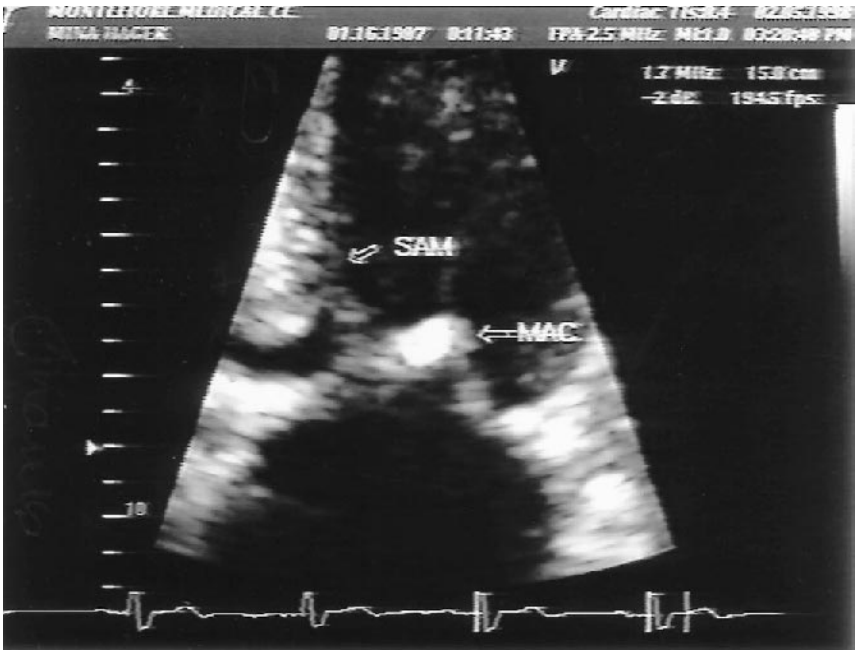

Figure 1 Systolic frame of a two-dimensional echocardiogram from an apical view in a 91-year-old female with hypertrophic cardiomyopathy of the elderly, showing extensive mitral annulus calcification and prominent systolic anterior motion of the mitral valve with near obliteration of the LVOT. SAM = Systolic anterior motion of the mitral valve leaflets. MAC = mitral annulus calcification.

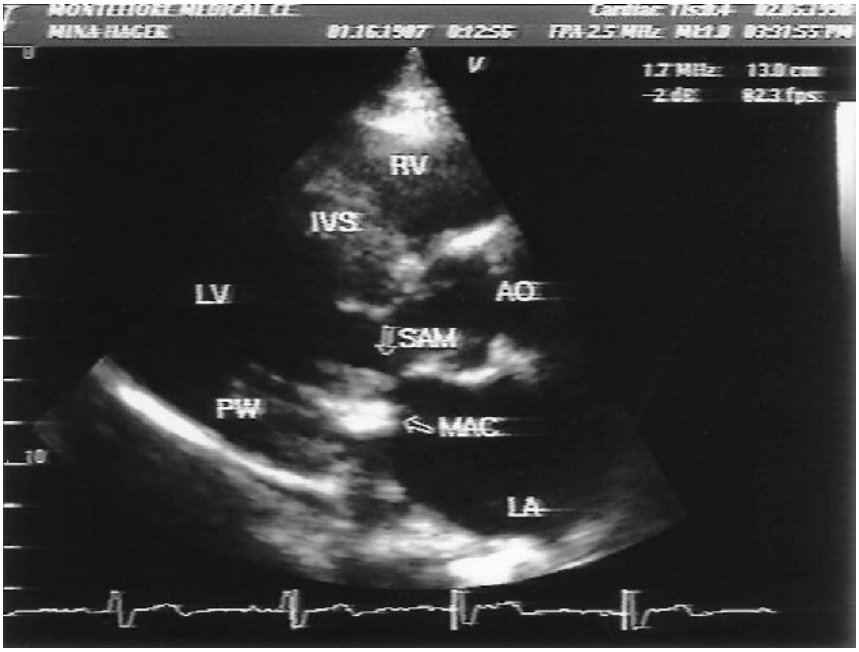

Figure 2 Early systolic frame from a two-dimensional parasternal long axis view in the same patient illustrated in Figure 1, showing a prominent septal bulge and systolic anterior motion of the mitral valve. RV=right ventricular cavity. IVS = interventricular septum. Ao = aortic root. LV = left ventricular cavity. LA = left atrium. PW = posterior wall. MAC = mitral annulus calcification. SAM=systolic anterior motion of the mitral valve leaflets.

concentric LV hypertrophy, a small LV cavity, and supernormal indexes of LV systolic function without concurrent and contributory medical illness or coronary artery disease. Pearson et al. (21) reported 17 patients (16 female) with hypertensive hypertrophic cardiomyopathy of the elderly. All their patients had symmetrical hypertrophy with involvement of both the LV septum and the LV free wall. The increased LV outflow tract velocities were late peaking, similar to those described in hypertrophic cardiomyopathy, and localized to the LVOT (Fig. 4). LV filling was characterized by increased peak atrial velocity and decreased ratio of peak early to peak atrial velocity compared to a control group. LV end-diastolic dimension was smaller and left atrial size not different compared to a control group.

Karam et al. (22) studied 39 patients with hypertrophic cardiomyopathy and hypertension and an age/gender-matched group of 29 patients with hypertrophic cardiomyopathy without hypertension. There were no significant differences between the two groups in regard to symptoms, functional class, electrocardiographic abnormalities, LVOT obstruction, or most echocardiographic abnormalities, including asymmetric hypertrophy. However, the patients with hypertension were more likely to have a thicker posterior LV wall. These investigators concluded that hypertrophic cardiomyopathy is a primary disorder whose manifestations can be worsened by the presence of hypertension. They suggested that the term ''hypertrophic cardiomyopathy with hypertension'' was preferable to the term ''hypertensive hypertrophic cardiomyopathy.''

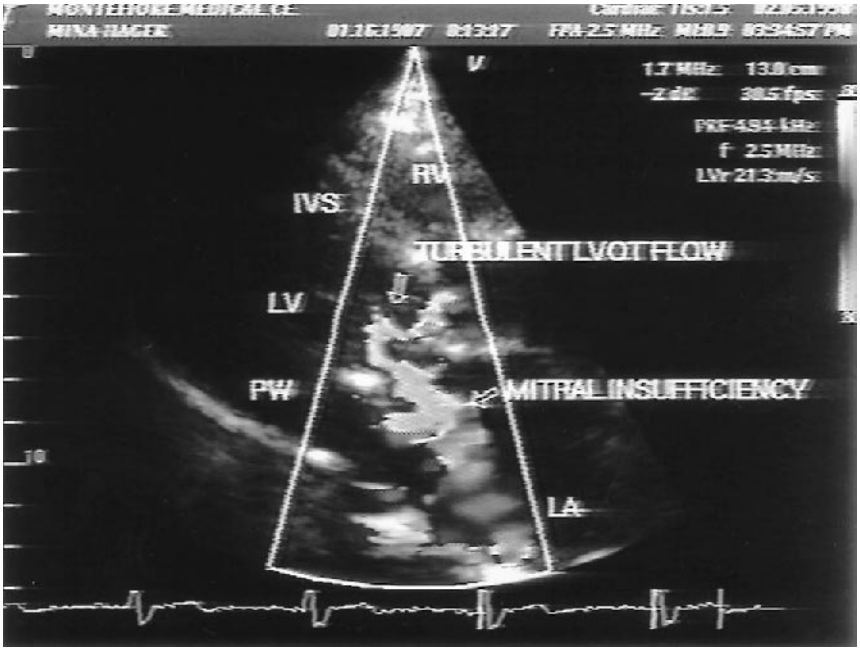

Figure 3 Color Doppler flow display superimposed on the same systolic frame from a parasternal long axis view shown in Figure 2, demonstrating turbulent LVOT flow. Abbreviations as in Figure 2.

Physiological Consequences of Hypertrophic Cardiomyopathy

When present, LVOT gradient is the most dramatic consequence of the complex anatomical and physiological derangements present in patients with hypertrophic cardiomyopathy (23). Impaired LV diastolic function, however, is the most important feature of hypertrophic cardiomyopathy. This is due to a combination of abnormalities in LV relaxation and compliance and affects both obstructive and nonobstructive forms. Abnormal LV diastolic function with abnormal Doppler diastolic indexes occurs with similar frequency in patients with hypertrophic cardiomyopathy with or without LVOT obstruction and with or without cardiac symptoms (24). LV diastolic dysfunction is a more prominent feature in elderly patients with hypertrophic cardiomyopathy compared to a younger patient population (25).

Decreased *compliance* in hypertrophic cardiomyopathy may be due to abnormal material properties secondary to a combination of fibrosis and cell disorganization (26–31). Fibrosis and cell disorganization, combined with an increase in LV mass, cause a shift to the left of the pressure-volume curve. Mechanisms that affect LV *relaxation* interfere with an active process by which calcium ions are recaptured in the sarcoplasmic reticulum, depriving the myofibrillar contractile proteins of an essential element for the actin-myosin bond. Furthermore, impaired calcium handling in the senescent heart may contribute to delayed relaxation. In a situation of normal, rate-controlled sinus rhythm, ventricular filling may be preserved; an increase in heart rate, however, leads to shortening in diastolic filling time, which may result in myocardial ischemia and worsening in LV relaxation.

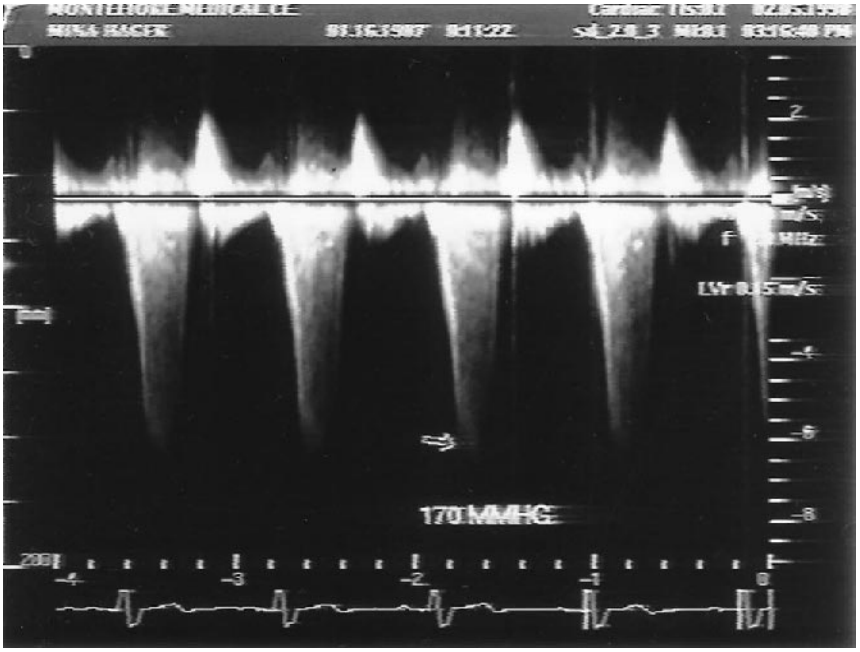

Figure 4 CW Doppler obtained from interrogation of the LVOT flow in the same patient illustrated in Figure 1, demonstrating a large increase of LVOT velocity (maximum = 6 m/s) and a Bernoulli-derived gradient of 170 mmHg.

LV diastolic filling abnormalities in hypertrophic cardiomyopathy are independent of the magnitude of LV hypertrophy and are common in patients with both marked and diffuse LV hypertrophy and more mild and localized LV hypertrophy (32). These findings suggest that the primary process causing impaired LV diastolic filling in hypertrophic cardiomyopathy is not confined to the thickened portions of the LV wall. Wigle (33) concluded that impaired LV relaxation is often a more important cause of abnormal LV diastolic filling than increased passive chamber stiffness (decreased compliance) in patients with hypertrophic cardiomyopathy. However, both abnormalities may coexist.

Hypertrophic cardiomyopathy is frequently associated with LVOT dynamic obstruction. Its mechanism is still controversial. Recent studies have attributed LVOT dynamic obstruction to the presence of predisposing structural abnormalities (i.e., elongated mitral valve leaflets and chordal apparatus, basal septal hypertrophy, mitral annulus calcification) that trigger the obstructive mechanism by ''dragging'' and pushing the protruding mitral leaflet into the septum (34–36), resulting in a time-dependent LVOT gradient (37). This proposed mechanism excludes a Venturi effect as the initiating phenomenon.

Figures 5 through 10 illustrate M-mode echocardiographic findings (Fig. 5), two-dimensional echocardiographic findings (Figs. 6, 7), pulsed Doppler echocardiographic findings (Fig. 8), color Doppler echocardiographic findings (Figs. 3, 9), and continuous-wave Doppler echocardiographic findings (Figs. 4, 10) in elderly patients with hypertrophic cardiomyopathy. Mitral annular calcification (MAC) associated with hypertrophic cardiomyopathy in the elderly is also illustrated in Figures 1, 2, and 5–7.

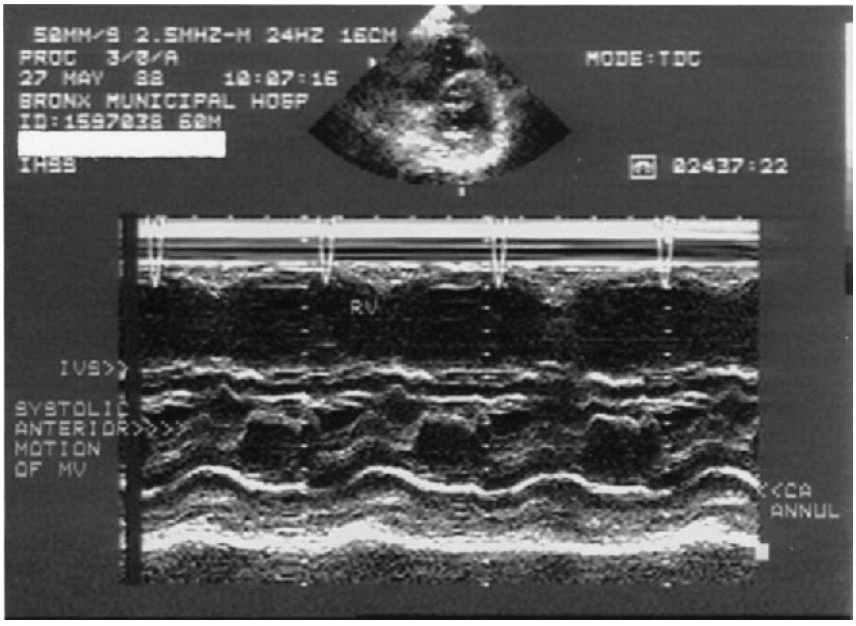

Figure 5 M-mode echocardiogram at the mitral valve level in an elderly patient with obstructive hypertrophic cardiomyopathy. During midsystole, a smooth anterior motion at the mitral valve is noted. The mitral valve assumes a flattened curve appearance as it approaches the septum, and the contact with the septum is facilitated by the posterior motion of the septum. Mitral annular calcification is present behind the posterior leaflet. IVS = interventricular septum; RV = right ventricular cavity; MV = mitral valve; CA ANNUL = mitral annular calcification.

Mitral Annular Calcium

Deposition of calcium at the level of the mitral annulus is common in patients with hypertrophic cardiomyopathy. By increasing LV systolic pressure, hypertrophic cardiomyopathy may accelerate MAC: this finding is characteristic of the older patient population (38–40). Kronzon and Glassman (38) observed that MAC occurred in 12 of 18 patients (67%) older than 55 and in 4 of 28 patients (14%) younger than 55 years with hypertrophic cardiomyopathy. Motamed and Roberts (39) demonstrated the presence of MAC in 30 of 100 autopsy patients older than 40 years and in none of 100 patients (0%) younger than 40 years with hypertrophic cardiomyopathy. Nair et al. (40) showed that MAC was present in 12 of 42 patients (29%) with hypertrophic cardiomyopathy. Patients with hypertrophic cardiomyopathy and MAC were older than those with hypertrophic cardiomyopathy without MAC. Fulkerson et al. (41) found that hypertrophic cardiomyopathy occurred in 5 of 80 patients (6%) with MAC and a mean age of 73 years. Aronow and Kronzon (5) showed that MAC was present in 13 of 17 elderly patients (76%) with hypertrophic cardiomyopathy and in 176 of 362 elderly patients (49%) without hypertrophic cardiomyopathy ($p = 0.025$). Lewis and Maron (8) demonstrated MAC in 52 of 52 elderly patients (100%) with hypertrophic cardiomyopathy. Calcification was severe in 39 of 52 patients (75%), mild to moderate in 13 patients (25%). The sizable deposits of calcium in the mitral annulus posterior to the mitral valve appeared to contribute to the narrowing of the LVOT.

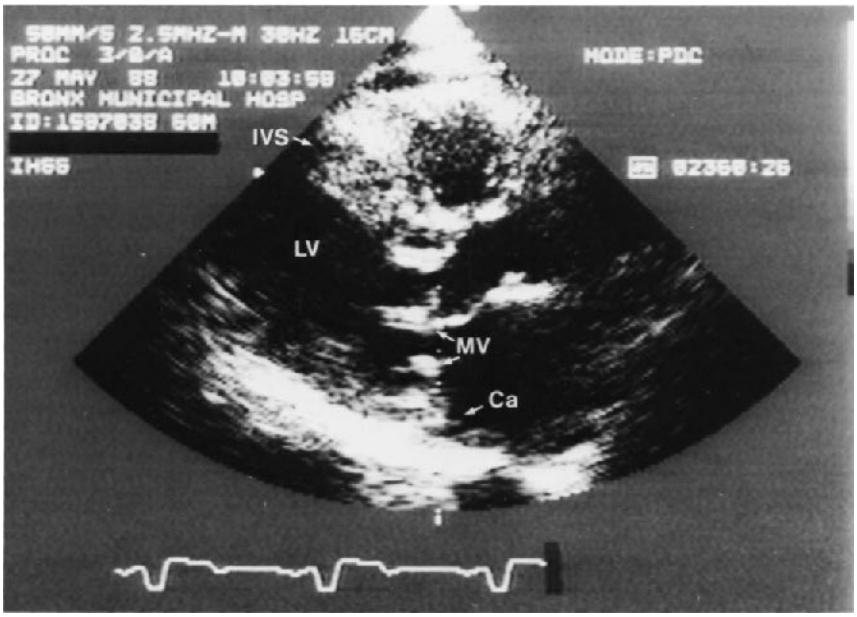

Figure 6 Diastolic frame of a two-dimensional echocardiogram from a parasternal long-axis view in an elderly patient with hypertrophic cardiomyopathy shows a small LV chamber, a hypertrophic interventricular septum (IVS), a fibrotic mitral valve (MV), and a calcified mitral annulus (Ca).

Other Mitral Valve Abnormalities

Klues et al. (42) also demonstrated that the disease process in hypertrophic cardiomyopathy is not confined to cardiac muscle. Of 94 mitral valves examined from patients with hypertrophic cardiomyopathy, 62 (66%) had structural abnormalities of the mitral valve unlikely to be acquired or secondary to mechanical factors. The structural abnormalities included increased mitral leaflet area and elongation of the leaflets or anomalous papillary muscle insertion directly into the anterior mitral leaflet. These abnormalities are thought to play a significant role in the pathogenesis of the obstructive physiology (34–37).

Clinical Manifestations

Dyspnea, palpitations, syncope, and angina are common clinical manifestations in patients with hypertrophic cardiomyopathy. Lever et al. (4) demonstrated in 28 elderly patients with hypertrophic cardiomyopathy that 24 (86%) had dyspnea, 17 (61%) had palpitations, 13 (46%) had angina pectoris, and 6 (21%) had syncope. Lewis and Maron (8) observed in 52 elderly patients with hypertrophic cardiomyopathy that 48 (92%) had exertional dyspnea and fatigue, 33 (63%) had chest pain, 22 (42%) had orthopnea or paroxysmal nocturnal dyspnea, and 12 (23%) had syncope or near-syncope. Agaston et al. (25) observed in 44 elderly patients with hypertrophic cardiomyopathy that 12 (27%) had congestive heart failure and 13 (30%) had angina pectoris. Fay et al. (43) demonstrated in 95 elderly patients with hypertrophic cardiomyopathy that 47 (49%) had chest pain, 16 (17%) had syncope, 32 (34%) had New York Heart Association functional class II dyspnea, 12

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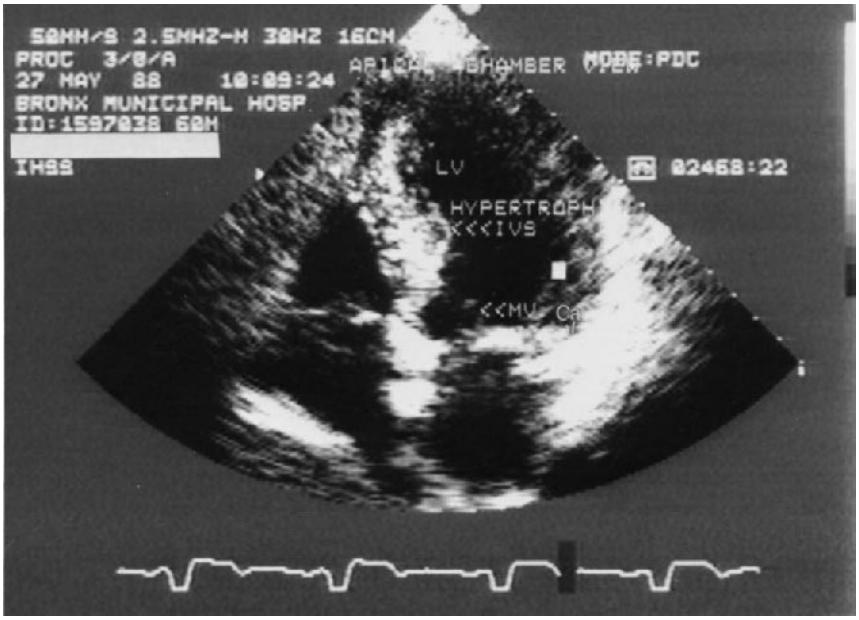

Figure 7 Two-dimensional apical four-chamber systolic still frame from an elderly patient with obstructive hypertrophic cardiomyopathy shows hypertrophy of the interventricular septum (IVS), a small LV cavity, fibrotic mitral valve (MV) leaflets, and a calcified mitral annulus (Ca).

(13%) had New York Heart Association functional class III dyspnea, and 24 (25%) had no symptoms.

Impaired LV filling due to LV diastolic dysfunction in patients with hypertrophic cardiomyopathy results in an elevated LV diastolic, left atrial, and pulmonary venous pressure causing dyspnea. Syncope or near-syncope may result from an inadequate cardiac output with exertion or from cardiac arrhythmias. Angina pectoris unassociated with coronary artery disease may result from an increased myocardial oxygen demand and a reduced myocardial oxygen supply due to an increase in coronary vascular resistance and a decrease in coronary vascular reserve associated with LV hypertrophy (44–48). The greater the degree of LV hypertrophy, the larger is the reduction in coronary vascular reserve. The ratio of subendocardial to epicardial blood flow in the LV becomes abnormal. Intraventricular compressive forces may cause a reduction in coronary blood supply to the myocardium, while myocardial oxygen demand is increased. This may result, especially during tachycardia, in subendocardial hypoperfusion and ischemia. Autopsy studies have demonstrated LV necrosis, widespread fibrosis, or transmural scarring in patients with hypertrophic cardiomyopathy (26,30,45,46). Coexistent coronary artery disease in elderly patients may also contribute to myocardial ischemia, causing chest pain.

Physical Examination Findings

Patients with obstructive hypertrophic cardiomyopathy may have a double apical impulse due to a prominent apical precordial impulse and a prominent presystolic apical impulse or a triple apical impulse, the third impulse being a late-systolic bulge. A fourth heart sound

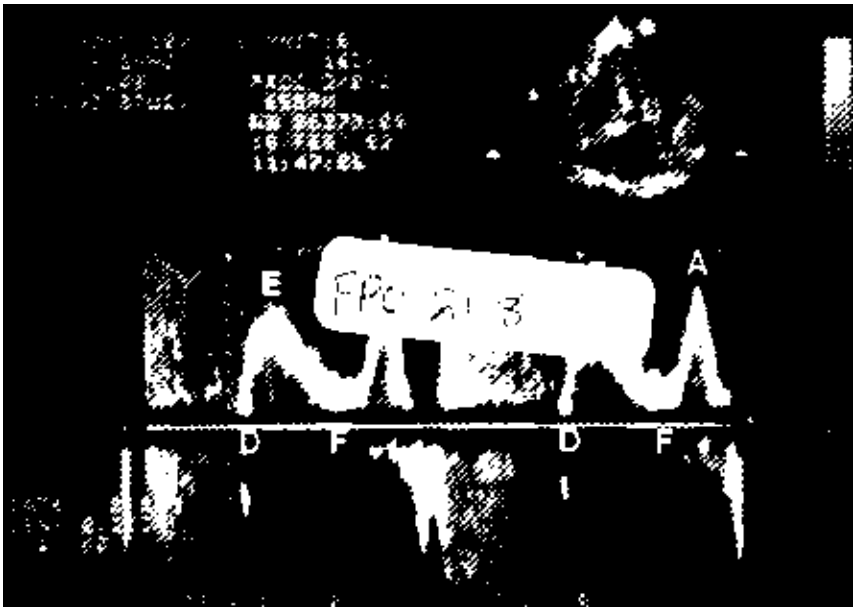

Figure 8 LV diastolic waveforms obtained with pulsed Doppler echocardiography in an elderly patient with hypertrophic cardiomyopathy show reduced maximal flow velocity of early peak (E), slow deceleration of early diastolic flow velocity (from E of F), prolongation of early filling components (from D to F) at the expense of diastasis, and increased maximal velocity of the late peak as a result of atrial systole (A).

is characteristically heard. A late-systolic murmur may be due to dynamic obstruction of the LVOT. Lever et al. (4) reported that a systolic murmur was heard in 26 of 28 elderly patients (93%) with hypertrophic cardiomyopathy. Fay et al. (43) stated that a systolic murmur was heard in 92 of 95 elderly patients (97%) with hypertrophic cardiomyopathy. Chandraratna and Aronow (49) concluded that the murmur of obstructive hypertrophic cardiomyopathy in patients with marked systolic anterior motion of the mitral valve is due to a composite of turbulence in the LVOT and mitral regurgitation, whereas when only mild and systolic anterior motion of the mitral valve is present, the systolic murmur originates in the LVOT. Cassidy et al. (50) demonstrated that during handgrip exercise, the systolic murmur associated with obstructive hypertrophic cardiomyopathy becomes inaudible or decreased in intensity by auscultation. In the squatting position, the systolic murmur due to hypertrophic cardiomyopathy also decreases in intensity. The systolic murmur increases in intensity during the Valsalva maneuver or in the standing position.

The carotid arterial pulse of obstructive hypertrophic cardiomyopathy characteristically reveals a rapid initial upstroke and commonly a bifid pulse contour (50,51). Cassidy et al. (50) demonstrated a bifid carotid arterial pulse in seven of nine patients (78%) with obstructive hypertrophic cardiomyopathy. During handgrip exercise, the bifid carotid arterial pulse disappeared in five patients and greatly decreased in the other two patients. In the elderly patient population, however, carotid arterial pulse findings may be altered by the presence of concomitant independent disease processes in this vascular district.

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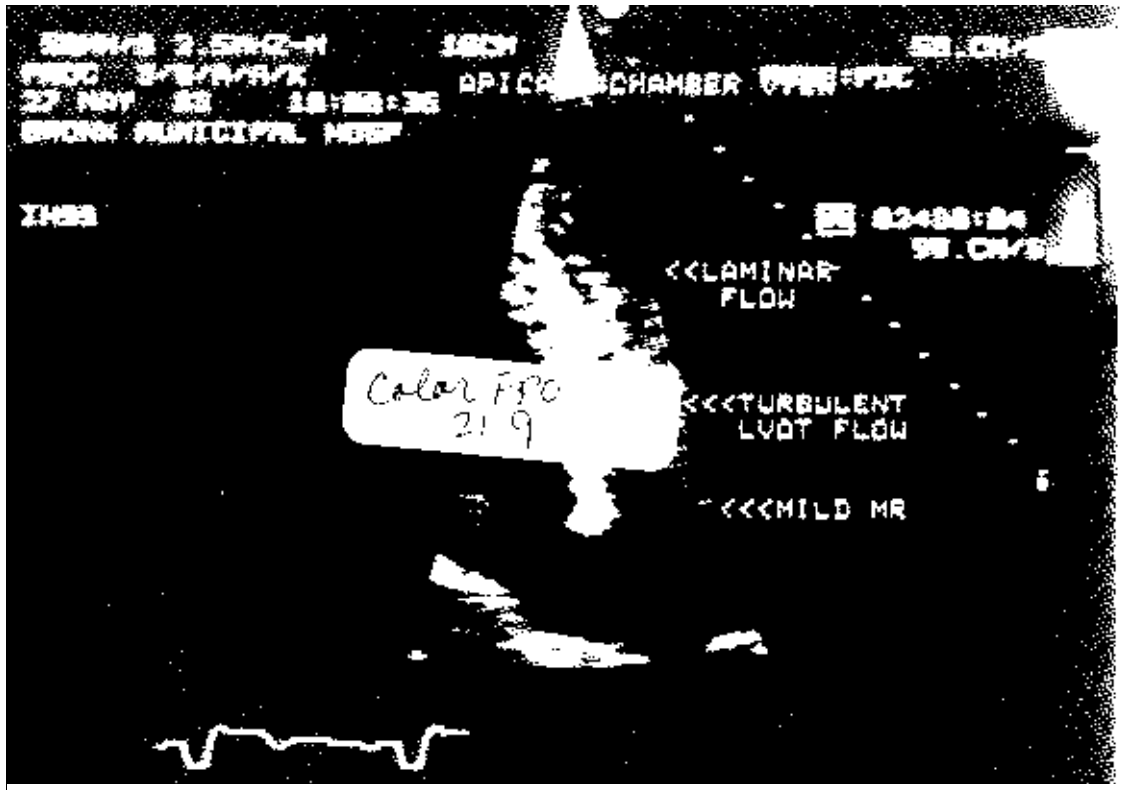

Figure 9 Color Doppler flow display from a patient with obstructive hypertrophic cardiomyopathy shows turbulent flow in the LVOT and mild mitral regurgitation (MR).

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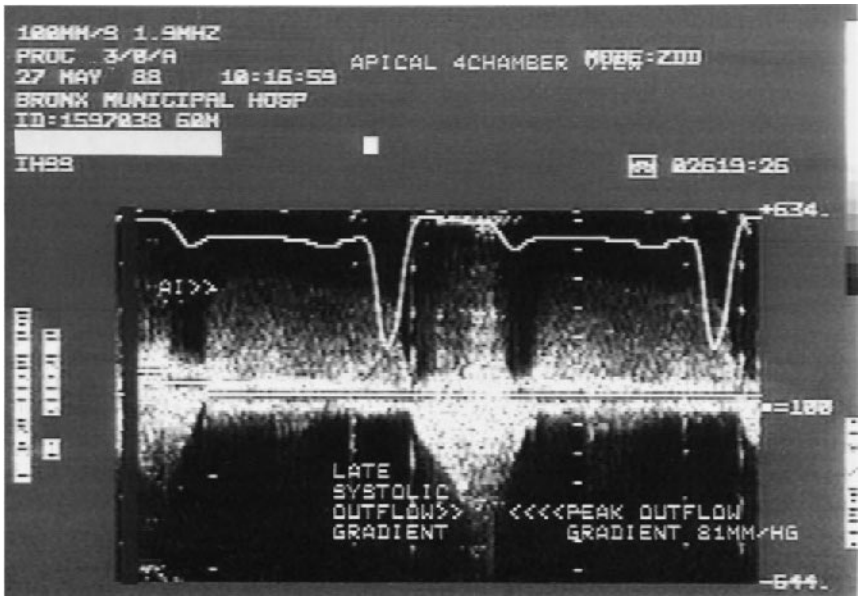

Figure 10 Continuous-wave Doppler recording obtained in the LV outflow tract of an elderly patient with obstructive hypertrophic cardiomyopathy. Note the increased late-systolic LV outflow tract velocity, which translates to a peak LVOT gradient of 81 mmHg. In diastole, a characteristic aortic insufficiency velocity pattern is noted.

Electrocardiogram

Electrocardiographic evidence of LV hypertrophy was observed in 18 of 28 (64%) and 56 of 95 (60%) elderly patients with hypertrophic cardiomyopathy (4,43). Lever et al. (4) described the presence of Q waves in the anteroseptal and lateral leads in 8 of 28 elderly patients (29%) with hypertrophic cardiomyopathy. Lemery et al. (52) demonstrated electrocardiographic abnormal Q waves in 19 of 67 patients (28%) with hypertrophic cardiomyopathy and attributed them primarily to a function of the ratio of upper anterior septal thickness to right ventricular wall thickness. Lever et al. (4) also reported in 28 elderly patients with hypertrophic cardiomyopathy that the electrocardiogram showed right bundle branch block in 4 patients (14%), left bundle branch block in 2 patients (7%), and no abnormality in 1 patient (4%).

Development of atrial fibrillation in patients with hypertrophic cardiomyopathy may cause symptomatic deterioration and increased risk of systemic embolization (8,52–56). Symptomatic deterioration is due to a rapid ventricular rate and to the loss of increased left atrial systolic filling in presence of impaired LV relaxation (56). Lewis and Maron (8) reported that atrial fibrillation (paroxysmal in 16 patients and chronic in 6 patients) occurred in 24 of 52 elderly patients (42%) with hypertrophic cardiomyopathy. The development of atrial fibrillation was associated with the onset of severe symptoms in 8 of 22 patients (36%), and the progression of preexisting symptoms in another 5 patients (23%). Lever et al. (4) showed that atrial fibrillation occurred in 7 of 28 elderly patients (25%) with hypertrophic cardiomyopathy. Spirito et al. (57) demonstrated that most patients with

hypertrophic cardiomyopathy and chronic atrial fibrillation have nonobstructive hypertrophic cardiomyopathy and relatively mild LV hypertrophy.

Ventricular Arrhythmias

Spirito et al. (58) showed a strong association between magnitude of echocardiographic LV hypertrophy and ventricular tachycardia detected by 24-h ambulatory electrocardiography in patients with hypertrophic cardiomyopathy. Aronow et al. (59) found an increased prevalence of ventricular tachycardia and complex ventricular arrhythmias detected by 24-h ambulatory electrocardiography in elderly patients with echocardiographic LV hypertrophy associated with hypertrophic cardiomyopathy. Maron et al. (60), using 24-h ambulatory electrocardiography, demonstrated that brief runs of asymptomatic ventricular tachycardia were associated with an increased risk of sudden cardiac death in patients with hypertrophic cardiomyopathy. At 3 years follow-up, sudden cardiac death occurred in 4 of 17 patients (24%) with asymptomatic ventricular tachycardia associated with hypertrophic cardiomyopathy and in 2 of 66 patients (3%) with hypertrophic cardiomyopathy and no ventricular tachycardia ($p = 0.02$). Aronow et al. (61) observed that ventricular tachycardia and complex ventricular arrhythmias detected by 24-h ambulatory electrocardiography in elderly patients with hypertrophic cardiomyopathy were a risk factor for new cardiac events at 2 years follow-up. During a 27-month follow-up period, Aronow et al. (62) found that elderly patients with hypertrophic cardiomyopathy, echocardiographic evidence of LV hypertrophy, and ventricular tachycardia or complex ventricular arrhythmias detected by 24-h ambulatory electrocardiography had an increased incidence of primary ventricular fibrillation or sudden cardiac death.

Hemodynamic and electrophysiological studies were performed by Fananapazir and Epstein (63) in 30 patients with hypertrophic cardiomyopathy who survived sudden cardiac death. Potential causes of sudden cardiac arrest were found in 30 of 30 patients (100%). Inducible, sustained ventricular arrhythmias were found in 21 patients (70%): polymorphic ventricular tachycardia in 18 patients, monomorphic ventricular tachycardia in 2 patients, and ventricular fibrillation in 1 patient. Severe LVOT obstruction was observed in 8 patients (27%), bradycardia in 5 patients (17%), myocardial ischemia associated with hypotension in 5 patients (17%), and atrial tachycardia causing hypotension in 4 patients (13%).

Natural History

Elderly patients with hypertrophic cardiomyopathy are predisposed to develop sudden cardiac death, congestive heart failure, and syncope. Lewis and Maron (8) observed that severe symptoms were not present early in life but developed after age 55 in 50 of 52 elderly patients with hypertrophic cardiomyopathy. Spirito and Maron (64) observed that most asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy who die suddenly have marked and diffuse LV hypertrophy. They concluded that a relation exists between the extent of LV hypertrophy and the occurrence of sudden and unexpected cardiac death in patients with hypertrophic cardiomyopathy. Kogure et al. (65) reported that 6 of 66 patients (9%) with hypertrophic cardiomyopathy developed systemic thromboembolism during 3.7 years follow-up. All thromboembolic events occurred in patients

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with atrial fibrillation. Hypertrophic cardiomyopathy also predisposes to infective endocarditis (66).

A total of 95 elderly patients (mean age 71.8 years) with hypertrophic cardiomyopathy were followed for a mean duration of 4.2 years (43). The survival rates at 1 and 5 years were 95 and 76%, respectively, compared with 97 and 82%, respectively, for control subjects. Patients with class III dyspnea had a 1-year mortality rate of 36%. Advanced functional class dyspnea ($p = 0.0002$), increased indexed left atrial size ($p = 0.004$), and increased indexed ventricular septal thickness ($p = 0.0003$) were associated with an increased incidence of cardiac death.

Therapy

Negative inotropic agents are generally recommended in the treatment of patients with hypertrophic cardiomyopathy. Negative inotropes exert several beneficial effects including a reduction in LVOT gradient by decreasing flow acceleration and ''dragging'' forces on the protruding mitral leaflets resulting in a lower pressure gradient (37).

β-adrenergic blockers can relieve the symptoms of exertional angina pectoris, dyspnea, and light-headness or syncope in patients with hypertrophic cardiomyopathy. In one-half to one-third of all symptomatic patients, improvement of cardiac symptoms is seen after treatment with propranolol at doses of 160–320 mg daily (53). Transient β-adrenergic hypersensitivity occurs after β-blocker withdrawal in patients with hypertrophic cardiomyopathy and is associated with clinical deterioration (67). Therefore, abrupt withdrawal of β-blockers should be avoided in patients with hypertrophic cardiomyopathy.

Calcium channel blockers, especially verapamil, have also been shown to be effective in reducing cardiac symptoms in patients with hypertrophic cardiomyopathy (56, 68,69). Almost 60% of 227 patients with hypertrophic cardiomyopathy receiving verapamil (median dose 360 mg daily) because of severe cardiac symptoms despite β-blocker therapy had clinical improvement after 3 to 53 months (mean 25 months) (69). β-blockers and verapamil are contraindicated in patients with important conduction system abnormalities unless a pacemaker has been implanted. Of 47 elderly patients with severe cardiac symptoms initially treated with drugs, only 12 (26%) showed clinical improvement (8). The drug treatment included verapamil in eight patients, propranolol in one patient, calcium channel blockers plus β-blockers in two patients, and disopyramide plus verapamil in one patient.

Digitalis should be avoided in patients with hypertrophic cardiomyopathy unless LV systolic dysfunction develops. Nitrates should be used with caution. Diuretics should be avoided in patients with hypertrophic cardiomyopathy and pulmonary venous congestion associated with normal LV systolic function unless administered concomitantly with a β-blocker or verapamil (53). β-blockers or verapamil may be used to slow the ventricular rate in patients with atrial fibrillation associated with hypertrophic cardiomyopathy. Restoration of sinus rhythm in patients with atrial fibrillation should be attempted by electrical cardioversion. Once atrial fibrillation has developed, anticoagulant therapy should be started immediately and continued indefinitely (53). Patients with hypertrophic cardiomyopathy should also receive prophylactic antibiotics during procedures predisposing to infective endocarditis (66).

Of 30 patients with hypertrophic cardiomyopathy surviving cardiac arrest who underwent hemodynamic and electrophysiological evaluation, Fananapazir and Epstein (63) studied patients with inducible, sustained ventricular arrhythmias and treated 17 of 21 of

them with an implantable defibrillator and 4 with antiarrhythmic drugs. A total of 7 patients underwent LV septal myectomy; 3 patients received antiarrhythmic drugs for atrial tachycardia; 1 patient had catheter ablation of a concealed posteroseptal accessory pathway; and 3 patients with myocardial ischemia were treated with propranolol plus verapamil (2 also had a defibrillator implanted). During 18 months follow-up (range 1 to 75 months), 4 patients (13%) died suddenly, and 4 (13%) received a total of 13 defibrillator shocks. The 1-year survival rate was 93%. The 1-year sudden death or shock event-free rate was 80%.

Patients with obstructive hypertrophic cardiomyopathy with severe cardiac symptoms not responding well to medical therapy should have surgical treatment. The preferred operation for most patients with obstructive hypertrophic cardiomyopathy is ventricular septal myotomy–myectomy (53,70). However, mitral valve replacement has a role in selected patients (53,71). A group of 18 severely symptomatic elderly patients with obstructive hypertrophic cardiomyopathy (LVOT obstruction 50 mmHg) underwent surgery: 12 had ventricular septal myotomy–myectomy and 6 had mitral valve replacement. Of 18 patients, 2 (11%) died as a result of surgery. Of the 16 surgical survivors, 14 (88%) had improvement in clinical symptoms. Of the 14 patients, 2 (14%) died during follow-up: 1 patient died suddenly 8 months after surgery, and 1 patient died of congestive heart failure 16 months after surgery.

DILATED CARDIOMYOPATHY

Idiopathic dilated cardiomyopathy is a primary disease of ventricular muscle, with increased LV or biventricular volumes, without an appropriate increase in ventricular septal or free wall thickness, and with depression of LV systolic function (72). Other etiological factors that can cause diffuse LV systolic dysfunction must be excluded (73). In a large cohort of 554 unselected men and 1243 women aged >60 years in a long-term health care facility (6), the prevalence of idiopathic dilated cardiomyopathy was 1% in both sexes. In the same cohort, the prevalence of abnormal LV ejection fraction ($<50\%$) was 29% in men and 21% in women (6). Approximately 10% of patients with dilated cardiomyopathy are older than 65 (73–77). The diagnosis of dilated cardiomyopathy can be confirmed by echocardiography (Figs. 11–13), and by pulsed Doppler echocardiography (Fig. 14) in elderly patients. Figure 13 shows a large apical thrombus that can complicate this condition. Coronary angiography should be considered in patients with dilated cardiomyopathy and chest pain. Recently, transthoracic coronary echocardiography has been proposed as a useful method for distinguishing between ischemic and nonischemic dilated cardiomyopathy (78).

Symptoms

Symptoms due to dilated cardiomyopathy include fatigue and weakness resulting from decreased cardiac output, exercise intolerance, dyspnea due to pulmonary congestion, chest pain, and syncope. Symptoms due to systemic or pulmonary emboli may also occur. Physical examination reveals moderate-to-severe cardiomegaly and audible third and fourth heart sounds. Signs of LV or biventricular failure may be present.

Fuster et al. (76) reported 104 patients at the Mayo Clinic with idiopathic dilated cardiomyopathy followed for 6 to 20 years. Of these 104 patients, 73% had congestive

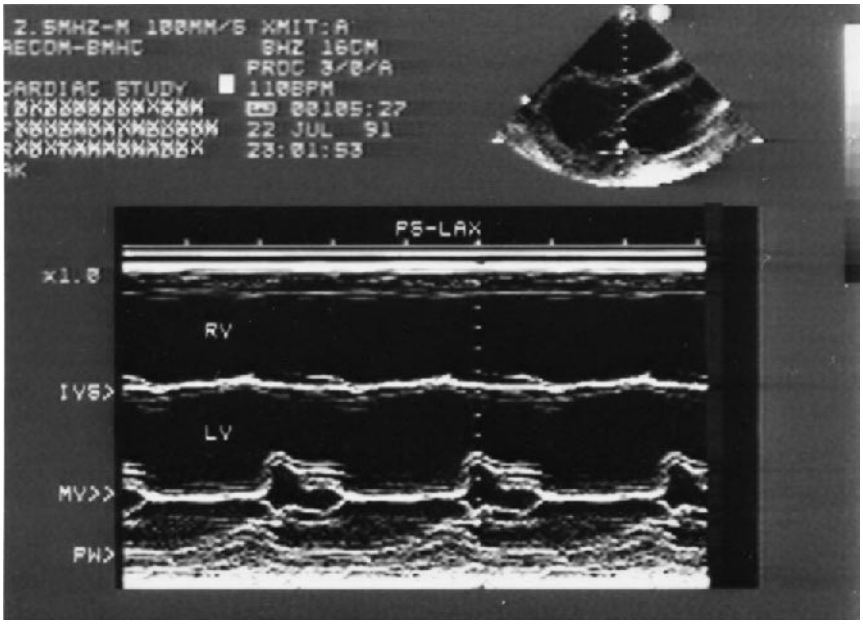

Figure 11 M-mode echocardiogram at the mitral valve level in an elderly patient with dilated cardiomyopathy shows thinning of the interventricular septum (IVS), a markedly dilated LV cavity (LV), and increased E point septal separation. RV = right ventricle; MV = mitral valve; PW = posterior wall.

heart failure at the time of diagnosis, and 96% had congestive heart failure at follow-up. Systemic emboli were present in 4% of the patients at the time of diagnosis and in 18% of the patients at follow-up. Systemic thromboembolism developed in 8 of 24 patients (33%) with atrial fibrillation and in 11 of 80 patients (14%) with sinus rhythm (p = NS). Systemic thromboembolism developed in 18% of patients who did not receive anticoagulant therapy and in none of those who did ($p = 0.05$). Of 104 patients, 80 (77%) died at follow-up, two-thirds of the deaths occurring within 2 years.

Roberts et al. (77) reported that 148 of 152 necropsy patients (97%) with idiopathic dilated cardiomyopathy had clinical evidence of chronic congestive heart failure. Sudden death was the initial manifestation in 114 of 152 patients (75%), and in most patients it became intractable and caused death. The mean duration from the onset of chronic congestive heart failure to known death in 120 patients was 54 months. The cause of death was chronic congestive heart failure in 58% of patients, sudden death in 27% of patients, pulmonary emboli in 9% of patients, and other in 6% of patients. Clinical evidence of pulmonary emboli was present in 39% of patients. Clinical evidence of systemic emboli was present in 20% of patients. Of 131 patients, 79 (60%) had either clinical or necropsy evidence, or both, of pulmonary or systemic emboli.

Falk et al. (79), studying 25 patients with nonischemic dilated cardiomyopathy who were not receiving anticoagulant therapy, demonstrated that a LV thrombus was present on initial echocardiogram in 11 patients (44%), developed during 21.5 months follow-up in 4 additional patients (16%), and disappeared in 2 patients (8%) during follow-up. Systemic thromboembolism developed in 5 of 25 patients (20%) during follow-up. Of the five

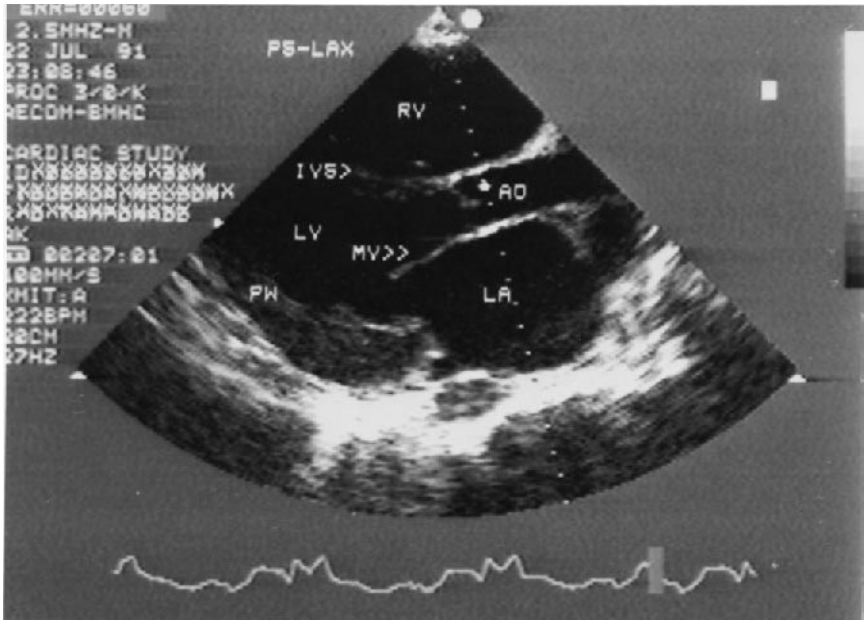

Figure 12 Diastolic frame of a two-dimensional echocardiogram from a parasternal long-axis view in an elderly patient with dilated hypertrophic cardiomyopathy shows thinning of the interventricular septum (IVS) and a large LV cavity (LV). RV = right ventricle; AO = aorta; MV = mitral valve; PW = posterior wall; LA = left atrium.

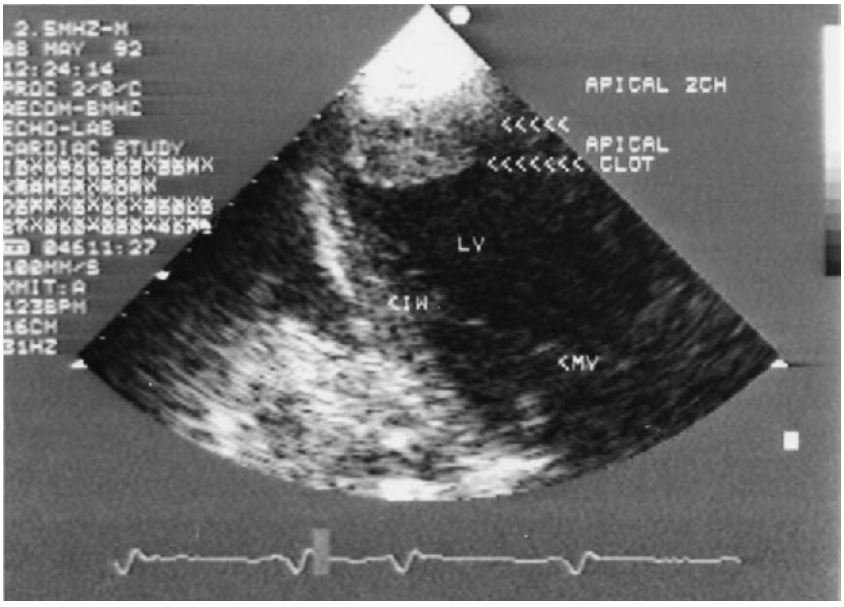

Figure 13 Two-dimensional apical two-chamber view in an elderly patient with dilated cardiomyopathy shows a large apical thrombus. LV = left ventricle; IW = inferior wall; MV = mitral valve.

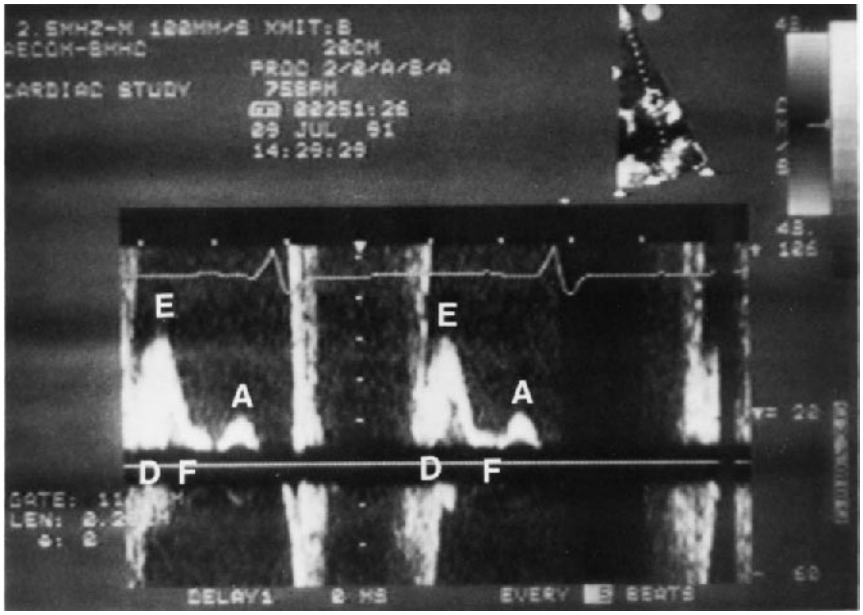

Figure 14 LV diastolic waveforms obtained with pulsed Doppler echocardiography in an elderly patient with dilated cardiomyopathy show increased flow velocity of early peak (E), fast deceleration of early diastolic flow velocity from (from E to F), shortening of early diastolic filling component from (D to F) with visible diastasis, and decreased maximal velocity of the late peak as a result of atrial systole (A).

thromboembolic events, four occurred in patients with echocardiographic evidence of a LV thrombus. These five patients with thromboembolic events were treated with warfarin. No further embolic events occurred in these patients at 15 months follow-up.

Congestive heart failure in patients with dilated cardiomyopathy should be treated with salt restriction, diuretics, digitalis, and angiotensin-converting enzyme inhibitor therapy. β-Blocker therapy may improve symptoms in patients with dilated cardiomyopathy (80). Anticoagulants should be administered even if there is no echocardiographic evidence of LV thrombus. There is no evidence that antiarrhythmic drugs prolong life or prevent sudden cardiac death in patients with dilated cardiomyopathy. The role of endomyocardial biopsy in the diagnosis of dilated cardiomyopathy and as a guide to therapy in the elderly is unknown (73). Immunosuppressive therapy may be poorly tolerated in elderly patients with dilated cardiomyopathy (81).

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy may be caused by myocardial infiltrative, noninfiltrative, and storage diseases and by endomyocardial disease and is uncommon in the elderly. Primary amyloidosis is a frequent cause of restrictive cardiomyopathy but is uncommon in the elderly (73). Characteristically in cardiac amyloidosis, the ventricles are small and the

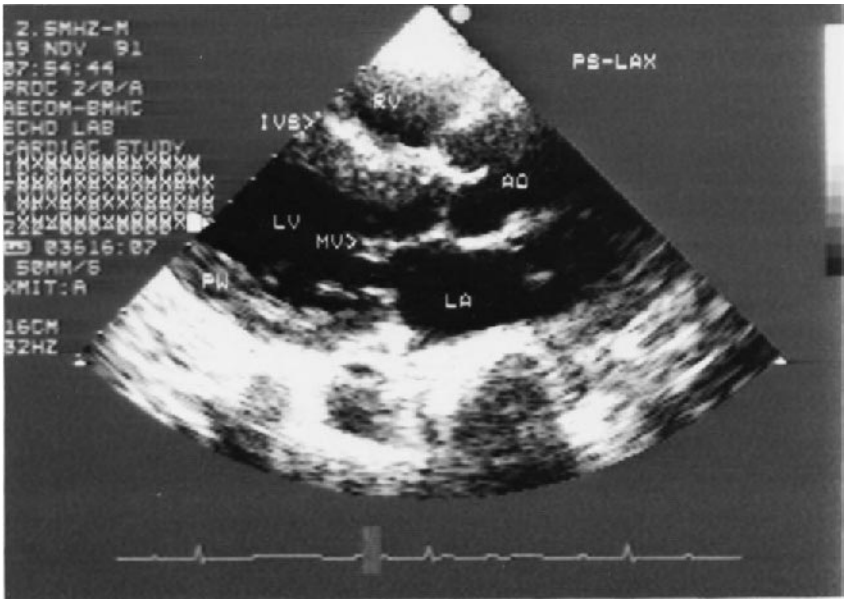

Figure 15 Two-dimensional echocardiogram from a parasternal long-axis view in an elderly patient with cardiac amyloidosis shows a hypertrophic interventricular septum with the characteristic ''sparkling'' appearance of the septal myocardium. RV = right ventricle; IVS = interventricular septum; AO = aorta; LA = left atrium; MV = mitral valve; LV = left ventricle; PW = posterior wall.

atria large, with increased filling pressures and thickened walls (73). The echocardiogram shows a characteristic ''sparkling'' of the ventricular myocardium (Fig. 15). Stiffness of the LV in cardiac amyloidosis produces a characteristic restrictive mitral inflow pattern with a tall E wave and a small A wave (Fig. 16). Low QRS voltage, atrial fibrillation, and conduction defects may be present on the electrocardiogram (73). The low voltage on a 12-lead ECG stands in striking contrast with the prominent hypertrophy by echocardiography. Small or absent R waves in the right precordial leads or Q waves in the inferior leads may mimic myocardial infarction. Complex ventricular arrhythmias are frequently present.

Symptoms due to cardiac amyloidosis include exertional dyspnea, fatigue, and chest pain. Peripheral edema is prominent. Congestive heart failure and postural hypotension may develop. A low systolic blood pressure, a narrow pulse pressure, jugular venous distention with prominent X and Y descents, mild-to-moderate cardiomegaly, a third heart sound gallop, a systolic murmur of tricuspid or mitral regurgitation, hepatomegaly, and peripheral edema may occur. An increase in neck and vein distention with inspiration (Kussmaul's sign) may be present.

The diagnosis of cardiac amyloidosis can be confirmed by biopsy of rectal, gingival, or endomyocardial tissue (73). There is no specific treatment for cardiac amyloidosis (73). Diuretics and vasodilators should be used very cautiously in patients with congestive heart failure due to cardiac amyloidosis. Patients with cardiac amyloidosis are especially sensi-

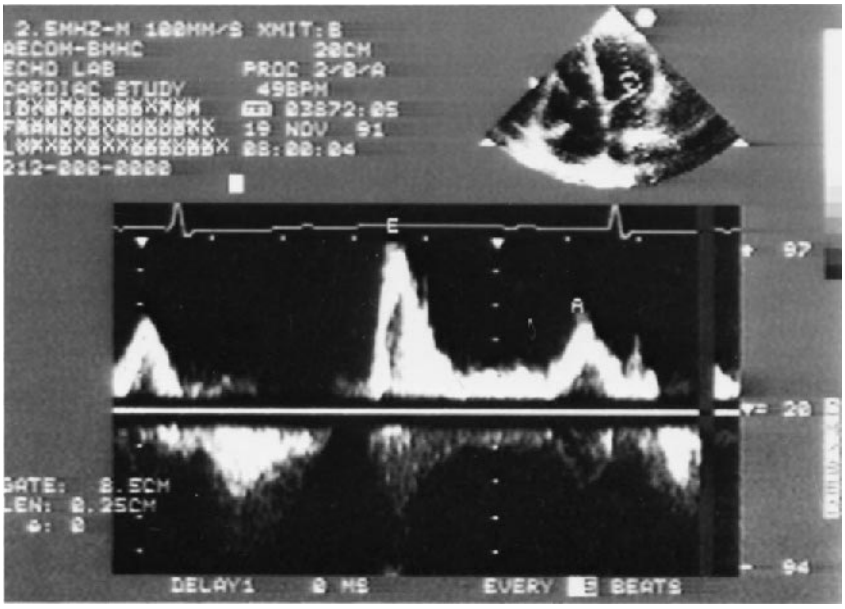

Figure 16 LV diastolic waveforms obtained with pulsed Doppler echocardiography in an elderly patient with cardiac amyloidosis show increased flow velocity of early peak (E) and decreased maximal velocity of the late peak as a result of atrial systole (A).

tive to digitalis. Patients with symptomatic conduction system abnormalities may benefit from permanent pacemaker implantation.

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22

Thyroid Heart Disease in the Elderly

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INTRODUCTION

The cardiovascular manifestations of both hyperthyroidism and hypothyroidism are well known and continue to serve as the focus of considerable research efforts. Cardiovascular manifestations are usually among the earliest and most consistent findings of an abnormality of the thyroid axis and are often responsible for the diagnostic testing that eventually leads to the diagnosis. This is particularly true when considering the elderly hyperthyroid population in that most of the classic signs and symptoms of hyperthyroidism are lacking at this time of life. Although there are receptors for thyroid hormone in heart tissue, thyroid hormone also affects cardiovascular function through an indirect effect on the adrenergic system, particularly in the setting of thyroid hormone excess. Age may modify some of the sequelae as well as the treatment of both hyper- and hypothyroidism, but it is important to understand the effect of these disorders on the cardiovascular system in general and consider each case individually.

HYPERTHYROIDISM

Classic symptoms of hyperthyroidism include tachycardia, palpitations, and an increased pulse pressure. In the elderly person with hyperthyroidism, however, associated findings often include atrial fibrillation, congestive heart failure, and angina. This latter problem results from the increase in oxygen demand placed on the aged heart by excessive amounts of thyroid hormone and thus increased metabolic demands by both the heart and other body organs. A definite adrenergic contribution to the clinical manifestations of hyperthyroidism was suggested in an animal model that showed that a total or nearly total sympathetic block produced by a subarachnoid injection of procaine could successfully relieve or prevent thyroid storm (1). It was also observed that alterations in cardiovascular function in hyperthyroid dogs were ameliorated after spinal epidural procaine blockade (2). This resulted in the use of sympatholytic agents, including reserpine, guanethidine, and propran-

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olol, to treat cardiovascular manifestations of hyperthyroidism (3–6). Since these agents are effective in reducing many of the cardiac manifestations, it appears that a significant component of these symptoms results from catecholamine–thyroid interactions. This latter phenomenon has received a great deal of attention in recent years and has been used as a model to support a membrane action for thyroid hormone because of the almost immediate effect noted on a number of systems when thyroid hormone and catecholamines interact in a synergistic manner. Interactions between thyroid hormone and the catecholamines may result from several mechanisms, including (1) an enhanced sensitivity of target cells to the activating effects of catecholamines; (2) an increase in the number of adrenergic receptor sites available to interact with catecholamines; (3) an increase in tissue levels of free catecholamines; (4) similar but separate and additive effects of thyroid hormone and catecholamines; and (5) thyroid stimulation of adrenergic nerve terminals. It has been noted for several decades that thyroid hormone is capable of potentiating both the chronotropic and pressor effects of the catecholamines (7,8). Using a model of euthyroid and hyperthyroid dogs, it was observed that thiopental anesthesia and spinal epidural block with procaine prevented the otherwise observed increase in heart rate, cardiac index, left ventricular stroke volume, and oxygen consumption noted in hyperthyroid dogs. There was also a greater increase in heart rate, cardiac index, and oxygen consumption following an infusion of either epinephrine or norepinephrine in the setting of hyperthyroidism (3). This study and several subsequent studies (7,8) were criticized for their lack of proper design and statistical analysis. More recent studies failed to demonstrate an increased sensitivity of the cardiovascular system to the action of sympathoadrenergic agents in the setting of hyperthyroidism (9–13). The parameters that were studied included blood pressure, heart rate, and contractile effects on isolated papillary muscles. In addition, studies on humans demonstrated a similar alteration in heart rate and mean atrial and arterial pressures before and after triiodothyronine (T_3)-induced hyperthyroidism (9,13). This is in contrast to studies that demonstrated an enhanced sensitivity to the chronotropic and arrhythmogenic effects of norepinephrine when combined with T_3 (14). One study reported an enhanced effect with T_3, but only with β-adrenergic agents (15).

Although thyroid hormone is thought to exert most of its calorigenic effects through a nuclear receptor and the process of transcription, both mitochondrial and membrane-bound receptors have been demonstrated. The membrane-bound receptor is most likely responsible for the thyroid hormone–catecholamine interaction because of the almost instantaneous synergistic response noted when catecholamines and thyroid hormone are introduced into certain systems. It has been demonstrated that chronic administration of thyroid hormone to rats increases the number but not the affinity of plasma β-adrenergic receptors in heart tissue (16,17). There has been a reported decline in the α-adrenergic receptors in response to chronic thyroid hormone administration as well (16,18). Although both mechanisms may help explain some of the reported findings showing an enhanced response of cardiac tissue in the setting of hyperthyroidism, additional studies are needed before arriving at a definite conclusion. It appears that this would only partially explain the observed findings in any case, because the time it takes for new receptor formation would exceed that of the observed synergistic effect noted in certain models. Although studies have reported no change in receptors for thyroid hormone with age, none have examined cardiac tissue, and therefore no conclusions regarding an age effect can be made at this time.

Some have proposed an alteration in the synthesis and/or release of sympathetic neuronal or adrenal medullary catecholamines in the setting of hyperthyroidism to help explain, at least in part, the data demonstrating an enhanced cardiovascular response, but

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this has not received universal acceptance. Hearts from hyperthyroid animals have been shown to have normal or low norepinephrine concentrations and turnover (10,19). Patients who are thyrotoxic reportedly have normal plasma concentrations of epinephrine, normal or low concentrations of norepinephrine, and normal rates of epinephrine and norepinephrine secretion by the adrenal (20–22). Urinary excretion of norepinephrine is normal or low, and the excretion of epinephrine, metanephrine, and 4-hydroxy-3-methoxylmandelic acid, the latter two representing catecholamine metabolites, are within normal range (23). A decrease in neuronal catecholamine synthesis has also been suggested based on a decrease in the plasma concentration of the enzyme dopamine β-hydroxylase (24). This makes it highly unlikely that hyperthyroidism mediates its effects by increasing endogenous catecholamine levels. It has been reported that aging is associated with higher basal levels of circulating norepinephrine. Whether the effects of hyperthyroidism are due to the same mechanism throughout life is not known at this time.

Another popular theory about why hyperthyroidism may result in an enhanced cardiovascular response relates to the way in which the catecholamines are metabolized by myocardial tissue. Although the two enzymes that metabolize catecholamines, catechol-*o*-methyltransferase and monoamine oxidase, were found not to be altered by thyroid hormone, at least in a rat model, hyperthyroidism was associated with a greater quantity of radiolabeled epinephrine and norepinephrine reaching the heart (25). There was a decrease in catecholamine binding to cardiac tissue, however, and a greater percentage of free catecholamine within the myocardium itself.

Studies have reported a decrease in the production of catecholamines in the setting of thyroid hormone excess. Nevertheless, because both thyroxine (T_4 and T_3) are concentrated and metabolized within adrenergic nerve endings, thyroid hormone may serve as a neurotransmitter, much like one of its precursors, tyrosine (26). The role of the central nervous system in regulation of cardiac function also remains a possible mechanism for the enhanced effect of thyroid hormone on the cardiovascular system. There is ample evidence showing an effect of thyroid hormone on neurotransmitters, such as β-endorphin and ACTH. Whether this may indirectly affect cardiac function remains a topic of future consideration.

Although much attention has been given to the effect that thyroid hormone may exert on cardiac tissue through a catecholamine interaction, thyroid hormone was first shown to exert a direct effect on myocardial tissue in the early part of the twentieth century (27). These studies were done before our current knowledge of receptors and cell mediators. Nevertheless, when T_4 was incubated with fragments of cardiac tissue from chicken embryos in the absence of adrenergic tissue, it was noted that the heart rate increased after a 12-h period. Thyroid hormone continued to exert a chronotropic effect even after pharmacological blockade, also implying a direct effect (4,6). It is currently agreed that the tachycardia that results from hyperthyroidism results from a combination of direct effects of thyroid hormone, as well as from an increase in adrenergic stimulation and parasympathetic inhibition.

Thyroid hormone also exerts a positive effect on cardiac contractility and inotropy. Most studies demonstrating this effect have used cat papillary muscles. Thyroid hormone increased the rate of isometric tension, decreased the time it took to achieve peak tension, and increased the velocity of muscle shortening. Since these findings were not affected by prior depletion of catecholamines, this also supports a direct effect of thyroid hormone (10). These data are consonant with those of studies using isolated atria from guinea pigs (28). There is a consensus that the majority of cardiac effects noted during the hyperthyroid state result from the direct action of thyroid hormone, with a smaller contribution from

adrenergic mechanisms. With this in mind, investigators examined the dynamics of cardiac function in the setting of hyperthyroidism. It has been reported, for example in a model of hyperthyroid rabbits, that the tachycardia characteristic of hyperthyroidism is associated with an increased rate of diastolic depolarization and a decrease in the duration of the action potential in sinoatrial node cells (28). A shortening of the refractory period and a reduction in the electrical threshold of atrial cells have been implicated in the pathogenesis of cardiac arrhythmias in the setting of excess thyroid hormone (3). Although a rise in adenylate cyclase activity by thyroid hormone is the suggested mechanism for the enhanced myocardial contractility (29), not all studies have come to the same conclusion (30). This enzyme system has also been implicated in the thyroid–catecholamine interaction on cardiac function. Thyroid hormone has been reported to exert an effect on the heart through its effect on cardiac sarcoplasmic reticulum. This intracellular organelle has the capacity to accumulate and release calcium during the contractile process of the heart, using calcium as a cell mediator (31,32). The ATPase system, notably Na,K-ATPase, has also been implicated in the increased effects of thyroid hormone on cardiac function, especially in ventricular tissue (33,34).

Clinical Manifestations

Clinically, it has been noted that hyperthyroidism is commonly associated with tachycardia and atrial fibrillation. In the elderly, congestive heart failure, angina, and ventricular arrhythmias may also be seen in greater frequency. Many argue that this is due to the greater likelihood of underlying cardiovascular disease; others argue that age may alter the end-organ effect of thyroid hormone. The literature is replete with studies that demonstrate that an excess amount of thyroid hormone can lead to cardiac hypertrophy, somewhere in the range of 20 to 90%, depending on the species studied and the duration of exposure to excess thyroid hormone. This effect is thought to be completely reversible upon cessation of thyroid hormone stimulation (35–39). Thyroid hormone excess results in cardiac hypertrophy, but there appears to continue to be an increase in contractile function (40). Treating the hyperthyroid state with antithyroid medications has been shown capable of reversing the cardiac hypertrophy (41). One recent study, on persons with subclinical hyperthyroidism, reported no effect on blood pressure, heart rate, left ventricular systolic function, or stroke volume index, but confirmed an increase in left ventricular mass index (42). Although there is no definite explanation of the pathogenesis of the cardiac hypertrophy, foci of lymphocytic and eosinophilic cells, fibrosis, and fatty infiltration have been described, along with myofibril hypertrophy. Mitochondria have been reported to be increased in number and hypertrophied, with localized areas of vacuolization and an aberrant configuration of intracellular structures (43,44). Thyroid hormone has recently been hypothesized to activate the cardiac renin–angiotensin system without involving the sympathetic nervous system or the circulating renin–angiotensin system. The activated renin–angiotensin system is thought to contribute to cardiac hypertrophy in hyperthyroidism. Administration of losartan, an angiotensin-II (AII) receptor blocker was associated with regression of thyroxine-induced cardiac hypertrophy (45). Another study using cultured myocardial cells reported that angiotensin-II was the principal mediator of the renin–angiotensin system and a regulator of cardiac hypertrophy corresponding to changes in the amount and composition of certain tissue proteins including the expression of beta-myosin heavy-chain iso-mRNA and isoprotein (46). A study using hyper- and hypothyroid rats reported on the renal expression of renin mRNA using a semiquantitative reverse transcriptase-polymerase chain reaction. Compared with control animals, plasma renin

activity, renal level of renin, and renal expression of renin mRNA were reduced (82, 94, and 71%, respectively) in hypothyroid animals and elevated (155, 182, and 152%, respectively) in hyperthyroid animals. Sympathetic denervation had no independent effect on these renin values. These results indicated that thyroid hormone stimulated renin synthesis without involving the sympathetic nervous system (47). A study using hyperthyroid rabbits reported elevated plasma–atrial natriuretic peptide levels and serum ACE activity. The authors concluded that thyroxine had both direct and indirect effects on the release of atrial natriuretic peptide (48).

There was no exercise-induced increase in ejection fraction in hyperthyroid subjects, in contrast to the increase usually noted (49,50). This observation was reversed upon return to the euthyroid state. Once again, no elderly subjects were studied. Although it has been demonstrated that congestive heart failure can result from hyperthyroidism even in the absence of underlying cardiovascular abnormalities and regardless of one's age, the older person is more prone to develop compromised cardiac functioning and more attention should be given to reverse the thyroid abnormality promptly before the development of a life-compromising situation. Coexisting problems, such as tachycardia and increased demand for oxygen by metabolically stimulated myocardial cells, may also lead to serious cardiac compromise, angina, cardiac ischemia, or arrhythmias.

As stated previously, hyperthyroidism is classically associated with increased cardiac output, stroke volume, heart rate, and ejection time. There is a decrease in peripheral vascular resistance, a widening of the pulse pressure, and a general increase in circulating blood volume. The electrocardiogram may be normal but more commonly demonstrates a tachycardia. ST- and T-wave abnormalities may be noted and tend to be nonspecific. There may be evidence of cardiac ischemia, voltage changes reflecting left ventricular hypertrophy, notching and slurring of the P wave, P-R interval shortening or prolongation, Q-T interval shortening, and/or transient atrioventricular conduction abnormalities, including complete heart block (51–53). Atrial fibrillation is found in approximately 15 to 20% of cases, with a slower rate more commonly reported in older persons. It occurs more commonly in persons with underlying cardiovascular disease, and it appears to be more common in the setting of hyperthyroidism even in an otherwise normal heart. Of note, elderly persons who develop atrial fibrillation in the setting of hyperthyroidism have a greater chance of remaining in this rhythm despite a return to the euthyroid state compared to younger persons in whom reversibility is usually the rule. Paroxysmal supraventricular tachycardia, atrial flutter, and ventricular tachycardia are less commonly noted. Although there has been a report of a greater risk of developing the Wolff–Parkinson–White syndrome in association with hyperthyroidism (54), this finding remains uncommon.

In measuring systolic time intervals, the preejection and left ventricular ejection time are reportedly shortened during the hyperthyroid state. The ratio of preejection to ejection time, however, remains unchanged (55,56). Although not well studied in the elderly, one study reported on seven patients with a mean age 47, with hyperthyroidism and coexisting dilated cardiomyopathy with low output failure. Five of the seven studied had a complete resolution and two a partial resolution of the dilated cardiomyopathy following treatment of the hyperthyroid state (57).

Management

Many cardiac findings in the setting of hyperthyroidism appear to be well tolerated and without an apparent risk of producing an immediate crisis, but it is essential that any

symptom or sign of cardiac compromise be evaluated promptly and treated as needed. In general, the goal is to treat the hyperthyroid state as quickly as possible while managing the patient in totality. Radioactive iodine therapy is the treatment of choice for most older persons with hyperthyroidism, but the time from beginning treatment with radioactive iodine until such time that euthyroidism is reached is of the order of weeks to months. Therefore, most agree that antithyroid medication should be used early in an attempt to decrease thyroid hormone production and metabolism. When an immediate effect is needed because of significantly compromised cardiac function, administration of iodine in the form of Lugol's can more quickly reduce circulating levels of thyroid hormone by blocking the uptake and organification process necessary for thyroid hormone production. If Lugol's solution is to be an asset, however, one must always ensure that antithyroid medication is administered before and during the iodine treatment to prevent the iodine from being converted into thyroid hormone by an already highly efficient thyroid nodule or diffusely toxic goiter, the end result being actual worsening of the hyperthyroid state. β-Blockers primarily compete with β-adrenergic receptors in the heart and other tissues, as well as reduce the conversion of thyroxine to 3,5,3′-triiodothyronine by approximately 15%. Although β-blockers have been used successfully to reduce end-organ responsiveness, caution is advised because they may precipitate cardiac failure. Reserpine and guanethidine have also been used with a great deal of success to ameliorate symptoms of tachycardia and palpitation, but once again both these agents have significant side effects for which the patient should be monitored. Both are capable of depleting tissues of catecholamines and may further depress cardiovascular reflexes, as well as induce other side effects, including altered mental function and orthostatic hypotension. In the setting of congestive heart failure, the use of diuretic therapy and digitoxin may be required until the heart becomes less of a target for the action of thyroid hormone excess. Clearly, the physician must provide close observation in all cases of hyperthyroidism in whom a compromised cardiovascular state exists, regardless of the age of the person, and seek the advice of an experienced cardiologist when uncertain concerning management. In most cases, the antithyroid medication begins working within 2 weeks, and attention can then be given to a more definitive therapy with radioactive iodine. Since it takes weeks to months for the radioactive therapy to become effective, however, it is important to continue antithyroid medications while the radioactivity has a chance to work. As the hyperthyroid condition improves, oral medication should be tapered to keep the person in a euthyroid state. Overtreatment at this time may precipitate hypothyroidism, with its own cardiac problems. Since many persons treated with radioactive iodine become hypothyroid, careful follow-up is advised, and if necessary, thyroid hormone replacement may be initiated.

HYPOTHYROIDISM

Cardiovascular manifestations of hypothyroidism have long been recognized and classically include bradycardia, cardiomegaly, and low voltage on electrocardiographic monitoring (58,59). Congestive heart failure and evidence of cardiomyopathy are frequent diagnoses in persons with insufficient amounts of thyroid hormone. What makes the diagnosis of hypothyroidism so difficult, however, is that hypothyroidism is an age-prevalent disorder and many of the signs and symptoms resemble those of other diseases that occur with increasing frequency with age. Physicians frequently treat target symptoms without regard

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to the etiology of the problem; for example, congestive heart failure may be treated with diuretics and digoxin for presumed atherosclerotic heart disease. The American Thyroid Association now recommends that all persons over 50 have annual screening for thyroid hormone abnormalities after studies showed the cost-benefit from such practice.

''Myxedema heart'' was a term used to connote a cardiomyopathy that resulted from insufficient quantities of thyroid hormone and that was reversible with thyroid hormone replacement. It is now recognized that hypothyroidism exerts its effects on the cardiovascular system through a direct effect of thyroid hormone deficiency as well as through an indirect effect from reduced metabolism.

Myocardial Tissue and Hypothyroidism

Studies have reported that the heart in persons with hypothyroidism may be dilated, pale, and flabby, but there is no evidence of hypertrophy (60). Histologically, swelling of the myofibrillar elements, interstitial fibrosis, basophilic degeneration, and tissue edema have been described (61). There appears to be deposition of mucopolysaccharide, likely reflecting the decline in certain enzymes necessary for the breakdown of these substances. Electron microscopic studies reveal thickening of the capillary basement membrane similar to that observed in diabetes mellitus and in persons of advanced age (62,63). Numerous other ultrastructural changes have been described, including loss of mitochondrial cristae.

Thyroid Hormone Deficiency and Cardiovascular Function

Perhaps the most widely accepted change that has been noted in the setting of hypothyroidism is a reduction in myocardial contractility. Using isolated right ventricular papillary muscles from hypothyroid cats and dogs, a decrease was noted in isometric tension and the rate of tension development. The time it took to reach peak tension increased at all muscle lengths, and isotonic force-velocity relations were shifted downward and to the left, supporting a depressed contractile state (64,65). In all animal studies reported, congestive heart failure was not noted despite significant reductions in circulating levels of thyroid hormone. It has been postulated that decreased myocardial contractility in hypothyroidism may result from a reduction in the thyroid–adrenergic relationship, with either a diminished response to a given amount of catecholamine or a reduced amount of free catecholamine available to interact at the cardiac receptor site. Studies have reported an increase, decrease, and no change in cardiovascular sensitivity to catecholamine stimulation in the setting of hypothyroidism (66–69). Levels of norepinephrine in myocardial tissue of hypothyroid cats were not reported to be affected by thyroid status (64), and thus it appears unlikely that a lower level of catecholamine exposure to the cardiac receptor is the cause of significant cardiac effects. Studies have shown a reduction in β-adrenergic receptor activity in atria from hypothyroid rats and an increase in α-receptor activity (70) in the same tissue. This reduction in the number and/or affinity of β-receptors in cardiac tissue could result in a depressed myocardial response. Because contractile function is depressed in isolated papillary muscles from hypothyroid rats (64), thyroid hormone deficiency seems to have a direct effect and is responsible for at least a component of the cardiovascular change induced by the hypothyroid state. It has been noted that the rate of calcium uptake and calcium-dependent ATP hydrolysis by isolated myocardial sarcoplasmic reticulum is reduced in the setting of hypothyroidism (71). A reduction in cardiac myosin ATPase activity has been described in both rat and mouse models of hypothyroidism (72–74), although not in a rabbit model (74). Bradycardia is a well-recognized accom-

paniment of hypothyroidism and is thought to result from the lack of thyroid stimulation of sinoatrial node cells (75), further impacted by a reduction in sympathoadrenal stimulation. A decreased rate of diastolic repolarization and prolonged action potential duration has also been described.

Recent studies have focused on changes in lipoprotein composition in altered states of thyroid function. Clearly this has implications on atherogenesis. Short-term hypothyroidism was associated with an increase in plasma lipoprotein (a); T_3 therapy rapidly lowered lipoprotein (a) together with apolipoprotein B and LDL cholesterol. These findings support the hypothesis that thyroid hormone is capable of regulating plasma lipoprotein (a) and apolipoprotein B in a parallel manner. Elevated concentrations of lipoprotein (a) in combination with LDL cholesterol may be involved in the increased risk of cardiovascular disease assumed to be associated with hypothyroidism (76). Hyperthyroidism, on the other hand, has been recently reported to lower the serum concentration of lipoprotein (a). Changes in LDL receptor activity were significantly correlated with changes in LDL cholesterol, but not changes in lipoprotein (a). The authors concluded that the serum concentration of lipoprotein (a) was lowered in hyperthyroidism, probably by a mechanism other than the enhanced activity of the LDL receptor, and that the LDL receptor pathway is involved in the catabolism of lipoprotein (a) to a limited extent (77). Another recent study reported an association of hypothyroidism, with elevated levels of total and HDL cholesterol, total/HDL cholesterol ratio, apolipoprotein AI, and apolipoprotein E. The increase in apolipoprotein AI without a concomitant increase in apolipoprotein AII suggested a selective elevation of HDL2. In contrast, hyperthyroidism was associated with a decrease in the total and HDL cholesterol, total/HDL cholesterol ratio, and apolipoprotein AI levels. These effects were found to be reversible with treatment of the underlying disorder (78).

Clinical Manifestations of Hypothyroidism

Cardiac manifestations of hypothyroidism occur only in association with a significant reduction in the levels of circulating thyroid hormone. Studies using oxygen consumption as a corollary of thyroid hormone status have reported few cardiac symptoms in otherwise healthy persons until oxygen requirements decline by 75%. This is highly variable, however. Many persons with hypothyroidism have coexisting medical conditions that compromise the cardiovascular system and may lower the threshold for cardiac problems. For the most part, the reduced requirement for oxygen by the hypothyroid myocardium is protective against angina. In fact, many persons develop angina only after therapy with thyroid hormone has been initiated. Dyspnea on exertion and easy fatigability are common complaints of persons who are hypothyroid. Less frequent are complaints of orthopnea, paroxysmal nocturnal dyspnea, and angina. Bradycardia is common, and weak pulse, mild hypertension, distant heart sounds, and evidence of cardiomegaly are classic findings. In general, there is no change in the jugular venous pressure. In severely diminished thyroid function, however, evidence of peripheral edema, nonpitting edema of the lower extremities, pleural effusion, and even ascites may be noted and may lead one to assume that the patient has congestive heart failure (CHF). The presence of nonpitting edema should be a tip that some other process is present. The electrocardiogram may be normal despite the presence of hypothyroidism. More commonly, there is a bradycardia, flattening or inversion of the T wave, particularly in lead II, and a low-amplitude P, QRS complex, and T wave (79). These findings may result from a direct effect of thyroid hormone deficiency, but the presence of a pericardial effusion is also known to affect the electrocardio-

graphic picture that may accompany hypothyroidism. Although not common, incomplete and complete right bundle branch block occur with greater frequency (80). With replacement therapy, these changes return to normal and may even precede the return to normal of other clinical features of the disease.

Studies suggest that in the absence of other coexisting diseases, congestive heart failure is an extremely uncommon finding in hypothyroidism (81). In the setting of shortness of breath, pleural effusions, cardiomegaly, and other symptoms, it is often difficult to distinguish CHF from what has been termed myxedema heart. The absence of pulmonary congestion, diminished plasma volume, high protein content of the effusion, and normal resting venous, atrial, pulmonary artery, and right ventricular end-diastolic pressures is highly suggestive of myxedema itself. It has also been reported that exercise results in an increase in cardiac output and ejection fraction in persons with myxedema, in contrast to the impaired response in those with congestive failure (82,83). The hemodynamic changes associated with hypothyroidism appear to respond to thyroid hormone, but they are not very responsive to diuretic and digoxin therapy. Since in many persons both conditions occur together, there is a great deal of variability in clinical response. Although subclinical hypothyroidism has been associated with a prolongation of the Q-T interval, little has been reported regarding its clinical consequences despite its relatively high incidence among the elderly. A recent Japanese study evaluated the relationship between subclinical hypothyroidism and/or autoimmune thyroid disease and coronary heart disease (CHD). Ninety-seven patients diagnosed as having CHD by a coronary angiogram (CHD group) and 103 healthy subjects matched for age, sex, and body mass index (control group) were included in the study. Thyroid function, thyroid autoantibodies and serum lipid concentrations were measured in the CHD and control groups. The CHD group exhibited significantly decreased levels of serum free T_3 and free T_4 and significantly increased serum TSH levels as compared with the control group, indicating a significant decrease in thyroid function in the CHD patients. Serum HDL cholesterol levels were significantly decreased in the CHD group (84).

Management of Hypothyroidism

Because so many elderly persons with hypothyroidism may have underlying cardiovascular abnormalities, it is wise to begin thyroid hormone replacement therapy with a small dose of L-thyroxine (0.0125 mg daily). The use of diuretic therapy and digoxin should be reserved for persons in whom there is clear evidence of coexisting congestive heart failure. Younger persons or those with no evidence of cardiovascular compromise may be started on higher doses of L-thyroxine, although extreme caution is advised. The starting dose should be increased slowly over the next several weeks, realizing that both age and hypothyroidism prolong the half-life of L-thyroxine. Because it takes approximately five half-lives to reach a steady state, caution is advised against too rapid a rise in dosing. In general, it is appropriate to increase the dose of thyroxine to 0.025 mg daily within 2 weeks if the dosage is well tolerated and to 0.050 mg daily within several weeks thereafter. If there are no clinical problems, the dose should be increased by 0.0125 mg increments every 4 to 6 weeks thereafter, depending on the age and cardiovascular status of the patient, until the level of serum thyroid stimulating hormone has declined to within the normal range or the patient develops signs of toxicity. In general, elderly persons who are hypothyroid require a replacement dose of between 0.100 and 0.125 mg daily compared to an approximate dose of 0.150 mg for younger persons. L-thyroxine is the preferred thyroid

hormone for replacement because T3 exerts a ''burst'' effect on the myocardium and is less well tolerated. It also has a shorter half-life, thereby having a less equilibrated metabolic profile. USP thyroid or other combination therapies also share the disadvantage of T3, a component in all these medications. In certain cases in which severe cardiac disease exists, it may not be possible to return the patient to the euthyroid state. In all cases, close clinical observation is necessary.

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23

Congestive Heart Failure in the Elderly

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BACKGROUND

Despite the decline in the overall age-adjusted mortality rate from coronary artery and hypertensive heart disease, the prevalence and incidence of congestive heart failure (CHF) are increasing (1,2). Congestive heart failure is the leading admitting diagnosis for patients older than 65 and is the most costly diagnosis in the Medicare population, with over $8 billion in annual expenditures (2). The prevalence of heart failure increases with age. In the Framingham study, men in their sixth decade were five times more likely to develop CHF than those in their fourth dacade (3). The progressive aging of the population is the foremost reason for the increasing incidence of CHF. While the overall prevalence of CHF in the U.S. is 0.4 to 2%, it increases to 10% in patients over 80 years old (Fig. 1) (4). The number of patients who will be diagnosed with CHF is expected to double over the next 40 years as a result of the progressive aging of the population. The second factor contributing to the rise in CHF is the decline in prevalence of hypertensive heart disease and ischemia. Thus older patients with or without residual left ventricular (LV) dysfunction will live longer and develop overt CHF later due to progression of their disease or because of the normal aging process. Last, advances in treatment of renal disease and other chronic conditions have improved mortality but indirectly increased the incidence of heart failure (2).

The clinical diagnosis of the syndrome of heart failure is especially challenging in the elderly since it becomes increasingly difficult to differentiate symptoms attributed to left ventricular dysfunction from exertional symptoms that are so common in the elderly. The most common complaint volunteered by young and middle-aged patients suffering from CHF is progressive development of exertional symptoms, such as shortness of breath and fatigue. However, shortness of breath on exertion and fatigue are increasingly common complaints volunteered by the elderly even without evidence of cardiopulmonary disease. Elderly people with undiagnosed heart failure may curtail their daily activity as they become progressively more dyspneic on exertion and match their lifestyle to their ability to perform daily activities of living. These individuals may therefore volunteer little information as to their exertional symptoms. As such, many elderly patients only consult their physicians when they experience dyspnea with minimal exertion or at rest. At such an advanced stage, the control and stabilization of CHF becomes more difficult and often requires hospitalization.

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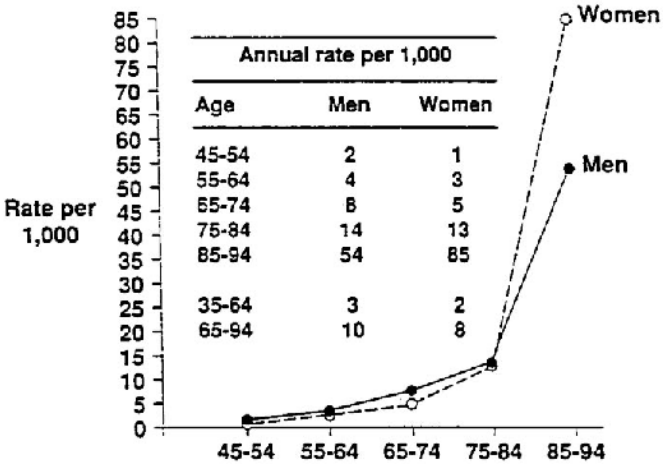

Figure 1 Incidence of heart failure by age and sex: 30-year follow-up from the Framingham study. (Ref. 1.)

PATHOPHYSIOLOGY

As previously mentioned, the higher incidence of CHF in the elderly results from age-related changes in the cardiovascular system and the increase in prevalence of cardiovascular disease, particularly coronary heart disease and hypertension (see Table 1). The elderly heart is characterized by having a normal left ventricular ejection fraction at rest. In fact, resting LV systolic function is preserved until very advanced age. Age-related changes in the heart reduce its ability to cope with stress. Cardiovascular reflexes involving the β-adrenergic system become impaired with aging (2,5). The decrease in adrenergic modulation limits the ability to maximally increase heart rate and contractility in response to stress (5).

The development of LV diastolic dysfunction is a major determinant of CHF. Thirty-four to 59% of elderly patients with CHF have normal left ventricular ejection fraction (6–9). Several age-related alterations in the cardiovascular system contribute to depressed LV diastolic function. Impaired relaxation of the myocardium leads to depressed LV diastolic function. Cardiac output fails to increase appropriately with stress as the left ventricle cannot adequately dilate (Frank–Starling mechanism) and the heart rate does not increase sufficiently (reduced adrenergic modulation) (10). Left ventricular hypertrophy and reduced left ventricular cavity size are two features of the aging heart even in the absence of cardiovascular disease, which can result in progressive rise in systolic and diastolic blood pressure as patients age (9,11). Changes in cross-linking of intercellular connective tissue, interstitial fibrosis, as well as amyloid deposition result in increased myocardial stiffness (9,12). Age-related myocyte loss causing a relative ventricular pressure overload and compensatory myocyte hypertrophy (13) result in impaired myocyte relaxation. Age-associated loss of myocytes has been estimated to be up to 35% (13). Diastolic abnormalities of the ventricles may also be due to age-linked decreases in calcium sequestration by the sarcoplasmic reticulum and an increase in calcium influx with myocyte contraction (14).

Table 1 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 degradation 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
Decreased norepinephrine synthesis
Decreased acetylcholine synthesis
Numerous changes in enzyme content and activity affecting most metabolic pathways
Conduction System
Degradation of sinus node pacemaker and transition cells
Decreased number of conducting cells in AV-node and HIS-Purkinje system
Increased connective tissue and amyloid deposition
Increased calcification around conduction system
Vasculature
Decreased distensability 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 maneuver and baroreceptor stimulation
Decreased heart rate variability

Source: Ref. 2.

Age-linked impaired LV relaxation and increased myocardial stiffness affects LV filling pattern, which can be studied noninvasively by Doppler echocardiographic mitral velocity curves (15). In normal subjects, a diastolic mitral flow velocity curve is characterized by a predominant E wave, representing rapid LV filling, and a smaller A wave corresponding to atrial contraction. In older individuals with age-related increase in ventricular stiffness, this filling pattern changes significantly and ventricular filling becomes more dependent on atrial contraction for adequate end-diastolic volume to develop (16). The

A/E ratio is significantly increased in the elderly. The E-wave upslope is delayed and its downslope is prolonged and therefore time to achieve diastases is increased. As a result of these changes, even in the absence of pathology, as much as 30 to 40% of diastolic volume in the elderly heart is dependent on the atrial contraction (3). To compensate for the increased left ventricular stiffness, the left atrium dilates and hypertrophies. This change in left atrial dimension explains in part why the elderly have an increased risk of developing atrial fibrillation with a risk exceeding 10% in patients older than 80 years (17,18). Atrial fibrillation can cause heart failure even in the setting of normal left ventricular systolic function. The loss of atrial contraction and thus impaired diastolic filling as well as the rapid ventricular rate that shortens the diastolic filling period contribute to the development of heart failure.

There are significant changes in the vasculature that contribute to diastolic and systolic abnormalities. The endothelial cells of the arterial intima become more heterogeneous so that blood flow in the vessels becomes less laminar. This contributes to an increase in sites for deposition of lipids (19). There is a significant increase in media smooth muscle cells as well as an increase in collagen deposition in the media and adventitia. These changes contribute to an increase in vascular stiffness. As a result of these changes in the medium- and large-sized arteries, there is an increase in afterload as well as a higher propensity to develop systolic hypertension.

Changes in renal blood flow and glomerular filtration appear to be important determinants of the syndrome of congestive heart failure in the elderly. It is known that elderly patients are very volume-sensitive and a small increase in fluid loads places them into pulmonary edema. This may be partly due to a relative decline in the glomerular filtration rate in the elderly. In general, there is a decrease in the GFR of 8 cc/min/decade. Such a decrease can contribute to defects in maintaining volume and electrolyte homeostasis. In addition, the intrarenal hemodynamic compensatory mechanisms during congestive heart failure defer significantly in the young patient compared to the elderly. In young patients with congestive heart failure as a result of the activation of the renin-angiotensin system, there is an increase in the filtration fraction due to efferent vasoconstriction. This has not been found to occur in the elderly patients who predominantly experience afferent vasoconstriction (20). Whether this discrepancy in intrarenal hemodynamic alterations noted between the elderly and young patients is the result of different neuroendocrine pathway activation is unclear. The elderly patients with congestive heart failure have a higher level of norepinephrine activation and renin-angiotensin concentration than middle-aged patients with heart failure (20).

ETIOLOGY

In general, the etiology of heart failure is similar in younger and older patients, with hypertension and coronary artery disease being the most common causes. In the Framingham study, 76% of men and 79% of women with CHF had hypertension or had received antihypertensive medications and 46% of men and 27% of women had coronary artery disease (21). Valvular heart disease, although an uncommon cause of heart failure in older patients, occurs at a higher frequency than in younger individuals. Calcified aortic stenosis and mitral insufficiency are the most common lesions seen in older persons with CHF due to valvular disease (2). CHF due to rheumatic heart disease and infective endocarditis

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occur less frequently in the elderly. High-output heart failure due to anemia, hyperthyroidism, or A-V fistulas occurs in older adults and is often overlooked.

DIAGNOSIS AND PRESENTATION

As mentioned previously, the elderly present a special challenge to the diagnosis and treatment of heart failure. Although the usual signs and symptoms of heart failure are similar in elderly and younger patients, the elderly may have more atypical presentations and tend to present later due to their lower functional expectations. Dyspnea at rest has been found to be the most common presenting symptom volunteered by patients with CHF. Orthopnea and paroxysmal nocturnal dyspnea are also common. In the elderly, however, somnolence, confusion, weakness, fatigue, disorientation, and anorexia are extremely common and may be the only presenting symptoms (22,23). At the bedside, jugular venous distention, S3 gallop, and hepatojugular reflux are reliable signs of CHF. Ankle edema, however, is a common geriatric finding and should not be assumed to be cardiac in origin unless other symptoms of cardiac dysfunction are present (24). Elderly people are frequently hypoproteinemic, sedentary, and have venous and lymphatic obstruction, which may contribute to edema formation.

Congestive heart failure due to systolic dysfunction tends to present with gradual worsening of symptoms throughout the day and paroxysmal nocturnal dyspnea. X-rays are useful in diagnosis of systolic heart failure when it shows cardiomegaly. Heart failure due to diastolic dysfunction, on the other hand, is often associated with abrupt clinical deterioration and ''flash'' pulmonary edema (see Table 2) (14). However, other clinical entities such as volume overload, valvular regurgitation, hypertrophic cardiomyopathy, pericardial constriction (tamponade or chronic constriction), restrictive cardiomyopathy, or high-output failure, which may resemble CHF, must also be considered. Differentiating systolic from diastolic LV dysfunction is important for therapeutic considerations, but at times can be difficult to make the diagnosis at bedside. Two-dimensional Doppler echocardiography is extremely useful to determine the nature of LV dysfunction (25). Recently, blood levels of brain natriuretic peptide (BNP) and N-terminal atrial natriuretic peptide (Nt-ANP) have been used to screen for patients with asymptomatic left ventricular dysfunction (26). Since routine use of echocardiography for the diagnosis of asymptomatic

Table 2 Diagnostic Characteristics of Heart Failure in the Elderly

Variable	Systolic dysfunction	Diastolic dysfunction	Combined systolic–diastolic dysfunction
Onset of symptoms	Gradual	Abrupt	—
Rate of decline	Progressive	Rapid	—
Peripheral edema	Frequent	Rare	—
Dilated left ventricle	Frequent	Rare	—
Ischemic heart disease	—	—	Frequent
Valvular heart disease	—	—	Frequent

Source: Modified from Ref. 14.

ventricular dysfunction is not cost-effective, screening patients for LV dysfunction with BNP and Nt-ANP may prove to be a more reasonable alternative.

MANAGEMENT

The first step in the management of patients with heart failure should be to educate patients about changes in their lifestyle, diet, and medications, since the most common cause of CHF decompensation in elderly patients is noncompliance with prescribed medications and dietary recommendations (see Table 3). A low-sodium diet is essential in patients with CHF and is a cornerstone of therapy especially in elderly patients with LV diastolic dysfunction. Daily sodium intake should be reduced to 1.6 g of sodium per day, substituting salt with other spices to make food more palatable (27). Tailoring the dose of diuretics to the amount of sodium intake, especially during holidays, can prevent CHF decompensation in these patients.

The goals of therapy for the elderly are somewhat different than from young patients in that the goal for the younger patient is not only to achieve symptomatic improvement but also to reach maximal functional capacity. In contrast to younger patients, the goal of therapy in the elderly should be mainly to improve symptoms at rest and during daily activities without attempting to improve maximal functional capacity, which is of no use to elderly with sedentary lifestyles.

Diuretics

Diuretic therapy is important for patients with CHF in whom a low-sodium diet alone is not sufficient to prevent sodium and fluid retention. Loop diuretics such as furosemide

Table 3 Common Precipitating Factors of Congestive Heart Failure in Older Patients

Dietary sodium excess
Inadequate treatment
Nonadherence to appropriate medications
Inappropriate medications (e.g. nonsteroidal anti-inflammatory drugs)
Excess fluid intake
Uncontrolled hypertension
Infection
Anemia
Hypoxia
Hot, humid environment
Alcohol
Myocardial infarction or ischemia
Pulmonary embolism
Renal insufficiency
Hyperthyroidism
Hypothyroidism

Source: Ref. 27.

and butamide should be used rather than thiazide diuretics. When sodium and fluid retention cannot be controlled by loop diuretics alone, short-term administration of metolazone together with loop diuretics is helpful. Nonsteroidal anti-inflammatory drugs should be avoided, as they provoke sodium retention. Age-related decrease in renal function and circulating plasma volume decrease the efficacy of diuretics. It is of note that patients with LV diastolic dysfunction do not tolerate high doses of diuretics since they rely on elevated LV end-diastolic pressure to achieve adequate LV filling. These patients would benefit from low doses of diuretics with rapid adjustment according to their sodium intake. In contrast, patients with depressed LV systolic function tolerate higher doses of diuretics, and the goal of therapy for patients is to achieve a body weight loss of 3 pounds per day. Older patients treated with diuretics should be monitored for electrolyte abnormalities, especially hypokalemia and hypomagnesemia, both of which can precipitate cardiac arrhythmias.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin-II Receptor Antagonists

Angiotensin-converting enzyme inhibitors have been shown to have important prognostic, hemodynamic, and symptomatic benefits in patients with CHF. ACE inhibitors do not improve cardiac output as much as nonspecific vasodilators or positive inotropic agents; however, their clinical benefits in improving life expectancy are more impressive than inotropes and vasodilators (28,29). ACE inhibitors reduce rather than activate neurohumoral mechanisms. Neurohumoral activation occurs early in the development of heart failure and levels of vasopressors (norepinephrine, vasopressin, and endothelin) steadily increase as the syndrome of CHF progresses (29,30). Diuretics and inotropes stimulate neurohumoral response mechanisms. Long-term administration of ACE inhibitors decreases circulating norepinephrine levels and potentiates the effects of vasodilating agents such as bradykinin, enkephalins, prostaglandin, and nitric oxide. Long-term use of ACE inhibitors also tends to restore parasympathetic tone (31,32). Angiotensin-II has been shown to stimulate myocyte and nonmyocyte cell growth and death. Thus ACE inhibitors may attenuate the effects of increased angiotensin-II levels (33). Long-term administration of ACE inhibitors can alter left ventricular remodeling and reduce dilation of the left ventricle after an ischemic event. In the rat model of myocardial infarction, captopril administration reduces LV filling pressure as well as the degree of LV hypertrophy and LV dilation (34). Increased myocardial fibrosis as a result of increased activity of the renin–angiotensin–aldosterone axis contributes to impaired LV diastolic filling. ACE inhibitors may improve LV diastolic filling by reducing the amount of myocardial interstitial fibrosis.

Long-term treatment with ACE inhibitors has been shown to reduce mortality and decrease the frequency of hospitalizations in patients with moderate-to-severe left ventricular dysfunction (35–37). The SOLVD treatment trial studied the effects of enalapril on mortality in patients with left ventricular ejection fractions less than 35% and NYHA class II–III heart failure. Enalapril reduced mortality by 16% and reduced the number of hospitalizations by 30% over the 2-year study period (36). In the CONSENSUS study, enalapril reduced mortality by 40% in class IV heart failure patients (35). When compared to nonspecific vasodilators, long-term ACE inhibitor therapy has a greater effect on reducing mortality and improving NYHA functional class in severely symptomatic patients (38). The SOLVD prevention trial studied the incidence of heart failure or need for hospi-

talization in asymptomatic patients with reduced left ventricular ejection fraction (LVEF). In this study, the risk of developing heart failure was reduced by 29% and there was a 20% reduced risk of being hospitalized in patients treated with ACE inhibitors (37). ACE inhibitors have been shown to reduce mortality and risk of hospitalization after myocardial infarction. Several studies have shown that treatment of patients with ACE inhibitors after myocardial infarction and with reduced left ventricular systolic function can reduce mortality by as much as 32% (39–41). Therefore, based on current evidence, ACE inhibitors are indicated in patients with moderate-to-severe LV systolic dysfunction independently of symptoms.

ACE inhibitors may be useful in patients with heart failure associated with normal systolic function. A study of enalapril versus placebo in older patients with history of myocardial infarction and normal LVEF showed an improvement in NYHA functional class, exercise time, LVEF, and left ventricular diastolic function in patients receiving enalapril (42). These agents should be used together with diuretics for the treatment of heart failure associated with normal left ventricular systolic function. Further prospective studies need to be performed to clearly define the role of ACE inhibitors in heart failure with intact systolic function.

The most common side effect of ACE inhibitors is hypotension, which occurs early after initiation of therapy. Hyponatremia and volume depletion due to vigorous diuresis is the most common cause of hypotension in patients. Even symptomatic hypotension after initiation of ACE inhibitor therapy is usually transient, and patients remain excellent candidates for therapy provided that measures are taken to prevent recurrence. Renal insufficiency is another common side effect and usually occurs in patients who rely on angiotensin-converting enzyme and angiotensin-II for adequate glomerular filtration. It is more common in patients with severe CHF and occurs in 25 to 50% of patients with NYHA class III–IV heart failure, and in 5 to 15% of patients with class II–III heart failure (43). Hyperkalemia can occur with ACE inhibitors and is more common in diabetics and in patients with renal insufficiency and congestive heart failure. Patients older than 70 years are at increased risk of developing recurrent hyperkalemia (44). Potassium supplements and potassium sparing diuretics should be avoided in patients.

Although ACE inhibitors have been effective in improving outcome for patients with congestive heart failure, there has been increasing evidence that after chronic treatment with ACE inhibitors many patients develop elevated angiotensin-II levels. This ''ACE escape'' has been thought to be due to production of angiotensin-II through pathways other than ACE (45). Elevated angiotensin-II levels are a sign of poor prognosis (46). The angiotensin-II receptor inhibitors are relatively new products that were developed with the rationale that they would be used in patients who could not tolerate the side effects of ACE inhibitors and that they might also block the action of angiotensin-II produced from pathways other than through ACE (47–49). Some evidence to date has shown that the angiotensin receptor inhibitor losartan may improve mortality in elderly patients with heart failure (50). More evidence is needed in order to evaluate efficacy of these agents in the treatment of heart failure. They are good alternatives for patients who cannot tolerate the side effects of ACE inhibitors.

Digoxin

Digoxin administration improves cardiac index, stroke work, and pulmonary capillary wedge pressure in patients with heart failure. The hemodynamic benefits from digoxin

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result from a positive inotropic effect due to inhibition of the sodium–potassium ATPase, which increases the concentration of intracellular calcium, and from the normalization of the impaired baroreflex mechanism that tends to lower sympathetic activation and thereby cardiac afterload.

The usefulness of digoxin in patients with moderate-to-severe heart failure and sinus rhythm has recently been evaluated in a long-term prospective case-control study. The Digitalis Investigation Group studied the effect of digoxin on patients with left ventricular ejection fractions of 0.45 or less (51). Although they found that there was no improvement in mortality for patients treated with digoxin, there was a significant reduction in the number of hospitalizations due to heart failure (7.9% risk reduction). Among subgroups of patients, digoxin seems to be more beneficial in reducing the number of hospitalizations in patients with NYHA class III–IV and in patients with low ejection fraction and dilated left ventricles (51). While the role of digoxin in improving symptoms in patients with systolic LV dysfunction can be understood based on the mechanism of digoxin action, there is little evidence to support its use for heart failure due to diastolic LV dysfunction. Indeed, digoxin may exacerbate this syndrome in patients with diastolic dysfunction. It is thought that increase in intracellular Ca^{2+} may result in increased cardiac stiffness and potentially worsen abnormal myocardial relaxation in these patients. Thus, based on the available data, it is recommended to begin digoxin in patients with abnormal LVEF who are in NYHA class II–IV or who cannot tolerate ACE inhibitors or isosorbide dinitrate and hydralazine.

In elderly patients, particular emphasis must be placed on the potential adverse effect of digoxin therapy. Compared to the middle-aged patient, the elderly are at increased risk of having adverse effects from digoxin therapy. Progressive renal insufficiency with aging places the elderly at high risk of developing digoxin toxicity. Digoxin bioavailability can be affected by concomitant administration of other drugs. In addition, hypothyroidism, hypokalemia, hypocalcemia, hypomagnesemia, hypoxia, acidosis, and myocardial ischemia can all cause digoxin toxicity despite normal serum digoxin levels (27). Decrease in muscle mass in the elderly reduces the volume of distribution of this drug and older patients can have blood levels twice as high as in young patients for the same dose of digoxin (52).

Other Inotropic Agents

An increasing yet controversial body of evidence supports the use of intravenous adrenergic agonists such as dobutamine, dopamine, and phosphodiesterase inhibitors (i.e., milrinone, amrinone) for short-term management of acute and severely decompensated congestive heart failure. Phosphodiesterase inhibitors induce peripheral vasodilatation and improve left ventricular contractility independently of their vasodilator effects. Clinical use of these agents improves symptoms and hemodynamic parameters. However, chronic use of phosphodiesterase inhibitors in patients with CHF has been associated with increased mortality (53–55). Until further studies are done to evaluate chronic use of these agents, they are contraindicated for treatment of chronic CHF.

Calcium Channel Blockers

Calcium channel blockers reduce afterload, blood pressure, heart rate, and myocardial oxygen demand and decrease intracellular calcium stores improving myocardial relax-

ation. These properties make calcium channel blockers logical choices for the treatment of CHF with normal left ventricular systolic function. These agents, however, can exacerbate CHF and reduce life expectancy in patients with depressed LV systolic function.

Therapy with calcium channel blockers is advocated in patients with hypertrophic cardiomyopathy, since it improves symptoms and exercise tolerance (56,57). Calcium channel blockers have also been shown to improve exercise capacity, peak left ventricular filling rate, and clinicoradiographic heart failure score in patients with CHF and normal LVEF (58). Thus calcium channel blockers are recommended for patients with normal LVEF and CHF when they continue to be symptomatic despite ACE inhibitor therapy.

Beta-Blockers

Initial studies with β-blocker therapy found that they decrease mortality and risk of sudden death as well as the risk of hospitalization in patients with myocardial infarction and CHF (59–61). In patients with CHF, large controlled studies have shown that these drugs can improve functional capacity, reduce symptoms, and improve left ventricular function. The carvedilol heart failure study group found that carvedilol therapy significantly reduced mortality and risk of hospitalization in patients with chronic congestive heart failure. Patients treated with carvedilol had a 65% reduction in mortality and a 27% reduction in risk of hospitalization for cardiovascular causes when compared to placebo (62). Carvedilol is a nonspecific β-adrenergic blocker, with α-adrenergic blocking and potent antioxidant effects.

β-blockers have also been used in the treatment of heart failure associated with LV diastolic dysfunction. Aronow et al. studied 158 patients with a mean age of 81 years, with prior history of myocardial infarction and CHF, who had LVEF $\geq$ 40% and were being treated with ACE inhibitors and diuretics (63). Propranolol decreased mortality by 35% in these patients.

Based on the available data, β-blockers should be started in patients with prior history of myocardial infarction with normal or abnormal LVEF or in patients with congestive heart failure who have failed treatment with ACE inhibitors and diuretics (55). Additional studies are needed to determine the effect of β-blockers on morbidity and mortality in patients with minimal or no symptoms. Beta-adrenergic blockers should be initiated cautiously in the elderly since they are prone to have significant side effects (e.g., hypotension, dizziness, worsening heart failure).

PROGNOSIS

In the absence of correctable causes such as valvular heart or pericardial disease, CHF is a very lethal condition. In the Framingham study, less than 50% of men with heart failure survived more than 5 years. This mortality rate is four to eight times that in the general population in the same age (3). The mortality rates for CHF increase exponentially with advancing age in the U.S. in all subgroups of the population (Fig. 2). Aronow et al. reported a 22% 1-year mortality rate among elderly patients (mean age 84 years) with a high prevalence of coronary disease (64). Sudden death is an especially common cause of cardiac mortality. In the Framingham study, mortality due to sudden death was five times that in the general population. Predictors of poor prognosis were rapid heart rate, decreased vital capacity, enlarged heart, and ECG abnormalities. In a study of prognosis of heart failure

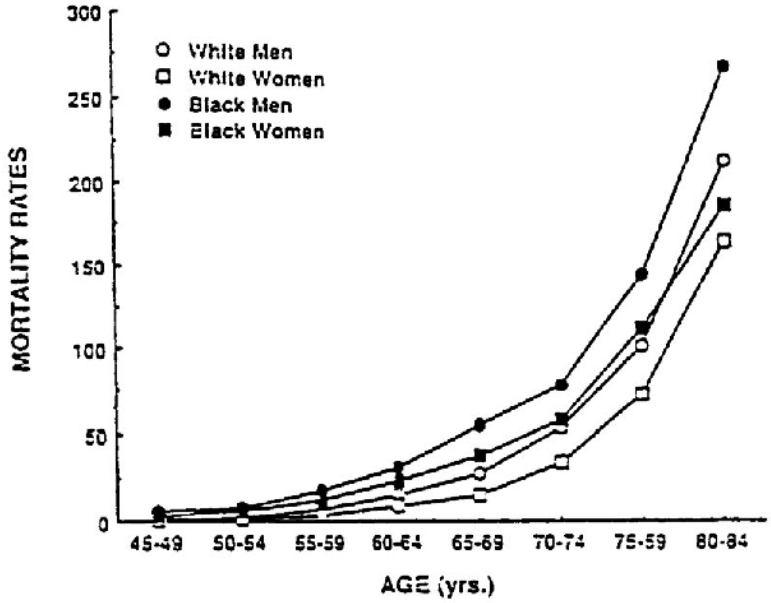

Figure 2 Mortality rates per 100,000 for congestive heart failure in the U.S., by age, sex, and race, 1990. (Ref. 2.)

in the elderly, the predictors of mortality were lower systolic blood pressure, lower activities of daily living score, increased BUN, and lower NYHA functional class (65). The effects of current therapies, including ACE inhibitors and blockers, on mortality have not been adequately studied in elderly patients with CHF. Further studies should include large randomized trials of these interventions versus active controls in elderly patients.

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24

Management of Supraventricular Tachycardia in the Elderly

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INTRODUCTION

Over the last 15 years, significant advances have been made in the ability to detect, diagnose, and treat a broad spectrum of complex arrhythmias. Although much of the emphasis during this time has focused on the management of sustained ventricular tachycardia and patients with aborted sudden cardiac death, equally dramatic advances have been made in the management of supraventricular arrhythmias including, atrial fibrillation, atrial flutter, atrioventricular (AV) node reentry, and AV reciprocating tachycardia. The following reviews the most common supraventricular arrhythmias, with emphasis on their current management. The putative mechanisms responsible for these arrhythmias are discussed, along with current tenets of acute and chronic management. Currently available diagnostic modalities and their potential role in patients with paroxysmal or infrequent arrhythmias are also reviewed. Finally, some of the recently appreciated risks associated with pharmacological therapy are discussed.

REENTRY AS THE BASIS OF SUPRAVENTRICULAR ARRHYTHMIAS

The term ''supraventricular arrhythmias'' constitutes a wide variety of arrhythmias that arise primarily from a level superior to the division of the common bundle of His into left and right bundle branches and/or activate the ventricles utilizing the native conduction pathways (i.e., His-Purkinje network) as an integral part of the circuit. The vast majority of supraventricular arrhythmias are thought to be based on reentry, as apart from abnormal or enhanced automaticity, which account for a minority (less than 5%) of clinically significant arrhythmias (1). For a reentrant circuit to result in a sustained arrhythmia, three basic requirements must be fulfilled. These include (1) physical contiguity of two electrophysiologically (but not necessarily anatomically) distinct tissues, (2) unidirectional block of conduction in one of the electrophysiological ''pathways,'' and (3) slow conduction in part of the pathway, to allow repolarization and subsequent conduction along the initial

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depolarized path (2–4). If a critical balance is maintained, with the leading wave front timed to engage tissue capable of sustaining conduction, a sustained arrhythmia perpetuates. Often the latent substrate for supraventricular arrhythmias based upon reentry is ''activated'' by properly timed atrial or ventricular premature depolarizations, which allow the dissociation of the conduction properties of the two component pathways, resulting in initiation of a sustained circuit. The hallmark of these arrhythmias is their paroxysmal nature, insofar as they are based upon a latent substrate that can be provoked by a variety of factors, including atrial and ventricular premature depolarizations, ischemia, changes in sympathetic tone, scarring, and even pharmacological agents (5–9). Abnormalities of automaticity, either enhanced or triggered, are believed to be responsible for the minority of these arrhythmias (10).

SPECTRUM OF SUPRAVENTRICULAR ARRHYTHMIAS

The most common supraventricular arrhythmia is atrial fibrillation, with an estimated prevalence of over 1 million (11). It is characterized by a continuous depolarization of the atrium, with often rapid and irregularly irregular conduction to the ventricle. Although the mechanism of this arrhythmia has in the past been controversial, work by Allessie, Moe, and others has suggested that it is reentrant in nature (11–14). In the absence of pharmacological therapy and in the setting of normal AV nodal conduction, the mean ventricular response to atrial fibrillation in a patient free of medication is often in the 150–170 bpm range.

The second most common supraventricular arrhythmia is atrial flutter, and this may represent one end of a continuous spectrum with atrial fibrillation. Once again, studies have suggested that the mechanism of this rhythm is reentry (15,16). This rhythm is characterized by a rapid regular rate of atrial depolarization, often 300 bpm, although this can vary from between 220 and 350 bpm, depending upon the patient. The usual form of atrial flutter is characterized electrophysiologically by organized atrial activity (so-called F waves), which resemble a ''sawtooth'' or ''picket fence'' pattern as seen in standard leads II, III, and AVF. Atrial flutter most commonly conducts to the ventricle with a 2:1 pattern, such that the ventricular rate during flutter is often 150 bpm and is usually characterized by a normal QRS morphology. There appears to be a continuous spectrum between atrial flutter and atrial fibrillation, and it has been demonstrated that atrial flutter can degenerate into atrial fibrillation and then reorganize into atrial flutter (17). Atrial mapping studies have suggested that the common form of atrial flutter involves a counterclockwise depolarization of the atrium, moving from an inferior to posterior to superior direction (16). The uncommon form of atrial flutter is usually more rapid (atrial rates in the 400 bpm range) and is usually characterized by a positive F wave in the inferior leads (superior to inferior direction).

AV nodal reentrant tachycardia accounts for approximately 60% of the supraventricular arrhythmias termed paroxysmal supraventricular tachycardia (PSVT) (18). It is often characterized as a narrow complex tachycardia that is regular in nature, exhibiting rates in the 150–180 bpm range, although in younger individuals rates of the 200–240 bpm range may be seen (19,20). A hallmark of this arrhythmia is its regularity. A 12-lead electrocardiogram during PSVT in two-thirds of patients does not show evidence of discreet P wave activity, because the atrium and ventricle are simultaneously depolarized,

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with the larger amplitude QRS masking the presence of P wave (atrial) activity. In approximately 30% of patients with AV node reentry, there is evidence of discreet atrial activity in the ST segment following the QRS. This occurs when the retrograde conduction time to the atrium is slow in comparison with antegrade conduction to the ventricle. In approximately 6% of patients with AV node reentry, the retrograde conduction time to the atrium is slow enough so that the ''R-P'' interval (as measured from the onset of the QRS to the onset of retrograde P wave activity) is $>$ 50% of the succeeding R-R interval. In this circumstance, differentiating an AV node reentrant tachycardia from either an intraatrial tachycardia or sinus node reentry can be difficult.

Paroxysmal supraventricular tachycardia secondary to accessory pathway conduction occurs in approximately 30% of patients with sustained PSVT (18). Accessory pathway conduction can either be overt, as in the Wolff-Parkinson-White syndrome, or concealed, because accessory pathways can be capable of either unidirectional or bidirectional conduction. Unidirectional retrograde conduction is electrocardiographically silent (i.e., one does not see evidence of delta waves); however, such accessory pathways are capable of sustaining a macroreentrant tachycardia, so-called AV reciprocating tachycardia, which involves antegrade conduction from atrium to ventricle utilizing the His-Purkinje system, with retrograde conduction mediated by the accessory pathway. This mechanism is identical to that utilized in so-called orthodromic tachycardia related to Wolff-Parkinson-White syndrome. In patients with Wolff-Parkinson-White syndrome, during sinus rhythm the ventricle is depolarized as a fusion between antegrade conduction across the AV node and antegrade conduction across the accessory pathway. Although the majority of PSVT related to Wolff-Parkinson-White syndrome (estimated prevalence of 0.3% in the general population, with equal prevalence in the young and the elderly) involves orthodromic tachycardia, in a minority of patients the sustained arrhythmia involves antegrade conduction across the bypass tract, with retrograde conduction along the His-Purkinje and AV node (so-called antidromic tachycardia) (21–23). This presents as a maximally preexcited QRS and is often mistaken for ventricular tachycardia. It generally responds to the same maneuvers as orthodromic tachycardia.

MAKING THE DIAGNOSIS

Appropriate management of supraventricular tachycardia requires making the correct arrhythmic diagnosis. Among the points essential to interpretation of arrhythmia is defining whether the observed QRS are wide or narrow, as well as assessing the regularity of each successive QRS. The relationship (if any) of atrial depolarization to that of the QRS complexes can yield important information about the mechanism of arrhythmia. The majority of supraventricular arrhythmias conduct to the ventricle with a narrow QRS, assuming normal baseline conduction. A wide QRS supraventricular tachycardia can of course occur in the setting of preexisting conduction disturbances (right bundle branch block and left bundle branch block), as well as rate-related conduction disturbances. As the relative refractory period of His-Purkinje and ventricular tissue is directly proportional to the preceding R-R interval, atrial fibrillation often manifests the so-called Ashman's phenomenon (24). This presents as wide QRS complexes that are supraventricular in nature, occurring when close coupled QRS complexes follow a preceding pause. Because the relative refractory period of the right bundle branch is somewhat longer than that of the left bundle

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branch, the majority of ''Ashman's beats,'' and indeed rate-related aberration in general, are of right bundle branch morphology. More specifically, approximately 85% of bundle branch aberrancy is right bundle in nature, with the remaining 15% presenting as left bundle branch block aberration. Therefore, wide complex tachycardias that are left bundle branch block in morphology are more likely, from a statistical perspective, to be of ventricular origin. Supraventricular tachycardias with bundle branch block aberration generally have QRS durations < 140 ms and most often exhibit a normal frontal plane axis. Moreover, a 12-lead electrocardiogram of aberrated PSVT will demonstrate a ''classic'' right bundle or left bundle branch block, not a nonspecific intraventricular conduction deficit (i.e., QRS that looks like right bundle branch block in lead I but manifests a left bundle branch block pattern in V_1). Such characteristics as extremely wide QRS, exhibiting an abnormal frontal plane axis and so-called concordance across the precordium (where lead V_1 has a morphology similar to that seen in lead V_2, V_3, and so on), strongly favor a ventricular origin of the tachycardia.

As mentioned, establishing the relationship between atrial activity and QRS depolarization is important in determining the type of supraventricular arrhythmia. The hallmark of atrial fibrillation is the absence of discreet atrial activity in the setting of a chaotic and irregularly irregular baseline, and the ventricular response to atrial fibrillation is classically irregular, although this may be difficult to appreciate at rapid ventricular rates. Approximately 60% of PSVT secondary to AV node reentry is free of evidence of atrial activity insofar as the atrium and ventricle are depolarized simultaneously. When one observes retrograde atrial activity following the QRS, as evidenced by a high-frequency depolarization in the ST segment or proximal T wave, 50% of these tachycardias represent AV node reentry; the remaining 50% represent so-called AV reciprocating tachycardia, with retrograde conduction mediated by an accessory pathway. If the R-P interval is $> 50\%$ of the R-R interval, intraatrial tachycardia or sinus node reentry should be suspected (18). Invasive electrophysiological study, by determining the atrial activation sequence during tachycardia and its relationship to ventricular depolarization, can help to determine the mechanism of a patient's tachycardia more definitively (Figs. 1 and 2).

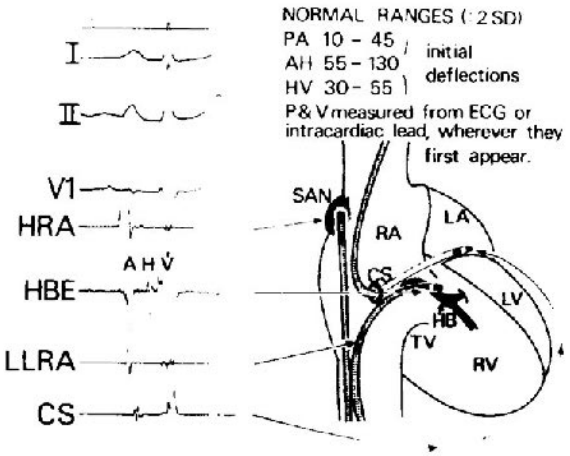

Figure 1 Catheter placement for routine electrophysiological study. Intracavitary electrograms are displayed. Normal ranges for intracardiac conduction intervals are shown.

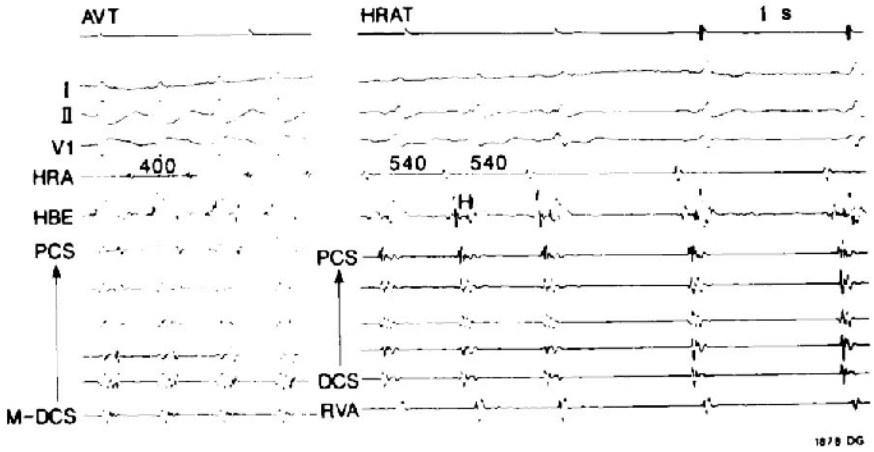

Figure 2 Electrograms taken from a patient with two forms of paroxysmal supraventricular tachycardia. Surface electrocardiograms are displayed, along with intracavitary electrograms from the high right atrium (HRA), His bundle region (HBE), and numerous sites in the mid- and distal coronary sinus (M-DCS). On the left, AV reciprocating tachycardia demonstrating the presence of a left-sided accessory pathway is seen, with evidence of early atrial activation in the distal coronary sinus. On the right, a high right atrial tachycardia is shown, demonstrating high to low atrial activation sequencing.

ACUTE MANAGEMENT OF SUPRAVENTRICULAR TACHYCARDIA

The acute management of any arrhythmia must involve assessment of the patient's hemodynamic status. This is of extreme importance in the elderly patient with underlying cardiovascular disease. In a setting in which the patient is compromised, that is, hypotensive, in severe congestive heart failure, or with persistent anginal type of chest pain, the treatment of choice is DC cardioversion. This should be done under brief anesthesia using a short-acting barbiturate or benzodiazepam, such as diazepam or midazolam. AV reciprocating tachycardia and AV node reentrant tachycardia are often vulnerable to 25 or 50 J synchronized shocks, but atrial fibrillation usually requires higher energies of 100 J or more. DC cardioversion is usually effective in terminating an acute episode of sustained supraventricular tachycardia, although it does not preclude arrhythmia recurrence. DC cardioversion is not of use in frequently recurring arrhythmias or rhythms thought to be secondary to enhanced automaticity, such as multifocal atrial tachycardia.

If the patient is tolerating the arrhythmia well, one should attempt to ascertain the specific nature of the arrhythmia to help guide specific treatment. The importance of establishing the relationship, if any, between atrial and ventricular activity in this assessment was discussed previously. Vagal maneuvers (i.e., Valsalva maneuver and carotid message), by transiently increasing the level of AV block, can be used to differentiate the type of arrhythmia. Atrial fibrillation and atrial flutter, for example, often exhibit a slowed ventricular response to carotid massage, allowing clear fibrillatory or flutter waves to be seen, whereas abrupt termination of the arrhythmia is often the response of AV reciprocating or AV node reentrant tachycardia. Other maneuvers that can assist in accentuating

Table 1 Maneuvers Used to Accentuate Atrial Activity

Recording leads II, III, AVF, V_1
Carotid massage
Valsalva maneuver
Lewis leads
Double speed, standard
Esophageal lead
Intraatrial recording

atrial activity are listed in Table 1. The following agents are often utilized in acute management of paroxysmal supraventricular tachycardia (Table 2).

Adenosine

A purine nucleoside with a half-life of approximately 1.5 s, this agent exhibits a relatively selective electrophysiological effect on the AV node. Administered initially as a 6 mg bolus to be followed by 12 mg if the initial dose is ineffective, adenosine is extremely effective in slowing AV nodal conduction and terminating PSVT secondary to AV node reentry or AV reciprocating tachycardia in more than 85% of patients (25–27). Transient atrial fibrillation, presumably due to the shortening of the atrial refractory period by adenosine, has been described. Its effect on atrial fibrillation and atrial flutter is modest; however, transient slowing of the ventricular response is often seen. In view of its relative specificity for the AV node, adenosine has been advocated as a ''pharmacological probe'' to help better elucidate the mechanism of specific arrhythmias. Side effects include transient flushing and chest pain; however, because of its extremely short half-life, these side effects are self-limited (28–30). It is therefore particularly useful in elderly patients with underlying left ventricular dysfunction who might otherwise not tolerate other agents.

Verapamil and Diltiazem

Introduced in the early 1980s, verapamil is successful in terminating AV node reentrant tachycardia and AV reciprocating tachycardia in 60–90% of patients (31,32). It is adminis-

Table 2 Options in the Acute Management of Paroxysmal Supraventricular Tachycardia

Pharmacological therapy
Adenosine
Verapamil
β-blockers
Digoxin
Procainamide
Ibutilide
Pacing
Cardioversion

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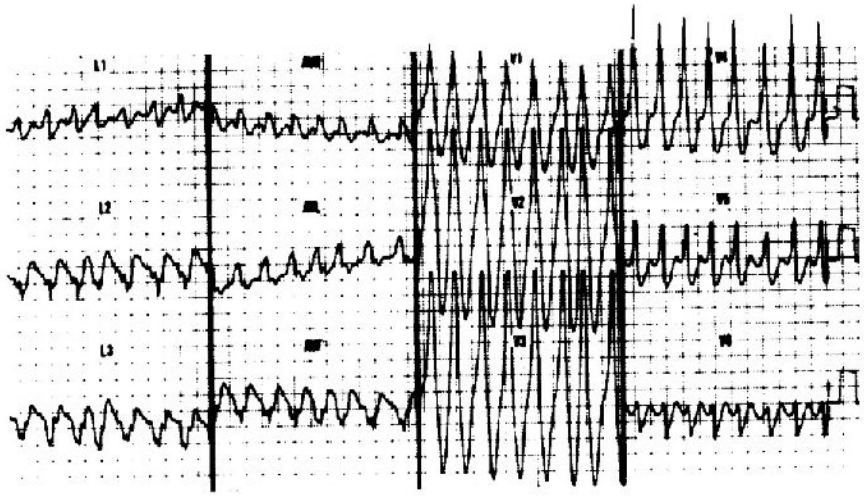

Figure 3 A 12-lead electrocardiogram demonstrating atrial fibrillation in a patient with Wolff-Parkinson-White syndrome. Of note, the irregularly irregular QRS complexes demonstrate varying degrees of preexcitation (so-called concertina effect).

tered as an initial dose of 10 mg over 2 min, although in elderly patients, who may be more prone to its hypotensive effect, an initial dose of 5 mg is recommended. The half-life of the intravenous agent is 20–30 min, and it is in general well tolerated, although transient hypotension is not uncommon. Verapamil has an effect on both the sinus and AV node, and it can be useful in slowing the ventricular response to atrial fibrillation and atrial flutter. Continuous infusion of intravenous verapamil can be used to mitigate the ventricular response to atrial fibrillation in patients who do not absorb or cannot take oral medications. Verapamil should be avoided in patients with atrial fibrillation and evidence of preexcitation (Fig. 3). Intravenous diltiazem is approved by the U.S. Food and Drug Administration (FDA) for the temporary control of rapid ventricular response to both atrial fibrillation and atrial flutter, as well as for the conversion of PSVT to sinus rhythm. Although diltiazem has less of an antidromotrophic effect than verapamil, intravenous diltiazem is easily titratable and is often used to mitigate the ventricular response of acute atrial fibrillation.

β-Blocking Agents

These agents exhibit a negative chronotropic as well as a negative dromotropic (slowing AV node conduction) effect, such that the response to supraventricular arrhythmias is similar to that seen with verapamil, although the response rate appears less with these agents. Intravenous β-blockers should not be used in combination with intravenous verapamil because of the negative inotropic effects of these agents. β-Blocking agents can also be effective in preventing atrial fibrillation in patients undergoing open-heart surgery (33–35). Esmolol, a nonselective beta blocker with a half life of approximately 8 min is often effective in acutely managing atrial fibrillation with rapid ventricular response. In view of the very short life of this agent, it can be of use in patients in whom there is

concern about their ability to tolerate the negative inotropic effects of longer acting beta blockers.

Digoxin

With a time to peak onset of 90 min, intravenous digoxin is not very effective in rapidly controlling supraventricular arrhythmias. This agent acts primarily by slowing conduction through the AV node. Although there have been reports of conversion with atrial fibrillation to sinus rhythm after digoxin administration, recent reports suggest that the conversion rate to sinus rhythm after digoxin is similar to that seen with placebo (36–38).

Procainamide

A sodium channel blocking agent that moderately prolongs the refractory period of atrial and ventricular tissue (a so-called Ia agent of the Vaughn/Williams classification), procainamide can be effective in converting atrial fibrillation and atrial flutter to sinus rhythm. It can be administered intravenously at a rate of 20 mg/min to a target dose of 10–15 mg/kg. This agent can also be effective in terminating AV node reentrant tachycardia, as well as AV reciprocating tachycardia, although the effect of procainamide on the AV node is modest (39,40). Hypotension and QRS widening can be seen with IV administration, so that careful attention must be paid to the infusion rate of the drug.

Ibutilide is an agent recently approved by the FDA for the acute conversion of either atrial fibrillation or atrial flutter to sinus rhythm. Efficacy rates of up to 60% for the termination of atrial flutter have been reported (40a,40b). The drug's success rate in converting atrial fibrillation to sinus rhythm is more modest, averaging on the order of 35 to 40%. Ibutilide has been called a ''pure'' class III antiarrhythmic agent. Its predominant electrophysiological effect is prolongation of the myocardial action potential duration. Electrophysiological studies have suggested that this is achieved by a combination of effects including activation of a late inward sodium current as well as blockade of the rapidly activating component of the delayed rectifier potassium current. The recommended initial dose is 1 mg for patients weighing 60 kg or more. For patients less than 60 kg, a dose of 0.01 mg/kg is recommended. The drug is administered by infusion over a 10-min interval. If sinus rhythm is not restored within 10 min of completion of the drug infusion, a second 10-min infusion of equal strength can be administered. In a randomized comparison between ibutilide and procainamide, ibutilide was more successful in restoring sinus rhythm both for atrial fibrillation and atrial flutter (40c,40d). Nevertheless, ibutilide has potentially serious side effects. Torsade de pointes has been reported following ibutilide administration with an incidence of 2 to 5% (40e). Preexisting bradycardia may increase the risk of torsade de pointes.

Pacing Maneuvers

In suitable candidates, programmed stimulation of the atrium or ventricle using overdrive, underdrive, or premature extrastimuli can be used to terminate reentrant arrhythmias. Conversion rates in the 60–80% range have been reported (41,42). Pacing maneuvers are ineffective in terminating atrial fibrillation, although atrial flutter can be entrained and terminated by rapid atrial pacing (43).

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Table 3 Options for Chronic Management of Supraventricular Tachycardia

Pharmacological
''AV nodal'' agents
Atrial stabilizing agents
Anticoagulation
Nonpharmacological
Pacing
single site
dual site
Ablation
Surgery
Atrial defibrillator

CHRONIC THERAPY

Historically, the mainstay of chronic therapy for sustained supraventricular arrhythmias has been pharmacological (Table 3). Broadly speaking, the available agents can be subdivided into those agents whose predominant electrophysiological effect is upon the AV node and those that affect working myocardial cells (''atrial stabilizing effect''). This classification is not absolute, however, insofar as many agents exhibit both types of effects, although perhaps not of equal magnitude. Historically, digoxin and quinidine have constituted the mainstay of therapy for a variety of supraventricular arrhythmias, the former agent confining its primary electrophysiological effect to the AV node and the latter acting as an ''atrial stabilizing'' agent (44–46). Indeed quinidine, with its vagolytic effect, can actually enhance AV nodal conduction, and therefore its use as monotherapy for atrial fibrillation has not been advocated. However, the last 15 years have seen a variety of newer agents with either AV nodal blocking and/or atrial stabilizing characteristics (Table 3).

Agents with Predominant Effects on the AV Node

Both verapamil and diltiazem, as calcium channel antagonists, have been shown to affect AV nodal conduction (47–52). These agents have demonstrated success rates in the 55–70% range in chronically controlling recrudescence of PSVT. Their use in atrial fibrillation is largely limited to moderation of ventricular response, and although effective at rest, they often fail to control ventricular rates during modest activity (50,51). Although generally well tolerated, these agents can cause annoying side effects, including peripheral edema, constipation, and nausea. Hypotension and exacerbation of congestive heart failure have been reported with verapamil administration secondary to its negatively inotrophic effect (53–55). When administered acutely to patients with wide complex tachycardias mistakenly believed to represent PSVT with aberration, verapamil has resulted in cardiovascular collapse and cardiac arrest. β-Blocking agents are effective in reducing the frequency of PSVT and have been shown to exhibit a significant effect in controlling the

ventricular response to atrial fibrillation. In postoperative patients, β-blocking agents appear to be effective in preventing atrial fibrillation (52,54).

Agents with Atrial Stabilizing Effects

Class Ia Agents

Quinidine, procainamide, and disopyramide are agents that exhibit moderately potent sodium channel antagonist activity and also moderately prolong the effective refractory period of atrial and ventricular tissue. These drugs have been used to treat both paroxysmal supraventricular tachycardia and paroxysmal atrial fibrillation (PAF). Of these drugs, however, only quinidine is approved by the Food and Drug Administration for this indication. Although agents of this type have efficacy rates of approximately 50–60% for the maintenance of sinus rhythm in patients with paroxysmal atrial fibrillation, as well as control of recurrence of paroxysmal supraventricular tachycardia, side effects limit their long-term use (55–58). Positive antinuclear antibody titers develop in the majority of individuals treated with long-term procainamide, and a lupuslike syndrome can occur in these patients. Hematological abnormalities have been reported in patients treated with either procainamide or quinidine (thrombocytopenia and neutropenia), but this appears to be less common with disopyramide. Nausea, abdominal discomfort, and diarrhea occur in 5–15% of patients treated with quinidine. In view of the negative inotropic effects of disopyramide, its use should be avoided in individuals with a history of congestive heart failure (59). Frequently, anticholinergic side effects (dry mouth, urinary hesitancy, and blurred vision) can be ameliorated through the use of a cholinergic agent, such as pyridostigmine. Mestinon-SR in doses of 90 mg administered on either an every 8 h or every 6 h regimen has been shown to effectively ameliorate these symptoms (60). Recently, concerns over the safety of quinidine in the treatment of atrial fibrillation have been raised by a retrospective metaanalysis by Coplen et al., which demonstrated a threefold excess mortality in patients treated with quinidine for paroxysmal atrial fibrillation compared with controls (58).

Class Ic Agents

Flecainide, a class Ic antiarrhythmic agent, was first introduced in 1985 for the treatment of ventricular arrhythmias. This agent was recently approved by the Food and Drug Administration for use in the treatment of a variety of supraventricular arrhythmias. As an agent of the Ic class, with potent sodium channel blocking effect, flecainide markedly slows cardiac conduction by blunting the upstroke during phase 0 of cardiac depolarization (61–64). At normal heart rates, flecainide exerts a minimal effect on the refractory period; at more rapid rates, however, flecainide markedly prolongs action potential duration and refractoriness. The drug in normal individuals has a half-life of elimination of approximately 20 h. It is metabolized in the liver and excreted by the kidney both as inactive metabolites and as unchanged drug. Flecainide has been demonstrated to reduce the frequency of episodes of PSVT and to prolong the interval between episodes in susceptible patients when compared with placebo. Flecainide has also been demonstrated to be effective in approximately 31% of treated patients in preventing recurrent paroxysmal atrial fibrillation. It has been demonstrated to increase by greater than fourfold the interval between episodes of paroxysmal atrial fibrillation compared with control.

Flecainide has also been demonstrated to be effective in preventing both the clinical recurrence and induction by programmed stimulation of paroxysmal supraventricular tachycardia in patients with Wolff-Parkinson-White syndrome (64). Success rates of up

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to 75% have been reported during short-term treatment with this agent. In general, flecainide is well tolerated in the vast majority of treated patients. Adverse cardiac effects have been reported to occur in 7% of patients treated for supraventricular arrhythmias (4% of those with PSVT and 10% of those with PAF). These cardiac effects have included increasingly frequent supraventricular tachycardia (proarrhythmia), conduction disturbances, and congestive heart failure. Sudden death has rarely been reported in patients treated with flecainide for supraventricular arrhythmias. The majority of these cardiac effects have occurred within 4 weeks of initiating therapy, and most have occurred in the setting of known structural heart disease. Noncardiac side effects include dizziness, blurred vision, light-headedness, and nausea.

When used to treat patients with asymptomatic ventricular arrhythmias following myocardial infarction (during the Cardiac Arrhythmia Suppression Trial), flecainide was associated with a 2.2-fold increase in 10-month mortality (from 2.3 to 5.1%) (65). However, the data for patients treated with flecainide for supraventricular arrhythmias suggest that the risk of proarrhythmia is much less (66). A recent study that compared patients treated with either flecainide or encainide with patients treated at a tertiary medical center with a variety of agents for supraventricular tachycardia failed to demonstrate evidence of excess mortality in patients treated with agents of the Ic class (63). Nevertheless, in view of concerns over potential proarrhythmia, flecainide is not recommended for the treatment of patients with significant structural heart disease, and if chronic therapy with flecainide is considered, exercise testing should be performed in an attempt to exclude exertional proarrhythmia. Because flecainide has negative inotropic effects, it should not be used in patients with congestive heart failure or significantly reduced ejection fractions. The recommended starting dose for the treatment of PSVT and paroxysmal atrial fibrillation is 50 mg every 12 h. The dosage can be titrated upward in increments of 50 mg twice per day every 4 days. The maximum recommended daily dose is 300 mg (i.e., 150 mg twice per day).

Agents with Class III Effects

The primary electrophysiological effect of these agents is to prolong action potential duration markedly. Electrocardiographically, this results in QRS prolongation, mild QT prolongation in parallel with the degrees of QRS prolongation, and no effect on the ''J-T interval.'' Agents of this class include amiodarone and sotalol, the latter agent also exhibiting a mild to moderate β-blocking effect. Amiodarone, an agent with an extremely long half-time of accumulation (67), has been demonstrated in a number of European studies to be extremely effective in treating both paroxysmal atrial fibrillation and PSVT (68–70). However, the use of this agent in the United States for these indications has been extremely limited. At the present time, the Food and Drug Administration approves the use of amiodarone only for life-threatening ventricular arrhythmias in view of its broad profile of side effects, some of which are potentially life threatening (i.e., hepatic failure and pulmonary fibrosis). Amiodarone also possesses mild class I effect and is effective in mitigating the ventricular response to atrial fibrillation. Sotalol, an agent that has been available in Europe for over 20 years and which was approved by the FDA in 1993 for the treatment of life-threatening ventricular arrhythmias, combines a nonselective β-blocking effect with a class III effect. It has been demonstrated to be effective in maintaining sinus rhythm after DC cardioversion, as well as in controlling the ventricular response in patients with chronic atrial fibrillation (71–73). It exhibits a modest negative inotropic effect and has a low

incidence of central nervous system effects secondary to its hydrophilic properties (74). Although it is believed to have a limited potential for proarrhythmia, torsades de pointes has been reported during its use, especially at higher doses (75). Its use is contraindicated in patients with severe congestive heart failure.

Anticoagulation in Atrial Fibrillation

It is well established that patients with rheumatic valvular disease and chronic atrial fibrillation are at significantly increased risk for stroke (approximately 17-fold) (76). It has been more recently appreciated that individuals with chronic atrial fibrillation and nonrheumatic heart disease are at approximately 5-fold increased risk for stroke compared with the general population (77,78). Anticoagulation therapy has been demonstrated to significantly reduce the incidence of stroke in patients over the age of 60 by approximately 60% (79,80). The role of aspirin in reducing stroke risk is controversial (81), and in the recently reported Stroke Prevention in Atrial Fibrillation Study, the beneficial effect of aspirin was not seen in patients over the age of 75 (82). Individuals in the absence of structural heart disease or with paroxysmal atrial fibrillation may not require chronic anticoagulation (see Chap. 9 for further discussion).

NONPHARMACOLOGICAL MANAGEMENT OF SUPRAVENTRICULAR ARRHYTHMIAS

In view of the limited efficacy, the potential for proarrhythmia, and the cumulative toxicity of long-term pharmacological therapy for arrhythmias, it is not surprising that over the last 20 years much attention has focused on the nonpharmacological management of sustained, symptomatic arrhythmias. In the early 1970s, great enthusiasm was mustered for the use of implantable pacemakers in the management of recurrent supraventricular arrhythmias. This was followed by the development of surgical procedures for the treatment of PSVT. More recently, surgical techniques for the treatment of automatic atrial tachycardias, as well as atrial fibrillation, have been reported. Additionally, with the advent of the use of radiofrequency energy, catheter ablation techniques have now assumed center stage for the chronic management of a variety of supraventricular arrhthymias. Although once considered investigational, ablative techniques are now considered by some the gold standard for long-term management of symptomatic supraventricular arrhythmias. The following attempts to highlight the major advances and limitations of these differing approaches.

Antitachycardia Pacing

With the development of sophisticated electrophysiological testing techniques that provided greater understanding of the mechanisms responsible for sustained arrhythmias, coupled with the availability of multiprogrammable pacemakers, it appeared in the early and mid-1970s that antitachycardia pacing would become a major therapeutic modality for supraventricular arrhythmias. Pacemakers can be utilized in an attempt to prevent tachycardia occurrence by pacing at rates more rapid than that of baseline sinus rhythm (i.e., overdrive suppression), thereby reducing the number of premature complexes that often serve to trigger an arrhythmia (83–85). They can also improve hemodynamics during incessant tachycardia, for example, by pacing the atrium to produce 2:1 atrioventricular

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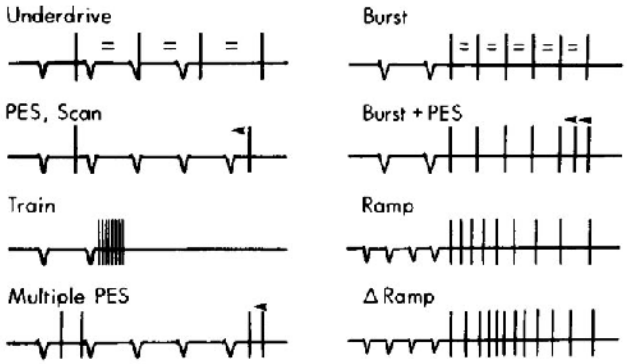

Figure 4 Different antitachycardia pacing algorithms that can be used to terminate PSVT. PES = premature extrastimuli. Arrows connote an automated change in timing interval, with stimuli brought closer to the last detected QRS or pacing stimulus.

conduction and thereby effectively slow the ventricular rate during tachycardia (86–88). Devices can also be utilized to assess the continuing efficacy of a pharmacological regimen. Specially designed pacemakers capable of performing noninvasive programmed stimulation allow such studies to be performed without the need for repeat catheterization. These devices can therefore be useful to identify the need for alterations in ongoing therapy, if such therapy is proven to be ineffective. However, the preeminent role of pacemakers for the treatment of supraventricular arrhythmias is the use of automated detection and termination algorithms to terminate recurrent episodes effectively. Currently available devices can define the presence of tachycardia by using characteristics of rate, mode of onset, and rate stability, such that a programmed sequence of pacing can be utilized in an attempt to terminate an arrhythmic event (89–92). A variety of complex pacing algorithms using pacing stimuli in a variety of patterns (single, multiple, bursts, incremental-decremental sequencing, and so on) have been used for this purpose (Fig. 4). Unfortunately, the long-term efficacy of antitachycardia pacing for PSVT is only fair. A series from Montefiore Medical Center (92) suggests 93% efficacy at 1 year; however, this declines to 86% at 2–4 years and ultimately to 68% at 8 years (Fig. 5). This progressive inefficacy is often due to the development of chronic atrial fibrillation or the precipitation of atrial fibrillation during attempts at rhythm termination. Other series have suggested that even in the absence of atrial fibrillation, implanted devices often need to be adjusted during follow-up to maximize algorithm efficacy (89). These factors suggest that antitachycardia pacing for PSVT may be most appropriate for patients with a limited life expectancy or whose cardiovascular status precludes more definitive therapy (i.e., surgery and catheter ablation).

Surgical Techniques

Surgical techniques have been developed over the last 15 years to treat a variety of supraventricular arrhythmias. Indeed, surgical therapy has been considered by some to have become the gold standard in the management of supraventricular tachycardia secondary to accessory pathways (Wolff-Parkinson-White syndrome and concealed bypass tracts).

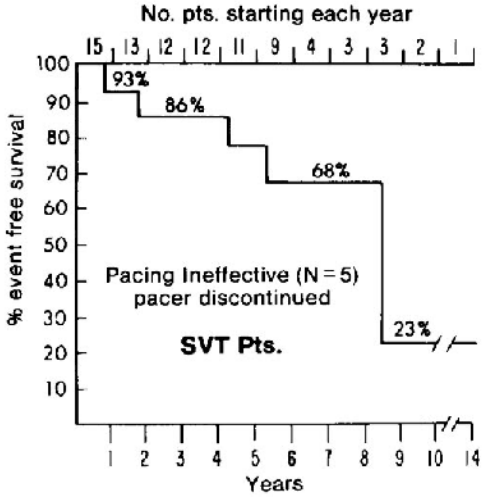

Figure 5 Actuarial survival of effective antitachycardia pacing in patients treated for PSVT. (Reproduced with permission from Fisher et al., Ref. 92.)

Success rates in excess of 95% with a surgical mortality of less than 1% have been consistently reported from centers that have performed this form of surgery since the mid-1970s (21–26,93–97). The surgical technique involves intraoperative confirmation of accessory pathway location, often using a computer-assisted mapping system with a multipole band electrode (Fig. 6). Although the original technique as described by Sealy and colleagues involved a combination of blunt and sharp dissection using an endocardial approach [i.e., incising from within the atrium out to the epicardial fat pad (93)], more recent techniques have involved epicardial dissection in concert with the application of cryolesions using nitrous oxide. Using the technique described by Guiraudon and others, the need for cardiopulmonary bypass can be avoided in many instances (94). Either right or left free-wall accessory pathway locations are particularly suited to this epicardial approach, whereas difficulties can arise in effectively ablating pathways in the posterior-septal region using solely an epicardial approach. This is secondary to the variable location of pathways in this region, which limit effective delivery of cryotherapy. High success rates coupled with major morbidity rates approaching the limits of general anesthesia alone make the surgical approach to Wolff-Parkinson-White syndrome extremely attractive. Successfully treated patients are ''cured'' of the arrhythmia in the broadest sense of the word and can be free of the need for chronic antiarrhythmic therapy and its attendant toxicities. Accurate pre- and intraoperative mapping is essential to the successful application of these techniques, because up to 10% of individuals may have multiple accessory pathways; in addition, a significant number of patients with accessory pathways may have other substrates for supraventricular arrhythmias, including dual AV nodal pathways. Definition of coronary anatomy to allow concomitant myocardial revascularization is useful in elderly patients with angina or a history of myocardial infarction.

AV node reentrant tachycardia is also amenable to direct surgical intervention using either sharp dissection, which can effectively interrupt the atrial insertion sites of input to the AV node, or through the selective application of cryolesions around the triangle of

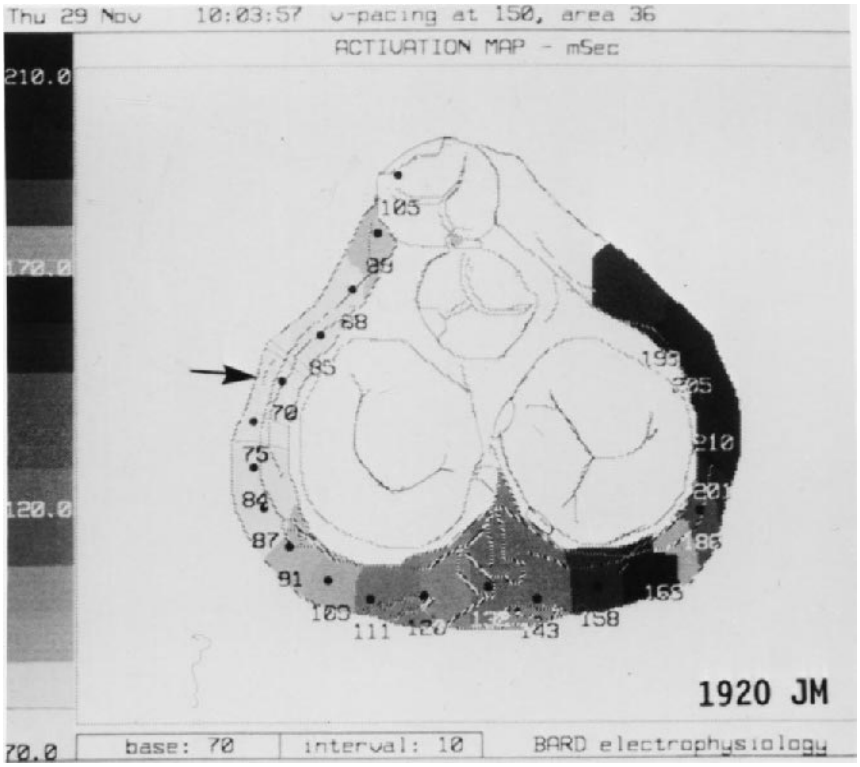

Figure 6 Computer-generated intraoperative atrial activation sequence map in a patient with Wolff-Parkinson-White syndrome. Arrow identifies the earliest site of atrial activation during ventricular pacing, confirming the presence of a left lateral bypass tract. Light-colored areas demonstrate areas of early activation, with darker areas coming progressively later. Numbers located along the AV groove represent local V-A conduction times in milliseconds.

Koch, as defined by the central fibrous body, the tendon of Todaro, the coronary sinus, and the septal leaflet of the tricuspid valve (98–102). With monitoring of AV conduction during the application of serial cryolesions, AV nodal modification can be accomplished with a low risk of high-degree AV block.

Automatic atrial tachycardias, which account for a minority of clinically significant atrial arrhythmias, can often be mapped to a focal point of origin, which can then be surgically removed. Often these arrhythmias, which encompass a spectrum of different sites of enhanced automaticity (i.e., so-called paroxysmal atrial tachycardia, inappropriate sinus tachycardia, and chronic atrial ectopic tachycardia), have historically proven to be resistant to a wide range of pharmacological therapy. The overall success rates for surgical therapy for these arrhythmias approaches 90%, as reported in a small series of patients from Duke University Medical Center, as apart from an approximately 34% success rate for medical therapy in similar patients (103,104) Because uncontrolled automatic atrial tachycardia can be associated with the development of a dilated cardiomyopathy, early surgical intervention of these arrhythmias has been advocated. Long-term efficacy of surgical treatment, however, may be limited by the development of enhanced automaticity in

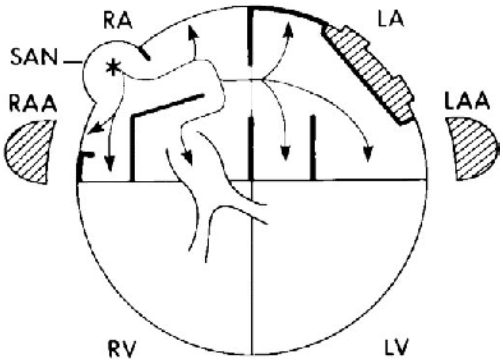

Figure 7 Suggested rationale behind the surgical incisions used for the Maze procedure. Incisions (heavy lines) are placed to ''channel'' the wave front of depolarization from the sinus node to the AV node region. Incisions are placed such that the wave front cannot ''double back'' on itself to form a localized area of reentry and recrudescence of atrial fibrillation.

other areas of the atrium, resulting in recrudescence of atrial tachycardia. There are limited data on the long-term efficacy of these procedures.

Cox has developed a procedure for the surgical treatment of atrial fibrillation, which has undergone a series of modifications over the last 5 years in an attempt to improve its efficacy and minimize its complication rate (105). This so-called ''maze'' procedure involves a series of anatomically defined incisions that attempt to ''channel'' the wave front of atrial depolarization in a path from the sinus to the AV node such that localized reentry cannot occur (Fig. 7). Conceptually, this provides organized atrial contraction synchronized to the sinus node, as well as an intact chronotropic response to activity. As electromechanical coupling exists in the atrium following this procedure, the risk of embolic phenomena should be reduced. This is in contradistinction to the so-called corridor operation proposed by Guiraudon et al., in which the majority of atrial tissue is electrically separated from a direct ''corridor'' connecting sinus and AV node (106). This latter procedure allows chronotropic competence by electrically ''connecting'' the sinus and AV node; the bulk of the atria remain fibrillating following this procedure such that the risk of emboli persists and anticoagulation following the operation is required. Sinus node dysfunction has developed in a subset of patients following both operations, and it is unclear whether this is a result of intraoperative damage to the sinus node or sinus node artery or reflects the natural history of sick sinus syndrome in atrial fibrillation. Postoperatively, patients undergoing the maze procedure often develop significant volume overload secondary to a depletion of atrial natriuretic factor such that vigorous diuresis during the postoperative period is mandatory.

Catheter Ablation Techniques

Catheter ablation was first reported in 1982 for the treatment of refractory supraventricular arrhythmias (107), although the first report of an ablative procedure was in 1979 by Vedel et al., when high-degree AV block was inadvertently produced during an electrophysiological study after cardioverting a sustained hemodynamically unstable tachycardia (108). The authors hypothesized that part of the defibrillating current passed through the intracav-

itary catheter, resulting in His bundle ablation. The first energy source used for ablative techniques was direct current, which utilized a conventional defibrillator to deliver energy to the patient. With this technique, the output from a defibrillator is channeled through the distal electrode of an intracavitary catheter (as cathode), using a backplate positioned on the posterior chest as the anodal sink. The energy delivered has a damped sinusoidal morphology, with resultant tissue injury from the procedure secondary to thermal and barotrauma, as well as direct electrical injury (109). Although in a given patient the direct contribution of each factor may be variable, it is believed by many that current flux created by the discharge is likely to be the major determinant of damage (110,111). Cellular studies in dogs undergoing DC shock ablation demonstrate local hemorrhage and contraction band necrosis. Chronically, volume loss, fibrosis, and fatty infiltration are common.

During ablation using a conventional electrophysiology catheter, currents up to 40 A occur, along with voltages in the range of 1000–2000 V. Defibrillator outputs of 300–400 J are used. This causes arcing, with the formation of a plasma arc. Significant localized barotrauma occurs, with transient increases in localized pressure to the $\leq$ 150 atm range (110).

DC shock ablation was first used in the management of atrial fibrillation to control ventricular response. Applying energy to the region of the AV node (with the catheter positioned to record an atrial electrogram that is larger than the ventricular electrogram and with a diminutive His bundle spike), applications of up to 360 J can create high-degree AV block in approximately two-thirds of patients. An additional 15–20% of patients following the procedure demonstrate effective slowing of ventricular response either in the absence of pharmacological therapy or during pharmacological therapy that was previously ineffective. Thus, DC shock ablation is effective in approximately 85% of patients in whom previous attempts at pharmacological therapy were ineffective in controlling the ventricular response to atrial fibrillation (107,109,111). The major ''down side'' of DC shock ablation for the management of atrial fibrillation is the need for permanent pacemaker implantation, insofar as the majority of patients treated become pacemaker dependent. With the advent of rate-responsive pacemakers, after DC shock ablation of the AV node a patient can be left with virtually physiological rate responsivity to exercise. Nevertheless, insofar as DC shock ablation of the AV node does not restore sinus rhythm, such patients should be anticoagulated indefinitely to reduce the embolic risk associated with atrial fibrillation.

DC shock ablation is performed under brief general anesthesia, optimally with chemically induced muscular paralysis using an agent like succinylcholine to prevent muscular contraction during the procedure. Complications reported with AV node ablation using DC energy are infrequent but include transient ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation immediately following the procedure, which can require DC cardioversion for termination. Tamponade secondary to atrial perforation has been reported, albeit rarely (112), such that whenever DC shock ablation is performed, a cardiac surgeon should be on standby in the event of cardiac perforation.

DC shock ablation can also be used to ablate appropriately located accessory pathways (109,111–116). Early attempts at ablating left lateral accessory pathways were associated with a significant risk of coronary sinus rupture and tamponade (112). This presumably occurs secondary to barotrauma in the relative confines of the coronary sinus. The risk of such trauma is significantly less with right-sided tracts: by positioning the endocavitary catheter in the right atrium at the level of the AV junction, transient increases in pressure during ablation can be dissipated in the distensible right atrium. However, spasm of the

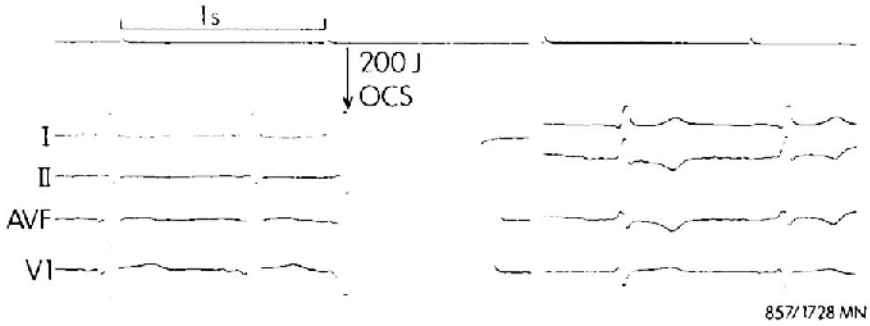

Figure 8 Surface electrocardiograms immediately before (left) and after (right) DC shock ablation in a patient with Wolff-Parkinson-White syndrome. Delta waves with a pseudoinferior wall myocardial infarction pattern are seen in leads 2 and AVF preablation. Following the application of a 200 J shock via a catheter positioned at the os of the coronary sinus (OCS), delta waves are not seen, and the initial vector of depolarization of the QRS in leads 2 and AVF is now positive.

right coronary artery has been reported (115). DC shock ablation can be used to ablate accessory pathways in the posterior septal location. Using this technique, the ablating catheter is positioned at the os of the coronary sinus, with the current flux directed from the catheter tip to an indifferent anterior or posterior electrode (Fig. 8). Morady et al. reported success in approximately two-thirds of patients treated with DC shock ablation for posterior septal accessory pathways. The risk of cardiac tamponade in this setting is approximately 1% (113). Since 1990, however, enthusiasm for DC shock ablation has waned with the development of radiofrequency ablation. Using this technique, localized lesions are created as a result of resistive heating of tissue at the site of the catheter tip. Using this more controllable energy source, arcing and subsequent barotrauma do not occur. With average impedances of approximately 100 Ω, 50 V at 0.5 A are applied to the target area for between 30 and 60 s. The lesions created using this form of energy are more focal, and selective AV nodal modification has been described that can result in control of AV node reentrant tachycardia without causing complete AV block. Jackman and others have described the selective modification of the AV nodal ''slow pathway'' with success rates of 85–90% in controlling PSVT (117–120). Morady and others have described using a somewhat different catheter location to ablate the AV nodal ''fast pathway,'' with similar success rates (118). The risk of high-degree AV block with fast pathway ablation is of the order of 1–2% and may be higher than that associated with slow pathway ablation.

Radiofrequency energy can also be used to ablate accessory pathways and thereby ''cure'' AV reciprocating tachycardia. A major advantage in this regard is that by avoiding arcing and the resultant barotrauma, ablation can be attempted for virtually all accessory pathway locations with minimal risk of cardiac perforation (121–123). Ablation of left-sided accessory pathways involves placing a specially designed ablating catheter with a large 4 mm distal electrode tip into the femoral artery and advancing it retrogradely across the aortic valve to position the tip either over or under the mitral valve apparatus at the level of the AV junction. Alternatively, transseptal puncture can be performed with subsequent deployment of a multipole catheter along the atrial side of the mitral annulus. The earliest site of atrial activation during reciprocating tachycardia can then be assessed using

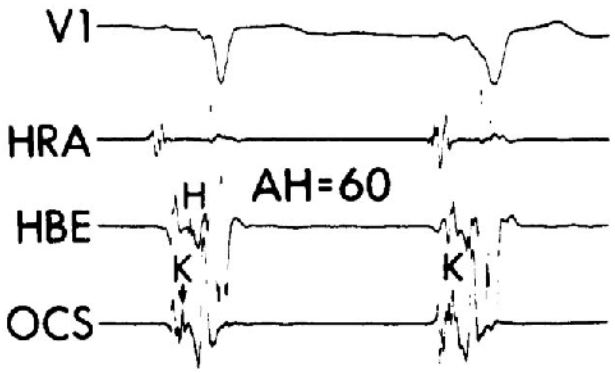

Figure 9 Intracavitary electrograms from a patient with Wolff-Parkinson-White syndrome. Notice the high-frequency deflection from a recorded catheter positioned at the os of the coronary sinus representing a Kent potential (K). A His bundle electrogram (H) is recorded from a catheter positioned in the His bundle region. The AH interval during sinus rhythm is normal at 60 ms. HRA = high right atrium, HBE = His bundle electrogram, OCS = os of coronary sinus.

the ablating catheter either alone or in concert with a catheter positioned in the coronary sinus. Jackman and others have described recording accessory pathway depolarizations (Fig. 9) using a special orthogonal electrode array on the catheter positioned on the coronary sinus. By targeting this accessory pathway depolarization (so-called ''Kent potential''), success rates in excess of 90% in ablating accessory pathway conduction have been reported (Fig. 10) (121). As in AV nodal modification, radiofrequency energy is directed between the distal ablating catheter tip and in an indifferent electrode usually placed on the patient's back (a commercially available patch used during routine electrophysiological studies or one of similar design used by surgical electrocautery devices). The impedance

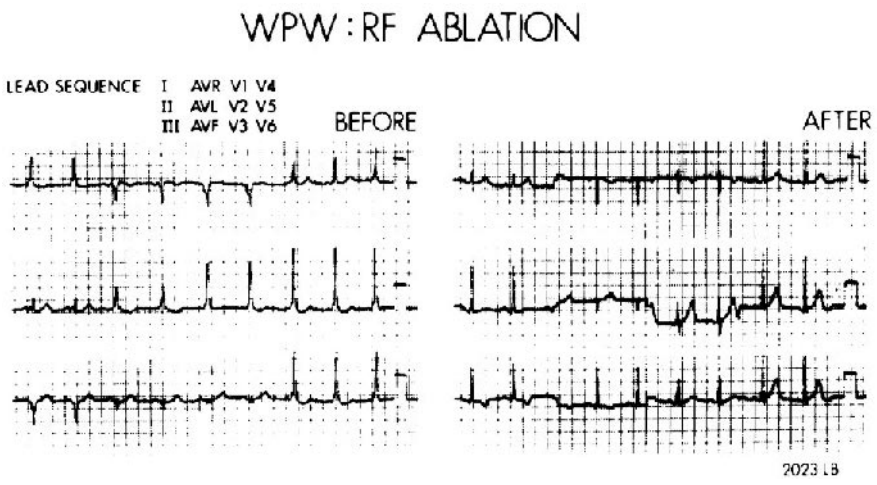

Figure 10 Example of 12-lead electrograms, before and after radiofrequency ablation of an accessory pathway. Notice the absence of delta wave activity following the procedure.

across the system is monitored during radiofrequency energy application, with ablation halted at the first sign of an impedance rise. Impedance rises are often associated with localized eschar formation along the catheter tip, resulting in diminution of current flow. The use of a large-tip electrode has been shown to minimize impedance rises; when they occur, however, the catheter must be removed and the tip cleaned of debris. Monitoring temperature of the ablating catheter during energy application can be used to minimize rises in impedance by reducing power output in an attempt to maintain a constant temperature of 60° to 70° Celsius.

In view of the discrete nature of the lesions formed by radiofrequency energy application, mapping must be precise. It is not uncommon for repeat applications of RF energy to be used before successful pathway ablation or AV node modification. Although there have been reports of successful ablation in studies lasting less than 4 h (118), during the early experience with radiofrequency ablation it was not uncommon for diagnostic electrophysiological studies involving ablation attempts to run in excess of 12 h. Total x-ray exposure time for both the patient and the operator can be significant, and the long-term sequelae of this have not been adequately characterized (123). Improved x-ray equipment, including devices capable of image retention as well as the use of ''pulsed fluoroscopy,'' have been effective in reducing the amount of radiation to which a patient is exposed.

Inappropriate sinus tachycardia is a form of supraventricular tachycardia characterized by normally vectored atrial depolarizations at rates of 130—170 bpm, exhibiting gradual but steep onset and termination. It is a rhythm that is often difficult to treat pharmacologically. Recently, electrophysiological techniques have been described to map the region of the sinus node allowing for radiofrequency modulation or ablation of this rhythm. The normal sinus node exhibits a hierarchical distribution of depolarization, with more rapid depolarization rates arising from a more cephalad point of origin along the superior aspect of the crista terminalis. Conversely, slower sinus rhythm appears to arise from a more caudal site in the sinus node. During inappropriate sinus tachycardia, regions of early atrial activation can be targeted for radiofrequency energy application. Acute and chronic modulation of sinus rate has been reported using this technique (123a,123b), although on occasion marked bradycardia has ensued requiring permanent pacemaker implantation.

Catheter ablation techniques can also be applied to the management of automatic atrial tachycardia, as well as atrial flutter. The common form of atrial flutter appears to involve a macroreentrant circuit with a zone of slow conduction in the posterior right atrium near the os of the coronary sinus. Successful ablation of atrial flutter has been reported with both DC shock ablation and radiofrequency ablation; however, success rates may be less than those for PSVT secondary to AV node reentry or accessory pathway conduction (124,125). Initial reports have suggested a success rate of 70 to 85% using radiofrequency ablation techniques for the treatment of atrial flutter of the common type (126–128). Although the most common technique described utilizes the placement of a series of radiofrequency lesions along the isthmus of atrial tissue between the tricuspid valve and inferior vena cava, placing lesions in a linear fashion between the tricuspid valve and coronary sinus has also been described. Initial reports utilized acute termination of atrial flutter and subsequent noninducibility by programmed stimulation as the endpoints by which to judge procedure success. Using this approach, a recurrence rate of 15 to 25% was seen during follow-up. Lesh and others have subsequently reported using a combination of techniques including concealed entrainment and differential atrial pacing with mapping of atrial depolarization sequence to assist in the creation of a line of conduc-

tion block to establish the efficacy of the ablative procedure (129). Using these techniques, success rates in the 85 to 90% range have been reported with a significantly lower arrhythmia recurrence rate.

DEVELOPING TECHNIQUES FOR ATRIAL FIBRILLATION MANAGEMENT

Ablation for Atrial Fibrillation Management

As noted previously, current ablative techniques used in the management of atrial fibrillation have only been palliative by using either DC shock or radiofrequency techniques to create iatrogenic heart block (130–133). Patients then undergo permanent pacemaker implantation to prevent symptomatic bradycardia. Significant amelioration of patient symptoms has been consistently noted following AV node ablation; however, as atrial fibrillation persists following AV node ablation, anticoagulation to reduce chronic embolic risk is required, and some investigators have been concerned about the potential adverse sequelae of pacemaker dependence. Dual-chamber pacing with mode-switching capability has been useful following ablation in providing AV synchrony during periods of sinus rhythm in patients with paroxysmal atrial fibrillation. Although it was hoped that atrial pacing following AV Node ablation would contribute to maintaining sinus rhythm, survival of the DDD pacing mode in these patients has been limited (40–50%) after 1 to 2 years of follow-up, with many patients ultimately reverting to constant atrial fibrillation.

Dual-Site Atrial Pacing

By decreasing dispersion of refractoriness and synchronizing both depolarization and repolarization, dual-site atrial pacing has been utilized in an attempt to prevent atrial fibrillation. Saksena and others have reported a marked reduction in atrial fibrillation recurrence following institution of dual-site atrial pacing, often, however, at a cost of continued antiarrhythmic therapy (134–136). Prolongation of the length of time between arrhythmic episodes using this technique has also been described. Pacing sites in the region of the atrial appendage and of the coronary sinus are most commonly utilized, although some have speculated that other sites such as the distal coronary sinus or atrial septum may be more effective alternatives.

Atrial Defibrillator

Spawned by the success of the implantable cardioverter defibrillator in treating patients surviving cardiac arrest, the development of an automated implantable atrial defibrillator has over the last several years received significant investigational attention (137–142). The device presently undergoing clinical investigation in the U.S. uses bidirectional R-wave synchronization and catheters placed at the RV apex, right atrial appendage, and coronary sinus to deliver a 0.5–3 J shock across the right atrial and coronary sinus leads to effect atrial defibrillation (143). This device is not capable of defibrillating in the ventricle, and as such proper R-wave synchronization is critical to prevent the inadvertent induction of ventricular fibrillation. Despite initial concern, in this regard, during both animal studies and during clinical trials, ventricular proarrhythmia has not been demonstrated with appropriate R-wave synchrony (144,145). In clinical trials, the atrial defibrillator has effectively terminated atrial fibrillation in over 85% of episodes. Although patients are aware of the sense of defibrillator discharge, in trials to date therapy has been well tolerated. More sophisticated atrial defibrillators, including those capable of dual-chamber de-

fibrillation, are already under development and are undergoing clinical evaluation in Europe (146,147).

AFFIRM

In view of the controversies surrounding the optimal management of patients with atrial fibrillation, planning for the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial began in 1992 (148). With a projected enrollment of 5300 patients from 200 clinical sites in the U.S. and Canada, AFFIRM compares two very different management strategies in patients with atrial fibrillation. Enrolled patients are randomized to either rhythm control utilizing agents attempting to maintain sinus rhythm (''atrial stabilizing agents''), or to a rate control arm using AV nodal blocking agents and possibly AV node ablation with pacemaker insertion if necessary to effect rate control. Enrollment criteria include age over 65, or age less than 60, with risk factors for stroke including left atrial enlargement, hypertension, CVA, or other markers of cardiovascular risk. Patients must be acceptable candidates for anticoagulation. An anticipated duration of follow-up of 42 months is planned for the study.

Catheter-Based MAZE Procedure

At present, the ''Holy Grail'' of atrial fibrillation management is the development of an effective catheter-based procedure to directly ablate atrial fibrillation. As a critical mass of atrial myocardium is necessary to maintain the multiple reentrant circuits of atrial fibrillation, the initial surgical procedures for treatment of atrial fibrillation (atrial isolation, corridor operation, MAZE procedure) all involved dividing the atria into ''compartments'' in order to reduce the likelihood of atrial fibrillation (149–151). Swartz, Haussiguarre, and others have described different patterns of linear lesions placed via multipole catheters using radiofrequency energy application to create atrial ''compartmentalization'' (152,153). The procedures described to date have had only limited efficacy, in part because of difficulty in achieving a continuous line of transmural block using present-day catheter and imaging technology. Although specially designed catheters for atrial fibrillation ablation have been proposed and are under development, at the present time a catheter-based procedure to ''cure'' atrial fibrillation must still be considered investigational.

Dofetilide

Dofetilide is a class III antiarrhythmic agent with selective potassium channel blocking effects. It has been demonstrated to be effective in prevention and treatment of atrial fibrillation (154,155). Two recent Danish studies investigating the use of dofetilide in patients following myocardial infarction as well as patients with congestive heart failure have suggested that use of dofetilide is safe even in the setting of left ventricular dysfunction and recent myocardial infarction.

Intracavitary DC shocks have been described as effective in cardioverting atrial fibrillation to sinus rhythm, and there have been reports suggesting that this may result in long-term maintenance of sinus rhythm in a minority of patients. The mechanism behind the successful conversion to sinus rhythm is unknown; however, it may be related to barotrauma and the transient ''stretching'' of the right atrium.

The management of supraventricular tachyarrhythmias has undergone a marked evolution in the last decade. Although options for pharmacological therapy have significantly broadened during this time, the most striking advancements have been in the nonpharmacological realm, with impressive developments in surgical and ablative modalities of therapy. In view of the potential toxicity and limited efficacy of pharmacological therapy, if

the initial successes of nonpharmacological therapy are confirmed, these techniques may become the modalities of choice for the treatment of sustained arrhythmias in the elderly.

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25

Anticoagulation Therapy in the Elderly

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INTRODUCTION

The issue of anticoagulation in the elderly is important to consider because of the sheer frequency of thrombotic disorders in this age group. Clinicians caring for such patients need to know which individuals are at highest risk for the development of thrombotic complications so that preventive and treatment strategies can be targeted at those who will potentially benefit most from anticoagulation. Because elderly patients may also experience more hemorrhagic complications than their younger counterparts, strategies to identify and modify risk factors for bleeding deserve equal consideration.

In 1995, the fourth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy recommended a set of target treatment goals for long-term oral anticoagulation (1). For patients with mechanical heart valves, the target treatment goal is an INR of 2.5–3.5; for all other treatment indications, a target INR of 2.0–3.0 is recommended. Although the fifth ACCP Consensus Conference on Antithrombotic Therapy is in the process of revising and updating their recommendations, we do not anticipate that there will be any substantial changes in these target treatment goals.

In this chapter we will: (1) summarize the major indications for long-term oral anticoagulation; (2) discuss the risk factors responsible for patient-related and treatment-related hemorrhagic complications; and (3) review some practical considerations associated with the long-term use of warfarin. While we have attempted to focus our discussion on the specific risks and benefits of anticoagulating elderly patients, many of our remarks can also be applied to younger age groups.

INDICATIONS FOR CHRONIC ANTICOAGULATION

Current indications for treatment with long-term anticoagulants include: (1) nonvalvular atrial fibrillation; (2) valvular heart disease and prosthetic heart valves; (3) ischemic heart disease; (4) dilated congestive cardiomyopathy; (5) ischemic cerebral vascular disease; (6) peripheral vascular disease; and (7) venous thromboembolic disease.

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Nonvalvular Atrial Fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia occurring in elderly patients (2). While it has been estimated that 1 to 2% of Americans over age 60 have AF, the prevalence of AF in very elderly patients appears to be substantially higher (3). For example, in 1153 unselected nursing home patients with a mean age of 82 years, Aronow and associates documented a 13% prevalence of AF (4). The significance of this finding is underscored by the fact that one-third of all AF patients will eventually have a stroke (5), and that many of these strokes will be disabling or fatal.

To help put the attributable risk of AF in perspective, Wolf and colleagues examined the impact of nonrheumatic atrial fibrillation, hypertension, coronary heart disease (CHD), and congestive heart failure (CHF) on stroke incidence in over 5000 participants in the Framingham Study (6). In persons with either CHD or CHF, the presence of atrial fibrillation doubled the risk of stroke in men and trebled the risk in women. While the effects of hypertension, CHD, and CHF on the risk of stroke became progressively weaker with advancing age, the impact of atrial fibrillation did not decrease significantly. In fact, for persons in their ninth decade of life, AF was the sole cardiovascular risk factor to exert an independent effect on the incidence of stroke. In this study, the attributable risk of stroke for atrial fibrillation increased from 1.5% for those aged 50 to 59 to 23.5% for those aged 80 to 89.

Since 1989, eight large-scale, randomized clinical trials (Table 1) have demonstrated the safety and efficacy of warfarin in preventing strokes in predominantly elderly patients with nonvalvular atrial fibrillation (NVAF) (7–14). Overall, warfarin produced a 70% reduction in the rate of ischemic strokes and was associated with a low risk of major bleeding complications. Based on this convincing evidence, the clinical question about anticoagulating NVAF patients has changed over the years from ''should we or shouldn't we?'' to ''which patients will benefit most from treatment?'' Recent studies have begun to identify specific clinical, echocardiographic, and/or hematological variables that may help clinicians stratify risk in patients with NVAF and target treatment to those with the most favorable benefit/risk ratios (Table 2).

Clinical Risk Factors for Stroke in NVAF Patients

Using multivariate analysis, SPAF-I investigators identified three clinical variables in NVAF patients that were independently associated with a substantial risk for thromboembolism; these included congestive heart failure within the preceding 3 months, a history of hypertension, and a history of previous arterial embolus (15). Patients who had none of these clinical variables had a stroke risk of 2.5% per year, compared to 7.2% per year for patients with one clinical risk factor and 17.2% per year for patients with two or more.

Previous studies have demonstrated that patients with nonvalvular atrial fibrillation and a past history of clinically apparent stroke are at particularly high risk for subsequent cerebral infarctions. Szekely found that such patients have a rate of recurrent thromboembolism that averages about 9.6% per year (16). Data from the European Atrial Fibrillation Trial support this assessment; in the placebo arm of this secondary prevention trial of ''high-risk'' patients, the incidence of recurrent stroke was 12% in NVAF patients who had experienced a recent TIA or minor stroke (13).

Asymptomatic cerebral infarctions have also been found to be disturbingly common in patients with NVAF. Feinberg and colleagues evaluated 141 asymptomatic patients

Table 1 Summary of NVAF Clinical Trials

Study	Total No. of patients	Mean age (yrs.)	Mean follow-up (yrs.)	Target INR	ASA dose (mg)	Primary outcomes (annual rates in %)			Major bleeds (annual rates in %)		
						W	A	P/C	W	A	P
Primary Prevention Studies											
AFASAK (7)	1007	73	1.2	2.8–4.2	75	2.7	5.2	6.2	0.3	0.3	0.0
SPAF-I (8)	1330	65	1.3	2.0–4.5	325	2.3	3.6	6.3	1.5	1.4	1.6
BAATAF (9)	420	69	2.2	1.5–2.7	—	0.4	—	3.0[a]	0.9	—	0.4
CAFA (10)	383	68	1.3	2.0–3.0	—	3.5	—	5.2	1.5	—	0.5
SPINAF (11)	525	67	1.8	1.4–2.8	—	0.9	—	4.3	1.5	—	0.9
SPAF-II (12)	1100		2.7	2.0–4.5	325						
(<75 yrs)		65				1.3	1.9	—	1.7	0.9	—
(>75 yrs)		80				3.6	4.8	—	4.2	1.6	—
SPAF-III (14)	1044	72	1.1	2.0–3.0	—	1.9	—	—	2.1	—	—
				1.2–1.5	325	—	7.9[b]	—	—	2.4[b]	—
Secondary Prevention Studies											
EAFT (13)	1007	71	2.3	2.5–4.0	300	8	15	19	2.8	0.9	0.7

[a] 46% of BAATAF patients in the control group used aspirin.
[b] These patients received both 325 mg/ASA daily plus low-intensity, fixed-dose warfarin (mean INR during follow-up = 1.3).
Source: Adapted from Refs. 13, 14, and 36.

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Table 2 Risk Factors for Stroke in NVAF Patients

Clinical
Age > 75
Female sex
History of previous TIA or stroke
Hypertension (>160/90)
Congestive heart failure within last 3 months
Clinical coronary artery disease
Diabetes
Thyrotoxicosis
Echocardiographic
Decreased fractional shortening
Left atrial enlargement
Global LV systolic dysfunction
Mitral annular calcification
LA spontaneous echo contrast (TEE)
Hemostatic
Thrombin-antithrombin III complex (?)
Fibrin monomers (?)
d-dimer (?)
b-thromboglobulin (?)

with NVAF, 26% of whom had hypodense areas consistent with cerebral infarctions on unenhanced CT scans of the head (17). Increasing age and an enlarged left atrium were the only clinical features associated with these apparently silent CNS events. Patients older than age 65 with left atrial diameters greater than 50 millimeters had a 52% prevalence of ''silent strokes'' compared with an 11% prevalence in younger patients with smaller left atrial diameters. The functional and prognostic significance of these presumed silent cerebral infarcts is an area of active investigation. If such hypodense areas are shown to be associated with an increased risk of subsequent clinically apparent strokes, then head CT scans may prove to be a useful means of identifying high-risk AF patients who are candidates for long-term anticoagulation (17).

Although a subgroup analysis of the patients enrolled in each of the completed NVAF clinical trials does not yield a consistent risk profile across all studies, the following clinical variables are associated with a higher rate of ischemic stroke: advanced age (> 75 years), history of previous TIA or stroke, hypertension, congestive heart failure, clinical coronary artery disease, diabetes, and thyrotoxicosis (7–14,18,19).

Echocardiographic Risk Factors

A transthoracic echocardiogram (TT echo) is usually obtained in most patients with AF to delineate the underlying cause of their arrhythmia and to stratify their risk for systemic embolism. Specific findings on TT echo that have been found to be independent predictors of thromboembolism in NVAF patients include: left atrial (LA) enlargement (by standard M-mode echocardiography), global left ventricular (LV) systolic dysfunction, and mitral annular calcification (9,20). TT echo may be particularly useful in evaluating the ''lone atrial fibrillation'' status of patients who have no clinical risk factors. In a post hoc subgroup analysis by the SPAF-I investigators, one of every three subjects (mean age 67) without clinical risk factors for systemic embolism were found to have echocardiographic

abnormalities (LA enlargement or global LV systolic dysfunction) (20). These two findings on echo yielded important prognostic information; the risk of ischemic stroke in NVAF patients without clinical risk factors increased from 1% per year if neither echo abnormality was present, to 5% per year if either one was identified, and to 10% per year if both were present.

Does transesophageal echocardiography (TEE) add unique and important prognostic information to that already available from routine clinical evaluation and TT echo? The TEE finding of spontaneous echo contrast (SEC) has been associated with conditions favoring stasis of blood in the left atrium (AF, mitral stenosis, absence of mitral regurgitation, increased LA dimension) (21). Although the prevalence of SEC in patients with NVAF may approximate 50%, additional clinical studies are required to determine the prognostic significance of this finding and clarify the precise role of TEE in future risk stratification protocols.

Hemostatic Markers

Do NVAF patients have a higher prevalence of certain hemostatic abnormalities that increase their risk of stroke? Recent studies have shown that, compared to persons in normal sinus rhythm (NSR), patients with AF may have rheologic and hemostatic abnormalities that contribute to a prothrombotic or hypercoagulable state (22). Mitusch and colleagues studied the prevalence and extent of a presumed hypercoagulable state in NVAF patients and found elevated levels of molecular hemostatic markers such as thrombin–antithrombin III complex, fibrin monomers, and D-dimer (among others) in over 70% of patients with NVAF (23). These markers, however, were not found to be clinically useful in identifying high-risk subgroups of NVAF patients. Gustafsson and colleagues found an association between molecular hemostatic markers and age but were unable to detect any difference in hemostatic function between NVAF patients who suffered a previous ischemic stroke and those who did not (24).

More recent clinical trials provide additional evidence to support the hypothesis that NVAF patients may have an underlying hemostatic abnormality. NVAF patients enrolled in the Stroke Prevention in Atrial Fibrillation-III (SPAF-III) trial demonstrated increased platelet activity and increased fibrin turnover as reflected by high circulating levels of β-thromboglobulin (β-TG) and fibrin D-dimer (22). Although treatment with conventional doses of warfarin (target INR 1.5–2.5) reduced both of these markers, it is not yet clear whether measurement of plasma D-dimer and β-TG will be useful in predicting systemic embolism in AF patients.

We conclude that readily assessable clinical risk factors for ischemic stroke are among the most important variables to consider when deciding which patients with NVAF will benefit most from long-term anticoagulation. Transthoracic echocardiography provides additional useful information in many patients, but the exact role of TEE awaits further clinical study. While alterations in hemostatic function may increase the risk of stroke in elderly patients with NVAF, current laboratory tests are not useful in identifying high-risk subgroups of patients for more aggressive antithrombotic prophylaxis. Therefore, at the present time, we do not recommend the routine use of TEE and/or laboratory hemostatic markers to stratify risk in patients with NVAF.

Lone Atrial Fibrillation

Lack of a uniformly applied definition has created some confusion as to whether lone atrial fibrillation (LAF) is a significant risk factor for stroke. Some investigators refer to

LAF as idiopathic atrial fibrillation that is not associated with any underlying heart disease. Others require not only the absence of structural heart disease, but the absence of any other clinical risk factors for ischemic stroke (see above).

The Framingham investigators defined LAF as atrial fibrillation that occurred without any preexisting or coexisting evidence of CHD, CHF, rheumatic heart disease, or hypertensive cardiovascular disease (25). At the time of their 30-year follow-up, 376 of 5209 patients (7.2%) were noted to have atrial fibrillation, with 43 of these meeting their definition of LAF. Thus, LAF patients comprised only 0.8% of the entire study population, but accounted for 11.4% of all patients with atrial fibrillation. Patients who met the Framingham definition of LAF were found to have an age-adjusted rate of stroke that was about four times that of an age-matched control (28.2% vs. 6.8%).

These findings contrast sharply with those of Kopecky and colleagues who found that LAF patients from Olmsted County, Minnesota had less than half the number of strokes that were expected on a cumulative actuarial basis (3% expected vs. 1.3% actual) (26). Although these investigators incorporated more exclusion criteria (such as hypertension, diabetes, COPD) into their operational definition of LAF, significant age differences between patients from Olmsted County and Framingham may account for the discordant results of these two studies. Eighty-eight percent of Framingham LAF patients were older than age 60, with 56% older than age 70. By comparison, subjects in the Olmsted County study had a mean age of only 44 years at the time AF was first documented; any patient over age 60 was excluded from analysis.

The SPAF-I provides a third subset of patients who might be considered to have LAF (15,20). In this study, 26% of all patients randomized to the placebo group had none of the clinical or echocardiographic predictors of thromboembolism that we have previously discussed. Such patients had an extremely low rate of thromboembolism (about 1% per year) (20). Moreover, SPAF patients who were younger than 60 years of age and who did not have a history of hypertension, recent congestive heart failure, or previous systemic embolism did not experience any thromboembolic events (15).

Paroxysmal Atrial Fibrillation

Is the relative risk of stroke in patients with intermittent or paroxysmal atrial fibrillation (PAF) the same as patients who have chronic or persistent atrial fibrillation (CAF)? While some earlier studies reported that PAF patients are at a lower risk of systemic embolism than patients with CAF, data from the Framingham Study suggest that the risk in both subgroups is comparable (27). More recently, the SPAF-I (8) and BAATAF (9) trials, each of which enrolled a substantial percentage of patients with PAF, showed no difference in stroke risk when PAF patients were compared to those with CAF. Moreover, in a subsequent analysis of pooled data from five large-scale, randomized clinical trials, the Atrial Fibrillation Investigators concluded that the presence of underlying heart disease correlated more closely with the risk of stroke than did the paroxysmal or chronic nature of the arrhythmia (18).

The pool of potential candidates for antithrombotic prophylaxis increases substantially if PAF and CAF patients are routinely considered for long-term anticoagulation on an equal footing. Using population-based surveys and recent nationwide census data, Feinberg and colleagues estimated that there are 2.2 million people (median age 75 years) in the U.S. with atrial fibrillation (AF) (28). However, these figures may substantially underestimate the true prevalence of AF in the population. Because only about 25% of

PAF patients will develop chronic and persistent arrhythmias, many of these cases will escape clinical detection (29).

Holter monitor data suggest that asymptomatic PAF occurs more than 12 times as frequently as its symptomatic counterpart (29). The question of whether an incidental finding of asymptomatic PAF detected on ambulatory monitoring requires long-term anticoagulation needs to be addressed in future clinical trials.

Atrial Flutter

Previous guidelines have not routinely recommended anticoagulating patients with atrial flutter because maintenance of synchronous, mechanical atrial contraction was felt to decrease the thromboembolic risk of such patients compared to those with atrial fibrillation. Recent work by Black and colleagues, however, suggests that the potential thromboembolic risk associated with atrial flutter may have been underestimated (30). Using TEE, these investigators noted a 33% incidence of LA spontaneous echo contrast and a 5% incidence of LA thrombi in 20 patients with atrial flutter. Although these echocardiographic findings were less common than in patients with atrial fibrillation (53% SEC, 12% LA thrombi), the authors felt that they occurred frequently enough in patients with atrial flutter to warrant prophylactic anticoagulation.

Intensity of Anticoagulation

Because INR treatment goals in the NVAF clinical trials ranged from a low of 1.4 (SPINAF study) (11) to a high of 4.5 (SPAF-I and SPAF-II) (8,12), much debate has centered around the question ''What is the optimal intensity of anticoagulation for NVAF patients that maximizes stroke protection and minimizes the risk of bleeding?''

Hylek and colleagues reported a case-control study of 74 patients with atrial fibrillation who had a stroke while being treated with warfarin (64% $>$ 75 years) and compared the INR values of these patients to 222 warfarin-treated patients who did not have a stroke (31). The risk of stroke rose steeply at INRs below 2.0; the adjusted odds ratio (OR) for ischemic stroke was 2.0 for an INR of 1.7, 3.3 for an INR of 1.5, and 6.0 for an INR of 1.3. Other independent risk factors were previous stroke (OR = 10.4), current smoking (OR = 5.7), diabetes mellitus (OR = 2.9), and hypertension (OR = 2.5).

The SPAF-III trial demonstrated that, even when combined with aspirin, very low intensity warfarin was insufficient for stroke prevention in ''high-risk'' NVAF patients (14). Participants in this study were considered to be at high risk for thromboembolism if one or more of the following risk factors were present: female and age $>$ 75; history of prior TIA, ischemic stroke, or systemic embolism ($>$ 30 days prior to study entry); systolic BP $\geq$ 160 mmHg; recent congestive heart failure (defined clinically) or left ventricular systolic dysfunction (defined as fractional shortening $\leq$ 25% by M-mode echocardiography). These high-risk patients (mean age 72 years) were randomized to receive standard warfarin (target INR 2–3, mean achieved INR 2.4) vs. low-intensity fixed-dose warfarin (target INR 1.2–1.5, mean achieved INR 1.3) in combination with daily aspirin (325 mg). The excessively high rate of primary outcome events (ischemic stroke, systemic embolism) in the group receiving low-intensity warfarin plus aspirin compared to the group receiving standard warfarin (7.9% per year vs. 1.9% per year) led to premature termination of this part of the study after a mean follow-up period of only 1.1 years. Due to these discouraging results, another large-scale clinical trial (AFASAK-II) designed to

evaluate the antithrombotic effects of various combinations of low-dose aspirin and/or warfarin was also stopped prematurely in October, 1996.

The European Atrial Fibrillation Trial (EAFT), a secondary prevention trial in high-risk NVAF patients (mean age 71 years) with a history of previous TIA or minor stroke, also demonstrated that optimal levels of anticoagulation should achieve a minimal INR of 2.0 (32). In this study, the rate of ischemic events (death from cardiovascular causes, nonfatal stroke, nonfatal MI, systemic embolism) was 18% per 100 person years when the INR was < 2.0 compared to 3.5% per year if the INR was between 2.0 and 3.9.

Most patients with NVAF who are candidates for long-term anticoagulation should be treated with warfarin to achieve an INR of 2 to 3. Hylek's data suggest that some, albeit incomplete, protection is provided by INRs between 1.6 to 2.0 (31). However, even this ''subtherapeutic'' level of anticoagulation provides more than 80% of the stroke risk reduction compared with an INR of 1.0 (33) (Fig. 1). For this reason, it appears that some elderly patients, especially those with special risks for bleeding, may be appropriately managed with slightly lower levels of anticoagulation. For high-risk patients, such as those with a history of recurrent systemic emboli, previous ischemic strokes, or recent TIAs, a minimum INR of 2.0 is needed to prevent recurrent thromboembolic events.

Role of Aspirin

In contrast to warfarin's proven efficacy, the role of aspirin in preventing strokes in patients with NVAF remains unsettled. In the AFASAK trial, a nonsignificant 18% reduction in the rate of stroke was found in NVAF patients taking 75 mg of aspirin daily, compared to a control group taking placebo (7). Similar unfavorable results were found in the BAATAF (9,34) and EAFT (13) trials. Although the BAATAF trial was not designed primarily to evaluate the role of antiplatelet therapy, patients randomized to receive placebo rather than warfarin were allowed to use aspirin, if they or their physicians so desired. About half of the patients in the placebo arm used aspirin, on a more or less regular basis, without any demonstrable reduction in their rate of systemic embolism (34). In the EAFT

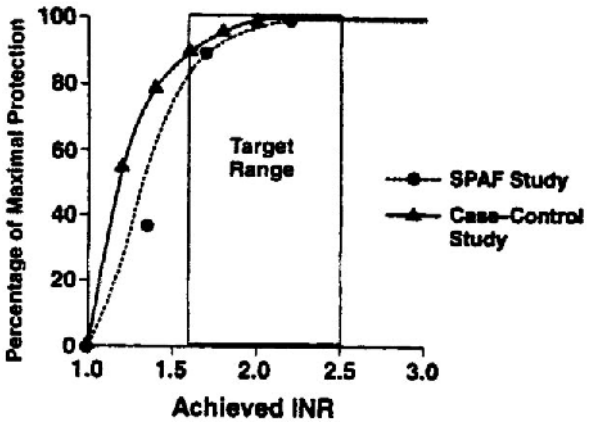

Figure 1 Intensity of Anticoagulation to Prevent Stroke in NVAF. Relative efficacy of target INRs of 1.6 to 2.5. Percentages calculated under the presumption that maximal protection is achieved with INRs greater than 2.0. SPAF = Stroke Prevention and Atrial Fibrillation. (From Ref. 34.)

study, aspirin decreased the absolute rate of stroke by only 2% per year compared to placebo (from 12% to 10% per year); this relative risk reduction of 17% was not statistically significant (13).

Aspirin's effect in reducing the rate of ischemic strokes reached statistical significance in only one randomized clinical trial that directly compared ASA with placebo. SPAF-I investigators found a 42% risk reduction in the group receiving 325 mg aspirin daily compared to placebo; this was a statistically significant and clinically important finding (8). Because the beneficial effects of aspirin were limited to patients less than 75 years of age, SPAF-II was designed to further investigate potential age-related differences in the responsiveness of NVAF patients to antiplatelet agents (12).

In the SPAF-II study (12), patients were stratified into two age groups (younger than 75, and 75 years and older) before randomization to aspirin (325 mg daily) or warfarin therapy (INR 2.8–4.2). Patients younger than 75 (mean age 65) receiving daily aspirin had a primary event rate (ischemic stroke or systemic emboli) of 1.7% per year compared with 1.2% per year for patients receiving warfarin (mean INR = 2.7). The rates of major hemorrhage did not differ significantly between treatment groups (0.9% per year for patients taking aspirin compared with 1.7% per year for those receiving warfarin).

For SPAF-II patients greater than age 75 (mean age 80), the rate of primary events was substantially higher in both treatment groups. Patients in this older age group had an event rate of 4.8% per year on aspirin compared with 3.6% per year on warfarin (mean INR = 2.6). However, when intracranial bleeds were factored into the analysis, the annualized rate of all strokes (hemorrhagic and ischemic) with residual deficits was similar in patients assigned to aspirin (4.3%) compared to those receiving warfarin (4.6%). The rate of major hemorrhage with warfarin was higher in this older cohort of patients, averaging 4.2% per year compared with 1.6% per year in the aspirin group. Despite a similar intensity of anticoagulation, older patients on warfarin also had a higher rate of major bleeding (4.2% per yr) compared to younger patients who were also being anticoagulated (1.7% per yr).

Cost-Benefit Analysis

Gage and colleagues have examined the cost-effectiveness of prescribing oral anticoagulants to patients with and without additional stroke risk factors (history of previous stroke or TIA, diabetes, hypertension, or heart disease) (35). They concluded that, except for highly selected patients, warfarin therapy is unlikely to be cost-effective in patients less than 65 years old with NVAF as their only risk factor for stroke (lone AF).

Warfarin was ''cost-effective'' in medium-risk patients (one additional risk factor) by prolonging life at a cost of $8000 per quality-adjusted life-year, a relatively inexpensive intervention compared with other routine health practices, such as the treatment of hypertension. Warfarin was also ''cost-saving'' in high-risk NVAF patients (more than one additional risk factor) who have an annual stroke rate between 4.9 and 17.6%. Because Gage and colleagues used a base case for their analysis that was 65 years of age, attempts to extend their findings to patients older than 65 may be invalid because the risk/benefit ratio may vary considerably in older patients.

Treatment Recommendations for NVAF Patients

The fourth ACCP Consensus Conference on Antithrombotic Therapy (36) considered the following variables to be important in stratifying risk in patients with NVAF: mitral steno-

sis, prosthetic heart valves, previous stroke or TIA, congestive heart failure, hypertension, diabetes, clinical coronary artery disease, and thyrotoxicosis. Regardless of age, patients with NVAF and other associated risk factors for stroke should be treated with warfarin. Specific recommendations for NVAF patients without associated risk factors depend on the patient's age. Patients younger than 65 without specific clinical or echocardiographic risk factors have a low risk of stroke and do not require long-term anticoagulation. Patients between ages 65 and 75 who are without risk factors can be treated with either aspirin or warfarin. NVAF patients age 75 years or older, regardless of the presence of other risk factors, should be treated with warfarin. The decision to use warfarin in patients over 75 years of age should take into account the patient's comorbidities and the probability of an age-related increase in the rate of serious bleeding complications. Anticoagulant therapy should be closely monitored so as to maintain the INR between 2 and 3. In patients who have contraindications to warfarin, 325 mg of aspirin is recommended. Based on the results of the SPAF-III study, combination therapy with aspirin and low-intensity warfarin (INR $\leq$ 1.5) does not appear to be beneficial as a stroke-prevention strategy. Questions about optimal dosing, patient selection, and the possible role of other antiplatelet agents, such as ticlopidine or clopidogrel, remain unanswered.

There is room for caution in generalizing the results of the NVAF clinical trials and applying them to typical practice settings. For example, up to 40% of the patients screened for randomization in these studies were excluded because of contraindications; if these patients are treated in clinical practice settings, risk/benefit ratios will undoubtedly be affected. Second, the risk of bleeding may vary significantly if patients on warfarin do not receive the type of regular follow-up and careful monitoring characteristic of these studies. Third, because the longest follow-up period for any of these clinical trials was only slightly more than 2.5 years, we can only speculate about the longer term risks of hemorrhage in patients who are chronically receiving oral anticoagulants. Fourth, because all of these trials, with the exception of AFASAK, enrolled an overwhelming proportion of male subjects, we should exercise caution in extrapolating these results to elderly female patients. Finally, the hemorrhagic risk noted in NVAF patients may not be directly applicable to other patients with different indications for anticoagulation, such as those with venous thromboembolism or ischemic cerebral vascular disease (37).

Anticoagulation and Cardioversion

The risk of thromboembolic events associated with elective cardioversion of atrial fibrillation to sinus rhythm is significantly reduced with anticoagulation (38). Bjerkelund and Orning noted that electrical cardioversion without anticoagulation resulted in a 5.3% incidence of emboli compared with an incidence of 0.8% in patients receiving anticoagulants (39).

For patients with the onset of atrial fibrillation or atrial flutter within the preceding 24 to 48 h, anticoagulant therapy before elective cardioversion is usually not necessary. ACCP Consensus Conference guidelines recommend that patients with atrial fibrillation or flutter of uncertain duration, or onset $>$ 48 h, should be anticoagulated with warfarin (INR 2–3) for 3 weeks before elective cardioversion (either electrical or pharmacological) and continued on oral anticoagulants until normal sinus rhythm has been maintained for 4 weeks (36).

The rationale for precardioversion anticoagulation appears to be related to thrombus resolution and prevention of new thrombus formation rather than to organization and/or

adherence of existing thrombus (40). Collins provided evidence to support this hypothesis by performing serial TEEs on 14 patients after atrial thrombi (5–20 mm) were noted on an initial echocardiographic study. After a median of 4 weeks of therapy with warfarin, 89% of these thrombi had completely resolved and no new thrombi were formed.

Postcardioversion ''stunning'' of the atria and atrial appendage and the delayed return of effective atrial contraction mandate that anticoagulants be continued for 4 weeks after the successful restoration of sinus rhythm (38). The recommendation to discontinue anticoagulants at that time should be reconsidered in light of the fact that only a minority of patients remain in sinus rhythm at 1 year. A large-scale prospective study by Van Gelder and colleagues on the long-term outcome of electrical cardioversion to manage chronic AF determined that the actuarial cumulative percentage of patients who maintained NSR after serial cardioversion attempts was 42% at 1 year and only 27% after 4 years (41). Multivariate analysis showed that the factors associated with failure to maintain NSR included duration of atrial fibrillation $>$ 36 months [risk ratio (RR) 5.0], functional class III to IV exercise tolerance (RR = 1.5), and age $>$ 56 years (RR = 1.5). Duration of atrial fibrillation as short as 3 months was inversely correlated with the chance of reinstitution of sinus rhythm. The decision to discontinue anticoagulation in patients who maintain normal sinus rhythm 4 weeks after elective cardioversion needs to be individualized according to the patient's risk factors for stroke and the likelihood that they will develop recurrent atrial fibrillation or flutter.

In a retrospective review of patients who underwent elective cardioversion, Schlicht and colleagues noted that physicians failed to follow at least one of the ACCP guidelines for pre/post anticoagulation at least 35% of the time (42). The majority of these cases involved failure to administer anticoagulants to patients for 3 weeks before cardioversion.

Role of Transesophageal Echocardiography in Precardioversion Screening

What is the role of TEE in screening precardioversion patients for the presence of left atrial thrombi and thereby guiding decisions about anticoagulant therapy? Based on their experience with patients who underwent DC cardioversion without adverse effects, Manning and colleagues reported that a prolonged course of oral anticoagulation was not necessary in patients with AF of unknown or prolonged duration if the precardioversion TEE excluded the presence of atrial thrombi (43). Over a period of 4.5 years, all patients who were admitted to the hospital with AF were screened and included in their study protocol if the duration of AF was $>$ 2 days or unknown. All patients (mean age 73 years) received initial anticoagulation with either warfarin or heparin and underwent transthoracic echo followed by TEE. Cardioversion was deferred in 34 patients (15%) who had atrial thrombi noted on TEE. Of the 196 patients without atrial thrombi, 95% had successful cardioversion to sinus rhythm and none experienced a clinical thromboembolic event.

Since the resolution of TEE is no better than 2 mm, the apparent exclusion of atrial thrombi by this technique does not guarantee that cardioversion without pretreatment anticoagulation will be risk-free (44). Black and colleagues identified 17 patients with negative TEE who developed systemic emboli during a period 2 to 7 days postcardioversion (45). Subsequently, a pooled analysis of 25 trials by Moreyra and colleagues demonstrated that the risk of thromboembolism using TEE guidance was 1.3% compared with 0.3% using traditional precardioversion anticoagulation (46). Thus, it appears that even with a negative

TEE study, NVAF patients may be at some risk, albeit small, if they are not anticoagulated before elective cardioversion.

At this time, TEE is not recommended for routine screening of precardioversion patients to determine their need for prophylactic anticoagulation. ACC/AHA guidelines for the use of TEE before elective cardioversion are summarized in Table 3 (47).

Valvular Heart Disease and Prosthetic Heart Valves

Native Valve Disease

Patients with rheumatic mitral valve disease complicated by episodes of systemic embolism, chronic or paroxysmal atrial fibrillation, or echocardiographic evidence of left atrial size greater than 55 mm are candidates for long-term anticoagulation (48). Patients with isolated aortic valvular disease usually have a low risk of systemic embolism; routine anticoagulation of such patients is not recommended (48).

Prosthetic Heart Valves

Because many elderly patients with valvular heart disease may eventually be candidates for valve replacement surgery, the subject of anticoagulating patients with either tissue heart valves or mechanical prostheses deserves attention. By obviating the need for long-term anticoagulation, bioprosthetic heart valves (tissue valves) may appear to offer a special advantage over mechanical heart valves in the elderly. However, when making the decision about which type of prosthesis to implant, clinicians must carefully weigh the potential risks of warfarin-induced hemorrhagic complications against the long-term durability of tissue valves. Bioprosthetic valves carry the potential for tissue degeneration, valve dysfunction, and the need for subsequent reoperation to place a second prosthesis (49).

Table 3 ACC/AHA Guidelines for Precardioversion TEE

Indicated
Urgent cardioversion but extended period of anticoagulation not desirable
Prior cardioembolic event thought to be related to intra-atrial thrombus
Anticoagulation contraindicated and a decision for cardioversion will be influenced by the TEE results
Previously demonstrated intra-atrial thrombus
Decision about cardioversion based on knowledge of prognostic factors (mitral valve disease, LV dysfunction)
Atrial fibrillation of $<$ 48 h and other heart disease is present
Not Indicated
Atrial fibrillation $<$ 48 h duration and no other heart disease
Patient anticoagulated long-term at therapeutic level
Atrial flutter
Emergency cardioversion deemed necessary
Previous TEE and no clinical suspicion of an interval change

Source: From Refs. 47 and 44.

Bioprosthetic (tissue) valves. Long-term anticoagulant use is not necessary in patients who are in sinus rhythm and who have a bioprosthetic valve in the aortic position (50). All patients with a bioprosthesis in the mitral position should be anticoagulated for the first 3 months after valve insertion (50,51). Patients with a bioprosthesis in either position who have a history of thromboembolism, left atrial thrombus at the time of surgery, or atrial fibrillation should be treated with long-term anticoagulation (50).

Mechanical heart valves. Chronic anticoagulation with warfarin is recommended for all patients with mechanical heart valves. In a prospective study of patients with mechanical heart valves, Mok has shown a relative risk reduction of 60 to 79% in the incidence of thromboembolism in warfarin-treated patients compared to those who received either dipyramidole-aspirin or pentoxifylline-aspirin (52).

Optimal Intensity of Treatment

Turpie and colleagues randomly assigned 284 consecutive patients (mean age 62.3 years, 53% male) with tissue heart valves to receive either less intense (INR = 2.0–2.3) or more intense (INR = 2.5–4.0) treatment regimens with oral anticoagulants (51). Although the incidence of embolic complications was the same in each arm of the study, only 6 of 102 patients (6%) in the less intense treatment group experienced hemorrhagic complications compared with 15 of 108 patients (14%) receiving more intense levels of anticoagulation. All five patients with major bleeding complications were in the more intense treatment group.

Altman and colleagues evaluated 99 patients (mean age 52, 72% male) with mechanical heart valves and compared groups receiving less intense (INR 2–3) and more intense levels of anticoagulation (INR 3–4.5) for evidence of thromboembolic and hemorrhagic complications (53). A direct comparison of their results with those of other investigators is complicated by the fact that all patients in this study received concurrent treatment with 330 mg of aspirin and 75 mg of dipyramidole twice each day. The frequency of thromboembolism was equal in both groups. Two of 51 patients (3.9%) in the less intense treatment regimen experienced bleeding complications (3.8 events per 100 patient years of follow-up) compared with 10 of 48 patients (20.8%) in the more intense treatment group (24.7 events per 100 patient years of follow-up).

Pengo and colleagues studied 205 patients who had undergone mechanical heart valve replacement surgery at least 6 months earlier (54). Patients (mean age 59 years) were randomized to either moderate intensity anticoagulation (target INR = 3, mean achieved INR = 3.06) or moderate-high intensity therapy (target INR = 4, mean achieved INR = 3.67) and followed for a mean of 3 years. Both major bleeding rates (1.2 vs. 3.8 per 100 patient years) and minor bleeding rates (26 vs. 43 per 100 patient years) were significantly less in the moderate intensity group. The number of thromboembolic complications (all transient ischemic attacks) and vascular deaths did not differ between the treatment groups. Based on these results, the authors suggested that a target INR of 3.0 was appropriate for patients with mechanical heart valves.

Acar and colleagues studied 380 patients (mean age 59 years) who were randomized to low-dose vs. ''standard-dose'' anticoagulation after single heart valve replacement surgery. Patients were treated postoperatively with acenocoumarol and followed for a mean of 2.2 years (55). Subjects in this study were in normal sinus rhythm with a left atrial diameter < 50 mm; the vast majority had a St. Jude's prosthesis placed in the aortic

position. Patients in the low-dose treatment arm [target INR of 2–3 (mean of median values = 2.74)] experienced 10 thromboembolic complications compared to nine events in patients receiving ''standard-dose'' anticoagulation [target INR of 3.0–4.5 (mean of median values = 3.21)]. While total hemorrhagic complications (major + minor bleeding) were higher in the 3.0 to 4.5 INR group (56 patients vs. 34 patients), major bleeding rates did not differ significantly between the two groups. Based on these results, Acar and colleagues concluded that, in selected patients with mechanical prostheses, anticoagulation with a target range INR of 2 to 3 reduces the incidence of hemorrhagic events while preventing thromboembolic complications as effectively as more intense regimens of anticoagulation.

Cannegieter and colleagues attempted to determine the optimal intensity of oral anticoagulant therapy for patients with mechanical heart valves by calculating the incidence of both thromboembolism and bleeding at every level of anticoagulation (56). A total of 1608 patients were followed for 6475 patient years. Cerebral embolism occurred in 43 patients (0.68 per 100 patient years), major extracranial bleeding occurred in 128 patients (2.1 per 100 patient years), and 36 patients experienced intracranial and spinal bleeding (0.57 per 100 patient years). The authors determined that the optimal intensity of anticoagulation (the lowest incidence of both thromboembolic and hemorrhagic complications) was achieved when the INR was between 2.5 to 4.9. Patient age, the type of prosthesis, and the implantation site (aortic, mitral, both) influenced the estimation of the optimal intensity of anticoagulation. Subjects over age 70 had an increased risk of bleeding. Characteristics associated with a lower risk of thromboembolism included: age younger than 50, prosthetic valve in the aortic position, and a bileaflet valve. Conversely, patients with older valves, especially those in the mitral position, had a higher risk of thrombotic complications; for such patients, an INR of 3.0 should be considered a minimally acceptable level of anticoagulation.

Taken as a group, these studies support the current guidelines from the fourth ACCP Consensus Conference on Antithrombotic Therapy which recommended that patients with mechanical heart valves should be anticoagulated to achieve an INR between 2.5–3.5 (50).

Combined Therapy with Warfarin Plus Aspirin

In a large-scale, double-blind, placebo-controlled, randomized clinical trial, Turpie and colleagues assessed the efficacy and safety of adding 100 mg of aspirin to warfarin (target INR 3.0–4.5) in 370 patients with mechanical heart valves or ''high-risk'' bioprostheses (preoperative atrial fibrillation or a history of thromboembolism) (57). Table 4 summarizes the striking risk reductions that were achieved during the follow-up period (average 2.5 years) by adding this small dose of aspirin to full-dose anticoagulation (mean achieved INR = 3.0) The annualized rate of major systemic embolism or death was decreased by 65% in the warfarin plus aspirin group (4.2% vs. 11.6%; $p < 0.001$). As expected, the incidence of minor bleeding complications (hematuria, epistaxis, bruising) was significantly increased in the warfarin plus aspirin group (35% per year) compared to the warfarin plus placebo group (22% per year). However, there was no significant increase in the risk of major bleeding (Hgb decrease > 2 g, blood transfusion of ≥ 2 units, or any intracranial, intraocular, intra-articular, or retroperitoneal bleed). Major hemorrhagic events occurred in a total of 43 patients, 19 in the warfarin plus placebo group (6.6% per year) and 24 in the warfarin plus aspirin group (8.5% per year). Turpie concluded that, although there was some increase in bleeding, the risk of combined treatment was more than offset by

Table 4 Outcome Analysis for Treatment with Warfarin Plus Aspirin in Heart Valve Patients

Outcome	Aspirin (n = 186) annualized		Placebo (n = 184) annualized			
	No. of events	Event rate %	No. of events	Event rate %	p value	Observed risk reduction % (95% CI)
Major systemic embolism or death from vascular causes	6	1.9	24	8.5	<0.001	77 (44–91)
Major systemic embolism, non-fatal intracranial hemorrhage, death from hemorrhage, or death from vascular causes	12	3.9	28	9.9	0.005	61 (24–80)
Major systemic embolism or death	13	4.2	33	11.6	<0.001	65 (33–82)
Death	9	2.8	22	7.4	0.01	63 (19–83)

Source: From Ref. 57.

its considerable benefit. Whether combination therapy of this sort will benefit other patients with different indications for long-term anticoagulation is the focus of ongoing research.

Ischemic Heart Disease

As many as 1.5 million Americans suffer myocardial infarctions (MI) each year, with over half of these events occurring in patients older than 65 years of age (58). While clinicians now widely accept the critical role that thrombosis plays in the vast majority of MI patients (59), the debate of the past 30 years over the role of long-term anticoagulation in post-MI patients continues.

Chronic Anticoagulation in Postmyocardial Infarction Patients

Jafri and colleagues recently reviewed the results of 12 large-scale randomized clinical trials that evaluated the role of long-term anticoagulation in the chronic management of post-MI patients (60). While two-thirds of these studies showed significant decreases in either mortality, reinfarction, or embolic events, direct comparisons of patient groups and/or pooling of study results was not possible because of substantial differences in study design, entry criteria, and treatment protocols. Three studies that address issues relevant to the management of elderly post-MI patients are reviewed in more detail in the following paragraphs.

The *Sixty Plus Reinfarction Trial* was a double-blind, multicenter study designed to assess the efficacy of long-term anticoagulation after myocardial infarction in patients over 60 years of age (61,62). In this study, investigators from the Netherlands evaluated 878 patients (mean age 67.6 years) who had already received oral anticoagulants for at least 6 months following their first transmural MI. Subjects were randomized at entry to an intervention group that continued oral anticoagulation or a control group that was placed on placebo. Two-year mortality was significantly lower in the group receiving anticoagula-

tion (7.6%) compared to the group receiving placebo (13.4%). The incidence of recurrent myocardial infarction was also significantly lower in the treatment group (5.7%) compared to the control group (15.9%). Although both major and minor bleeding episodes were more frequent in the group receiving anticoagulation, about 75% of these occurred when the prothrombin time was excessively prolonged.

The *Norwegian Warfarin Re-Infarction Study* (WARIS) was a more contemporary clinical trial designed to evaluate the effect of warfarin on mortality and reinfarction in patients who were recovering from an acute MI (63). Smith and colleagues enrolled over 1200 patients (mean age 61 years) in this double-blind, placebo-controlled trial at a mean interval of 27 days post-MI. After randomization to placebo or adjusted dose warfarin (target INR 2.8–4.2), patients were followed for an average of 37 months. Using an ''intention to treat'' analysis, the warfarin-treated group had the following risk reductions compared to placebo: death decreased by 24%, reinfarction decreased by 34%, and strokes decreased by 55%. These highly significant results were achieved with a combined incidence of major bleeding that was calculated at 0.6% per year.

More recently, the ASPECT trial (*Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis*) evaluated the effect of long-term anticoagulant treatment on cardiovascular morbidity and mortality after myocardial infarction (64). In this double-blind, placebo-controlled, multicenter trial from the Netherlands, over 3400 patients (mean age 61 years) were randomized to placebo vs. anticoagulant therapy (target INR 2.8–4.8) within 6 weeks of hospitalization for an acute MI. During the mean follow-up period of 37 months, patients receiving anticoagulants (either nicoumalone or phenprocoumon) had a significant reduction in the incidence of recurrent myocardial infarction (2.3 vs. 5.1 per 100 patient-years), but overall mortality did not differ between the two groups (3.2 vs. 3.6 per 100 patient years). Major bleeding was more common in patients receiving anticoagulants than in those receiving placebo (1.4% vs. 0.4% per 100 patient years); gastrointestinal bleeding accounted for about half of all extracranial bleeding episodes.

Lack of a well-designed clinical trial directly comparing warfarin to aspirin in post-MI patients has made it difficult to assess the relative merits of these two drugs. A pooled analysis of post-MI studies by the Antiplatelet Trialists Group showed a 12% reduction in mortality, a 31% reduction in myocardial infarction, and a 39% reduction in strokes in aspirin-treated patients (65). Pooled results of anticoagulant trials in post-MI patients demonstrated a 19% mortality reduction and a 44% reduction in both myocardial infarction and stroke (66). Pending the results of ongoing clinical trials that are evaluating head-to-head comparisons of warfarin vs. aspirin, we recommend that clinicians follow current ACC/AHA guidelines for anticoagulating patients after myocardial infarction (67) (Table 5).

Combination Therapy with Warfarin Plus Aspirin

A 13-year primary prevention trial of 5085 British men has recently shown that the chance of a first myocardial infarction was reduced by one-third when men at high risk for ischemic heart disease took small doses of aspirin combined with warfarin (68). Subjects randomized to receive aspirin (75 mg daily) plus warfarin (4.1 mg) had a 34% lower risk of first MI compared to a 20% decrease in those who took only aspirin and a 21% decrease in those who took only warfarin. There were 12 fatal cerebral events in those taking ASA and warfarin compared to only one such event in the placebo group. The authors estimated that for every 12 myocardial infarctions that were avoided, one fatal hemorrhagic stroke would occur.

Table 5 ACC/AHA Guidelines for Anticoagulation After Myocardial Infarction

Class I recommendations[a]
Post-MI patients with persistent atrial fibrillation
Post-MI patients with evidence of left ventricular mural thrombus
Secondary prevention of MI in postinfarct patients who are unable to take daily aspirin
Class IIa recommendations[a]
Post-MI patients with extensive wall motion abnormalities
Post-MI patients with paroxysmal atrial fibrillation
Class IIb recommendations[a]
Post-MI patients with LV systolic dysfunction, with or without congestive heart failure

[a] Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.

[b] Conditions for which there is conflicting evidence and/or a divergence of opinion about then usefulness/efficacy of a procedure or treatment. II*a*—weight of evidence or opinion is in favor of usefulness/efficacy. II*b*—usefulness/efficacy is less well established by evidence/opinion.

Source: Ref. 67.

These results conflict with those of the Coumadin Aspirin Reinfarction Study (CARS), a secondary prevention trial, in which 8803 post-MI patients were randomly assigned to one of three treatment groups; 160 mg aspirin daily; 3 mg warfarin plus 80 mg aspirin; or 1 mg warfarin plus 80 mg aspirin daily (69). Primary outcome events (reinfarction, nonfatal ischemic stroke, or cardiovascular death) averaged 8.4 to 8.8% per year and did not differ significantly between the treatment groups. The risk of spontaneous major hemorrhage was low in all treatment groups averaging 0.7% per year in the aspirin group compared with 1.4% per year in the group receiving 3 mg warfarin plus 80 mg aspirin (mean INR at 6 months = 1.19). During the follow-up period (maximum of 33 months, median of 14 months) no benefit was found from combining warfarin with aspirin compared to a regimen of aspirin alone. The lower dose of warfarin used in this study may explain the discrepant results between CARS and the British primary prevention trial noted above.

The Combination Hemotherapy and Mortality Prevention Study (CHAMPS) is another large-scale (projected enrollment 8000) secondary prevention trial of oral anticoagulation vs. aspirin in post-MI patients (70). In this ongoing study whose primary outcome is all-cause mortality, patients with a recent MI (<14 days) are being randomized to receive either 162 mg aspirin per day or 81 mg aspirin per day plus warfarin adjusted to maintain the INR between 1.5 and 2.5. Further studies such as this will be needed to help clinicians develop optimal strategies for preventing cardiovascular morbidity and mortality after MI.

Warfarin Use in Patients with Coronary Stents and Coronary Artery Bypass Graft (CABG) Surgery

Schomig and colleagues recently compared clinical outcomes 30 days after coronary artery stenting in patients receiving antiplatelet therapy vs. those receiving conventional anticoagulation (71). After successful placement of Palmaz-Schatz stents, all patients (mean

age 61.5 years) received a continuous heparin infusion (dose adjusted to achieved aPTT between 80–100 s) and 100 mg of aspirin twice daily. In the 257 patients randomized to antiplatelet therapy, ticlopidine (250 mg bid) was started immediately after the procedure and heparin was discontinued 12 h later. In the 260 patients randomized to anticoagulant therapy, warfarin was started immediately after stent placement with dose adjustments to maintain the INR between 3.5 and 4.5. Heparin was continued in this group for 5 to 10 days, until a stable level of anticoagulation was achieved. Hemorrhagic complications occurred in 6.5% of the patients, all of them in the group receiving warfarin. Of the patients assigned to antiplatelet therapy, there was an 82% reduction in the risk of myocardial infarction, a 78% reduction in the need for reintervention [CABG or repeat percutaneous transluminal coronary angioplasty (PTCA)] and an 87% reduction in the risk of peripheral vascular events. Occlusion of the stented vessel occurred in 0.8% of the antiplatelet group and 5.4% of the anticoagulated group. The authors concluded that, compared to conventional anticoagulant therapy, combined antiplatelet therapy with aspirin and ticlopidine for 4 weeks after placement of coronary artery stents reduced the incidence of cardiac events as well as hemorrhagic and vascular complications. There appears to be no role for long-term anticoagulation in patients who have undergone successful deployment of coronary artery stents. Despite the early benefits of combined antiplatelet therapy, angiographic follow-up at 6 months showed equivalent rates of restenosis (26.8% in the combined antiplatelet treatment group vs. 28.9% in the anticoagulant treatment group (72).

Does long-term anticoagulation have a role to play in reducing graft occlusions and decreasing cardiovascular morbidity and mortality in patients who have undergone CABG surgery (73)? A recent study by the Post Coronary Artery Bypass Graft trial investigators concluded that, unlike aggressive lowering of LDL cholesterol below 100 mg/dL, low-dose warfarin (mean INR 1.40) plus 81 mg aspirin daily did not significantly reduce the angiographic progression of atherosclerosis in bypass grafts (74). Questions as to whether a higher target INR or earlier initiation of warfarin therapy would make anticoagulant treatment more effective have not been addressed in any placebo-controlled clinical trials.

Left Ventricular Thrombus

The risk of systemic embolism (SE) is highest in the first few days following an acute myocardial infarction with two-thirds of all SE occurring in the first week post-MI (75). Patients at highest risk for the development of SE include those with transmural anterior wall MIs who display evidence of akinesis or dyskinesis of the cardiac apex, regardless of whether these findings are associated with a left ventricular mural thrombus.

Johannsen and colleagues studied a large group of patients with anterior wall MIs and found that, in addition to thrombus mobility and protuberance, patients older than age 68 years were at significant risk for subsequent embolization (76). While Stratton and Resnick also confirmed that thrombus protrusion and mobility were predictive of embolization, they did not uncover any clinical features, including age, that distinguished those patients with thrombus who were more likely to embolize (77).

Current ACC/AHA guidelines for anticoagulating patients after myocardial infarction including those with left ventricular mural thrombi and extensive wall motion abnormalities are summarized in Table 5 (67).

Dilated Congestive Cardiomyopathy

Besides the setting of acute myocardial infarctions that involve the cardiac apex, idiopathic dilated cardiomyopathy (IDC) is another substrate for the formation of left ventricular

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mural thrombi. Whether patients with IDC should receive prophylactic anticoagulation to prevent systemic emboli is a matter of ongoing clinical debate.

Fuster and colleagues evaluated 104 patients with IDC diagnosed on the basis of clinical and angiographic data (78). Univariate analysis at the time of diagnosis revealed that age greater than 55 was one of three factors that was highly predictive of poor clinical outcome, the other two being cardiothoracic ratio on chest x-ray > 0.55 and cardiac index < 3.0 L/min/m^2 measured at the time of cardiac catheterization. Systemic emboli occurred in 19 of 103 patients not receiving long-term anticoagulation, an event rate of 3.5 emboli per 100 patient years of follow-up. Conversely, no embolic events or major hemorrhagic complications were noted in 32 patients who were maintained on long-term anticoagulation during 101 patient years of exposure.

Baker and Wright recently reviewed the issue of anticoagulating patients with heart failure due to left ventricular systolic dysfunction (79). The incidence of arterial embolism or stroke in untreated patients ranged from 0.9 to 5.5% per 100 patient years, with the largest studies reporting an incidence of 2.0% and 2.4%. Thromboembolic events appeared to increase somewhat as the ejection fraction declined, but this analysis was confounded by a higher prevalence of atrial fibrillation in patients with more severe left ventricular dysfunction. Because no controlled clinical trials have adequately assessed the efficacy and risks of anticoagulating CHF patients who remain in normal sinus rhythm, the authors concluded that such patients should not be routinely treated with warfarin. Until better evidence is available, clinicians and their patients must continue to make individual decisions about the potential risks and benefits of using anticoagulants in this clinical setting.

Ischemic Cerebral Vascular Disease

Disabling strokes are among the most common and feared illnesses of the elderly (80). Based on data from Framingham, it has been estimated that approximately 500,000 Americans suffer strokes each year (81). While long-term anticoagulation is clearly beneficial in preventing strokes in those patients with atrial fibrillation (7–14), NVAF patients comprise only a small percentage of the total stroke population (82). Eighty-five percent of acute strokes are attributable to cerebral infarctions, the vast majority secondary to atherothrombotic cerebral vascular disease (81,82). Even though it is well accepted that thrombosis plays a central role in the pathophysiology of ischemic stroke and that, in selected patients, early administration of lytic therapy may prevent the irreversible consequences of a brain attack, the role of antithrombotic therapy in this large group of patients remains largely unsettled.

Unstable or Progressing Thrombotic Stroke

Although a few small studies have shown favorable trends, there is no convincing evidence from large-scale clinical trials to support the use of routine anticoagulation in patients with unstable or progressing thrombotic strokes (82). Nonetheless, some clinicians feel that an ischemic stroke that progresses, or one that has a fluctuating clinical course, may be an indication for acute anticoagulation with heparin. Treatment of such ''strokes in evolution'' is typically reserved for patients who display progressive deterioration within 48 h of stroke onset and who have no other apparent cause to explain their clinical course (80).

Cardioembolic Stroke

In the setting of an acute cardioembolic stroke, the use of intravenous heparin to prevent an early recurrent neurological event should be considered empiric. It is recommended that heparin followed by warfarin (target INR 2–3) be instituted in nonhypertensive patients with small-to-moderate sized embolic strokes only after a CT scan done 48 h or more after stroke onset documents the absence of spontaneous bleeding. Anticoagulation should be postponed 5 to 14 days in patients with large embolic strokes because of a predisposition for these patients to develop hemorrhagic transformations. In patients with atrial fibrillation as the presumed embolic source, initiation of warfarin therapy (following CT scan $>$ 48 h) without initial heparin therapy is reasonable in view of the relatively low risk of early embolic recurrences (82). If there are no specific contraindications to anticoagulation, patients with a potential cardiac source for cerebral emboli should be considered candidates for long-term prophylaxis with warfarin (83) (Table 6).

Transient Ischemic Attack

The annual U.S. incidence of transient ischemic attacks (TIAs) is 1 per 1000 in patients over 55 years of age (82). Despite the fact that TIA patients face a 10% annual risk of stroke or death, anticoagulants are not routinely recommended in this setting (82). The few randomized clinical trials that have evaluated the risks and benefits of anticoagulating TIA patients have enrolled small numbers of subjects and produced conflicting results (82).

Oral anticoagulants are often administered empirically to TIA patients who are judged to be at high risk for stroke (84–87). Such patients include those who: (1) fail treatment with antiplatelet aggregating drugs; (2) develop crescendo symptoms; (3) have high-grade narrowing of intracranial arteries; and/or (4) have symptoms that reflect brain stem ischemia. No current data support or refute the use of warfarin in these settings.

Table 6 Risk Factors for Cardiogenic Emboli That May be Ameliorated by Long-Term Anticoagulatiion

Major Risk Factors
Atrial fibrillation
Mitral stenosis
Prosthetic heart valves (mechanical $\gg$ bioprostheses)
Recent myocardial infarction (within past 3 months, especially if LV apex involved)
LV thrombus (especially if mobile, protruding)
Dilated cardiomyopathy (LV EFx $<$35%)
Minor Risk Factors
Severe mitral annular calcification
Patent foramen ovale
Atrial septal aneurysm
LV wall motion abnormalities
Aortic arch atheromatous plaques
Spontaneous echo contrast on TEE

Source: Adapted from Refs. 83 and 89.

A recent national survey examined the stroke prevention practices of 2000 U.S. physicians and reported that long-term anticoagulant use was higher for three subgroups of patients: (1) those with more than 70% stenosis of the extracranial carotid artery (compared to those with 50–70% stenosis); (2) those with symptoms of a recent TIA or minor stroke (compared to asymptomatic patients); and (3) those who had surgical contraindications (compared to those who did not) (88). One should note, however, that most physicians still used aspirin or other antiplatelet agents regardless of the degree of carotid stenosis, symptom status, or the presence of surgical contraindications.

Current guidelines from the Stroke Council of the American Heart Association recommend that, pending the results of ongoing clinical trials, prolonged anticoagulation not be routinely carried out in patients with TIA or minor stroke due to cerebrovascular disease (89). Warfarin therapy is an acceptable option in patients who develop a TIA or stroke during aspirin therapy or those who have a contraindication to aspirin.

The decision to anticoagulate patients with ischemic cerebral vascular disease should be balanced by an appreciation of the risk of serious, and potentially fatal, bleeding complications. ISCOAT investigators noted that patients being anticoagulated for arterial vascular disease (peripheral vascular and/or cerebral vascular disease) had a higher frequency of bleeding (12.5 per 100 patient years of follow-up) compared to patients being treated for venous thrombolic event (VTE) or other indications (6.8–7.1 per 100 patient years of follow-up) (90). Using a pooled analysis of the results from multiple published studies, Levine and colleagues also found an increased risk of major and fatal bleeding events in patients who were being anticoagulated for ischemic cerebral vascular disease compared to patients with other indications for treatment (37). Increased rates of fatal bleeding are presumably due to higher rates of intracerebral bleeding; these, in turn, may be related to associated hypertension or underlying cerebrovascular disease per se (37).

Peripheral Vascular Disease

Symptomatic occlusive peripheral vascular disease (PVD) occurs in 2 to 3% of all men and 1% of all women over age 50 to 65 (91). The decision to anticoagulate such patients should take into account the morbidity directly related to PVD as well as the morbidity and mortality related to associated cardiovascular disease. Using a prospective cohort study design, Criqui and colleagues followed 67 patients with PVD over a 10-year period (92). After multivariate adjustments for age, sex, and other risk factors for cardiovascular disease, these investigators noted that the relative risk of death among subjects with large vessel peripheral arterial disease was 3.1 times higher than those who had no evidence of PVD. Additional analysis showed a 15-fold increase in mortality rates due to cardiovascular disease and CHD among subjects with large-vessel PVD.

At least two studies lend support to the decision to anticoagulate selected patients with PVD. In the first study, Kretschmer and colleagues randomized 88 patients with reversed autologous saphenous vein femoropopliteal bypasses and demonstrated significant benefit in maintaining bypass graft patency in patients receiving warfarin (93). At a mean follow-up of 30 months, 37% of the controls had bypass occlusions compared with only 18% of those on oral anticoagulants. However, 12% of the patients receiving long-term anticoagulation had to discontinue warfarin because of major bleeding complications.

In a second study by the same investigators, 119 patients (79% male, mean age 63.1 years) who had undergone elective femoropopliteal bypass surgery were randomized to receive treatment with either anticoagulants or placebo (94). During the follow-up period,

a total of 30 patients died, 10 (17%) in the warfarin group and 20 (34%) in the control group. Graft occlusions occurred in 28 patients, 11 (18%) in the warfarin group, and 17 (29%) in the control group. Further analysis showed that anticoagulation significantly influenced patient survival irrespective of graft performance, probably by decreasing fatal cardiovascular events. While it is premature to recommend long-term anticoagulation for all patients after femoral-popliteal bypass or other vascular reconstructions, these two studies provide suggestive evidence that anticoagulants may play an important role in preventing vascular-related morbidity and mortality. More specific recommendations should be forthcoming from a large VA cooperative trial that is evaluating the relative benefits of warfarin vs. aspirin in patients who have undergone lower extremity vascular reconstructive procedures.

Current guidelines from the 1995 ACCP Consensus Conference recommend that patients with PVD who suffer arterial thrombi or emboli should receive intravenous heparin in order to prevent clot propagation if surgical revascularization is delayed (95). Warfarin should then be administered in a dose sufficient to achieve a target INR of between 2.0 and 3.0.

Venous Thromboembolic Disease

The high frequency of VTE disease in elderly patients appears to be related to the coexistence of age-related comorbidities that serve as predisposing risk factors for thrombosis. For example, decreased mobility due to strokes, recent surgery (particularly orthopedic surgery of the hips and knees), or congestive heart failure may be prominent factors leading to stasis and thrombosis in some elderly patients. Others may have hypercoagulable states induced by malignancy (see below). Several predisposing risk factors are frequently present in the same patient; Anderson found that 80 to 85% of patients with an initial episode of deep venous thrombosis (DVT) or pulmonary emboli (PE) had at least three factors that placed them at increased risk for the development of VTE (96).

Randomized studies provide solid evidence that treatment with standard heparin followed by longer-term oral anticoagulation is effective in decreasing mortality in patients with pulmonary emboli (97) and in preventing recurrences in patients with proximal vein thrombosis or symptomatic calf vein thrombosis (98–100). For most patients with submassive DVT or PE heparin and warfarin can be started together on Day 1 and heparin therapy can be discontinued on Day 5 if the INR is therapeutic.

Hull and colleagues found that low-dose warfarin (INR of 2–2.3) provided the same degree of protection as more intense treatment regimens (INR 2.5–4.1) and that low-dose therapy was associated with a lower incidence of hemorrhagic complications (101). Ninety-six consecutive patients (56% $>$ 60 years, 56% male) with proximal-vein thrombosis received a standard course of intravenous heparin before being randomized to less intense or more intense oral anticoagulant treatment regimens. While both treatment groups experienced a similar incidence of recurrent thrombotic events, only 2 of 47 patients (4%) in the less intense treatment group developed hemorrhagic complications compared to 11 of 49 patients (22%) receiving more intense treatment with warfarin. All patients with major bleeding in this study (two in each group) had protimes that were prolonged beyond the target treatment range and each of these patients had an underlying predisposition to hemorrhage. Two patients who experienced serious bleeding had un-

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suspected duodenal ulcer disease while the other two patients with significant bleeding had recently undergone major surgery.

Duration of Therapy

Although the Fourth ACCP Consensus Conference on Antithrombotic Therapy recommended that warfarin be continued for at least 3 months after a first episode of DVT and/or PE, the optimal length of time that oral anticoagulants should be continued remains unsettled (102). Several recent studies provide additional guidance and clarification regarding the optimal duration of therapy for these treatment indications.

Schulman and colleagues performed a multicenter study comparing 6 weeks of oral anticoagulant therapy with 6 months of treatment; both groups had a target INR of 2.0 to 2.85 (103). After 2 years of follow-up, 80 recurrences were documented in the 6-week treatment group (18.1%) compared with 43 recurrences in the 6-month treatment group (9.5%; OR = 2.1). No difference was noted in mortality or the rate of major hemorrhagic complications between the two groups.

Levine and colleagues also evaluated the optimal duration of anticoagulant therapy by studying 214 patients with venographically confirmed acute proximal DVT. All patients in this study were thought to be at low risk for recurrence based on a normal IPG exam obtained 4 weeks after initial anticoagulant therapy was begun (104). At that point, patients were randomly allocated to receive placebo or 8 weeks of additional therapy with warfarin (INR of 2–3). All patients were classified as having either continuous or transient risk factors for VTE based on clinical characteristics that were present at the time of their initial thrombosis. For the purpose of this study, continuing risk factors included cancer, a history of previous VTE, or idiopathic thrombosis (no recognized clinical or laboratory risk factors). Although warfarin-treated patients had a lower rate of recurrence during the initial 8 weeks following randomization (0.9% vs. 8.6%), this treatment advantage was lost during the 11-month follow-up period. Recurrent events were strongly clustered in the group with continuing risk factors compared to the group with only transient risk factors (12.9% recurrence rate vs. 1.6%). Based on these results, Levine and colleagues concluded that 4 weeks of oral anticoagulation may be all that is required in patients without continuing risk factors; for others, the occurrence and clustering of events after stopping warfarin suggests that the potential for thrombogenesis is probably still present after 3 months. Other investigators have also suggested that a high level of thrombogenic activity may continue for at least 6 months after a first episode of DVT (105).

Prandoni and colleagues conducted a prospective, cohort study of 355 consecutive patients to determine the long-term clinical outcome of patients after a first episode of symptomatic venous thrombosis (106). The 5-year mortality rate of almost 30% was, in large part, attributable to cancer deaths (hazard ratio 8:1). The cumulative incidence of recurrent VTE and postthrombotic syndrome were 24.6% and 28%, respectively; the incidence of postthrombotic syndrome was strongly related to the development of ipsilateral recurrent DVTs. The high incidence of recurrent thrombotic events after cessation of oral anticoagulant therapy lends additional support to the argument that prolonged anticoagulant treatment should be considered in selected patients with VTE.

To address the issue of how to deal with recurrent DVT, Schulman and colleagues conducted a multicenter trial in which they randomly assigned 227 patients with a second DVT to receive either 6 months of oral anticoagulation vs. anticoagulant therapy that was

continued indefinitely (105). The target INR for both groups was 2.0 to 2.85. After 4 years of follow-up, the recurrence rate of VTE in the group assigned to 6 months of therapy was 20.7% compared with 2.6% in the group assigned to continuing therapy (RR = 8.0). There was no difference in mortality between the two groups; the risk of major hemorrhage was 2.7% in the 6-month group compared to 8.6% in the indefinite treatment group (RR = 0.3).

In the aggregate, these studies suggest that continuing anticoagulation beyond 3 months may be beneficial for some patients with an initial episode of VTE. Further work is needed to identify subgroups at high risk for recurrence and to determine whether mortality rates and the incidence of postthrombotic syndrome will be favorably influenced by a more prolonged course of treatment. At this time, patients with recurrent venous thrombosis or a continuing risk factor such as antithrombin III deficiency, Protein C or S deficiency, lupus anticoagulant, or malignancy should be treated indefinitely (102).

Risk Factors for Heparin-Induced Bleeding

Landefeld identified four factors that were independently related to the development of major bleeding complications in hospitalized patients who were being started on anticoagulation for various reasons (107). These factors included (1) heparin use in patients aged 60 or older; (2) supratherapeutic levels of anticoagulation with maximal prothrombin or partial thromboplastin time greater than 2 or more times the control value; (3) worsening liver dysfunction on therapy; and (4) the number of specific comorbid conditions (serious cardiac illness, liver dysfunction, renal insufficiency, cancer, or severe anemia).

In a recent review article, Hirsh identified four variables that have been reported to influence bleeding during treatment with heparin (108). These include the dose of heparin, the patient's anticoagulant response, the method of administration, and other patient-related factors including serious concurrent illnesses, chronic heavy consumption of alcohol, renal failure, age, and sex (109–111).

Several additional studies have specifically evaluated the risk for heparin-induced bleeding during treatment of acute venous thromboembolism. In the first study, Hull stratified patients with proximal venous thrombosis into high-or low-risk subgroups depending on the presence or absence of risk factors for bleeding (112). High-risk patients had one or more of the following characteristics: (1) surgery within the previous 14 days; (2) history of previous peptic ulcer disease; (3) bleeding into the gastrointestinal or genitourinary tract; (4) disorders predisposing the patient to bleeding; (5) thrombotic stroke within the previous 14 days; or (5) a platelet count less than 150,000. All patients received an i.v. bolus of 5000 units of unfractionated heparin followed by a continuous i.v. heparin infusion. Low-risk patients received an i.v. heparin dose of 40,000 units/24 h while high-risk patients received 30,000 units/24 h. Despite the fact that low-risk patients received a much higher daily dose of heparin, they experienced far fewer major bleeding episodes than high-risk patients who received a much lower dose of heparin. Major bleeding occurred in only 1% of the low-risk patients compared with 11% of the high-risk patients. All patients with major bleeding had an underlying predisposing cause. This study suggests that patient-related risk factors may be far more important than treatment-related risk factors in determining an individual's short-term risk for bleeding while receiving therapeutic doses of heparin.

Nieuwenhuis and colleagues identified four independent risk factors for heparin-induced bleeding in hospitalized patients who were receiving either unfractionated heparin

or low-molecular-weight heparin (LMWH) (dalteparin) (113). These risk factors included WHO performance status, a history of bleeding, recent trauma or surgery, and body surface area. In a subsequent, prospective, randomized clinical trial by the same investigators, only body surface area $< 2.2\ m^2$ (OR = 2.3) and malignancy (OR = 2.4) could be confirmed as independent risk factors for heparin-induced bleeding (114). An increased incidence of hemorrhage (combined major and minor bleeding) was also observed in patients treated with high doses of heparin, independent of the concomitant aPTT ratios.

Low-Molecular-Weight Heparin

Because of its longer plasma half-life and more predictable dose response, LMWH has several distinct advantages over the continuous intravenous administration of unfractionated heparin (UH) (115). Weight-adjusted doses of LMWH can be administered subcutaneously once or twice daily without the need for subsequent dose modification or laboratory monitoring. This ease of administration and a safety profile that is at least as good as UH make LMWH an attractive option for the treatment of VTE. Although not currently approved by the FDA for the treatment of established deep venous thrombosis or pulmonary emboli, several studies have already demonstrated the safety and efficacy of using LMWH to treat proximal deep venous thrombosis in an out-of-hospital setting. These studies may be particularly relevant to the care of elderly patients at home or in extended care facilities.

Levine and colleagues randomly assigned 253 patients with acute proximal DVT to receive i.v. unfractionated heparin in the hospital and 247 patients to receive LMWH (1 mg/kg enoxaparin subcutaneously twice per day) at home (116). Each patient received at least 5 days of heparin (either UH or LMWH). Warfarin was begun on day 2 and the study medication was discontinued when the target INR was maintained for at least 2 days. The incidence of recurrent thrombosis was similar in the treatment groups (5.3% in the LMWH group and 6.7% in the UH group). Five patients receiving LMWH experienced major bleeding complications compared with three patients receiving UH.

Using a similar study design, Koopman et al. randomly assigned 198 patients to adjusted-dose i.v. unfractionated heparin in hospital and 202 patients to fixed-dose subcutaneous LMWH (fraxiparin) administered at home (117). The incidence of recurrent thromboembolism was similar in the two groups (6.9% in the LMWH group and 8.9% in the group receiving standard heparin). Only one patient who received LMWH experienced major bleeding compared with four patients receiving UH. Both studies suggest that outpatient treatment of DVT with LMWH is at least as effective and safe as in-hospital treatment with UH.

Hormone Replacement Therapy and the Risk of VTE

The question of whether to withhold postmenopausal hormone replacement therapy (HRT) from women at risk for VTE is an important one to consider. Three large epidemiological studies have recently provided evidence to support a positive link between postmenopausal HRT and VTE (118–120).

The Boston Collaborative Drug Surveillance Project estimated a VTE risk of 3.2 per 10,000 woman years for current estrogen users compared with 0.9 for nonusers (118). The risk associated with HRT use also appeared to be dose dependent; the matched relative risk estimates for daily estrogen doses of 0.325 mg, 0.625 mg, and 1.25 mg or more daily

were 2.1, 3.3, and 6.9, respectively. Daly and colleagues also reported that the increased risk of VTE in current HRT users seemed to be concentrated in new users (119). Although the adjusted odds ratio for VTE was 3.5 in current users of HRT compared with nonusers, the number of extra cases attributable to HRT appears to be quite low, on the order of 1 in 5000 per year.

Using data from the Nurses Health Study, Grodstein and colleagues reported that current users of postmenopausal hormones also had an increased risk of PE (120). After adjusting for multiple risk factors, such as age and smoking status, the relative risk of PE associated with current postmenopausal hormone use was 2.1. However, the overall rate of PE was quite low with an absolute risk of 1.1 per 10,000 woman years. The authors estimated that among postmenopausal women aged 50–59, five additional PE cases per 100,000 person years could be attributable to current postmenopausal estrogen use.

Thus, while these studies demonstrate a two- to fourfold increase in VTE risk associated with the use of HRT (either estrogen alone or combined estrogen and progesterone), the absolute risk of VTE appears to be quite low. In terms of actual clinical practice, it seems prudent to take into account other risk factors for VTE (family history, previous DVT, gross obesity, prolonged immobilization), when weighing the risks and benefits of therapy (121). Additional management suggestions are summarized in Table 7.

DVT and Malignancy

The incidence of newly diagnosed malignancy is increased in patients with unexplained (idiopathic) VTE during the first year after the initial thromboembolic event (OR = 3.9–36) (122). Because of age-related increases in both the incidence of DVT and malignancy, several questions relevant to the management of VTE in elderly patients have been raised. Should all elderly patients who present with a spontaneous DVT or PE be worked up for an occult malignancy? If so, what should this work-up include?

In one study in which malignancy was diagnosed in patients who presented with an idiopathic DVT, all the patients with cancer had one or more abnormalities on either the history, physical exam, basic lab testing, or chest radiography (123). In other retrospective studies in which no extensive screening tests beyond the routine were performed, the incidence of newly diagnosed malignancy varied from 1.5 to 8.8%. Despite the fact that a higher incidence of occult malignancy (9.1–11.5%) was reported in studies that per-

Table 7 Suggested Use of HRT in Women with a History of Previous VTE or Known Thrombophilia[a]

Clinical setting	Suggested management strategy
Known thrombophilia	Avoid HRT use
Recent VTE (within past 2 yrs)	Either avoid HRT or use HRT in combination with warfarin (INR 2–3)
Remote VTE (>2 yrs)	Use of HRT is acceptable, especially if substantial benefits are expected

[a] Known thrombophilic states include AT-III deficiency, protein C deficiency, protein S deficiency, resistance to activated protein C (factor V Leiden), antiphospholipid antibody syndrome, and hyperhomocysteinemia.

Source: Adapted from Ref. 121.

formed more extensive screening procedures (122), it is not clear that a more aggressive search strategy utilizing CT scans, endoscopy, and/or tumor markers will improve overall morbidity and mortality.

Questions also remain as to whether VTE patients with malignancy are at greater risk for anticoagulant-induced bleeding. Using decision analysis, Sarasin and Eckman concluded that, in the setting of cancer-related hypercoagulability, vena caval filter placement was safer and more effective than anticoagulation, especially for patients who decided to pursue active treatment of their underlying malignancy (124). A more recent review by Bona and colleagues concluded that oral anticoagulation was not associated with a significant increase in the risk of major bleeding compared to the hemorrhagic risk in patients without cancer. However, the risk of recurrent thrombosis appeared to be higher in patients with underlying malignancy (125).

RISK FACTORS FOR ORAL ANTICOAGULANT-INDUCED BLEEDING

The risk of developing a major hemorrhagic complication attributable to long-term anticoagulation is influenced by multiple variables (126–128). These variables can be conveniently divided into patient-related and treatment-related risk factors. Patient-related risk factors for bleeding include advanced age, underlying indication for anticoagulation, noncompliance with the prescribed treatment program, and the presence of specific comorbid conditions such as GI bleeding (but not peptic ulcer disease alone), recurrent falls, previous stroke or cerebral vascular disease, hypertension (especially if uncontrolled), and renal insufficiency (126). Treatment-related risk factors for bleeding include the intensity, duration, and variability of anticoagulation as well as the adequacy of follow-up and monitoring (126). Increasing numbers of prescribed medications, especially the use of drugs that interfere with hemostasis (aspirin, nonsteroidal anti-inflammatory drugs), also increase the risk of bleeding (see below).

Does Advanced Age Confer Independent Risk for Bleeding?

Studies that contain information about age as an independent risk factor for the development of anticoagulant-induced hemorrhage report conflicting results (129–133).

Several studies refute the contention that age is an independent risk factor for anticoagulant-induced bleeding. Gurwitz and colleagues evaluated 321 patients with a mean age of 59 $\pm$ 16 years (range 13–92 years) who were followed in the outpatient anticoagulation clinic of a university hospital (129). Over the 8-year period (1978–1986) of this retrospective study, 4.4% of the patients developed major bleeding complications and 19% developed minor bleeding events. No significant differences in the risk of initial major or minor bleeding complications were observed between four age groups ($<$50, 50–59, 60–69, 70$>$) despite the fact that these groups varied significantly in the distribution of underlying indications for anticoagulation (AF alone, AF with stroke, PE, prosthetic heart valve). A multivariate regression analysis confirmed the lack of association between age and bleeding events.

Fihn and colleagues found that patient age was a much weaker predictor of bleeding than the intensity of anticoagulation and deviation from the therapeutic range (134). In this multicenter, long-term study of 2376 patients (mean age at start of therapy 58 years,

73% male, 16.7% with AF as treatment indication), the overall incidence of any type of hemorrhage (major and minor bleeding combined) was no higher in elderly patients receiving warfarin than in younger patients who were also taking anticoagulants. It should be noted, however, that the unadjusted, combined incidence of life-threatening bleeding or fatal complications was significantly higher among patients over 80 years of age compared to patients aged 60 to 69 years (3.4% vs. 1.1%; RR = 3.1).

Hylek and Singer studied 121 consecutive adult patients taking warfarin (54% had AF) who were hospitalized with intracranial hemorrhage (135). In those patients who developed subdural hematomas, age and INR > 4 were the only significant independent risk factors for hemorrhage, with OR of 7.6 and 2.0, respectively. However, in the patients with intracerebral hemorrhages, age was of only borderline significance (OR = 1.3) after controlling for the intensity of anticoagulation (OR = 4.1) and two other independent risk factors: history of cerebral vascular disease (OR = 3.1) and presence of prosthetic heart valves (OR = 2.8).

Other studies in the literature support the contention that older age is an independent risk factor for anticoagulant-induced bleeding. Two large-scale, retrospective reviews have identified age as the most powerful risk factor for the development of major bleeding episodes in patients on long-term anticoagulation. In the first study, Landefeld and colleagues evaluated an inception cohort of 565 patients (54% female) with a mean age of 61 ± 14 years (range 18–92) who were discharged from a university hospital between 1977 and 1983 after being started on warfarin (130). The treatment indication for these patients included cardiac surgery in 57% and venous thromboembolism in 15%. During 876 patient years of outpatient therapy with warfarin, the cumulative incidence of major bleeding at 12 months was 11% with fatal bleeding occurring in 10 patients (2%). Using multivariate regression analysis, age greater than 65 (RR = 3.2) was determined to be one of five independent risk factors associated with the development of major bleeding complications. The four other factors and their respective relative risks included: (1) the presence of serious comorbid conditions such as recent MI, renal insufficiency, or severe anemia (RR = 3.0); (2) history of gastrointestinal bleeding (RR = 2.9); (3) history of stroke, either past or current (RR = 2.5); and (4) atrial fibrillation (RR = 2.2).

In the second study, Launbjerg and colleagues evaluated 551 Danish patients (60% male) with a mean age of 63 years (range 14–97) who received anticoagulants during the period between 1981–1987 (131). The treatment indication for 60% of the patients in this study included either deep venous thrombosis or pulmonary embolism. During 1010 treatment years of follow-up, the incidence of bleeding that necessitated hospital admission was 2.7% per year. Using multivariate analysis, age > 75 years was found to increase the risk of major bleeding by 10.5%. Other factors that also independently contributed to bleeding risk included current treatment with thiazide diuretics, hypertension (defined as blood pressure greater than 160/95), number of INR values above 7, and the duration of treatment (in years).

Two large-scale, prospective studies also support the view that advanced age is an important and independent risk factor for anticoagulant-induced bleeding. The Italian Study on Complications of Oral Anticoagulant Therapy (ISCOAT) prospectively evaluated an inception cohort of 2745 consecutive patients (43% female) from 34 anticoagulation clinics in Italy (90). Nearly three-fifths of the patients were aged 60 to 79; 8% were over age 80. During the mean follow-up period of 267 days, the rates of fatal, major, and minor bleeding were respectively 0.25, 1.1, and 6.2 per 100 patient years of follow-up. Bleeding rates were higher in those over age 70 (10.5 per 100 patient years of follow-

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up) compared with those under age 70 (6.0 per 100 patient years of follow-up) with a relative risk of 1.75 for patients over age 70 compared with all others. Additional risk factors for bleeding included anticoagulation during the initial 90 days of therapy and the underlying indication for treatment. Patients who were anticoagulated for arterial vascular disease (peripheral vascular and/or cerebral vascular disease) had a higher frequency of bleeding (12.5 per 100 patient years of follow-up) compared to patients being treated for VTE or other indications (6.8–7.1 per 100 patient years of follow-up). Intensity of anticoagulation was also related to bleeding complications; although about 20% of all bleeding events occurred at an INR < 2.0, the risk of bleeding was much higher for INR values > 4.5 (RR = almost 8).

The SPAF-II investigators also prospectively evaluated the precise impact of age on the safety and efficacy of warfarin therapy in NVAF patients (12). The rate of major hemorrhage was 1.7% per year in anticoagulated patients 75 years and younger vs. 4.2% per year in patients older than 75 (RR = 2.6). Furthermore, the age-related incidence of intracranial hemorrhage, which accounted for one-third of all the strokes in the warfarin-treated group was 0.6% per year in the ''young–old'' group (mean age 65) and 1.8% per year in the ''old–old'' group (mean age 80). This higher rate of intracranial bleeding in older patients canceled warfarin's beneficial effect and, in most cases, was associated with major or permanent disability.

Duration of Therapy and Risk of Bleeding

Several retrospective studies have attempted to quantitate the relationship between the duration of anticoagulation and the cumulative risk of developing a major bleeding complication. Petitti and colleagues used hospital discharge data collected during a 10-year period (1970–1980) to determine the association between duration of warfarin therapy for venous thromboembolic disease and the cumulative risk of hemorrhage (136). These investigators evaluated the medical records of over 2400 patients with a diagnosis of pulmonary embolism, thrombophlebitis, or both, and found that the probability of major hemorrhage increased almost linearly between 1 week and 5 years (10% at 3 months, 18% at 1 year, 26% at 2 years, and 41% at 5 years).

Landefeld studied an inception cohort of 565 patients (mean age 61 years) who began anticoagulant treatment between 1977 to 1983 and found that the cumulative incidence of major bleeding at 1, 12, and 48 months was 3%, 11%, and 22%, respectively (130). Using a retrospective chart review of 560 outpatients (mean age 63) who received anticoagulants between 1981 and 1987, Launbjerg determined that each year of treatment increased the risk for major bleeding by 2.0% (131).

Besides this expected cumulative increase in bleeding complications over time, several investigators have also detected a clustering of bleeding events around the time of initiation of anticoagulation. In a study of 321 patients (mean age 59 ± 16 years) followed over an 8-year period, Gurwitz noted that the risk of minor bleeding was greatest during the first 3 months of therapy (129). Landefeld found that the risk of major bleeding decreased from 3% during the first month of outpatient therapy to 0.3% per month after the first year of treatment (130). After controlling for the intensity of treatment, Launbjerg calculated a relative risk of 1.7 when the incidence of serious bleeding during the first 3 months of anticoagulation was compared with the second 3 months of therapy (131). Similar results were reported by the ISCOAT investigators who found that one-third of

all bleeding episodes occurred during the first 3 months of therapy; after this time, the rate of bleeding complications stabilized (90).

The reason for this early clustering of bleeding complications has several possible explanations: (1) suspicion bias may lead to more intense monitoring during the early phases of treatment; (2) instability of laboratory values with occasional marked fluctuations of the prothrombin time may lead to episodes of overanticoagulation that provoke bleeding; and (3) clinically ''occult'' lesions that are predisposed to bleeding may be unmasked by therapeutic levels of anticoagulation (90,130).

Summary

The major risk factors for anticoagulant-induced bleeding are summarized in Table 8. Available studies strongly suggest that advanced age (> 75 years), intensity of anticoagulation (especially INR > 4.0), history of cerebral vascular disease (recent or remote), and concomitant use of drugs that interfere with hemostasis (aspirin or NSAIDs) are among the most important variables determining an individual's risk for major or life-threatening bleeding complications on warfarin. All patients, especially the elderly, require meticulous screening and careful monitoring to minimize their risks of anticoagulant-related bleeding.

PRACTICAL CONSIDERATIONS IN USING WARFARIN

Initiating Therapy

For patients who require initial treatment with heparin, warfarin can be commecned on day 1 by administering the estimated daily maintenance dose (usually 2.5–5.0 mg) or by

Table 8 Risk Factors for Anticoagulant-Induced Bleeding

Patient-Related
Age
Gender?
Underlying indication for anticoagulation
Presence of serious comorbid conditions
GI bleeding
Hypertension
Renal insufficiency
Previous stroke or cerebral vascular disease
? underlying malignancy
Recurrent falls
Noncompliance with prescribed treatment
Increasing numbers of prescription medications
Use of drugs that interfere with hemostasis
Treatment-Related
Duration of therapy
Increased risk during first 3 months of Rx
Cumulative risk over time
Intensity of treatment (INR > 4.0)
Variability of control
Adequacy of monitoring and follow-up

using a flexible dose-induction protocol such as the ones described by Fennerty (137), Cosh (138), and others (139).

Harrison and colleagues recently compared the relative clinical efficacy and safety of 5 mg versus 10 mg as an initial ''loading dose'' of warfarin (140). The initial 5-mg dose produced less excess anticoagulation and avoided the development of a potential hypercoagulable state caused by the transient depletion of protein C, a vitamin-K-dependent protein with intrinsic anticoagulant and fibrinolytic effects. Patients who received the initial 10-mg warfarin dose experienced more rapid decreases in protein C and factor VII levels during the first 36 h of warfarin therapy and achieved INRs > 2.0 sooner than the 5-mg group. However, these early INR changes were caused by a more rapid reduction in factor VII levels ($t_{1/2}$ of 4–6 h) and did not reflect a true antithrombotic state, which is more accurately assessed by measuring reduced factor II ($t_{1/2}$ of 42–72 h) and factor X levels ($t_{1/2}$ of 60 h). Levels of factors II and X declined slowly after the initiation of warfarin therapy and did not differ significantly between the 5- and 10-mg groups; both regimens resulted in a therapeutic INR in most patients by day 5 of treatment.

Transient reductions in the level of protein C (before levels of factors II and X are substantially reduced) appear to be responsible for the syndrome of warfarin-induced skin necrosis (WISN) (141–143). Although reliable data on the incidence of this phenomenon are not available, it has been estimated that WISN occurs in 1:100 to 1:10,000 patients treated with anticoagulants (142). Some clinicians are concerned about the possibility of provoking WISN in patients who begin therapy with warfarin if there is not an appropriate overlap period with therapeutic doses of heparin. Because the NVAF clinical trials did not uncover any problems with early strokes or other thrombotic events that might be attributable to protein-C-mediated hypercoagulability, we believe that the possibility of coumadin necrosis in such patients is more of a theoretical than a practical concern. It has been our practice to treat hemodynamically stable NVAF patients in the outpatient clinic by initiating oral anticoagulant therapy without heparin overlap. We begin treatment with the anticipated maintenance dose of warfarin (2.5–5 mg daily) and follow the INR at 2- to 3-day intervals until a stable level is reached.

Dose Adjustment in the Elderly

Although most patients on long-term warfarin therapy require a daily dose of about 4 to 5 mg to maintain a steady-state level of anticoagulation, there is tremendous dose variation between individual patients. In general, when older patients are compared to younger ones, the elderly seem to require smaller doses of medication to achieve an equivalent anticoagulant effect (144).

Examples of some conditions that are prevalent in the elderly and known to enhance the prothrombin time response include congestive heart failure, malignancies, malnutrition, and unsuspected vitamin K deficiency (145). While age-related diseases and concurrent drug therapy may account for a major portion of the increased warfarin sensitivity noted in some older patients, mechanisms that account for this effect in other elderly patients are complex and not yet fully understood (Table 9). For example, healthy elderly volunteers taking no other medications still seem to exhibit greater sensitivity to the effects of warfarin than do younger patients.

Shepherd and colleagues have noted that, for a given plasma level of warfarin, older subjects demonstrated greater reductions in the rates of synthesis of coagulation factors than did a younger group of controls (146). Russman and colleagues reported that older

Table 9 Potential Reasons for Increased Warfarin Sensitivity in Older Patients

Concurrent drug therapy
Congestive heart failure
Advanced malignancy
Malnutrition
Diarrheal illness
Unsuspected vitamin K deficiency
Hepatic abnormalities
Decreased synthesis of vitamin K-dependent clotting factors
More pronounced inhibitory effect of vitamin K epoxide reductase
Diminished albumin concentration (increases unbound fraction of drug)
Reduced intrinsic clearance of drug
Fall in racemic warfarin clearance
Decreased liver size

patients (> 70 years) with recent heart valve replacements were more sensitive to the anticoagulant, phenoprocoumon, than younger patients (age < 60) (147). As a result, older patients required a dose reduction of approximately 30% compared to their younger counterparts. Gurwitz et al. have also demonstrated that the mean daily dose of warfarin decreases significantly with advancing age (Fig. 2) (148).

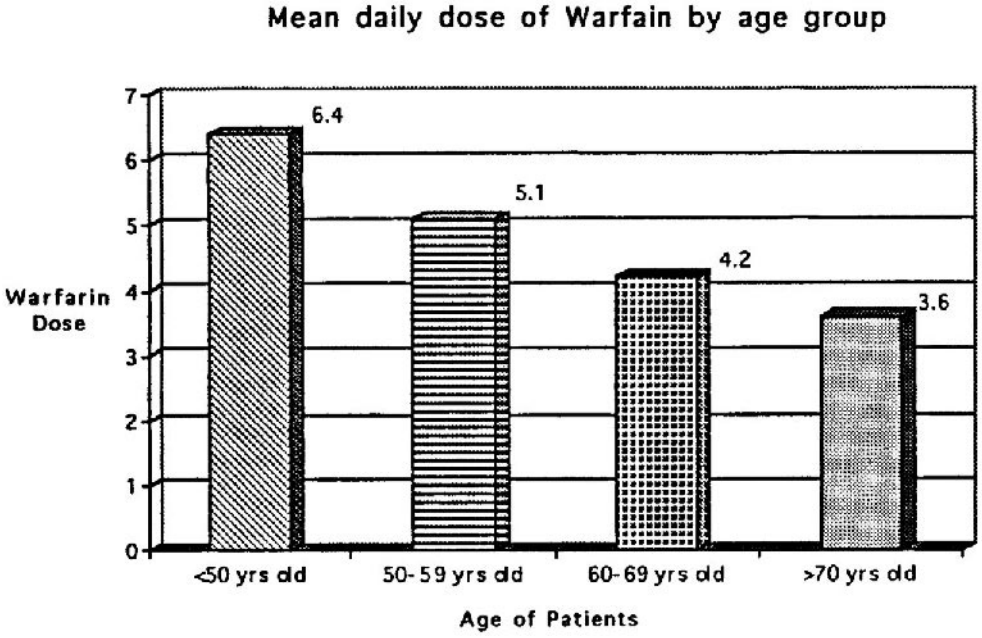

Figure 2 Daily warfarin requirements decline with age. (From Ref. 148.)

Wynne and colleagues designed a longitudinal study to establish the rate of age-related changes in warfarin dose requirements (149). They retrospectively studied 104 community-dwelling patients (median age at the start of therapy = 59 years) who had been stabilized on warfarin for a median period of 10 years. Warfarin dose requirements were significantly correlated with age differences; a derived regression equation noted a 21% fall in warfarin dose requirements over a 15-year period. These results suggest that the fall in warfarin dose requirements is a true age-related phenomenon and not explainable as a secondary effect. James et al. have also reported that daily warfarin dose requirements decreased by about 0.5 mg per every 10 years of advancing age, with an average decrease of almost 11% per decade (150).

Using a retrospective analysis of anticoagulation clinic records, Gladman and Dolan examined the effect of age upon the degree of control of anticoagulation (151). Because the initial dose of warfarin was not reduced in these elderly patients ($>$ 75 years), 58% had an INR $>$ 4 and 17% had an INR $>$ 6.0 during the first 2 weeks of therapy. By comparison, only 24% of patients younger than 65 had an INR $>$ 4, while only 8% had an INR $>$ 6 during the induction phase of treatment. Despite the fact that patients $>$75 received lower doses of warfarin during the maintenance phase of therapy (23.9 mg/week compared with 33.5 mg/week for those $<$ 65 years), the INR still rose with increasing age ($p < 0.001$); the number of patients with an INR $>$ 6.0 remained higher in the older age group (6% vs. 2%). In order to minimize bleeding complications, physicians need to account for the fact that older patients may display increased sensitivity to the effects of warfarin, both in the induction period and during the maintenance phase of therapy.

Drug Interactions with Warfarin

Drug–drug interactions are among the most frequent problems encountered in the management of elderly patients on long-term anticoagulants (Table 10). Although several recent reviews (152,153) and computer-based drug-interaction programs provide excellent summaries of warfarin–drug interactions, we recommend that all physicians routinely caution their patients about the potential for warfarin–drug interactions any time a medication is added or deleted from a patient's drug list [both prescription and over-the-counter (OTC) drugs]. All drugs should be considered suspect until their safety is well established. For example, while it is well known that erythromycin inhibits hepatic cytochrome p450 enzymes and the CYP34A isozymes responsible for the metabolism of (R) warfarin, most patients experience only a small increase in their INR when erythromycin and warfarin are used concurrently. However, some newer macrolide antibiotics, such as clarithromycin, are much more potent inhibitors of CYP3A4; as such, these drugs may be more likely to potentiate the effect of warfarin and cause substantial increases in its hypoprothrombinemic effect (154).

Nonsteroidal Anti-Inflammatroy Drugs

Because of concerns about hemorrhagic gastropathy and inhibition of platelet function, we discourage our patients on warfarin from using prescription-strength or over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDS) or aspirin-containing compounds. Shorr and colleagues placed this risk in perspective by evaluating the concurrent use of NSAIDS and oral anticoagulants in a retrospective cohort study of Medicaid enrollees aged 65 and older (155). Among current users of oral anticoagulants, the adjusted inci-

Table 10 Drug Interactions with Warfarin (Level I Evidence)

Potentiate effect of warfarin	Inhibit effect of warfarin	No effect
Antibiotics		
Cotrimoxazole	Nafcillin	
Erythromycin	Rifampin	
Fluconazole	Griseofulvin	
Isoniazid		
Metronidazole		
Miconazole		
Cardiac Drugs		
Amiodarone	Cholestyramine	Atenolol
Propranolol		Metoprolol
CNS Drugs		
	Barbiturates	Fluoxetine
	Carbamazepine	
	Chlordiazepoxide	
GI Drugs		
Cimetidine	Sucralfate	Antacids
Omeprazole		Psyllium
		Famotidine
		Nizatidine
		Raniditine
NSAIDS		
Phenylbutazone		Ketorolac
Piroxicam		Naproxen
Sulfinpyrazone		

Source: Refs. 153 and 186.

dence of hospitalization for peptic ulcer disease (PUD) was 14.3 per 1000 patient years compared with 6.4 for nonusers (RR = 2.2). The risk of hospitalization for the subset of patients who presented with hemorrhagic PUD (frank hematemesis or melena) was 10.2 per 1000 patient years in current users of oral anticoagulants compared with 3.1 for nonusers (RR = 3.3). The risk of hospitalization with hemorrhagic PUD for current users of both NSAIDS and oral anticoagulants was 26.3 per 1000 patient years, compared with 2.1 for patients who were not currently using either drug (RR = 12.7). These results suggest that NSAIDS should be prescribed with extreme caution in elderly patients who are also being treated with anticoagulants (156).

While some of NSAIDS' deleterious effect may be due to impaired platelet aggregation, much of the increased risk of bleeding is probably due to inhibition of cytoprotective prostaglandins in the gut. Treatment with potent acid-suppressing agents, use of misoprostol, and/or cure of *Helicobacter pylori* may provide protection from ulcer development in patients using NSAIDS. Chan and colleagues reported that eradication of *H. pylori* with triple therapy (bismuth, tetracycline, and metronidazole) before treatment with naproxen reduced the development of drug-induced ulcers from 26% to 7% (157). It is not clear whether these results are generalizable to other *H. pylori* treatment regimens or applicable to patients on both NSAIDS and warfarin.

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Acetaminophen

Hylek and colleagues have recently reported a prospective case-control study that identified factors associated with an elevated INR in outpatients (mean age of 70 years) who were taking warfarin (target INR 2–3) (158). Acetaminophen use was independently associated with having an INR > 6.0. This relationship was highly significant and dose-dependent; for patients taking more than 9100 mg/wk of acetaminophen (more than four 325-mg tablets daily for > 1 week) the odds of having an INR > 6.0 were increased tenfold compared to patients taking between 0 to 6 tablets per week. Other factors that were independently associated with an INR > 6.0 were advanced malignancy (OR $= 16.4$), newly started potentiating medication (OR $= 8.5$), warfarin dose more than prescribed (OR $= 8.1$), decreased oral intake (OR $= 3.6$), and acute diarrheal illness (OR $= 3.5$).

Dietary Interactions with Warfarin

The current recommended dietary allowance of vitamin K_1 for adults is 80 μg/day for men and 65 μg/day for women (159). Karlson and colleagues have noted that a continuous daily intake of > 250 μg of vitamin K may affect plasma coagulant activity (160). Data from Pedersen and colleagues suggest that ingestion of 1000 μg of dietary vitamin K for even a single day may cause similar undesirable changes; this effect may last for several days after resumption of the patient's habitual diet (161). While all of our patients on warfarin receive dietary instructions, we only limit the regular intake of a few foods and nutritional supplements known to have very high vitamin K contents (162,163).

Alcohol

Alcohol intoxication may substantially increase the INR in patients on warfarin; smaller amounts of alcohol appear to have little effect in most patients unless there is underlying liver disease (152). Fihn and colleagues noted that elderly patients on warfarin may be at particular risk for alcohol-related bleeding complications; the relative risk for serious warfarin-induced bleeding was 1.4 among binge drinkers, but 2.0 among binge drinkers over than 65 years of age (164).

Interruption of Anticoagulant Therapy for Elective Surgical Procedures

The appropriate perioperative management of anticoagulated patients who are scheduled to undergo elective noncardiac surgery or other invasive procedures depends on multiple factors including the underlying indication for anticoagulation, the nature of the surgical procedure, and the type of anesthesia that is being planned (Table 11). We suggest that patients who need anticoagulation for only a limited period of time should postpone elective surgical or major dental procedures until their course of treatment is completed. For all others, the decision to continue or interrupt warfarin therapy should carefully weigh: (1) the thrombotic risk of allowing the INR to fall below the treatment threshold; (2) the inherent hemorrhagic risk of the surgery or procedure under consideration; and (3) the additional risk of bleeding if anticoagulants are continued without modification.

It short-term discontinuation of anticoagulation is deemed safe, how long does it

Table 11 Approach to Patients on Long-Term Anticoagulants Who Require Elective Noncardiac Surgery or Invasive Procedures

Ask the following questions

1. Can the procedure be delayed until the treatment course with anticoagulants is completed?
2. What is the underlying indication for chronic anticoagulation?
3. What is the thrombotic risk if anticoagulants are discontinued?
4. What surgical procedure is being planned?
5. Is this a major or a minor procedure?[a]
6. What is the baseline risk of bleeding associated with this procedure?
7. How will this bleeding risk be affected if anticoagulants are continued at their usual dose?
8. Will bleeding complications compromise or jeopardize the surgical result?
9. At what INR would the surgeon be comfortable operating?
10. What type of anesthesia is being planned?

[a] A major procedure is one in which either a bone or body cavity is entered.

take the INR to normalize? White and colleagues helped to answer this question by simulating the preoperative discontinuation of warfarin and measuring the decrease in INR over time in 22 patients (average age 55 years) receiving a fixed dose of warfarin (165). From a mean steady-state value of 2.6, the INR began to decrease exponentially 24 to 36 h after the last dose of warfarin; 3 days later, the mean INR was 1.61. Wide interpatient variation was noted in both the time until this decrease began and the actual rate of decrease. Age was a significant independent predictor of smaller decreases in INR between day 1 and day 3; for every 10-year increase in age, the fall in INR decreased by approximately 7%. White's data suggest that 4 to 5 days after warfarin is discontinued almost all patients with an initial INR between 2 to 3 will have an INR less than 1.5. If one assumes that an INR < 1.5 is associated with an acceptable risk of postoperative bleeding, it would be prudent to delay surgery for this length of time, especially in older patients who eliminate warfarin more slowly.

Several recent reviews provide general recommendations for managing anticoagulation during surgery and other invasive procedures (166,167). From their review, Kearon and Hirsh concluded that most patients do not require temporary heparinization after oral anticoagulants have been discontinued (166). While we agree with their general recommendations, we believe that decisions regarding perioperative management of anticoagulation can be further individualized by considering additional variables that may contribute to thrombotic risk. For example, some patients with mechanical heart valves are at relatively high risk for arterial thrombosis if anticoagulants are discontinued for even short periods of time. Additional variables contributing to this thrombotic risk may include the position of the valve, the design and material used for the prosthesis, the presence of atrial fibrillation, and the presence and severity of left ventricular dysfunction (59). An example of a patient with a high thrombotic risk profile would include one with congestive heart failure, long-standing atrial fibrillation, and an older valve prosthesis in the mitral position. This type of individual risk assessment is supported by a decision analysis that examined the cost effectiveness of various strategies for treating patients with mechanical heart valves undergoing noncardiac surgery (168). The authors concluded ''that the marginal

cost of prolonging hospitalization to administer heparin was prohibitively high compared with most contemporary therapies, except when the patient has the most thrombogenic of valves.''

Bleeding Risk Associated with Specific Procedures

The risk of bleeding during specific surgical procedures needs further study so that realistic risk appraisal can replace anecdotal experience. Because dental, prostate, cataract, and cutaneous surgeries are among the most common procedures performed in elderly patients, the next few sections specifically review the risks of bleeding during these procedures if full-dose anticoagulation is continued without interruption.

Dental Procedures

Wahl and Howell recently surveyed practicing physicians in Delaware to determine whether they recommended any alterations of warfarin or aspirin therapy for patients about to receive dental care (169). There was no consensus of opinion among respondents (internists, cardiologists, and family practitioners), but physicians who had been in practice for more than 10 years were less likely to modify antithrombotic therapy before dental procedures. Despite the fact that numerous studies have shown that patients on warfarin can safely undergo general dental procedures, 73% of physicians said they would alter warfarin therapy for at least one dental procedure; 11% would instruct patients to modify warfarin before a routine professional cleaning; 33% before restorative treatment; 42% before a conventional root canal; and 56% before a single simple extraction. Since root canal therapy causes little or no bleeding, Wahl and Howell concluded that many practicing physicians may misunderstand the nature of certain dental procedures and the likelihood that those procedures will cause significant postoperative bleeding.

Benoliel and colleagues have reported their protocol for managing patients with prosthetic heart valves who were undergoing general dental treatment (170). Study participants did not have their warfarin dose adjusted if the prothrombin time was less than 2.5 times the control value; it was not possible to determine the exact level of anticoagulation because the sensitivity of the thromboplastin reagent was not specified. Only one episode of excessive bleeding occurred during 490 dental procedures, including 87 simple extractions.

Ramstrom and colleagues have also reported that patients on warfarin can safely undergo oral surgery without reducing the dosage of anticoagulants, provided that the INR is within the therapeutic range and local antifibrinolytic treatment with tranexamic acid solution is instituted (171). They designed a double-blind, placebo-controlled clinical trial to evaluate the hemostatic effect of a 4.8% solution of tranexamic acid in 93 patients (INR 2.1–4.0) who underwent oral surgery without altering their anticoagulants. Ten patients in the placebo group (21%) developed bleeding requiring treatment while none of the patients using tranexamic acid had significant bleeding. Additional local measures including sutures, microfibillar collagen, packed collagen, gelfoam impregnated with thrombin, and fibrin glue may also help decrease the incidence of postprocedure bleeding in anticoagulated dental patients (172).

Based on this information, it seems reasonable to maintain most dental patients on their anticoagulant regimen without alteration or interruption (172,173). However, we strongly recommend consultation between dentists and primary care physicians to deter-

mine whether warfarin dose adjustments are necessary before more complicated dental treatments (such as soft tissue-flap reflections) are undertaken (174).

Prostate Surgery

By age 80, an estimated one-third of all U.S. men will require surgical treatment of bladder outlet obstruction due to benign prostatic hyperplasia (175). In order to reduce the risk of increased bleeding from the prostatic fossa during transurethral resection of the prostate (TURP), it has been the usual urological practice to discontinue or avoid any form of anticoagulant therapy before and after this procedure.

In 1989, Parr and colleagues reported 13 patients (mean age 67 years) who underwent 12 TURPs and 1 transurethral resection of an extensive bladder tumor without withdrawal of their chronic anticoagulant therapy (176). Four patients (31%) required blood transfusions but no other serious complications were reported. Despite the considerable increased risk of hemorrhage, the authors recommended continuing warfarin therapy because of the risk of thromboembolic complications associated with its temporary withdrawal.

In 1995, Kingston and colleagues reported 20 patients who underwent transurethral laser ablation of the prostate gland (LAP) without withdrawal of warfarin therapy (177). Patients in this study had a mean age of 70.2 years (range 58–82) and a mean preoperative INR of 2.6 (range 1.19–5.25). One patient required revision TURP for intractable hematuria, three patients (15%) developed hematuria requiring transfusion (one of these had an INR of 5.25 at the time of surgery), and four patients developed mild hematuria requiring no intervention.

The reduction in local bleeding complications with LAP may be due to several factors (177). The thermal conduction properties of the laser produce a sphere of acute coagulation necrosis and an area of delayed tissue necrosis in the surrounding transition zone. Because the prostatic venous sinuses are not disrupted as they are in standard TURP, acute morbidity from blood loss is minimized. Deep thrombosis of the prostatic arteries also appears to contribute to hemostasis. Laser ablation in the transition zone is thought to be responsible for the slow, nonhemorrhagic sloughing of prostatic tissue that normally occurs over a period of several weeks; the fact that no significant delayed hemorrhage was noted suggests that deeper vessels are most likely sealed by the effect of the laser. Thus, unlike standard TURP, laser ablation of the prostate can be used successfully in patients who are fully anticoagulated; in such patients, LAP appears to be a more appealing surgical option.

Cataract Surgery

Several recent reports have addressed the issue of whether it is safe to continue full-dose anticoagulation in patients who are scheduled for cataract surgery. Gainey analyzed 50 patients receiving long-term anticoagulation who underwent ocular surgery; there was no significant difference in bleeding complications between patients in whom warfarin was continued and those in whom it was stopped (178). McCormack and colleagues reviewed the outcomes of 50 surgical procedures in 41 patients who were anticoagulated at the time of surgery (INR 1.1–4.9) (179). Local anesthesia was used in 39 operations and 11 were performed under general anesthesia. Thirty-three patients had extracapsular cataract extraction with posterior chamber lens implantation. No major hemorrhagic complications were associated with either the surgical procedure or the local anesthetic. In his report of 69 additional cases, Hall reinforced the contention that anticoagulants should not be termi-

nated for cataract surgery (180). In his series, the majority of surgeries (64%) utilized topical anesthesia and all were performed through clear corneal wounds. One procedure done under regional anesthesia was complicated by a retrobulbar hemorrhage.

Anticoagulated patients undergoing cataract surgery showed no increase in sight-threatening complications when compared to nonanticoagulated patients (181). Because of the relatively avascular field present in cataract surgery, routine cataract extraction can be safely recommended in most patients even in the face of systemic anticoagulation.

Cutaneous Surgery

Otley and colleagues performed a retrospective review of 633 patients who underwent excisional and Mohs micrographic surgery to determine the frequency of surgical complications in patients who were receiving warfarin and platelet inhibitors and to evaluate whether preoperative discontinuation reduces complications (182). Severe complications occurred in only 1.6% of cases, a rate not significantly increased compared to control subjects. No significant reduction in the rate of severe complications was noted in patients who had their medications held preoperatively. This study suggests that, in most cases, cutaneous surgery can be performed at a very low rate of severe hemorrhagic complications in patients who continue to take warfarin or platelet inhibitors in the perioperative period (183).

Anesthesia

In their review of anticoagulants and anesthesia, Stow and Burrows concluded that ''the use of epidural or spinal analgesia in combination with systemic anticoagulation is contraindicated by the standards of most anesthesiologists'' (184). Even when given in prophylactic doses, anticoagulants may pose particular risks for patients undergoing lumbar puncture or neuraxial anesthesia. A recent FDA Public Health Advisory (December, 1997) summarized reports of more than 30 patients who developed epidural or spinal hematomas when prophylactic doses of low-molecular-weight heparin were used concurrently with spinal/epidural anesthesia or lumbar puncture (185). Approximately 75% of these patients were elderly women undergoing orthopedic surgery; many of the epidural or spinal hematomas caused serious neurological injury including long-term or permanent paralysis. The risk of such adverse events appears to be increased by the use of in-dwelling catheters for administering epidural anesthesia, the concomitant use of other drugs known to affect hemostasis (platelet inhibitors, NSAIDS), and by traumatic or repeated epidural/spinal puncture.

Approach to Patients with Excessive Degrees of Anticoagulation

For many patients receiving warfarin, excessive anticoagulation without associated hemorrhage can usually be managed by simply withholding one or several doses of the medication. Although the fourth ACCP Conference on Antithrombotic Therapy (186) and others (187) have published guidelines for the management of excessive anticoagulation, limited data are available to support these recommendations. A recent retrospective review of 301 episodes of excessive anticoagulation among 248 patients (mean age $>$ 62) enrolled in a group model HMO concluded that moderate elevations of the INR (6.0–10) can be managed conservatively without the administration of phytonadione (188).

If more rapid reversal of warfarin's anticoagulant effect is deemed necessary, small doses of vitamin K_1 can be administered either orally or intravenously. When there was no evidence of significant bleeding, Weibert and colleagues found that withholding warfarin and administering 2.5 mg of oral vitamin K_1 (phytonadione) was a safe, painless, and inexpensive treatment for outpatients with an INR $>$ 5.0 (189). Excluding 10 patients who presented with an INR $>$ 10, this oral dose of vitamin K_1 corrected the INR to less than 5.0 in 96% of the remaining 71 patients. The INR was reduced to less than 2.0 in 17% of the treated patients and to less than 1.8 in only 5 patients (6%). No INR fell below 1.5 and no patient developed clinically evident thromboembolism. When warfarin therapy was resumed, no patient demonstrated vitamin K_1-induced resistance to anticoagulation.

Shetty and colleagues have also recommended the use of small doses of vitamin K_1 as an effective and convenient method of predictably controlling excessive oral anticoagulation (190). They administered 0.5 to 1.0 mg of intravenous vitamin K_1 to 21 patients with INRs greater than 5.5 (INR range 5.6 to 25.9) and found that the INR fell below 5.5 in all patients after 24 h. There were no reported instances of overcorrection; the INR did not fall below 2.0 in any patient. No patient had a thrombotic or hemorrhagic complication and no difficulty was encountered in reestablishing anticoagulant control after 24 h.

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26

Ventricular Arrhythmias in the Elderly

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Sudden cardiac death remains a significant medical concern. Approximately 300,000 to 400,000 persons die suddenly in the U.S. annually (1,2). Advanced age is a risk factor for sudden cardiac death and the prevalence increases with age (3,4).

In most cases of sudden cardiac death the metabolic substrate is myocardial ischemia or hypertrophy with underlying coronary artery disease or hypertension; and the electrical substrate is ventricular fibrillation, most often arising from ventricular tachycardia (5). Due to the increase in coronary artery disease and hypertension, plus the effect of aging changes, both metabolic and electrical substrates are common in the elderly person, which most likely explains the increased incidence of sudden cardiac death in this age group (Fig. 1).

PREVALENCE OF VENTRICULAR ARRHYTHMIA

Ventricular arrhythmias are common in elderly persons and the incidence increases when underlying heart disease is present (6–11). Various studies have reported that 70 to 80% of persons over 60 years of age will exhibit ventricular arrhythmias. The frequency of premature ventricular contractions (PVC) is often high, and complex forms are common in this age group, although the person is often asymptomatic.

Early studies assessing ventricular arrhythmia in elderly populations found PVCs to be common even in ''healthy'' persons. Glasser and associates (6) reported 30% of ''apparently healthy'' subjects aged 60 to 84 years demonstrated complex ventricular ectopy on 24-h electrocardiographic (ECG) monitoring. In a larger study population of ''healthy'' older persons leading active independent lives, Camm (11) and associates reported that 12% of 106 subjects demonstrated greater than 100 PVCs/h, 22% had multiform PVCs, and 4% had ventricular tachycardia (VT). Similar findings were reported in separate studies by Kantelip (7) and Fleg (10). Fleg reported 80% of ''healthy'' elderly subjects from the Baltimore Longitudinal Study of Aging (BLSA) demonstrated ventricu-

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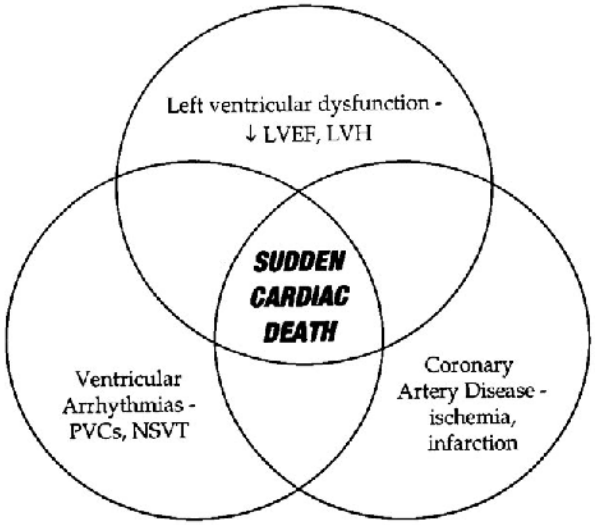

Figure 1 Relationship of factors that predispose to sudden death in elderly patients. (Adapted from Ref. 59, with permission.)

lar arrhythmias and 50% of the group had complex ventricular arrhythmias with VT seen more frequently in subjects aged 70 and older (10).

More recent studies that assessed larger sample size have also reported ventricular arrhythmias to be common in nonselected elderly persons. In the Bronx Study of Aging (12), which included 423 community-dwelling subjects 75 to 85 years of age with and without cardiovascular disease, 93% of the subjects demonstrated PVCs on 24-h ECG monitoring, and 19% had 10 to 100 PVCs/h, 38% had multifocal PVCs, and 5% had nonsustained VT. Manolio and associates (13) reporting on the findings of the Cardiovascular Health Study, a population-based study of 5200 nonselected independent-living adults, age >65 years, found VT in 13% of men and 4% of women who had interpretable 24-h ECG monitored tapes. The increased prevalence of VT in males was noted in every 5-year age group.

In assessing the determinants of ventricular arrhythmia in elderly patients, Aronow and associates (14) found the prevalence of PVCs and VT to be related to left ventricular dysfunction. Eight-one percent of 453 nursing home patients, mean age 82 years, demonstrated ventricular arrhythmias on 24-h ECG monitoring. Sixty-seven percent of the patients with left ventricular ejection fraction (LVEF) < 50% demonstrated complex ventricular arrhythmias, compared to 52% of patients with LVEF > 50% and VT was found in 14% of patients with LVEF < 50%, whereas only 8% of patients with LVEF > 50% had VT. Besides LVEF, left ventricular hypertrophy (LVH) is a significant determinant of ventricular arrhythmias (15–17). Left ventricular mass increases with age and hypertension, and approximately 50% of elderly patients with mild hypertension have LVH (15). Messerli and associates, (15) in a study of patients 56 to 72 years of age (mean 68 years of age) found 24-h premature PVC rate to be 40 to 50 times greater in patients with LVH

than in patients without LVH, and the higher prevalence was closely related to the degree of hypertrophy.

PROGNOSTIC SIGNIFICANCE OF VENTRICULAR ARRHYTHMIAS AND STRATIFICATIONS OF PATIENTS

Significance of Underlying Heart Disease: Younger and Middle-Aged Persons

The presence and severity of underlying heart disease, particularly left ventricular function, greatly influences prognosis in patients with ventricular arrhythmias. It is well documented that ventricular arrhythmias in persons without significant underlying heart disease are not predictive of increased total mortality or sudden cardiac death (18–24). Kennedy and associates, (24) in a study of mainly young, asymptomatic, apparently healthy men, mean age 46 years, found on 24-h ECG monitoring complex ventricular ectopy in 63% and VT in 26% of the subjects. At 6 years mean follow-up, only five subjects experienced cardiac events: two subjects had myocardial infarctions (MI); one had heart failure; one had cardiac arrest; and one had syncope. The authors concluded that the long-term prognosis of asymptomatic healthy persons with frequent and complex ventricular ectopy is similar to that of the healthy population and suggests no increased risk of death.

In contrast to the favorable prognosis in asymptomatic healthy patients with ventricular arrhythmias, in the presence of underlying heart disease ventricular arrhythmias are highly predictive of mortality, especially sudden cardiac death (25–28). Studies have shown that nonsustained VT is the arrhythmia of most concern and is a marker for the patient at risk for increased mortality and sudden cardiac death (29–31). Ruberman and associates (25), in one of the earliest studies assessing prognostic significance of ventricular arrhythmias in post-MI patients, found ventricular arrhythmias to be a significant determinant of total mortality, particularly sudden cardiac death. In this study, the prevalence of ventricular arrhythmias significantly increased with age, as did the probability of total death and sudden cardiac death; however, the presence of complex PVCs was an independent risk, regardless of age, for all forms of death, including sudden cardiac death. In a more recent study of post-MI patients, Bigger and associates (31) found the risk of sudden cardiac death to be two to three times greater in patients with, than in patients without, nonsustained VT.

Significance of Underlying Heart Disease: Elderly Persons

Studies addressing the prognostic significance of ventricular ectopy, in specifically elderly patients, have reported similar findings as those reported in studies of younger and middle-aged patients (16,22,32–34) (Table 1). In studies of elderly nursing home patients (32), Aronow and associates found no correlation between complex ventricular arrhythmias and new cardiac events in patients without heart disease. Similar findings were reported by Fleg and associates (21–23) in their studies of healthy elderly BLSA subjects. No difference in cardiac events, including sudden death, was found at 10 years follow-up between subjects with or without ventricular arrhythmias on 24-h ambulatory ECG monitoring or between subjects with or without exercise-induced PVCs or nonsustained VT.

Compared to the favorable prognosis in elderly patients with ventricular arrhythmias

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Table 1 Relationship of Ventricular Arrhythmias to Future Cardiac Events in Older Patients

Study	No. of patients	Age (years)	Cardiac status	Variable	Mean follow-up period	Incidence of cardiac events
Fleg (21)	10	>65[a]	Healthy[b]	Exercise induced VT	24 mos	No correlation
Fleg (22)	98	69	Healthy[b]	VPCs, VT	120 mos	No correlation
Kirkland (33)	30	79	Healthy[b]	VPCs	29 mos	No correlation
Aronow (32)	843	82[c]	Heart disease	Complex VA	39 mos	Approximately 2× incidence of patients with complex VA
	104		No heart disease	Complex VA	39 mos	No correlation
Aronow (16)	391	82[c]	Heart disease	Complex VA, VT, & LVEF	24 mos	Greater than 2× incidence in patients with complex VA or VT. 3× incidence in patients with abnormal LVEF and complex VA or VT.
	76		No heart disease	Complex VA, VT, & LVEF	24 mos	No correlation
Aronow (34)	468	82[c]	Heart disease	Complex VA, VT, & LVH	27 mos	3 × incidence of SCD or VF in patients with complex VA, VT or LVH. 7 × incidence of SCD or VF in patients with LVH and complex VA or VT.
	86		No heart disease	Complex VA, VT, & LVH	27 mos	No correlation

[a] 1 patient < 65 years.
[b] See text for definition.
[c] Age of total patients, including patients without heart disease.
LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; SCD = sudden cardiac death; VA = ventricular arrhythmias; VPC = ventricular premature beat; VT = ventricular tachycardia; VF = ventricular fibrillation.
Source: Adapted from Ref. 100, with permission.

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in the absence of underlying heart disease, ventricular arrhythmias in elderly patients, as in younger patients, portends increased mortality, including sudden cardiac death, when heart disease is present. Aronow and associates (32) found 58% of nursing home patients, mean age 82 years, with documented heart disease, who demonstrated complex ventricular arrhythmias on 24-h ECG monitor had new coronary events, including MI, primary ventricular fibrillation, and sudden cardiac death, within 39 months follow-up. In contrast, only 34% of the patients without ventricular arrhythmias had new coronary events. In another study of 121 elderly nursing home patients, mean age 81 years, who were all at least 6-months post-MI, Mercando and associates (35) reported significantly higher incidence of both sudden cardiac death and total cardiac deaths in patients with nonsustained VT than in patients without such arrhythmias. A significant correlation between ventricular arrhythmias and cardiac death was also reported in the patients enrolled in the Bronx Aging Study (12); in multivariate analysis, nonsustained VT was an independent predictor of death (R.R. = 2.8; CI 1.4–5.8), and was almost as powerful as a predictor of death as the occurrence of MI (R.R. = 3.2; CI 1.2–9.4).

Association of Left Ventricular Function and Ventricular Arrhythmias

Left ventricular dysfunction, in association with ventricular arrhythmias, has been shown to increase the risk of sudden cardiac death and total mortality. Ventricular arrhythmias and left ventricular dysfunction are independent predictors of mortality, including sudden cardiac death: the more severe the left ventricular dysfunction and the more malignant the ventricular arrhythmia, the worse the prognosis. The Multicenter Post Infarction Program Study (28), in which maximum age of patients was 65 years, reported a 2-year mortality rate of 38% in patients with both left ventricular ejection fraction of $<30\%$ and >3 PVC/h, whereas the 2-year mortality rate of the remaining patients was 10%. The odds of dying within 2 years were almost six times as great for patients with a left ventricular ejection fraction $<30\%$ and >3 PVCs/h compared with all other patients. Similar findings have been reported in patients with nonischemic heart disease: Holmes (36) and Meinertz (37), in separate studies of mainly younger patients, found complex ventricular arrhythmias and left ventricular dysfunction to be powerful predictors of sudden death in patients with idiopathic dilated cardiomyopathies.

Studies that have specifically involved elderly patients have also found the combination of ventricular arrhythmia and left ventricular dysfunction to portend poor prognosis. In one of their nursing home studies, Aronow and associates (16) found at 2-year follow-up, 61% of elderly nursing home patients (mean age 80 years) with complex ventricular arrhythmias had new cardiac events, including sudden cardiac death if their LVEF was $<50\%$, whereas only 20% of the patients with complex ventricular arrhythmias had cardiac events if their LVEF was $\geq 50\%$

Association of Left Ventricular Hypertrophy and Ventricular Arrhythmias

Left ventricular hypertrophy is another finding that needs to be considered when assessing elderly patients with ventricular arrhythmias. Not only does the prevalence of ventricular arrhythmias significantly increase in correlation to the degree of LVH, but also LVH is a risk factor for sudden cardiac death and total mortality. The Framingham Heart Study

(17) reported the risk for sudden cardiac death in patients with LVH to be five to six times greater than that in patients without LVH. Aronow and associates (34) found a correlation between LVH and sudden cardiac death in nursing home patients with the risk of sudden death significantly increasing when ventricular arrhythmias are present. The incidence of sudden cardiac death and ventricular fibrillation increased from 4% at 2 years follow-up in the patients without LVH or complex ventricular ectopy to 29% in patients with both LVH and complex ventricular ectopy. The incidence of sudden death and ventricular fibrillation was even higher (57%) in those patients with LVH and VT.

Electrophysiological Studies and Signal-Averaged Electrocardiography

Electrophysiological studies (EPS) and signal-averaging ECG have been used to further stratify patients with nonsustained VT, and both procedures can be performed accurately and safely in elderly patients (35,38). Most studies of EPS (39,40) have shown sustained VT to be inducible in 18 to 45% of patients with clinical nonsustained VT, and the probability of inducibility is higher in patients with left ventricular dysfunction. In some studies (41,42), inducibility of VT correlated with a risk of subsequent arrhythmic events, whereas other studies (43,44) have not substantiated these findings. Similar inconclusive findings have been reported in studies of EPS when used to stratify specifically post-MI patients into high- and low-risk groups for future arrhythmic events. Therefore, on the basis of the present data, EPS in conjunction with clinical parameters may be beneficial in stratifying certain individual elderly patients with nonsustained VT into high- and low-risk groups for subsequent sudden cardiac death. No conclusions, however, can be made about the value of routine EPS in elderly patients with ventricular arrhythmias.

Signal-averaged ECG is a computer-aided, noninvasive method of detecting high-frequency, low-amplitude potentials at the terminal portion of the QRS complex (45). It is thought these ''late potentials'' originate from damaged myocardial tissue. Some investigators have reported that the presence of late potentials will identify a group of patients post-MI who are at risk for an arrhythmic event, including sudden death (45–49). Unfortunately, other studies of signal-averaged ECG in post-MI patients have suggested that the use of this technique to identify patients at risk for sudden cardiac death is associated with a high proportion of false-positive results and the significance of late potentials is uncertain (50,51). Thus, as with EPS, signal-averaged ECG may be beneficial in stratifying certain elderly patients with ventricular arrhythmias, but the routine use of this test cannot be recommended.

Some investigators (46–48) consider the combination of ventricular arrhythmias on Holter monitoring, LVEF, and late potentials on signal-averaged ECG to provide the best predictor of future arrhythmic events, including sudden cardiac death. Gomes and associates (48) reported the presence of any two of the three abnormal assessments [presence of late potentials, LVEF $<40\%$, and ten ventricular premature contractions per hour (couplets or triplets)] or all three to be associated with a future arrhythmia event rate of 36 to 50% in post-MI patients at 2 years follow-up. The presence of late potentials and an abnormal LVEF was found to be the best predictor of a future arrhythmic event. When these two findings were absent, no arrhythmic events were noted. Other studies have reported similar findings; El-Sherif and associates (46a) found at 12 months of follow-up a 37% arrhythmia event rate in post-MI patients who exhibited late potentials and an abnormal LVEF, whereas the incidence of an arrhythmic event was only 1% when these two findings were absent. When late potentials were present in association with both an abnor-

mal LVEF and high grades of ventricular ectopy, the arrhythmic event rate increased to 50% during a 1-year period.

THERAPEUTIC OPTIONS

Pharmacological Therapy

The empirical use of antiarrhythmic drugs in the treatment of ventricular arrhythmias has been shown by numerous studies to be ineffective in preventing sudden cardiac death, and, in certain situations, such therapy may be detrimental (52–63). The recent and much publicized Cardiac Arrhythmia Suppression Trial (CAST I and II) (60,61), in which approximately 2500 patients with previous MI and ventricular arrhythmias were randomized to receive antiarrhythmic drug therapy or placebo, showed at 10 months of follow-up a 2.5 increase in total mortality and a more than threefold increase in sudden cardiac death and nonfatal cardiac arrest in patients treated with encainide or flecainide, compared with patients in the placebo group. Approximately one-third of the patients in the study were older than 65 years of age, and the observed increased risk from the antiarrhythmic drugs was found to be present regardless of the patient's age. Another recent study that assessed the efficacy of empirical use of antiarrhythmic therapy in reducing mortality in post-MI patients was the Survival With Oral D-Sotalol (SWORD) trail (62). Over 3000 high-risk patients who had LVEF $<$ 40%, recent MI (6–47 days), or symptomatic heart failure and remote MI ($>$ 42 days) were randomized to treatment with D-sotalol vs. matching placebo; ventricular arrhythmias were not required for entry into this study, although nonsustained VT was present in the majority of patients. Patient's mean age was 62 years, range 33 to 73. As in CAST (60,61), the trial was stopped early because of increased mortality in the antiarrhythmic drug group; the increased mortality was presumed to be due to arrhythmic deaths.

In studies of antiarrhythmic drugs specifically involving elderly patients, Aronow and associates (63) found that in 406 elderly nursing home patients (mean age, 82 years; range, 62 to 100 years) with ventricular arrhythmias who were treated with either quinidine (213 patients), procainamide (7 patients), or a placebo (186 patients), antiarrhythmic drugs did not reduce sudden cardiac death or total mortality. At 24-month follow-up, 21% of 220 patients treated with quinidine or procainamide and 23% of the 186 patients treated with placebo sustained sudden cardiac death. Sixty-five percent of patients in the treatment group died compared with 63% of the patients in the placebo group. In addition to the lack of efficacy of the antiarrhythmic drugs, approximately 50% of patients treated with drugs developed side effects.

Based on the results of the many studies that have failed to document any objective efficacy of drug therapy in improving mortality in patients with ventricular arrhythmias, plus the results of the recent CAST and SWORD studies, it is difficult to justify the empirical use of antiarrhythmic drugs in most elderly patients with ventricular arrhythmias. The use of adrenergic β-blocking agents and/or the class III antiarrhythmic drug, amiodarone, however, do need to be considered when evaluating elderly patients with ventricular arrhythmias.

Repeated studies (64–67) assessing the use of β-blockers (with exception of β-blockers with significant intrinsic agonist activity, such as pindolol and oxprenolol) in post-MI patients have found the drugs to be beneficial in reducing total mortality, sudden cardiac death, and recurrent myocardial infarction. Data pooled from the major studies show a 28% reduction in total mortality and a 33% reduction in sudden cardiac death. Beneficial

effects of β-blockers have been shown to be as impressive in elderly patients as in younger patients, and the incidence of side effects and rate of drug withdrawal have not been greater in elderly patients. Furthermore, in a post hoc analysis of the CAST trial, patients treated with antiarrhythmic drugs who received β-blockers were found to have a lower sudden death rate than patients treated only with antiarrhythmic drugs (68). Such findings suggest that β-blockers may reduce proarrhythmic effects of certain antiarrhythmic drugs. Studies have also demonstrated that when amiodarone is used in combination with β-blockers in treatment of post-MI patients with life-threatening ventricular arrhythmias, the reduction in total mortality and sudden cardiac death is significantly greater than when amiodarone alone is used (69,70).

Although the specific mechanism by which β-blockers reduces sudden death is unknown, the benefit of β-blockers after MI in elderly patients is so overwhelming that it behooves the physician to consider myocardial ischemia as a possible etiology of ventricular arrhythmias whenever confronting all elderly patients with such arrhythmias. In many elderly patients, myocardial ischemia may be silent, and stress testing (exercise or pharmacological) is necessary to elicit and document the ischemia. Regardless of the documentation of ischemia, β-blockers are indicated in all elderly post-MI patients and should be considered in all elderly patients with ventricular arrhythmias.

Despite the benefits of β-blockers after myocardial infarction, it has been shown that these agents are disproportionately used in elderly patients (71,72). Soumerai and associates (71), in a study of over 3000 Medicare post-MI patients who were eligible for β-blockers, found only 21% of the patients received the drug. Patients were three times more likely to receive a new prescription for a calcium channel blocker than for a new β-blocker after their acute MI. At follow-up, the mortality rate among the β-blocker recipients was 43% less than for norecipients, and use of a calcium channel blocker instead of a β-blocker was associated with double risk of death.

Until recently, the findings of studies concerning efficacy of amiodarone in preventing sudden cardiac death in high-risk patients have been inconclusive. The Cardiac Arrest in Seattle: Conventional versus Amiodarone Drug Evaluation (CASCADE) (73) trial reported a significant improvement in prognosis in survivors of cardiac arrest treated with amiodarone, compared to those treated with conventional antiarrhythmic drugs even when guided by EPS or Holter monitoring. In two studies (74,75) of patients with heart failure and ventricular arrhythmias, the findings, however, were contradictory. In the Congestive Heart Failure-Survival Trial of Arrhythmic Therapy (CHF STAT) (74), no difference in mortality was seen in patients with class II–VI CHF treated with amiodarone as compared to placebo. There was, however, a marginal benefit seen in the patients with nonischemic cardiomyopathies who received amiodarone. In contrast to the CHF STAT trial, in the Grupo de Estudrio de la Sobrevida en la Insufficiencia Cardiaca en Argentine (GESICA) (75) trial, which also included patients with class II–VI heart failure, a significant reduction in mortality was found in patients treated with amiodarone.

In the early studies that assessed the benefit of amiodarone in high-risk MI patients, a reduction in total mortality and sudden death was usually seen in patients treated empirically with amiodarone compared to placebo, although the reduction did not usually reach statistical significance (Table 2) (76–79). In all of these earlier studies of amiodarone therapy, including the CHF studies, elderly patients were not specifically assessed, although patients 70 years or older were included and the findings were independent of patient's age.

Recently, two large multicenter studies, the Canadian Amiodarone Myocardial In-

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Table 2 Randomized Prophylactic Amiodarone Trials After Myocardial Infarction

Study[a] (year of publication)	No. of patients	Entrance criteria besides MI	Change in total mortality	Change in cardiac mortality	Reduction in sudden death
BASIS (1990) (76)	212	Low Class 3 or 4B on Holter	↓65%[b]	↓58%	↓56%
CAMIAT pilot (1991) (77)	77	≥ VPC/h or VT < 10 beats	↓55%	↓44%	↓87%
PAS (1992) (78)	613	None	↓67%	↓45%[b]	↓51%
SSSD (1993) (79)	238	LVEF 20–45% and ≥ 3 VPC/h or VT ≤ 15 beats	↓53%	↓73%	↓36%
EMIAT (1997) (70)	1486	LVEF ≤ 40%	↓1%	↓6%	↓35%[b]
CAMIAT (1997) (69)	1202	≥ 10 VPC/h or > 1 run NSVT	↓18%	↓22%	↓38%[b]

[a] See text for specific name of study.
[b] $p < .05$.
LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; VPC = ventricular premature contractions; VT = ventricular tachycardias.
Source: Adapted from Ref. 80, with permission.

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farction Arrhythmic Trial (CAMIAT) (69) and the European Myocardial Infarction Amiodarone Trial (EMIAT) (70), which separately assessed prophylactic use of amiodarone in over 1000 high-risk-post-MI patients, reported a significant reduction in sudden death with amiodarone, although total mortality was not affected. Patient enrollment criteria in CAMIAT (69) included $\geq$ 10 PVC/h or $\geq$ one run of VT on ambulatory ECG monitoring. In the EMIAT (70), findings of baseline ambulatory monitoring were not used as enrollment criteria, but inclusion criteria included LVEF $\leq$ 40%. The age of the patients in these two studies was between 18 to 91 years; in the CAMIAT, 20% of the patients were 70 years or older and in these older patients the relative risk reduction of cardiac arrest was greater compared to younger patients, although the benefit of amiodarone was independent of patient's age.

Early permanent discontinuation of amiodarone was common in both studies. Approximately 37% of the patients stopped taking the drug for reasons other than outcome events. The main reason for discontinuation of the drug was high rate of adverse effects. Biochemical thyroid disorders were common, but clinical hypothyroidism and hyperthyroidism were rare. In CAMIAT (69), no patient died of pulmonary toxic effects, although in EMIAT (70), there were three deaths in the amiodarone group from pulmonary fibrosis. Two of the three patients who died from pulmonary fibrosis, however, had preexisting pulmonary disease and should not have been included in the study.

Based upon the findings of these studies, the investigators concluded that physicians may be encouraged to consider amiodarone for patients with symptomatic or potentially dangerous ventricular arrhythmias, even after MI. The failure of the studies to demonstrate a significant reduction in total morality is thought possibly to be related to inadequate sample size. Investigators who addressed the issue of sample size reported a significant 12% reduction in total mortality with meta-analysis of 13 randomized controlled trials of 6553 post-MI patients and patients with heart failure who were randomized to amiodarone therapy (80). It should be noted that none of the amiodarone studies were specifically designed to assess elderly patients, but patients $>$ 70 years were included in all the studies. In some studies a subgroup of patients who were 70 years or older was assessed, and the benefit of amiodarone was not significantly different in these elderly patients. Therefore, the recommendations concerning amiodarone therapy should apply to elderly patients, as well as younger patients.

Amiodarone, however, is a drug associated with a complex array of side effects and physicians, prior to prescribing the drug, need to be aware of the pharmacodynamics and the possible side effects of the drug. This is particularly pertinent when treating elderly patients who are prone to develop side effects with drugs and are commonly on multiple drugs, which increases the risk of side effects. In addition, physicians need to understand dosing schedules for amiodarone, including loading and maintenance dosage; and physicians should have a long-term management plan for following a patient taking the drug (see Appendix A for summary of amiodarone use (81,82).

INTERVENTIONAL INVASIVE THERAPY

The use of invasive interventions, both for evaluation and treatment, has been shown to be beneficial in the management of patients with life-threatening ventricular arrhythmias. Programmed ventricular stimulation has proven beneficial in guiding antiarrhythmic drug

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therapy in patients who have had spontaneous and induced VT and in patients who have been resuscitated from cardiac arrest (83,84). Cardiac surgery, including coronary artery bypass graft (CABG) surgery, ventricular resection, and ablation, is beneficial in certain patients with life-threatening ventricular arrhythmias (85,86). More recently, repeated studies (87–89) have shown the internal cardioverter defibrillator (ICD) to be the most effective therapy in preventing sudden death in patients with life-threatening ventricular arrhythmias.

The first large multicenter study to demonstrate that ICD therapy has a positive impact on survival in high-risk post-MI patients was the Multicenter Automatic Defibrillator Implantation Trial (MADIT) (90). One hundred and ninety-six post-MI patients, with a LVEF $\leq$ 30%, documented asymptomatic nonsustained VT, and inducible, nonsuppressible VT on EPS, were randomly assigned to receive an ICD or conventional antiarrhythmic therapy, primarily amiodarone, which was used in 80% of the patients. The mean age of the patients in each group was 64 years and clinical characteristics of the two groups were similar. At an average follow-up of 27 months, total deaths and cardiac deaths were significantly higher in the antiarrhythmic-treated group. Patients treated with ICD demonstrated a 54% reduction in overall mortality as compared to the antiarrhythmic therapy group.

More recently, a larger multicenter study comparing ICD and amiodarone therapy in high-risk patients for sudden cardiac death was completed. The Antiarrhythmics vs. Implantable Defibrillators (AVID) (91) Trial included 1013 post-MI patients, who had either been resuscitated from near-fatal ventricular fibrillation or who had undergone cardioversion from sustained VT. Patients were randomized to either ICD implantation or treatment with class III antiarrhythmic drugs; as in MADIT, amiodarone was the primary antiarrhythmic drug used. Total survival was greater with ICD, with 89% survival, as compared to 82% in the antiarrhythmic drug group at 1 year; 82% vs. 75% at 2 years; and 75% vs. 64% at 3 years ($p < 0.02$). The mean age of the patients in each group was 65 years.

Another recent study that assessed the benefit of ICD as primary prevention was the CABG patch trial (92) that randomized 900 CABG patients at the time of surgery to either ICD or conventional therapy. The patients were considered at high risk for arrhythmic events and sudden death on the basis of an LVEF $\leq$ 35% and ''late potentials'' on signal-averaged ECG. At 32-month follow-up, there was no overall difference in survival between the two groups. The contrary results of this study compared to the findings of the MADIT and AVID studies are unclear, although the high surgical mortality of 6% may have caused both groups to start lower on the curve and made any splaying in the survival curves difficult to demonstrate. Also, the bypass surgery that all the patients underwent may have markedly reduced risk of sudden death and influenced the survival curves.

Overall, findings of the MADIT and AVID studies demonstrate the superiority of ICD over antiarrhythmic drug therapy in prolonging survival among patients with life-threatening ventricular arrhythmias. Therefore, it is the recommendation of the investigators that ICD be offered as first-line therapy in both younger and older patients with such arrhythmias. In certain high-risk patients who do not meet all the criteria of patients in the two published studies, or who are not candidates for ICDs, amiodarone therapy should be considered. Neither study specifically assessed elderly patients, although older patients were included in the study, and age did not appear to influence the favorable benefits of ICD implantation.

Despite the documented benefits of an aggressive approach, including cardiac surgery and ICD implantation in patients with life-threatening arrhythmias, many physicians are hesitant to subject elderly patients to such interventions, and the role of these therapies in elderly patients has been questioned. Elderly patients, compared with younger patients, are known to have increased complications associated with interventional diagnostic testing and are more likely to have higher operative morbidity and mortality rates associated with cardiac surgery (93). Studies (94–99), however, have shown that an aggressive approach in managing patients with life-threatening ventricular arrhythmias is as beneficial in elderly patients as in younger patients (Table 3). In one of the earlier studies, Tresch compared outcomes in a group of 49 elderly patients, age range 68 to 84 years, to that of 44 younger patients, age range 44 to 53 years who were referred to the Johns Hopkins Arrhythmia Service for treatment of recurrent life-threatening ventricular tachyarrhythmias (94). More than 80% of the elderly patients had at least one myocardial infarction before onset of the life-threatening arrhythmia compared with 57% of the younger patients, and twice as many elderly patients had a history of heart failure. Patients underwent coronary angiographic studies and electrophysiological testing before the initiation of definitive treatment. Anatomically, elderly patients exhibited more severe coronary artery disease, with 80% of the elderly patients having three-vessel disease compared with 30% of the younger patients. Therapy consisted of programmed ventricular stimulation, directed antiarrhythmic drug therapy, cardiac surgery (CABG with or without left ventricular resection), and implantation of ICDs. Despite the difference in cardiac history and anatomical disease, no significant difference in complications from the aggressive evaluation was noted between the two age groups, and long-term survival rates were similar. Surgical mortality rates, however, were greater in the elderly patients.

More recently, Tresch and associates (95) studied a group of 54 elderly patients (range 66–80 years of age; mean 70 years) who had ICDs implanted for life-threatening ventricular arrhythmias. The outcome of the elderly patients was compared with that of a group of 79 younger patients (range 18–65 years of age; mean 53 years), who were treated in a similar manner. All patients in each age group underwent extensive evaluation, including coronary angiography and repeated electrophysiological studies. Most patients in each age group had coronary artery disease, and left ventricular function was significantly impaired. The mean left ventricular ejection fraction was 35% in the younger patients and 31% in the elderly patients. An ICD device was implanted in all patients, and 37% of elderly patients and 29% of younger patients had concomitant heart surgery. Concomitant heart surgery consisted of CABG, left ventricular resection, left ventricular cryoablation, or a combination of these. No significant difference was noted in complications from the evaluation or therapy (medical or surgical) between the age groups, and at a mean follow-up of 25 months, only one younger patient and three elderly patients had died suddenly. It was concluded that an ICD is very effective in the treatment of life-threatening ventricular arrhythmias, and this benefit applies to elderly patients as well as to younger patients. Similar findings were found by Scott and associates (96) in a study that compared the use of an ICD in elderly patients 70 years of age or older and in patents under 60 years of age with life-threatening ventricular arrhythmias. No difference was found between the age groups in operative mortality and complications. Four elderly patients did require concomitant cardiac pacemakers. At 1 to 3 years follow-up, no significant difference was observed between the age groups in hospital readmissions, and only one elderly patient had sudden death compared with two younger patients.

More recent studies (97–99) have correlated the findings of the studies of Tresch

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Table 3 Implantable Cardioverter-Defibrillator[a] in the Elderly

Study (year of publication)	Number of Patients	Age (year)	F/U (months)	Survival[b] (percent)	SCD (No. of patients)
Tresch (1987) (94)	49[c]	>65	25	62	8
Tresch (1991) (95)	54	>65	26	87	2
Scott (1988) (96)	20	≥70	36	—	1
Geelen (1997) (97)	32	≥70	48	75	0
Saksena (1998) (98)	—	>65	36	87	—
Panagiotis (1996) (99)	74	≥75	24	80+	0

[a] Many patients underwent cardiac surgical procedure (CABG, ventricular resection) in addition to ICD.
[b] No difference between elderly and younger patients unless denoted.
[c] 45% of patients had ICD (see text for details).
+ = significant difference in 5-year survival between elderly and younger age groups (57% vs. 75%); CABG = coronary artery bypass graft; ICD = implantable cardioverter-defibrillator; SCD = sudden cardiac death.

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and Scott. In separate studies by Geelan (97) and Sakena (98), ICD implantation was performed with low complication rate in elderly patients and long-term survival was similar in elderly and younger patients who received the device. Geelan and associates (97) reported total survival to be 75% after 48 months for the elderly patients compared to 74% after 68 months for younger patients. Furthermore, sudden death was low in both groups; 4% of younger patients died suddenly and no sudden deaths occurred in the elderly patients. In Sakena's study (98) there was no perioperative mortality in the elderly patients and 1-year survival was 96%, 3-year survival was 87%, and 5-year survival was 73%. Survival in a subgroup of patients, 75 years or older, was not significantly different than that of the younger patients. Panagiotis and associates (99) recently reviewed their experience with 699 patients who received ICDs and compared the outcomes in 74 patients ≥75 years of age to that of the other patients. Most of the patients had the ICD implanted because of aborted sudden cardiac death, spontaneous VT, or syncope with inducible VT, and clinical characteristics were similar between age groups. The majority of patients had coronary artery disease and over 40% had LVEF ≤ 30%. Perioperative mortality was low (1.5%) and not significantly different between the groups. As in the other studies, survival curves demonstrated sudden cardiac death to be rare and not different between elderly

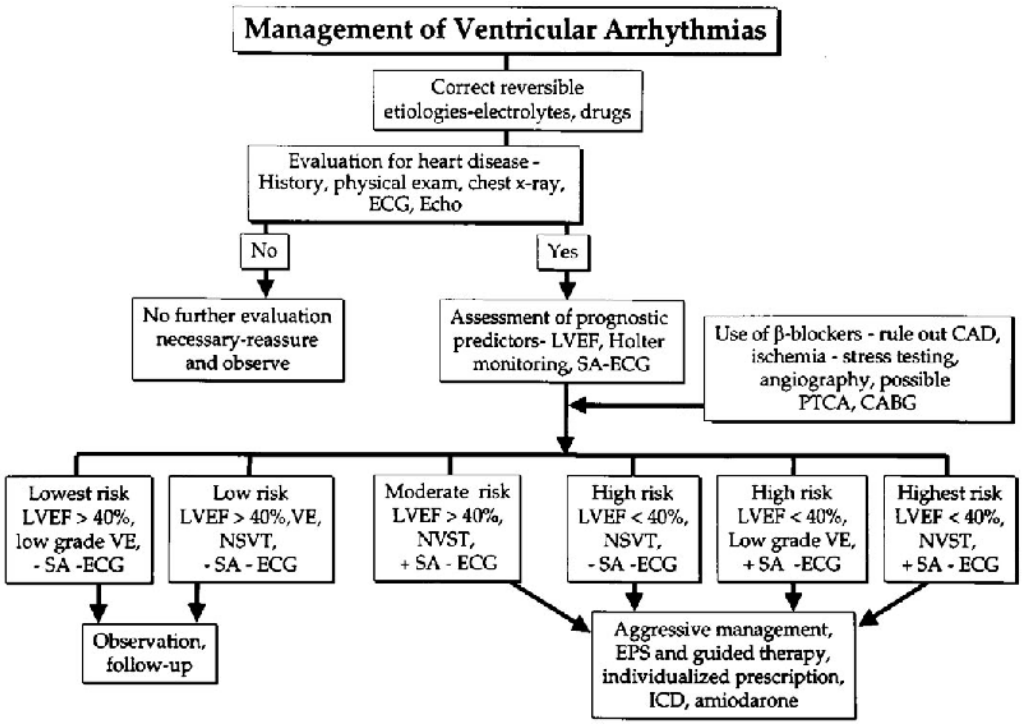

Figure 2 An approach to the elderly person with ventricular arrhythmias. CAD = coronary artery disease; CABG = coronary artery bypass grafting; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; SA-ECG = signal-averaged ECG; VE = ventricular ectopic; VT = ventricular tachycardia. (Adapted from Ref. 59, with permission.).

and younger groups; at 2 years of follow-up, freedom from sudden death was 100% and 98%, respectively, and 100% and 97% at 4 years. A difference in total survival, however, was noted between the two age groups. Actuarial survival at 2 and 4 years of follow-up was 80% and 50%, respectively, in elderly patients and 90% and 78% in younger patients. Besides patient's age, New York Heart Association functional class III, left ventricular ejection fraction $< 30\%$, and appropriate shocks during follow-up were independently associated with increased mortality. The authors concluded that ICD can be placed in elderly patients with minimal risk and is as effective in preventing sudden cardiac death in elderly as in younger patients. However, nonsudden cardiac death is significantly higher in elderly patients.

Based upon the results of these various studies, it appears that ICD can be implanted safely in elderly patients with life-threatening ventricular arrhythmias and, in general, is as beneficial in selected elderly patients as in younger patients. As in younger patients, ICDs should be considered as first therapy in elderly patients with life-threatening ventricular arrhythmias. It should be emphasized, however, that patient selection is mandatory in order to obtain optimum success in all age groups, particularly in elderly patients.

In Conclusion

Elderly patients with ventricular arrhythmias, particularly VT, with underlying heart disease are at risk for increased mortality, including sudden death. Intensive evaluation and stratification into high-a low-risk groups is necessary, in order to decide the optional therapy (Fig. 2). Patients at high risk for future arrhythmic events should be approached aggressively, with consideration of invasive interventional evaluation and therapy including implantation of ICD. In elderly patients who are not candidates for ICD, amiodarone should be considered.

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APPENDIX A: CONSIDERATIONS FOR ORAL USE OF AMIODARONE[a]

Important Pharmacodynamic and Electrophysiological Properties

Parameters	*Chronic oral amiodarone*
Extent of absorption	Poor and slow
Elimination of half-life	3.2–20.7 H (acute)
Therapeutic serum	1.0–2.5 μg/mL range
Heart rate	Slow onset and offset of action
QT/QT_c intervals	Decreased
AV nodal conduction	Prolongation
Noncompetitive beta-blocker	Decreased
Net antiadrenergic effect	Increased
Proarrhythmic effects	Increased
Ventricular function	Rare
Special features	No depression

Drug Interactions with Amiodarone

Agents	*Consequences*
Class IA antiarrhythmic agents	Prolongation of QT interval; torsade de pointes; infranodal atrioventricular block
Beta-blockers	Bradyarrhythmias; sinus arrest; atrioventricular block; sinoatrial block
Calcium antagonists (verapamil and diltiazem)	As with beta-blockers
Warfarin	Increased serum warfarin levels
Digoxin	Increased serum digoxin levels
Dilantin	Increased serum dilantin levels
Antiarrhythmic drugs, in general	May increase serum antiarrhythmic drug level

Side Effects Attributable to Amiodarone Therapy

Occurring early	
Gastrointestinal	Nausea, vomiting, constipation
Central nervous system	Headache, insomnia, impaired memory, hallucinations, ataxia
Cardiac	Bradycardia, sinus arrest, aggravation of arrhythmia (rare)
Occurring late	
Gastrointestinal	Constipation, nausea, weight loss (or sometimes weight gain)
Central nervous system	Headache, ataxis, insomnia, hallucinations, impaired memory, peripheral neuropathy

Cardiac	Bradycardia, sinus arrest, atrioventricular block, torsade de pointes (rare)
Pulmonary	Pulmonary fibrosis with or without respiratory failure
Dermatological	Photosensitivity, ecchymosis, pigmentation
Musculoskeletal	Proximal myopathy (rare)
Hematopoietic	Thrombocytopenia (rare)
Endocrinological	Hyperthyroidism, hypothyroidism (common)
Ophthalmological	Corneal deposits, reduced visual acuity (rare), haloes, macular degeneration (uncommon)
Hepatic	Elevation of liver enzymes, hepatoxicity (uncommon)
Miscellaneous	Gynecomastia, mastalgia; epididymitis

All adverse reactions shown are reversible, although rarely pulmonary fibrosis may prove fatal especially if diagnosed and treated late; death from hepatotoxicity, especially in the setting of preexisting liver disease, has been reported.

Routine Baseline Measurements in Patients Receiving Amiodarone

Complete blood count
Serum electrolytes and serum creatinine
Liver function tests
Thyroid function tests
Serum digoxin or other drugs, the levels of which tend to increase during amiodarone therapy
Chest x-ray
Pulmonary function tests
12-Lead electrocardiogram

Dosing Schedule

Principles: Elimination half-life unusually long, and attainment of steady state in individual patient is empirical.[b]

Initial loading dosage = 800–1200 mg/day (in 2 or 3 equally divided daily doses) for 1 to 2 weeks
Intermediate dosage = 600–800 mg (2 equally divided doses) for 2 to 3 weeks.
Maintenance dosage = 400 mg/day for first year; in some cases dose may be reduced to 300–200 mg/day.

[a] For i.v. use and further details, see Refs. 81 and 82. Adapted from Ref. 81
[b] Dose reduction may be necessary at any time point in loading or maintenance regimens if side effects occur. Dose adjustments at either phase is not reliably ascertained by serum levels of amiodarone or electrocardiographic changes.

Table A1 Protocol for Follow-Up Assessment of Amiodarone

	Duration of therapy				
Test	Baseline	3 mos	6 mos	12 mos	Symptoms
Electrocardiogram	X	X	X	X	
Pulmonary function	X				X
Chest x-ray	X				X
Thyroid	X		X	X	
Liver enzymes	X		X	X	
Ophthalmic exam					X

The time intervals for clinical and laboratory monitoring may vary considerably relative to the complexity of the arrhythmias and the overall clinical condition of the patient.

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27

Cardiopulmonary Resuscitation in the Elderly

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INTRODUCTION

Aging of the American population is the most important demographic factor affecting the prevalence of cardiac arrhythmias because heart disease increases in prevalence with advancing age. Sudden cardiac death is one of the leading causes of death and a major public health problem, representing 30% of all nontraumatic and 50% of all coronary artery disease (CAD)-related deaths. In the U.S., approximately 300,000 to 400,000 sudden deaths occur annually and about two-thirds of these victims are above the age of 65 years (1,2).

Sudden cardiac death may be a terminal event after a prolonged debilitating and painful illness such as cancer, or it may occur following many years of symptoms related to a cardiac disorder. Cardiac arrest in many elderly persons, however, may be the first manifestation of cardiac disease in a supposedly healthy and physically active elderly individual. Depending upon the clinical situation and the person's beliefs, sudden cardiac death may be viewed as a blessing or a tragedy. Certainly, age of the individual will influence the manner in which sudden cardiac arrest is perceived.

Whether cardiopulmonary resuscitation (CPR) should be performed in elderly patients who sustain cardiac arrest is a significant issue confronting the medical profession, as well as the general public. The issue has both ethical and economic implications. Several questions must be answered to put this matter in the right perspective.

1. What percent of elderly patients will survive the CPR, and are elderly survivors, compared with younger survivors, more likely to have significant neurological impairment?
2. Will elderly survivors of cardiac arrest be able to live independent, functional lives or will they spend their remaining years in a long-term care institution?
3. What about the hospital course in elderly patients who are successfully resuscitated?

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4. Will the hospital stay be significantly longer in elderly survivors, and will medical costs be extremely expensive in this group of patients whose long-term survival is problematic?

Such questions require answers in a society that is struggling with ethical issues of providing meaningful life versus prolonging suffering in an environment of medical care cost containment.

In this chapter, we will explore the issues raised above and attempt to decide if CPR is beneficial in elderly patients compared with younger patients following a cardiac arrest. We will examine the data regarding the site of the cardiac arrest, including in-hospital, out-of-hospital, and nursing home settings. The functional status of survivors and the duration of hospitalization and stays in intensive care units will be assessed. We will determine if there are any significant differences in the clinical characteristics between elderly and younger patients who sustain cardiac arrest and determine whether any prearrest or arrest characteristics are predictive of survival. Last, a possible difference in the mechanism of the cardiac arrest between the age groups will be investigated.

The specific age criterion for the elderly in this chapter will vary depending upon the specific study discussed. In most studies, the elderly are classified as 70 years or older. We are unaware of any specific study of very elderly patients, although in all studies the elderly groups included some patients 80 years or older, and some studies included patients 100 years old or older.

IN-HOSPITAL CARDIAC ARRESTS

Results of CPR in hospitalized elderly patients following cardiac arrest have been variable (Table 1). Many early studies (3–6) of CPR in hospitalized patients, which mainly included small numbers of patients, did not find the patient's age to be a significant determinant of survival. Gulati and associates (4), in a prospective study of 52 patients aged 64 to 91 years, hospitalized in Lancashire, England, found 27% of patients who sustained cardiac arrest in 1983 were initially resuscitated and 17% survived to be discharged. Age was not a determinant of survival, although the initial documented cardiac rhythm at the time of the arrest was highly predictive. Twenty-three patients with ventricular fibrillation (VF) as their initial rhythm survived, compared to only 5% of patients with asystole. Similar findings as those in Gulati's study were reported by Bedell and associates in one of the largest prospective studies of CPR performed in hospitalized patients (5). Of 294 consecutive patients hospitalized in Beth Israel Hospital, Boston, who received CPR for a cardiac arrest during an 18-month period between 1981 to 1983, 42 (14%) survived to be discharged. Patients' ages ranged from 18 to 101 years and was not a significant predictor of survival. Prearrest determinants of survival included severity of illness and level of patient's functional activity. At the time of arrest, as in Gulati's study, the presence of VF was the most favorable determinant of survival: 27% of patients with VF survived compared with only 8% of those with other rhythms. Other predictors of survival at the time of arrest included duration of CPR and whether intubation was necessary.

In contrast to the results of many early studies of CPR, some studies have reported less favorable survival rates in elderly hospitalized patients receiving CPR (7–10). George and associates (7), in a prospective study of 140 consecutive hospitalized patients in 1985, reported a 24% survival rate (hospital discharge). The survival rate increased to 36%

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Table 1 Survival Rates After In-Hospital Cardiac Arrest

Study (location, year)	Percent survival to hospital discharge		
	Younger patients	Elderly patients	Total patients
Gulati (Lancashire, UK, 1982) (4)			
All rhythms	18	17	17
VF	—	—	—
Bedell (Boston, USA, 1981–82) (5)			
All rhythms	—	—	14[a]
VF	—	—	27[a]
Woog (Sydney, Aus, 1984) (6)			
All rhythms	15	17	16
VF	—	—	22
George (Nashville, USA, 1985) (7)			
All rhythms	—	—	24[b]
VF	—	—	36[b]
Tortolani (Manhasset, USA, 1990) (8)			
All rhythms	—	—	15[b]
VF	—	—	21[b]
Taffet (Houston, USA, 1984–85) (9)			
All rhythms	16	0	—
VF	—	0	—
Murphy (Boston, USA, 1977–87) (10)			
All rhythms	—	6.5	—
VF	—	21	—
Robinson (York, USA, 1989) (11)			
All rhythms	—	—	29[a]
VF	—	—	50[a]
Roberts (Winnipeg, Canada, 1985–86) (12)			
All rhythms	—	—	10[a]
VF	—	—	19[a]
Rosenberg (Portland, USA, 1989–90) (13)			
All rhythms	25	22	23
VF	—	—	—
Berger (Lexington, USA, 1985–89) (14)			
All rhythms	—	—	11[a]
VF	—	—	15[a]
Tresch (Milwaukee, USA, 1989–90) (18)			
All rhythms	27	24	26
VF	35	39	37

[a] Age not determinant of survival.
[b] Older age unfavorable determinant of survival.
VF = Ventricular fibrillation.
Source: Reprinted with permission from Ref. 41.

in the patients who demonstrated VF or ventricular tachyarrhythmias (VT). A statistical difference in survival was found when patients were partitioned at age 65 years, but ''chi square'' analysis did not demonstrate a significant association between mortality and age partitioned at 60, 63, 67, 70, or 80 years. Eleven percent of patients older than 80 years

survived to hospital discharge. Hypotension and azotemia were the only significant prearrest predictors of survival; however, the collective effect of various clinical characteristics that assessed the patient's prearrest comorbidity significantly correlated with survival. The higher the patient's prearrest comorbidity classification, the less chance the patient had of surviving the cardiac arrest with CPR. The authors concluded that increased comorbidity was a more important prognostic factor than the patient's age in determining success of CPR. Tortolani and associates (8), in a retrospective study published in 1989, reported a survival rate following CPR of 19% in younger hospitalized patients, compared to a 10% survival rate in patients 68 years or older. The authors did not explain their reasoning for why age 68 years was used for dividing the age groups. Therefore, the possibility of post hoc selection must be considered.

Two other studies published in 1988 and 1989, which have been highly publicized, reported very dismal results with CPR in hospitalized elderly patients. Taffet and associates (9), in a retrospective study of CPR in a Veterans Administration hospital in Houston, Texas, found that elderly patients (aged $\geq$70 years) who received CPR in 1988 could be initially resuscitated as successfully as younger patients, although none of the elderly patients survived hospitalization. In comparison, 16% of the patients $<$ 70 years survived to be discharged from the hospital. In this study, the authors did not assess the cardiac arrest rhythm, but, besides patient's age, the presence of sepsis, cancer, increased number of prearrest medications, and absence of witnessed arrest were all felt to be predictors of poor outcome. In the other study, Murphy and associates (10) retrospectively analyzed the success of CPR in 503 persons aged $\geq$70 years who sustained cardiac arrest between 1977 and 1987 in the city of Boston. Of the 503 persons, 259 were hospitalized at the time of cardiac arrest and 244 were living in the community (out-of-hospital arrest). Of the 259 hospitalized patients, 36% were initially resuscitated, although only 6.5% of the patients survived to be discharged. Moreover, at the time of discharge, approximately 50% of survivors had significant neurological or functional impairments and over 50% of the patients were discharged to either a rehabilitation institution or a long-term care facility. As in Taffet's study, prearrest clinical characteristics that favored survival included lack of chronic and multiple acute illnesses. There was a trend, although the difference was not significant, that patients with functional or mental impairments had worse outcomes than patients without such impairments. The presence of VF at the time of the arrest was a significant favorable predictor of survival. Twenty-one percent of the elderly survived if their cardiac arrest rhythm was VF or VT compared with a survival rate of only 2.6% in those with other rhythms. However, VF/VT was not a common initial cardiac rhythm; VF/VT was observed in only 27% of the patients at the time of arrest. Electromechanical dissociation or asystole was the more common rhythm in these elderly patients. Other arrest characteristics that favored survival were a witnessed arrest and CPR duration $<$5 min. Upon the basis of the unfavorable results, both Taffet (1988) and Murphy (1989) concluded that CPR is rarely beneficial in hospitalized elderly patients who sustained cardiac arrest and questioned whether the procedure should be performed.

Contrary to the dismal findings of Taffet and Murphys' studies, findings of more recent published studies of CPR performed on hospitalized elderly patients have reported more favorable results (11–20). Robinson and associates (11) reported a 29% hospital discharge survival rate in hospitalized patients who received CPR following cardiac arrest; and, in this study, the patient's age was not a significant determinant of survival. As reported in most previous studies, patients demonstrating VT/VF had a significantly better chance of surviving compared to patients with other arrhythmias. None of the patients

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who demonstrated asystole and only 1% of patients with electrical mechanical dissociation survived. Duration of CPR was the other arrest determinant of survival; CPR of ≤10 min duration was associated with favorable results, compared with CPR > 10 min. Prearrest functional status was not specifically assessed, although all but one of the survivors lived at home prior to the hospital CPR and none of the survivors had any limitations in their daily activities prior to the hospital admission. Follow-up evaluation of the patients at mean 31 months demonstrated that 54% of the patients were alive and the majority of the patients were living independently at home without any compromise in activities. In another retrospective study published in 1993, Rosenberg and associates (13) assessed success of CPR in two university-affiliated community hospitals located in Portland, Oregon. Survival to hospital discharge was 23% in the total patient population. The patient's age was not a significant determinant of survival, although, as in other studies, VT/VF and short CPR duration were favorable determinants of survival. Survival to hospital discharge was also significantly influenced by the patient's prearrest comorbidity. The specific comorbidities, however, differed in each of the two hospitals and an increased number of comorbidities was much more predictive of survival than a specific comorbidity.

In a more recent study (1994) comparing success of hospital CPR between elderly and younger cardiac arrest victims, Tresch and associates (18) found no significant difference in hospital or long-term survival between patients ≥70 years and patients <70 years. Over 25% of all patients survived to be discharged, and if their initial cardiac rhythm was VT/VF at the time of arrest, over 35% survived. At 2 years follow-up, over 70% of all patients were alive, and the majority were functioning at their prearrest status, regardless of their age. In assessing prearrest clinical characteristics, the only significant difference between elderly and younger patients was that the elderly had a higher prevalence of atrial fibrillation. Prior to hospitalization, the patients, including the elderly, were very active and functionally independent, with most patients free of significant chronic illnesses or disabilities. The majority of patients were hospitalized for acute coronary syndromes, including unstable angina and acute myocardial infarction, and over 80% of the patients had their rhythm monitored either in an intensive care unit or on telemetry at the time of arrest. In over 50% of patients the arrest was witnessed. Based upon the results of this study, the investigators concluded that hospitalized patients who received CPR in the 1990s were a more selected group, compared to patients who received CPR in previous years. Regardless of age, the patients who receive CPR are usually highly functional, are commonly hospitalized for acute coronary syndromes, and the majority are closely monitored prior to a cardiac arrest. In these patients, CPR can be very gratifying and elderly patients will benefit from the procedure as well as younger patients. Other recent studies (19) have confirmed that elderly patients whose primary illness is a cardiac disorder have a much better chance of surviving with CPR than patients whose primary illness is noncardiac.

OUT-OF-HOSPITAL CARDIAC ARREST

In general, most studies (20–26) of out-of-hospital cardiac arrest have reported that elderly victims do benefit from CPR (Table 2). Tresch and associates (20), in a study of paramedic-administered advanced cardiac life support in Milwaukee, Wisconsin, reported that elderly patients (≥70 years) could be initially resuscitated as successfully as younger patients, although elderly patients were less likely to survive hospitalization. Nine percent of elderly

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Table 2 Survival Rates After Out-of-Hospital Cardiac Arrest

Study (location, year)	Percent survival to hospital discharge	
	Younger patients	Elderly patients
Murphy (Boston, USA, 1977–87) (10)		
All rhythms		0.8
VF		2.0
Tresch (Milwaukee, USA, 1983–85) (20)		
All rhythms	16	9
VF	23	16
Tresch (Milwaukee, USA, 1980–85)[a] (38)		
All rhythms	24	10
VF	47	24
Bonnin (Houston, USA, 1987) (21)		
All rhythms	12	7
VF	20	14
Denes (Minneapolis, USA, 1987–88) (22)		
All rhythms	—	—
VF	16	18
Eisenberg (King City, WA, USA, 1975–89) (23)		
All rhythms	22	9
VF	32	20
Longstreth (Seattle, USA, 1983–88) (24)		
All rhythms	14	10
VF	30	24
Juchems (Aschaffenburg, GDR, 1981–91) (26)		
All rhythms	14	11
VF	—	—

[a] Arrest witnessed by paramedics.
VF = Ventricular fibrillation.
Source: Reprinted with permission from Ref. 41.

patients survived to be discharged from the hospital compared with 16% of younger patients. As in studies of in-hospital CPR, the survival significantly improved in those patients with VT/VF. Sixteen percent of elderly patients and 23% of younger patients survived if their cardiac rhythm was VT/VF. Even in patients over 80 years of age, 14% survived if their initial documented arrhythmia was VT/VF. Unfortunately, only 44% of elderly patients demonstrated VT/VF, which was significantly less compared to younger patients. Electromechanical dissociation and asystole were the more common initially documented arrhythmias in the elderly. Besides rhythm differences, elderly patients' arrests were more commonly witnessed compared with younger patients, although elderly patients were less likely to be receiving bystander CPR upon arrival of paramedics.

Other recent studies have reported similar favorable findings to those of Tresch and associates. Bonnin and associates (21) in Houston, Texas, and Denes and associates (22) in Minneapolis, Minnesota, reported survival rates of 14% and 18%, respectively, in elderly patients who received CPR following out-of-hospital cardiac arrest if the initial arrest rhythm was VT/VF. Eisenberg and associates (23), in one of the largest patient series in the U.S., reported even more favorable results. Twenty percent of 569 patients aged ≥75 years in King County, Washington, who sustained out-of-hospital cardiac arrest between

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1975 and 1989 survived following CPR if their arrest rhythm was VF. More recently, Longstreth and associates (24) reported a 24% survival in elderly patients aged ≥70 years who received out-of-hospital CPR in Seattle, Washington, if their initial cardiac rhythm was VF. Outcome was independent of patient's age until the ninth decade. As in all the studies, patients in Longstreth's study who demonstrated asystole or electromechanical dissociation at the time of cardiac arrest had little chance of surviving. Only 1% of elderly and 2% of younger patients survived the cardiac arrest if their rhythm was electromechanical dissociation or asystole at the initiation of CPR.

It should be noted that, as in their study of elderly hospitalized patients, Murphy and associates (10) reported very poor survival rates in elderly patients who sustained out-of-hospital cardiac arrest in Boston between 1977 and 1987. Less than 1% of patients 70 years or older survived. The authors did not report survival in younger patients receiving CPR; thus we do not know if the poor results in the elderly patients were related to patient's age, or merely reflected the poor success of CPR in the Boston area during this period. Two other recent studies (26,27) of out-of-hospital CPR, in large metropolitan areas (Chicago and New York), have also reported very poor success. In New York City, during a 6-month period in 1990 to 1991 only 1.4% of all residents who received out-of-hospital CPR by paramedics survived, and even in the patients who demonstrated VF only 5.3% survived (27). Similar dismal results were noted in the Chicago study, and the findings of this study suggested that age was a determinant of survival (28). Such poor survival rates are very troublesome. The explanation for these poor results, compared to other studies, is unclear. Possibilities include differences in the predictors of survival: initial cardiac rhythm, down-time before CPR is initiated, availability of advanced cardiac life support in the field and training level of paramedics, among other variables.

NURSING HOME CARDIAC ARREST

The issue of CPR in the nursing home has not received much interest from the medical profession until recently. However, in the last decade, with the increased emphasis on long-term care and the increased pressure from society for medical cost containment, the issue has attracted increasing attention. Due to the complexity of the issue, which involves both medical and ethical questions, answers remain controversial and emotional, as well as unresolved.

In general, CPR is infrequently used in nursing homes. Studies have reported that CPR is used in only 2 to 5% of all nursing home deaths with some nursing homes never performing CPR (29). In reference to success, most studies (30–33) have reported a very poor survival rate in the majority of nursing home patients who received CPR (Table 3). Applebaum and associates (30) reported only 2 of 11 (2%) nursing home residents in Baltimore City or Baltimore County who received CPR in 1987 by trained ambulance teams survived. In comparison, 11% of non-nursing home residents ≥65 years or older who received CPR survived. The mean age of the nursing home residents was 82 years; for nonresidents it was 75 years. Similar dismal findings were reported in separate studies by Awoke (31) and Gordon (32). In both studies no residents in long-term care facilities who received CPR survived. Cardiopulmonary resuscitation in both studies was performed by trained in-site physicians and resuscitation teams. Upon the results of these studies, the use of CPR in nursing homes has been questioned.

Two recent studies, by Tresch (34) and Ghusn (35), however, found success of CPR

Table 3 Survival Rates After Nursing Home Cardiac Arrest

Study (location, year)	No. of patients	Mean age (yr)	Survival to hospital discharge
Kaiser (Rochester, USA, 1977–85) (33)			
All rhythms	32	72	16[a]
Applebaum (Baltimore, USA, 1987) (30)			
All rhythms	177	82	2
Awoke (Washington DC, USA, 1987–90) (31)			
All rhythms	57	75	0
Gordon (Toronto, Canada, 1988–91) (32)			
All rhythms	41	81	0
Tresch (Milwaukee, USA, 1986–91) (34)			
All rhythms	196	79	5
VF	39	—	15
VF witnessed arrests	22	—	27
Ghusen (Houston, USA, 1986–91) (35)			
All rhythms	114	81	11
VF	16	—	13
Unwitnessed arrests	—	—	0

[a] Alive at 30 days.
Source: Reprinted with permission from Ref. 41.

to be quite variable among nursing home patients, and in a subset of patients, the survival rate was not significantly different than that reported in community living elderly persons who receive out-of-hospital CPR. In both studies, the success of CPR was highly dependent upon whether the arrest was witnessed and whether the initial documented cardiac arrest rhythm was VF. In Tresch's study of 196 nursing home patients, mean age 78.5 years (range 31–107), 27% of the patients whose arrest was witnessed and who demonstrated VF survived with CPR. At follow-up, the majority of patients were without a significant functional change from their prearrest status. Without the presence of the two determinants (witnessed arrest and presence of VF), the survival rate was only 2.5%. Unfortunately, patients' prearrest clinical characteristics did not separate survivors from nonsurvivors. The mean length of hospital stay for the total patients who were initially successfully resuscitated was 9.9 days and 63% of the patients who died in the hospital died within 24 h. From their findings, Tresch and Ghusn concluded that a subset of nursing home patients sustaining cardiac arrest may benefit from CPR. Therefore, CPR should be offered to those nursing home residents who desire it, but CPR should only be initiated if the arrest is witnessed, and only continued if the patient's initial documented rhythm is VT or VF.

FUNCTIONAL STATUS OF SURVIVORS OF CARDIAC ARREST

Most studies of elderly survivors of cardiac arrest show that the majority of survivors are without significant neurological or functional impairments and return to their prearrest

activities. Tresch and associates (36) found that the deterioration of prearrest functional status to hospital discharge status was no different between elderly and younger survivors of out-of-hospital cardiac arrest; and the majority of survivors, regardless of age, were functionally independent at hospital discharge. Furthermore, duration of hospitalization and length of stay in an intensive care unit did not differ between the age groups. Long-term survival was also similar between the age groups with approximately two-thirds of elderly and younger survivors alive and functionally independent at 2 years follow-up.

In another study Tresch and associates (18) assessed the functional status of 39 survivors of in-hospital cardiac arrest. As in their study of out-of-hospital survivors of cardiac arrest, pre-arrest to post arrest functional deterioration was not different between elderly and younger survivors. Functional status was good in these survivors and most patients were completely independent at the time of hospital discharge. Moreover, at mean follow-up of 29 months, all living survivors were functioning independently.

The lack of significant neurological and functional impairment in elderly survivors of cardiac arrest has been further corroborated by the findings from other recent studies. As in the studies by Tresch and associates (18,36), Longstreth and associates (24) found no significant difference between the age groups in the number of survivors of out-of-hospital cardiac arrest who were discharged to nursing homes. And, in a prospective study of CPR in a VA medical center in Lexington, Kentucky, published in 1994, Berger and associates (14) reported that the majority of survivors were discharged home, regardless of age, and had no significant neurological or functional impairment.

In contrast to these favorable findings concerning functional status of elderly survivors of cardiac arrest, some studies (10,37) have found significant deterioration of prearrest functional status following CPR in survivors and the deterioration has been noted to be more severe in elderly survivors. As previously noted, Murphy and associates (10), in a study of elderly persons who received CPR, reported approximately 50% of survivors of cardiac arrest aged $\geq$70 years had significant neurological and functional impairment and over 30% of the survivors required placement in nursing homes following hospital discharge. Fitzgerald and associates (37) also found significant deterioration in functional status in survivors of in-hospital cardiac arrest and worse functional deterioration was associated with greater age and longer hospital stay prior to the cardiac arrest. Multivariant logistic regression analysis demonstrated that survivors older than 75 years were 5.3 times as likely to have deterioration of function after CPR than patients 55 years or younger.

We are unclear concerning the explanation for the differences between the unfavorable findings of Murphy and Fitzgeralds' studies and the previous studies that reported favorable results. In the studies that reported favorable findings, only patients who survived to hospital discharge were analyzed, whereas it appears that some of the patients analyzed by Fitzgerald died before hospital discharge. Thus, it is possible that the patients who died before hospital discharge had severe neurological impairments, which may partially explain the increased number of patients with functional impairment in Fitzgerald's study, compared to the other studies. Furthermore, the patients in Fitzgerald's study were patients enrolled in the Study to Understand Prognosis and Preferences for Outcomes and Risks of Treatment (SUPPORT), a group of patients who are seriously ill with an aggregate 6-month survival of only 47%. Some of the SUPPORT patients had metastatic cancer, nontraumatic coma, severe heart failure, or end-stage renal disease. Therefore, the patients in Fitzgerald's study had much worse prearrest comorbidities than the patients in the other studies, which may be another reason for the worse postarrest functional status of their survivors. And, the elderly patients in support more commonly have increased prearrest

comorbidities compared to younger patients, which may explain why the elderly survivors in Fitzgerald's study demonstrated severe functional deterioration following successful resuscitation: minor changes would produce significant functional deterioration in these frail chronically ill patients.

POSSIBLE DIFFERENCE IN CHARACTERISTICS OF CARDIAC ARREST BETWEEN AGE GROUPS

In some studies of CPR (18,20,21), VF has been found to be the most common initial documented arrhythmia in younger patients, whereas bradyasystole was the more common initial documented arrhythmia in elderly patients. In addition, elderly patients who sustained cardiac arrest more commonly had a history of heart failure and were more likely to be taking digitalis at the time of the arrest. To assess whether the bradyasystole arrhythmia in elderly patients was not merely degeneration of an initial ventricular tachyarrhythmia, Tresch and associates studied a subset of patients whose out-of-hospital arrest was witnessed by paramedics (38). In this group of patients, the cardiac arrest occurred after arrival of paramedics. The patient's cardiac rhythm was therefore monitored at the time of the arrest. As noted in their previous studies, the investigators found a significant difference in cardiac rhythm between age groups. Only 22% of patients $\geq$ 70 years demonstrated VF as their initial cardiac rhythm at the time of the onset of arrest, compared with 42% of younger patients. In turn, elderly patients more commonly demonstrated bradyasystole rhythms. Besides rhythm, symptoms preceding the arrest were found to be age-related. Younger patients were more likely to complain of chest pain, whereas elderly patients complained of dyspnea. Regardless of age, patients with chest pain before the arrest were more likely to demonstrate VF at the time of arrest, whereas patients with dyspnea demonstrated bradyasystole. Survival was dependent upon both the patient's cardiac rhythm at the time of arrest and the patient's symptoms preceding arrest. Approximately 60% of the younger and elderly patients survived if they complained of chest pain before the arrest and demonstrated VF at the time of arrest. Patients who complained of dyspnea were less likely to survive, as were patients who did not demonstrate VF.

The explanation for the difference in the cardiac rhythm at the time of arrest and the difference in symptoms before the arrest between age groups is unclear. Tresch and associates, in some of their studies (36,38), found that more elderly patients who sustained out-of-hospital cardiac arrest had a history of heart failure and were receiving digoxin and diuretics compared with younger patients. The investigators hypothesized that cardiac arrest in many elderly patients may be related predominantly to left ventricular dysfunction with underlying heart failure, which would explain the dyspnea in the elderly patients preceding arrest, and might also explain the bradyasystole noted at the time of arrest. In contrast, cardiac arrest in younger patients may more frequently be related to acute myocardial ischemia or infarction manifested as acute chest pain with the development of VF and resultant cardiac arrest. Other investigators (39) have reported severe bradycardia or electromechanical dissociation to be a common cardiac arrhythmia in patients with advanced heart failure who sustained cardiac arrest, which would be compatible with the proposal of Tresch and associates. Investigators other than Tresch and associates have also found VF to be less common in elderly patients who sustain cardiac arrest, compared with younger patients. Furthermore, a low prevalence of VF associated with cardiac arrest has been found in nursing home residents who sustain cardiac arrest and many nursing

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home patients are elderly, have a history of heart failure, and are taking digitalis and diuretics. In turn, not all investigators have found a significant difference in rhythms between elderly and younger patients who experience cardiac arrest.

CONCLUSIONS AND CONSIDERATIONS

Age alone does not appear to be the most significant determinant of survival in patients who receive CPR following cardiac arrest and CPR can be beneficial in elderly patients, as well as younger patients. Based upon the results of numerous studies, we now understand what factors do influence success of CPR. Patients' prearrest comorbidity is one of the most significant determinants. Patients with acute cardiac illness have more favorable success with CPR than do patients with such chronic illnesses as renal failure or cancer. Not only the specific comorbidity, but also the number of chronic illnesses present appear to be an important determinant of survival; the more illnesses present and the more medications taken, the less chance of survival with CPR. In addition to comorbidity, functional status is important. Patients with chronic disabilities, physical or mental, are less likely to do well with CPR. The influence of such variables may be the reason that hospitalized patients who sustain cardiac arrest do worse with CPR than do out-of-hospital persons who receive CPR. The presence of such variables may also partially explain the poor results with CPR in nursing homes.

Besides prearrest variables, certain arrest characteristics are important determinants of survival with CPR. The most important arrest variable is the initial cardiac rhythm. All studies show that patients with VF or VT are the patients most likely to survive with CPR. Some investigators have found witnessed arrest another favorable variable for survival. Duration of CPR is also an important factor, as is the need for intubation.

Recognizing that there are always exceptions, it appears, in general, we can now predict which patients are not likely to survive with CPR. Based upon this information, patient selection is critical, and guidelines need to be developed for initiation, continuation, and duration of CPR in the elderly. Too often the patient or the patient's family is not properly informed about the chances of successful CPR and decisions concerning CPR or DNR are emotional responses, instead of rational, reasoned decisions. Other times the decision concerning CPR reflects the physician's, or in some cases, the nurse's, preferences, rather than the patient's.

It is gratifying that some recent studies show that patients receiving CPR are becoming a more ''selective group'' and in these patients results of CPR are as rewarding in elderly as well as younger patients. Such selection, however, occurs too infrequently and if we, as a profession, fail to accomplish the task of ''selecting'' patients we most likely will lose the right to participate in CPR decision making at all. And that would invite continued erosion of the clinical skill, art, and judgment that results in appropriate individual care (40), which is so important in caring for elderly patients.

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28

Bradyarrhythmias and Cardiac Pacemakers in the Elderly

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DIAGNOSIS

While bradycardia is used to describe any slow heart rhythm, usually under 60 bpm, it is always caused by specific abnormalities in cardiac impulse formation or conduction. Mean heart rates decline with age, but the prevalence and significance of bradyarrhythmias in the elderly remain controversial (1–5). Degenerative disease in the sinus node can lead to pathological sinus bradycardia, sinus arrest, or sinus exit block. Sick sinus syndrome is a condition that includes one or several abnormalities in sinus node or atrioventricular (AV) node function. AV block and block in the His-Purkinje system can occur as a result of ischemic heart disease or various degenerative processes. Baroreceptor and autonomic abnormalities can produce symptomatic sinus slowing or AV node block. Bradyarrhythmias are in the differential diagnosis of syncope and presyncope in the elderly. The identification of bradycardia as a cause of syncope is crucial because pacemaker therapy usually relieves the problem.

History

Bradycardia should be suspected in patients who present with symptoms of syncope, presyncope, episodes of light-headedness, or palpitations. Patients should be questioned about the relationship of these symptoms to time of day, activity, and position, since the causes of bradycardias are usually intermittent or precipitated by specific events. Often there are associated symptoms, such as dyspnea or chest pain, that can give a clue to the etiology of an arrhythmia. The patient should be asked to tap out any associated palpitations to help in differentiating rapid from slow and regular from irregular rhythms. If symptoms are associated with activity or rapid palpitations, a bradycardia is unlikely to be an isolated cause of the patient's complaints. History of associated illness, such as thyroid disease, and use of sedative drugs or medications that can produce bradycardia (such as beta-blockers, digoxin, or calcium channel blockers) should be elicited (6). Family members should be instructed to take the patient's pulse during episodes and to comment on the regularity and rate of the pulse.

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Physical Examination

During an arrhythmia, pulse rate, rhythm, and blood pressure abnormalities may be detected. In addition, AV dissociation and variability of systolic blood pressure from beat to beat may give clues to the types of arrhythmia. The changes associated with AV dissociation may be seen as abnormalities in the venous pulse, such as intermittent high-volume A waves.

Electrocardiography

The findings obtained during history and physical examination may be nonspecific, and the diagnosis of symptomatic bradyarrhythmias rests with demonstration of the abnormality by electrocardiography (possibly with carotid sinus massage) and electrophysiological testing. Because of the intermittent nature of sinus node and conduction system abnormalities, a single 12-lead electrocardiogram (ECG) or a longer ECG rhythm strip are usually inadequate to make a diagnosis. Twenty-four-hour ambulatory (Holter) recordings should be obtained early in the evaluation of the patient. Careful evaluation of the rate and relationship of P waves and QRS complexes should be made. All pauses greater than 1.5 s on Holter monitoring should be examined to identify the mechanism of the event. In all cases, symptoms should be correlated with ECG abnormalities, and the patient should be instructed to keep a detailed diary of symptoms during the time of the Holter recording. Pauses of greater than 2 to 3 s may occur in normal individuals. If the event does not produce symptoms and is due to sinus node dysfunction, Mobitz Type I AV block, or excess vagal tone, a pacemaker is usually not indicated. Lack of heart rate increase with exercise may be pathological and could result in presyncope.

In many individuals, 24- or 48-h Holter monitoring may be inadequate to identify symptomatic bradycardias. In these cases, a patient-activated event recorder or continuous memory loop recorder may be useful. Event recorders store several seconds or minutes of ECG data when an event button is activated. The stored tracing can be sent to a central location via telephone after the patient has recovered from the event. If episodes produce immediate syncope and do not allow the patient sufficient time to activate an event recorder, a 24-h memory loop recorder is more appropriate. These devices are more cumbersome, since they remain on the patient for prolonged periods of time (up to 1 month or more), but for recording and correlating rare symptoms their use may be necessitated.

Provocative Testing

When the preceding techniques fail to provide a diagnosis, exercise testing, carotid sinus massage, or pharmacological testing can be employed. All such tests are generally insensitive and nonspecific, so they must be used in concert with other diagnostic tests. Failure of the sinus node rate to increase with exercise has been reported in sick sinus syndrome (7,8). An abnormally long pause during carotid sinus massage (greater than 3 s) may indicate hypersensitive carotid sinus reflex, but this may occur in asymptomatic elderly patients (9). Determination of intrinsic heart rate following autonomic blockade with propranolol and atropine may identify sinus node function that falls outside population-determined norms. Since all these tests fail to correlate abnormalities with symptoms, however, their usefulness is limited.

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Electrophysiological Testing

The technique of electrophysiological testing can be useful in the diagnosis and management of a wide variety of atrial and ventricular arrhythmias (10). Pacing wires are inserted via a subclavian and/or femoral vein, with electrodes in the high right atrium and the right ventricular apex, and via the right femoral vein across the tricuspid valve, with electrodes in the region of the bundle of His (Fig. 1). Recordings are made from these sites and from others as necessary. By analyzing conduction times, sites of block can be defined; by pacing the atrium and ventricle, the integrity of the conduction system can be studied and arrhythmias can be reproduced.

Sinus node function is usually evaluated during electrophysiological testing using sinus node recovery time and sinoatrial conduction time. The sinus node recovery time examines the ability of the sinus node to recommence firing after overdrive suppression with atrial pacing. A normal value in most laboratories is less than 1500 ms. The measurement can be corrected for baseline sinus rate, in which case normal values range from 350 to 550 ms, depending upon the laboratory. Sinoatrial conduction time is an indirect measurement of the time it takes for an impulse to travel into and then exit from the sinus node. The sensitivity of these techniques, even when combined, is only about 64%, with a specificity of about 88% (11).

Atrial conduction, AV node function, and His-Purkinje system function are assessed by measuring intracardiac conduction intervals and by atrial pacing. An electrophysiological study can be useful in identifying the site of atrioventricular block and in assessing the competence of the His-Purkinje system at rest and during pacing.

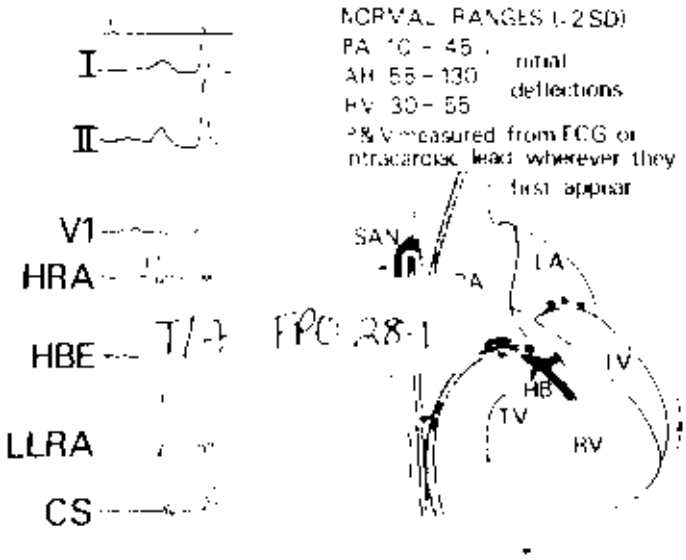

Figure 1 Surface electrocardiograms and intracardiac electrograms recorded during an electrophysiologic study. Arrows show location of electrodes in the heart. I, II, VI = standard surface ECG leads; HRA = high right atrium; HBE = His bundle electrogram; LLRA = low lateral right atrium; CS = coronary sinus; P = P wave; V = ventricular depolarization. (From Ref. 10, with permission.)

An electrophysiological study should be performed in patients with suspected sinus node disease or AV block who are symptomatic with syncope or presyncope and in whom the relationship between symptoms and a bradyarrhythmia has not been established. Patients who have symptoms documented to be due to bradyarrhythmias or patients with degrees of heart block that require permanent pacing (see section on indications for pacemaker therapy) do not require an electrophysiological study. When the site of AV block cannot be determined by electrocardiography or Holter monitoring and differentiation of the site would help in the decision to implant a pacemaker, a His bundle study should be performed. This may be necessary in patients with fixed 2:1 AV block and bundle branch block or in patients with Mobitz type II block with a normal QRS in whom block in the Bundle of His is suspected. The use of electrophysiological testing to diagnose patients with syncope of undetermined origin is discussed in Chapter 24.

NORMAL CARDIAC CONDUCTION SYSTEM

The understanding of bradyarrhythmias and their management is enhanced by a knowledge of the normal cardiac conduction system (Fig. 2). Normal cardiac activation originates in a group of cells in the high right atrium, known as the sinus node. The node is composed of nodal cells, which are the source of normal impulse formation, transitional cells, which may form the pathway for impulse conduction to the atrium, and working atrial myocardial cells, which extend into the node from surrounding atrial tissue. The sinus node receives innervation from postganglionic adrenergic and cholinergic nerve endings. Vagal stimulation slows sinus node discharge and prolongs conduction times within the node through

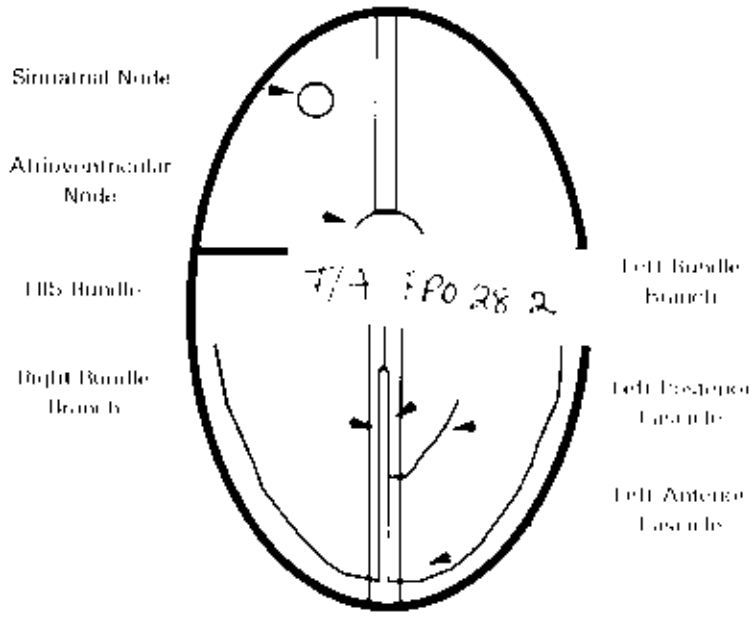

Figure 2 Components of the cardiac conduction system (see text).

release of acetylcholine, which hyperpolarizes the cell membrane producing an increase in the time for the cell to reach firing threshold. Adrenergic stimulation of beta-1 receptors increases sinus rate by increasing the slope of diastolic depolarization. From the sinus node, the normal cardiac impulse travels through atrial tissue and possibly through internodal and interatrial pathways, although this latter point is controversial (12,13). Conduction from right to left atrium appears to travel preferentially over a band of muscle fibers known as Bachmann's bundle.

The signal eventually reaches the AV node, located in the lower part of the right atrium near the septal leaflet of the tricuspid valve, anterior to the ostium of the coronary sinus. The AV node conducts the impulse from the atrium to the Bundle of His. In normal hearts, the remainder of the interface between atria and ventricles is electrically insulated. In patients with Wolff-Parkinson-White syndrome, this insulator and the AV node are short-circuited via a bypass tract known as a Kent bundle.

AV nodal tissue exhibits a characteristic known as decremental conduction: the more rapidly impulses stimulate and attempt to pass through the AV node, the more slowly the node will conduct, even to the point of intermittent block. Like the sinus node, the AV node is richly innervated by cholinergic and adrenergic nerve endings. Vagal stimulation increases AV node conduction time and can produce block. Sympathetic stimulation shortens AV node conduction time and refractory periods.

From the AV node, the cardiac impulse travels to the Bundle of His, the first part of the specialized ventricular conduction system. From the Bundle of His, the impulse travels through the bundle branches and eventually to terminal Purkinje fibers. These fibers form interweaving branches on the endocardial surface of both ventricles and allow rapid transmission of the impulse to the entire ventricular myocardium in a period of 60 to 100 ms. Without the specialized ventricular conduction system, muscle conduction of the cardiac impulse would require longer periods of time, typically on the order of 120 to 160 ms, resulting in a prolonged QRS duration on the surface ECG. The anatomy of the bundle branches is variable between individuals, although the most common configuration is that of a main right bundle branch and a left bundle branch that bifurcates into an anterior and a posterior fascicle.

Bradyarrhythmias can result from abnormalities in impulse formation in the sinus node or impulse conduction in the sinus node, atrial myocardium, AV node, Bundle of His, or bundle branches. Total or subtotal destruction of the sinus node or transitional zone tissue may be found in patients with sick sinus syndrome. Inflammatory and degenerative changes can also be seen in some cases. AV nodal block may be due to infiltration of the node by fibrosis or calcification from adjacent structures (Lev's disease), like that in calcific aortic stenosis. The ventricular conduction system can be affected by degeneration caused by chronic ischemic heart disease or by a sclerotic degenerative process (Lenegre's disease) (14).

SINUS NODE DYSFUNCTION

Sinus Bradycardia

Sinus bradycardia is defined as a sinus node rhythm with a rate of less than 60 bpm. The arrhythmia may result from excessive vagal tone or diminished sympathetic tone, medications such as beta-blockers, digoxin, or calcium channel blockers, or because of sick sinus syndrome and its associated anatomical abnormalities. Well-trained athletes can

exhibit sinus bradycardia, but this is a less common cause in the elderly population. Sinus bradycardia can also occur during sleep, with manipulation of the eye during surgery, or secondary to hypothyroidism, hypothermia, intracranial tumors, meningitis, or increased intracranial pressure. Excessive vagal tone, as is seen during intense vomiting, can also produce symptomatic sinus bradycardia. Besides beta-blockers and calcium channel blockers, lithium and clonidine have been reported to cause sinus bradycardia. Beta-blocker eye drops may be absorbed and produce sinus slowing or AV node block (15,16).

The ECG during sinus bradycardia shows normal-appearing P waves before each QRS complex and occurring at a rate less than 60 bpm. Normal-appearing P waves imply that the impulse originates in the sinus node. There can be coexisting AV block, which can further lower the ventricular rate.

Treatment of sinus bradycardia is usually not necessary, unless the patient is symptomatic during the periods of slow rhythm. In the acute setting, such as following a myocardial infarction, symptomatic patients can be treated with 0.5 mg intravenous (i.v.) atropine, repeated every 5 min up to 2 mg. If atropine fails, an external transthoracic pacemaker or a temporary transvenous pacemaker should be employed. If temporary pacing is not available, consider cautious use of i.v. dopamine (5–20 μg/kg/min) or i.v. epinephrine (2–10 μg/min). Isoproterenol should be used, if at all, with extreme caution, especially in patients with myocardial ischemia, since it can increase myocardial oxygen demand and is proarrhythmic even at low doses. If the patient exhibits chronic symptomatic sinus bradycardia not attributable to medications, permanent pacing is the treatment of choice.

Sinus Arrest

Sinus arrest occurs because of an abnormality in impulse formation caused by medications or any of the disease processes mentioned previously. Bradycardia occurs if lower pacemakers such as the AV node fail to produce an appropriate escape rhythm.

On the ECG, P waves are identified before each QRS and are normal in configuration, as they are in sinus bradycardia. The tracing shows a pause in the sinus rhythm, with a P-P interval that is not equal to a multiple of the patient's basic P-P interval (Fig. 3).

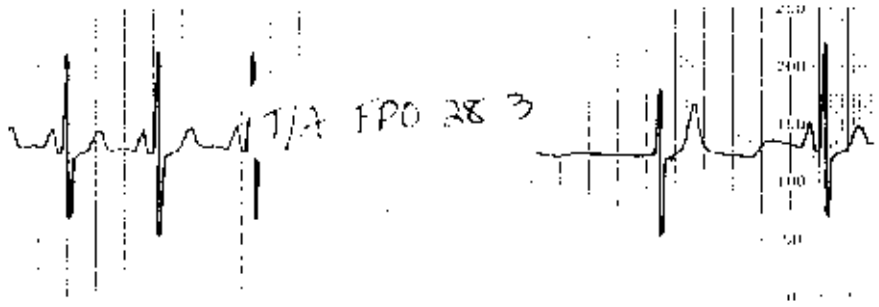

Figure 3 Sinus arrest. The escape beat is from the AV node, and the peaked T wave following this beat implies that a P wave is buried in the T wave.

Treatment for asymptomatic sinus arrest is usually not required. For symptomatic patients, treatment is similar to that outlined for sinus bradycardia.

Sinoatrial Exit Block

Sinoatrial exit block represents an abnormality in impulse conduction from the sinus node to surrounding atrial tissue. It can be caused by medications, including type IA antiarrhythmic drugs such as quinidine and procainamide. The arrhythmia can also be caused by the other sinus node abnormalities described earlier. On the ECG, there is a pause in the sinus rhythm, which is equal to a multiple of the underlying P-P interval.

The treatment for patients with symptomatic sinoatrial exit block is similar to that for sinus bradycardia. For asymptomatic patients, no treatment is required and the block may be transient, resolving after any offending medications are discontinued.

Sick Sinus Syndrome

Sick sinus syndrome includes a number of abnormalities of the sinus node, atrial myocardium, and AV node. It is often considered synonymous with the bradycardia–tachycardia syndrome, which consists of paroxysmal regular or irregular atrial tachycardias alternating with episodes of bradyarrhythmias, but bradycardia–tachycardia is only one manifestation of sick sinus syndrome. Also included in the definition are persistent sinus bradycardia not caused by medications, episodes of sinus arrest or sinus exit block, abnormalities of sinus node and atrial function in conjunction with AV conduction abnormalities (such as atrial fibrillation with slow ventricular response), or any combination of these conditions (Fig. 4). The etiology of sick sinus syndrome is probably multifactorial, varying from patient to patient. There may be inflammatory or degenerative changes in the sinus node and perinodal tissues. Autonomic abnormalities are also common (17,18).

Treatment of sick sinus syndrome can be problematic, since medications used to suppress or slow chronic or paroxysmal atrial tachycardias may exacerbate the associated bradycardias. Digoxin in particular can cause profound bradyarrhythmias in these patients. Often ventricular pacing must be used with drug therapy to treat patients with the bradycardia–tachycardia syndrome.

Although prophylactic pacing is not indicated, patients who require digoxin, beta-blockers, calcium channel blockers, or antiarrhythmic medications should be monitored

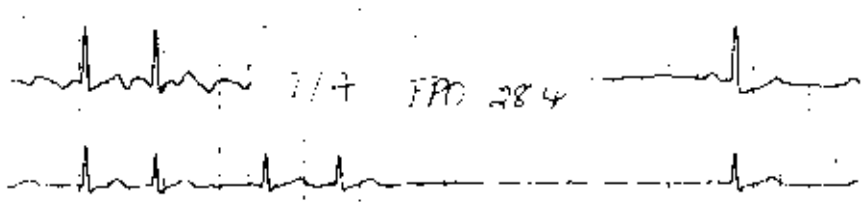

Figure 4 Long sinus pause after spontaneous conversion of atrial fibrillation to sinus rhythm in a patient with sick sinus syndrome. Prolonged recovery of the sinus node is characteristic of this condition and can also produce long pauses following electrical cardioversion.

after these medications are started. If long ventricular pauses occur or if patients become symptomatic, they should receive permanent pacing.

CAROTID SINUS HYPERSENSITIVITY

Hypersensitive carotid sinus syndrome is defined as ventricular asystole greater than 3 s during carotid sinus stimulation, although the definition is arbitrary. Studies have shown conflicting results regarding the significance of the 3-s pause during carotid sinus massage (19–21). Hypersensitive carotid sinus response can be found in elderly patients complaining of syncope or presyncope, but many of these patients have multiple causes for their symptoms.

The cause of hypersensitive carotid sinus syndrome is not known but may involve an abnormal baroreceptor set point, excessive release of acetylcholine, inadequate cholinesterase to metabolize the acetylcholine, or abnormal central autonomic response. Carotid sinus hypersensitivity may manifest clinically following carotid stimulation from head turning or from tight collars. On the ECG during carotid sinus stimulation, either sinus arrest or sinus exit block is found. Although AV node block can occur, it is infrequent because the sinus slowing usually masks its manifestation.

Atropine can blunt the cardioinhibitory effects of carotid sinus hypersensitivity, but long-term treatment requires ventricular pacing. Medications such as beta-blockers, calcium channel blockers, digitalis, and clonidine should be avoided in patients who do not have an implanted ventricular pacemaker.

ATRIOVENTRICULAR BLOCK

Atrioventricular block is a nonphysiological delay in conduction or a lack of conduction of the electrical impulse from atria to ventricles. Block can result from abnormal conduction in any part of the electrical system of the heart. Blocks that occur during a period of time in which the AV conduction system should be refractory (for example, an atrial premature contraction that occurs early after a normally conducted beat) must be excluded. The causes of block have been discussed previously and include ischemic heart disease, degenerative and infiltrative diseases, drug toxicities, and excess vagal activity. Atrioventricular block can be paroxysmal or fixed. A patient can exhibit different degrees of AV block at different times and under different pathophysiological conditions.

Electrocardiographic criteria are used to define degrees of block. First-degree AV block refers to a delay in AV conduction without nonconduction. On the ECG, normal sinus P waves are each followed by QRS complexes, but with a P-R interval that is prolonged at greater than 0.20 s. Occasionally, the P-R interval can be as long as 1.0 s. P-R interval prolongation can be due to slowed conduction in the atrium (prolonged P-A interval), in the AV node (prolonged A-H interval), or in the His-Purkinje system (prolonged H-V interval). The presence of a narrow QRS usually indicates disease in the AV node, but first-degree AV block with a widened QRS morphology does not localize disease to the AV node or the His-Purkinje system (22).

Second-degree AV block is manifested by intermittent lack of conduction from atria to ventricles. Mobitz type I second-degree AV block (also called Wenckebach block) is usually, but not always, due to disease in the AV node and produces a gradual prolongation

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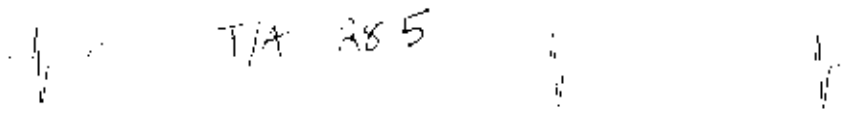

Figure 5 Second-degree AV block, type I (Wenckebach). Note the prolongation of the P-R interval before the blocked P wave.

of P-R intervals in successive beats until a P wave is completely blocked for one beat (Fig. 5). Mobitz type II second-degree block, which usually involves disease below the AV node in the His-Purkinje system, produces intermittent block in AV conduction without prior prolongation of the P-R interval (Fig. 6). Type I block is usually considered benign, since AV node disease is the usual site of block and the prognosis is good. There is less tendency for the process to progress to complete heart block and frank syncope.

Type I block can occur with inferior wall myocardial infarction and tends to be transient. Patients are generally asymptomatic, and temporary or permanent pacing is not required. Type II block occurs more commonly after anterior wall myocardial infarction and usually indicates a large area of myocardial damage. Type II block also leads to complete heart block more frequently than type I and consequently produces more symptoms. Temporary and permanent pacing are usually indicated for type II block because of this propensity to advance to complete heart block. Following anterior wall myocardial infarction, mortality remains high, despite permanent pacing, because of the association with extensive myocardial damage.

There is a special case of second-degree block in which every other P wave is blocked. This is known as 2:1 block. Since two successive P-R intervals cannot be examined, it is not possible to further classify the rhythm as type I (Wenckebach) or type II second-degree block. When the QRS interval is narrow, the block is usually in the AV node. When the QRS interval is wide, the block can be in either the AV node or the His-Purkinje system. In such cases, it is necessary to examine long rhythm strips or 24-h Holter recordings in an attempt to find evidence for Wenckebach or non-Wenckebach conduction.

The term ''high-grade AV block'' is used by many cardiologists but is not uniformly defined. Usually the term refers to a situation in which multiple consecutive P waves are blocked. Usually, the P-R interval does not change in conducted beats, so this rhythm resembles type II second-degree AV block.

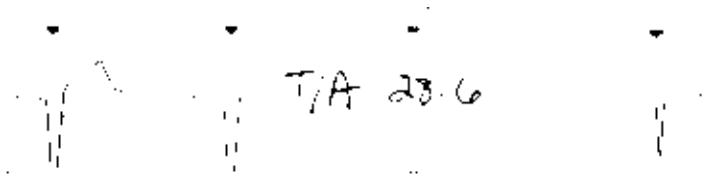

Figure 6 Second-degree AV block, type II. Note that the P-R intervals are not prolonged before the blocked P wave.

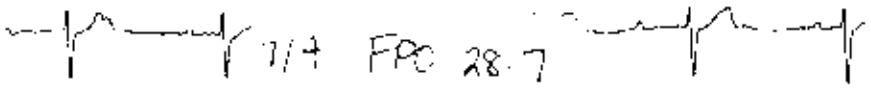

Figure 7 Complete heart block, with narrow complex escape rhythm (AV nodal escape). Note the blocked P waves, A-V dissociation, and regular ventricular response (from the escape rhythm).

In third-degree or complete AV block, there is a total lack of conduction and communication between atria and ventricles. The atrial rhythm does not affect the ventricular rhythm, which is produced by an escape focus in the AV node (junctional escape rhythm) or, more commonly, in the ventricle (idioventricular escape rhythm). The ECG during complete heart block usually exhibits three features: (1) nonconducted P waves; (2) atrioventricular dissociation (atrial and ventricular rhythms are independent); and (3) a regular ventricular response produced by the escape rhythm (Fig. 7).

An algorithm can be constructed to aid in the correct identification of the degree of heart block based on the surface electrocardiogram (Fig. 8). By answering several simple yes–no questions, an accurate diagnosis can be established. One must first determine whether there are blocked P waves. If there are none and the P-R interval is greater than 0.20 s, the patient has first-degree AV block. If there are blocked P waves, then the P-R intervals must be examined. The algorithm does not require that an assessment be made of whether a particular P wave is causing a QRS. Simply identify a QRS, find the P wave that precedes that QRS, and define that as a P-R interval. If the intervals are not variable,

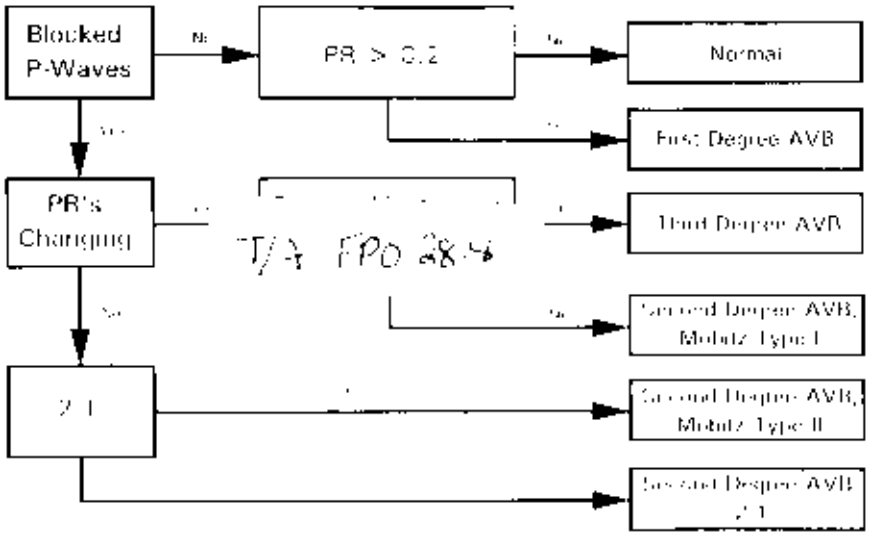

Figure 8 Algorithm for the ECG diagnosis of AV block (see text).

then the special case of second-degree block with 2:1 conduction must be excluded. If 2:1 conduction is present, it is not possible to further categorize the block as Mobitz type I or Mobitz type II, and the diagnosis of second-degree AV block, 2:1 is made. If the patient has constant P-R intervals and is not in 2:1 block, then the diagnosis of second-degree AV block, Mobitz type II, is made. If the P-R intervals are changing and the ventricular rhythm is not regular, then the diagnosis of second-degree AV block, Mobitz type I, is present. If the ventricular response is regular, then the criteria for third-degree (complete) AV block have been met.

Electrophysiological testing can be used to identify the site of the atrioventricular block. In the nonmedicated state, the patient's rhythm is recorded and the P-A, A-H, and H-V intervals are determined (Fig. 1). Lack of a His bundle depolarization following a blocked P wave signifies that the AV node is the site of the block. Presence of the His bundle signal following a blocked P wave indicates that the impulse has traveled through the AV node, has stimulated the bundle of His, and has been blocked below that point. Block below the bundle of His generally requires permanent pacing.

First-degree block alone does not require treatment. Second-degree block, Mobitz type I, in an asymptomatic patient does not require treatment. Symptomatic Mobitz type I can be treated acutely with temporary pacing and eventually with permanent pacing. A permanent pacemaker should be used only after possible causative medications have been discontinued. Permanent pacing is indicated in patients with symptomatic and probably asymptomatic Mobitz type II block and probably in Mobitz type II block acquired during an acute myocardial infarction. Even with permanent pacing, however, the mortality rate in this group of patients with anterior wall myocardial infarction remains high. Acquired third-degree block requires permanent pacing, since the patient is dependent upon an escape rhythm that may be unreliable. If the patient exhibits symptoms with complete heart block, a temporary pacemaker should be inserted while the patient waits for definitive therapy with a permanent pacemaker.

PACEMAKER THERAPY FOR BRADYCARDIAS

Indications

Indications for permanent pacemaker implantation have been developed by the American Heart Association and the American College of Cardiology (23), and the Health Care Financing Administration has published guidelines for reimbursement for pacemaker implantation. In general, permanent pacing is indicated to treat symptomatic bradyarrhythmias. If a causative drug can be identified and stopped, this should be done. Pacing should be undertaken only if the symptomatic arrhythmia persists. When symptoms cannot be temporally related to a bradyarrhythmia, controversies regarding indications for implantation exist.

Class I indications are those in which a permanent pacemaker is generally considered acceptable and necessary if the cause is not transient. These include acquired complete heart block with symptoms, such as syncope, seizures, congestive heart failure, dizziness, or limited exercise tolerance; symptomatic Mobitz type II second-degree AV block; symptomatic Mobitz type I second-degree block with hemodynamic instability related to the block; symptomatic sinus bradycardia, with heart rate less than 50 bpm, and documented hemodynamic instability related to the bradycardia; symptomatic sinus bradycardia or atrial fibrillation, with slow ventricular response resulting from required long-term drug

treatment and without acceptable alternative drugs; symptomatic sinus node dysfunction (sick sinus syndrome); sinus node dysfunction without symptoms when the bradycardia leads to potentially life-threatening ventricular arrhythmias; and patients with severe carotid sinus hypersensitivity and syncope.

Class II indications are those with some divergence of opinion but in which the pacemaker can assist in the management of the patient. These indications include asymptomatic acquired complete AV block; bifascicular or trifascicular block with syncope after other causes of syncope have been excluded; prophylactic use after acute myocardial infarction during which the patient exhibited transient Mobitz type II second-degree block or complete heart block; asymptomatic Mobitz type II second-degree AV block; mildly symptomatic sinus bradycardia secondary to required long-term drug treatment; and for overdrive pacing in some patients with recurrent ventricular tachyarrhythmias.

Class III indications are those in which pacing is not routinely indicated and scientific evidence cannot support its use. These include syncope of unidentifiable origin; asymptomatic sinus bradycardia; asymptomatic sinoatrial node block or sinus arrest; asymptomatic ventricular pauses during atrial fibrillation; bradycardia during sleep; asymptomatic right bundle branch block with left anterior hemiblock; asymptomatic Mobitz type I second-degree AV block; and first-degree AV block. Asymptomatic type I second-degree AV block in which the block is located in or below the bundle of His may be an indication for permanent pacing, but supra-Hisian block is not.

Modes of Cardiac Pacing and Cardiac Pacemaker Codes

The earliest cardiac pacemakers were simple devices that paced the ventricle or atrium and lacked the ability to sense the patient's underlying heart rhythm. As the technology advanced, the ability to sense the patient's native heart beat was added, as was dual-chamber pacing. In the 1980s, multiprogrammability became common, allowing adjustments in many pacemaker parameters using an external programming device. Several newer pacemakers have the capability of providing antitachycardia therapy. Most recently, some pacemakers can modulate their pacing rates using physiological sensors (such as activity, acceleration, body temperature, and minute ventilation) that are independent of sinus node activity. Some newer pacemakers even incorporate dual sensors.

A pacemaker code system was developed by committees of the Intersociety Commission for Heart Disease Resources the North American Society of Pacing and Electrophysiology (NASPE), and the British Pacing and Electrophysiology Group (BPEG) (Table 1) (24). The code initially consisted of three positions: the first to indicate the chambers paced, the second the chambers sensed, and the third the response that the pacemaker exhibited to a sensed event. A fourth position was added to identify programmability and rate modulation, and an optional fifth position to indicate antitachycardia functions. Pacemakers with no sensing capabilities are identified as VOO or AOO. A ventricular demand pacemaker is designated VVI and, with rate modulation, VVI,R. The same pacemaker used in the atrium is designated AAI or AAI,R. A pacemaker that senses atrial activity but paces the ventricle following an atrial sensed event is designated VAT. Such a pacemaker is useful in treating patients with complete heart block in whom sinus node activity is normal and can be used to modulate the ventricular pacing rate (AV synchronous pacemaker). A pacemaker that paces both chambers but senses only the ventricle is desig-

Table 1 Pacemaker Codes

Chamber paced	Chamber sensed	Response to sensed event	Programmability and rate modulation	Antitachycardia rate modulation
0 = None	0 = None	0 = None	0 = None	0 = None
A = Atrium	A = Atrium	T = Triggered	P = Simple programmable	P = Pacing (antitachycardia)
V = Ventricle	V = Ventricle	I = Inhibited	M = Multiprogrammable	S = Shock
D = Dual	D = Dual	D = Dual	C = Communicating	D = Dual (P + S)
			R = Rate modulation	

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nated DVI and is useful in patients with symptomatic sinus bradycardia in whom AV synchrony is desired (AV sequential pacemaker). A pacemaker that combines both dual-chamber pacing with dual-chamber sensing is designated DDD and is capable of tracking atrial activity and providing AV synchrony under all conditions. This is the most common dual-chamber mode used in modern pacemakers. Rate modulation has been added to DDD pacing (DDD,R) and is useful in patients with an inadequate sinus node response to exercise. Dual-chamber pacing was once considered inappropriate for patients with frequent atrial tachyarrhythmias, in particular paroxysmal atrial fibrillation, because sensing of an atrial tachyarrhythmia would result in unwanted rapid ventricular pacing. However, newer pacemakers have the capability to switch modes from DDD to VVI or VVI,R during paroxysmal atrial tachycardias (24,25). Consequently, the only absolute contraindication to dual chamber pacing is chronic, continuous atrial fibrillation.

Programming rate-modulated parameters should involve the use of rate response tailoring, such as through some form of exercise testing to achieve an optimum rate response prescription. Rate modulated devices typically allow the physician to determine a threshold level for rate increase and a slope of heart rate increase in response to the sensed physiological parameter.

Pacemaker Follow-Up

Although modern pacemakers and leads are extremely reliable, periodic evaluation of the pacemaker-lead-patient system is required. Initial thresholds for stimulation of the heart may change with time or with partial or complete dislodgement of the implanted leads. Follow-up is also required to predict impending battery depletion to allow elective replacement of the pulse generator when the time arrives. Pacemakers are usually followed via trans-telephone monitoring and periodic patient visits. Medicare guidelines for pacemaker follow-up frequency are based upon the demonstrated longevity of the particular pacemaker model being tested (Table 2). The telephone monitor permits transmission of a rhythm strip in the free-running mode and with magnet application but does not give information about sensitivity or output thresholds in most cases. Some pacemakers allow threshold checking via telephone. The follow-up also involves patient reassurance and answering questions that the patient or family members may have regarding the pacemaker.

Future of Cardiac Pacing

The future promises devices with more sophisticated (but more ''user friendly'') programming capabilities, more reliable and more physiological metabolic rate sensors, and more capacity for providing useful telemetric information from the patient. Great strides are being made in the application of devices to the treatment of atrial and ventricular tachyarrhythmias using antitachycardia pacing, low-energy cardioversion, and high-energy defibrillation. Because of the high incidence of bradyarrhythmias in patients with tachyarrhythmias, implantable cardioverter-defibrillators will be designed with more sophisticated bradycardia pacing capabilities, such as dual-chamber pacing and sensing, and rate-responsive pacing.

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Table 2 Pacemaker Follow-Up

Pacemaker type[a]	Months after implantation	Scheduled trans-telephone contacts
Single-chamber		
	1	Every 2 weeks
	2–48	Every 12 weeks
	49–72	Every 8 weeks
	> 72	Every 4 weeks
Dual-chamber		
	1	Every 2 weeks
	2–30	Every 12 weeks
	31–48	Every 8 weeks
	> 48	Every 4 weeks
Pacemaker type[b]	Months after implantation	Scheduled trans-telephone contacts
Single-chamber		
	1	Every 2 weeks
	2–36	Every 8 weeks
	> 36	Every 4 weeks
Dual-chamber		
	1	Every 2 weeks
	2–6	Every 4 weeks
	7–36	Every 8 weeks
	> 36	Every 4 weeks

[a] Pacemakers with demonstrated longevity greater than 90% at 5 years, and whose output voltage decreases < 50% over 3 months and whose magnet rate decreases < 20% or 5 pulses/min over that period.
[b] Pacemakers that do not meet the above criteria.

CONCLUSIONS

Bradycardias and the sick sinus syndrome, symptomatic and asymptomatic, are common in elderly individuals. Treating patients for such arrhythmias involves careful history taking, physical examination, and diagnostic testing. Correlating symptoms with abnormalities of the rhythm can be challenging and in some cases impossible. However, such a correlation is important to allow proper therapy by medications and implanted devices. There is debate about the use of pacemakers for certain indications, but the demonstration of bradycardia-induced symptoms usually makes the decision straightforward.

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29

Evaluation of Syncope in the Elderly

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Syncope is a sudden, temporary, brief loss of consciousness associated with loss of postural tone from which the patient recovers spontaneously. The causes of syncope range from benign to life-threatening. Because some of the causes of syncope can result in death, complaint of syncope results in frequent hospital admissions and performance of multiple diagnostic tests. Evaluation frequently focuses on identifying a singular cause. This may be especially inappropriate in the elderly, who more often than not have multiple disease processes (diseases that may specifically contribute to the occurrence of syncope). Furthermore, the elderly take medications for these and other diseases which may make syncope more likely (1). Because of the complex etiology and pathophysiology of syncope in the elderly, evaluating this entity merits a practical and directed approach.

PATHOPHYSIOLOGY

Elderly patients frequently have multiple medical conditions that interact with the normal changes associated with aging to contribute to syncopal episodes; they do this by decreasing blood flow to the brain, both at baseline and with physiological stressors. For instance, both hypertension and atherosclerotic disease decrease baseline cerebral blood flow (2), narrowing the margin of reserve before compromise becomes clinically apparent. Insults of significance may be as seemingly innocent as the enhanced vagal tone associated with micturition or defecation, or they might be drugs prescribed for the patient such as antihypertensives and psychotropic medications.

Baroreflex sensitivity diminishes with aging, blunting the response of increased vascular tone to hypotensive challenges. One possible cause of this is the diminished beta-adrenergic-mediated vasodilatation seen with aging. Additionally, there is an increase in baseline plasma norepinephrine as well as a greater rise in norepinephrine with acute hypotension in the elderly, suggesting impaired end-organ responsiveness to adrenergic stimulation; this also suggests normal central and afferent components of the baroreflex circuit. Decreased baroreceptor sensitivity may not allow the elderly to increase heart rate

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or vascular tone adequately to maintain cerebral blood flow in the setting of hypotension. Thus the elderly are more sensitive to hypotensive drugs as well as to hypotension from other causes—volume loss, hemorrhage, and upright posture.

Long-standing systolic hypertension, prevalent in 30% of people over the age of 75, also diminishes baroreflex sensitivity and decreases vascular and ventricular compliance. Hypertension increases the threshold for cerebral autoregulation, with resultant decrease in cerebral blood flow with modest acute decreases in blood pressure to levels within normotensive ranges (2). Hence, age-related physiological changes may be worsened by systolic hypertension.

The ability of kidneys to conserve sodium when salt intake is restricted is impaired with aging. Additionally, basal plasma levels of renin and aldosterone are decreased. These changes may enhance the susceptibility of the elderly to orthostatic hypotension and syncope. Because of these changes, the effects of diuretics, salt restriction, and upright posture may be more pronounced in the elderly.

CLINICAL CLASSIFICATION

The etiologies of syncope can be classified into the four major categories (Table 1).

Neurally Mediated Syndromes

Neurally mediated and neurocardiogenic syncope are terms that describe syncope resulting from reflex mechanisms associated with inappropriate vasodilatation and/or bradycardia (3,4). These terms encompass more specific syndromes such as vasovagal, vasodepressor, micturition, and carotid sinus syncope.

The origins of afferent signals triggering the various neurally mediated syncopal syndromes (3,4) are thought to be the receptors that respond to pain, mechanical stimuli, and temperature. For example, left ventricular baroreceptors (mechanoreceptors) may serve as triggers for vasovagal syncope and syncope during tilt testing. Similar receptors in the aortic arch, carotid arteries, atrial and ventricular myocardium, respiratory tree, bladder, and the gastrointestinal tract may trigger various other neurally mediated syndromes (3). From these receptors, afferent pathways transmit signals to the central nervous system (mainly the medulla, the nucleus tractus solitarius). The efferent outflow from medulla leads to vasodilation and bradycardia.

Vasovagal syncope is common in the elderly (5), and is often associated with pallor, nausea, vomiting, and sweating but may occur without associated symptoms. Precipitating factors can include fatigue, prolonged standing, venipuncture, blood donation, heat, fear, injury and local procedures, such as dental or eye surgery.

Syncope associated with a variety of common daily activities is termed situational syncope (micturition, defecation, postural change, and meals). In one study, these activities were associated with 20% of cases of syncope (6). Other situational causes include laughing, swallowing, and coughing. The mechanism of situational syncope is similar to vasovagal syncope. In elderly patients, impaired homeostasis and orthostatic hypotension can decrease the threshold for situational syncope to occur.

Postprandial hypotension may result in syncope during or after a meal. Studies of nursing home elderly population show up to 36% prevalence of systolic blood pressure decline of more than 20 mmHg after a meal (generally at 45 to 60 min) (7). However, this

Table 1 Etiologies of Syncope

Neurally mediated syndromes	Decreased cardiac output
Vasovagal	Obstruction to flow
Situational	aortic stenosis
micturition	IHSS
cough	mitral stenosis
swallow	myxoma
defecation	
Carotid sinus syncope	Other Heart Disease
Neuralgias	pump failure
High altitude	MI
Psychiatric disorders	CAD
Others (exercise, selected drugs)	coronary spasm
Orthostatic hypotension	Arrhythmias
	bradyarrhythmias
Neurological diseases	sinus node disease
	atrioventricular block
Migraines	second degree
TIAs	third degree
Seizures	tachyarrhythmias
	ventricular tachycardia
	torsade de pointes (congenital or acquired QT prolongation)
	supraventricular tachycardia

rarely results in symptoms since 8% of institutionalized elderly patients had postprandial syncope (6). Postprandial hypotension is likely due to impaired compensation for the pooling of blood in the splanchnic blood vessels following meals. Failure to maintain elevated plasma norepinephrine levels despite hypotension may play a role (8).

Stimulation of baroreceptors located just above the bifurcation of the common carotid artery results in carotid sinus hypersensitivity. Cardioinhibitory carotid sinus hypersensitivity is defined as asystole greater than or equal to 3 s and vasodepressor variety is defined as a decline in systolic blood pressure of greater than or equal to 50 mmHg. Cardioinhibitory response is common (80% of patients); vasodepressor in about 10% of cases of carotid sinus hypersensitivity; the remainder are cases of mixed responses. Carotid sinus syncope, the clinical result of carotid sinus hypersensitivity, occurs in 5 to 20% of patients. This type of syncope may be triggered by tight collar, shaving, or sudden turning. Other risk factors include neck pathology such as enlarged lymph nodes, scar tissue and carotid body, parotid, thyroid, and other head and neck tumors, as well as drugs such as digitalis, a-methyldopa, and propranolol. However, syncope is often without any specific triggers.

Generalized anxiety disorder, panic disorder, and major depression probably cause syncope by lowering the threshold for vasovagal reactions (9). Syncope associated with exercise, especially immediately postexercise in individuals without structural heart disease, is often due to reflux mechanisms. In this instance, mild volume depletion and shifts of blood flow to dissipate heat may trigger neurally mediated syncope. Drugs that decrease

venous return to the heart in upright position such as nitroglycerin can cause vasovagal syncope (3).

Orthostatic Hypotension

Upon standing, blood pools in the lower extremities and the splanchnic circulation resulting in reduced venous return to the heart and a decrease in cardiac output, which lead to stimulation of aortic, carotid, and cardiopulmonary baroreceptors. As a result of this, there is an increase in sympathetic outflow and a decrease in parasympathetic activity, resulting in an increase in heart rate and vascular resistance to maintain systemic blood pressure. Orthostatic hypotension results from several pathophysiological processes, disease states, and medications that may alter blood pressure homeostasis.

Physiological changes associated with aging and systolic hypertension contribute to the development of orthostatic hypotension in the elderly. Volume depletion is another major cause of orthostatic hypotension due to impairment of salt and water homeostasis. The elderly are especially vulnerable to volume depletion with the use of even low-dose diuretics and in the face of even mild acute illnesses resulting in increased insensible losses. One reason for this is the diminished thirst experienced by the elderly, even when their plasma is hyperosmolar. Medications are also a common cause of orthostatic hypotension in the elderly, even in the usual therapeutic doses.

Diseases affecting the autonomic nervous system may cause chronic orthostatic hypotension. Idiopathic orthostatic hypotension is a rare illness that more commonly affects men. Clinical manifestations include sphincter disturbances, impotence, impaired erection and ejaculation, and impaired sweating. Supine basal plasma norepinephrine levels are markedly low and remain unchanged upon standing, suggesting a peripheral dysfunction with depletion of norepinephrine from sympathetic nerve endings. Shy-Drager syndrome consists of autonomic failure and involvement of the corticospinal, extrapyramidal, and cerebellar tracts, including a Parkinsonlike syndrome. Basal norepinephrine levels are normal at rest but do not increase substantially upon standing, suggesting an inability to stimulate normally functioning peripheral neurons.

Neurological Diseases

Neurological disorders rarely cause of syncope. Approximately 6% of patients with ischemic stroke or transient cerebral ischemia have associated syncope and, in one study of patients with syncope seen in an emergency room, 7.7% had transient ischemic attacks (10). Concurrent neurological symptoms, most frequently vertigo, ataxia, and paresthesia are present in almost all patients. Almost all patients had vertebrobasilar transient ischemic attacks. Other symptoms heralding transient posterior circulation ischemia are diplopia, dysarthria, and hemiparesis (11).

Migraines can cause vasovagal reaction secondary to pain. Approximately 2% of patients presenting with syncope are diagnosed as having a seizure (12), which include atonic seizures and sudden falls associated with temporal lobe epilepsy, called temporal lobe syncope. Unwitnessed grand mal seizures can be mistaken for syncope if the patient cannot provide detailed information.

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Cardiac Syncope

Cardiac causes of syncope fall under three main categories: outflow obstruction due to structural abnormalities, arrhythmias, and other forms of organic heart disease. Obstruction to outflow may be due to structural lesions of either the left or right side of the heart. Exertional syncope is a common symptom of all types of heart disease in which cardiac output is fixed and does not rise with exercise. Exercise results in a marked increase in left ventricular systolic pressure, which may lead to excessive stimulation of left ventricular mechanoreceptors with subsequent inhibition of sympathetic and activation of parasympathetic tone through cardiac vagal nerves.

Syncope is reported in 10 to 15% of patients with pulmonary embolism and is more common with massive embolism. The mechanism may be acute right ventricular failure with decreased cardiac output or stimulation of cardiopulmonary mechanoreceptors leading to vasovagal reactions.

Bradyarrhythmias and tachyarrhythmias may result in a sudden decrease in cardiac output and syncope. Physiological impairments with aging, the effects of multiple medications, and comorbidity may predispose elderly to syncope in the setting of brief arrhythmias, whereas such arrhythmias may not lead to symptoms in the young since the elderly are less able to compensate for sudden decrease in cardiac output due to arrythmias.

Sinus node disease and ventricular tachycardia were the most common arrhythmic causes of syncope in the elderly, occurring in 22% of this group (13). Syncope is a common manifestation of sick sinus syndrome, and electrocardiographic findings include sinus bradycardia, pauses, arrest, and exit block. When these bradyarrhythmias are associated with supraventricular tachycardia or atrial fibrillation they are termed tachycardia–bradycardia syndrome. Ventricular tachycardia commonly occurs in the setting of known structural heart disease. Prolonged QT syndromes may lead to polymorphic ventricular tachycardia, called torsade de pointes. In the elderly, torsade de pointes occurs in the setting of acquired long QT syndromes associated with drugs, electrolyte abnormalities, and central nervous system disorders. Antiarrhythmic drugs such as quinidine (quinidine syncope), procainamide, disopyramide, flecainide, and encainide are the most common causes of torsade de pointes.

Syncope may be the presenting symptom in 5 to 12% of elderly patients with acute myocardial infarction. This presentation may be due to (1) sudden pump failure producing a decrease in perfusion pressure of the brain or (2) rhythm disturbance that may include ventricular tachycardia or bradyarrhythmias due to vasovagal reactions during acute inferior infarction or ischemia involving the right coronary artery.

DIAGNOSTIC EVALUATION

There are three important elements in the diagnostic evaluation of syncope:

1. Does the patient have syncope? Using history from the patient and a witness, syncope can be separated from other entities such as dizziness, vertigo, drop attacks, coma, and seizure. Syncope and seizure are often difficult to separate. Videometric analysis of syncope has shown myoclonic activity in 90%, predominantly consisting of multifocal arrhythmic jerks both in proximal and distal muscles (14). Historical features that suggest seizures include: blue face (not pale), frothing at the mouth, tongue biting, disorientation, aching muscles, sleepiness after the event and duration of unconsciousness of more than

5 min. Symptoms associated with syncope are sweating or nausea before the event and being oriented after the event. Disorientation after the episode best discriminates seizure from syncope (15). Elderly often provide unreliable history of loss of consciousness; thus drop attacks (sudden loss of posture without loss of consciousness) should be fully investigated with high index of suspicion for syncope (16).

2. Is the patient at high risk? Risk stratification may help in the initial management decisions such as admission to the hospital and the use of cardiac testing. The assessment of risk includes the likelihood of sudden death and cardiac syncope. In the assessment of risk, the cause of syncope, and presence of underlying cardiac disease and ECG abnormalities are important. Previous studies have consistently shown patients with cardiac causes as a high-risk subset with increased mortality and sudden death rates. Examples include aortic stenosis, pulmonary hypertension, and arrhythmic syncope. Arrhythmias are mainly found in patients with structural heart disease or abnormal ECG. Thus, the presence of heart disease and certain abnormalities on ECG help stratify patients into low-and high-risk groups. Congestive heart failure, valvular heart disease, hypertrophic cardiomyopathy and other types of organic heart disease constitute a high-risk group. Atrioventricular (AV) block, old myocardial infarction and Wolff-Parkinson-White syndrome are examples of high-risk findings on ECG. Echocardiogram, stress test, and ventricular function studies may be needed for risk stratification if evidence of structural heart disease cannot be determined clinically.

3. Can diagnostic tests be used selectively? The evaluation of syncope is best approached by using the history and physical examination, ECG, and risk stratification to guide further diagnostic tests.

History and Physical Examination

Details of loss of consciousness, prodromal symptoms, and complaints following the episode are crucial to diagnosing specific entities (see Table 2). Physical examination is used to help assign specific causes and to exclude others. Attention should be paid to orthostatic hypotension, cardiovascular findings, and neurological examination.

Orthostatic hypotension is commonly defined as a decline of 20 mmHg or more in systolic pressure upon standing. This finding is commonly reported in up to 24% of the elderly and is frequently not associated with symptoms. Thus, orthostatic hypotension as a cause of syncope should incorporate the presence of dizziness or syncope in association with decline in blood pressure.

In detection of orthostatic hypotension, supine blood pressure and heart rate should be measured after the patient has been lying down for at least 5 min. Standing measurements should be obtained immediately and for at least 2 min.

Several cardiovascular findings are important diagnostically. Differences in blood pressure (generally $>$20 mmHg) and the pulse intensity in the two arms are suggestive of aortic dissection or subclavian steal syndrome. Special attention to cardiovascular examination for aortic stenosis, idiopathic hypertrophic subaortic stenosis, pulmonary hypertension, myxomas, and aortic dissection may help diagnose these.

In the elderly, a history and physical examination led to 40% of the diagnoses that could be assigned in one study (13). Furthermore, in an additional 15%, a diagnosis was suggested by history and physical examination and confirmed by specific tests (e.g., echocardiogram or catheterization for aortic stenosis) (13). In the elderly, arrhythmias are more

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Table 2 Clinical Features Suggestive of Specific Causes

Symptom or finding	Diagnostic consideration
After sudden unexpected pain, unpleasant sight, sound or smell	Vasovagal syncope
During or immediately after micturition, cough swallow, or defecation	Situational syncope
With neuralgia (glossopharyngeal or trigeminal)	Vasodepressor reaction or bradycardia
Upon standing	Orthostatic hypotension
Prolonged standing at attention	Vasovagal
Well-trained athlete after exertion	Neurally mediated
Changing position (from sitting to lying, bending, turning over in bed)	Atrial myxoma, thrombus
Syncope with exertion	Obstructive heart disease, coronary artery disease, neurally mediated
Syncope with head rotation, pressure on carotid sinus (as in tumors, shaving, tight collars)	Carotid sinus syncope
Associated with vertigo, dysarthria, diplopia, and other motor and sensory symptoms of brain stem ischemia	TIA, subclavian steal, basilar artery migraine
With arm exercise	Sublclavian steal
Confusion after episode	Seizure

Adapted from Ref. 2a.

often diagnosed as the etiology as compared to the young. Several entities were primarily found in the elderly including aortic stenosis, TIAs, and carotid sinus syncope (13).

The elderly patients in whom a cause of syncope is not established by the initial history and physical examination, further evaluation should focus on the following issues: (1) arrhythmia detection; (2) tilt testing; and (3) multiple abnormalities causing symptoms.

Tests for Arrhythmia Detection

In evaluating syncope, every attempt should be made to attain symptomatic correlation with arrhythmias. At the current time there are no valid criteria for attributing syncope to most arrhythmias by the use of electrocardiographic or electrophysiological abnormalities during asymptomatic periods.

Arrhythmias are evaluated using prolonged electrocardiographic monitoring or electrophysiological studies. Rarely (in 2–9%), the initial electrocardiogram or a rhythm strip may show an arrhythmia (12,13). In one study, a cause of syncope was assigned by ECG in 9% of the elderly as compared with 4% of the young group (13). The yield of stress testing for arrhythmias is very low. Exercise ECG can be used to evaluate syncope with exercise for the diagnosis of ischemia and exercise-induced tachyarrhythmias or bradyarrhythmias after abrupt termination of exercise.

Prolonged Electrocardiographic Monitoring

The usefulness of ambulatory monitoring in syncope can be determined by assessing the presence or absence of arrhythmias in patients who develop symptoms during monitoring.

In studies of patients with syncope or presyncope monitored 12 h or more and when symptoms were reported, only 4% had symptomatic correlation with arrhythmias (17). In approximately 17% of patients, symptoms were present, but there were no arrhythmias, thus potentially excluding rhythm disturbance as an etiology for syncope (17). In the majority (approximately 80% of patients), no symptoms were reported but arrhythmias were often found. The causal relation between syncope and these arrhythmias is therefore uncertain. Furthermore, finding brief or no arrhythmias in absence of symptoms during monitoring does not exclude arrhythmic syncope because arrhythmias can be episodic. In patients with high likelihood of arrhythmias, event monitoring or electrophysiological studies are often needed. Extending the duration of monitoring to 72 h increases the yield of brief arrhythmias detected, but does not increase detection of symptomatic arrhythmias (18).

Patient-activated intermittent loop recorders can capture the rhythm during syncope after the patient has regained consciousness because several minutes of retrograde electrocardiographic recording can be obtained. Loop monitoring can be worn for weeks to months and is most useful in patients with history of recurrent, unexplained syncope because their probability of recurrence is higher, making it more likely for arrhythmias to be captured during an event.

Electrophysiological Studies

Abnormal or ''positive'' electrophysiological studies are found mainly in patients with structural heart disease (including abnormal ventricular function), abnormalities on electrocardiogram, or ambulatory monitoring (19). Predictors of ventricular tachycardia by electrophysiological studies include organic heart disease, PVCs by ECG, and nonsustained ventricular tachycardia by Holter monitoring (19). Predictors of bradycardia outcome (20) include sinus bradycardia, first-degree AV block, and bundle branch block by ECG.

Negative electrophysiological studies are found in absence of heart disease, ejection fraction $>$40%, normal electrocardiogram and Holter monitoring, absence of injury during syncope, and multiple or prolonged ($>$5 mins) episodes of syncope.

Approximately 60% of patients being evaluated for syncope with electrophysiological testing have negative studies. The most common findings are inducible ventricular tachycardia, found in approximately 45% of patients. In the elderly, a study of 75 patients who were 75 years old or older showed electrophysiological testing to be abnormal in 68%. The abnormalities were mostly conduction disturbances such as sinus node disease in 55% and His-bundle conduction abnormalities in 39%. Inducible ventricular tachycardia was found in 14% of the patients (21).

There are several limitations of electrophysiological testing for evaluating syncope. Symptomatic correlation is often not possible and the criteria for significant abnormalities are controversial. For example, criteria for significantly abnormal HV interval have ranged from greater than 55 ms to greater than 100 ms. Furthermore, some of the abnormalities, such as polymorphic ventricular tachycardia, are nonspecific.

Electrophysiological studies identify a group of patients who are at high risk of mortality. Mortality rates as high as 61% and sudden death rates of 48% have been reported at 3 years in patients with abnormal studies as compared with 15% and 9% in the negative group (22). These differences appear largely due to higher prevalence of cardiac comorbidity in patients with positive findings. A low rate of mortality and sudden death in patients

with negative studies can also be reassuring because this defines a low-risk group of syncope patients.

Rates of recurrence of syncope in follow-up are lower in patients with abnormal electrophysiological studies as compared with patients with normal findings. At a mean of 3 years, recurrence rate of syncope in the elderly with positive electrophysiological studies was 16% as compared with 25% in the negative group (22).

Upright Tilt Testing

Neurally mediated syncope can be precipitated in the laboratory by standing the patient upright on a tilt table. The mechanism by which tilt testing provokes syncope is poorly understood but most authorities believe that stimulation of cardiac mechanoreceptors is probably involved. Upright posture leads to pooling of blood in the lower limbs, resulting in decreased venous return. Normally, compensatory response to standing upright is reflex tachycardia, more forceful contraction of the ventricles, and vasoconstriction. In individuals susceptible to neurally mediated syncope, this forceful ventricular contraction in the setting of a relatively empty ventricle may excessively stimulate the cardiac sensory nerves or mechanoreceptors. Afferent impulses from these receptors are relayed to the medulla, resulting in a decrease in sympathetic and an increase in parasympathetic tone. Catecholamine release (as may occur with anxiety, fear, and panic) by increasing ventricular contraction may also activate the nerve endings responsible for triggering this reflex.

There are two general types of upright tilt testing protocols: tilt testing without chemical stimulation (passive) and tilt testing in conjunction with a chemical agent (such as isoproterenol infusion or nitroglycerine) (5). Blood pressure is monitored using cuff blood pressure measurements or continuous noninvasive or intraarterial blood pressure recording and rhythm is monitored continuously. During passive tilt test, after measurements of supine baseline blood pressure and heart rate, patients are suddenly brought to an upright position at an angle of 60 to 80 degrees and remain upright until a positive response occurs (hypotension and/or bradycardia in association with syncope or presyncope) or 45 min elapse.

The most widely used protocol in the U.S. employs isoproterenol. In protocols using isoproterenol, patients undergo a drug-free upright tilt table testing for 10 to 30 min. If an endpoint is not reached, the patient is returned to a supine position and isoproterenol infusion is started. The patient is again tilt tested at the same angle for 5 to 30 min (most commonly 10 min). This procedure is continued with gradually increasing doses of isoproterenol until an endpoint is reached (maximum dose of isoproterenol or syncope/presyncope). Isoproterenol should be avoided in the elderly whenever possible. Protocols using nitroglycerine are more commonly used in Europe and may be preferable in the elderly (23).

Most studies of upright tilt testing in syncope of unknown origin in the elderly (studies of patients with a mean age greater than or equal to 60 years old specified as elderly) have used passive protocols. The overall percent positive response is 54% (range 26–90%) (5,24–26). The rate of positive response in elderly control subjects without syncope is approximately 11% with a range of 0 to 100% (5). Intravenous cannulation leads to lower specificity and should be avoided. Studies using nitroglycerine have similar positive response rates in patient with unexplained syncope (23). In general, the likelihood of

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positive response is lower in the elderly who are less likely to develop syncope and less able to mount a relative bradycardia (27)

Multiple Abnormalities

The evaluation of the elderly should initially focus on a single disease as explaining the loss of consciousness. If a single disease is found (such as severe aortic stenosis, symptomatic bradycardia, or symptomatic orthostatic hypotension), treatment of that disease can be planned. However, a single disease as the cause of syncope is often not apparent. In these patients, inability to compensate for common situational stresses in the setting of multiple medical problems, medication, and physiological changes associated with aging may be responsible for the loss of consciousness. Once these potential processes are identified, treatment should be directed at correcting these factors. As an example, consider an elderly patient presenting with syncope, who has taken enalapril 10 mg/day, has anemia (hemoglobin 9.0), mild orthostatic hypotension, and a recent upper respiratory tract infection. In this patient, if no other etiology of syncope is apparent based on clinical findings and selective use of laboratory tests, then volume repletion, treatment of anemia, and adjustment or change of antihypertensive medication may help prevent further episodes of syncope.

Other Tests

Prior studies show that skull films, lumbar puncture, radionuclide brain scan, and cerebral angiography do not generally yield diagnostic information for a cause of syncope in the absence of clinical findings suggestive of a specific neurological process (12,13). EEG shows an epileptiform abnormality in 1 to 2% of patients, but almost all of these are suspected clinically. Head computed tomography scans are needed if subdural bleed due to head injury is suspected or in patients suspected to have a seizure as a cause of loss of consciousness, but the yield is low when used in a nondirected fashion (12,13).

APPROACH TO EVALUATION

A careful history and physical examination identify the majority of causes of syncope or may suggest specific entities as possible causes (e.g., findings of aortic stenosis or neurological signs and symptoms suggestive of a seizure disorder). These entities can then be evaluated in a directed fashion by performing noninvasive or invasive tests for establishing a diagnosis. An electrocardiogram is generally needed for the initial evaluation of syncope. Although the diagnostic yield of electrocardiogram for arrhythmias or suspicion of myocardial infarction is low, abnormalities can be acted upon quickly if found.

In patients with negative history, physical examination, and ECG, further testing can be approached by stratifying patients into those with and without structural heart disease and ECG findings. Patients with structural heart disease (e.g., coronary artery disease, congestive heart failure, valvular heart disease, obstructive cardiomyopathy) or ECG abnormalities such as bundle branch block have a higher likelihood of arrhythmic syncope. In elderly patients without clinical heart disease and unexplained syncope, cardiac assessment with stress testing or echocardiogram may be needed to define the presence of occult heart disease. Prolonged electrocardiographic monitoring provides an initial

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step in the evaluation of patients with syncope and heart disease or when arrhythmias are clinically suspected. If prolonged monitoring is nondiagnostic, these patients may be candidates for electrophysiological studies. Since, in the elderly, diseases may present in an atypical fashion or multiple abnormalities may be of concern, the clinical assessment should be particularly focused on these issues. If multiple abnormalities are found that could have led to loss of consciousness, a trial of empirical treatment of those factors is warrented prior to considering an invasive workup.

The prognosis of patients with negative electrophysiological studies is favorable. Upright tilt testing may define a potential etiology in these patients but therapy is recommended only for patients with recurrent or disabling symptoms because the effectiveness of therapy has not been established, especially in patients with single or rare episodes. In elderly patients without heart disease and with a normal electrocardiogram, the likelihood of arrhythmias is low. Many of these patients probably have vasovagal syncope. If there is a clinical suspicion of arrhythmias, ambulatory or loop monitoring (when there is recurrent syncope) may help define an etiology. Because the yield of electrophysiological studies is low in this group, these studies should generally be avoided in these patients. In these patients tilt testing may provide a potential etiology and is recommended in those with recurrent syncope.

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30

Acute Pulmonary Embolism in the Elderly

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Pulmonary embolism (PE) is more prevalent in elderly patients than in younger patients (1,2). A first PE was diagnosed by high-probability ventilation/perfusion lung scan or pulmonary angiogram in 0.40% of hospital admissions of patients 70 years of age or older, in 0.30% of admissions of patients 40 to 69 years of age, and in 0.07% of patients under 40 years of age (1). Others reported a similar trend, but observed an order of magnitude fewer PE in each age group (2). Above age 90, a trend toward a reduction of the incidence of PE was observed (1). Such very old patients may not have been considered appropriate candidates for diagnostic tests.

Although in the past the diagnosis of pulmonary embolism among elderly patients was thought to be particularly difficult because the expected signs and symptoms may be absent or ignored (3–5), this, in general, did not seem to be the case in the experience of the Prospective Investigation of the Pulmonary Embolism Diagnosis (PIOPED) (6). The nonspecific manifestations of pulmonary embolism, even among patients ≥70 years old, occurred with sufficient frequency to suggest the possibility of pulmonary embolism in the differential diagnosis (6).

PREDISPOSING FACTORS IN ELDERLY PATIENTS

Among patients ≥70 years old, 67% were immobilized before the pulmonary embolism, and surgery preceded the pulmonary embolism in 44% (6). Malignancy was more frequent among patients ≥70 years than among younger patients, occurring in 26% (6).

SYNDROMES OF PULMONARY EMBOLISM IN ELDERLY PATIENTS

The usual syndromes of pulmonary embolism are (1) pulmonary hemorrhage or infarction syndrome characterized by pleuritic pain or hemoptysis; (2) isolated dyspnea, unaccompa-

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Table 1 Symptoms of Acute Pulmonary Embolism Among Elderly Patients ($n = 72$)

	≥ 70 Years, (%)
Dyspnea	78
Pleuritic pain	51
Cough	35
Leg swelling	35
Leg pain	31
Palpitations	13
Wheezing	10
Anginal pain	10
Hemoptysis	8

nied by hemoptysis, pleuritic pain or circulatory collapse; and (3) circulatory collapse. The syndrome of pulmonary hemorrhage or pulmonary infarction is the most common syndrome of acute PE among patients in whom a diagnosis is made antemortem (7,8). These syndromes were observed with comparable frequency among elderly patients and younger patients (6). However, 11% of patients ≥70 years of age, in contrast to younger patients, did not show these syndromes (6). Pulmonary embolism in these patients was suspected on the basis of unexpected radiographic abnormalities, which may have been accompanied by tachypnea or a history of thrombophlebitis. Unexplained radiographic abnormalities in elderly patients may be an important clue to the diagnosis of pulmonary embolism (3,6).

SYMPTOMS OF PE IN ELDERLY PATIENTS

In considering all elderly patients, including those who may have had prior cardiopulmonary disease, dyspnea and pleuritic pain were the most frequent symptoms (Table 1). Dyspnea occurred in 78% of elderly patients with PE and pleuritic pain occurred in 51% (6). Hemoptysis occurred less frequently among patients ≥70 years than among younger patients (6). Other symptoms occurred with comparable frequency among all age groups.

Among elderly patients with the pulmonary hemorrhage/infarction syndrome who did not have prior cardiopulmonary disease, pleuritic pain was more frequent than hemoptysis (88% vs. 12%) (9).

SIGNS OF PE IN ELDERLY PATIENTS

Among all patients ≥70 years of age, regardless of prior cardiopulmonary disease, tachypnea (respiratory rate ≥ 20/min) was the most frequent sign of PE. Tachypnea occurred

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Table 2 Signs of Acute Pulmonary Embolism Among Elderly Patients ($n = 72$)

	≥ 70 Years, (%)
Tachypnea ≥ 20/min	74
Rales (crackles)	65
Tachycardia > 100/min	29
Increased P_2	15
Deep venous thrombosis	15
Diaphoresis	8
Wheezes	8
Temperature > 38.5°C	7
Third heart sound	7
Pleural friction rub	6
Homan's sign	4
Cyanosis	3

in 74% and tachycardia (heart rate > 100/min) occurred in 29% of elderly patients with PE (6) (Table 2). All signs occurred with comparable frequency among all age groups (≥70 years, 40 to 69 years, and <40 years).

CHEST RADIOGRAPH AMONG ELDERLY PATIENTS WITH PE

The chest radiograph was normal in 4% of all elderly patients with PE, including those with prior cardiopulmonary disease (6). Atelectasis or pulmonary parenchymal abnormalities were the most frequent radiographic abnormalities (Table 3). All radiographic abnormalities occurred with a comparable frequency among all age groups.

Table 3 Chest Radiograph in Acute Pulmonary Embolism Among Elderly Patients ($n = 72$)

	≥ 70 Years, (%)
Normal	4
Atelectasis or pulmonary parenchymal abnormality	71
Pleural effusion	57
Pleural-based opacity	42
Prominent central pulmonary artery	29
Elevated diaphragm	28
Cardiomegaly	22
Decreased pulmonary vascularity	19
Pulmonary edema	13
Westermark's sign[a]	7

[a] Prominent central pulmonary artery and decreased pulmonary vascularity.

Table 4 Combinations of Signs and Symptoms Among Elderly Patients with Acute Pulmonary Embolism ($n = 72$)

	≥ 70 Years, (%)
Dyspnea or tachypnea[a]	92
Dyspnea or tachypnea or hemoptysis	92
Dyspnea or tachypnea or signs of deep venous thrombosis	92
Dyspnea or tachypnea or pleuritic pain[b]	94
Dyspnea or tachypnea or pleuritic pain or signs of deep venous thrombosis[b]	94
Dyspnea or tachypnea or radiographic atelectasis or parenchymal abnormality	100
Dyspnea or tachypnea or pleuritic pain or radiographic atelectasis or parenchymal abnormality[b]	100

[a] Tachypnea = respiratory ratio ≥ 20/min.
[b] The addition of hemoptysis did not improve the sensitivity of the combination for the detection of pulmonary embolism.

COMBINATIONS OF SYMPTOMS AND SIGNS IN ELDERLY PATIENTS

Dyspnea or tachypnea or pleuritic pain occurred in 94% of all elderly patients, including those with prior cardiopulmonary disease. Dyspnea or tachypnea or radiographic evidence of atelectasis or a parenchymal abnormality occurred in 100% (6) (Table 4).

THE ELECTROCARDIOGRAM IN ELDERLY PATIENTS WITH PE

Among all elderly patients, some of whom had prior cardiopulmonary disease, nonspecific ST segment or T-wave changes were the most frequent electrocardiographic abnormalities (6). Either or both occurred in 56% of patients ≥70 years old (6) (Table 5). With the

Table 5 Electrocardiographic Findings in Elderly Patients with Acute Pulmonary Embolism ($n = 57$)

	≥ 70 Years, (%)
Normal	21
ST segment or T-wave changes	56
Left axis deviation	18
Left ventricular hypertrophy	12
Acute myocardial infarction pattern	12
Low-voltage QRS	9
Complete right bundle branch block	7
Right ventricular hypertrophy	4
Right axis deviation	2
Right atrial enlargement	2
Incomplete right bundle branch block	2

exception of left anterior hemiblock (left axis deviation) among patients ≥70 years of age, other electrocardiographic abnormalities occurred in 12% or fewer elderly patients. No difference in the frequency of any electrocardiographic abnormalities occurred among different age groups (6).

Among elderly patients with the pulmonary hemorrhage/infarction syndrome and no prior cardiopulmonary disease, the electrocardiogram was normal in 62% (9). If abnormal, the most frequent abnormalities were nonspecific ST segment or T-wave changes (38%).

BLOOD GASES IN ELDERLY PATIENTS WITH PE

The partial pressure of oxygen in arterial blood (P_aO_2) was lower among elderly patients with PE than among younger patients (6). The P_aO_2 among elderly patients with PE, some of whom had prior cardiopulmonary disease, was 61 ± 12 mmHg (mean ± standard deviation).

The alveolar–arterial oxygen difference (gradient) among elderly patients with PE was 47 ± 14 mmHg, which was higher than among younger patients. The alveolar–arterial oxygen difference in normal adults increases with age (10–13).

Elderly patients with the pulmonary hemorrhage/infarction syndrome who had no prior cardiopulmonary disease had a higher pulmonary artery mean pressure (25 ± 9 mmHg) and lower P_aO_2 (64 ± 10 mmHg) than patients less than 40 years of age (9).

CLINICAL ASSESSMENT IN ELDERLY PATIENTS

When physicians were 80 to 100% confident that pulmonary embolism was present in elderly patients on the basis of clinical judgment and simple laboratory tests, they were correct in 90% of a small sample of patients (9 of 10 patients) (6). When they believed that there was less than 20% likelihood of pulmonary embolism, they correctly excluded the diagnosis in 81% of patients. In most elderly patients, physicians were uncertain of the diagnosis, believing that there was a 20 to 79% chance of pulmonary embolism. The accuracy of clinical assessment was comparable among patients in all age groups (6).

VENTILATION/PERFUSION LUNG SCANS IN ELDERLY PATIENTS

The utility of ventilation/perfusion lung scans among patients ≥70 years old was comparable with that in younger patients (6). Among patients ≥70 years of age with ventilation/perfusion lung scans indicating a high probability of pulmonary embolism, 94% had pulmonary embolism (Table 6). The positive predictive value of all probabilities of ventilation/perfusion lung scans using original PIOPED criteria (14) were comparable in all age groups (6).

The sensitivity of ventilation/perfusion scans interpreted as a high probability of pulmonary embolism among patients ≥70 years of age was 47% (6). The sensitivity did not differ significantly among age groups. The specificity of ventilation/perfusion scans

Table 6 Ventilation-Perfusion Scans in Elderly Patients with Acute Pulmonary Embolism (PE)

	≥70 Years	
	Number of patients	%
High	34/36	94
Intermediate	27/100	27
Low	10/71	14
Near normal/normal	1/8	13

interpreted as a high probability of pulmonary embolism among patients ≥70 years of age was 99%. The specificity was similar among all age groups (6).

Elderly patients with no prior cardiopulmonary disease who had the pulmonary hemorrhage/infarction syndrome tended to show more mismatched perfusion defects than patients under age 40, regardless of whether the defects were large or moderate in size (9).

In patients with no prior cardiopulmonary disease, a high positive predictive value can be achieved with fewer mismatched perfusion defects than are required for a high-probability interpretation in patients with prior cardiopulmonary disease (15,16). Stratification according to the presence or absence of prior cardiopulmonary disease was particularly useful for the evaluation of V/Q lung scans in patients ≥70 years, although only 23% of elderly patients had no prior cardiopulmonary disease. Among patients ≥70 years, who had no prior cardiopulmonary disease, ≥ 2 mismatched large- or moderate-size perfusion defects showed a sensitivity of 74%, a specificity of 100%, and a positive predictive value of 100% (17).

COMPLICATIONS OF PULMONARY ANGIOGRAPHY AMONG ELDERLY PATIENTS

Major complications of pulmonary angiography occurred in 1.0% of 200 patients ≥70 years (6). Renal failure, either major or minor, was the most frequent complication of angiography among elderly patients. It occurred in 3% of patients ≥70 years of age (6). ''Minor'' complications of renal failure were important complications, although dialysis was not required. Patients with these complications showed either an elevation of the serum creatinine from previously normal levels to ≥2.1 mg/100 mL (range 2.1–3.5 mg/100 mL) or an increase in a previously abnormal serum creatinine level ≥2 mg/100 mL.

Minor complications of prior angiography included urticaria, pulmonary edema requiring only diuretics, nausea and vomiting, arrhythmias that were not life threatening, hematomas, interstitial staining with contrast material and narcotic overdose (18). Minor complications occurred in 7.0% of patients ≥70 years old.

Contrast-enhanced spiral computed tomography (CT) might be considered in elderly patients instead of standard pulmonary angiography (19–22). This technique has not yet been fully evaluated (23,24). It appears to be more sensitive for PE in central pulmonary arteries than peripheral arteries (23,24). If there is a likelihood that standard angiography may be required anyway because of a nondiagnostic contrast-enhanced spiral CT, renal

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insufficiency due to a large load of contrast material may be a problem in elderly patients. In that case, standard pulmonary angiography is recommended (23).

STRATEGIES OF DIAGNOSIS IN THE ELDERLY

Serial noninvasive leg tests accompanied by ventilation/perfusion lung scans may be a particularly useful diagnostic strategy in the elderly. This strategy may permit a diagnosis without the need for pulmonary angiography (25). Although elderly patients have been shown to tolerate pulmonary angiography, it is sensible to avoid the procedure if possible. The risk of fatal PE has been shown to be small if serial noninvasive leg tests show no deep venous thrombosis (26,27). Conversely, if deep venous thrombosis is present, the treatment with anticoagulants is the same as with PE (28).

ANTICOAGULANT THERAPY

Several studies found that the frequency of bleeding during warfarin therapy is higher in older patients, although this was not observed by some (29). In one study, the relative risk for major bleeding was 3.2 for patients age 65 or older (30). The risk of major hemorrhagic complications among patients of all ages with thromboembolic disease, treated with ''less intense'' warfarin, international normalized ratio (INR) = 2.0–3.0, based on pooled data, was 1.7% (31).

Older patients also have a higher risk of bleeding from heparin than younger patients (32,33). The frequency of major hemorrhagic complications from heparin among patients of all ages treated for thromboembolic disease was 4.9%, based on pooled data (31). The frequency of major bleeding from heparin in high-risk patients (surgery within previous 14 days, history of peptic ulcer disease, gastrointestinal or genitourinary tract bleeding, or platelet count $<150 \times 10^9$/L) was 10.8% (34). Among patients at low risk of bleeding, the frequency of major bleeding with heparin was 1.1%.

THROMBOLYTIC THERAPY

Intracranial bleeding appears to be more common in elderly patients following thrombolytic therapy, based on experience following myocardial infarction (35). The average reported risk of major bleeding in patients of all ages who underwent pulmonary angiography prior to the administration of t-PA for acute PE was 14.0% (36). Major bleeding was frequent at the site of insertion of the catheter. The estimated risk of major bleeding with t-PA in patients of all ages following a noninvasive diagnosis of PE was 4.2% (36). Some believe that the risks of serious and perhaps fatal bleeding with thrombolytic therapy are so great that a pulmonary angiogram must be obtained in all patients (37). Some believe that if there is a strong clinical suspicion of acute PE supported by a high-probability V/Q scan (or in an extreme emergency a noninvasive leg test showing DVT or an echocardiogram showing right ventricular dysfunction), then thrombolytic therapy may be administered on the basis of these noninvasive tests without a pulmonary angiogram (38). The most appropriate indication for thrombolytic therapy in patients with PE is massive PE

complicated by hypotension in the absence of contraindications to thrombolytic therapy (38).

CONCLUSION

In conclusion, the signs and symptoms known to occur among younger patients also occurred in elderly patients, although occasional exceptions were observed. Even among elderly patients, typical signs and symptoms occurred with sufficient frequency to suggest the possibility of pulmonary embolism in the differential diagnosis. In the absence of these signs and symptoms, unexplained radiographic abnormalities were important diagnostic clues. When the diagnosis of pulmonary embolism is uncertain, pulmonary angiography can be performed safely in elderly patients, although renal failure was a problem among elderly patients. Serial noninvasive leg tests in combination with ventilation/perfusion lung scans may eliminate the need for pulmonary angiography in many elderly patients.

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31

Peripheral Vascular Disease in the Elderly

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INTRODUCTION

Peripheral vascular disease will continue to be a major cause of morbidity and mortality in the geriatric population. This is especially pertinent since the elderly comprise the fastest growing element in our society. Between 1995 to 2005 there will be a projected growth of 24% in the age group over 75, increasing from 14.7 million to 18.3 million (1). The disease process, especially that due to atherosclerosis, is prevalent in virtually every organ system and can therefore manifest in a variety of symptoms. Carotid bifurcation disease contributes to stroke through sudden occlusion and/or cerebral embolization. Lower extremity arterial occlusive disease results in significant disability due to intermittent claudication, advancing to limb-threatening conditions of rest pain, ischemic ulceration, and gangrene. Aortic aneurysms are particularly life-threatening conditions, most commonly diagnosed in octogenarians, with an estimated incidence of 6% in men over 80 years of age. Other common clinical signs and symptoms in the elderly, including hypertension, renal insufficiency, and abdominal pain may be due to renovascular and mesenteric ischemia resulting from arterial luminal stenoses.

Management of each of these conditions in the geriatric population requires thorough knowledge of the natural history of these peripheral vascular disease processes. This is especially important in the older patient, since common comorbid conditions such as coronary artery disease, pulmonary disease, diabetes mellitus, and renal insufficiency can increase the risks associated with any necessary invasive diagnostic tests and operative procedures.

This chapter examines those common considerations related to the genesis and diagnosis of all types of vascular lesions, and then focuses on the current management of the most common peripheral vascular problems found in the geriatric patient.

GENERAL CONCEPTS

The aging process causes subtle changes to occur in the wall of peripheral arteries, independent of atherosclerosis. The shape and orientation of the endothelial cells become less

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homogeneous, predisposing them to increased turbulence at the critical blood–endothelial cell interface (2,3). The flexibility of the peripheral vascular artery is altered as the calcium and lipid content of the subendothelial layer increases, while, at the same time, the elasticity of the underlying muscular media is compromised by fractured cross-linking of elastin and other supportive protein moieties. As a result, this leads to increased ''stiffness'' of the arterial vasculature, making it less well suited to the reactive enlargement of the media and adventitia, which is the most important compensation to eccentric plaque deposition (4).

Cigarette smoking, hypertension, hypercholesterolemia, diabetes mellitus, obesity, sedentary lifestyle, and hereditary factors are known risk factors for the development and acceleration of atherosclerosis. The first four factors are of greatest importance and appear to be cumulative in their effect. Therefore, the greater number of risk factors a patient has, the more likely it is that they develop atherosclerosis. Modification of these risk factors may influence the progression of the atherosclerotic disease process. Adequate control of hypertension has the beneficial effects of reducing cardiac work and microvascular injury, especially the kidneys. Management of hyperlipidemia, especially low-density lipoproteins (LDL), has been shown to reduce the progression of coronary artery atherosclerotic plaque formation (5). Exercise has the benefit of reducing heart rate and increasing high-density lipoproteins (HDL) levels (6,7). Cessation of tobacco use has also been associated with decreasing the progression of coronary and peripheral arterial atherosclerosis. In one study (8), 11% of claudicants who continued smoking required amputation within 5 years, with no amputations in those who stopped or never smoked. Similarly, patency in lower extremity bypass grafts is worse in smokers than in nonsmokers (9). Additionally, the rigid control of serum glucose in diabetics appears to diminish the entire spectrum of associated secondary peripheral vascular complications. Diabetics have at least a fivefold increased risk of critical ischemia from peripheral vascular disease compared to nondiabetics. Ulcers and gangrene will occur in 10% of elderly diabetics. In one series, 6.8% of diabetics underwent lower extremity amputations compared to 0.6% of nondiabetics over a 5-year period (10,11). Approximately 20% of diabetics with claudication progress to amputation within 5 years, compared to about 3% of nondiabetics (12,13). Furthermore, diabetics who smoke have markedly worse prognosis for limb loss compared to nonsmokers.

Unfortunately, it is not unusual for geriatric patients to present with advanced symptoms of peripheral vascular disease, often related to delays in obtaining a proper diagnosis. For instance, symptoms of intermittent claudication may be easily rationalized or attributed to other musculoskeletal causes such as arthritis, so that the first recognized manifestation of lower extremity athero-occlusive disease is advanced limb-threatening ischemia. Vertigo, dizziness, or other intermittent neurological symptoms may likewise be attributed to other reasons without adequate evaluation of extracranial arterial lesions or proximal arterial–arterial embolic sources. The incidence of abdominal aortic aneurysm is highest in the geriatric population, yet it is not unusual for these patients to present with rupture of these lesions due to an overly conservative approach to their elective surgical repair. These scenarios emphasize the great importance of very careful history taking and vigilant physical examination during regular office visits in these elderly patients.

Prevalence of peripheral aortic occlusive disease (PAOD) varies with age and sex. A representative study is shown in Figure 1, depicting the relation between PAOD prevalence and age in Scotland. At all ages, men have a higher prevalence than women, but the gap narrows with advancing age. Scotsmen under 50 years have a less than 1% prevalence,

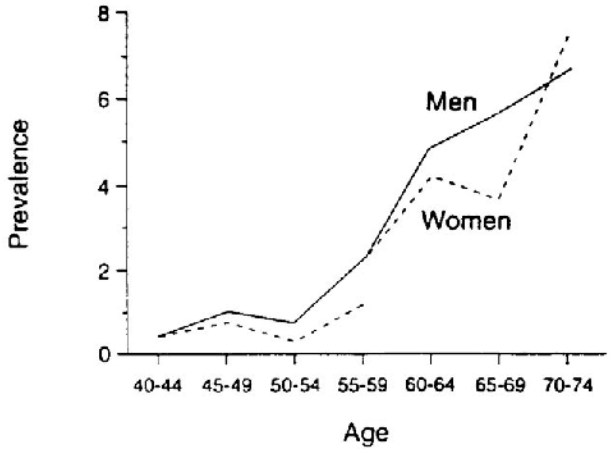

Figure 1 Prevalence of PAOD in men and women. (From Ref. 14, with permission.)

compared to men older than 60, who have a fivefold increased prevalence (14). Similar relations between age, sex, and PAOD prevalence have been found in other countries, although different absolute prevalences are reported. The low end of the spectrum is found in Danish men aged 40 to 59 who have a 0.4% prevalence compared with a 14% prevalence reported in American men and women over the age of 65 (15,16). At the other extreme, Italians 80 years and older have a reported prevalence of 30% (17).

Another important element that influences the natural history of PAOD is the response of the arterial wall to iatrogenic trauma from therapeutic manipulation such as surgery or balloon angioplasty. The response of the injured arterial wall is to elaborate a myointimal hyperplastic reaction. Smooth muscle cells, partially under the influence of platelet-derived growth factors elaborated at the site of injury, migrate from the media into the intima, and transform into unique myointimal cells, which proliferate and lay down fibrous tissue. The resulting lesion is histologically distinct from atherosclerotic plaque, but has many of the same consequences, including gradual reduction in blood flow that may promote arterial thrombosis (18,19). The development of myointimal hyperplasia remains the Achilles heel of vascular therapy.

DIAGNOSTIC STUDIES FOR PERIPHERAL VASCULAR DISEASE

The ready availability of noninvasive vascular tests should prompt primary care physicians to consider early evaluation in elderly patients presenting with even subtle changes in symptoms of physical findings suggestive of peripheral vascular disease. These studies can quantify the extent of disease and localize lesions in many areas prone to atherosclerotic disease without the risks of more invasive procedural studies such as arteriography. In this fashion, significant disease may be more aggressively pursued while noncritical lesions may be reassessed over time, thereby sparing both patients and physicians anxiety over missed pathology.

Noninvasive ultrasound tests are used to assess lower extremity blood flow using three main methods: determination of ankle blood pressures, characterization of velocity wave forms, and duplex ultrasound. Doppler ultrasound-based studies offer the most commonly utilized noninvasive examinations for a host of peripheral vascular disease processes. One common test is to measure ankle and brachial artery systolic pressures using a Doppler stethoscope and blood pressure cuffs. This allows calculation of an ankle-brachial index (ABI) which is normally 1.0 to 1.2. An ABI below 1.0 suggests arterial occlusive disease. The lower the ABI, the more severe the restriction of blood flow and the more serious the ischemia. ABIs of 0.6 to 0.9 usually correlate with mild-to-moderate claudication; values between 0.4 to 0.6 often accompany severe claudication; and between 0.25 to 0.4, rest pain and tissue loss are often found; ABIs below 0.25 predict high likelihood of limb loss. In addition to the ratio, the actual systolic pressure at the ankle has significance, with pressures below 50 mmHg marking critical ischemia. Occasionally, patients with calcified arteries from diabetes or renal failure have relatively noncompressible arteries leading to fictitiously elevated ABI values above 1.2.

In addition to measuring pressure in nonpalpable arteries, Doppler ultrasound methods allow characterization of the flow vs. time velocity waveform. The normal waveform at the level of the common femoral artery is triphasic, with distal arteries having either biphasic or triphasic flow. The finding of biphasic flow at the groin or monophasic flow more distally is good evidence of arterial obstruction even when ABI measurements are falsely elevated due to calcification (20).

Duplex ultrasound combines Doppler frequency measurements with two-dimensional images of blood vessels (see Fig. 2). Duplex ultrasound allows sophisticated hemodynamic analyses based on velocity power spectra, velocity waveforms, and ratios of systolic and diastolic flows. The severity of flow restriction induced by a stenosis can thus be accurately assessed and disturbed flow reliably detected (21). Duplex ultrasonography offers the most comprehensive noninvasive examination of a host of vascular lesions. This modality is especially useful in screening patients for extracranial carotid and vertebral disease, mesenteric arterial disease, renovascular stenoses, abdominal aortoiliac lesions, and infrainguinal arterial disease.

Other important noninvasive diagnostic methods include measurements of skin perfusion with laser Doppler techniques, determination of skin oxygen tension ($tcPO_2$), and assessment of walking distance on a low-speed treadmill. The vascular laboratory is particularly good in documenting hemodynamic responses to interventions aimed at improving the circulation. After arterial reconstruction, increased ABIs or improvements in blood velocity waveforms reliably indicate improved blood flow. Bypass grafts are easily assessed via ultrasound for patency and the presence of significant stenosis using duplex ultrasound. The information provided by ultrasound regarding flow of blood and vessel patency or occlusion allows critical management decisions to be made without depending on arteriography.

Percutaneous transcatheter contrast arteriography remains the conventional diagnostic test for a wide range of peripheral vascular problems. Commonly, noninvasive tests are performed initially as a screening study to identify specific lesions. Arteriography is reserved for validating the findings and allowing finalization of the decision-making process—to plan definitive intervention, whether an endovascular transcatheter-based treatment or open surgery. However, as noninvasive studies such as duplex ultrasonography become more sophisticated and accurate, they themselves are sometimes adequate to serve as the definitive diagnostic study. Furthermore, invasive studies such as arteriography

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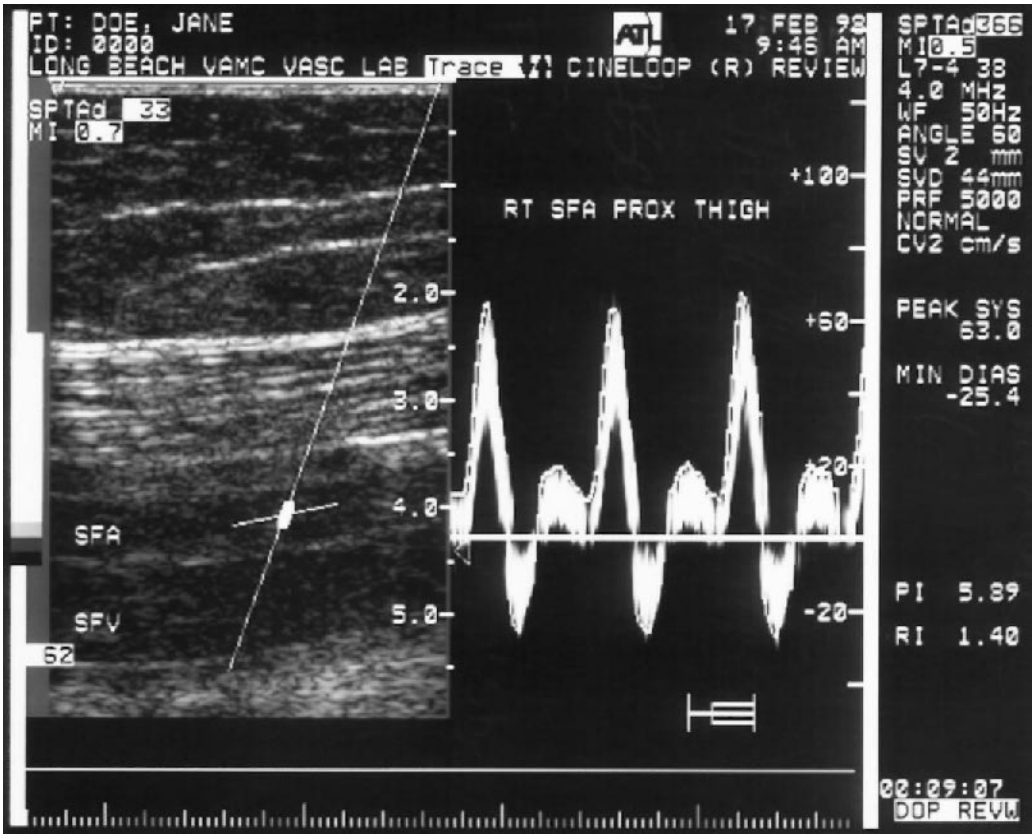

Figure 2 Noninvasive ultrasound. The figure shows a typical result of duplex ultrasound examination of flow in a superficial femoral artery. At the left is a gray scale image of the artery in longitudinal section, at the right is a depiction of the flow versus time waveform. Note the reversal of flow below baseline during diastole, indicating triphasic flow.

should be reserved only for those individuals in whom a decision has been made that some form of definitive therapy is warranted. This approach is prudent since regardless of the indication or peripheral vascular region of interest, contrast arteriography has associated morbidity and mortality. These adverse reactions may be categorized as being local, systemic, or neurological. Local complications, ranging in incidence from 5 to 15%, include hemorrhage, hematoma formation, arterial thrombosis, distal embolization, infection, and pseudoaneurysm formation at the puncture site. Systemic complications include allergic reactions to the radiological ionic contrast agents as well as renal and cardiovascular manifestations. Most series report a less than 2% incidence of serious allergic reactions; however, the incidence of anaphylactic reactions may be as high as 20% in patients with a history of contrast allergy (20). Allergic reactions may range from minor sequelae such as nausea, vomiting, hives, and chills, to major life-threatening reactions such as bronchospasm, hypotension, laryngospasm, and pulmonary edema. The ionic contrast agents may also have a deleterious effect on renal function, especially in patients with preexisting kidney insufficiency. One series reported that nonazotemic patients experienced a 2%

incidence of acute renal failure following all types of contrast arteriography, while patients with chronic azotemia suffered a 33% incidence (21). Finally, since these studies utilize percutaneous transluminal techniques, they may cause arterial-arterial embolization to the brain, causing strokes, especially when performing cerebrovascular examinations.

Alternative imaging techniques include magnetic resonance arteriography (MRA) and computerized tomographic arteriography (CTA). They both have the advantage over conventional percutaneous transcatheter arteriography in that there is no risk of stroke or local arterial injury. Moreover, since MRA does not require infusion of contrast agents, it avoids these inherent potential systemic reactions. However, since these imaging modalities have only recently become widely available, rigorous correlation between MRA, CTA, and actual arterial pathology has yet to be validated. In our early experience with CTA, there appears to be excellent correlation between actual degree of arterial stenoses with the operative findings, especially in extracranial carotid bifurcation disease.

When it becomes apparent that surgical intervention is warranted, critical attention should be directed toward the preoperative evaluation of cardiac, renal, and pulmonary function to minimize any perioperative morbidity and mortality. While the magnitude of the proposed intervention appropriately influences the extent of the preoperative evaluation, cardiac risk assessment must be rigorous, presuming the systemic nature of the atherosclerotic disease process. This is especially important in the diabetic patient who is more prone to have ''silent'' cardiac disease. Cardiac complications are the major cause of mortality in all types of peripheral vascular interventions. Furthermore, the symptoms of cardiac disease may be masked in elderly patients due to restrictions in daily activities as a result of claudication or musculoskeletal disorders. The utility of exercise or pharmacologically induced stress echocardiograms or radionuclide scans may uncover areas of myocardium with reversible ischemia, prompting more definitive diagnostic studies such as coronary arteriography. Formal pulmonary function tests and evaluation of renal clearance, in addition to simple measures of BUN and serum creatinine, offer helpful prognostic indicators. A forced expiratory capacity of < 1.0 L and a creatinine clearance of < 40 mL/min both indicate an increased incidence of perioperative complications, especially for major abdominal procedures. Such preoperative evaluations can significantly alter the operative approach to a particular peripheral vascular problem, allowing the surgeon to choose between alternative procedures. For example, for an individual patient, the most durable anatomical solution for advanced aortoiliac athero-occlusive (aortofemoral bypass) may be a less valid choice than other less stressful procedures (extra-anatomical axillobifemoral bypass or percutaneous transluminal angioplasty $\pm$ stenting). A vigilant, comprehensive approach by knowledgeable physicians and surgeons to the geriatric patient with advanced peripheral vascular disease assures the best potential outcome for this high-risk group.

SPECIFIC CLINICAL PRESENTATIONS OF PERIPHERAL VASCULAR DISEASE

Extracranial Carotid Disease

Carotid endarterectomy (CEA) is commonly performed for prophylaxis against stroke in patients with severe atherosclerotic stenosis of the internal carotid artery. The prevalence of this procedure in the U.S. peaked at 103,000 cases in 1984 but decreased in the late 1980s to 70,000 cases in 1989 (22,23). The number of patients undergoing CEA is now

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on the rise again after long-standing controversy regarding its effectiveness was settled by several large-scale clinical trials. These studies include the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the European Carotid Surgery Trial (ECST), the Veterans Administration Cooperative Studies 309 and 167 (VA 309, VA 167), and the Asymptomatic Carotid Atherosclerosis Study (ACAS) (24–28). Although these trials confirmed the efficacy of CEA for both symptomatic and asymptomatic patients with severe carotid stenosis, the procedure must be performed with acceptable perioperative morbidity and mortality to assure patient benefit. The combined mortality and stroke morbidity in the ECST study was 7.5% compared with 5.6% in VA 309 (25,26). In asymptomatic disease, mortality and morbidity are lowest, as demonstrated by ACAS with a total of 2.3% (28).

The prospect of any perioperative mortality suggests that special consideration be taken with the geriatric patient. In managing the older patient with symptomatic or asymptomatic carotid stenosis, the referring physician and surgeon must be certain that the carotid lesion warrants an operation. Additionally, the patient's associated risk status must be good enough to recommend operation for an asymptomatic stenosis.

Elderly patients are at highest risk for suffering stroke. Among those over age 65, the annual death rate from stroke is 394 per 100,000 (1). Since the elderly population is the fastest growing segment of our society, CEA could potentially provide great benefit for a large number of people. However, because the older patient is already at greater risk for perioperative mortality and morbidity, one must be quite discriminating in choosing the elderly patient who is fit enough to undergo carotid endarterectomy. If this is kept in mind and enough precautions are taken in patient selection, one may achieve acceptably low rates comparable to the 4.3% and 2.3% in the VA 167 (mean age 64.1) and ACAS (mean age 67) (27,28).

The specific indications for CEA in the geriatric patient should generally follow those for the population at large. CEA has been shown to be beneficial in minimizing subsequent ipsilateral stroke in symptomatic patients with internal carotid stenosis with diameter reduction of $\geq$70% (Fig. 3). Specific symptoms include focal hemispheric symptoms [i.e., transient ischemic attack (TIA), reversible ischemic neurological deficit (RIND); small completed stroke; and stroke in evolution or amaurosis fugax]. Nonhemispheric symptoms, such as dizziness, vertigo, or headache, should be assessed with caution. For patients with hemispheric symptoms, the benefits of operation are clear. Subsequent stroke rates for surgically vs. medically treated patients were found to be 7.7% vs. 19.4% at 11.9 months for stenosis $>$50% (VA 309); 10.3% vs. 16.8% at 36 months for stenosis $>$70% (ECST); and 9% vs. 26% at 24 months for stenosis $>$70% (NASCET) (24–26). For the patient with significant carotid stenosis but without symptoms, selection must be somewhat more restricted. After several other studies failed to conclusively prove the benefits of surgery, ACAS established that for asymptomatic patients with stenosis $>$60%, surgery reduces the risk of ipsilateral stroke provided that operative morbidity and mortality be held to $<$3% (28).

For the elderly patient, the difference in indications for carotid endarterectomy must be tempered by the increased operative risk. Older patients, who have been shown to have higher operative risk for coronary artery bypass and peripheral vascular reconstruction, tend to have significant concomitant morbidity (29–31). The incidence of diabetes mellitus, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and hypertension all increase with advancing age (32–33). Moreover, history of prior myocardial infarction (MI), especially if within the previous 6 months, is associated with higher

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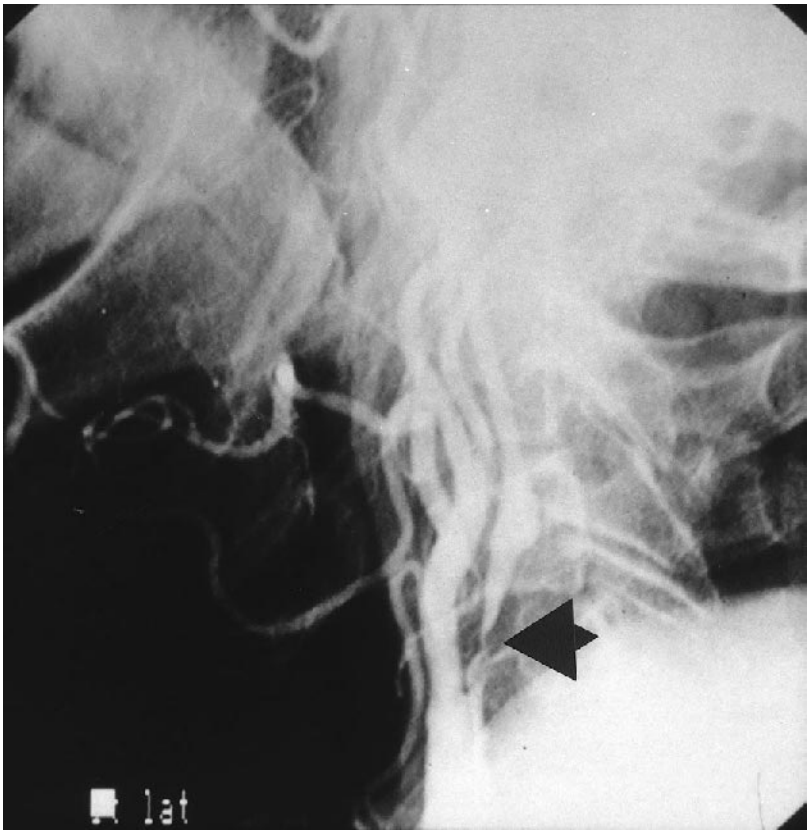

Figure 3 Arteriogram demonstrating severe atherosclerotic stenosis of the extracranial carotid artery bifurcation.

operative risk. This is not uncommon, with 10% of men and 5% of women over 65 years having such a history (33). Among patients undergoing CEA, angina, CHF, COPD, hypertension, and MI within the past 6 months, all were correlated with increased incidence of postoperative MI (34). This, along with postoperative stroke, is responsible for the majority of post-CEA morbidity. In two studies, advanced age (>70 years), in itself, was correlated with an increased incidence of postoperative MI for a wide variety of major surgical procedures (34,35).

The benefit of surgery for the elderly patient with asymptomatic carotid stenosis having significant concomitant disease imparts a major judgmental challenge to surgical decision making. Perioperative morbidity and mortality should be kept to <3% when the indication for operation is asymptomatic disease. However, significant medical comorbidities may by themselves increase the risk of postoperative MI, stroke, or death to 7% (34).

As with all age groups, the decision to operate is further made difficult by the prevalence of cerebrovascular disease of noncarotid etiology, such as lacunar infarct or vertebrobasilar disease. Lacunar infarct has been shown not to be due to carotid embolization but rather to intracerebral small vessel vasculopathy (36). The presence of vertebrobasilar

disease can result in such symptoms as dysarthria, dysphagia, diplopia, nystagmus, visual field defects, hoarseness, ataxia, and syncope (37). Presence of a combination of these symptoms may not be due to carotid disease, and distinguishing the two etiologies can be confusing. Nonhemispheric symptoms such as dizziness, lightheadedness, and blurry vision are presumably due to generalized hypoperfusion rather than embolus.

Preoperative evaluation of the elderly patient found to be a candidate for CEA must be performed vigilantly. Accurate assessment of surgical risk due to concomitant disease and assurance that symptoms are caused by extracranial carotid bifurcation stenosis or plaque are important. While a conservative approach is warranted, the life expectancy of older patients should not be underestimated. These geriatric patients stand to gain extension of productive years, provided their surgical risk is acceptably low. As of 1990, the remaining life expectancy was 10.9 years at age 75 and 8.3 years at age 80 (1). In fact, the fit patient at age 80 may have a longer life expectancy than a patient 20 years younger who has risk factors such as heavy tobacco use or diabetes mellitus.

Sixteen studies of carotid endarterectomy in the elderly published between 1981 and 1996 are summarized in Table 1 (30,38–52). The age cutoff for defining the ''elderly patient''varied in each of the studies (70, 75, or 80 years old). In those studies that included series of younger patients below the arbitrary age cutoff, none demonstrated a statistically significant difference between younger and older patients in either mortality or incidence of postoperative stroke. Other studies (53,54) have also corroborated these numerical results. However, when the individual studies are grouped and evaluated by the age cutoff ($>$70 years old; $>$75 years old; $>$80 years old, respectively), there is a statistically significant ($p < 0.05$) increase in both morbidity alone as well as combined mortality and morbidity for the $>$75-year-old group (Table 2). No increase in risk for the elderly was found when 70 or 80 years was used as the cutoff. Interestingly, there was a statistically significant increased morbidity and combined morbidity and mortality for younger patients with a cutoff of 70 years. It should be noted that in two of the studies, each progressively older age bracket had a correspondingly higher operative morbidity, mortality, and combined morbidity (48,52).

The failure of individual studies to find a difference in mortality and morbidity rates between younger and older patients can be attributed to various factors. Several studies report results from referral centers with uniform surgical technique and limited patient selection by a small number of surgeons with great familiarity in performing CEA. An additional factor is the operation itself; patients undergoing CEA have relatively little postoperative pain and therefore less respiratory impairment and pulmonary complications (44).

Generally, individual reports chronologically show a significant decrease in mortality and morbidity rates over the years in which the studies were conducted. However, the overall morbidity and mortality has changed very little over time (Table 3).

Age greater than 65 years was once considered a high-risk threshold for performing CEA. Over the last 20 years, the age limit for CEA has been extended to progressively older groups. Review of the literature suggests that age itself should not be the sole discriminating factor in weighing the value of CEA for clear-cut symptoms or high-grade asymptomatic stenosis. Recently, a statewide analysis of 9918 Maryland patients concluded that CEA, even among the very elderly, is a safe procedure, although the length of stay may be longer due to the concomitant medical illness (55).

There has been recent interest in endovascular stenting of carotid artery lesions in

Table 1 Summary of Carotid Endarterectomy Morbidity and Mortality Rates in Young vs. Old Patients

Author	Year	Age cutoff	Cases (young)	Cases (old)	Morbidity (young)	Morbidity (old)	Mortality (young)	Mortality (old)	Combined M + M (young)	Combined M + M (old)	Statistically significant difference?
Benhamou	1981	70		220		8 (3.6)		8 (3.6)		16 (7.3)	
Brott	1984	70	307	124	32 (10.4)	5 (4.0)	8 (2.6)	4 (3.2)	40 (13)	9 (7.3)	No
		80	412	19	36 (8.7)	1 (5.3)	12 (2.9)	0 (0)	48 (11.7)	1 (5.3)	No
Courbier	1985	75		76		2 (2.6)		1 (1.3)		3 (3.9)	
Plecha	1985	75	5220	782	94 (1.8)	17 (2.2)	77 (1.5)	18 (2.3)	171 (3.3)	35 (4.5)	No
Ouriel	1986	75	393	77	12 (3.1)	3 (3.9)	2 (0.5)	0 (0)	14 (3.6)	3 (3.9)	No
Rosenthal	1986	80	1008	90	20 (2.0)	4 (4.4)	6 (0.6)	2 (2.2)	26 (2.6)	6 (6.7)	No
Schultz	1988	80		116		1 (0.9)		2 (1.7)		3 (2.6)	
Loftus	1988	70		53		1 (1.9)		0 (0)		1 (1.9)	
Fisher	1989	65		2089		35 (1.7)		52 (2.5)		87 (4.2)	
		70		1356				44 (3.2)			
		75		685				25 (3.6)			
		80		212				10 (4.7)			
Schroe	1990	70	483	222	20 (4.1)	7 (3.2)	8 (1.7)	3 (1.4)	28 (5.8)	10 (4.5)	No
Pinkerton	1990	75	560	125	2 (0.4)	0 (0)	5 (0.9)	1 (0.8)	7 (1.3)	1 (0.8)	No
Meyer	1991	70		749		23 (3.1)		10 (1.3)		33 (4.4)	
		75		265		10 (3.8)		4 (1.5)		14 (5.3)	
		80		56		3 (5.4)		0 (0)		3 (5.4)	
Roques	1991	75		81		2 (2.5)		3 (3.7)		5 (6.2)	
Treiman	1992	80		183		3 (1.6)		3 (1.6)		6 (3.3)	
Coyle	1994	80	992	79	26 (2.6)	0 (0)	16 (1.6)	1 (1.3)	42 (4.2)	1 (1.3)	No
Perler	1996	75	124	63	2 (1.6)	3 (4.8)	2 (1.6)	1 (1.6)	4 (3.2)	4 (6.3)	No

Note: Morbidity indicates postoperative ipsilateral stroke.
Percentages are shown in parentheses.
Young and old refer to patients below and above the particular age cutoff for each study.

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Table 2 Carotid Endarterectomy Morbidity and Mortality: Studies Grouped by Age Cutoff

Cutoff	No. of studies compiled	Total no. of young patients	Total no. of old patients	Morbidity (young)	Morbidity (old)	Mortality (young)	Mortality (old)	Combined M + M (young)	Combined M + M (old)
>65	1		2089		35 (1.7)		52 (2.5)		87 (4.2)
>70	5	790	1368	52 (6.6)	44 (3.2)	16 (2)	25 (1.8)	68 (8.6)	69 (5)
>75	7	6297	1469	110 (1.7)	37 (2.5)	86 (1.4)	28 (1.9)	196 (3.1)	65 (4.4)
>80	6	2412	543	82 (3.4)	12 (2.2)	34 (1.4)	8 (1.5)	116 (4.8)	20 (3.6)

Note: Number of compiled studies totals to >16 because several studies listed results by more than one age cutoff.
Pairs of italicized figures indicate statistically significant difference ($p < 0.05$).

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Table 3 Carotid Endarterectomy Morbidity and Mortality by Year of Study Publication

Five-year period	Number of studies compiled	Total cases	Morbidity	Mortality	Morbidity + mortality
1981–1985	4	6279	158 (2.3)	116 (1.7)	274 (4.1)
1986–1990	7	5216	105 (2)	81 (1.6)	186 (3.6)
1991–1995	4	2084	54 (2.6)	33 (1.6)	87 (4.2)
1996–	1	187	5 (2.7)	3 (1.6)	8 (4.3)

lieu of standard operative CEA. This new development is still unproven and careful prospective studies need to be carried out before any recommendations can be made regarding the efficacy of these endoluminal therapies.

It is clear that elderly patients may benefit from CEA when performed for the proper indications. However, careful assessment of their associated comorbidities is most important to assure optimal long-term benefit from surgical intervention. If these caveats are respected, prevention of ischemic or embolic stroke can greatly enhance the quality of life for the geriatric patient.

Vertebrobasilar Insufficiency

The most common symptoms of vertebrobasilar insufficiency include nausea, vertigo, ipsilateral facial numbness, ipsilateral Horner's syndrome, and limb ataxia. While these ischemias may be very mild and often transient, there can be progression to actual posterior fossa infarction, which can be lethal due to extensive edema and midbrain compression. Although microembolization can contribute to posterior cerebral and cerebellar ischemic compromise, athero-occlusive disease of the vertebral arteries or the basilar artery is the most common etiology of this process. Thrombosis may occur in the basilar artery proper or the basilar branch vessels that penetrate into the brain stem.

Subclavian steal syndrome is a classic vertebrobasilar symptom complex associated with proximal subclavian or innominate artery stenosis. Since the vertebral arteries originate from the subclavian arteries, they can function as collaterals to the upper extremities. With a proximal stenosis, flow is reversed in the vertebral artery following ipsilateral arm exertion, decreasing blood flow and perfusion pressure through the basilar arterial system. This results in posterior cerebral and cerebellar ischemic symptoms, and is exacerbated in the presence of associated carotid occlusive disease. The left subclavian artery is more commonly involved, occurring in 65% of cases. The diagnosis of subclavian steal syndrome is supported by complaints of intermittent vertigo, light-headedness, nausea, diplopia, and vomiting exacerbated by arm exercise. Findings of a supraclavicular bruit and a significant ($>$40 mmHg) blood pressure discrepancy between arms on physical examination should prompt further evaluation. The differential diagnosis in geriatric patients includes inner ear disorders and chronic subdural hematomas that may occur even after fairly trivial trauma.

Symptomatic patients with vertebrobasilar occlusive disease should be considered for elective operative intervention. Procedures to treat this condition include proximal

vertebral artery endarterectomy, carotid-subclavian bypass, or vertebral artery transposition to restore adequate antegrade vertebral flow (56).

Abdominal Aortic Aneurysms

The natural history of aortic aneurysms is for progressive enlargement, usually without accompanying symptoms. Left undetected and untreated, it may lead to eventual rupture, often resulting in death. Early detection with appropriate screening of high-risk patients and elective operative repair of these aneurysms are the key to optimal management of this common vascular disease. Unlike some other atherosclerotic-related disease processes, the incidence of abdominal aortic aneurysms (AAAs) is increasing (57). This is due, in part, to increased utilization of diagnostic tests that detect smaller asymptomatic aneurysms, but it also reflects the aging of the population. The incidence of aneurysms increases dramatically after the age of 55 years in men and after 70 years in women (58). As a consequence of this chronologically staggered presentation, aneurysmal disease of the aorta has substantial male predominance by a ratio of about 3:1. It is estimated that 3 to 7% of men over age 70 have an AAA and approximately 100,000 abdominal aortic aneurysms will be diagnosed in the U.S. this year (59). About 15,000 deaths per year are attributable to AAAs.

The risk of rupture is clearly related to size, although the correlation is not perfect. That is, when considering a large group of patients, aneurysms greater than 6 cm in diameter are more likely to rupture (about 30% in 3 years) than smaller aneurysms (about 10% in 3 years) (Fig. 4). It has been well documented, however, that aneurysms as small as 4 cm do rupture (60). More importantly, documenting stability in size over time does not necessarily predict a continued benign course (61,62).

The prognosis for a ruptured abdominal aortic aneurysm is very poor. As many as half of patients with ruptured AAAs die before operative management can be rendered. Although great progress has been made in surgical technique, anesthesia, and postoperative care, the operative mortality rate for patients with ruptured aneurysms reaching the operating room still remains around 50% in most series (63–65). Conversely, over the past three decades, there has been a progressive improvement in the perioperative mortality rate associated with elective aortic abdominal aneurysmorrhaphy (66). Mortality rates of 1 or 2% are commonly reported in the literature, although the average national mortality rate is probably closer to 5% (67,68). Therefore, it is clear that if the mortality rate attributable to abdominal aortic aneurysms is to be reduced, the disease must be recognized in its asymptomatic state and treated before rupture occurs.

Diagnosis depends on careful physical examination and high index of suspicion for the geriatric patient. In nonobese patients, deep palpation of the abdomen between the xiphoid and umbilicus can usually outline the abdominal aorta and provide an estimate of its size. This gross measurement tends to overstate the actual diameter of the aneurysm by 1 to 2 cm. In a very thin patient, even the normal abdominal pulsation may be mistaken for an aneurysm. Conversely, large aneurysms may be missed in obese patients due to difficulty in manual palpation. During examination, attention should also be directed to the peripheral vasculature including the femoral, popliteal, dorsal pedal, and posterior tibial pulses. Ischemic changes in the foot (''blue toe syndrome'') or diminished pulses may suggest distal atheroembolism from the aneurysm. Furthermore, concomitant periph-

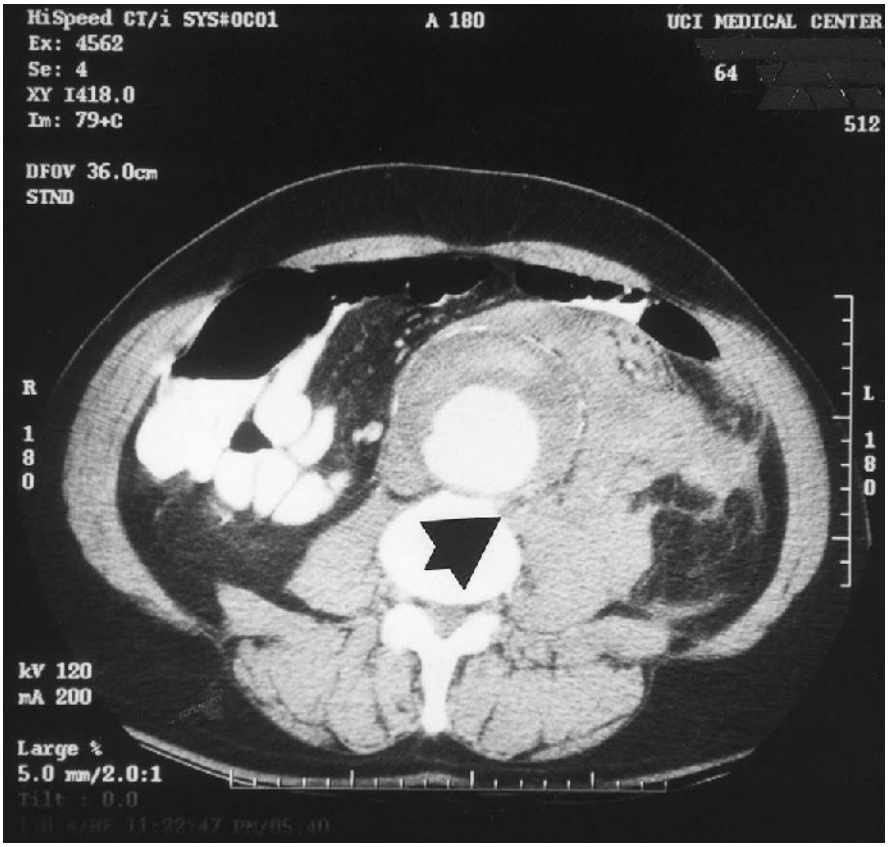

Figure 4 CT scan demonstrates a contained rupture of an 8-cm infrarenal abdominal aortic aneurysm. Note extravasation of blood into surrounding left retroperitoneum and small bowel mesentery.

eral aneurysms of the femoral and popliteal arteries may be found in 5 to 8% of patients with AAAs.

Ultrasound imaging is an accurate method of diagnosing an abdominal aortic aneurysm (Fig. 5A, 5B). This simple, noninvasive procedure can be tolerated by virtually all patients and is the best screening test for the disease. The biplanar cross-sectional visualization of the aorta allows for determinations of the size and extent of the aneurysm, as well as the detection of intraluminal thrombus and associated iliac aneurysms. Ultrasound determination of AAA diameter is readily reproducible and allows longitudinal assessments of changes in aneurysm size. This is especially useful when following a patient with a ''small'' (4-cm) AAA.

Computed tomography (CT) offers the most accurate assessment of AAA size. This modality is highly predictive of size and provides precise localization of the extent of the aneurysm and valuable accessory information such as the presence of renal cysts or ectopic or horseshoe kidneys. CT scans are superior to ultrasound imaging in the identification of those critical venous abnormalities, including retroaortic left renal veins or a left-sided

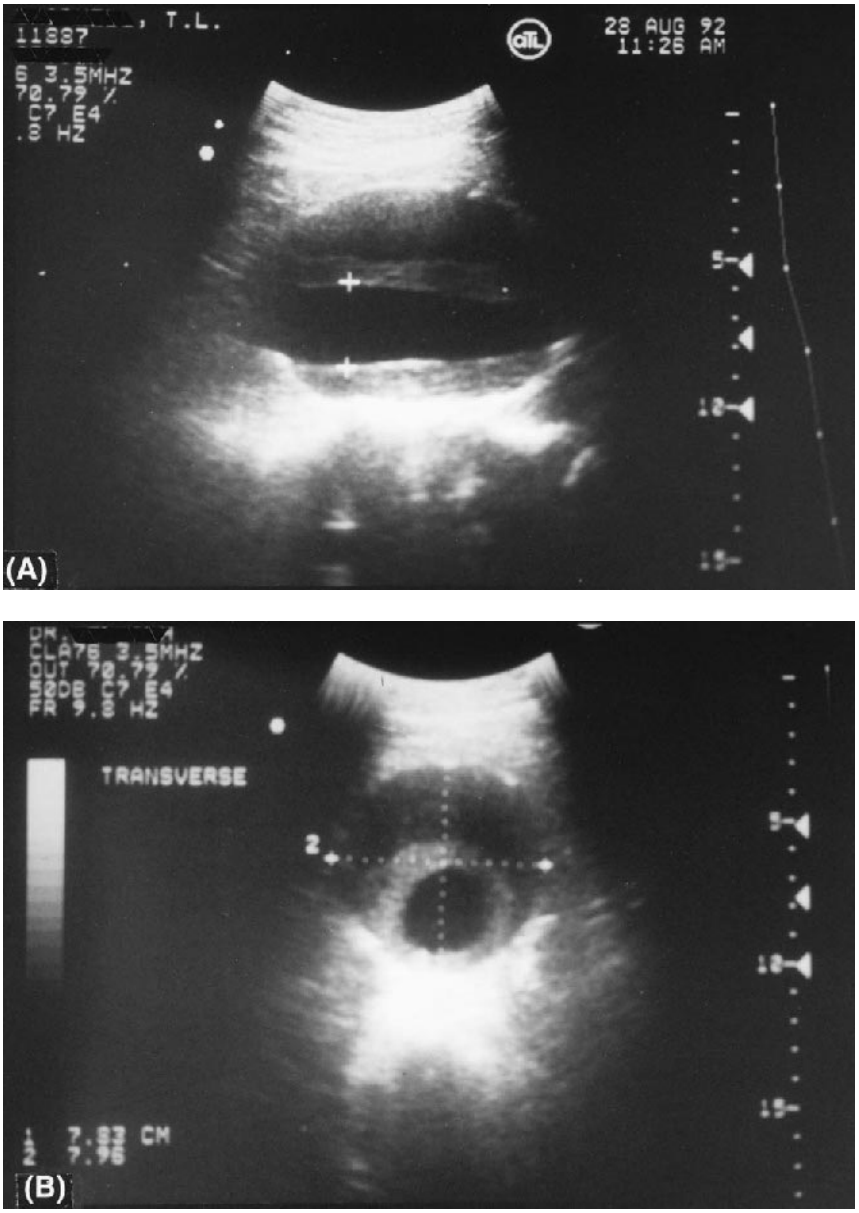

Figure 5 (A) Ultrasound with lateral view demonstrating a 6-cm infrarenal abdominal aortic aneurysm; (B) transverse ultrasound image of same aneurysm. Note large intramural thrombus within confines of the aneurysm.

vena cava, which can influence the operative approach. Although drawbacks include the increased expense over ultrasonography and exposure to contrast, the very detailed depiction of the abdominal aorta, retroperitoneum, and adjacent organs make this modality the preferred noninvasive method of preoperative evaluation. Modern helical CT scans allow for three-dimensional reconstruction of the aneurysms and adjacent organs, allowing for complete visualization of the involved aorta.

Aortography is a more invasive procedure, but is only selectively used for preoperative evaluation once the diagnosis of an AAA is made. Aortography determines critical associated arterial anatomy, such as the number and location of the renal arteries, the patency of the celiac axis, superior and inferior mesenteric arteries, and the condition of the iliac and distal runoff arteries. It should be kept in mind, however, that arteriography defines only that portion of the lumen not filled with clot, and for this reason should not, by itself, be used to determine the diameter of the aneurysm.

The majority of abdominal aortic aneurysms are asymptomatic. When symptoms do occur, they are related to compression of surrounding structures, arterial embolization, or rupture. Pain is usually described as an intermittent ache in the abdomen or back, although discomfort in the flank or scrotum may also be noted. In fact, abdominal aortic aneurysms can mimic virtually all intra-abdominal conditions. Since the pain of expansion cannot be reliably distinguished from retroperitoneal rupture, the acute onset of back pain in a patient with a known aneurysm is an indication for urgent operation.

Most clinicians agree that an infrarenal aortic aneurysm greater than 5 cm in diameter is an indication for surgery in good-risk patients (69). With elective mortality of aneurysm resection as low as 2%, patients can be returned to a normal life expectancy for age-matched controls with comparable cardiac disease. Severe pulmonary disease, ischemic heart disease, and renal dysfunction increase operative risk (70). Age per se is not a significant risk factor for perioperative mortality. Furthermore, the functional status of geriatric patients undergoing aneurysm repair rapidly returns to normal; most report resumption of full activities within 8 weeks of surgery (71,72). The consequences of a conservative, nonoperative approach to AAAs in geriatric patients was well documented in a 1970 report from the Cleveland Clinic concerning 152 patients 75 years of age or older (73). Of the 69 patients who were not operated upon, 37% eventually died of ruptured aneurysms. During the same interval, the perioperative mortality of those patients undergoing elective repair was not different from that experienced by younger patients (14% vs. 9%). Another series from Toronto documented an admirable 3% operative mortality in 34 patients 80 years of age or older (74).

The treatment of AAAs with endovascular stent-graft prostheses has recently received increasing attention as an alternative to major ''open'' abdominal surgery (75). Endovascular repair of an aortic aneurysm allows for exclusion of the aneurysm using a composite stent-graft inserted inside the aorta from a remote site, usually via the femoral or iliac artery percutaneously or through a small groin incision. Unfortunately, both the short-term and long-term durability of these nonoperative procedures is not yet defined. Prospective trials are currently underway to determine the feasibility of these novel devices. Since they are purported to be less invasive, such procedures may have considerable impact on the management of AAAs in elderly patients with significant comorbid conditions.

A ruptured aneurysm requires immediate surgery to avoid the prohibitive mortality associated with delay in diagnosis and therapy. For this reason, any patient presenting with signs or symptoms consistent with a ruptured aneurysm (classic triad of abdominal

pain, presence of a pulsatile abdominal mass, and hypotension) should be emergently transported to the operating room. Minimal, if any, diagnostic studies are indicated. With such an aggressive approach the mortality from ruptured aneurysm has been lowered to less than 25% in some centers, especially when the surgical procedure is begun prior to anuria and massive blood loss.

Unusual presentations of aneurysmal disease include inflammatory aneurysms, mycotic (infected) aneurysms, and aortocaval and aortoenteric fistulae. Inflammatory aneurysms are characterized by a dense desmoplastic soft tissue reaction around the aorta. These lesions cause abdominal and back pains, which often suggest the diagnosis of impending rupture. In some cases, patients present with ureteral or duodenal obstruction due to the retroperitoneal reaction.

Mycotic aneurysms are rare and are seen most commonly in patients with subacute bacterial endocarditis and histories of intravenous drug abuse. In our experience, they may also occur in debilitated patients receiving long-term steroid treatment. If the infection is acute, a severe systemic response is evident. Daily intermittent fevers, impressive leukocytosis, and cachexia complete the septic presentation. On occasion, however, infections are more indolent and may show only a mild leukocytosis or increased erythrocyte sedimentation rate (ESR). Preoperative diagnosis is crucial, since direct arterial reconstruction in the infected field is contraindicated and complex extra-anatomical approaches must be devised. A mycotic aneurysm should be suspected if the arteriographic image is inconsistent with the typical aortic aneurysm. In particular, irregular nonatherosclerotic supraceliac aneurysms or saccular aortic aneurysms at any location have a high incidence of complicating infection.

Aortocaval fistulae occur when the right lateral wall of an aortic aneurysm erodes into the infrarenal vena cava. While this is a most unusual presentation (probably less than 2% of all ruptured aneurysms), it must be suspected when a patient presents with the classic triad of a pulsatile abdominal mass, continuous midabdominal bruit, and sudden onset of congestive heart failure. Surgical treatment involves routine aneurysmorrhaphy with closure of the caval defect from within the aneurysm.

Primary aortoenteric fistulae follow the erosion of an aortic aneurysm into the third or fourth portion of the duodenum. Aneurysms may also perforate into the sigmoid colon or small bowel. More commonly, infected anastomotic pseudoaneurysms from previously inserted aortic prosthetic grafts may also form aortoenteric fistulae. Oddly, exsanguinating hemorrhage rarely occurs early in the course. Rather, patients present with multiple episodes of limited upper gastrointestinal bleeding, aptly called ''sentinel hemorrhages.'' Hence, the diagnosis should be suspected in any patient with a known aneurysm or previous aortic graft replacement with signs of gastrointestinal blood loss. Endoscopy is most useful in excluding the more common causes for bleeding such as peptic ulcer disease or gastritis. While arteriography (especially lateral views) may demonstrate extravasation or pseudoaneurysm formation, studies are often normal in patients who are not actively bleeding.

Thoracoabdominal Aortic Aneurysms

Although the incidence of thoracoabdominal aneurysms is lower than that of infrarenal AAAs, the potential for rupture is similar (76). The best assessments of the natural history of these lesions estimate a 50% rupture rate over 5 years for isolated thoracic or thoracoabdominal aneurysms greater than 7 cm (77). Unfortunately, surgical therapy of these lesions

is associated with a much higher mortality than the treatment of infrarenal AAAs. The incidence of perioperative morbidity, including paraplegia, is also significant (78).

Thoracoabdominal aneurysms are usually asymptomatic and are found incidentally. Most often, the findings of widening of the mediastinum or an abnormal vascular density behind the heart on routine chest x-ray are the first indication of the presence of a thoracoabdominal aneurysm. When symptoms occur; patients complain of nonspecific upper abdominal or chest discomfort or more severe chest pains secondary to direct compression of the intercostal nerves. When rupture does occur, the symptoms relate directly to the site and rate of bleeding. Rupture within the chest is often accompanied by exsanguinating hemorrhage because of the large potential space. On occasion, however, patients may leak slowly over days or weeks and complain of chest pain associated with left pleural effusion.

Even though thoracic aneurysms are almost initially discovered by chest x-ray, CT scan is needed to properly define the proximal and distal extent of the aneurysm (Fig. 6). It is also helpful in making some assessment regarding the condition of the aortic wall. Aortography remains an essential study in the preoperative evaluation of patients with thoracic and thoracoabdominal aneurysms. The mesenteric circulation and the distal extent of the aneurysm are best evaluated by conventional arteriography. Furthermore, it is sometimes possible to identify the dominant spinal blood supply from either proximal intercostal vessels or the dominant radicular artery (the artery of Adamkiewicz). The latter vessel usually arises on the left side of the aorta and can originate from the eighth thoracic to the fourth lumbar vessel (79).

Surgical treatment of these thoracoabdominal aneurysms are extensive procedures

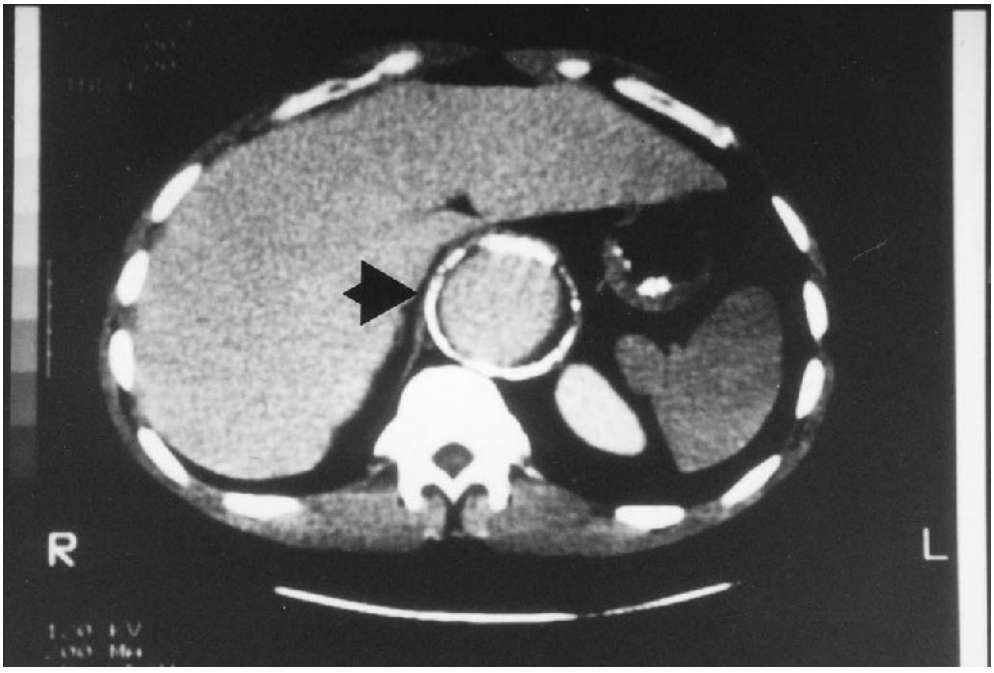

Figure 6 CT scan demonstrating large thoracoabdominal aortic aneurysm extending through the retrohepatic location.

requiring detailed evaluation of perioperative risk factors, especially pulmonary, cardiac, and renal function. Whenever possible, operation should be carried out by a team of surgeons and anesthesiologists experienced in the most current measures for spinal cord and myocardial protection (80,81). Even in the most experienced centers, 30-day mortality is high, particularly in patients over 75 years or age (10–20%). Nonetheless, once symptoms are evident, the risk of rupture and death mandates consideration of urgent repair. New developments in transluminally placed endografts may provide an alternative method of treatment, especially for aneurysms limited to the thoracic aorta (82). At the current time, application of this technology, even in carefully selected patients, is still unproven with regard to its long-term efficacy. Specialized centers are actively providing careful, prospective evaluation of these endovascular techniques.

Mesenteric Ischemia

The elderly patient is especially prone to the development of acute mesenteric ischemia but the diagnosis is often seriously delayed since concomitant medical problems can complicate accurate assessment of the symptom presentation. Geriatric patients with underlying cardiac disease, including valvular heart disease, congestive heart failure, cardiac arrhythmias, and recent myocardial infarction are more prone to present with acute mesenteric ischemia (83). These conditions often lead to arterial–arterial macroembolization leading to sudden occlusion of mesenteric arteries. Additionally, these serious comorbidities also decrease the likelihood of successful treatment. Alternatively, patients with chronic mesenteric ischemic syndromes due to advanced atherosclerotic involvement of mesenteric arteries may progress to sudden thrombosis leading to acute ischemic symptoms.

Classically, the presentation of acute mesenteric ischemia is abdominal pain out of proportion to physical findings. The pain is usually located in the midabdominal aorta, described as steady and severe. The patient typically is found writhing in bed in distress, being unable to find a comfortable position. yet, typically, the physical findings are paradoxically quite benign early in the clinical presentation. If peritoneal signs are elicited, it is likely that intestinal infarction has already occurred. As noted by Boley et al. (84), the mortality from a mesenteric event is directly related to the state of the bowel at the time of the diagnosis. The occurrence of bowel infarction greatly increases mortality and morbidity; in some series, infarction is associated with greater than 80% mortality. This fact underscores the importance of prompt diagnosis and treatment of acute ischemia with expeditious arterial reconstructions in chronic ischemic syndromes before acute ischemia supervenes.

Macroembolization from a proximal source is one of the most frequently encountered causes of acute ischemia, accounting for about one-third of all mesenteric vascular catastrophes (84). As noted earlier in this chapter, most emboli occur in association with cardiac arrhythmias (especially atrial tachyarrhythmias) or myocardial infarctions. The superior mesenteric artery (SMA) is the site of most embolic occlusions due to its near parallel course to the abdominal aorta. As many as 5% of all peripheral emboli lodge in this vessel.

Acute thrombosis of an already compromised vessel lumen occurs in another one-third of cases. Such preexisting atherosclerotic lesions are often associated with prodromal symptoms. In fact, over 50% of patients who die due to acute SMA thrombosis have a history of postprandial abdominal pain and weight loss (84). Intestinal angina typically

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occurs 15 to 60 min after meals and is more closely correlated with the volume of food consumed rather than any specific type of food. In situ thrombosis typically occurs at the origin of the superior mesenteric artery resulting in gut infarction from the proximal jejunum to the midtransverse colon.

Nonocclusive mesenteric ischemia makes up most of the remaining cases of mesenteric ischemia. It most commonly involves the viscera supplied by the superior mesenteric artery. The mechanisms leading to visceral ischemia are often multifactorial. Patients typically have moderate-to-severe mesenteric atherosclerosis with marginal cardiac reserve. The administration of vasoactive agents, especially digitalis preparations, further exacerbate the process (85). The onset is often predated by an acute decrease in cardiac function with reductions in mesenteric perfusion pressure. Paradoxic splanchnic vasonconstriction then ensues with microvascular collapse, formation of microthrombi, and capillary sludging.

Venous thrombosis, a relatively uncommon cause of mesenteric vascular compromise, may begin peripherally in the small veins of the mesenteric arcade or centrally in the major trunks of the portal system (86). Substantial splanchnic fluid sequestration and hemorrhagic intestinal infarction accompany venous occlusion. Although mesenteric venous thrombosis may also present with constant, diffuse abdominal pain, symptoms may be intermittent at first. About half of these patients complain of distention and nausea with low-grade fever. Many patients developing mesenteric venous thrombosis have a history of associated deep venous thrombosis of the extremities or hypercoagulable states.

The clinician's single greatest tool for the successful diagnosis of an acute mesenteric vascular event is a high index of suspicion in patients with multiple risk factors. Although many laboratory abnormalities occur with mesenteric ischemia and infarction, most are nonspecific and thus not diagnostic. These include hemoconcentration, leukocytosis with a significant ''left shift,'' metabolic acidosis, hyperamylasemia, and hyperphosphatemia.

Abdominal roentgenograms are useful in excluding other causes of abdominal pain such as mechanical small bowel obstruction or perforation of a hollow viscus. As many as 70% of patients with mesenteric ischemia show at least one of the following signs on abdominal radiographs: ileus, ascites, small bowel dilation, thickening of valvulae conniventes, and separation of the small bowel loops. On occasion, a ''gas-less'' abdomen is seen due to excessive fluid accumulation within the lumen.

Barium studies are actually contraindicated but, if performed, may show evidence of small bowel dilation and focal mucosal hemorrhage (''thumbprinting''). The considerable disadvantage of intraluminal contrast studies is the potential for interference with arteriography, which is the essential diagnostic study. The problems with all diagnostic tests except arteriography are the lack of specificity and reliability.

Successful arteriography mandates prior hemodynamic stabilization of the patient since hypotension alone may cause significant splanchnic vasoconstriction and preclude an adequate study. Infusion of any vasoactive drugs with splanchnic vasoconstrictive properties should be terminated. Both anterior/posterior (AP) and lateral views of the aorta are required. The anterior/posterior view best demonstrates collateral vessels while lateral aortography better visualizes the origins of major visceral arteries that overlie the aorta in the AP plane.

Arteriographic signs can generally differentiate embolic from thrombotic occlusions (87). As noted earlier, emboli to the SMA usually lodge just proximal or distal to the origin of the middle colic artery and may be associated with minimal preexisting atherosclerotic

changes. Thrombotic occlusions of preexistent stenotic lesions, on the other hand, occur more commonly at the SMA origin and are associated with both generalized atherosclerosis of the aorta and the presence of extensive collaterals (Fig. 7). Mesenteric venous thrombosis is characterized by general slowing of arterial blood flow in conjunction with nonopacification of the corresponding mesenteric or portal veins. Nonocclusive ischemia characteristically shows narrowing and irregularity of major branches of the SMA.

Nonocclusive mesenteric ischemia may be primarily treated with intraarterial infusion of a vasodilator such as papaverine into the superior mesenteric artery (88). Papaverine should be administered continuously, infusing at a rate of 30 to 60 mg/h for at least 24 to 48 h. Surgery may be avoided in these patients with nonocclusive ischemia if the diagnosis is clear on arteriography and abdominal signs and symptoms totally resolve with papaverine infusion.

In contrast, all patients with suspected embolic or thrombotic occlusions should undergo urgent exploratory celiotomy. Intravenous fluid resuscitation, infusion of continuous anticoagulation with heparin and administration of broad-spectrum antibiotics are indi-

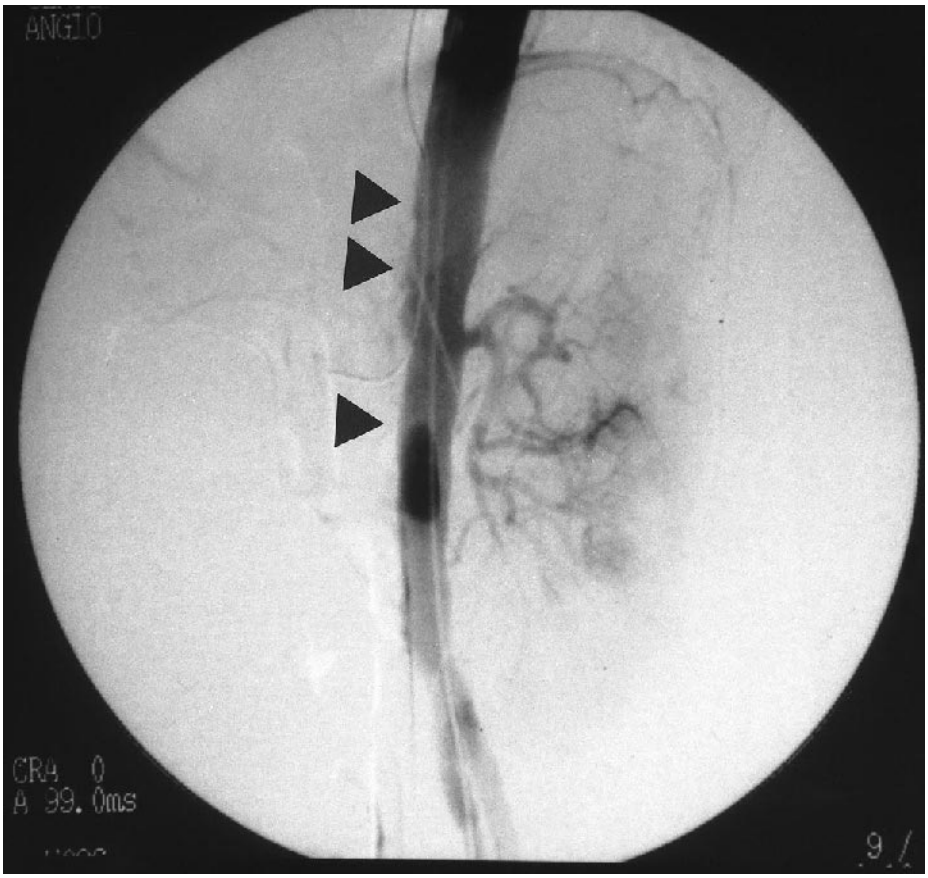

Figure 7 Lateral aortic arteriogram of patient presenting with advanced chronic mesenteric ischemic symptoms. Note complete occlusion of both celiac axis and superior mesenteric artery at origins. The inferior mesenteric artery was also occluded in this patient.

cated prior to surgery. Usually, an embolus can be directly extracted from the superior mesenteric artery through a transverse arteriotomy made at the base of the mesentery. If adequate inflow is obtained following the passage of an embolectomy catheter, no additional arterial reconstruction may be required. If thrombosis of an atherosclerotic lesion is suspected, or if extraction of the embolic material is not possible or incomplete, some form of aortomesenteric bypass should be considered. The operative approach to venous thrombectomy involves resection of infarcted bowel. Venous thrombectomy can be considered in the larger, more proximal veins, although the likelihood of recurrent thrombosis is relatively high.

Chronic mesenteric ischemia is most frequently associated with atherosclerotic occlusions or stenoses (89). Due to the abundant collateral network, multiple vessel involvement is usually required before classic postprandial symptoms occur. The presentation of chronic ischemia depends on the region of the gut affected. The most common syndromes involve the midgut (jejunum, ileum, and right colon) and reflect vascular insufficiency of the distribution of the SMA due to atherosclerosis or midaortic developmental abnormalities. Since consumption of a meal predictably induces severe incapacitating pain, eating is dramatically curtailed with patients developing ''food fear''which invariably results in loss of weight. The weight loss is usually substantial and may exceed 25% of body mass. Ischemia of the foregut (stomach and liver) is much less common and may be irregular in its symptomatology. Patients frequently complain of nonspecific symptoms such as bloating and early satiety. The more classic symptoms of postprandial abdominal pain and weight loss are often absent.

Finally, ischemias of the hindgut (left colon and rectum) rarely presents with postprandial pain or weight loss. Patients present with hemoccult positive diarrhea and chronic strictures due to mucosal ischemia. These syndromes reflect insufficiency of the inferior mesenteric artery (IMA) and collateral pelvic circulation through the hypogastric (internal iliac) arteries, usually due to advanced athero-occlusive disease. Colonic ischemia frequently follows vascular reconstructions of the infrarenal aorta, which may inadvertently compromise collateral blood flow through the internal iliac arteries.

The definitive diagnosis of chronic intestinal ischemia is based on (1) symptoms consistent with the visceral arterial occlusive disease; (2) exclusion of other gastrointestinal pathology; and (3) arteriographic demonstration of appropriate occlusive lesions and development of collaterals. Selective arterial catheterizations are usually required along with oblique or lateral views to adequately image the origins of the three main visceral vessels. Vascular reconstruction for chronic foregut and midgut ischemia can be accomplished by endarterectomy or aortomesenteric bypass. Antegrade bypasses from the supraceliac aorta to the celiac axis and superior mesenteric artery is currently our preferred method for visceral revascularization (90).

Renovascular Arterial Disease

Although renovascular disease is a relatively rare cause of hypertension (1–5% of adult hypertensives), it is the most amenable to surgical correction (91). Renovascular disease in the elderly is caused primarily by atherosclerotic narrowing of the renal arteries and may result in both progressive hypertension and diminished renal function. Recently, it has become apparent that clinically important ischemic nephropathy may occur without hypertension. The high probability of success in our ability to correct these functional alterations reinforces the need for the early diagnosis of renovascular disease, regardless

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of age. However, such an aggressive approach is controversial even today. Many clinicians feel elderly patients have such a high incidence of end-organ damage from atherosclerosis (especially coronary and cerebrovascular disease) that their response to surgical or other interventions would be poor and associated with untoward risk. Furthermore, there has been limited recognition of the availability of modern noninvasive screening tests to diagnose remediable renal artery lesions.

The exact prevalence of renovascular hypertension is difficult to determine. The incidence reported in any particular series is dependent on the age, sex, and race of the study population. Furthermore, it depends on the specific definition of hypertension being employed. Clinical features that increase the likelihood of a renovascular cause of hypertension in elderly patients include new onset of hypertension, rapid progression of previously stable hypertension, and hypertension associated with renal functional impairment. The presence of atherosclerotic disease in other vascular distributions increases the probability of associated renovascular disease. Hypertension resistant to standard three-drug treatment regimens (diuretics, beta-blockade, and angiotensin converting enzyme inhibitors) has been associated with a 30% prevalence of renovascular disease, while the coexistence of accelerated hypertension with renal failure predicts a 45% likelihood of renovascular disease (92). While the diagnosis may be suggested by detection of an abdominal or flank systolic-diastolic bruit, this finding is quite nonspecific. Most importantly, absence of a bruit should not deter a more definitive evaluation in a patient with positive demographics.

Traditional noninvasive screening methods for renovascular hypertension have included plasma renin measurements, intravenous pyelography, radioisotope renography, and split renal function tests. All of these have been disappointing as screening tests due to high false-negative rates (93,94). Additionally, these tests are not able to reliably address the critical issues in management, that is, which arterial lesions are functionally significant and which patients would benefit from renal revascularization. The refinement of two noninvasive modalities, captopril renography and duplex scanning, have helped resolve these issues.

Captopril renography is based on the principle that suppression of the renin-angiotensin system in the presence of a hemodynamically significant renal artery stenosis will result in a decrease in glomerular filtration rate (GFR) in the affected kidney. Theoretically, angiotensin inhibition decreases the resting vasomotor tone of the efferent arteriole, thereby reducing effective glomerular filtration pressure across the basement membrane. The clinical applicability of this effect was originally noted by Majd et al. (94), who observed that the diagnostic accuracy and sensitivity of renography with either technetium (Tc) 99m-diethylenetriamine pentaacetic acid (DTPA) uptake (measuring renal plasma flow and excretory function) was enhanced by captopril administration. In a selected patient population, Setaro et al. (95) reported a 91% sensitivity and a 94% specificity in the diagnosis of renal arterial stenosis as compared with angiography. Furthermore, they also noted that the detection of captopril-induced scintigraphic abnormalities predicted cure or improvement of blood pressure control in 83% of patients who underwent revascularization. Unfortunately, other studies have reported lower sensitivities and specificities, and large prospective series are lacking (96,97). A major limitation of this test is the requirement that antihypertensive medications be withdrawn for up to 2 weeks before testing. A further limitation is that interpretation of results is more difficult in bilateral disease since the response of one kidney cannot be compared with that of the other.

Renal duplex scanning has evolved into the principal noninvasive screening test for both the presence of renal arterial disease as well as its hemodynamic significance (98).

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This modality combines B-mode ultrasound imaging with pulsed Doppler ultrasound determinations of blood flow velocity (99,100). The ratio of renal artery peak systolic velocity to aortic peak systolic velocity (RAR) has been utilized to define hemodynamically significant lesions. By retrospectively comparing renal artery duplex scanning and arteriography, Kohler et al. (99) correlated RAR of greater than 3.5 with the presence of renal artery stenoses of greater than 60% diameter reduction. This study reported an overall sensitivity of 91% and specificity of 95%. Others have confirmed similar results (101). The B-mode imaging also allows anatomical definition of the stenoses especially whether the disease is localized to the orifice or the more distal vessel. Duplex scanning is particularly useful in postprocedural follow-up of lesions treated by surgical revascularization or angioplasty. Recurrent stenoses or thromboses can be identified with an accuracy of 93% when compared to arteriography (102).

Arteriography, however, is still the accepted standard for diagnosis of anatomical renovascular disease. Multiplanar views of the renal vessels, including anteroposterior and oblique views, are routinely obtained (Fig. 8). Newer digital subtraction techniques allow the utilization of smaller volumes of dye, lessening the chance for contract-mediated renal dysfunction following the necessary pararenal or selective injections.

Traditionally, the measurement of renal vein renin levels has been employed as an adjunct to arteriography to help identify functionally significant renal arterial stenoses (103). Such values can be expressed as renal vein renin ratios, which compare one kidney to the other (ratios of >1.5 are considered diagnostic), or renal/systemic renin indices, which quantify the contribution of each kidney to the total systemic renin level. Renal

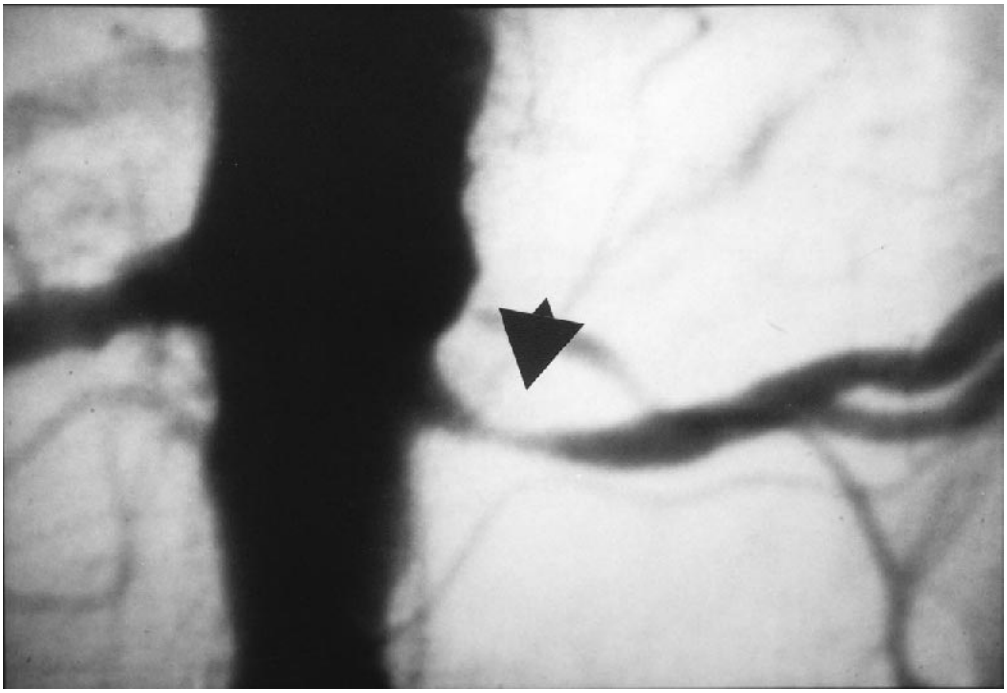

Figure 8 Arteriogram demonstrating severe orificial renal artery stenosis.

vein ratios are obviously less accurate in bilateral disease. In contrast, renal/systemic indices assess bilateral disease more precisely and have been a more reliable predictor of the response to revascularization (104). The most favorable situation is unilateral disease in which renin secretion is suppressed in the contralateral kidney.

A more aggressive approach in the treatment of renovascular disease has resulted from three recent distinct developments: (1) an increased recognition of ischemic nephropathy as an important consequence of renovascular disease separate from hypertension; (2) the widespread acceptance of percutaneous renal angioplasty; and (3) improved results of revascularization in elderly patients. In recent reports, substantial improvements in renal function have been noted even in patients over 65 years of age with significant and progressive azotemia (serum creatinine >4mg%) (105). Currently accepted indications for renal revascularization include the presence of a hemodynamically significant renal artery stenosis (>60% diameter) in patients with refractory hypertension or hypertension associated with renal functional impairment.

Percutaneous renal angioplasty is an attractive option in high-risk elderly patients whose medical risks would otherwise prohibit operative revascularization (106). However, it is optimally performed in midsegment renal artery stenoses and is not as well suited for treatment of the most prevalent orificial lesions. In appropriately selected stenoses, short-term patency rates with angioplasty are approximately 90% (107). The utility of balloon-expandable and self-expanding stents have a broadened number of renal artery lesions amenable to these catheter-based endovascular procedures.

Operative options include endarterectomy and aortorenal or hepatorenal bypasses. Endarterectomy through a transaortic route is most useful in bilateral orificial disease but requires suprarenal aortic exposure and clamping with resultant higher cardiac risk. Aortorenal bypass from a relatively disease-free area of the infrarenal aorta has been the most widely used technique in the past, although extra-anatomical hepatorenal and splenorenal bypasses are not uncommon. The latter procedures avoid manipulation of the often diseased aorta and obviate any need for aortic occlusion.

Irrespective of the origin of these bypass grafts, long-term patency is excellent, approaching 95% over 5 years if autogenous vein is used. In one recent series of 35 patients over 60 years of age, improvement or cure of hypertension was reported in 91% of patients and improvement in renal function in 37% (108). Overall morbidity and mortality in this group (5.4% mortality, 23% perioperative morbidity) appeared to be related to generalized atherosclerosis and accompanying risk factors rather than age per se. The argument for aggressive treatment of renovascular disease in the geriatric patient population is further supported by the experience of the physicians at the Cleveland Clinic, who compared medical to surgical management in 50 patients over 3 years (109). While this was not a randomized study, they noted better control of hypertension (90% improvement in the surgical group vs. 66% improvement in the medical group) as well as improvement or stabilization of renal function in those treated surgically (91% surgical vs. 50% medical group).

Acute Arterial Thrombosis

Sudden arterial thrombosis may result from (1) in situ thrombosis of preexisting atheroocclusive disease; (2) arterial–arterial embolization; (3) thrombosis of an aneurysm; and (4) vascular trauma. Obtaining a careful medical history can be very helpful in eliciting the underlying etiology. Patients with in situ thrombosis often describe a history of preexisting

claudication or rest pain that has recently worsened. In contrast, arterial embolization, vascular trauma, and aneurysm thromboses are usually not associated with any previous vascular symptoms. When the occlusion is very sudden and is not associated with prior development of collateral arteries, the symptoms tend to be much more severe.

Classically, the presentation of acute limb-threatening ischemia includes the six ''Ps.'' These include pallor, pain, paresthesias, paralysis, pulselessness, and poikilothermia (change in skin temperature). The level of coolness of the extremity is usually limited to the portion of the limb well beyond the occlusion. For example, with an acute femoral artery occlusion, the level of ischemia may not extend above the knee due to recruitment of collateral flow to the thigh. On the other hand, internal organs, especially the intestines, kidneys, and brain are especially prone to early loss of function and infarction with sudden arterial occlusion due to the end-artery nature of their blood supply.

With acute occlusions resulting from vascular graft thrombosis or emboli to native vessels, flow through collaterals may sometimes be inadequate to preserve limb viability. The heart is the most common source of emboli, which also originate from plaques and aneurysms in the thoracic and abdominal aorta. Bilateral extremity involvement is common when the origin is proximal; unilateral involvement is the rule with embolism from the iliac or more distal vessels. Atherosclerosis is not the only cause of thombosis. Trauma, collagen vascular disorders, myeloproliferative diseases, and dysproteinemias are other causes for sudden arterial thrombosis.

Acute arterial occlusion, regardless of the end organ, requires prompt recognition and treatment. The long nerves of the lower extremity are sensitive to ischemia and weakness, paralysis, or paresthesias indicate the presence of acute limb threat with the urgency of intervention correlating well with the degree of neurological impairment. Initial numbness may be rapidly followed by ischemic muscle necrosis and skin infarction without timely revascularization. Irrevocable tissue injury may occur within 6 h. Often, however, even when rest pain is present, collateral flow is sufficient to preserve the limb while diagnostic studies are obtained prior to operative intervention. Complete paralysis, muscle rigidity, and thrombosis of cutaneous vessels are markers of a high probability of limb loss even with successful revascularization. Delays can result in severe muscle ischemia and amputation.

Patients with a sudden onset of acute limb threat often have embolized clots from a cardiac or peripheral source into the infrainguinal arteries. In many instances the thrombosis of a previously patent bypass graft creates an identical clinical picture. Surgical management entails operative exposure of one or more of the vessels occluded, fashioning an incision (arteriotomy) into the artery, and extraction of the offending thrombus via the arteriotomy. Embolectomy catheters specifically designed for these procedures are passed via the arteriotomy into the proximal and distal arterial segments. A tip-mounted balloon is inflated and traps the thrombus, leading to its extraction as the catheter is gently dragged out of the artery. Repeated passes of the thrombectomy catheter will usually result in satisfactory removal of clot and restoration of blood flow.

Adjunctive therapy in patients requiring urgent thrombectomy includes the use of systemic heparin (75–100 units/kg bolus, followed by a continuous infusion. Diagnostic angiography before surgery is helpful in planning the operation, and intraoperative contrast angiography can be used to position thrombectomy catheters over guide wires and to confirm the restoration of blood flow. Arteriography is especially helpful in cases of sudden thrombosis of preexistent disease. However, arteriography is not essential in the diagnosis and treatment of obvious embolic occlusions, especially if thrombolysis is not an option due to advanced ischemia or other contraindications. Thrombolytic drugs may be

administered as part of the operation to dissolve clots either that are incompletely removed by embolectomy catheters or that are lodged in tibial or pedal vessels beyond their reach. The combination of fluoroscopic guidance of embolectomy catheters and the use of intraoperative thrombolytic drugs both improves the overall success of operative interventions and allows distal thrombi to be adequately managed via femoral and popliteal incisions (110,111). The use of proximal incisions is an advantage as they avoid arteriotomies of more distal vessels with the risk of intimal hyperplasia and late thrombosis. An additional concern is that incisions below the knee may compromise subsequent amputation stump healing if revascularization is unsuccessful.

The overall immediate success rate with surgical thrombectomy and embolectomy for limb salvage in the face of acute occlusion is good, on the order of 70 to 90%. Patient mortality after embolic episodes, however, is strikingly high, compared to elective bypass, the reported mortality ranges from 4 to 39%, with an average rate of about 20% in recent series (112). Some of the factors responsible for high mortality are the metabolic disturbances that accompany acute arterial occlusion of the lower extremity including hyperkalemia, acidosis, and renal failure secondary to rhabdomyolysis. Some of these disturbances are a consequence of cellular necrosis due to ischemia and may be exacerbated by the reperfusion injury that often attends successful revascularization after severe ischemia. Delay in operative treatment of limb-threatening ischemia correlates with poor outcomes. In one series, treatment instituted within 12 h of symptom onset led to a limb salvage rate of 93% and 12% mortality. After 12 h, limb salvage fell to 78% and mortality increased to 31% (113).

Another factor in the high mortality associated with embolism is the concomitant presence of severe cardiac disease and the frequency of other comorbid conditions. Increased mortality is associated with advanced age; in one series, those less than 70 years old were found to have 7% mortality compared to 22% for those older than age 70 (112).

Many elderly patients may have already undergone previous vascular reconstructions, which are susceptible to failure. Occluded bypass grafts are often treated by thrombectomy, using techniques similar to those employed with primary thromboembolism. Balloon catheter methods are usually sufficient to allow restoration of flow, and results are good if attendant technical defects restricting flow (most commonly stricture of the distal anastomosis or stenosis in the native artery just beyond) are also corrected. Saphenous vein grafts are more difficult to salvage with thrombectomy than prosthetic grafts. Often in graft thrombosis, clot propagates into the arteries beyond the distal anastomosis (e.g., the tibial origins may be occluded after a femoropopliteal graft clots) and successful thrombectomy will require supplemental removal of thrombus in distal segments.

After initial treatment of embolic occlusions, long-term postoperative anticoagulation must be strongly considered. Without anticoagulation, emboli may recur in about one-third of patients within 30 days. With the use of heparin and warfarin postoperatively, the recurrence rate decreases to less than 10%. Unfortunately, even with the best treatment, the mortality rate for acute arterial occlusion remains relatively high. This can be attributed to the often advanced age of these patients suffering from either in situ thrombosis or embolization, together with the severity of associated myocardial disease. The most common cause of death in these patients is myocardial infarction and pulmonary embolization.

Lower Extremity Athero-Occlusive Disease

Moderate arterial insufficiency induces pain with walking. As rest rapidly resolves the pain, moderate ischemia tends to be intermittent, with the effects known as intermittent

claudication. Muscle exercising near its maximum potential may experience a 30-fold increase in perfusion; overall, the ambulating limb has flow increased by a factor of 2 or more. Claudication pain often localizes to the calf, but may affect any portion of the limb. As the imbalance between the demands of exercising muscle and what is provided by the diseased arterial system is transient, claudication is considered a *functional* impairment. When flow cannot meet the requirements of resting metabolism, *critical ischemia* is present.

Rest pain from critical ischemia is usually experienced in the toes or foot. Patients dangle their legs from the bed or even stand to relieve symptoms. Without intervention, rest pain may progress to ulceration or gangrene. Ulcers tend to be bland and lack intense inflammation or infection, and commonly develop at the ankle, heel, or leg. Mummified, dry, black toes or devitalized soft tissue covered by a crust represent areas of gangrene from ischemic infarction. With time dry tissue often develops suppuration, as ''dry'' changes to ''wet'' gangrene.

Many subjects with complete occlusions of major vessels like the superficial femoral artery are more limited by weakness or shortness of breath and do not walk enough to claudicate. Elderly subjects frequently accommodate themselves to decreased mobility, whether from arthritis, neurological disease, or PAOD, and consider it a natural consequence of aging. Angiograms detect more cases than noninvasive ultrasound or symptom questionnaires. With increasingly stringent definitions of ischemia, measured prevalence falls, as subjects with mild ischemia greatly outnumber severe cases. Fifteen to 20% of claudicants will progress to limb threat, and the estimated crude incidence for vascular amputations in the U.S. is about 250 per million per year, compared to a crude incidence for critical ischemia of 1000 per million per year (114,115).

Isolated aortoiliac involvement is a favorable pattern, with better outcomes than when PAOD affects infrainguinal vessels (116). Infrainguinal disease is found in 65% of PAOD patients over 40 years compared to only 25% of younger patients. In addition to more distal patterns of involvement, multisegmental disease is also more common with aging (114,117). When multiple segments are involved, the chance of claudication progressing to limb threat increases (118). Multisegmental involvement is also associated with decreased survival and increased coronary disease. When matched to patients with identical risk factors except PAOD, claudicators have a three- to sixfold higher risk of cardiovascular mortality (119).

Diabetic patients have increased risks for PAOD and worse outcomes. In addition to athero-occlusive disease and enhanced susceptibility to infection, diabetics may have polyneuropathy with impairment of sensory, autonomic, and motor nerve function. Inability to experience pain often leads to unfortunate delays in the diagnosis of serious ischemia. Foot deformity may result from neuropathy leading to pressure ulcers forming over bony prominences such as the plantar aspect of the metatarsal heads. Such neuropathic ulcers need to be distinguished from neuroischemic ulcers, in which ischemia contributes independently to the pathological process. The liberal use of ultrasonic and angiographic investigations is warranted in diabetes when lower extremity circulation is an issue.

Current therapies and interventions for PAOD include medical management, arterial reconstruction with surgery or interventional radiology methods, and, finally, amputation.

Medical Therapy

Medical management revolves around reducing risk factors for atherosclerosis in the hopes of slowing disease progression, teaching proper local care of the foot, encouragement of

exercise, and appropriate drug therapy. Given that continued smoking increases disease progression, it is most helpful to influence the patient to cease smoking. Even when tissue loss is present, tobacco cessation may lead to healing. Exercise is very effective in claudication. Most patients can double their walking distance within 3 months with a daily exercise routine, leading to improved joint mobility, better neuromuscular function, and a lower incidence of cardiovascular events (120). These beneficial effects probably are achieved by promoting the formation of arterial collateral vessels, inducing changes in mitochondria and oxidative enzymes in the muscle cell, and, possibly, improved cardiac performance. With advancing age, ambulation consumes a greater proportion of the total possible energy expenditure an individual can achieve. As a consequence, most of the benefits of strenuous exercise in the young are achieved in the aged by simple walking (121). The usual prescription is for the patient to walk 30 to 60 min daily outside or on a treadmill.

Patients must be careful to avoid even minor trauma and wear properly fitted shoes. Small objects inside a shoe may cause serious wounding. Careless nail clipping or injuries incurred walking barefoot may lead to catastrophe. Feet should be washed daily and the skin kept moist with lanolin or other lotions to prevent cracking, which can be a portal of entry for bacterial infections. Similarly, fungal infections should be treated aggressively. Socks should be made of wool or other thick fabrics, and, as necessary, padding should be placed to prevent pressure sores. Special casts, boots, and methods of unweighting affected areas are useful, but more important is prevention, as neuropathic ulcers often are refractory to treatment and lead to amputation in the absence of ischemia.

Several medications have been shown to have benefit in chronic lower extremity ischemia. These include pentoxifylline, which has a modest ability to improve walking distance in claudicators; the cyclic AMP phosphodiesterase inhibitor cilastozol, which appears potentially more efficacious based on treadmill-based studies; and iloprost, a prostaglandin E1 analog, which has efficacy intravenously for healing ischemic wounds and which as an oral agent has promise for claudication. As of this writing, only pentoxyfilline is approved for use in the U.S. (122–124).

Reconstruction

Bypass surgery is the most common reconstruction employed for managing PAOD of the lower limb. The results of all interventions are evaluated based on patency, limb salvage, and patient survival rates using life table analysis. Patency refers to the percentage of bypass grafts (or treated native vessels) with blood flow at the end of a specified period. Primary patency represents uninterrupted blood flow without additional procedures to restore flow. Secondary patency is achieved if flow is present at the end of the time period under consideration, but corrective procedures to restore flow have been performed. If a corrective procedure such as angioplasty is undertaken, but the graft never has clotted, assisted primary patency has been achieved. Limb salvage is achieved if no major amputation is performed.

A variety of materials are employed for bypass, with autologous saphenous vein (in either the reversed or in situ configuration) and expanded polytetrafluoroethylene (PTFE) the most common conduits. Veins yield the best long-term patency, with the least intimal hyperplasia. The common procedures are above-knee femoropopliteal bypass, below knee femoropopliteal bypass, tibial (meaning distal anastomosis to a tibial vessel) bypass, and pedal (ankle level or lower) bypass.

Figure 9 shows the relations that emerge from numerous studies of lower extremity

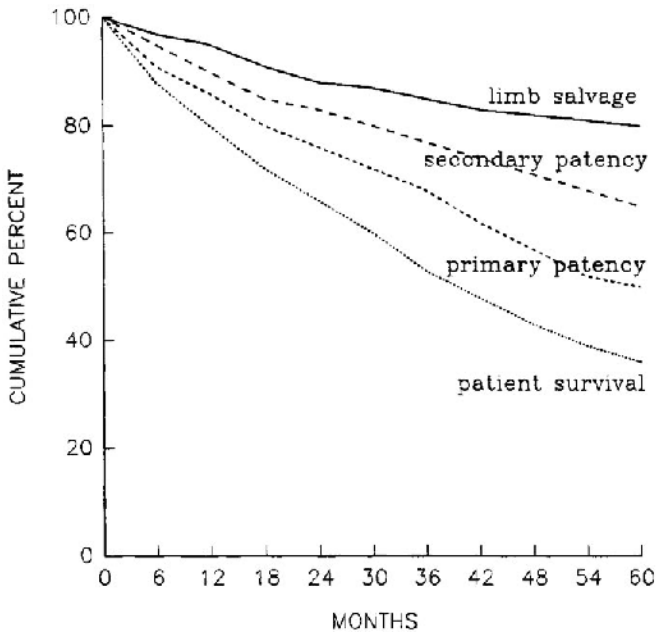

Figure 9 Life table analysis of results from infrainguinal bypass. The idealized relation between limb salvage, graft patency, and patient survival is shown. The relations shown could be for any particular bypass, such as above-knee saphenous vein femoropopliteal bypass. If a more distal anastomosis had been employed, overall rates of salvage, patency, and survival would be shifted downwards, but the relative positions of the curves would remain unchanged.

bypass (125–127). Secondary patency is better than primary patency, as the former includes grafts reopened after occlusion. Limb salvage usually exceeds graft patency—if operation is undertaken for claudication, graft failure should not mandate amputation. Additionally, sufficient collaterals sometimes develop so that even after a graft closes the limb survives. There is a tendency for patient survival to be worse than patency or limb salvage as bypass patients tend to die from vascular problems affecting the brain or heart. Most bypass patients die before renewed ischemia necessitates amputation.

Factors that influence patency, limb salvage, and survival after bypass are: (1) the severity of ischemia prior to operation; (2) the level of distal anastomosis; (3) the quality of runoff arteries below the distal anastomosis (distal resistance); and (4) the conduit employed (128). When claudication is the indication for bypass, long-term survival is highest; survival is intermediate with rest pain and lowest with tissue loss as the operative indication. The correlation of operative indications with mortality reflects the association between diffuse disease in the leg and more severe atherosclerosis in other territories. If limb salvage or graft patency was an endpoint, the same relations between operative indications and outcomes would hold, again because symptom intensity correlates with the diffuseness and severity of atherosclerotic occlusion. With increasing symptoms, more arterial segments tend to be involved, and more severe distal disease increases resistance to flow. The net effect is decreased graft patency and worse limb salvage. More severe PAOD

at the time of operation has increased risk of subsequent graft failure, limb loss, and death, even if reconstruction is successful.

Saphenous vein grafts to the popliteal artery provide 70 to 80% of 5-year patency in patients who survive that long. PTFE grafts above the knee remain patent in perhaps 50% of patients surviving 5 years, but have very poor (20%) patency rates when used below the knee. Saphenous vein is highly preferred for distal bypass because of its better patency (128–130). Because below-knee bypasses have lower patency and salvage rates and need autologous vein, distal bypass is generally reserved for limb threat and avoided in claudicants. Clotted PTFE grafts are often easy to revise with thrombectomy or lytic therapy, so more revisions and greater long-term costs are not as problematic as might be anticipated. Long-term survival after bypass is not greatly influenced by the choice of graft material, and the need to preserve saphenous vein for future coronary bypass is always a consideration.

Complications of bypass include perioperative death, early graft failure, wound complications, and leg edema. Thirty-day mortality (Table 4) after bypass is 2 to 5%, predominantly from MI (130,131). Wound complications occur in as many as 20% of infrainguinal bypasses, but generally are minor, entailing superficial necrosis or infection, delayed healing, and fluid collections from lymphatic disruption; the more serious problem of graft sepsis, which leads to further surgery or limb loss, occurs in only 1 to 2% (132).

Besides bypass, endarterectomy and sympathectomy are occasionally employed. Endarterectomy in the lower extremity uses the same methods employed in carotid surgery. Optimum results are achieved with short segments, as bypass is better than long endarterectomy. Sympathetic denervation of the lower extremity can provide good results in causalgia and vasospasm, and may occasionally be helpful in PAOD. The operation requires excision of two or more ganglia in continuity, and is adapted to minimally invasive endoscopy. It should be reserved for inoperable patients with an intact sympathetic nervous system and an ABI greater than 0.3 (133,134).

When arterial lesions of the lower extremity are amenable to either percutaneous transluminal balloon angioplasty (PTBA) or operative reconstruction, equivalent outcomes can be achieved with the two methods in selected patients (135). Success or failure of PTBA depends on (1) whether stenosis or complete occlusion is present; (2) lesion length;

Table 4 Mortality of Lower Extremity Bypass

Author	Year (Ref.)	No. of patients	Mean age	30-day mortality
Rosenblatt	(1990) (164)	171	64	0
Vieth	(1990) (165)	857	—	3.1
Taylor	(1992) (126)	484	68	2.3
Moody	(1992) (166)	226	68	1.8
Whittemore	(1995) (128)	3005	—	2.0
Plecha	(1985) (167)	2377	<75	2.2
		571	>75	6.7
Gregg	(1985) (143)	186	<70	3.5[a]
		89	>70	15.6[a]
Bunt	(1994) (144)	183	<70	2.2

[a] Hospital mortality.

(3) severity of symptoms, i.e., claudication or limb threat; (4) position of the lesion, i.e., femoral, popliteal, or tibial; and (5) quality of the distal runoff. The best results with PTBA are achieved with short (<5 cm) focal stenoses in large arteries (e.g., iliac segments), and the worst results with long occlusions (e.g., long SFA-popliteal occlusions). Reported 5-year patency may be as high as 72% for iliac PTBA if the runoff is good (patent SFA) compared to only 51% when the SFA is occluded (136–138). Similar factors influence patency after popliteal PTBA, depending on tibial runoff.

The ability of the stents to limit elastic recoil of atheroma into the lumen and prevent immediate and delayed restenosis is a major advance. A variety of balloon-expandable and self-expanding stents are currently in use or undergoing clinical trials. The largest experience with stents in PAOD has been with iliac lesions. Compared to PTBA alone, stenting improves 3-year patency by 26% (139,140). Our center has one of the larger experiences with stenting of infrainguinal occlusions, having treated over 60 limbs since 1994 with wire recanalization, balloon angioplasty, and deployment of stents to open chronic SFA occlusions. We find secondary patency to be close to 70% at 2 years, which is much better than our previous experience with PTBA alone for SFA occlusion. Although stenting has great promise, these patients require freqent further angiograms and repeated interventions (141), so that bypass appears to remain the preferred intervention. With improvements in endovascular device design or the development of adjuncts to prevent intimal hyperplasia, stenting may eventually realize its promise as an alternative to bypass.

Although PTBA is an important management technique for PAOD, its risks include distal embolization that may precipitate limb-threatening ischemia, bleeding, and delayed intimal hyperplasia stimulated by catheter trauma. Our appreciation of PTBA should be influenced by an awareness that long-term results (e.g., walking distances) with intense exercise programs for claudicants are as good as or better than those achieved with PTBA (142).

Amputation

Amputation may be required when tissue loss has progressed beyond the point of salvage, surgery is too risky, life expectancy is very low, or if functional limitations obviate the benefit of limb salvage. Amputation should remove all painful or nonviable tissue, and lead to primary stump healing if at all possible. As long a stump as possible should be fashioned, as a lower level of amputation improves the probability of successful rehabilitation. Minor toe amputation or a transmetatarsal level of amputation provides a foot suitable for walking without a prosthesis. Major amputations proximal to the ankle lead to increased costs and length of rehabilitation, and decreased chances of success. Below-knee (BKA) and above-knee (AKA) amputations are the common major amputations.

Death (Table 5) after vascular amputations is variably reported as 5 to 17% within 30 days, and is probably close to 15%. Mortality is higher when sepsis is present or AKA is required. Thirty-day mortality figures do not adequately reflect the serious nature of amputation, as during the second month after amputation, an equivalent number of patients die as within the first (143). Survivors of amputation have reduced longevity compared to age-matched controls. Table 6 shows long-term survival rates for vascular amputees. Survival after major amputations is approximately 50 to 60%, with BKA worse than AKA. A recent report found 50% 1-year survival after amputation in patients older than 70, compared to 84% in younger patients. An earlier study found 5-year survival was 75% in patients under 60 compared to 24% for those older than 60 (144,145).

Approximately 20% of below-knee amputations and 10% of above-knee amputa-

Table 5 Mortality of Lower Extremity Amputation

Author	Year (Ref.)	Procedure	No. of patients	Mean age	Mortality
Huston	(1980) (168)	AKA	100	65	15
Gregg	(1985) (143)	BKA	62	—	8[a]
		AKA	43	—	23[a]
Rush	(1981) (169)	BKA	110	64	7
		AKA	146	67	16
Couch	(1977) (145)		242	60	13
Houghton	(1992) (110)		440	72	17[a]
Plecha	(1985) (167)		783	<75	9.8
				>75	14.7
Bunt	(1994) (144)		212	<70	1.5
			253	>70	8.0

[a] Hospital mortality.

tions fail to heal primarily, leading to prolonged hospitalization and repeated surgery (146,147). These complications are a consequence of inadequate arterial inflow, which is the main factor determining the level of amputation, other than the extent of necrosis. The higher the level chosen for amputation, the greater the likelihood of primary healing.

It is crucial to understand the impact of amputation on elderly patients' ability to walk. Ambulation with a prosthesis requires more energy expenditure than ambulation with an intact limb. The higher the level of amputation, the more energy is required. Table 7 shows the expected increased total energy requirement for ambulation with a prosthesis. A unilateral BKA amputee requires 33% more energy to walk than a normal subject, a unilateral AKA amputee requires 87% more, and more than a 100% increase is required after bilateral BKAs. The second crucial point is that the energy of ambulation, measured as oxygen consumption (mL O_2/kg-min) remains fairly constant with age, but the overall

Table 6 Long-Term Survival After Amputation or Revascularization for Critical Ischemia

Author	Year (Ref.)	Procedure	No. of patients	Mean age	Survival
Huston	(1980) (148)	AKA	100	65	56% at 2 years
Couch	(1977) (145)	BKA + AKA	32	<60	75% at 5 years
			141	>60	24% at 5 years
Rush	(1981) (169)	BKA	121	64	63% at 5 years
		AKA	146	67	51% at 5 years
Bunt	(1994) (144)	BKA + AKA	212	<70	84% at 1 year
		BKA + AKA	253	>70	50% at 1 year
Whittemore	(1995) (128)	bypass	230	65	60% at 5 years
Vieth	(1981) (170)	bypass	522	—	48% at 5 years
Taylor	(1990) (126)	bypass	498	68	38% at 5 years
Hobson	(1985) (171)	BKA	172	67	58% at 5 years
		bypass	375	66	59% at 5 years
Ouriel	(1988) (151)	BKA + AKA	158	70	54% at 3 years
		bypass	204	68	80% at 3 years

Table 7 Energy Expenditure with Ambulation in Vascular Amputees[a]

Amputation	Oxygen cost mL O_2/kg-m)[b]	% Increase
Normals	0.15	—
Unilateral Symes	0.17	13
Unilateral BKA	0.20	33
Unilateral AKA	0.28	87
Bilateral BKA	0.31	106

[a] Ref. 172.
[b] Determined by oxygen consumption measurements during walking on a level surface at a comfortable walking speed.

ability to expend energy steadily decreases with age (Fig. 10). The result is that energy devoted to normal ambulation increases from about 30% of total energy output at age 25 to 55% at age 65 (148).

The consequence of these two relations is that less than one-third of geriatric BKA amputees will meet the physiological demands of prosthetic ambulation (149). The prospects for AKA or bilateral amputees are much worse. Another critical factor in the relation between age and potential for rehabilitation is that with advanced age, the average level required for amputation rises. Patients less than 55 years of age require AKA 12.5% of the time, those between 55 to 74 require AKA about 50% of the time, and patients 75 and older require AKA over two-thirds of the time (143). A recent survey of vascular amputees provides a grim but useful perspective. Four hundred forty patients (median age 72) at eight centers underwent amputation: 193 unilateral AKA, 193 unilateral BKA, and 54 other; 75 patients died in hospital, 113 were deemed unsuitable for rehabilitation, and the remaining 252 patients (57%) were actually referred for prosthesis fitting. Of the survivors referred for prostheses, only 12% achieved mobility independent of a wheelchair;

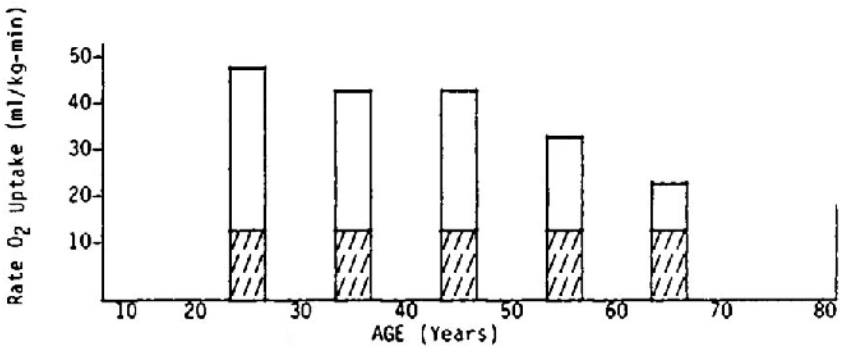

Figure 10 Relation between age, ambulation, and maximal aerobic capacity. The height of each bar corresponds to the maximal sustained O_2 consumption possible at each age. Hatched areas represent the rate of energy expenditure with ambulation. With increasing age the energy required for ambulation represents an increasing percentage of maximal energy expenditure. (From Ref. 172, with permission.)

another 29% were able to achieve limited mobility around their homes with the prosthesis. Nearly half the amputees actually fitted never wore their prostheses. Only 5% of the entire group ultimately achieved independent ambulation; an additional 12% achieved partial rehabilitation. As would be expected, rates of rehabilitation were approximately twice as high with BKA as AKA (150).

Arterial surgery should be reserved for limb-threat situations (rest pain or tissue loss) unless, based on anatomical considerations, the risk of surgery is low and the expected benefit high. With very severe claudication (e.g., the patient who experiences pain walking from bed to bath) and those who are incapacitated from employment, more judgment is required. An otherwise healthy patient with very severe claudication, an ABI of <0.5, and anatomy conducive to above-knee femoropopliteal bypass would probably be recommended for surgery by most U.S. surgeons if compliant medical treatment has failed. An otherwise identical patient who requires distal bypass to the ankle would probably be advised to forego surgery. The tendency to reserve distal bypass for limb threat is fairly standard. Much less uniform is the manner in which endovascular therapy is provided. Although less invasive than surgery, interventional radiology procedures carry significant risks. Particularly troublesome are the risks of delayed restenosis leading to worsened ischemia.

In the face of limb threat, the proposition that vascular surgery is better than amputation may seem self-evident. Nonetheless, based on comparative costs, morbidity, and mortality, primary amputation without prior revascularization may be a better approach in some, often elderly, patients. The average initial costs associated with amputation are somewhat less than those found with bypass, due to the occasional need for secondary procedures to maintain graft patency. More important, because of the risks of bleeding and longer operating times with reconstruction, amputation may be safer in very high-risk patients.

Outcome comparisons between arterial reconstruction and amputation are confounded by selection bias, as sicker and older patients have amputation chosen in lieu of revascularization. Retrospective studies examining perioperative mortality show that revascularization has a low mortality (2–4%), compared to amputation (15%). When risk is analyzed by age (Tables 2–4), two trends emerge. First, mortality in the elderly is greater than in younger patients with either amputation and revascularization. Second, compared to arterial reconstruction, at any age amputation is the more dangerous choice. A study comparing outcomes weighted by preoperative risk found low- and intermediate-risk patients undergoing amputation and revascularization to have comparable low mortality (0–3%). In contrast, high-risk patients had significantly greater ($p < 0.05$) 30-day mortality with amputation than bypass (16% vs. 6%). Most significantly, 29% of high-risk amputees were alive at 3 years compared to 76% of high-risk bypass patients (151).

Amputation appears to decrease survival independent of other factors, plausibly because immobility leads to a hypercoaguable state with increased thromboembolism, and increased rates of coronary and cerebrovascular thrombosis. The negative emotional and psychological impacts of amputation probably also contribute to worsened survival as well as the probability that health providers, perceiving a diminished quality of life, are less aggressive in providing care.

The cost of stay for uncomplicated bypass operations is about the same as successful primary amputations. Length of stay is more difficult to measure as rehabilitation is variable in or out of hospital, but probably length of stays are comparable. When either revascularization or amputation fails, the total cost of treatment approximately doubles, and

length of stay similarly increases (152–154). One factor that should be incorporated into economic analyses is the cost of long-term care for amputees. Perhaps one-third of amputees require nursing home placement (145,155). If one-third of successful revascularizations prevent a nursing home placement, each lasting 3 years, then a savings of about $45,000 should be associated with each successful arterial reconstruction (based on an estimated charge of $130 per diem for nursing home care in 1998). Even ultimately unsuccessful bypass may provide a cost savings, if several months of nursing home care are avoided. Equally important, there is better quality of life provided by successful revascularization compared to amputation, with preserved independence, improved overall health, and improved satisfaction as definite benefits of successful limb salvage (156,157).

Figure 11 shows the relation between angioplasty, bypass, and amputation utilization rates and age found in a recent study. Men were more likely than women at all ages to receive treatment for PAOD by a factor of approximately 1.7. Those between the ages of 65 to 74 had the highest rate (70 per 100,000) for angioplasty. Those between ages 75 to 84 had the highest rate (250 per 100,000) for bypass surgery, and those over 85 had the highest rate (225 per 100,000) for amputation. Poor patients and blacks had higher rates of amputation and lower utilization of revascularization methods. Women were found to have lower age-adjusted rates for any intervention, but, if requiring revascularization, were just as likely as men to have angioplasty or an amputation. The study illustrates the age-related progression of disease severity and the accommodation of therapy chosen to age (158).

Analysis of hospital charges and length of stay indicate that age independently affects resource consumption. Patients aged 80 to 84 admitted for PAOD have hospital charges nearly twice that of those aged 55 to 64. Mean length of stay for 80- to 84-year-old patients is 24 days compared to 14 days in those aged 55 to 64. The difference in resource consumption cannot be attributed to the number of associated comorbid conditions, as younger patients do not have more DRG or ICD-9 diagnoses (159,160). Probably care of PAOD becomes more costly with age due to increased severity of comorbid conditions.

Table 8 is a synopsis of the results of limb salvage surgery in octogenerarians, most of whom (90%) had critical ischemia. When the high expected mortality associated with embolectomy for acute thrombosis is separated out, the 30-day mortality for bypass is about 5%. There is good agreement in the reported limb salvage rates, ranging from 80 to 92% at 1 year, and 71 to 83% at 3 years. Figure 12 shows limb salvage and bypass patency results from one study of octogenarians. These were not significantly different from those found in younger patients, nor was the survival of patients >80 requiring bypass significantly different from those <80. Survival of octogenarians requiring infrainguinal bypass is reduced compared to age-matched controls (Fig. 13). The average life expectancy of the octogenarian who requires bypass for limb threat is about 4 years, compared to an average life expectancy at 80 of 7.9 years and a life expectancy at 85 of 5.9 years (161,162). The potential for preserving independent mobility in the very elderly after limb salvage is good. Scher found over 50% of patients survived 2 or more years with the threatened limb intact, and 76% of the patients who died had been successfully salvaged (163). O'Mara found 67% of octogenarians experienced amputation-free survival after distal bypass. Of 8 patients dying more than 30 days after surgery, 75% had a functional limb (162). Cogbill found 83% of survivors experienced limb salvage with graft patency confirmed in 78%. Only one surviving patient was bedridden and 13 were fully ambulatory at 5 years. Only one-third of the survivors were in nursing homes (161).

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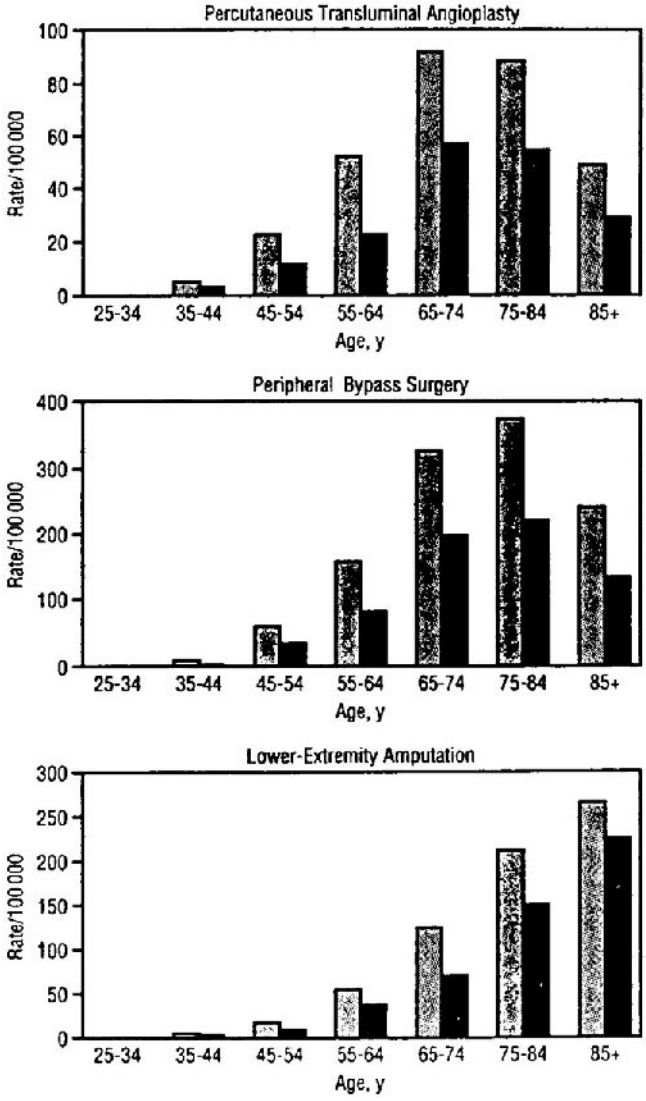

Figure 11 Influence of age and gender on utilization of angioplasty, bypass, and amputation. The histogram depicts the rate of procedure utilization (procedures per 100,000 per year) for individual age groups. Solid black bars represent men, stippled bars represent women. Note that the highest rate of angioplasty is in those aged 65 to 74, the highest rate of bypass is in those aged 75 to 84, and amputation rates are highest in those 85 and older. The data are drawn from all nonfederal hospitals in Maryland over a 2-year period. (From Ref. 158, with permission.)

Given the relations between age and rehabilitation after amputation, efforts toward limb salvage are more critical in the elderly than younger patients. The risks of bypass are not significantly increased by age, and the results of surgery are not worsened appreciably. The modest decrease in life expectancy created by PAOD, should not justify reduced efforts to preserve limbs, given the terribly morbid consequences of amputation.

Table 8 Limb Salvage in Octogenarians

Author	Year (Ref.)	No. of patients	Mean age	No. of procedures	Procedure type	Operative morality	Limb salvage	Survival
Scher	(1986) (163)	168	84	182	13% inflow		80% 1 year	78% 1 year
					13% angioplasty	6%	71% 3 year	54% 3 year
					85% infraing bypass			
O'Mara	(1987) (162)	34	85	40	tibial bypass	5%	91% 1 year	90% 1 year
							81% 3 year	54% 3 year
Cogbill	(1987) (161)	46	84	54	infraing bypass	0%	95% 1 year	85% 1 year
							87% 5 year	30% 5 year
		21	84	25	embolectomy	19%	89%[a]	67% 1 year
								25% 3 year
Edwards	(1982) (173)	55	84	85	7% inflow			
					5% embolectomy	5%	89%	—
					107%			
Friedman	(1989) (174)	50	84	69	16% inflow	3%	92% 1 year	92% 1 year
					84% infraing bypass		83% 3 year	59% 3 year

[a] Unspecified interval.

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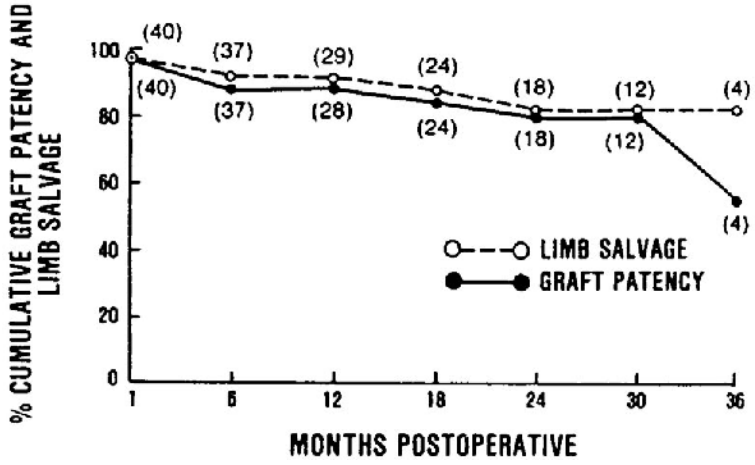

Figure 12 Limb salvage and graft patency rates in octogenarians. The patency and limb salvage rates were not significantly different from those found with patients younger than 80. (From Ref. 162, with permission.)

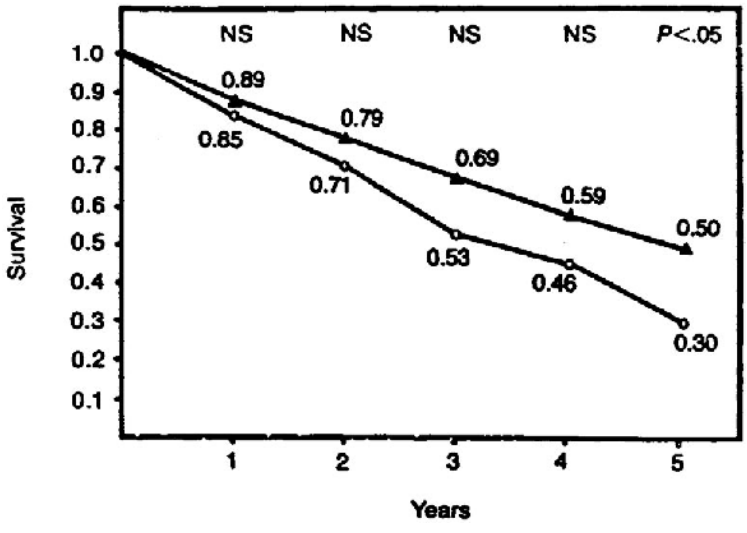

Figure 13 Cumulative survival after infrainguinal bypass in octogenarians. Survival after infrainguinal bypass for limb salvage in octogenarians (circles) is plotted in comparison to survival of age-matched controls (triangles). NS indicates not significant. The difference in survival at 5 years was significant. (From Ref. 161, with permission.)

SUMMARY

Management of peripheral vascular disease in geriatric patients requires a complete understanding of the diverse presentations of atherosclerosis including the influence of coronary artery disease on therapeutic options. There is ample evidence that the outcomes of treatment in patients of advanced age are highly acceptable and can positively impact both the length and quality of life.

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32

Perioperative Evaluation of Elderly Noncardiac Surgical Patients

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Over 30 million patients undergo noncardiac surgery annually in the U.S., 4 million of whom are at risk of having coronary artery disease on the basis of clinical risk factors. More than 1 million patients have cardiovascular complications postoperatively (1). The health care costs associated with these adverse cardiac outcomes have been estimated to be in excess of $10 billion annually.

In addition to a higher prevalence of symptomatic coronary artery disease, cardiovascular complications continue to be a significant source of adverse outcome in elderly patients undergoing noncardiac procedures in spite of improvements in surgical and anesthetic techniques, and perioperative medical management. This is due to the associated changes in the cardiovascular system with aging, such as systolic hypertension, diastolic left ventricular dysfunction, and blunted responses to the stressors of surgery. Notably, there is a decrease in heart rate and increase in stroke volume for any given cardiac output, complicating the expected hemodynamic responses.

The preoperative evaluation and preparation of the elderly patient undergoing noncardiac surgery represents a unique challenge for the primary care physician, cardiologist, anesthesiologist, and surgeon. The elderly have a higher prevalence of cardiovascular disease, and are more likely to need urgent or emergent surgical procedures. Therefore, the evaluation is frequently more complicated and may need to be performed on a more urgent basis.

In approaching the elderly surgical patient, the fundamental assumption is that the preoperative evaluation will result in changes in perioperative management. Since each practitioner who cares for the surgical patient has a different perspective with regard to potential perioperative interventions, it is important that the various consultants communicate with each other in order to reduce an individual patient's risk. For example, while the internist or cardiologist may be most concerned with the need for preoperative interventions or assessing the risks vs. benefits of a surgical intervention, a consultation in which the patient is ''cleared'' is inadequate for the anesthesiologist. From the anesthesiologist's perspective, information regarding the patient's ventricular reserve and ischemic potential is critical in determining the optimal intraoperative management. Therefore, com-

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munication is essential and an understanding of each practitioner's need for critical information is important for achieving the optimal perioperative outcome.

It is important to realize that the preoperative evaluation may also represent the patient's initial evaluation in the medical system. Therefore, both assessment of the perioperative cardiac risk and impact on long-term health can be accomplished. Although aging is associated with declines in basic organ function along with a higher incidence of concomitant disease states such as atherosclerosis, physiological age does not always correlate to chronological age.

The current chapter will attempt to review those factors which identify the high-risk patient, and the potential perioperative interventions that may modify that risk. Information regarding intra- and postoperative care will be reviewed in order to provide the practitioner with an understanding of some of the issues and concerns for the anesthesiologist and perioperative caregivers.

ASSESSMENT OF THE PATIENT BEFORE NONCARDIAC SURGERY

History

A thorough history should focus on cardiovascular risk factors and symptoms or signs of unstable cardiac disease states such as myocardial ischemia, congestive heart failure, valvular heart disease, and significant cardiac arrhythmias.

In patients with symptomatic coronary disease, the preoperative evaluation may lead to the recognition of a change in the frequency or pattern of anginal symptoms. Symptoms of cardiovascular disease should be carefully determined, especially characteristics of chest pain, if present. Certain populations of patients, for example, the elderly, women, or diabetics, may present with more atypical features. The presence of unstable angina has been associated with a high perioperative risk of myocardial infarction (MI) (2). The perioperative period is associated with a hypercoagulable state and surges in endogenous catecholamines, both of which may exacerbate the underlying process in unstable angina and increase the risk of acute infarction. The preoperative evaluation can impact on both a patient's short- and long-term health by instituting treatment of unstable angina.

The patient with stable angina represents a continuum from mild angina with extreme exertion to dyspnea with angina after walking up a few stairs. The patient who only manifests angina after strenuous exercise who does not demonstrate signs of left ventricular dysfunction and would not be a candidate for changes in management. In contrast, a patient with dyspnea on mild exertion would be at high risk for developing perioperative ventricular dysfunction, myocardial ischemia, and possible MI. These patients have an extremely high probability of having extensive coronary artery disease, and additional monitoring or cardiovascular testing should be contemplated, depending upon the surgical procedure and institutional factors.

In virtually all studies, the presence of active congestive heart failure preoperatively has been associated with an increased incidence of perioperative cardiac morbidity (3–5). Stabilization and treatment for pulmonary congestion is prudent prior to elective surgery. Also, it is important to determine the etiology of the left heart failure. Congestive symptoms may be due to nonischemic cardiomyopathy or mitral or aortic valvular insuffi-

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ciency and/or stenosis. Since the type of perioperative monitoring and treatments would be different, clarifying the cause of pulmonary congestion is important.

Patients with a prior MI have coronary artery disease, although a small group of patients may sustain a MI from a nonatherosclerotic mechanism. Traditionally, risk assessment for noncardiac surgery was based upon the time interval between the MI and surgery. Multiple studies have demonstrated an increased incidence of reinfarction if the MI was within 6 months of surgery (6–8) (Table 1). With improvements in perioperative care, this difference has decreased.

However, the importance of the intervening time interval may no longer be valid in the current era of thrombolytics, angioplasty, and risk stratification after an acute MI. Although many patients with an MI may continue to have myocardium at risk for subsequent ischemia and infarction, others patients may have had their critical coronary stenosis either totally occluded or widely patent. Therefore, patients should be evaluated from the perspective of their risk for ongoing ischemia. The American Heart Association/American College of Cardiology Task Force on Perioperative Evaluation of the Patient undergoing Noncardiac Surgery has advocated the use of an MI < 30 days as the group at highest risk, while after that period, risk stratification is based upon the presentation of disease and exercise tolerance. (9)

Patients at Risk for Coronary Artery Disease

For those patients without overt cardiac symptoms or history, the probability of coronary artery disease (CAD) varies with the type and number of atherosclerotic risk factors present. Peripheral arterial disease has been shown to be associated with CAD in multiple studies. Hertzer and colleagues studied 1000 consecutive patients scheduled for major vascular surgery and found that approximately 60% of patients had a least one coronary artery with a critical stenosis (10).

Diabetes mellitus is common in the elderly and represents a disease that impacts on multiple organ systems. Complications of diabetes mellitus are frequently the cause of urgent or emergent surgery, especially in the elderly. Diabetes accelerates the progression of atherosclerosis, which can be frequently silent in nature. Diabetics have a higher probability of CAD than nondiabetics do. There is a high incidence of both silent myocardial infarction and ischemia (11). Eagle et al. demonstrated that diabetes is an independent risk factor for perioperative cardiac morbidity (12). In attempting to determine the degree of this increased probability, the length of the disease and other associated end-organ dysfunction should be taken into account. Autonomic neuropathy has recently been found to be the best predictor of silent coronary artery disease (13). Since these patients are at

Table 1 Reinfarction Rates in Different Studies and Number of Patients Studied

Time elapsed between prior myocardial infarction and operation (months)	Tarhan (6)	Rao (7)	Shah (8)
0–3	37%, $n = 18$	5.8%, $n = 52$	4.3%, $n = 23$
4–6	16%, $n = 19$	2.3%, $n = 86$	0%, $n = 18$
>6	5.6%, $n = 322$	1.5%, $n = 595$	5.7%, $n = 174$
Time unknown	—	—	33.3%, $n = 60$

very high risk for silent MI, the electrocardiogram should be obtained to examine for the presence of Q waves.

Diabetes can also lead to changes in drug metabolism due to its effects on renal function. The optimal management strategy for patients with diabetes mellitus is to determine their history of glucose control and episodes of diabetic ketoacidosis or insulin shock. Frequent assessment of glucose levels and careful administration of insulin are often appropriate.

Hypertension has also been associated with an increased incidence of silent myocardial ischemia and infarction (11). Those hypertensive patients with left ventricular hypertrophy who are undergoing noncardiac surgery are at a higher perioperative risk than nonhypertensive patients (14). Investigators have suggested that the presence of a strain pattern on electrocardiography (ECG) suggests a chronic ischemic state (15). Therefore, these patients should also be considered to have an increased probability of CAD and developing cardiovascular morbidity. A more complete review of the hypertensive patient is described below.

Several other risk factors have been used to suggest an increased probability of CAD. These include the atherosclerotic processes associated with tobacco use and hypercholesterolemia. Although these risk factors increase the probability of developing coronary artery disease, they have not been shown to increase perioperative risk. When attempting to determine the overall probability of disease, the number and severity of the risk factors are important.

Obesity and postmenopausal status may increase the risk of cardiovascular events. The history should also include the patient's use of alcohol and other substances or medications that may affect the cardiovascular system. A past history of cardiac surgery or diagnostic or interventional cardiac procedures should be elicited. The presence of congestive heart failure preoperatively has been associated with an increased incidence of perioperative cardiac morbidity. The patient's functional status should be assessed by detailed questioning of activities of daily living, work habits, and regularity of exercise. Activity level is important as a predictor of perioperative mortality. Stabilization of clinical symptoms is prudent prior to elective surgery.

Physical Examination

General Comments

A complete physical examination is necessary. Blood pressure and heart rate should be determined in both the supine and standing positions to assess intravascular volume or autonomic dysfunction. Careful cardiac auscultation should be performed to detect clinically important findings. The pulmonary exam and evaluation for lower extremity edema can help determine clinical volume status. Peripheral arterial pulses may suggest valvular disease or the presence of atherosclerotic disease. Several studies have shown that the prevalence of coronary artery disease is as high as 70% in patients with evidence of early peripheral vascular disease.

Hypertension

Systemic arterial hypertension (Table 2) is common and its prevalence increases with age (16). According to the third National Health and Nutrition Examination Survey NHANES III, 24% of the adult population of the U.S. has hypertension (17) and, by age 70, the prevalence increases to more than 60% (16). Forty percent of patients with known hyper-

Table 2 Hypertension

Category	Systolic (mmHg)	Diastolic (mmHg)
Normal	<130	<85
High normal	130–139	85–89
Hypertension	140–159	90–99
stage 1 (mild)	160–179	100–109
stage 2 (moderate)	180–209	110–119
stage 3 (severe)	210	120
stage 4 (very severe)		

Adapted from the Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V), Arch Intern Med 1993; 153.

tension either go untreated or are managed inadequately with pharmacological therapy. Hypertension adds to the normal changes of aging by resulting in a more severe form of diastolic dysfunction, which may predispose the patient to congestive heart failure.

Hypertension is a known risk factor for cardiovascular, renal, and neurological disease, increasing the risk of developing these conditions severalfold (18). As a result, these patients may be at greater risk of perioperative myocardial ischemia and infarction. However, the large, multivariate analysis by Goldman et al. (3,19) did not establish mild-to-moderate hypertension as an independent predictor of postoperative cardiac complications such as cardiac death, postoperative myocardial infarction, heart failure, or arrhythmias.

More severe hypertension diastolic blood pressure $>$ 110 mmHg of a chronic nature should certainly be controlled before any elective noncardiac surgery (9). In contrast, a patient who is normally well controlled at home may demonstrate a markedly elevated blood pressure preoperatively due to anxiety. Although these patients are at increased risk of intraoperative hemodynamic lability, particularly with induction, most anesthesiologists will proceed with surgery in the absence of other signs of end-organ dysfunction. A hypertensive crisis in the postoperative period, defined as a diastolic blood pressure $>$ 120 mmHg and clinical evidence of impending or actual end-organ damage (20), poses a definite risk of myocardial infarction and cerebrovascular accident. Evidence includes papilledema or other evidence of increased intracranial pressure, myocardial ischemia, or acute renal failure. Several precipitants of hypertensive crises have been identified (20), including preeclampsia or eclampsia, pheochromocytomas, abrupt clonidine withdrawal prior to surgery, and the use of chronic monoamine oxidase inhibitors with or without sympathomimetic drugs in combination (21).

Causes of secondary hypertension should be investigated in a patient with severe hypertension (e.g., systolic $>$200 mmHg and/or diastolic $>$120 mmHg), particularly if it is of recent onset or if the blood pressure of a previously controlled individual becomes poorly controlled. The 1996 ACC/AHA Guidelines (9) note that mild-to-moderate hypertension is not an independent risk factor for perioperative cardiac morbidity. Therefore, the management of mild-to-moderate hypertension diastolic blood pressure $\geq$ 110 mmHg preoperatively before general anesthesia is controversial.

Chronic hypertension may indirectly predispose patients to perioperative myocardial ischemia since coronary artery disease is more prevalent in these patients. Even in the absence of coronary artery disease, patients with chronic hypertension may have episodes of myocardial ischemia (22), perhaps due to impaired coronary vasodilator reserve and

autoregulation (23) such that higher arterial pressures are required to maintain adequate perfusion of vital organs. Hypertensive patients with known peripheral and coronary vascular disease should have preoperative blood pressure levels maintained.

The Study of Perioperative Ischemia Research Group (24,14), in which patients had continuous perioperative ECG monitoring, showed that a history of hypertension was one of five independent predictors of postoperative ischemia (14) and one of three independent predictors of increased postoperative mortality (24). Patients with a history of hypertension had almost twice the risk of developing postoperative myocardial ischemia (14) and almost four times the risk of postoperative death (24) than did patients without hypertension in the first 48 h postoperatively. Severely limited activity level and renal insufficiency were also independent predictors of postoperative mortality.

The link between systemic hypertension and perioperative cardiac complications may relate to an increased risk of silent myocardial ischemia. Silent ischemia has been shown to be a major predictor of postoperative cardiac morbidity (25,26). In one study (27), patients underwent ambulatory ECG monitoring to determine the incidence of silent myocardial ischemia before elective noncardiac surgery. At least one episode of ST-segment depression consistent with silent ischemia occurred in 20%. Patients with hypertension despite antihypertensive therapy were at particularly high risk, with more than a 50% incidence of silent myocardial ischemia. Of all other cardiac risk factors, including age greater than 70 years, only hypertension predicted the presence of preoperative silent ischemia (27).

On the other hand, more recent studies of postoperative myocardial ischemia diagnosed by continuous ECG monitoring in the hypertensive patient (27,28) may overestimate its incidence, especially in the setting of left ventricular hypertrophy when criteria defining episodes of myocardial ischemia may be less reliable. In contrast, the effects of left ventricular hypertrophy on the ECG, which may affect the determination of ischemic ECG changes, could not explain the findings of one study (24), where there was an increased risk of postoperative death in the hypertensive patient.

Thus, whether patients with mild-to-moderate hypertension should be considered at greater than average risk of perioperative myocardial ischemia remains uncertain because of often conflicting reports from the last 20 years. Surgery should neither be postponed nor canceled in the otherwise uncomplicated patient with mild-to-moderate hypertension (9), antihypertensive medications should be continued perioperatively (9), and blood pressure should be maintained near preoperative levels to reduce the risk of myocardial ischemia (23). In patients with more severe hypertension, diastolic blood pressure >110 mmHg, the potential benefits of delaying surgery in order to optimize antihypertensive medications should be weighed against the risk of delaying the surgical procedure (29,30).

Factors Related to the Surgical Procedure

The surgical procedure itself has a significant impact on perioperative risks and the amount of preoperative information required to safely provide anesthesia. For surgical procedures that are not associated with significant stress or a high incidence of perioperative myocardial ischemia or morbidity, the cost of the preoperative specialized testing is often greater than any perceived benefits from the new information. For example, cataract surgery is associated with minimal stress, and exceeding low morbidity and mortality rates, even after a recent myocardial infarction (31). Similarly, outpatient procedures have also been shown to be associated with a low incidence of morbidity and mortality (32). In such patients, perioperative management is rarely changed by the cardiovascular status unless

Table 3 Cardiac Risk Stratification for Noncardiac Surgical Procedures[a]

High	Reported cardiac risk often >5%
	Emergent major operations, particularly in the elderly
	Aortic and other major vascular
	Peripheral vascular
	Anticipated prolonged surgical procedures associated with large fluid shifts and/or blood loss
Intermediate	Reported cardiac risk generally <5%
	Carotid endarterectomy
	Head and neck
	Intraperitoneal and intrathoracic
	Orthopedic
	Prostate
Low[b]	Reported cardiac risk generally <1%
	Endoscopic procedures
	Superficial procedure
	Cataract
	Breast

[a] Combined incidence of cardiac death and nonfatal myocardial infarction.
[b] Do not generally require further preoperative cardiac testing.
Source: Reproduced with permission from Ref. 9.

the patient demonstrates unstable angina or overt congestive heart failure. In contrast, the patient undergoing a procedure associated with a high incidence of morbidity and mortality can frequently benefit from a more extensive preoperative evaluation. For example, vascular disease is associated with a high risk of morbidity and the ischemic potential and incidence of perioperative cardiac morbidity increases with the level of aortic cross-clamp in patients undergoing aortic reconstruction (33). Since further determination of cardiac status may alter perioperative care, (i.e., coronary artery revascularization or invasive monitoring), the benefit of further evaluation and treatment can be greater than the associated costs or risks. Finally, intra-abdominal, orthopedic, and intrathoracic procedures are associated with an intermediate risk. In this group, the duration of surgery and extent of fluid shifts may modify the need for further evaluation. Using data from a long-term follow-up of the Coronary Artery Surgery Study, the guidelines have suggested three classifications of surgical risk (Table 3) (9).

The urgency, type, and duration of the surgical procedure, possible alternatives to surgery, and the expected blood loss and volume shifts are necessary to make an informed perioperative management plan. Importantly, patients with prosthetic heart valves, prior episodes of infective endocarditis, and specific valvular abnormalities may require antibiotic prophylaxis against endocarditis prior to specific surgical procedures. In addition, appropriate timing of anticoagulation may be necessary for patients with chronic atrial fibrillation, cardiomyopathy, or prosthetic heart valves.

ESTIMATION OF CARDIAC RISK

Cardiac Risk Indices

In early studies, clinical parameters suspected to be associated with coronary artery disease were proven predictors of perioperative morbidity. In the landmark study of Goldman (3),

Table 4 Computation of the Cardiac Risk Index

Criteria[a]	Multivariate discriminant function coefficient	Points
I. History:		
(a) Age > 70 yr	0.191	5
(b) MI in previous 6 mo	0.384	10
II. Physical examination:		
(a) S_3 gallop or JVD	0.451	11
(b) Important VAS	0.119	3
III. Electrocardiogram:		
(a) Rhythm other than sinus or PACs on last preoperative ECG	0.283	7
(b) >5 PVCs/min documented at any time before operation	0.278	7
IV. General status:		
$Po_2 < 60$ or $PCO_2 > 50$ mmHg, $K < 3.0$ or $HCO_3 < 20$ meq/L, BUN > 50 or Cr > 3.0 mg/dL, abnormal SGOT, signs of chronic liver disease or patient bedridden form noncardiac causes	0.132	3
V. Operation:		
(a) Intraperitoneal, intrathoracic or aortic operation	0.123	3
(b) Emergency operation	0.167	4
Total possible		53

[a] MI, myocardial infarction; JVD, jugular-vein distention; VAS, valvular aortic stenosis; PACs, premature atrial contractions; ECG, electrocardiogram; PVCs, premature ventricular contractions; PO_2, partial pressure of oxygen; PCO_2, partial pressure of carbon dioxide; K, potassium; HCO_3, bicarbonate; BUN, blood urea nitrogen; Cr, creatinine; and SGOT, serum glutamic oxaloxetic transaminase.

Source: From Ref. 3, with permission.

with patients over the age of 40 years undergoing noncardiac surgery, there were nine independent correlates of cardiac complications (Table 4). A point system was applied to these predictors and to help stratify patients at highest risk for postoperative cardiac complications. Detsky (4) validated the Goldman criteria a decade later in a small patient population using a modified version of the cardiac risk index (Table 5), which included other clinical parameters such as the severity of angina pectoris and prior history of pulmonary edema. The disadvantage with both indexes is that many cardiac events occurred even in patients with low-risk scores, thereby lowering the sensitivity of these methods. Additionally, use of these risk indices may provide a probability of perioperative morbidity, but do not provide information regarding cardiovascular status and reserve required by the anesthesiologist in determining the optimal intraoperative management plan. Therefore, simply providing an overall risk score without defining specific information regarding the potential for developing myocardial ischemia and ventricular reserve is insufficient.

Alternative Approach to Defining Baseline Risk

The 1996 American College of Cardiology/American Heart Association ACC/AHA Guidelines for Perioperative Cardiovascular Evaluation for Noncardiac Surgery chose to define three classes of clinical risk based upon the association of an individual risk factor

Table 5 Modified Cardiac Risk Index by Detsky

Variables	Points
Angina	
class IV	20
class III	10
unstable angina < 3 months	10
Suspected critical aortic stenosis	20
Myocardial infarction	
< 6 months	10
> 6 months	5
Alveolar pulmonary edema	
< 1 week	10
ever	5
Emergency surgery	10
Sinus plus atrial premature beats or rhythm other than sinus on preop ECG	5
>5 PVCs at any time before surgery	5
Poor general medical status	5
Age >70 years	5

Source: Reproduced, with permission, from Ref. 4.

with known coronary artery disease (Table 6). The degree of clinical risk is then the starting point in the decision to undergo further evaluation.

IMPORTANCE OF EXERCISE TOLERANCE

Exercise tolerance is one of the most important determinants of perioperative risk and the need for invasive monitoring (34). An excellent exercise tolerance, even in patients with stable angina, suggests that the myocardium can be stressed without becoming dysfunctional. 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 with chest pain during minimal exertion, then the probability of extensive coronary artery disease is high. A greater degree of coronary artery disease has been associated with a higher perioperative risk (35). Additionally, these patients are at risk for developing hypotension with ischemia, and therefore may benefit from more extensive hemodynamic monitoring or possibly preoperative coronary revascularization. Exercise tolerance can be assessed with formal treadmill testing or with a questionnaire that assesses activities of daily living (Table 7) (9).

PREOPERATIVE TESTING BEFORE NONCARDIAC SURGERY

General Comments

The approach to the preoperative evaluation of an elderly patient for noncardiac surgery includes consideration of noninvasive cardiac stress testing. The sensitivity, specificity, and accuracy of the stress testing modality, along with the cost, must be considered along with the prevalence of disease in the population. A positive stress test for myocardial

Table 6 Clinical Predictors of Increased Perioperative Cardiovascular Risk (Myocardial Infarction, Congestive Heart Failure, Death)

Major
Unstable coronary syndromes
Recent myocardial infarction[a] with evidence of important ischemic risk by clinical symptoms or noninvasive study
Unstable or severe[b] angina (Canadian class III or IV)[c]
Decompensated congestive heart failure
Significant arrhythmias
High-grade atrioventricular block
Symptomatic ventricular arrhythmias in the presence of underlying heart disease
Supraventricular arrhythmias with uncontrolled ventricular rate
Severe valvular disease
Intermediate
Mild angina pectoris (Canadian class I or II)
Prior myocardial infarction by history or pathological Q waves
Compensated or prior congestive heart failure
Diabetes mellitus
Minor
Advanced age
Abnormal ECG (left ventricular hypertrophy, left bundle branch block, ST-T abnormalities)
Rhythm other than sinus (e.g., atrial fibrillation)
Low functional capacity (e.g., inability to climb one flight of stairs with a bag of groceries)
History of stroke
Uncontrolled systemic hypertension

ECG indicates electrocardiogram.

[a] The American College of Cardiology National Database Library defines recent MI as greater than 7 days but less than or equal to 1 month (30 days).

[b] May include ''stable'' angina in patients who are unusually sedentary.

[c] Ref. 33a.

Source: Reproduced, with permission, from Ref. 9.

ischemia may not have the same meaning in a population with a low prevalence of coronary artery disease as in a population of patients in whom a high prevalence for coronary disease exists. This type of decision making should be considered for all patients so that stress testing will be applied to the patient population in which it is most appropriate and useful.

The optimal approach for cardiac risk stratification for patients undergoing noncardiac surgery remains controversial. Several algorithms exist for approaching cardiac risk assessment. Some studies raise questions about the usefulness of preoperative noninvasive stress testing before noncardiac surgery while other studies consider it useful in certain populations (36,37,12,38). There is also a lack of evidence showing that intensive antianginal therapy or coronary revascularization lowers the postoperative risk in patients with evidence of stress-induced myocardial ischemia.

The negative predictive values of the specific stress testing modalities studied in these patient populations are high. Therefore, in a patient with a negative stress test for myocardial ischemia, the risk of a perioperative cardiac event is relatively low. On the other hand, the positive predictive values of these same stress tests are consistently low

Table 7 Estimated Energy Requirement for Various Activities

1 MET	Can you take care of yourself?	4 METs	Climb a flight of stairs or walk up a hill?
4 METs	Eat, dress, or use the toilet?	>10 METs	Walk on level gound at 4 mph or 6.4 km/h?
	Walk indoors around the house?		Run a short distance
	Walk a block or two on level gound at 2–3 mph or 3.2–4.8 km/h?		Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?
	Do light work around the house like dusting or washing dishes		Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football?
			Participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing?

MET, metabolic equivalent.
Source: Adapted from the Duke Activity Status Index and AHA Exercise Standards. Reproduced, with permission, from Ref. 9.

in all studies. A patient with evidence of stress-induced myocardial ischemia may be at higher risk, but this does not always predict a poor perioperative outcome.

Myocardial infarction or unstable angina pectoris may be caused by an unstable, but not flow-limiting, coronary artery plaque. The precise mechanism of perioperative myocardial ischemia and infarction is unknown, but it is postulated that this same mechanism may play a role (39). Stress testing demonstrates myocardial ischemia by revealing flow-limiting stenoses but it has been shown that myocardial infarctions may not always occur in these areas. Therefore, the poor positive predictive value of stress testing may be due to the fact that the presence of myocardial ischemia may only serve as a marker for unstable, less critical, coronary stenoses.

Perioperative changes in adrenergic tone, plasma catecholamine levels, body temperature, fluid balance, and pain control fluctuate and may precipitate myocardial ischemia. Therefore, many cardiac events may be less often clinically evident perioperatively due to an altered pain threshold. Monitoring for silent ischemia and more intensive control of postoperative hemodynamic changes may be more critical to prevention of postoperative cardiac events perioperatively.

Approach to the Patient

The algorithm to determine the need for testing proposed by the American College of Cardiology/American Heart Association Task Force is based upon the available evidence and expert opinion and integrates clinical history, surgery specific risk, and exercise tolerance (Fig. 1) (9). First, the clinician must evaluate the urgency of the surgery and the appropriateness of a formal preoperative assessment. Next, it must be determined if the patient has undergone a previous revascularization procedure or coronary evaluation. Those patients with unstable coronary syndromes should be identified, and appropriate

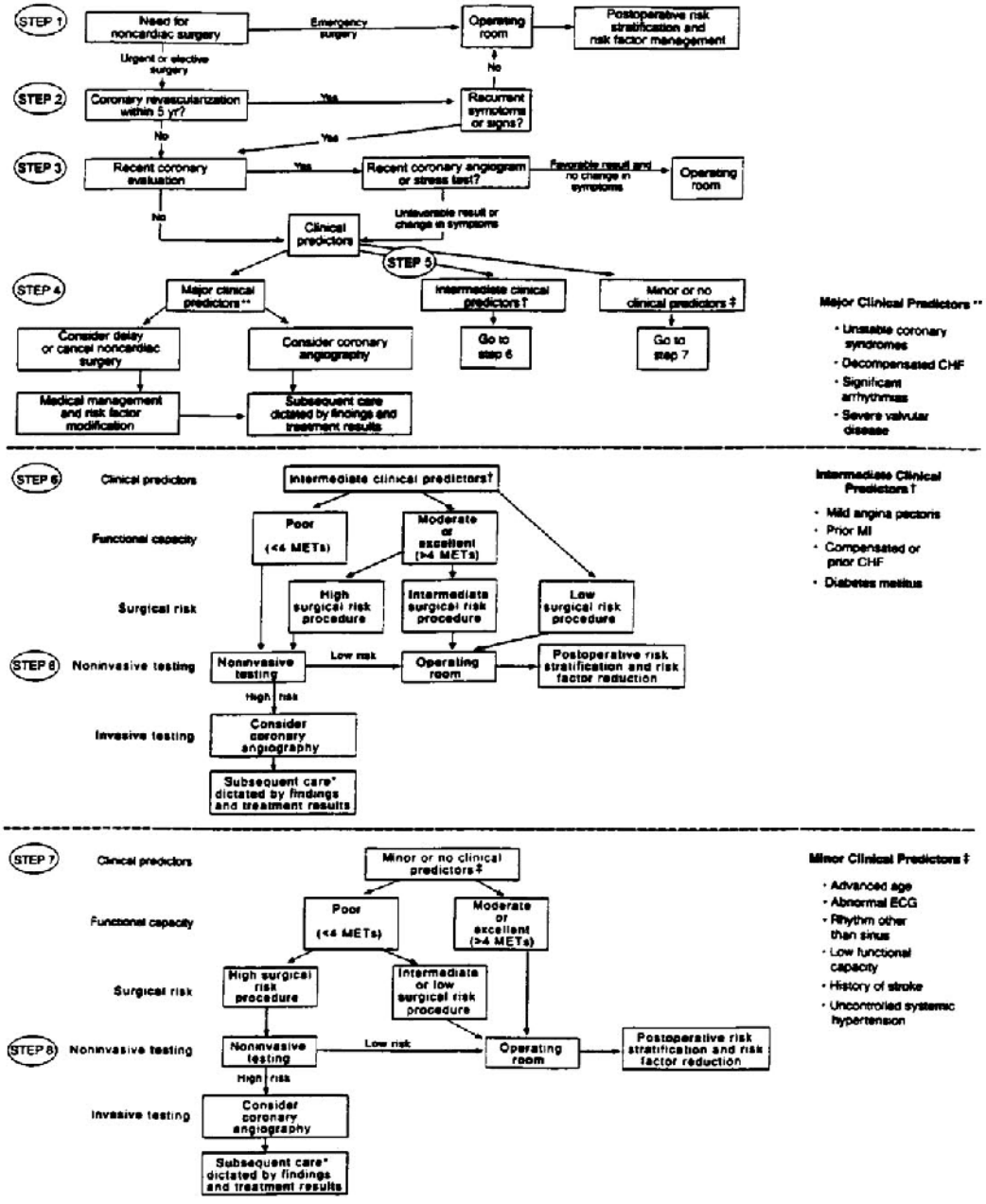

Figure 1 The American Heart Association/American College of Cardiology Task Force on Perioperative Evaluation of Cardiac Patients Undergoing Noncardiac Surgery has proposed an algorithm for decisions regarding the need for further evaluation. This represents one of multiple algorithms proposed in the literature. It is based upon expert opinion and incorporates six steps. The clinician must evaluate the urgency of the surgery and the appropriateness of a formal preoperative assessment. He or she 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. (Adapted, with permission, from Ref. 9.)

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treatment instituted. Finally, the decision to undergo further testing depends upon the interaction of the clinical risk factors, surgery-specific risk, and functional capacity. For patients at intermediate clinical risk, both the exercise tolerance and the extent of the surgery are taken into account with regard to the need for further testing. Importantly, no preoperative cardiovascular testing should be performed if the results will not change perioperative management.

The American College of Physician guidelines attempts to apply the evidence-based approach (Fig. 2) (40). The initial decision point is the assessment of risk using the Detsky modification of the Cardiac Risk Index (4). If patients are class II or III, they are considered high risk. If they are class I, the presence of other clinical factors according to work by Eagle et al. or Vanzetto et al. is used to further stratify risk (12,41). Those with multiple markers for cardiovascular disease according to these risk indices and undergoing major vascular surgery are considered appropriate for further diagnostic testing by either dipyridamole imaging or dobutamine stress echocardiography. The guidelines suggest that there is insufficient evidence to recommend diagnostic testing for nonvascular surgery patients.

NONINVASIVE PREOPERATIVE TESTING

Resting Electrocardiography

Patients over the age of 40 years undergoing preoperative evaluation for noncardiac surgery should have a resting ECG. The sensitivity of abnormalities on the ECG to determine specific cardiac diseases depends on the prevalence of coronary disease in the patient population. It has been estimated that up to 30% of myocardial infarctions are silent and only detected on routine ECG, especially in diabetics and patients with hypertension. Long-term prognosis is not altered by the lack of cardiac symptoms. The baseline ECG has limited applicability in the assessment of myocardial ischemia but may be useful for the diagnosis of significant conduction disturbances and arrhythmias. High-grade atrioventricular block, symptomatic ventricular arrhythmias in the presence of underlying heart disease and supraventricular arrhythmias with uncontrolled ventricular rate are considered high-risk clinical predictors by the AHA/ACC guidelines (9). Pathological Q waves are intermediate predictors of risk. The presence of left ventricular hypertrophy, left bundle branch block, ST abnormalities, and rhythm other than sinus are considered minor predictors.

In a retrospective study conducted in the early 1970s, no surgical procedures were delayed based on the findings of the resting preoperative ECG. The value of a preoperative ECG in the elderly has not been studied. Any abnormalities may not lead to delay of a surgical noncardiac procedure but may lead to increased vigilance by the anesthesiologist that may influence intraoperative monitoring and treatment.

Assessment of Left Ventricular Systolic and Diastolic Function

Baseline left ventricular systolic function can be assessed using echocardiography, radionuclide angiography, and/or contrast ventriculography. Dyspnea of unknown etiology warrants a careful preoperative assessment to determine its etiology. Left ventricular ejection fraction has been correlated with short- and long-term prognosis in multiple studies in patients undergoing noncardiac surgery (9). The greatest risk of perioperative ischemic events is believed to be in patients with a resting left ventricular ejection fraction $< 35\%$,

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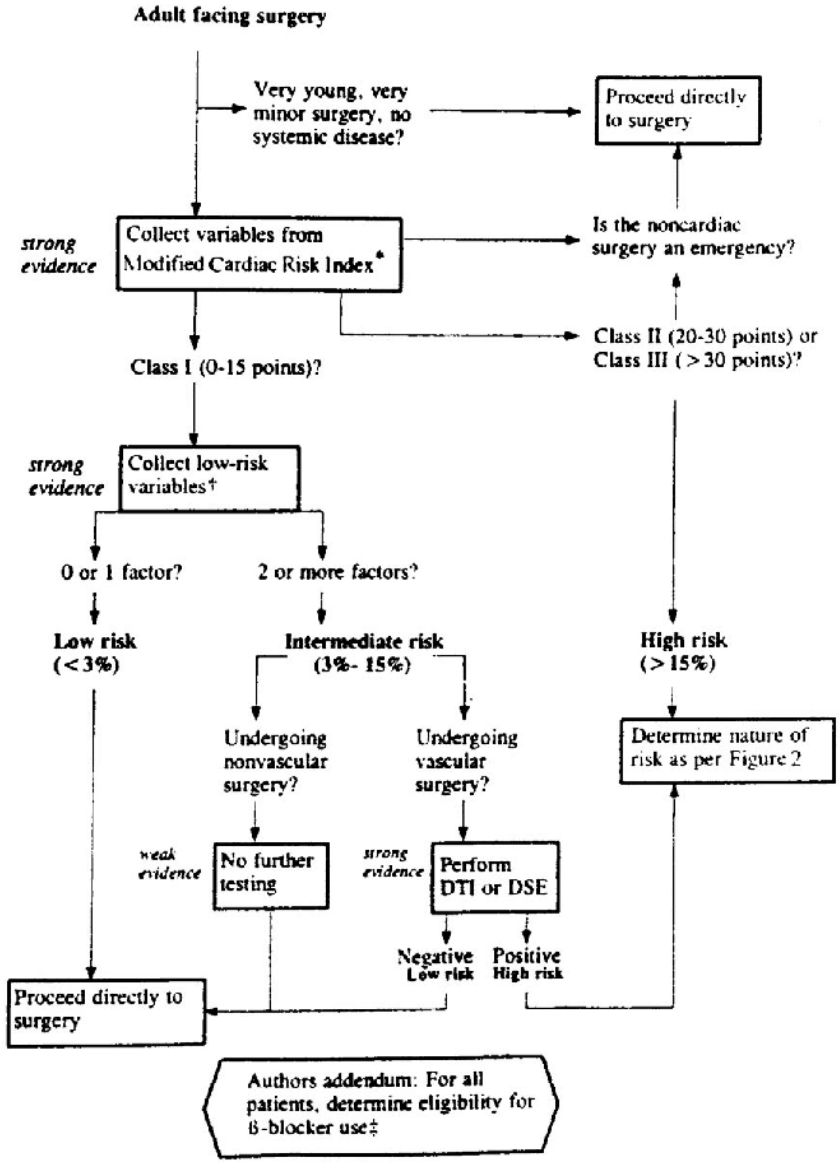

Figure 2 The American College of Physicians Guidelines for assessing and managing the perioperative risk from coronary artery disease associated with major noncardiac surgery. The commentary in italics represents the strength of evidence to support each decision process in the algorithm. An evidence-based analysis of the literature accompanied the algorithm in a paper by Detsky and Palda. Initially, patients are assessed using the Detsky modification of the cardiac risk index to determine if they are class I (low risk), class II, or III (high risk). If they are class I, clinical predictors such as those identified by Eagle are collected to determine if they represent low or high clinical risk. Only those patients with several clinical predictors are then determined to be at intermediate perioperative risk. Those patients with an intermediate risk and undergoing vascular surgery should be considered for noninvasive imaging with dipyridamole thallium imaging or dobutamine stress echo-

but this has not been a consistent predictor (9) and some recent studies have found that left ventricular systolic dysfunction does not predict cardiac complications after vascular surgery (9,42–44).

Ambulatory Electrocardiography: Holter Monitoring/Event Recorder

The choice of perioperative ECG ST monitoring is dependent on the interaction of patient-specific risk, surgical procedure performed, and location of care. Multiple studies have demonstrated the predictive value and association of perioperative ECG ST-segment changes and major cardiac events. Furthermore, the duration, either cumulative or continuous, of perioperative ECG ST changes has been shown to be the strongest predictor of poor outcomes (22,23). Therefore, ST-segment monitoring is becoming a standard during the intraoperative period for high-risk patients. However, low-to-moderate risk patients may also develop ST-segment changes. These changes may not reflect true myocardial ischemia, as suggested by several recent case series (39,40).

The value of ST-segment monitoring during the postoperative period is controversial. Most currently installed intensive care unit monitors do not include ST-segment monitoring, although virtually all of the new machines do have it available. The period of greatest risk may be the time when the patient is on the ward and unmonitored. Many companies have developed ST telemetry monitors, but they have not been tested in the perioperative period. This issue is whether early treatment of prolonged ST-segment changes will lead to improved outcome. Until such studies are completed, the efficacies of such monitors are debatable. In fact, overly aggressive treatment of ST-segment changes of nonischemic origin could theoretically increase morbidity, costs, or both.

The incidence of myocardial ischemia and infarction peaks at 48 to 72 h postoperatively, is often clinically silent, and can predict adverse perioperative outcomes (45). Ambulatory ECG can be an important tool to document perioperative myocardial ischemia but many patients either do not manifest ECG changes or have baseline ECG abnormalities (9–39%) that preclude interpretation of further changes (9). It is important to note that many patients were excluded from the studies performed due to this. The value of detecting preoperative ischemia by this method to predict postoperative cardiac events was evaluated in two studies by Raby (46). Preoperative ischemia was the most significant independent predictor of postoperative cardiac events. The absence of ischemia carried a very high negative predictive value (99%). Cardiac events occurred more often in patients with higher postoperative heart rates if patients had a history of diabetes, clinical manifestations of coronary artery disease, or age $\geq$ 70 years. Intraoperative ischemia was a significant,

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cardiography. No further testing is suggested in those patients undergoing nonvascular surgery. If the noninvasive testing is positive or the patient is at high clinical Detsky risk, then it is important to determine the nature of the risk. If the risk is largely due to ischemic heart disease, then it is important to determine if the patient would be eligible for coronary revascularization based on AHA Guidelines independent of noncardiac surgery. If the risk is due to nonischemic origins, then the ideal choice is to optimize and reassess. Finally, if it is due to largely nonmodifiable factors, then either canceling the case or modifying the noncardiac surgery should be considered. (Reproduced, with permission, from Ref. 40.)

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but relatively weak, predictor of postoperative events, especially in patients with a low prevalence of coronary disease. All patients with preoperative ischemia who went on to have cardiac events had postoperative ischemia that occurred most often in the first 24 h postoperatively.

Subsequent studies have also shown that postoperative ischemic ST-segment changes by ambulatory ECG were the strongest independent predictors of perioperative cardiac events for both nonvascular and vascular surgical procedures, especially if the ischemic events were prolonged (47,48). Postoperative ischemia has been found to be common, but is difficult to detect because it is often silent (45). Extended monitoring and aggressive therapy for pain control and heart rate may be indicated during the perioperative period to lower immediate stressors (45). Of note, preoperative clinical variables such as hypertension, previous myocardial infarction, and a high cardiac risk index failed to predict ischemic events (3).

The ambulatory ECG provides a means of continuously monitoring the electrocardiogram for significant ST-segment changes during the preoperative period. Raby demonstrated that the presence of silent ischemia is a strong predictor of outcome, while its absence was associated with a good outcome in 99% of patients (46). Other investigators have demonstrated the value of ECG ST-segment monitoring, although the negative predictive values have not been as high as originally reported (35). Fleisher et al. demonstrated a similar predictive value of dipyridamole thallium imaging and ambulatory ECG monitoring; however, the quantity of silent ischemia episodes could not be used to identify those patients at greatest risk who might benefit from further testing and coronary revascularization (35).

Specialized Testing

Preoperative Noninvasive Stress Testing as a Predictor of Cardiac Disease

Early studies assessed only clinical parameters from a population with a relatively low risk of coronary artery disease (3,4). Applying these clinical indexes to elderly patients undergoing vascular surgery, in whom the prevalence of coronary artery disease is high and exercise capacity limited, may not be as reliable (44). This has led to the development of multiple noninvasive cardiac stress-testing modalities. The ultimate goal of a preoperative stress test is to identify patients with myocardial ischemia in whom further cardiac interventions would significantly lower the perioperative cardiac risks. In patients undergoing elective major vascular surgery, which carries the highest perioperative cardiac risk, noninvasive cardiac testing has been found to be helpful for cardiac risk stratification (12,36,38,49,50–54). Unfortunately, there are few prospective, randomized studies that establish the value of preoperative stress testing and how therapy based on these test results affects perioperative outcomes. In most studies, biases were present and may have led to preoperative cardiac interventions that would alter postoperative outcomes. Also, clinical predictors and determination of abnormal test results varied among studies, limiting applicability to generalized populations. Large, randomized trials are needed to assess the indications for preoperative cardiac stress testing and to determine how the information is best utilized.

The pretest probability estimated prevalence of coronary artery disease in each patient must be considered (55,56). This concept, Bayes' theorem, addresses not only the

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sensitivity and specificity of the stress-testing modality being used, but also considers the prevalence of disease for the entire group of patients under consideration. Bayes' theorem states that the predictive value of the test is predetermined by the incidence of disease in the population being evaluated. For example, a false-positive test result is most likely to occur in a patient group in whom the particular disease, such as coronary artery disease, is very uncommon.

Various stress-test modalities have been evaluated for estimating perioperative cardiac risk in patients having noncardiac surgery. A limited number of prospective studies have investigated the predictive value of noninvasive stress tests in determining the risk of postoperative cardiac events. The likelihood of an adverse cardiac event after noncardiac surgery, even in patients with evidence of coronary artery disease, is less than 10% (57,58). The positive predictive values have been shown to be poor (10–20%), so that a patient with evidence of myocardial ischemia often will not have a postoperative cardiac event even though the estimated cardiac risk is high. On the other hand, negative predictive values have been high (95–100%), so that patients without evidence of ischemia are at the lowest risk for an adverse perioperative outcome. Therefore, universal screening with stress testing before noncardiac surgery is not warranted since the findings would potentially not alter prognosis in a large subset of patients. Also, it is important to remember that stress testing of any type should be reserved for patients in whom cardiac interventions would be considered.

There are no data to compare the impact of intensive medical therapy to coronary revascularization procedures based on the finding of myocardial ischemia with any stress-testing modality. Stress testing should be limited to patients in whom the risk of significant coronary disease is high and to those undergoing the highest risk surgical procedures, so that the test result might selectively and accurately modify perioperative management.

Stress-Testing Modalities

The 1996 ACC/AHA Task Force guidelines state that the choice of specialized testing in the preoperative evaluation for noncardiac surgery in ambulatory patients is a treadmill exercise ECG to determine functional capacity and to detect myocardial ischemia (9). In patients with ECG abnormalities or in those who are unable to ambulate, nuclear scintigraphic or echocardiographic imaging should be used, depending on the expertise of interpreters. Dobutamine echocardiography, stress treadmill echocardiography, and dipyridamole thallium have been shown to the same positive and negative predictive values, sensitivities, and specificities when performed by clinicians with expertise with these studies (59–62).

Exercise Stress Testing

In patients with a normal baseline ECG without a prior history of coronary disease, the exercise ECG response is abnormal in up to 25% and increases up to 50% in those with a prior history of MI or an abnormal resting ECG (63). If an ischemic response occurs at a low cardiac workload, the positive predictive value of the test for determining a high cardiac risk is further increased (34,64,65). Reduced exercise duration and exercise-

induced ST-segment depression, in most studies, have been shown to correlate with an increased likelihood of postoperative cardiac events (38,64). But, some series have found that results of preoperative exercise tests are not independent predictors of cardiac risk, especially for nonvascular surgical procedures (9,66).

In the general population, the usefulness of an exercise ECG test is somewhat limited. The mean sensitivity and specificity are 68% and 77% for detection of single-vessel disease, 81% and 66% for detection of multivessel disease, and 86% and 53% for detection of three-vessel or left main coronary disease (9). The older age of patients undergoing noncardiac and, especially, vascular surgery reduces the sensitivity and prognostic utility of exercise stress testing in this group (63,67). Often these patients will have a submaximal treadmill exercise study, not being able to achieve their maximum predicted heart rate due to medical therapy, such as beta-blocker use, or to comorbid states, which can limit the results. The results of these tests must be analyzed incorporating clinical parameters and knowledge of the risk of the proposed surgery.

Functional capacity, or cardiac workload, can be estimated by aerobic demands during activities of daily living and is expressed in metabolic equivalent levels (MET) (Table 7) (63). A 40-year-old, 70-kg man at rest has an oxygen consumption of 1 MET or 3.5 mL oxygen/kg/min. Patients with intermediate- to high-risk profiles who reach a cardiac workload $>$ 5 METs or a greater than 75 to 85% of maximum age-predicted heart rate with a nonischemic ECG response are at low-risk for postoperative cardiac events (67). Perioperative cardiac risk is increased in patients unable to achieve a 4 MET demand during normal daily activities (9,24).

A patient's performance on a treadmill or bicycle ergometer may also be predictive of postoperative cardiac outcomes (68). Patients unable to reach 85% maximum predicted heart rate had a significantly higher postoperative cardiac complication rate compared to those able to reach that target heart rate in one study (34). In addition, if there was evidence of ischemia, those unable to achieve the predicted heart rate (30%) had a 33% complication rate. Those who were able to achieve the predicted heart rate had no cardiac complications, making them a low-risk group.

The level at which ischemia is evident on an exercise ECG can be used to estimate the ''ischemic threshold'' for a patient to guide perioperative medical management. This may support further intensification of perioperative medical therapy in high-risk patients, which may impact on perioperative cardiovascular events (69).

Nonexercise Pharmacological Stress Testing

Pharmacological stress testing has been advocated for preoperative cardiac risk assessment for patients in whom exercise tolerance is limited, both by comorbid diseases or symptomatic peripheral vascular disease. Often, these patients may not stress themselves sufficiently during daily life to provoke symptoms of myocardial ischemia or congestive heart failure. The noncardiac surgical procedure may represent a stress significantly greater than encountered in daily life. Pharmacological stress-testing techniques either increase myocardial oxygen demand (dobutamine) or produce coronary vasodilatation, leading to coronary flow redistribution (dipyridamole/adenosine). Echocardiographic or nuclear scintigraphic imaging is used in conjunction with the pharmacological therapy. These pharmacological stress-testing modalities have been studied extensively in preoperative cardiac risk assessment for noncardiac, and especially vascular, surgery (9).

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Dipyridamole-Thallium Scintigraphy

An abnormal preoperative dipyridamole-thallium scan has been shown to be a sensitive marker for patients likely to have a postoperative cardiac event (36,38,49,51,54,56,70–73). Pooled data, though, show that the positive predictive value for adverse cardiac outcomes is low, ranging from 36 to 45%. The negative predictive value, on the other hand, is high (approximately 97%). In several studies, the presence of a fixed defect was shown to have no predictive value for adverse cardiac outcomes postoperatively (36,38,41, 49,51,54,70,74), although, in two studies, there was a higher risk compared to patients with no thallium defect (55,58).

Preoperative dipyridamole thallium scintigraphy was found to be superior to the clinical assessment alone for the determination of cardiac risk in early studies (49). More recent studies support the use of preoperative dipyridamole thallium scintigraphy, in combination with clinical parameters, to identify patients at high risk for adverse cardiac outcomes after noncardiac surgery. In the initial study by Eagle of patients undergoing vascular surgery, an abnormal preoperative dipyridamole thallium scan was the most significant predictor of postoperative ischemic events, increasing the likelihood of an event from 7%, if the scan was negative, to 45% (36). Other predictors of postoperative events were pathological Q waves on ECG. Patients with no clinical predictors were stratified into the lowest perioperative cardiac risk group and it was felt that they may not have needed preoperative stress testing since their perioperative outcomes were not affected by the results. Notably, a large subset of patients with a reversible thallium defect did well postoperatively, suggesting that occult coronary disease did not have a significant clinical impact perioperatively in this group.

In a second study by Eagle (12), in a similar patient population, five clinical variables were predictors of postoperative cardiac events: (1) age $>$ 70 years; (2) Q waves on baseline ECG; (3) history of angina; (4) ventricular ectopic activity requiring therapy; and (5) diabetes mellitus. Dipyridamole thallium scintigraphy was found to be most useful in further stratifying patients considered at intermediate clinical risk (one or two clinical variables). In this group, the presence of a redistribution defect on dipyridamole thallium testing was associated with a 30% event rate compared to a 3% event rate in those without a thallium redistribution defect. In more than 50% of cases, the dipyridamole thallium stress test did not add incremental information to the preoperative assessment after clinical variables were evaluated.

One study by Lette (67) has challenged the findings of Eagle (12). Clinical criteria were not found to be useful in estimating postoperative risk. Using 18 clinical parameters and several scoring systems, including Eagle's clinical criteria, clinical parameters were not predictors of postoperative events. The dipyridamole thallium scan results were the only predictors of events. Patients without thallium evidence of ischemia or with only a fixed defect had no adverse cardiac outcomes. Some studies have also found that dipyridamole thallium scans with an increased number and size of redistribution defects, presence of left ventricular dilatation after stress, or pulmonary radiotracer uptake are predictive of a higher postoperative cardiac risk (54,67,70,74).

The accuracy of dipyridamole-thallium in the preoperative evaluation of patients before noncardiac surgery has been challenged by more recent trials (75–78). In one study, intraoperative myocardial ischemia was assessed using continuous ECG monitoring and transesophageal echocardiography in patients undergoing vascular surgery (75). All had dipyridamole thallium scintigraphy preoperatively and all treating physicians were blinded to the results. There was a 5% incidence of adverse postoperative cardiac outcomes, with

no association between redistribution defects and adverse cardiac outcomes. The sensitivity and specificity of thallium scintigraphy for all adverse outcomes were low (40 to 54% and 65 to 71%, respectively). The positive predictive value was low 27 to 47%, and the negative predictive value relatively high 61 to 82%. It was proposed that routine use of dipyridamole thallium scans for preoperative screening of patients before vascular surgery may not be warranted. A study by Baron (76) confirmed these findings.

There are few studies that evaluate the long-term postoperative outcomes of patients with abnormal dipyridamole thallium scans. In one such study (53), an abnormal dipyridamole thallium scan was associated with a significantly increased risk of cardiac death in the perioperative period (7%) and in late follow-up (17%) in comparison to those with a normal scan. A reversible defect was the only predictor of death or myocardial infarction during late follow-up and was associated with a twofold greater risk of a cardiac event than if the defect was fixed. The number of perfusion defects, a history of angina, and the presence of chest pain during the dipyridamole study were independent predictors of perioperative cardiac events. Fleisher et al. utilized criteria from the TIMI-IIIB trials for quantification of dipyridamole thallium results (35). They reported a significantly increased long-term risk only in the subset of patients with high-risk thallium markers, including increased lung uptake and multiple segments of reversible defects.

Newer Myocardial Perfusion Tracers

Initial data using technetium 99m sestamibi, a newer myocardial perfusion tracer, indicates that it has the same diagnostic accuracy as thallium 201 for the detection of myocardial ischemia (79). Further studies will be necessary before it is known if this tracer provides equivalent prognostic information in the preoperative evaluation of patients before noncardiac surgery as other stress testing modalities. The ACC/AHA guidelines on indications for stress testing with myocardial perfusion imaging have recommendations for use of this testing modality in the general population and there are no additional recommendations specifically for patients undergoing noncardiac surgery (63).

Recently, the ACC/AHA Task Force algorithm for perioperative cardiovascular risk stratification before noncardiac surgery was applied to high-risk patients before major vascular surgery (80). An evaluation of functional status was also incorporated and patients were stratified according to predicted cardiac risk. Higher risk patients were randomized to dipyridamole thallium scintigraphy. Overall mortality was 3.5%, while cardiac mortality was 1%. There was no significant difference in cardiac morbidity between groups and no single independent predictor of morbidity. This algorithm for high-risk patients demonstrated an excellent clinical outcome and proved to be a safe and economical strategy.

Dobutamine Stress Echocardiography

Dobutamine stress echocardiography involves the identification of new or worsening myocardial wall motion abnormalities using two-dimensional echocardiography during infusion of intravenous dobutamine, and has been shown to have the same accuracy as dipyridamole thallium scintigraphy for the detection of coronary artery disease (62, 81–83). More recently, this stress-testing modality has been found to be useful for the assessment of preoperative cardiac risk in patients undergoing noncardiac surgery (9,60,84,85). The estimated low positive predictive values of 17 to 43% and high negative predictive values of 93 to 100% are similar to those for dipyridamole

thallium (36,49,51,60,62,75,86). There are several advantages to dobutamine stress echocardiography compared to dipyridamole thallium scintigraphy. The dobutamine stress echocardiography study can also assess left ventricular function and valvular abnormalities. The cost of the procedure is significantly lower (60,62), there is no radiation exposure, the duration of the study is significantly shorter, and results are immediately available.

Several studies have assessed the value of dobutamine stress echocardiography in preoperative risk assessment. In one of the first studies, postoperative cardiac events were noted in 21% of patients undergoing noncardiac surgery who had evidence of preoperative dobutamine stress-induced myocardial ischemia, while no patient had a cardiac event if ischemia was not induced (52). Other authors have reported similar findings (61,62,87). The results of dobutamine stress echocardiography add significantly to the clinical risk assessment of patients undergoing major vascular surgery (62), particularly in patients with intermediate clinical risk (87). As with other forms of preoperative risk assessment, however, dobutamine stress echocardiography has a relatively low positive predictive value (61), and many patients with abnormal test results do not have postoperative cardiac events.

Presently, there are few studies that evaluate long-term outcomes after noncardiac surgery in patients with abnormal preoperative dobutamine stress echocardiograms. In one study, patients were followed for up to 2 years (60). Of patients with a negative dobutamine stress echocardiogram, there were two cardiac events (3%). Of patients with a positive dobutamine stress echocardiogram, 68% subsequently underwent coronary revascularization before the noncardiac surgery was performed and there were no perioperative events in this group. Of the patients with a positive dobutamine stress echocardiogram who did not have coronary revascularization, 40% had perioperative adverse cardiac outcomes. Long-term complications were noted in 3% with a negative dobutamine stress echocardiogram, and in 15% with a positive study. Dobutamine stress echocardiography was found to be safe and predicted perioperative and long-term outcome in patients undergoing major vascular surgery, with a high negative predictive value.

In a second study, patients undergoing major vascular surgery were evaluated by clinical parameters and results of dobutamine stress echocardiography and followed for an average of 19 months postoperatively (88). The presence of extensive dobutamine-induced wall motion abnormalities and a previous history of myocardial infarction independently predicted late cardiac events, increasing risk up to sixfold. These findings may support the need for more intensive perioperative management in this population.

A meta-analysis of 15 studies to compare dipyridamole-thallium and dobutamine echocardiography for risk stratification before vascular surgery in intermediate-risk patients found that the prognostic value of both techniques is comparable but that the accuracy varies with coronary artery disease prevalence (86).

CORONARY ANGIOGRAPHY AND REVASCULARIZATION BEFORE NONCARDIAC SURGERY

Coronary Angiography

Modification of perioperative care based upon the preoperative evaluation can take the form of coronary revascularization, changes in anesthetic technique, utilization of expen-

sive resources such as intensive care units, and of aggressive treatment of hemodynamic fluctuations (89). Historically, the use of coronary angiography as a screening procedure before elective peripheral vascular surgical procedures was advocated (10) due to the high perioperative mortality associated with a high prevalence of asymptomatic coronary artery disease (30–50%) (53). Many argue that using coronary angiography as a preoperative screening tool is too costly and places patients at further risk due to the cumulative risks of these procedures, especially in the elderly with higher risks from comorbid diseases. This has led to increased interest in preoperative noninvasive stress testing to assist in risk stratifying patients before elective surgery (90). It is generally assumed that coronary angiography should be performed preoperatively in patients with evidence of ischemia on stress testing (49,51,53) although there are no published randomized trials to support this approach. These trials would require large sample sizes and would include multiple potential confounders.

The present indications for use of coronary angiography in the preoperative evaluation before noncardiac surgery are adapted from the ACC/AHA guidelines for coronary angiography for the general population. There is general agreement that performance of coronary angiography should be considered in patients with unstable symptoms of angina pectoris, with high-risk or equivocal preoperative noninvasive stress-test results, or patients with high-risk clinical parameters who are undergoing a high-risk noncardiac surgical procedure. It is generally agreed that performance of coronary angiography is not indicated in patients with low-risk results on preoperative noninvasive testing, in those who are asymptomatic up to 5 years after prior coronary revascularization if they exhibit excellent exercise capacity $>$ 7 METs, or for screening for coronary artery disease without a prior noninvasive test.

Percutaneous Transluminal Coronary Angioplasty

The benefit of percutaneous transluminal coronary angioplasty (PTCA) before noncardiac surgery to reduce the incidence of perioperative cardiac events has not been studied in a prospective randomized fashion. In a small, retrospective study of patients who underwent PTCA prior to noncardiac surgery, 10% required urgent coronary artery bypass grafting (CABG) (91). Successful preoperative PTCA in high-risk patients was shown to be associated with a low perioperative cardiac risk during noncardiac surgery.

In a large 10-year study of patients who underwent PTCA and/or CABG prior to elective abdominal aortic aneurysm surgery from 1980–1990, there were no perioperative deaths in patients with prior coronary revascularization compared to a 2.9% perioperative mortality within 1 year for the group as a whole (92). Of note, the trend to perform coronary revascularization preoperatively increased as the decade progressed. CABG did delay time to noncardiac surgery but this was not significant. Three-year survival was the same with either revascularization procedure (92% PTCA vs. 83% CABG), although patients with PTCA had a significantly higher number of late events at 3 years (56.5% vs. 27.3%). This study may suggest that in a select group of patients undergoing specific noncardiac procedures that preoperative coronary revascularization may improve perioperative outcomes.

The risk of significant complications during PTCA limits its generalized use, especially in elderly population (91–93). Indications for the use of PTCA in the preoperative

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setting before noncardiac surgery are similar to the 1993 ACC/AHA guidelines for the use of PTCA in the general population. Current evidence does not support the use of PTCA beyond established indications for nonoperative patients, especially in the elderly population, where the risk associated with coronary revascularization are increased compared to younger patients.

Coronary Artery Bypass Surgery

Studies have shown that the preoperative presence of coronary artery disease significantly increases the risk for a perioperative cardiac event after noncardiac surgery (94–97), although there are no randomized trials to assess whether preoperative CABG lowers this risk (98). Some evidence exists that preoperative revascularization may decrease postoperative cardiac risk two- to fourfold in patients undergoing elective vascular surgery (99–101). In one study (10), CABG was performed in patients before noncardiac surgery. The overall surgical mortality for the noncardiac procedures was 3.4%, but only .08% in those patients who underwent prior revascularization. The risk of adverse cardiac outcomes after noncardiac surgery in these patients may be reduced with CABG, but with the added risk of the CABG procedure itself (5.2% mortality). Many patients referred for noncardiac surgeries, and especially vascular surgery, are elderly with comorbid conditions, and it is in these patients where the risks of CABG itself are significant (10,102). Several studies suggest that preoperative CABG can reduce postoperative risk if the patient is felt to be at low risk for the CABG itself (10,103–108).

In a subset of patients in the Coronary Artery Surgery Study (CASS) Registry enrolled from 1978 to 1981, the influence of CABG on perioperative cardiac risks prior to noncardiac surgery was studied (108). The operative mortality for patients with CABG prior to noncardiac surgery was 0.9%, but was significantly higher (2.4%) in patients without prior CABG. However, there was a 1.4% mortality rate associated with the CABG procedure itself (98).

Few data support the use of CABG solely to improve perioperative outcomes in patients undergoing noncardiac surgery. The indications for CABG are based on ACC/AHA Task Force guidelines of indications for CABG for the general population. Indications include patients with significant left main stenosis ($>50\%$), three-vessel coronary artery disease with left ventricular dysfunction, two-vessel disease with severe proximal left anterior descending artery disease and intractable ischemia after maximal medical therapy. Timing of CABG prior to noncardiac surgery is an individualized decision and there are no prospective, randomized data to suggest the optimal strategy.

Risks vs. Benefits of Coronary Revascularization

An alternative approach to determining the optimal strategy for medical care in the absence of clinical trials is construction of a decision analysis. Two decision analyses have been published on the issue of cardiovascular testing before major vascular surgery (101,109) (Fig. 3). Both assumed that patients with significant coronary artery disease would undergo CABG prior to noncardiac surgery. Both models found that the optimal decision was sensitive to local morbidity and mortality rates within the clinically observed range (Fig. 4). These models suggest that preoperative testing for the purpose of coronary

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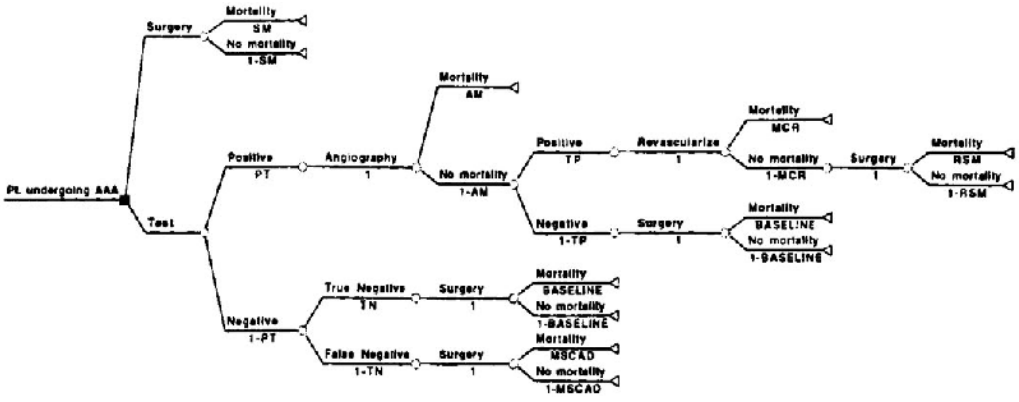

Figure 3 A decision algorithm evaluating the decision between vascular surgery alone or coronary artery revascularization before vascular surgery. There are currently no randomized trials to address the optimal strategy. By outlining the multiple decision points at which a patient can sustain mortality by choosing to undergo coronary revascularization first, the optimal strategy for preoperative evaluation can be demonstrated. Specifically, variation in mortalities at each decision point can change the optimal strategy. (Reproduced, with permission, from Ref. 109.)

revascularization is not the optimal strategy if perioperative morbidity and mortality are low.

Importantly, the primary cost both in dollars and morbidity of preoperative testing and revascularization is the revascularization procedure itself. Therefore, the indications for revascularization, and thus the frequency of its use, have a significant impact on the model. Second, potential long-term benefits of coronary revascularization in this population were not included in the analysis, potentially biasing against the revascularization arm. If long-term survival is included in the models, then coronary revascularization may lead to improved overall outcome and can be considered a cost-effective intervention. However, a patient's age should be included in the equation. For example, an 80-year-old diabetic patient with significant comorbid diseases may gain little additional life years and may actually have a decrease in the quality of their final years by undergoing coronary revascularization. In contrast, a 55-year-old man with an abdominal aortic aneurysm who is found to have occult left main disease would have a substantial increase in both the length and quality of his life from preoperative cardiovascular testing and coronary revascularization.

PERIOPERATIVE INTERVENTIONS TO REDUCE RISK

Intra-Aortic Balloon Counterpulsation

In patients with unstable angina or severe coronary artery disease, placement of an intraaortic balloon counterpulsation device has been used before induction of anesthesia in patients considered high-risk for noncardiac surgical procedures. In several small case series, perioperative morbidity and mortality was low (110).

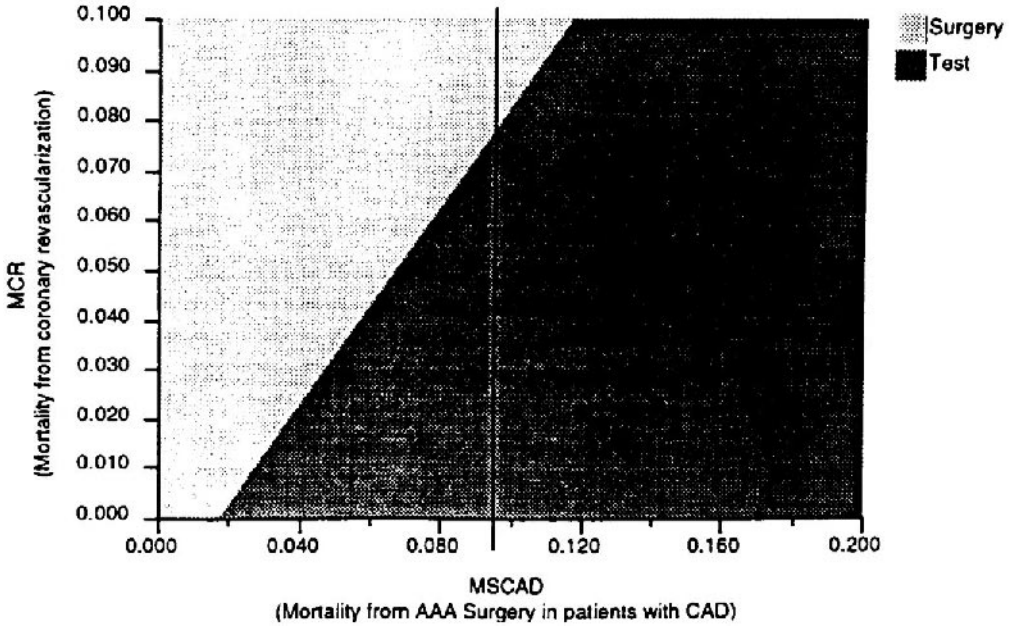

Figure 4 A two-way sensitivity analysis demonstrating the optimal preoperative strategy of surgery alone or coronary revascularization before vascular surgery. As the probability of mortality from coronary revascularization increases, vascular surgery alone becomes the preferred strategy. In contrast, as the probability of mortality from aortic surgery in patients with significant coronary artery disease increases, then coronary revascularization before vascular surgery is the optimal strategy. The average mortality for vascular surgery in patients with significant coronary artery disease is 9.5%, suggesting that the strategy with the lowest mortality is very sensitive to local morbidity and mortality of the procedure. However, if long-term mortality is included in the model, the coronary revascularization might prove to be more beneficial. (Reproduced, with permission, from Ref. 109.)

Management of Perioperative CHF

It is critical to optimize the medical management of CHF before an elective noncardiac surgical procedure. For systolic left ventricular dysfunction, this often involves the use of diuretics and angiotensin converting enzyme inhibitors. These medications can alter hemodynamic and metabolic parameters that may impact on perioperative cardiac risk so their use must be carefully monitored. Patients at risk for CHF postoperatively are those with a history of dysrhythmias and diabetes (3,108) and those undergoing prolonged surgical procedures. Patients who develop CHF postoperatively have a better long-term prognosis than those in whom a postoperative myocardial ischemic event occurs (47).

The 1996 ACC/AHA Task Force guidelines recommend that preoperative assessment of left ventricular systolic function prior to noncardiac surgery should be limited to patients with poorly controlled, decompensated CHF (9). In patients with a history of CHF and with dyspnea of unknown etiology, the indications are less clear. It should generally not be used in patients without prior CHF. This would limit the unnecessary cost of these tests in patient populations in which there is no known benefit gained from the information.

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Beta-Blockers

Several subsequent studies in the late 1970s indicated that beta-blocker therapy could be safely continued preoperatively, often resulting in a reduction in the incidence of myocardial ischemia (111). These studies, and the concern for beta-blocker withdrawal-induced tachycardia, hypertension, and myocardial ischemia (112,113) led to recommendations to continue beta-blocker therapy before surgery (114).

By decreasing adrenergic stimulation of the heart, beta-blockers have the potential to lower the incidence of perioperative tachycardia and reduce the incidence of perioperative arrhythmias and myocardial ischemia. In a study of unmedicated patients with mild-to-moderate hypertension undergoing general anesthesia, the use of a single, low-dose oral beta-blocker produced a thirteenfold reduction in the incidence of intraoperative myocardial ischemia by ECG (28). In patients not receiving beta-blocker therapy, ischemia was detected in 28%. All episodes were either during tracheal intubation or emergence from anesthesia. In those treated with beta-blocker therapy, only 2.2% had evidence of myocardial ischemia. Those who received beta-blockers more frequently had bradycardia, had a greater fall in mean arterial pressure during premedication, and had less of a pressor response during tracheal intubation and emergence from anesthesia. The prophylactic use of beta-blocker therapy has been studied in patients considered to be at high risk of postoperative cardiac complications and appears to be safe and effective (115).

Recently, the effect of the use of atenolol was examined in a randomized, placebo-controlled study of patients either with, or at risk for, coronary artery disease who were undergoing noncardiac surgery (69). The majority of these patients (66%) had a history of hypertension. Six died during the hospitalization, four in the atenolol group and two in the placebo group, three from noncardiac causes. Treatment with atenolol during the hospitalization was associated with a reduction in mortality and cardiac complications, which was noted for the 2-year follow-up period of the study. The effect was particularly prominent in the first 6 months postoperatively (69). Based on the findings of this trial, the American College of Physician guidelines advocates the perioperative use of atenolol in all high-risk patients (40).

In summary, beta-blockers should not be discontinued prior to noncardiac surgery. Although the relationship between preoperative beta-blocker use and perioperative myocardial ischemia is not clear, the perioperative use of beta-blockers appears to be well-tolerated and may lower the incidence of cardiac events in some high-risk patients.

Nitroglycerin

Continuous intravenous infusions of nitroglycerin, a venodilator, are most useful for the management of perioperative hypertension. The postoperative patient with congestive heart failure and/or ischemic heart disease may also benefit from its use. Nitroglycerin may also reduce preload and improve myocardial oxygen supply. Prolonged use should be avoided due to potential tachyphylaxis.

There have been multiple trials investigating the value of intra- and postoperative pharmacological agents in decreasing perioperative cardiac morbidity. Nitroglycerin has been a mainstay of anti-ischemic therapy, but its value during the perioperative period is controversial. Two randomized clinical trials have focused on high-risk noncardiac surgery patients. Coriat et al. studied a cohort of patients undergoing carotid endarterectomy using

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a high-dose narcotic technique (116). They demonstrated a significantly reduced incidence of myocardial ischemia with 1.0 μg/kg/min of nitroglycerin compared to 0.5 μg/kg/min; however, there were no patients who sustained a perioperative myocardial infarction. Dodds et al. compared nitroglycerin at 1.0 μg/kg/min to placebo using a balanced anesthetic technique in high-risk patients undergoing a diverse group of noncardiac surgeries and demonstrated no difference in perioperative myocardial ischemia or infarction (117). Many of the effects of nitroglycerin are mimicked by the anesthetic agents, minimizing nitroglycerin's potential beneficial effects and potentially leading to more profound hypotension. Therefore, the evidence does not support the routine prophylactic use of this agent.

Alpha-2 Agonists

Alpha-2 agonists have received a great deal of attention as adjuvants to the anesthetic management. Ellis et al. randomized high-risk noncardiac surgery patients to receive either clonidine vs. placebo and demonstrated a significantly decreased incidence of intraoperative, but not postoperative, ischemia (118). Stuhmeier et al. randomized 297 elective vascular surgery patients and demonstrated a significantly reduced incidence of perioperative myocardial ischemia with fewer nonfatal myocardial infarctions (119). Clonidine may be useful for the management of postoperative hypertension, since it is available for oral and transdermal use. Clonidine stimulates central α_2-receptors and thereby decreases sympathetic nervous outflow to the vasculature, producing vasodilation and lowering blood pressure (20). It is particularly appropriate for the patient taking clonidine preoperatively in order to avoid the clonidine withdrawal syndrome (120). Clonidine should not be used in patients with high-grade conduction disturbances (121).

Perioperative administration of mivazerol, a new intravenous alpha-2 agonist, was associated with a significantly reduced incidence of myocardial ischemia with no difference in cardiac events (122). A large-scale trial of mivazerol is currently being analyzed, the results of which should provide important data for management of high-risk patients.

Calcium Channel Antagonists

The calcium channel blockers may also be useful in the management of postoperative hypertension. These agents lower arterial blood pressure by reducing afterload but may produce reflex tachycardia; this is particularly true of the dihydropyridine compounds like nifedipine (123). Recently, the use of sublingual nifedipine capsules for the treatment of hypertensive emergencies has been questioned, since there have been numerous reports of drug-induced cerebrovascular ischemia and infarction, acute myocardial infarction, and death (124).

Perioperative Transvenous Pacemaker Use: General Comments

Over 460,000 individuals in the U.S. have permanent cardiac pacemakers, 85% of which are in the population over the age of 65 (125). It is important that the type of pacemaker implanted is known in order to guide perioperative management if issues arise. Major pacemaker manufactures provide technical support for particular devices, as does the cardiologist who implanted the device, if available. A conservative recommendation is that

a pacemaker be interrogated at least 2 months prior to an elective procedure. Indications for use of perioperative pacemakers and management of preexisting devices are generally based on expert opinion. No established evidence-based guidelines are available. In general, noncardiac surgery should be delayed for 48 h after permanent pacemaker implantation, if possible, to minimize the risk of acute dislodgement of the leads.

In general, perioperative pacemakers are indicated for high-grade conduction abnormalities and intraventricular conduction delays with associated symptoms. In cases where symptoms are not present and an intraventricular conduction delay is not present, easy access to temporary transvenous pacing equipment in the operating room is advised. As with all invasive procedures, the risk of pacemaker placement must be considered.

Electrocautery may interfere with pacemakers by causing oversensing in patients with unipolar and, rarely, bipolar systems. In this case, it is recommended that the electrocautery electrode be kept at least 4 to 6 in. away from the pacemaker to minimize electrical interference (126). A pacemaker could be programmed to a fixed-rate mode to avoid reprogramming problems. Preoperatively, in cases of emergent surgery or situations in which the pacemaker is not able to be interrogated, a magnet should be placed over the pacemaker and an ECG recorded to evaluate the back-up mode and function of the pacemaker. A programming device specific for the interrogation of the pacemaker being used should be available in the operating room when the potential for electrocautery interference is high, the use of defibrillation or cardioversion is expected, or when there has been a noted change in the function and pacing mode of the pacemaker. Pacing thresholds may be decreased due to hypoxia and myocardial ischemia and may be raised due to hyperkalemia and acid/base disturbances (126). Endocarditis prophylaxis for patients with permanent pacemakers before noncardiac surgery is not recommended in most cases (127).

Recommendations for temporary or permanent pacemaker implantation in patients undergoing noncardiac surgery are the same as those for elective pacemaker implantations for patients not undergoing surgical procedures.

Perioperative Management of Automatic Implantable Cardiac Defibrillators

Management of the automatic implantable cardiac defibrillator (AICD) in the perioperative setting is also based predominantly on expert opinion and no standards are available. It is advisable that the consultant knows the manufacturer of the device. In general, the device should be inactivated and appropriate resuscitation equipment should be available in the operating room. If the electrophysiologist who implanted the device is available, they could provide expert assistance. Also, the technical support provided by the major AICD manufacturers may provide specific recommendations. The AICD can be left in the inactivated mode until the patient is transferred to an unmonitored hospital bed. Endocarditis prophylaxis before noncardiac surgery for patients with an AICD is not generally recommended (127).

SPECIFIC MEDICAL CONDITIONS

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is not frequently encountered in the perioperative period. It is important to identify hypertrophic cardiomyopathy preoperatively, since there may

be increased risk of hemodynamic compromise in the perioperative period. These patients typically have marked degrees of left ventricular hypertrophy, reduced ventricular compliance, hyperdynamic left ventricular systolic function and systolic anterior motion of the mitral valve with or without a dynamic pressure gradient in the subaortic area.

There may be a family history of cardiomyopathy or of sudden, unexpected death at a young age. A history of cardiac symptoms should be carefully determined, especially chest pain, dyspnea, and syncope. The systolic murmur of hypertrophic cardiomyopathy is quite characteristic and dynamic auscultation during passive leg elevation or with the patient changing from the standing to the squatting position typically demonstrates a decrease in the intensity of the murmur (128). Two-dimensional and Doppler echocardiography are useful in these patients.

There is little published information available that defines the perioperative risk of patients with hypertrophic cardiomyopathy. Although based on limited evidence, it has been recommended that spinal anesthesia be avoided in patients with hypertrophic cardiomyopathy (129,130) because it can decrease systemic vascular resistance and increase venous capacitance.

As a result of the pathophysiology of hypertrophic cardiomyopathy, these patients are particularly susceptible to factors that alter left ventricular filling, such as diminished intravascular volume, alterations in systemic vascular resistance, and increases in heart rate. Special care should be taken to maintain adequate intravascular volume, minimize pain and anxiety, and avoid treatment with catecholamines (9). Intensive care unit monitoring may be useful postoperatively to limit periods of hypotension and avoid volume depletion, which may include pulmonary artery catheter monitoring, although the usefulness of these has not been established.

Diastolic Dysfunction

The hypertensive heart is characterized by concentric left ventricular hypertrophy, normal or above normal systolic function and diastolic dysfunction (131). In the elderly patient with marked concentric left ventricular hypertrophy and small end-systolic chamber sizes, diastolic dysfunction can lead to pulmonary congestion (132). This population may be particularly sensitive to factors that affect diastolic filling of the left ventricle, such as increased heart rate, atrial fibrillation, or volume depletion. Identifying chronically hypertensive patients with diastolic dysfunction with reliable echocardiography parameters (132–134) could guide optimal perioperative fluid and blood pressure management.

Echocardiography should be considered in the patient with chronic hypertension and a history of exertional or stress-induced dyspnea, particularly if there is evidence of left ventricular hypertrophy on the ECG. Exercise may produce a suboptimal increase or even a decrease in left ventricular ejection fraction in these individuals, apparently in some cases, due to impaired diastolic filling (135). The hemodynamic response to the stress of anesthesia and surgery might be expected to produce a similar response in these individuals.

Increased sympathetic nervous system activity, producing increases in blood pressure and heart rate, may occur as the patient emerges from anesthesia (136). This response may compromise diastolic filling so it is critical to assess volume status at this time. In certain patients, this may be extremely difficult without continuous invasive hemodynamic

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monitoring, especially in procedures involving large volume shifts. While a pulmonary artery catheter cannot be routinely recommended, it may provide important information (see section on use of pulmonary artery catheterization).

Valvular Heart Disease

Prevalence and Risk

Valvular heart disease is frequently encountered in patients undergoing surgical procedures. The prevalence of diagnosed valvular heart disease might be greater today due to the more widespread use of echocardiography. Mitral and aortic valvular disease is more likely to be associated with perioperative cardiac events. The 1996 ACC/AHA Task Force Guidelines indicate that severe valvular disease is a major clinical predictor of increased perioperative cardiovascular risk (9). A very early study of only 23 patients (3,19) considered severe aortic stenosis, defined by physical examination criteria and by other supportive data when available, to be the most significant valvular lesion (9,3). A later study (137), in which all patients underwent echocardiography, showed that selected patients with moderate-to-severe aortic stenosis can undergo noncardiac surgical procedures at a relatively low risk. Patients with mitral regurgitation, mitral stenosis, or aortic regurgitation may have an increased risk of developing new or worsening heart failure (19), but do not appear to have an increased risk of perioperative cardiac mortality.

Mitral Stenosis

The major issues of concern in the patient with mitral stenosis undergoing noncardiac surgery are: (1) maintaining hemodynamic stability; (2) decreasing the incidence of perioperative arrhythmia such as atrial fibrillation; and (3) prevention of infective endocarditis.

Increases in heart rate reduce left ventricular filling across the stenotic mitral valve and increase the transmitral pressure gradient (138). Patients can become symptomatic with activities associated with tachycardia and similarly during the perioperative period, when tachycardias are common due to many mechanisms. Beta-blockers may be used to reduce heart rate in an attempt to maximize hemodynamic conditions. Antiarrhythmic agents may be considered to prevent the development of atrial fibrillation in patients in whom this arrhythmia is particularly likely, such as those who have frequent premature atrial contractions. Unrecognized mitral stenosis must be included in the differential diagnosis of the patient who abruptly develops pulmonary edema in the perioperative period.

Mitral Regurgitation

Mitral regurgitation is more common than mitral stenosis and has many causes. When the regurgitation is severe, left ventricular function is often reduced, left atrial and pulmonary vascular pressures are elevated, and atrial fibrillation may be present. Mitral regurgitation is less likely to cause abrupt clinical deterioration in the perioperative period, unless there are associated valvular lesions (e.g., aortic stenosis or left ventricular dysfunction). In the Goldman series (19), mitral regurgitation was a significant univariant correlate of perioperative cardiac morbidity and postoperative cardiac mortality, but the predictive value did not persist after controlling for other criteria of heart disease in a multivariate analysis.

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Patients with significant mitral regurgitation or mitral valve prolapse with regurgitation should receive antibiotic prophylaxis against infective endocarditis for certain surgical procedures.

Aortic Stenosis

The patient with suspected aortic stenosis merits further evaluation prior to surgery, since those with severe aortic stenosis are considered to be at high risk for noncardiac surgery (9,3,19). Aortic stenosis is more common in men, is a condition of the elderly in particular, and usually results from degenerative calcific aortic disease or calcification of a congenitally bicuspid valve (139). Although cardiac output may increase normally with exercise in asymptomatic patients with aortic stenosis, stroke volume may decrease slightly (140). Thus, a normal hemodynamic response to exercise or to the stress of the perioperative period may be critically dependent on an increase in heart rate. In symptomatic and more severe aortic stenosis, the cardiac output may not increase normally with increasing metabolic demand. Typically, patients with moderate-to-severe valvular aortic stenosis develop concentric left ventricular hypertrophy and may, therefore, develop diastolic left ventricular dysfunction.

Asymptomatic patients with significant aortic stenosis may also be considered for valve replacement prior to noncardiac surgery (141) unless this is not feasible such as with urgent noncardiac surgical procedures or in patients considered to be at unacceptably high risk. The 1996 ACC/AHA Guidelines recommend that elective noncardiac surgery be postponed or canceled until aortic valve replacement is performed in patients with severe, symptomatic aortic stenosis (9). A more recent report (137) indicates that selected patients with aortic stenosis, even when severe, may be able to safely undergo noncardiac surgery. This may be due to more meticulous perioperative monitoring and care.

Aortic stenosis is most commonly a disease of older individuals and cardiac stress testing may be indicated prior to noncardiac surgery. It may be difficult to distinguish whether a patient's chest pain or dyspnea is due to significant valvular aortic stenosis or to myocardial ischemia. The safety of performing exercise stress testing in patients with aortic stenosis has been questioned since exercise-induced cardiac events, particularly effort syncope, have been described (142). The ACP/ACC/AHA Task Force Statement on exercise testing (63) lists severe aortic stenosis as a general contraindication to exercise testing. Nevertheless, some studies have indicated that patients with varying degrees of valvular aortic stenosis may safely undergo treadmill stress testing (140,143–145). Although based on a study of a small number of patients (146), adenosine myocardial perfusion imaging with nuclear scintigraphy can be safely performed in patients with moderate-to-severe aortic stenosis as an alternative to treadmill exercise testing. Dobutamine echocardiography has been safely performed in patients with severe aortic stenosis even without invasive hemodynamic monitoring (147) and may be another alternative to treadmill exercise.

Patients with moderate-to-severe aortic stenosis may also benefit from close postoperative hemodynamic monitoring in an intensive care unit to limit periods of hypotension and avoid volume depletion. Also, in asymptomatic patients with mild aortic stenosis, general anesthesia may be preferable to spinal anesthesia, since the hemodynamic effects of spinal anesthesia (hypotension and tachycardia) may be undesirable (141).

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Aortic Regurgitation

Patients with chronic aortic regurgitation may have marked degrees of left ventricular hypertrophy and dilatation and eventually develop systolic dysfunction. As is true of patients with mitral regurgitation, those with isolated chronic aortic regurgitation typically do not deteriorate abruptly in the perioperative period. Again, these patients require infective endocarditis prophylaxis for certain surgical procedures.

Preoperative Angiography in the Patient with Valvular Disease

The ACC/AHA Guidelines for Coronary Angiography list coronary angiography as a Class I recommendation when valve surgery is being considered in adult patients with chest discomfort, ECG changes, or both, suggesting the presence of coronary artery disease or in men >35 years old or in postmenopausal women.

Balloon Valvuloplasty Prior to Noncardiac Surgery

While the long-term outcome of patients who undergo aortic balloon valvuloplasty is generally poor (148,149), due primarily to restenosis (150), this procedure may be used for palliation prior to noncardiac surgery (151). Balloon aortic valvuloplasty results in improvement in the severity of aortic stenosis in the majority of patients (148,149), although the procedure is not without risk. Fatal cardiac arrest complicating the procedure has been reported in approximately 3% (150), but the procedural mortality may be even higher. In a report of 492 patients who underwent balloon aortic valvuloplasty, 4.9% died within the first 24 h after the procedure and 7.5% died during the hospitalization (152). Acute catastrophic complications, including ventricular perforation, acute severe aortic regurgitation, cerebrovascular accident, and limb amputation have been reported in approximately 6% of patients (153). The considerable procedure-related morbidity and mortality risk must be carefully considered before recommending this to lower the risk of noncardiac surgery. In a study of 55 elderly patients who underwent balloon aortic valvuloplasty for severe aortic stenosis, Doppler echocardiography showed that while the aortic valve mean gradient decreased significantly after the procedure from 48 to 33 mmHg, it had increased again to 46 mmHg approximately 6 months later (149).

In contrast to aortic valvuloplasty, mitral valve balloon valvuloplasty is often a reasonable alternative to mitral valve surgery. Results have been favorable, especially in younger patients with mitral stenosis but without severe mitral valve leaflet thickening or significant subvalvular fibrosis and calcification (154,155).

PROSTHETIC HEART VALVES

More than 60,000 cardiac valve replacements are performed each year in the U.S. (156). Issues important in the perioperative period include the management of chronic anticoagulation therapy, reducing the risk of infective endocarditis, preventing valve thrombosis, and ruling out significant valve-related hemolysis.

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There are two major types of mechanical prosthetic heart valves, the caged-ball and the tilting-disk valves. The St. Jude valve, a type of tilting-disk valve, is the most commonly used prosthetic valve in the world (157). While mechanical prosthetic valves have greater durability than bioprosthetic valves, they are more thrombogenic. The risk of valve thrombosis is greatest in patients with caged-ball prosthetic valves (Starr-Edwards) single-tilting-disk prosthetic valves (Bjork-Shiley, Medtronic-Hall, and Omnicarbon) have an intermediate risk of valve thrombosis, and bileaflet tilting-disk prostheses (St. Jude, Carbomedics, Edwards Duromedics) pose the lowest risk of the mechanical prosthetic valves (156). The possibility of prosthetic valve dysfunction may be suggested by new cardiac symptoms and abnormal auscultatory findings on physical examination. The valve may be evaluated with cinefluoroscopy for mechanical prosthetic valves or echocardiography; cardiac catheterization may be warranted in some situations (156).

Perioperative Anticoagulation of Prosthetic Valves

The management of chronic warfarin anticoagulation in the perioperative period is of major importance in patients with mechanical prosthetic heart valves. The risk of temporarily discontinuing anticoagulation must be weighed against the benefit of a reduced risk of perioperative bleeding for all patients on chronic anticoagulation, especially those with prosthetic heart valves. In general, the incidence of thromboembolism in patients with valvular heart disease depends on the valve involved, the presence and type of prosthetic heart valve, the existence of concomitant heart disease, the presence of left atrial enlargement, and whether atrial fibrillation is present (158).

For most elective noncardiac surgical procedures in which blood loss is anticipated to be significant, it is generally recommended that patients maintained on warfarin anticoagulation have this therapy stopped 3 to 5 days before surgery (156). Some have recommended briefly reducing the level of warfarin anticoagulation to the low therapeutic or subtherapeutic range for minimally invasive surgical procedures (159) and then resuming the usual warfarin dose after the procedure. This recommendation can only be made with information about the usual risk of bleeding, and the potential for blood loss if the surgery does not go as planned.

The risk of thromboembolism varies by which heart valve is involved. Mechanical prosthetic mitral valves appear to pose a greater risk of thromboembolism than prosthetic aortic valves. Caged-ball valves are more thrombogenic than tilting-disk valves (156). Those patients with the greatest risk of thromboembolism should be therapeutically anticoagulated with intravenous heparin during the 3 to 5 preoperative days in which warfarin is discontinued (160) and the heparin infusion should be continued until several hours before surgery (156,160). Subcutaneous heparin may be used both during and soon after the operation (158). Warfarin should be restarted as soon as possible following surgery and intravenous heparin should be resumed and continued until oral anticoagulation is in the therapeutic range.

INTRAOPERATIVE MANAGEMENT

Choices of Anesthetic Agents

There are many different approaches to the anesthetic care of the patient with CAD. The specific choice of anesthetic technique and intraoperative monitors depends upon the inte-

gration of patient and surgery-specific factors, and is best left to the discretion of the anesthesiologist according to the American Heart Association/American College of Cardiology Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery (9). Importantly, in large-scale studies of unselected patients, patients' coexisting disease and surgical procedure were the most important determinants. Although important in univariate analysis, type of anesthesia was not an independent predictor of 30-day mortality in the multivariate analysis (161). Outcome studies specifically addressing anesthetic technique in high-risk patients will be discussed after a review of these agents' physiology and pharmacology.

There are three classes of anesthetics: general, regional, local/sedation and monitored anesthetic care (MAC). General anesthesia can best be defined as a state including unconsciousness, amnesia, analgesia, immobility, and attenuation of autonomic responses to noxious stimulation. General anesthesia can be achieved with inhalational agents, intravenous agents, or a combination (frequently termed a balanced technique). Additionally, general anesthesia can be achieved with or without an endotracheal tube. Laryngoscopy and intubation were traditionally thought to be the time of greatest stress and risk for myocardial ischemia, but recent studies suggest that extubation is the time of greatest risk (162). Alternative methods of delivering general anesthesia is via a mask or a laryngeal mask airway, which is a newer device that fits above the epiglottis and does not require laryngoscopy or intubation. The laryngeal mask airway is extremely popular for shorter cases that do not require muscle relaxation.

There are five currently approved inhalational anesthetic agents in the U.S. in addition to nitrous oxide. All have advantages and disadvantages, which differ among the various agents (Table 8). All inhalational agents have reversible myocardial depressant effects and decrease myocardial oxygen demand. The degree to which they depress cardiac output is a function of their concentration, effects on systemic vascular resistance, and effects on baroreceptor responsiveness.

Halothane is the inhalation agent that has been in clinical use the longest of the currently available ones. It has both negative inotropic and chronotropic effects, and causes a small decrease in systemic vascular resistance. Halothane is rarely used in adult patients today because of its slow onset and offset as well as its association with hepatitis. Enflurane and isoflurane are stereoisomers. Both demonstrate negative inotropic effects, but enflurane moderately decreases systemic vascular resistance and depresses the baroreceptor function. In contrast, isoflurane is a more potent vascular smooth muscle dilator and has minimal effects on baroreceptor function. Two newer inhalation agents have recently been approved for clinical use, both of which are associated with a faster onset and offset of action. Desflurane has the fastest onset and is commonly used in the outpatient setting. Sevoflurane is the newest approved agent for use in the U.S. Its onset and offset of action are intermediate to that of isoflurane and desflurane. Its major advantage is that it is extremely pleasant smelling and therefore is frequently used as the agent of choice in children.

There have been several issues regarding the safety of the inhalational agents in patients with coronary artery disease. Isoflurane, because of its vasodilating properties, has been shown to cause a coronary artery steal phenomenon leading to myocardial ischemia in an animal model (163). There are also several case reports of myocardial ischemia associated with isoflurane. This led to an editorial suggesting that isoflurane should not be used in patients with coronary artery disease (164). However, several large-scale randomized

Table 8 Clinical Qualities of Inhaled Anesthetics

Agent	Advantages	Disadvantages
Nitrous oxide	Rapid uptake and elimination	Supports combustion
	Minimal respiratory depression	Expansion of closed air spaces
	Minimal circulatory depression	Inactivates vitamin B_{12}
	Odorless, nonpungent	Lack of anesthetic potency
Halothane	Potent anesthetic	Requires preservatives
	Nonpungent	Slow uptake and elimination
	Stable heart rate	Undergoes biotransformation
		Idiosyncratic hepatic necrosis
		Sensitization to catecholamine-induced cardiac dysrhythmias
Enflurane	Stable heart rate	EEG seizure activity
	Skeletal muscle relaxation	Depression of myocardial contractility
Isoflurane	Decreases cerebral metabolic rate	Tachycardia at greater concentration
	Cardiac output maintained	
Desflurane	Rapid uptake and elimination	Airway irritation
		Tachycardia with rapid increase in inspired concentration
		Requires specialized vaporizer for administration
		Expensive unless low flows are used
Sevoflurane	Rapid uptake and elimination	Reacts with CO_2 absorbents
	Nonpungent	Inorganic fluoride release
	Less depression of myocardial contractility	Expensive unless low flows are used
	Stable heart rate	

and nonrandomized studies of the inhalational agents in patients undergoing coronary artery bypass grafting have not demonstrated any increased incidence of myocardial ischemia or infarction in patients receiving isoflurane compared to other inhalation agents or narcotic-based techniques (165,166). In a subsequent analysis of one of the randomized trials, those patients who demonstrated steal-prone anatomy on coronary angiography did not have a higher incidence of myocardial ischemia (167). Based upon the accumulated data from human studies, most anesthesiologists do not believe that coronary steal presents a major threat of using isoflurane and it has become the most widely used anesthetic, including for those patients with coronary artery disease.

There are theoretical concerns regarding the safety of desflurane. Desflurane has been shown to be associated with airway irritability and leading to tachycardia in volunteer studies (168). In a large-scale study comparing a narcotic-based anesthetic to a desflurane-based anesthetic, the desflurane group had a significantly higher incidence of myocardial ischemia, although no difference in myocardial infarction rate (169). By including a narcotic with desflurane, this tachycardia can be ablated. Studies are ongoing to determine the safety profile of desflurane in patients undergoing major vascular surgery. Sevoflurane has been studied in one randomized trial compared to isoflurane and patients at high risk for cardiovascular disease. No differences in the incidence of myocardial ischemia were

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observed; however, the incidence of myocardial infarction was too low to detect any difference. Overall, there appears to be no one best inhalation anesthetic for patients with coronary artery disease.

High-dose narcotic techniques offer an advantage of hemodynamic stability and lack of myocardial depression. In the early 1980s, Lowenstein and colleagues proposed a high-dose narcotic technique for patients undergoing coronary artery bypass grafting (170). Narcotic-based anesthetics were frequently considered the ''cardiac anesthesia'' and advocated for use in all high-risk patients including those undergoing noncardiac surgery. The disadvantage of these traditional high-dose narcotic techniques is the requirement for postoperative ventilation. Recently, an ultrashort-acting narcotic (remifentanil) was introduced into clinical practice, negating the need for prolonged ventilation. It has been used in patients undergoing cardiac surgery and shown to facilitate early extubation.

Despite the theoretical advantages of a high-dose narcotic technique, in several large-scale trials in patients undergoing coronary artery bypass grafting, there was no difference in survival or major morbidity compared to the inhalation-based technique (165,166). This has in part led to the abandonment of high-dose narcotics in much of cardiac surgery and the trend toward early extubation. Most anesthesiologists use a ''balanced'' technique. This involves the administration of lower doses of narcotics with an inhalational agent. This allows the anesthesiologist to derive the benefits of each of these agents, while minimizing the side effects.

An alternative mode of delivering general anesthesia is with the intravenous agent, propofol. Propofol is an alkyl phenol that can be used for both induction and maintenance of general anesthesia. It can result in profound hypotension secondary to reduced arterial constriction with no change in heart rate. The major advantage of propofol is its rapid clearance with few residual effects on awakening; however, it is expensive and its use tends to be limited to short cases. Despite its hemodynamic effects, it has been used extensively to facilitate early extubation after coronary artery bypass surgery.

The current evidence supports the contention that there is no one best general anesthetic technique for patients with coronary disease undergoing noncardiac surygery and led to the abandonment of the concept of a ''cardiac anesthetic.''

Regional Anesthesia

Regional anesthesia includes the techniques of spinal and epidural, as well as peripheral, nerve blocks. Each technique has its advantages and risks. Peripheral techniques, such as brachial plexus or Bier blocks, offer the advantage of being associated with minimal or no hemodynamic effects. In contrast, spinal or epidural techniques are associated with sympathetic blockade, which can lead to reduction in blood pressure, reflex sympathetic activation above the level of the blockade, and slowing of heart rate if the cardioaccelerator fibers are blocked.

The primary difference between epidural and spinal anesthesia is the speed of onset of the anesthetic and the ability to provide continuous anesthesia or analgesia via placement of an epidural catheter. Although the speed of onset is dependent upon the local anesthetic agent used, spinal anesthesia, and its associated autonomic effects, occur sooner than the same agent administered epidurally. Since a catheter is usually left in place for epidural anesthesia, it can be more easily titrated. Epidural catheters can also be used postoperatively to provide analgesia, which will be discussed later in this chapter. Continuous catheters can be used with spinal anesthesia, but most anesthesiologists only use spinals as a single administration technique.

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There has been a great deal of research focused on comparing regional vs. general anesthesia for patients with coronary artery disease, particularly in patients undergoing infrainguinal bypass surgery. Yeager et al. demonstrated improved outcome in a combined regional and general anesthetic vs. general alone for a mixed population of intraabdominal and thoracic surgery; however, there were many flaws with this study, leading other investigators to design more rigorously controlled trials (171). Three major trials have been published involving patients undergoing infrainguinal surgery. Tuman et al. evaluated a combined general plus regional vs. general anesthesia alone and noted a decreased incidence of all-cause cardiac morbidity with no difference in acute myocardial infarction or cardiac death (172). Importantly, the group that included regional anesthesia demonstrated a decreased hypercoagulable state using thromboelastography compared to the general anesthesia group. Christopherson et al. randomized 100 patients to epidural plus epidural analgesia vs. general anesthesia plus postoperative intravenous patient-controlled analgesia (173). They noted no difference in cardiac morbidity, although the regional anesthesia group did demonstrate a significantly reduced incidence of graft thrombosis and reoperations. Bode et al. randomized such patients to epidural, spinal, and general anesthesia and found no difference in cardiac outcome or graft thrombosis (174). Importantly, those patients who had a failed regional technique had the highest incidence of cardiac morbidity. In an accompanying editorial, an informal meta-analysis suggests that no difference in cardiac morbidity could be detected between regional and general anesthesia unless the effect was extremely small (175). Baron et al. compared general anesthesia with regional plus general anesthesia for aortic surgery and was also unable to find a difference in cardiac morbidity (176).

Monitored anesthesia care encompasses local anesthesia administered by the surgeon both with or without sedation. In a large-scale epidemiological study, MAC was associated with increased 30-day mortality in a univariate analysis, although it did not remain significant in multivariate analysis (161). The major issue with MAC is the ability to adequately block the stress response, since inadequate analgesia associated with tachycardia may be worse than the potential hemodynamic effects of general or regional anesthesia. Although MAC can include supplemental analgesia, the ability to provide good local anesthesia is important. However, with the newer short-acting intravenous agents, essentially general anesthesia can be administered without an endotracheal tube. This can allow the anesthesiologist to provide intense anesthesia for short or peripheral procedures without the potential effects of endotracheal intubation and extubation.

INTRAOPERATIVE PULMONARY ARTERY CATHETERIZATION

The use of intraoperative pulmonary artery (PA) catheterization to optimize hemodynamics in patients with CHF has been assessed in only a few prospective randomized trials in patients undergoing vascular surgery (177,178) and remains controversial. Care must be exercised in the use of PA catheters due to the potential risk of complications such as pneumothorax, infection, and arrhythmias.

The value of pulmonary artery catheter monitoring has come under close scrutiny since an article by Connors and colleagues and an accompanying editorial in JAMA (179). Using a variation of a case-controlled design to match patients enrolled in a study of end-of-life decision in patients admitted to an intensive care unit with an anticipated 50%

mortality within 6 months, they demonstrated an increased mortality in those patients who received a PA catheter. This has led the National Institutes of Health and the Food and Drug Administration to convene a panel to plan several large-scale randomized trials. From a perioperative perspective, the patients in the Connors study are not those seen for elective surgery and the results may not be generalizable.

There are several randomized trials attempting to address issues of outcome in vascular surgery patients with respect to the use of a PA catheter. For patients undergoing aortic surgery, a PA catheter was not associated with improved outcomes compared to those patients who had a central venous pressure catheter if the ejection fraction was >50% in one small study or if the patient had a negative cardiovascular workup or prior coronary intervention in a second study (180,181). In contrast, Berlauk et al. randomized unselected patients undergoing infrainguinal bypass surgery patients to either (1) a PA catheter placed preoperatively with optimization of hemodynamics or (2) a PA catheter placed immediately prior to surgery or (3) only if indicated (177). Those patients who had a PA catheter placed had a lower incidence of postoperative graft thrombosis but no difference in major cardiac morbidity. In fact, two patients in the cohort who had preoperative PA catheter placement and hemodynamic optimization had a preoperative myocardial infarction.

In contrast, in a recent study, patients undergoing elective vascular surgery were randomized to have PA catheterization the day of major vascular surgery or if clinically indicated. There was no difference in intraoperative and postoperative complications, overall length of hospital or intensive care unit stay, or mortality between the groups (178).

Based upon a review of the available literature, the American Society of Anesthesiologists advocate reserving the PA catheter for those circumstances in which a high-risk patient is undergoing a high-risk surgery when the PA catheter will make a difference in management (182). For example, if there is a high probability of significant fluid shifts and the patient has signs of LV dysfunction, then the PA catheter may provide important therapeutic information.

Certain noncardiac surgical procedures are listed in the 1990 ACP/ACC/AHA Task Force statement on clinical competence in hemodynamic monitoring. The use of a PA catheter preoperatively may be recommended in patients with known cardiac disease in the following groups: (1) recent myocardial infarction < 6 months; (2) unstable angina; (3) refractory CHF; and (4) symptomatic valvular heart disease (183). In the postoperative setting, use of a PA catheter may be considered in the following groups of patients with known cardiac disease: (1) acute significant blood losses > 10 units and (2) early postoperative hypoxia.

CONDITIONS THAT MAY LEAD TO PERIOPERATIVE MYOCARDIAL ISCHEMIA

Hemodynamic Changes

Increases in heart rate cause increases in myocardial oxygen demand that can precipitate myocardial ischemia in patients with known coronary artery disease. Studies have supported a causal relationship between tachycardias and intraoperative myocardial ischemia (184). Both attenuation of the heart rate response and control of exaggerated sympathetic responses in the perioperative period may limit the development of cardiac ischemia and possible subsequent myocardial infarction. Increases in heart rate have a greater impact.

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Slogoff and Keats (26) studied 1023 patients undergoing coronary artery bypass surgery to determine the predictors of postoperative myocardial infarction. This population may be particularly useful in determining the relationship between hemodynamic instability and perioperative myocardial ischemia/infarction, since by definition all have significant, flow-limiting coronary artery disease. Not surprisingly, these authors found that the incidence of perioperative ischemia, detected by ischemic ST-segment depression on continuous electrocardiographic monitoring, was relatively high in this group of patients (36.9%). However, this study emphasized the relationship between tachycardia, but not hypertension or hypotension, and perioperative myocardial ischemia.

Anemia

Anemia has also been associated with an increased incidence of myocardial ischemia. In a small retrospective study of patients undergoing infrainguinal bypass surgery, hematocrit $< 27\%$ was associated with a significantly increased risk of postoperative myocardial infarction (185). Until definitive randomized trials are conducted to determine the value of transfusions for low hematocrit, it would seem prudent to maintain hematocrit $> 27\%$ for high-risk patients.

Hypothermia

Hypothermia has also been associated with an increased incidence of myocardial ischemia in vascular surgery patients (186). In a recent randomized trial involving patients either undergoing vascular surgery or with known risk factors for coronary artery disease, use of forced air warming to maintain normothermia was associated with a significant reduction in cardiac morbidity and myocardial ischemia for the first 24 h (187). Therefore, there is strong evidence that maintenance of normothermia should be a goal of intraoperative management.

MANAGEMENT OF PERIOPERATIVE ARRHYTHMIAS

The incidence of arrhythmias during noncardiac surgery varies from 0.9 to 70% (69). Atrial and ventricular arrhythmias are common and are usually benign in patients without known cardiac disease. In the presence of coronary artery disease or left ventricular dysfunction, arrhythmias increase perioperative cardiac risk (9). This is especially true in elderly patients in whom arrhythmias and conduction disturbances can be a marker of underlying cardiopulmonary disease. The prognostic importance of perioperative arrhythmias is not known since the incidence of arrhythmias from the preoperative period was not often studied (188). Also, very limited periods of preoperative ECG monitoring were performed in most studies so that it could not be determined whether perioperative arrhythmias were new or related to preexisting arrhythmias. The management of perioperative ventricular arrhythmias in patients undergoing noncardiac surgery is also not well studied and is generally considered to be that for the nonsurgical patient. Reversible causes such as electrolyte disturbances, acid-base abnormalities, or decompensated congestive heart failure should be corrected. A search for an underlying cardiac or pulmonary disease or potential drug toxicity is essential. Significant perioperative ventricular arrhythmias do not

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often require therapy unless they are associated with ongoing cardiac ischemia, significant valvular disease, left ventricular dysfunction, or hemodynamic compromise (9). Postoperative arrhythmias are often due to metabolic and sympathetic causes. Cardioversion is indicated in some cases. No studies support the suppression of preoperative arrhythmias with antiarrhythmics to reduce surgical morbidity and mortality. The use of perioperative beta-blockers may be beneficial (69).

The most recent and largest prospective study of perioperative ventricular arrhythmias in patients undergoing noncardiac surgery (189) showed that major ventricular arrhythmias (> 30 ventricular ectopic beats/h) or ventricular tachycardia, detected with the use of continuous ECG monitoring, occurred in 44% of patients and predominantly in the postoperative period. Most occurred without clinical symptoms. Patients with CHF, ECG evidence of myocardial infarction, or a history of tobacco use had a higher incidence of preoperative arrhythmias. The severity of preoperative arrhythmias increased in 10% of patients postoperatively. Nonfatal myocardial ischemia or cardiac death was not more frequent in those with perioperative arrhythmias. Therefore, these arrhythmias may not require aggressive perioperative therapy.

Postoperative Surveillance for a Perioperative Myocardial Infarction

The optimal and most cost-effective strategy for monitoring high-risk patients for major morbidity after noncardiac surgery is unknown. Myocardial ischemia and infarctions that occur postoperatively are usually silent, most likely due to the confounding effects of analgesics and surgical pain. Creatine kinase (CK)-MB have been found to be less specific for myocardial necrosis postoperatively, since it has been shown to be released during aortic surgery and after mesenteric ischemia (190). Further confounding the issue is that most perioperative myocardial infarction are non-Q-wave in nature, and nonspecific ST-T wave changes are common (191,192). Therefore, the diagnosis of a perioperative myocardial infarction is particularly difficult using these traditional tests. In one older study of diabetic and hypertensive patients, Charlson et al. determined the best combination of these three tests for detecting a perioperative event, and demonstrated a daily electrocardiogram plus symptom-directed CK-MB isoenzymes yielded the best sensitivity and specificity (193).

The sensitivity and specificity for detecting a perioperative myocardial infarction have recently been simplified by the use of troponin-T and I. Adams et al. studied 108 patients undergoing high-risk surgery and obtained measures of CK-MB, total CK, cardiac troponin I, daily electrocardiograms and pre- and postoperative echocardiograms (194). Eight vascular surgery patients sustained a perioperative myocardial infarction, as confirmed by the presence of new segmental-wall motion abnormalities. All eight patients had elevations of cardiac troponin I, while six patients had elevated CK-MB. Troponin I had a specificity of 99%, while CK-MB had a specificity of 81%. Lee et al. measured CK-MB and Troponin T levels in 1175 patients and created receiver-operating characteristic curves (195). They found that Troponin T had a significantly better correlation with major cardiac complications of an acute myocardial infarction. Metzler et al. examined the sensitivity of variable cut-off (0.6 ng/mL) and demonstrated a positive predictive value of 87.5% and a negative predictive value of 98% (196). Both Troponin I and T hold great promise as sensitive and specific markers of perioperative myocardial injury.

The implications of a perioperative myocardial infarction are controversial. Tradi-

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tionally, perioperative myocardial infarctions were associated with a 30 to 50% short-term mortality (6,197). With the improved sensitivity of the assays and perioperative surveillance protocols, asymptomatic myocardial infarctions are being detected. Recent series have reported the incidence of fatal perioperative myocardial infarctions to be less than 20% (48,191). Mangano et al. demonstrated significantly worse survival in those patients who have sustained a cardiac event compared to those who did not (198). Yeager et al. used a case-controlled method to retrospectively compare their cohort of patients who underwent major vascular surgery (199). Survival was significantly reduced for those patients who had symptomatic myocardial infarctions. In contrast, myocardial infarctions that were diagnosed by elevated CK-MB without cardiovascular signs of symptoms were not associated with worse survival when matched with patients who had similar degrees of coronary artery disease. Lopez-Jimenez et al. found that abnormal Troponin-T levels were associated with an increased incidence of cardiovascular complications within 6 months of surgery (200). Further research will be required to determine the implications of elevated postoperative cardiac enzymes or nonspecific electrocardiographic changes.

Postoperative Analgesia

There is recent interest in the value of postoperative analgesia regimens in reducing perioperative cardiac morbidity. If postoperative tachycardia and catecholamine surges are one of the etiologies of perioperative cardiac morbidity, then more intense analgesia regimens may reduce these changes. Additionally, there is growing interest in the role of postoperative analgesia in reducing the hypercoagulable state. Several studies comparing general with regional anesthesia have demonstrated reduced platelet aggregability in the epidural group (172,201). Future research will focus on how best to deliver postoperative analgesia to maximize the potential benefits and to reduce complications.

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33

Cardiovascular Drug Therapy in the Elderly

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Cardiovascular disease is the greatest cause of morbidity and mortality in the elderly, and cardiovascular drugs are among the most widely prescribed drugs in this population. Since many cardiovascular drugs have narrow therapeutic toxic ranges in the elderly, the incidence of adverse effects from using these drugs is also highest in the elderly. The appropriate use of cardiovascular drugs in the elderly requires knowledge of age-related physiological changes, the effects of concomitant diseases that alter the pharmacokinetic and pharmacodynamic effects of cardiovascular drugs, and drug–drug interactions.

PHARMACOKINETIC CONSIDERATIONS IN THE ELDERLY

Absorption

Age-related physiological changes that may affect absorption include reduced gastric secretion of acid, decreased gastric emptying rate, reduced splanchnic blood flow, and decreased mucosal absorptive surface area (Table 1). Despite these physiological changes, the oral absorption of cardiovascular drugs is not significantly affected by aging, probably because most drugs are absorbed passively (1).

Bioavailability

There are almost no data available for age-related changes in drug bioavailability for routes of administration other than the oral route. The bioavailability of cardiovascular drugs depends on the extent of drug absorption and on first-pass metabolism by the liver and the wall of the gastrointestinal (GI) tract. In the elderly, the bioavailability of drugs such

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Table 1 Physiological Changes with Aging Potentially Affecting Cardiovascular Drug Use

Process	Physiological change	Result	Drugs affected
Absorption	Reduced gastric acid production	Reduced tablet dissolution and decreased solubility of basic drugs	
	Reduced gastric emptying rate	Decreased absorption for acidic drugs	
	Reduced GI mobility, GI blood flow, absorptive surface	Less opportunity for drug absorption	
Distribution	Decreased total body mass. Increased proportion of body fat	Increased V_d of highly lipid-soluble drugs	↓ β blockers, central α agonists
	Decreased proportion of body water	Decreased V_d of hydrophilic drugs	↑ digoxin & ACE inhibitors
	Decreased plasma albumin, disease-related increased α_1-acid glycoprotein, altered relative tissue perfusion	Changed % of free drug, V_d, and measured levels of bound drugs	↑ disopyramide and warfarin, lidocaine, propranolol
Metabolism	Reduced liver mass, liver blood flow, and hepatic metabolic capacity	Accumulation of metabolized drugs	↑ propranolol, nitrates, lidocaine, diltiazem, warfarin, labetalol, verapamil, mexiletine
Excretion	Reduced glomerular filtration, renal tubular function, and renal blood flow	Accumulation of renally cleared drugs	digoxin, ACE inhibitors, antiarrhythmic drugs, atenolol, sotalol, nadolol

Source: Adapted from Ref. 1a.
GI = gastrointestinal; ACE = angiotensin converting enzyme.

as propranolol, verapamil, and labetalol is increased because of reduced first-pass hepatic extraction (2). However, the bioavailability of prazosin in the elderly is reduced (3).

Drug Distribution

With aging, there is a reduction in lean body mass (4) and in total body water (5), causing a decrease in volume of distribution of hydrophilic drugs. This leads to higher initial plasma concentrations of hydrophilic drugs such as digoxin and angiotensin converting enzyme inhibitors in the elderly (6). The increased proportion of body fat that occurs with aging also causes an increased volume of distribution of lipophilic drugs. This leads to lower initial plasma concentrations for lipophilic drugs such as most beta-blockers, antihypertensive drugs, and central alpha-agonists.

The level of alpha$_1$-acid glycoprotein increases in the elderly (7). Weak bases such as disopyramide, lidocaine, and propranolol bind to alpha$_1$-acid glycoprotein. This may cause a reduction in the free fraction of these drugs in the circulation, a decreased volume

of distribution, and a higher initial plasma concentration (8). In the elderly, there is also a reduction in plasma albumin concentration (9). Weak acids, such as salicylates and warfarin, bind extensively to albumin. Decreased binding of drugs such as warfarin to plasma albumin may result in increased free-drug concentrations, resulting in more intense drug effects (10).

Half-Life

The half-life of a drug (or of its major metabolite) is the length of time in hours that it takes for the serum level of that drug to decrease to one-half of its original serum level. This can be described by the kinetic equation: $t_{1/2} = 0.693 \cdot Vdt_{1/2}/Cl$, where $t_{1/2}$ is directly related to drug distribution and inversely to clearance. Therefore, changes in $Vdt_{1/2}$ and/or Cl due to aging, as previously mentioned, can affect the half-life of a drug. In elderly patients, an increased half-life of a drug means a longer time until steady-state conditions are achieved. With a prolonged half-life of a drug, there may be an initial delay in maximum effects of the drug and prolonged adverse effects. Table 2 lists the pharmacokinetic changes, routes of elimination, and dosage adjustment for common cardiovascular drugs used in the elderly.

Drug Metabolism

Decreased hepatic blood flow, liver mass, liver volume, and hepatic metabolic capacity occur in the elderly (11). There is a reduction in the rate of many drug oxidation reactions (phase 1) and little change in drug conjugation reactions (phase 2). These changes in the elderly may result in higher serum concentrations of cardiovascular drugs metabolized in the liver, including propranolol, lidocaine, labetalol, verapamil, diltiazem, nitrates, warfarin, and mexiletine.

Drug Excretion

With aging, there is a reduction in glomerular filtration, renal plasma flow, and the total number of functioning nephrons (12,13). Age-related decline in renal function is the single most important physiological change causing pharmacokinetic alterations in the elderly. Decreased renal function in the elderly may occur with a normal serum creatinine because creatinine production from skeletal muscle also decreases with aging. An estimate of creatinine clearance in the elderly may be made with the following equation (14): creatinine clearance (mL/min) = (140 − age) × body weight (kg) divided by 72 × serum creatinine (mg/dL). For women, this result would be multiplied by 0.85 to correct for the smaller body size.

The reduced clearance of many drugs primarily excreted by the kidneys causes their half-life to be increased in the elderly. Cardiovascular drugs that are excreted by the kidney include digoxin, diuretics, angiotensin converting enzyme (ACE) inhibitors (benazepril, captopril, enalapril, lisinopril, perindopril, quinapril, ramipril), antiarrhythmic drugs (disopyramide, flecainide, *N*-acetyl procainamide, quinidine, tocainide), and the beta-blockers (atenolol, bisoprolol, carteolol, nadolol, sotalol).

Table 2 Pharmacokinetic Changes, Route of Elimination, and Dosage Adjustment of Selected Cardiovascular Drugs in the Elderly

Drug	$T_{1/2}$	Vd	Cl	Primary (secondary) route of elimination	Dosage adjustment
Alpha 1-Selective Adrenergic Blockers					
Prazosin	↑	↑	NSC	Hepatic	Initiate at lowest dose
Terazosin	↑	—	—	Hepatic (renal/fecal)	Initiate at lowest dose
Doxazosin	↑	↑	↑*	Hepatic	Initiate at lowest dose
ACE Inhibitors					
Benazepril	↑	—	↓	Renal (biliary)	No adjustment needed
Captopril	NSC	—	↓	Hepatic/renal	Initiate at lowest dose
Enalapril	—	—	—	Renal (fecal)	Initiate at lowest dose
Fosinopril	—	—	—	Renal/biliary	No adjustment needed
Lisinopril	↑	NSC	↓	Renal	Initiate at lowest dose
Quinapril	—	—	—	Renal (fecal)	Initiate at lowest dose
Ramipril	—	—	—	Renal (fecal)	Initiate at lowest dose
Moexipril	—	—	—	Fecal (renal)	No adjustment needed
Trandolapril	—	—	—	Fecal (renal)	No adjustment needed
Angiotensin-II Receptor Antagonists					
Irbesartan	NSC	—	—	Hepatic/fecal (renal)	No adjustment needed
Losartan	—	—	—	Fecal/hepatic (renal)	No adjustment needed
Valsartan	↑	—	—	Fecal/hepatic (renal)	No adjustment needed
Antiarrhythmics					
Moricizine	—	—	—	Hepatic (biliary/renal)	Use lower dose
Quinidine	↑	NSC	↓	Hepatic (renal)	Use lower dose
Procainamide	—	—	↓	Renal	Use lower dose
Disopyramide	↑	—	↓	Renal (hepatic/biliary)	Use lower dose
Lidocaine	↑	↑	NSC	Hepatic (renal)	Use lower dose
Mexiletine	—	—	—	Hepatic (renal)	No adjustment needed
Tocainide	↑	—	↓	Hepatic/renal	Use lower dose
Flecainide	↑	↑	↓	Hepatic/renal	Use lower dose

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Propafenone	—	—	—	Hepatic (renal/fecal)	Use lower dose
Amiodarone	—	—	—	Hepatic/biliary	Use lower dose
Bretylium	—	—	—	Renal	Use lower dose
Ibutilide	—	—	—	Hepatic (renal/fecal)	No adjustment needed
Atropine	—	—	—	Hepatic/renal	Use adult dose with caution
Adenosine	—	—	—	Erythrocytes/vascular endothelial cells	No adjustment needed
Anticoagulants					
Heparin	—	—	—	Hepatic/reticuloendothelial system	Use adult dose with caution
Ardeparin	—	—	—	Renal	Use adult dose with caution
Enoxaparin	—	—	—	Renal	Use adult dose with caution
Danaparoid	NSC	NSC	NSC	Renal	No adjustment needed
Warfarin	NSC	NSC	NSC	Hepatic	Use lower dose
Antithrombotics					
Aspirin	—	—	↓	Hepatic/renal	Use adult dose with caution
Anagrelide	—	—	—	Hepatic (renal/fecal)	Use adult dose with caution
Dipyridamole	—	—	—	Hepatic/biliary	No adjustment needed
Ticlopidine	—	—	↓	Hepatic (renal/fecal)	No adjustment needed
β-Adrenergic Blockers: Nonselective					
Nadolol	NSC	—	—	Renal	Use lower dose
Propranolol	↑	NSC	↓	Hepatic	Use lower dose
Sotalol	—	—	—	Renal	Adjust to renal function
Timolol	—	—	—	Hepatic (renal)	Use lower dose
Beta 1-Selective					
Atenolol	↑	NSC	↓	Renal (hepatic)	Use lower dose
Betaxolol	—	—	—	Hepatic (renal)	Use lower dose
Bisoprolol	—	—	—	Hepatic/renal	Use lower dose
Esmolol	—	—	—	Erythrocytes	Use adult dose with caution
Metoprolol	NSC	NSC	NSC	Hepatic/renal	Use lower dose
With ISA: Nonselective					
Carteolol	—	—	—	Renal (hepatic)	Adjust to renal function
Penbutolol	—	—	—	Hepatic (renal)	Use adult dose with caution

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Table 2 Continued

Drug	$T_{1/2}$	Vd	Cl	Primary (secondary) route of elimination	Dosage adjustment
Pindolol	—	—	—	Hepatic/renal	Use lower dose
With ISA: Beta 1-Selective					
Acebutolol	↑	↓	—	Hepatic/biliary (renal)	Use lower dose
Dual Acting					
Carvedilol	—	—	—	Hepatic/biliary	No adjustment needed
Labetalol	—	—	NSC	Hepatic (renal)	No adjustment needed
Calcium Channel Blockers					
Verapamil	↑	NSC	↓	Hepatic (biliary/renal)	Initiate at lower dose
Amlodipine	↑	—	↓	Hepatic (renal)	Initiate at lower dose
Felodipine	—	NSC	↓	Hepatic	Initiate at lower dose
Isradipine	—	—	—	Hepatic	Initiate at lower dose
Nicardipine	NSC	—	—	Hepatic	No adjustment needed
Nifedipine	↑	NSC	↓	Hepatic	Initiate at lower dose
Nimodipine	—	—	—	Hepatic	Use adult dose with caution
Nisoldipine	—	—	—	Hepatic (biliary/renal)	Initiate at lower dose
Diltiazam	↑	NSC	↓	Hepatic	Use lower dose
Bepridil	—	—	—	Hepatic	No adjustment needed
Centrally Acting Anti-hypertensives					
Clonidine	—	—	—	Hepatic/renal	Initiate at lower dose
Guanabenz	—	—	—	Hepatic	Initiate at lower dose
Guanfacine	—	—	↓	Hepatic/renal	Adjustment not needed
Methyldopa	—	—	—	Hepatic/renal	Adjust to renal function
Neuronal and Ganglionic Blockers					
Guanadrel	—	—	—	Hepatic/renal	Initiate at lower dose

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Guanethidine	—	—	—	Hepatic/renal	Initiate at lower dose
Reserpine	—	—	—	Hepatic	Initiate at lower dose
Mecamylamine	—	—	—	Renal	Use lower dose
Diuretics Loop					
Bumetanide	—	NSC	↓	Renal (hepatic)	Use lower dose
Ethacrynic acid	—	—	—	Hepatic/renal	Use lower dose
Furosemide	↑	NSC	↓	Renal (hepatic/fecal)	Individualize dosage
Torsemide	—	—	—	Hepatic (renal)	Individualize dosage
Thiazide					
Chlorothiazide	—	—	—	Renal	Individualize dosage
Chlorthalidone	—	—	—	Renal (hepatic)	Use lower dose
Hydrochlorothiazide	—	—	↓	Renal	Use lower dose
Metolazone	—	—	—	Renal (biliary)	Individualize dosage
Potassium-Sparing					
Amiloride	—	—	↓	Renal/fecal	Initiate at lower dose
Spironolactone	—	—	—	Hepatic/biliary/renal	Initiate at lower dose
Triamterene	↑	—	—	Hepatic/renal	Use lower dose
Inotropic Agents					
Amrinone	—	—	—	Hepatic/renal	Individualize dosage
Milrinone	—	—	—	Renal	Adjust to renal function
Dopamine	—	—	—	Hepatic/renal/plasma	Individualize dosage
Dobutamine	—	—	—	Hepatic/tissue	Individualize dosage
Norepinephrine	—	—	—	Hepatic (renal)	Individualize dosage
Digoxin	↑	↓	↓	Renal (GI tract)	Use lower dose
Lipid-Lowering Agents					
Atorvastatin	↑	—	—	Hepatic/biliary	No adjustment needed
Cerivastatin	—	—	—	Hepatic/fecal (renal)	Adjust to renal function
Fluvastatin	—	—	—	Hepatic	No adjustment needed
Lovastatin	—	—	—	Hepatic/fecal (renal)	No adjustment needed
Pravastatin	—	—	—	Hepatic/fecal (renal)	Use lower dose
Simvastatin	—	—	—	Hepatic/fecal (renal)	Use lower dose
Nicotinic acid	—	—	—	Hepatic/renal	Initiate at lower dose

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Table 2 Continued

Drug	$T_{1/2}$	Vd	Cl	Primary (secondary) route of elimination	Dosage adjustment
Clofibrate	—	—	—	Hepatic/renal	Adjust to renal function
Cholestyramine	—	—	—	Not absorbed from GI tract	No adjustment needed
Colestipol	—	—	—	Not absorbed from GI tract	No adjustment needed
Gemfibrozil	—	—	—	Hepatic/renal	No adjustment needed
Fenofibrate	—	—	—	Renal (hepatic)	Initiate at lowest dose
Thrombolytics					
Alteplase	—	—	—	Hepatic	Use adult dose with caution
Anistreplase	—	—	—	—	Use adult dose with caution
Streptokinase	—	—	—	Circulating antibodies/reticuloendothelial system	Use adult dose with caution
Urokinase	—	—	—	Hepatic (biliary/renal)	Use adult dose with caution
Reteplase	—	—	—	Hepatic/renal (blood)	Use adult dose with caution
Vasodilators					
Cyclandelate	—	—	—	—	Initiate at lower dose
Diazoxide	—	—	—	Hepatic/renal	Use lower dose
Fenoldopam	—	—	—	Hepatic	No adjustment needed
Hydralazine	—	—	—	Hepatic (renal/fecal)	Initiate at lower dose
Isosorbide dinitrate	—	—	—	Hepatic (renal)	Initiate at lower dose
Isosorbide mononitrate	NSC	—	NSC	Hepatic	No adjustment needed
Isoxsuprine	—	—	—	Renal (hepatic/blood)	Initiate at lower dose
Minoxidil	—	—	—	Hepatic (renal)	Initiate at lower dose
Nitroglycerin	—	—	—	Hepatic (renal)	Use lower dose
Nitroprusside	—	—	—	Hepatic/renal/erythrocytes	Use adult dose with caution

* Increase in Cl is small compared to increase in Vd. NSC = No significant change; GI = Gastrointestinal. Minus sign = no information or not relevant; ACE = angiotensin-converting enzyme.

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Table 3 Characteristics of the Elderly Relative to Drug Response

Physiological changes	Changes in response
Decreased cardiac reserve	Potential for heart failure
Decreased LV compliance due to thickened ventricular wall, increased blood viscosity, decreased aortic compliance, increased total and peripheral resistance	Decrease of cardiac output
Decreased baroreceptor sensitivity	Tendency to orthostatic hypotension
Diminished cardiac and vascular responsiveness to β-agonists and antagonists	Decreased sensitivity to β-agonists and antagonists
Suppressed renin-angiotensin-aldosterone system	Theoretically decreased response to ACE inhibitors, but not observed
Increased sensitivity to anticoagulant agents	Increased effects of warfarin
Concurrent illnesses	Increased drug–disease interactions
Multiple drugs	Increased drug–drug interactions
Sinus and AV node dysfunction	Potential for heart block

Source: Adapted from Ref. 1a.
LV = left ventricular; ACE = angiotensin converting enzyme; AV = atrioventricular.

PHARMACODYNAMICS

There are numerous physiological changes with aging that affect pharmacodynamics with alterations in end-organ responsiveness (Table 3). Increased peripheral vascular resistance is the cause of systolic and diastolic hypertension in the elderly (15). Inappropriate sodium intake and retention may cause increased arteriolar resistance and/or plasma volume. Cardiac output, heart rate, renal blood flow, glomerular filtration rate, and renin levels are reduced. Increased arterial stiffness, resulting from changes in the arterial media and an increase in arterial tonus and arterial impedance, increases systolic blood pressure. Maintenance of alpha-adrenergic vasoconstriction with impaired beta-adrenergic-mediated vasodilation may contribute to increased peripheral vascular resistance. The cardiovascular response to catecholamines is reduced. Carotid arterial baroreflex sensitivity is decreased. Left ventricular (LV) mass and left atrial dimension are increased. There is a reduction in both the LV early diastolic filling rate and volume (15).

The pharmacodynamic, chronotropic, and inotropic effects of beta agonists and beta-blockers on $beta_1$-adrenergic receptors are diminished in the elderly (16–18). The density of beta receptors in the heart is unchanged in the elderly, but there is a decrease in the ability of beta-receptor agonists to stimulate cyclic adenosine monophosphate production (19).

There are also age-related changes in the cardiac conduction system, as well as an increase in arrhythmias in the elderly. In the Framingham Study, the prevalence of atrial fibrillation was 1.8% in persons 60 to 69 years old, 4.8% in those 70 to 79 years old, and 8.8% in those 80 to 89 years old (20). In a study of 1153 elderly patients (mean age 82 years), the prevalence of atrial fibrillation was 13% (21).

In elderly patients with unexplained syncope, a 24-h ambulatory electrocardiogram (ECG) should be obtained to rule out the presence of second- or third-degree atrioventricular block or sinus node dysfunction with pauses >3 s not seen on the resting ECG. These phenomena were observed in 21 of 148 patients (14%) with unexplained syncope (22).

These 21 patients included 8 with sinus arrest, 7 with advanced second-degree atrioventricular block, and 6 with atrial fibrillation, with a slow ventricular rate not drug-induced.

Unrecognized sinus node of atrioventricular node dysfunction may become evident in elderly persons after drugs such as amiodarone, beta-blockers, digoxin, diltiazem, procainamide, quinidine, or verapamil are administered. Clinical use of these drugs in the elderly, therefore, must be carefully monitored.

USE OF CARDIOVASCULAR DRUGS IN THE ELDERLY

Digoxin

Digoxin has a narrow toxic-therapeutic ratio, especially in the elderly (23). Decreased renal function and lean body mass may increase serum digoxin levels in this population. Serum creatinine may be normal in elderly persons with a marked reduction in creatinine clearance, causing increased serum digoxin levels. Older persons are also more likely to take drugs that interact with digoxin by interfering with bioavailability or elimination. Quinidine, cyclosporin, itraconazole, calcium preparations, verapamil, amiodarone, diltiazem, triamterene, spironolactone, tetracycline, erythromycin, propafenone, and propantheline increase serum digoxin levels. Hypokalemia, hypomagnesemia, hypercalcemia, hypoxia, acidosis, acute and chronic lung disease, hypothyroidism, and myocardial ischemia may cause digitialis toxicity despite normal serum digoxin levels. Digoxin may also cause visual disturbances (24), depression, and confusional states in older persons, sometimes with therapeutic blood levels.

Indications for using digoxin are slowing a rapid ventricular rate in patients with supraventricular tachyarrhythmias such as atrial fibrillation, and treating patients with congestive heart failure (CHF) in sinus rhythm associated with abnormal LV ejection fraction that does not respond to diuretics and ACE inhibitors, or in patients unable to tolerate ACE inhibitors or other vasodilator therapy. Digoxin should not be used to treat patients with CHF in sinus rhythm associated with normal LV ejection fraction. By increasing contractility through increasing intracellular calcium ion concentration, digoxin may increase LV stiffness and increase LV filling pressures, adversely affecting CHF associated with LV diastolic dysfunction. Since almost half the elderly patients with CHF have normal LV ejection fractions (25,26), LV ejection fraction should be measured in all older patients with CHF, so that appropriate therapy may be given (27). Many older patients with compensated CHF who are in sinus rhythm and who are on digoxin may also have digoxin withdrawn without recurrence of the CHF (28,29).

Therapeutic levels of digoxin do not reduce the frequency or duration of episodes of paroxysmal atrial fibrillation detected by 24-h ambulatory ECGs (30). In addition, therapeutic concentrations of digoxin do not prevent the occurrence of a rapid ventricular rate in patients with paroxysmal atrial fibrillation (30,31). Many elderly patients are able to tolerate atrial fibrillation without the need for digoxin therapy because the ventricular rate is slow as a result of concomitant atrioventricular nodal disease.

Some studies have suggested that digoxin may decrease survival after acute myocardial infarction in patients with LV dysfunction (32,33). Leor et al. (34) showed that digoxin may exert a dose-dependent deleterious effect on survival in patients after acute myocardial infarction. Other studies have not confirmed this finding (35,36). Eberhardt et al. (37) demonstrated in the Bronx Longitudinal Aging Study that digoxin use in the elderly without evidence of CHF was an independent predictor of mortality. The results of the Digitalis

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Investigators Group Trial demonstrated that digoxin could be used in older subjects with heart failure, but in lower doses than that previously employed in clinical practice (38).

Diuretics

Diuretics are eliminated by the kidneys. The Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure recommends as initial drug treatment of hypertension, the use of diuretics or beta-blockers because these drugs have been demonstrated to reduce cardiovascular morbidity and mortality in controlled clinical trials (39). The results of the Systolic Hypertension in the Elderly (SHEP) treatment trial showed the safety and efficacy of a diuretic and beta-blocker in the treatment of isolated systolic hypertension in the elderly (40). We recommend that the choice of antihypertensive drug selected as monotherapy depend on associated medical conditions. Older hypertensive patients with CHF associated with abnormal LV ejection fraction (41–43) or normal LV ejection fraction (44) should receive both a diuretic and an ACE inhibitor.

Diuretics are the first-line drug in the treatment of patients with CHF. Diuretics reduce venous return, decrease ventricular filling pressures, cause loss of fluid from the body, and relieve symptoms of pulmonary and systemic congestion and edema. Age-related decrease in renal function and circulating plasma volume may reduce the efficacy of diuretics in elderly patients.

A thiazide diuretic, such as hydrochlorothiazide, may be used to treat older patients with mild CHF. However, a thiazide diuretic is ineffective if the glomerular filtration rate is <30 mL/min. Older patients with moderate or severe CHF should be treated with a loop diuretic such as furosemide. Older patients with severe CHF or concomitant renal insufficiency may need metolazone added to a loop diuretic. Nonsteroidal anti-inflammatory drugs may decrease the antihypertensive and diuretic effects of furosemide. Severe volume overload should be treated with intravenous diuretics and hospitalization.

Serum electrolytes need to be monitored closely in older patients treated with diuretics. Hypokalemia and hypomagnesemia, both of which may precipitate ventricular arrhythmias and digitalis toxicity, may occur. Hyponatremia with activation of the renin-angiotensin system may develop.

Older patients with CHF are especially sensitive to volume depletion. Dehydration with hypotension and prerenal azotemia may occur if excessive doses of diuretics are used. The minimum effective dose of diuretics should be administered. Older patients with CHF associated with normal or abnormal LV ejection fraction should be treated with diuretics. However, patients with CHF associated with abnormal LV ejection fraction tolerate higher doses of diuretics than do patients with CHF associated with normal LV ejection fraction.

Beta-Adrenergic Blockers

Beta-blockers are used in various cardiovascular disorders, with resultant beneficial and adverse effects (45). Beta-blockers are very effective antianginal agents in older, as well as younger, patients. Combined therapy with beta-blockers and nitrates may be more beneficial in the treatment of angina pectoris than either drug alone (45).

Diuretics or beta-blockers have been recommended as initial drug therapy for hypertension in older persons because these drugs have been shown to decrease cardiovascular morbidity and mortality in controlled clinical trials (39). Beta-blockers are especially use-

ful in the treatment of hypertension in older patients who have concomitant prior myocardial infarction, angina pectoris, silent myocardial ischemia, complex ventricular arrhythmias, supraventricular tachyarrhythmias, or hypertrophic cardiomyopathy.

Teo et al. (46) analyzed 55 randomized controlled trials that investigated the use of beta-blockers in patients after myocardial infarction. Mortality was significantly decreased (19%) in patients receiving beta-blockers, compared with control patients. In the Beta Blocker Heart Attack Trial (BHAT), propranolol significantly decreased total mortality by 34% in patients aged 60 to 69 years, and insignificantly reduced total mortality by 19% in patients aged 30 to 59 years (47). In the Norwegian Timolol Study, timolol significantly decreased total mortality by 43% in postinfarction patients aged 65 to 75 years, and significantly reduced total mortality by 34% in postinfarction patients <65 years of age (48). Despite the utility of beta-blockers in postmyocardial infarction patients, they are still underutilized in older patients (49,50).

Beta-blockers decrease complex ventricular arrhythmias including ventricular tachycardia (51–54). Beta-blockers also increase the ventricular fibrillation threshold in animal models, and have been shown to reduce the incidence of ventricular fibrillation in patients with acute myocardial infarction (55). A randomized, double-blind, placebo-controlled study of propranolol in high-risk survivors of acute myocardial infarction at 12 Norwegian hospitals demonstrated that patients treated with propranolol for 1 year had a significant (52%) decrease in sudden cardiac death (52).

In addition, beta-blockers decrease myocardial ischemia (53,54,56), which may reduce the likelihood of ventricular fibrillation. Stone et al. (56) demonstrated by 48-h ambulatory ECGs in 50 patients with stable angina pectoris that propranolol, not diltiazem or nifedipine, caused a significant decrease in the mean number of episodes of myocardial ischemia and in the mean duration of myocardial ischemia compared with placebo. Furthermore, beta-blockers reduce sympathetic tone.

Studies have demonstrated that beta-blockers reduce mortality in older and younger patients with complex ventricular arrhythmias and heart disease (Table 4) (47,53,54,57–59). In the BHAT of 3290 patients comparing propranolol with placebo, propranolol reduced sudden cardiac death by 28% in patients with complex ventricular arrhythmias and by 16% in patients without ventricular arrhythmias (47).

Hallstrom et al. (57) did a retrospective analysis of the effect of antiarrhythmic drug use in 941 patients resuscitated from prehospital cardiac arrest due to ventricular fibrillation between 1970 and 1985. Beta-blockers were administered to 28% of the patients, and no antiarrhythmic drug to 39%. There was a reduced incidence of death or recurrent cardiac arrest in patients treated with beta-blockers versus no antiarrhythmic drug (relative risk 0.47; adjusted relative risk 0.62).

Aronow et al. (53) performed a prospective study in 245 elderly patients (mean age 81 years) with heart disease (64% with prior myocardial infarction and 36% with hypertensive heart disease), complex ventricular arrhythmias diagnosed by 24-h ambulatory ECGs, and LV ejection fraction $\geq 40\%$. Nonsustained ventricular tachycardia occurred in 32% of patients. Myocardial ischemia occurred in 33% of patients. Mean follow-up was 30 months in patients randomized to propranolol and 28 months in patients randomized to no antiarrhythmic drug. Propranolol was discontinued because of adverse effects in 11% of patients. Follow-up 24-h ambulatory ECGs showed that propranolol was significantly more effective than no antiarrhythmic drug in reducing ventricular tachycardia ($>90\%$), in decreasing the average number of ventricular premature complexes per hour ($>70\%$), and in abolishing silent ischemia.

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Table 4 Effect of β-Blockers on Mortality in Elderly Patients with Complex Ventricular Arrhythmias and Heart Disease

Study	Age (years)	Mean follow-up (months)	Results
BHAT (46)	60–69 (33%)	25	Compared with placebo, propranolol reduced sudden cardiac death by 28% in patients with complex VA and 16% in patients without VA.
Hallstrom (56)	62 (mean)	108	Reduced incidence of death or recurrent cardiac arrest in patients treated with β-blockers vs. no antiarrhythmic drug (adjusted relative risk 0.62).
Aronow et al. (52)	62–96 (mean 81)	29	Compared with no antiarrhythmic drug, propranolol caused a 47% significant decrease in sudden cardiac death, a 37% significant reduction in total cardiac death, and a 20% insignificant decrease in total death.
Aronow et al. (53)	62–96 (mean 81)	29	Among patients taking propranolol, suppression of complex VA caused a 33% reduction in sudden cardiac death, a 27% decrease in total cardiac death, and a 30% reduction in total death; abolition of silent ischemia cause a 70% decrease in sudden cardiac death, a 72% reduction in total cardiac death, and a 69% decrease in total death.
Aronow et al. (57)	62–96 (mean 81)	29	Incidence of sudden cardiac death or fatal myocardial infarction was significantly increased between 6 a.m. and 12 a.m., with peak hour at 8 a.m. and secondary peak at 7 p.m. in patients with no antiarrhythmic drug treatment; propranolol abolished the circadian distribution of sudden cardiac death or fatal myocardial infarction.
CAST (58)	66–79 (40%)	12	Patients on β-blockers (30% of study group) had a significant reduction in all-cause mortality of 43% at 30 days, 46% at 1 year, and 33% at 2 years: in patients on β-blockers, arrhythmic death or cardiac arrest was significantly reduced by 66% at 30 days, 53% at 1 year, and 36% at 2 years; multivariate analysis showed β-blockers to be an independent factor for reduced arrhythmic death or cardiac arrest by 40% and for all-cause mortality by 33%.

Source: Reproduced from Ref. 59A.
BHAT = Beta Blocker Heart Attack Trial; VA = ventricular arrhythmia; CAST = Cardiac Arrhythmia Suppression Trial.

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Multivariate Cox regression analysis showed that propranolol caused a significant (47%) decrease in sudden cardiac death, a significant (37%) reduction in total cardiac death, and an insignificant (20%) decrease in total death (53). Univariate Cox regression analysis showed that the reduction in mortality and complex ventricular arrhythmias in elderly patients with heart disease taking propranolol was due more to an anti-ischemic effect than to an antiarrhythmic effect (54).

Table 4 also shows that there was a circadian distribution of sudden cardiac death or fatal myocardial infarction, with the peak incidence occurring from 6 a.m. to 12 a.m. (peak hour 8 a.m. and secondary peak around 7 p.m.) in patients treated with no antiarrhythmic drug (58). Propranolol abolished this circadian distribution of sudden cardiac death or fatal myocardial infarction (58).

In a retrospective analysis of data from the Cardiac Arrhythmia Suppression Trial (CAST), Kennedy et al. (59) found that 30% of patients with a LV ejection fraction $\leq$40% were receiving beta-blockers. Forty percent of these 1735 patients were between 66 and 79 years of age. Patients on beta-blockers had a significant reduction in all-cause mortality of 43% at 30 days, 46% at 1 year, and 33% at 2 years. Patients receiving beta-blockers had a significant decrease in arrhythmic death or cardiac arrest of 66% at 30 days, 53% at 1 year, and 36% at 2 years. Multivariate analysis showed that beta-blockers were an independent factor for reducing arrhythmic death or cardiac arrest by 40%, for decreasing all-cause mortality by 33%, and for reducing the occurrence of new or worsening CHF by 32%. On the basis of these data (47,53,54,57–59), beta-blockers can be utilized in the treatment of older and younger patients with ventricular tachycardia or complex ventricular arrhythmias associated with ischemic or nonischemic heart disease, and with normal or abnormal LV ejection fraction, if there are no contraindications to the drugs.

Beta-blockers are also useful in the treatment of supraventricular tachyarrhythmias in older and younger patients (60,61). If a rapid ventricular rate associated with atrial fibrillation persists at rest or during exercise despite digoxin therapy, then verapamil (62), diltiazem (63), or a beta-blocker (64) should be added to the therapeutic regimen. These drugs act synergistically with digoxin to depress conduction through the atrioventricular junction. The initial oral dose of propranolol is 10 mg q 6 h. This dose may be increased to a maximum of 80 mg q 6 h if necessary.

Most recently, beta-blockers, specifically carvedilol, an alpha-beta-blocker, have been shown to be safe and efficacious in patients with ventricular dysfunction who have class II and III NYHA symptoms, when added to stable doses of diuretics and ACE inhibitors (65).

Numerous drug interactions may occur with beta-blockers in the elderly (45). Recently, quinidine was shown to decrease the hepatic metabolism of topically applied ophthalmic timolol, causing systemic effects (66).

ACE Inhibitors

ACE inhibitors are effective antihypertensive agents. A meta-analysis of 109 treatment studies showed that ACE inhibitors are more effective than other antihypertensive drugs in decreasing LV mass (67). Older hypertensive patients with CHF associated with abnormal (41–43) or normal (44) LV ejection fraction, LV hypertrophy, or diabetes mellitus, should initially be treated with an ACE inhibitor.

ACE inhibitors reduce mortality in patients with CHF associated with abnormal LV ejection fraction (41–43). The Survival and Ventricular Enlargement (SAVE) trial (68) and the combined Studies of Left Ventricular Dysfunction (SOLVD) treatment and pre-

vention trials (69) also demonstrated that ACE inhibitors such as captopril or enalapril should be standard therapy for most patients with significant LV systolic dysfunction with or without CHF. In addition, ACE inhibitor therapy has been shown to be beneficial in the treatment of elderly patients (mean age 80 years) with CHF caused by prior myocardial infarction associated with normal LV ejection fraction (44).

ACE inhibitors should be initiated in elderly patients in low doses after correction of hyponatremia or volume depletion. It is important to avoid overdiuresis before beginning therapy with ACE inhibitors since volume depletion may cause hypotension or renal insufficiency when ACE inhibitors are begun or when the dose of these drugs is increased to full therapeutic levels. After the maintenance dose of ACE inhibitor is reached, it may be necessary to increase the dose of diuretics. The initial dose of enalapril is 2.5 mg daily and of captopril is 6.25 mg t.i.d. The maintenance doses are 5 to 20 mg daily and 25 to 50 mg t.i.d, and the maximum doses are 20 mg b.i.d. and 150 mg t.i.d., respectively.

Older patients at risk for excessive hypotension should have their blood pressure monitored closely for the first 2 weeks of ACE inhibitor or angiotensin-II receptor blocking therapy, and whenever the dose of ACE inhibitor or diuretic is increased. Renal function should be monitored in patients on ACE inhibitors to detect increases in blood urea nitrogen and serum creatinine, especially in older patients with renal artery stenosis. A doubling in serum creatinine should cause the physician to consider renal dysfunction due to ACE inhibitors, a need to reduce the dose of diuretics, or exacerbation of CHF. Potassium-sparing diuretics or potassium supplements should not be administered to patients receiving ACE inhibitors routinely because hyperkalemia may result from ACE inhibitor therapy.

Angiotensin-II Receptor Blockers

Angiotensin-II receptor blockers are the newest class of antihypertensive drugs to be approved. They have also been used in patients with CHF. Although the published experience with these drugs in the elderly is limited, the drugs appear to be safe if used with similar caution to those recommended for ACE inhibitors, as described above. These drugs significantly reduce the incidence of nonproductive cough seen with ACE inhibitors. One study suggested a greater benefit on morbidity and mortality in elderly patients with CHF when using angiotensin-II receptor blockers versus ACE inhibitors (69a).

Nitrates

Nitrates are effective therapies for older individuals; however, caution should always be used because of the dangers of orthostatic hypotension, syncope, and falls, especially if the treatment is combined with diuretics and other vasodilators. Recently, it was shown that nitrate headaches are less frequent in older patients and in individuals with renal dysfunction (70).

Calcium Channel Blockers

Calcium channel blockers are effective antihypertensive and antianginal drugs in older patients. Verapamil (62) and diltiazem (63) are especially valuable in treating hypertensive patients who also have supraventricular tachyarrhythmias. However, recent reports have suggested an increased mortality risk with these drugs, especially the use of short-acting dihydropyridines in older subjects (71–73). With the use of longer-acting calcium block-

ers, such as the dihydropyridine nitrendipine, a benefit was seen in patients with isolated systolic hypertension (74), although many were receiving concurrent β-blocker therapy. In contrast, nisoldipine was shown to be less effective in protecting against mortality in diabetic patients with hypertension (75).

Verapamil improved exercise capacity, peak LV filling rate, and a clinicoradiographic heart failure score in patients with CHF, normal LV ejection fraction, and impaired LV diastolic filling (76). However, calcium channel blockers such as verapamil, diltiazem, and nifedipine exacerbate CHF in patients with associated abnormal LV ejection fraction (77). In addition, some calcium channel blockers have been shown to increase mortality in patients with CHF and abnormal LV ejection fraction after myocardial infarction (78). Therefore, calcium channel blockers such as verapamil, diltiazem, and nifedipine may be used to treat older patients with CHF associated with normal LV ejection fraction, but are contraindicated in treating older patients with CHF associated with abnormal LV ejection fraction.

Amlodipine and felodipine are two vasculospecific dihydropyridine agents that appear to be safer in patients having CHF.

The age-associated decrease in hepatic blood flow and hepatic metabolic capacity may result in higher serum concentrations of verapamil, diltiazem, and nifedipine. Therefore, these drugs should be given to older persons in lower doses.

Alpha$_1$-Adrenergic Blockers

Alpha$_1$-adrenergic blockers are effective treatments for patients with hypertension and have become first-line treatments for males with symptomatic prostatism. Caution should be exercised when using these agents because of a significant incidence of postural hypotension, especially in patients receiving diuretics or other vasodilator drugs (79,80). A more selective alpha$_1$-blocker, tamsulosin, has become available, which improves prostatism without having vasodilator effects (80a).

Lidocaine

Intravenous (i.v.) lidocaine may be used to treat complex ventricular arrhythmias during acute myocardial infarction (60). Lidocaine toxicity is more common in the elderly and older patients should be monitored for dose-related confusion, tinnitus, paresthesias, slurred speech, tremors, seizures, delirium, respiratory depression, and hypotension. Older patients with CHF or impaired liver function are at increased risk for developing central nervous system adverse effects from lidocaine (81). In these patients, the loading dose should be decreased by 25 to 50%, and maintenance infusion should be initiated at a rate of 0.5 to 2.5 mg/min, with the patient monitored closely for adverse effects. The dose of lidocaine should also be reduced if the patient is receiving beta-blockers (82) or cimetidine, since these drugs reduce metabolism of lidocaine.

Other Antiarrhythmic Drugs

The use of antiarrhythmic drugs in the elderly is extensively discussed elsewhere (61,83). In the CAST I trial, encainide and flecainide significantly increased mortality in survivors of myocardial infarction with asymptomatic or mildly symptomatic ventricular arrhythmias, when compared to placebo (84). In the CAST II, moricizine insignificantly increased mortality when compared to placebo (85). Akiyama et al. (86) found that older age in-

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creased the likelihood of adverse events, including death, in patients treated with encainide, flecainide, or moricizine in these two studies.

In a retrospective analysis of the effect of empirical antiarrhythmic treatment in 209 cardiac arrest patients who were resuscitated out of hospital, Moosvi et al. (87) found that the 2-year mortality was significantly lower for patients treated with no antiarrhythmic drug than for patients treated with quinidine or procainamide. Hallstrom et al. (57) showed an increased incidence of death or recurrent cardiac arrest in patients treated with quinidine or procainamide versus no antiarrhythmic drug.

In a prospective study of 406 elderly subjects (mean age 82 years) with heart disease (58% with prior myocardial infarction) and asymptomatic complex ventricular arrhythmias, the incidence of sudden cardiac death, total cardiac death, and total mortality were not significantly different in patients treated with quinidine or procainamide or with no antiarrhythmic drug (88). In this study, quinidine or procainamide did not reduce mortality in comparison with no antiarrhythmic drug in elderly patients with presence vs. absence of ventricular tachycardia, ischemic or nonischemic heart disease, and abnormal or normal LV ejection fraction. The incidence of adverse events causing drug cessation in elderly patients in this study was 48% for quinidine and 55% for procainamide.

A meta-analysis of six double-blind studies of 808 patients with chronic atrial fibrillation who underwent direct current cardioversion to sinus rhythm demonstrated that the 1-year mortality was significantly higher in patients treated with quinidine than in patients treated with no antiarrhythmic drug (89). In the Stroke Prevention in Atrial Fibrillation Study, arrhythmic death and cardiac mortality were also significantly increased in patients receiving antiarrhythmic drugs compared with patients not receiving antiarrhythmic drugs, especially in patients with a history of CHF (90).

Teo et al. (46) analyzed 59 randomized controlled trials, comprising 23,229 patients, which investigated the use of class I antiarrhythmic drugs after myocardial infarction. Patients receiving class I antiarrhythmic drugs had a significantly higher mortality than patients receiving no antiarrhythmic drugs. None of the 59 trials demonstrated that a class I antiarrhythmic drug decreased mortality in postinfarction patients. Therefore, it is not recommended that class I antiarrhythmic drugs be used for the treatment of ventricular tachycardia or complex ventricular arrhythmias associated with heart disease.

Amiodarone is very effective in suppressing ventricular tachycardia and complex ventricular arrhythmias. However, there are conflicting data about the effect of amiodarone on mortality (91–97). The Veterans Administration Cooperative Study comparing amiodarone vs. placebo in heart failure patients with malignant ventricular arrhythmias was recently completed and showed that amiodarone was very effective in decreasing ventricular tachycardia and complex ventricular arrhythmias, but it did not affect mortality (97). The incidence of adverse effects from amiodarone has been reported to approach 90% after 5 years of treatment (98). In the Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation Study, the incidence of pulmonary toxicity was 10% at 2 years in patients receiving an amiodarone dose of 158 mg daily (99). On the basis of these data, one should reserve the use of amiodarone to the treatment of life-threatening ventricular tachyarrhythmias or in patients who cannot tolerate or who do not respond to beta-blocker therapy.

Amiodarone is also the most effective drug for treating refractory atrial fibrillation in terms of converting atrial fibrillation to sinus rhythm and slowing a rapid ventricular rate. However, because of the high incidence of adverse effects caused by amiodarone, amiodarone should be used in low doses in patients with atrial fibrillation when life-threatening atrial fibrillation is refractory to other therapy (100).

Lipid-Lowering Drugs

The safety of lipid-lowering drugs, specifically 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors, was demonstrated in the Cholesterol Reduction in Seniors Program (CRISP) (101). Based on CRISP, the Antihypertensive Lipid Lowering Heart Attack Trial (ALLHAT), a large primary prevention trial, is now in progress using pravastatin in older subjects to reduce morbidity and mortality (102).

In the Scandinavian Simvastatin Survival Study (103), 4444 men and women with coronary artery disease were treated with double-blind simvastatin or placebo. At a 5.4-year follow-up, patients treated with simvastatin had a 35% decrease in serum low-density lipoprotein cholesterol, a 25% reduction in serum total cholesterol, an 8% increase in serum high-density lipoprotein cholesterol, a 34% decrease in major coronary events, a 42% reduction in coronary deaths, and a 30% decrease in total mortality. The decreases in coronary events and in total mortality were similar in men and in women between the ages of 60 and 70 years and in those younger in age. Similar effects have been seen in older subjects with pravastatin (104).

On the basis of the available data showing increased risk of cardiovascular disease from abnormal lipoprotein patterns (105), we recommend dietary therapy for older patients with dyslipidemia, regardless of age, in the absence of other serious life-limiting illnesses such as cancer, dementia, or malnutrition. If hyperlipidemia persists after 3 months of dietary therapy, hypolipidemic drugs should be considered, depending on serum lipid levels, presence or absence of coronary artery disease, presence or absence of other coronary risk factors, and the patient's overall clinical status. In older women, the use of estrogen plus cyclic micronized progesterone, as used in the Postmenopausal Estrogen/Progestin Intervention (PEPI) trial (106), might be considered an adjunctive hypolipidemic approach for treating high-serum low-density and low-serum high-density lipoprotein cholesterol levels (107,108). This is being analyzed in the Women's Health Initiative Study, where estrogen alone or in combination with progesterone is being looked at as primary prevention to reduce coronary artery disease risks in postmenopausal women, 20% of whom are 70 to 80 years of age. In older men and women, the HMG-CoA reductase inhibitors would be the drugs of choice for treating a high-serum low-density lipoprotein cholesterol level. Recently the Heart and Estrogen/Progestin Replacement Study (HERS) showed that there was no benefit in using adjunctive hormonal replacement therapy in postmenopausal women with known coronary artery disease (108a).

Anticoagulants

Anticoagulant therapy in the elderly is discussed extensively elsewhere (61,109). Anticoagulants are effective in the prevention and treatment of many thromboembolic disorders, including venous thromboembolism and pulmonary embolism, acute myocardial infarction, and embolism associated with prosthetic heart valves or atrial fibrillation. These conditions, necessitating the use of anticoagulants, are more common in elderly than in younger patients. In the report from the Sixty Plus Reinfarction Group who evaluated the effects of oral anticoagulant therapy on total mortality after myocardial infarction in patients older than 60 years, it was shown that active therapy lowered both mortality and reinfarction compared with placebo (110). However, the treatment group also had more major bleeding complications.

The anticoagulant response to warfarin is increased with age (111). Chronic diseases that increase the risk for bleeding during anticoagulant therapy are also more common in

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Table 5 Cardiovascular Drugs Regularly Detected as the Culprit in Some Common Disorders of the Elderly

Confusion states	β-blockers, digoxin, methyldopa and related drugs, quinidine
Tinnitus, vertigo	Aspirin, furosemide, ethacrynic acid
Depression	β-blockers, methyldopa, reserpine
Falls	All drugs liable to produce postural hypotension, glycerol trinitrates
Postural hypotension	All antihypertensives, antianginal drugs, β-blockers, diuretics
Constipation	Anticholinergics, clonidine, diltiazem, diuretics, verapamil
Urinary retention	Disopyramide, midodrine
Urinary incontinence	β-blockers, diuretics, labetalol, prazosin

Source: Adapted from Ref. 1a.

elderly patients than in younger patients. In addition, elderly patients are at higher risk for bleeding during anticoagulant therapy because of increased vascular or endothelial fragility (112). Furthermore, older patients may be at increased risk for bleeding due to anticoagulant therapy because they may be taking other drugs that potentiate the anticoagulant effect. Drugs such as aspirin, cephalosporins, and penicillins increase the risk of bleeding in patients treated with heparin. Drugs such as allopurinol, amiodarone, aspirin, cimetidine, ciprofloxacin, clofibrate, cotrimoxazole, dextroproproxyphene, disulfiram, erythromycin, fluconazole, isoniazid, ketoconazole, meclofenamic acid, metronidazole, miconazole, norfloxacin, phenylbutazone, phenytoin, quinidine, sulfinpyrazone, sulindac, thyroxine, and trimethoprim-sulfamethoxazole potentiate the effect of warfarin, causing an increased prothrombin time and risk of bleeding.

ADVERSE EFFECTS OF DRUGS IN THE ELDERLY

Cardiovascular drugs are often associated with adverse effects that simulate common disorders of the elderly (Table 5). In addition, important drug–disease interactions (Table 6), drug–drug interactions (Table 7), and drug–alcohol interactions (113) (Table 8) occur in older patients.

MEDICATIONS BEST TO AVOID IN THE ELDERLY

Careful selection of drugs and dosages of drugs in the elderly can minimize adverse outcomes while maximizing clinical improvement. In their first attempt to identify medications and doses of medication that may be best to avoid in the elderly, Beers and colleagues developed a set of explicit criteria after an extensive review of the literature and assistance from 13 well-recognized experts in geriatric medicine and pharmacology (114). These criteria included 30 statements that described medications that should generally be avoided in nursing home residents as well as statements that described doses, frequencies, and duration of medications that should generally not be exceeded. Since the publication of the explicit criteria, several research studies have utilized these criteria to evaluate the appropriateness of medication prescribing in the elderly (115–118). The most striking study of this type was performed by Willcox and colleagues (118), who reported a potentially inappropriate medication prescription in 23.5% of the elderly in the community.

Table 6 Important Drug–Disease Interactions in Geriatric Patients

Underlying disease	Drugs	Adverse effect
Congestive heart failure	β-blockers, verapamil	Acute cardiac decompensation
Cardiac conduction disorders	Tricyclic antidepressants	Heart block
Hypertension	NSAIDs	Increased blood pressure
Peripheral vascular disease	β-blockers	Intermittent claudication
Chronic obstructive pulmonary disease	β-blockers	Bronchoconstriction
Chronic renal impairment	NSAIDs, contrast agents, aminoglycosides	Acute renal failure
Diabetes mellitus	Diuretics	Hyperglycemia
Prostatic hypertrophy	Drugs with antimuscarinic side effects	Urinary retention
Depression	β-blockers, centrally acting antihypertensives	Precipitation or exacerbation of depression
Hypokalemia	Digoxin	Cardiac arrhythmias
Peptic ulcer disease	Anticoagulants, salicylates	GI hemorrhage

Source: Adapted from Ref. 112a.
NSAIDs = nonsteroidal anti-inflammatory drugs; GI = gastrointestinal.

Willcox and colleagues were criticized, however, for applying criteria that were designed for frail elderly patients in nursing homes to healthier elderly residents in the community, along with other things such as using criteria that need to be updated (119).

Acknowledging the limitation of this first set of criteria, Beers updated and expanded it to encompass elderly patients who are in the ambulatory setting, as well as medications that should be avoided in the elderly known to have certain conditions (120). With the assistance of six nationally recognized experts in geriatric medicine and pharmacology, a set of 63 criteria were developed using the first set of criteria plus a more recent literature review. Out of the 63 criteria, 28 criteria described medications or categories of medication that were considered to be potentially inappropriate when used by all older patients, 35 criteria described medications or categories of medications that were considered to be potentially inappropriate when used by elderly patients with any of 15 known medical conditions such as heart failure, diabetes, hypertension, asthma, and arrhythmias. These criteria were further rated by the six panelists regarding their importance. The panelists considered a criterion to be severe when an adverse outcome was both likely to occur and, if it did occur, would likely lead to a clinically significant event (120). Table 9 lists the cardiac medications that were recognized by the expert panel as having the highest risk for potential problems from their use and the reasons for their avoidance. Table 10 lists medications that were identified by the expert panel as having the highest risk for potential problems and the reasons for their avoidance in the elderly when certain cardiac-related conditions exist.

Although these criteria serve as useful tools for assessing the quality of prescribing to the elderly, they do not identify all cases of potentially inappropriate prescribing (120). In fact, these criteria may identify appropriate prescribing as inappropriate at times (120). The latter case may be particularly likely when physicians and pharmacists carefully adjust medication regimens for the specific needs of individual patients (120).

Table 7 Selected Clinically Significant Drug-Drug Interactions in Geriatric Patients

Primary drugs	Interacting drugs	Mechanism of interaction	Possible effects
Augmented Drug Effects			
Antidiabetic sulfonylureas (tolbutamide, chlorpropamide)	Chloramphenicol, warfarin	IM	Hypoglycemia
	Phenylbutazone	IM, DP, IE	
	Quinidine	OM	
Azathioprine	Allopurinol	IM	Bone marrow suppression
Carbamazepine	Diltiazem, verapamil	IM	Increase serum carbamazepine concentration and risk of toxicity (e.g., nausea, ataxia, nystagmus)
Cyclosporine	Diltiazem, verapamil	IM	Increase serum cyclosporine concentration and risk of toxicity (e.g., hepatotoxicity, nephrotoxicity)
Digoxin	Amiodarone, diuretics, quinidine, verapamil	OM	Increase serum digoxin concentration and risk of toxicity (e.g., nausea, confusion, cardiotoxicity)
Disopyramide	Diltiazem, verapamil	OM	Bradycardia
Lidocaine	β-blockers, cimetidine	HBF	Increase serum lidocaine concentration and risk of toxicity (e.g., sedation, seizures, cardiotoxicity)
Methotrexate	Aspirin, indomethacin, phenylbutazone	DP, IE	Bone marrow suppression
	Probenecid	IE	
	Sulfisoxazole	DP	
Procainamide	Diltiazem, verapamil	OM	Bradycardia
Propranolol	Cimetidine	HBF	Bradycardia
	Diltiazem, verapamil	OM	Bradycardia and hypotension
Phenytoin	Amiodarone, chloramphenicol, cimetidine, fluconazole, isoniazid, phenylbutazone	IM	Increase serum phenytoin concentration and risk of toxicity (e.g., nystagmus, sedation)
	Valproic acid, warfarin	DP, IM	
Quinidine	Diltiazem, verapamil	IM	Increase serum quinidine concentration and risk of toxicity (e.g., nausea, cinchonism, arrhythmias)

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Table 7 Continued

Primary drugs	Interacting drugs	Mechanism of interaction	Possible effects
Warfarin	Aspirin, Indomethacin	DP	Hemorrhage
	Amiodarone, cimetidine, metronidazole	IM	
	Phenylbutazone, sulfonamides	DP, IM	
Decreased Drug Effects			
All medications	Cholestyramine	IA	Delay or reduce absorption of other drugs. Administer other drugs 1–2 h before or 4–6 h after cholestyramine
Antidiabetic sulfonylureas (tolbutamide, chlorpropamide)	β-blockers (nonselective)	IIS, MCM, IIR	Decrease hypoglycemic effects
	Corticosteroids, thiazide diuretics	OM	
Digoxin	Sucralfate	IA	Reduce absorption of digoxin. Administer sucralfate at least 2 h apart form digoxin.
Lincomycin	Kaolin-pectin	IA	Decrease drug bioavailability
Phenytoin	Calcium, sucralfate	IA	Decrease serum phenytoin concentration and anticonvulsant effect
	Rifampin	SM	
Prednisone	Barbiturates	SM	Decreased steroid effects
Quinidine	Barbiturates, rifampin	SM	Decrease antiarrhythmic effect
Tetracycline	Antacids-iron	IA	Decrease drug bioavailability
Warfarin	Barbiturates, carbamazepine, glutethimide, rifampin	SM	Loss of anticoagulant control
	Vitamin K	SP	
Other Drug Effects			
ACE inhibitors	Potassium-sparing diuretics, potassium-containing medications	RAP	Hyperkalemia
HMG-CoA reductase inhibitors	Cyclosporine, gemfibrozil, niacin	Unknown	Rhabdomyolysis, acute renal failure
	Erythromycin	IM	

Source: Adapted from Ref. 112b.
IM = inhibition of drug metabolism; DP = displacement of protein binding; IE = inhibition of renal excretion; OM = other mechanisms (pharmacodynamic effects of drugs on tissue responses); HBF = decreased hepatic blood flow; IA = inhibition of drug absorption; IIS = inhibition of insulin secretion; MCM = modification of carbohydrate metabolism; IIR = increased peripheral insulin resistance; SM = stimulation of drug metabolism; SP = increased hepatic synthesis of procoagulant factors; RAP = reduction of aldosterone production; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A.

Table 8 Selected Clinically Significant Drug–Alcohol Interactions in Geriatric Patients

Primary drugs	Interacting drug	Possible effects
Antidiabetic sulfonylureas	Alcohol	Disulfiram-like reactions (especially with chlorpropamide)
ACE inhibitors	Alcohol	Hypotension
Isoniazid	Alcohol	Decreased therapeutic effect of isoniazid, increased risk of hepatic toxicity
Nitrates	Alcohol	Hypotension
Phenytoin	Alcohol	Decreased serum phenytoin concentration and effectiveness (chronic use of alcohol); increased serum phenytoin concentration and risk of toxicity (acute intake of alcohol)
Rifampin	Alcohol	Decreased therapeutic effect of rifampin, increased risk of hepatic toxicity
Sedatives-hypnotics	Alcohol	Excessive sedation
Vitamins	Alcohol	Decreased absorption and storage of folic acid and thiamine
Warfarin	Alcohol	Increased anticoagulant activity (acute intoxication); decreased anticoagulant activity (chronic abuse)

SAFER USE OF MEDICATION IN THE ELDERLY

Although the elderly make up only 14% of our population, they receive more than 30% of all prescribed medication (121). The increased exposure of medications in the elderly may lead to higher incidence of adverse drug reactions and drug–drug interaction in this population (122). Physiological changes with aging may also alter the elimination of drugs that can contribute to adverse outcomes with medication usage. With these concerns in

Table 9 Medications Best to Avoid in All Older Patients

Medications	Prescribing concerns
Disopyramide	Of all antiarrhythmics, disopyramide is the most potent negative inotrope and therefore may induce heart failure in the elderly. It is also strongly anticholinergic. When appropriate, other antiarrhythmic drugs should be used.
Digoxin[a]	Because of decreased renal clearance of digoxin, doses in the elderly should rarely exceed 0.125 mg daily, except when treating atrial arrhythmias.
Methyldopa[a] and methyldopa/HCTZ[a]	Methyldopa may cause bradycardia and exacerbate depression in the elderly. Alternate treatments for hypertension are generally preferred.
Ticlopidine	Ticlopidine has been shown to be no better than asprin in preventing clotting and is considerably more toxic. Avoid in the elderly.

[a] Panelists believed that the severity of adverse reaction would be substantially greater when these drugs were recently started. In general, the greatest risk would be within about a 1-month period.
HCTZ = hydrochlorothiazide.
Source: Adapted from Ref. 120.

Table 10 Medications Best to Avoid in Older Patients with Specific Diseases and Conditions

Diseases/conditions	Medications	Prescribing concerns
Heart Failure	Disopyramide	Negative inotrope; may worsen heart failure
Hypertension	Diet pills; amphetamines	May elevate blood pressure
Blood-clotting disorders, limited to those receiving anticoagulant therapy	Aspirin, NSAIDS, dipyridamole, and ticlopidine	May cause bleeding in those using anticoagulants
Syncope or falls	Long-acting benzodiazepine drugs	May contribute to falls
Arrhythmias	Tricyclic antidepressant drugs[a]	May induce arrhythmias

Source: Adapted from Ref. 120.

[a] Panelists believed that the severity of adverse reaction would be substantially greater when these drugs were recently started. In general, the greatest risk would be within about a 1-month period.

mind, several authors have suggested some steps that clinicians may employ to ensure careful prescribing (121,123,124). These suggestions include:

Acquire a full history of the patient's habits and medication use.
Evaluate the need for drug therapy. Consider alternative nondrug approaches when appropriate.
Know the pharmacology of the drugs prescribed.
Start with low dose of medication and titrate up slowly.
Titrate medication dosage according to the patient's response.
Minimize the number of medications used.
Educate patients regarding proper usage of medications.
Be aware of medication cost, which may have an impact on compliance.
Provide patient with a portable prescription record.
Review the treatment plan regularly and discontinue medications no longer needed.

With proper monitoring and adequate understanding of the effects of medications in the elderly, the use of medication can be a positive experience for both the elderly patient and the clinician.

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34

Ethical Decisions and Quality of Life in Elderly Patients with Cardiovascular Disease

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Clinical decision making for elderly patients with cardiovascular disease or risk factors consumes a good part of a physician's day. The epidemiology of cardiovascular disease in the elderly is outlined in other chapters. To emphasize the extent of these problems, we can simply ask clinicians who care for elderly patients the following question. What percentage of your practice for elderly patients is devoted to preventing and treating cardiovascular disease? More specifically, what percent of your practice is devoted to preventing or treating hypertension, atrial fibrillation, angina, congestive heart failure, peripheral vascular disease, or stroke? Most clinicians will answer greater than 50%. The magnitude of these concerns is no surprise to clinicians.

What may surprise clinicians is the ethical complexity involved with these routine, seemingly mundane decisions. Consider, for example, an 80-year-old woman with hypertension whose blood pressure has been running a bit high while she has been treated with a thiazide diuretic. Do you recommend another agent to help lower her blood pressure? A seasoned clinician might wonder why this decision, one that is made every day in a busy practice, can pose an ethical challenge. Yet it does.

Principle-based ethics encourages clinicians to consider four fundamental principles when making decisions about health care. We will briefly review these four principles and then discuss how they might apply to four categories of health care, including: (1) screening tests for asymptomatic patients; (2) prophylactic medications for patients with well-defined conditions, such as hypertension; (3) diagnostic tests for symptomatic patients; and (4) treatments for patients with well-defined diseases. Most clinical activities fall into one of these four categories. At the end of the chapter, we will focus on four of the most controversial areas in bioethics (genetic testing, futile treatment, the allocation of resources based on age, and physician-assisted suicide) and explore how these controversies may affect the quality of life and decision making for seniors with cardiovascular disease.

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THE FOUR FUNDAMENTAL ETHICAL PRINCIPLES

A caveat is needed before reviewing the four ethical principles. The principles provide a framework for addressing ethical problems. If we expect them to lead to clear, easy-to-follow clinical algorithms, we expect too much from them. Clinical decision making is often too complex for many algorithms, no matter how well the algorithm may be grounded by principles. Physicians and patients bring many biases to the office or bedside, and often these biases have little to do with principles. Yet these biases, which we will discuss briefly in this chapter, have much to do with ethical decision making. When clinicians can balance the four principles with their own biases and with their patients' biases in clinical decision making, they are practicing virtue or care-based ethics. The medical and ethics literature is replete with articles about principle-based ethics. Unfortunately, the literature is short on articles dealing with virtue or care-based ethics, the ethics that guide most clinicians in their busy everyday practices.

Nonmaleficence is the first principle (i.e., first, do no harm). This principle is easy to preach from an ivory tower. In the real world of health care, however, it is not always easy to follow. Any test or medication a clinician prescribes carries some risk of an adverse outcome. Clinicians cannot help their patients unless they are willing to accept the small risk of harming them. A good clinician helps the patient weigh the potential benefits and burdens in deciding what course to follow, but cannot guarantee that there will be no harm in pursuing that course.

Beneficence is the second principle. It is the obvious corollary to nonmaleficence. Once again, we have a principle that is easy to preach form the ivory tower. In the office, however, the beneficent course is not always well marked.

Autonomy is the third principle. This principle suggests that patients (or surrogate decision makers) should decide what course is best for themselves. In a society built on rugged individualism, such as the U.S., autonomy tends to be the decisive principle in solving most ethical problems. It, too, can be difficult to translate into medical practice on a routine basis.

Although quality of life is not one of the four principles, it deserves mention in this introduction because of its central importance in the care of elderly patients. With rare exceptions, guidance from the first three principles leads to considerations of quality of life. When patients follow courses that are very unlikely to harm them, that are very likely to benefit them, and that they perceive to be in their best interests, they are, in essence, expecting to improve the quality of their lives.

Justice is the fourth principle. It encourages us to practice medicine that is fair to the individual patient and to the communities (e.g., family, nursing home, city, state, HMO, indemnity insurance pool, Medicare, etc.) in which the patient and physician must share resources. Justice is perhaps the least developed principle because it asks that we work to improve the lives of others, not just of ourselves or of our patients.

Whereas nonmaleficence and beneficence can be viewed as two sides of the same coin, autonomy and justice can be viewed as two different currencies. A challenge for all clinicians in the 21st century will be to balance the needs and desires of individuals (autonomy) with the needs and desires of communities, particularly the disenfranchised (justice).

With a focus on cardiovascular disease in elderly patients, we will now turn to common measures from four categories of health care. Although the four principles form

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the framework for this discussion, we will see that many biases enter into—and many simplify or complicate—medical decision making.

SCREENING TESTS FOR ASYMPTOMATIC PATIENTS

The majority of screening tests detect cancers. However, a large number of screening tests detect cardiovascular disease. We will focus on two such tests, the routine (or preoperative) electrocardiogram (EKG) and cholesterol levels.

The rationale for these tests is straightforward. The screening tests may detect a risk factor for cardiovascular disease (e.g., high cholesterol levels) or early cardiovascular disease (e.g., an arrhythmia or left ventricular hypertrophy) in a patient who has no cardiovascular symptoms and is aware of no risk factors or early disease. Early intervention could lead to therapies that reduce the risk of cardiovascular disease, or at least delay the onset of symptomatic disease. Assuming there are no significant side effects from the therapy, we conclude that the therapy benefits the patient. Although one could argue about the degrees of benefit or the risks of harm from screening tests, most would agree that screening tests pose few challenges to the principles of nonmaleficence and beneficence.

Screening tests present more challenges to the principles of autonomy and justice. An autonomous decision is an informed one. When physicians order screening tests, patients do not ordinarily have a full understanding of the likelihood that information from the test will either benefit or harm them (1,2). Patients trust that their physicians encourage tests that are potentially beneficial. Consider, for example, cholesterol screening for an 80-year-old woman who has no history of cardiovascular risk factors. Assume her total cholesterol level is 260. Based on analyses of absolute risk reduction, we can estimate that there is less than a 1% chance that cholesterol reduction will improve her quality of life (by delaying onset of cardiovascular symptoms or death) (3,4). Many seniors would opt for cholesterol reduction even if the absolute risk reduction was less than 1%, but many would not (5). Without knowing the probability of benefit, patients will not be able to make truly informed decisions. On the other hand, providing too much information can confuse patients and make medical practice impractical. A virtuous physician strives for a balance that meets the informational needs of his patients. He does not necessarily screen all and then prescribe treatments to lower cholesterol, simply because his colleagues or a professional society suggest that he do so. He helps individual patients make autonomous decisions.

Preoperative EKGs illustrate a challenge to the principle of justice. The problem can be framed with this question. At a time when millions of citizens are uninsured or underinsured, should the medical profession encourage practices that benefit so few? Stated differently, are preoperative EKGs cost-effective? If we are considering seniors with angina who are having revascularization for peripheral vascular disease, the answer is yes. Cost-effectiveness analyses may show that the cost of obtaining one quality-adjusted life year from preoperative EKGs in this population ranges from $10,000 to $30,000 (6), a range considered quite cost effective by today's standards (7–10). If, however, we are considering seniors with no cardiovascular disease who are having cholecystectomies, the answer is probably no. Extrapolating from various studies, we can estimate that the cost per quality-adjusted life year for preoperative EKGs in this population may be greater than $200,000 (11–13), a figure that few would consider cost-effective. Although

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preoperative EKGs are the norm, it his hard to justify preoperative EKGs for low-risk patients when many other cost-effective measures are not available to all members of society.

PROPHYLACTIC MEDICATIONS FOR PATIENTS WITH WELL-DEFINED CONDITIONS

Antihypertensives for systolic hypertension and anticoagulation for atrial fibrillation are common prophylactic measures that seem to raise few, if any, ethical questions. However, the use of prophylactic medications raise the same ethical concerns discussed for screening tests. In prescribing medications prophylactically, clinicians strive to minimize potential harm, maximize potential benefit, encourage autonomous decisions, and practice cost-effective care.

For patients to make informed decisions, they must understand the likelihood that medications will prevent an adverse outcome. Specifically, they must know the likelihood that antihypertensive therapy will help prevent a stroke or congestive heart failure. Similarly, they must know the likelihood that anticoagulation for atrial fibrillation will help prevent a stroke. The relative risk reduction, which is often highlighted in the medical literature and in the media, does not inform a patient (or physician) about the likelihood that medication will prevent adverse outcomes. It is the absolute risk reduction that a patient and physician must know if they are to make truly informed decisions (14,15).

Antihypertensives and anticoagulation are both associated with absolute risk reductions ranging from 3 to 6% (16–23). Given these odds, the vast majority of healthy 65-year-olds would opt for treatment, though a few individuals might not (5). On the other hand, many 90-year-olds with comorbidities may opt to forego treatment for hypertension or atrial fibrillation if they understand the likelihood of benefit.

It is unrealistic to expect physicians to present—and patients to understand—all of the probabilities that might be associated with a treatment decision. In most cases, clinicians distill information, present options to patients, and make recommendations. Clinicians use a model of decision making that is similar to the enhanced autonomy model proposed by Quill and Brody (24), who suggest that clinicians can enhance patient autonomy by sharing the clinician's biases.

Consider the decision to treat mild systolic hypertension in a 90-year-old. One clinician, who leans toward therapeutic nihilism, might strongly discourage antihypertensives for this patient. Another clinician, who leans toward therapeutic evangelism, might strongly encourage tight control of blood pressure in this patient. As long as they both share their biases, and allow patients to agree or disagree, they can promote patient autonomy.

Cost-effectiveness must also be considered in these routine decisions. Consider, again, the 90-year-old with mild systolic hypertension. Treatment with less expensive alternatives such as diuretics, beta-blockers, or reserpine (25) may be cost-effective whereas treatment with more expensive alternatives, such as ACE inhibitors or calcium channel blockers, may not be cost-effective. Much, of course, depends on other risk factors, potential side effects, and concurrent disease. Nevertheless, first-line treatment with expensive antihypertensives, no matter who is paying for the medication, may not be cost-effective in this case.

Options for treating atrial fibrillation are much more limited than options for treating hypertension. However, clinicians and patients still have choices, specifically aspirin or

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warfarin. One study showed that for 65-year-old patients with nonvalvular atrial fibrillation alone, warfarin therapy costs $370,000 per quality-adjusted life-year saved, as compared with aspirin therapy (26). The cost per quality-adjusted life year was $110,000 for 75-year-old patients with nonvalvular atrial fibrillation alone (26). These are significant sums that cannot be ignored as our society struggles to define cost-effective therapy.

DIAGNOSTIC TESTS FOR SYMPTOMATIC PATIENTS

We now shift attention from patients who are asymptomatic to patients with symptoms. The ethical equation changes somewhat. Patients with symptoms probably have different thresholds for potential burdens and benefits than patients with no symptoms. A patient with undiagnosed chest pain, for example, is willing to assume more risk from diagnostic tests than a patient with no chest pain. The potential benefit is much greater for the symptomatic patient.

Autonomous decisions become more complex than simply considering probabilities of benefit. The physician and patient must also consider the meaning of suffering (that is, the symptoms) in the patient's life. The physician's biases may take on more importance. A symptomatic patient is vulnerable and more likely to be swayed by the recommendations of the physician. Consider a 70-year-old man with atypical chest pain. Although the pain may not appear to be cardiac in origin, the man is frightened by the possibility of coronary artery disease. It may be the patient's level of fear, rather than the nature and severity of the pain, that influences the physician to recommend cardiac catheterization. The physician cannot expect an objective, dispassionate assessment of the pros and cons of all reasonable tests from the patient who is worried that he may die suddenly from a heart attack. Similarly, the physician cannot expect a set of guidelines to determine which tests to use to diagnose the problem. The physician must guide the patient. As long as the physician is aware of the many biases that influence decisions to recommend cardiac catheterization and is willing to share those biases with the patient, he or she is likely enhancing the autonomy of her patient.

The cost-effectiveness of various diagnostic tests for atypical chest pain is difficult to determine. Assuming we could study a homogeneous population of patients with atypical chest pain, we could follow those who had cardiac catheterizations and compare their outcomes (at 1, 5, or 10 years) with those who did not have cardiac catheterizations. Measuring quality of life and mortality, we could calculate the cost per quality-adjusted life year associated with cardiac catheterization in patients with atypical chest pain. However, two obstacles may preclude accurate determination of cost-effectiveness for these patients. First, gathering a homogeneous population of patients with atypical chest pain—or many other symptoms—is difficult. Second, cost-effectiveness analyses, including those using sophisticated quality-of-life measurements, do not reliably account for the peace of mind (or perhaps anxiety) that patients may experience 1, 5, or 10 years after a cardiac catheterization. These are not excuses for neglecting cost-effectiveness studies in patients with complex signs or symptoms. Similarly, these are not excuses for clinicians to neglect the cost of diagnostic tests when evaluating patients with symptoms. Rather, these are reasons we cannot always reduce the art of medicine to scientific formulas that tell us what is cost-effective and what is not. In summary, symptoms may strongly influence how clinicians weigh the four fundamental principles.

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TREATMENTS FOR PATIENTS WITH WELL-DEFINED DISEASES

We will focus on thrombolytics for acute myocardial infarctions to illustrate how the four fundamental principles may apply to decision making for a patient who presents with symptomatic disease. Consider, for example, an 80-year-old man who presents to the emergency room 1 h after the onset of severe chest pain. The evaluation reveals an acute anterior myocardial infarction. Should the emergency physicians treat this patient with a thrombolytic agent? Is there an ethically correct standard for this decision in 1998?

Assuming the patient has no contraindications to thrombolytic therapy, the physicians can reassure him that the risk of harm is very small, certainly smaller than the potential benefit. The absolute risk reduction associated with thrombolytic therapy ranges from 3% to 7% (27–29). The chance that a thrombolytic agent will cause serious harm, such as a life-threatening bleed, is less than 1%. A decision based on the principles of nonmaleficence and beneficence favors thrombolytic therapy.

Can a patient make an autonomous decision when he has severe chest pain and physicians are presenting options that he has never had to consider? It is doubtful. The idealized decision-making model, with patient autonomy guiding the way, simply does not work in an emergency room (or other clinical settings) where patients and providers are stressed and decisions must be made without careful consideration of all of the factors that might apply. Again, enhanced autonomy is a more appropriate model.

Is thrombolytic therapy for this 80-year-old man a fair use of limited resources? Recognizing that cost-effectiveness analyses have shortcomings and biases (30,31), we turn to such studies to provide some clarity. An analysis by Krumholz and colleagues suggested that the cost per year of life saved to use streptokinase for 80-year-old patients with acute myocardial infarctions is about $21,200 (32). Depending on a number of assumptions, the cost per year of life saved may be as high as $55,000 (32). Nevertheless, the cost-effectiveness of streptokinase therapy for octogenarians appears very reasonable.

We can conclude that, based on the four principles that guide ethical decision making in our culture, treating older patients with thrombolytic therapy is appropriate. Our society should indeed encourage more appropriate use of thrombolytic therapy for seniors (33,34).

But this analysis seems too easy. Let us complicate the decision by allowing the emergency room physician to choose either streptokinase or tissue plasminogen activator (tPA), which costs ten times more than streptokinase (35) but can further reduce the absolute risk of death by 1% (36,37). The following is a series of thoughts that may enter the physician's mind.

First, I want to provide the best treatment possible. I must ask myself, what if this was my father? Wouldn't I want him to have tPA? Second, how is this patient insured? What if his managed care company doesn't cover tPA? Third, all of my colleagues use tPA. Shouldn't I follow the standard of care in my community? Fourth, I own stock in the manufacturer of tPA. I know I shouldn't let that influence my decision, but it does to some extent. Fifth, a friend of mine was sued for not offering tPA in a similar situation. What if that happens to me? Sixth, a patient I treated with tPA 4 years ago died from an intracranial hemorrhage. Could that happen again? Seventh, tPA is a lot more expensive than streptokinase. I know that some studies show that tPA is more effective than streptokinase, but some studies show they are equally effective. Can I justify the additional cost? Eighth, our pharmacy and therapeutics committee has asked that we consider using streptokinase more frequently.

No doubt there are other thoughts that enter the physician's mind. The conflicts of

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interest inherent in this routine decision—streptokinase or tPA?—suggest that the four fundamental principles will not necessarily provide answers about what clinicians ought to do. Rather, they are simply guideposts. The physician must rely on her knowledge, biases, and virtues to reach a decision she believes is ethically sound.

We now turn to four of the most controversial areas of medical ethics and consider how these controversies may affect care for seniors with cardiovascular disease or risk factors.

GENETIC TESTING

Although genetic testing is rarely used in the treatment or counseling of seniors in 1998, developments in genetic testing regarding Alzheimer's disease (38,39) and cancer (40) suggest that the use of these tests may increase significantly in the next 5 to 10 years. Progress in this area will of course depend on beneficial treatments for these diseases.

We can expect that similar tests will be developed to identify patients at high risk for cardiovascular disease. Considering the number of options already available to prevent cardiovascular disease, it is likely that genetic screening for cardiovascular disease will gain wide support. Not everyone will perceive these advances as helpful. Consider the following scenario in the year 2010. A 65-year-old male wonders about his chance of developing symptomatic coronary artery disease when he is 75. Based on his family history, his lifestyle, and genetic testing, a computer program estimates that he has a 6% chance of dying with a myocardial infarction, a 27% chance of having unstable angina, and a 53% chance of having stable angina by the time he is 75. More elaborate genetic testing indicates that he can cut these odds in half by taking vitamin E and aspirin daily and by lowering his cholesterol by 30% with medication. Will this prognostic information be helpful or not?

Some will say yes (41). They will want to know as much as possible about outcomes so that they can pursue measures to minimize their risk of disease. They would rather know what dangers await them so that they can try to ward them off.

Some will say no. They will not want to worry about a future that, no matter what they do, may never come to pass. The potential years added to their lives may not be worth the anxiety caused by this prognostic information.

Currently we have the ability to risk-stratify patients based on a variety of risk factors, such as level of activity, family history, concomitant diseases, smoking history, and others. Genetic testing has the potential to significantly improve our ability to risk-stratify (42). The timing of these tests and the use of information from them will largely depend on patients' values and preferences. The factors we addressed for screening asymptomatic patients will become even more important as genetic testing leads to accurate risk stratification.

FUTILITY

Interest in futile interventions has accelerated in the last 10 years. Concerns about quality of care at the end of life, about responsible stewardship of limited health care resources, and about professional integrity have driven this debate. Many speak of inappropriate, rather than futile, interventions. The reason is that health care professionals rarely, if ever,

provide interventions that are truly futile. On the other hand, professionals commonly provide interventions that are very unlikely to succeed, are very costly, and are unlikely to improve the patient's quality of life.

No matter what language we use to describe interventions that may be considered futile or inappropriate, cardiopulmonary resuscitation (CPR) for chronically ill seniors is an example we use to illustrate this type of care. Studies show that it is the burden of disease, not chronological age, that determines the likelihood of survival to leave the hospital (43–45). However, we will use the example of a very old individual to highlight some of the issues that the futility debate will help us address in the coming years.

Imagine a 90-year-old who has lived in a nursing home for the last 3 years. He has moderate dementia, an advanced cardiomyopathy (ejection fraction about 20%), type II diabetes with chronic renal insufficiency (creatinine about 3.0), and a history of severe depression. He has only one relative, a grandson who sees him about once a year. Two years ago, the primary care physician asked the patient if he would want CPR in the event of a cardiac arrest. Despite the dementia, the patient could comprehend the question to some degree, but he wasn't sure what he would want. Now the patient is admitted to the hospital with pulmonary edema. When the physician asks the grandson what to do if his grandfather has a cardiac arrest, the grandson responds, ''anything you can to bring him back.''

Almost all physicians would agree that a cardiac arrest would be fatal for this patient. CPR simply would not work (46) (granted, if someone cardioverted him from ventricular tachycardia within a couple of minutes of the onset of the arrhythmia, he might have a chance). For the sake of illustration, let's assume CPR would be futile. A skeptic could ask, why bother to define CPR in this case as futile or inappropriate? Whether CPR is given or not, the patient will die when he has a cardiac arrest. He will not feel pain one way or another. Furthermore, the costs savings from withholding CPR would be trivial (47,48).

Defining futile or inappropriate interventions is important for two key reasons. The first reason is that the process of building a community consensus about futile interventions will ultimately lead to better communication about, and delivery of, end of life care. Advance directives have not been the panacea that many had hoped for, at least not as they are currently pursued in the U.S. (49,50). Community dialogues about futile interventions, such as those occurring in Sacramento, Houston, Wisconsin, and Colorado (51–53), are unlikely to lead to a consensus about futile care policies, but they are likely to lead to better end-of-life care. As a strong majority opinion (if not consensus) emerges, clinicians will feel more comfortable counseling their patients about appropriate end-of-life care. This is another example of how clinicians can enhance patients' autonomy by sharing their clinical biases (24). In the example above, the primary care physician should have counseled his then 88-year-old patient to avoid CPR, rather than approaching him like a waiter would, presenting a menu and asking the patient to select from the menu. Discussions about futile care should give clinicians more confidence serving as counselors.

The second reason is that defining futile interventions will help our society deal with the much larger question about marginally effective health care. We can consider futile care the tip of the iceberg. The vast mass of ice under the surface, which represents marginally effective care across the clinical spectrum, presents the real danger in a society struggling to control health care costs (54). Once our society can define futile interventions—and determine how to pay for such interventions—we will be much closer to setting priorities in health care. Oregon Health Decisions is the first and preeminent experi-

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ment in our country in setting priorities (55). Other communities that are trying to define futile interventions are, to a limited degree, following a similar path.

How might such a consensus change the way we deliver care 10 years from now? Let us return to the 90-year-old nursing home resident who is hospitalized with pulmonary edema. When his grandson insists on CPR, he will be informed that his grandfather's managed care company has been directed by its community of subscribers not to pay for interventions the community believes are inappropriate. If the grandson persists in requesting CPR, he will be informed that he will be responsible for paying for all care related to the CPR and subsequent intensive care. The threat of a lawsuit will have little impact because many cases will have been tested in the courts, and the courts will have supported communities' decisions to limit inappropriate interventions.

AGE-BASED RATIONING

The debate about age-based rationing began earnestly in 1988 with the publication of Setting Limits (56), the controversial book by Daniel Callahan, then director of the Hastings Center. Callahan argued that there is a natural lifespan and that seniors ought to conserve resources for younger generations rather than use these limited resources to extend the natural lifespan just a little longer. Others have made similar arguments (57–60). At the risk of oversimplying these arguments, I will summarize the rationale for age-based rationing with the following question. If our society must set limits (i.e., conserve health care resources), what is a more fair criterion for setting limits than something we all share? With the exception of premature catastrophic illness, we all share aging. We do not all share race, creed, gender, socioeconomic status, or other factors that may divide us.

Currently our society rations health care based on ability to pay. The rationing may not be explicit, but it is real nonetheless. Our society may go to great lengths to rationalize the status quo, but few commentators would claim that our system is fair. Some consider age a more fair criterion than socioeconomic status.

Opponents of age-based rationing argue that such rationing is not only discriminatory, it is unnecessary. With appropriate measures (e.g., eliminating fraud and abuse, eliminating waste, etc.), there will be no need to single out any group in society for conserving resources. There should be enough to meet everyone's needs, if not their desires. Our society's confidence in free market solutions to rising health care costs, particularly in managed care, has led to a simmering of the debate on age-based rationing. The debate is likely to boil over again only if the current approaches to controlling health care costs are unsuccessful.

Why should our optimism for current solutions be guarded? The primary reason is that the savings resulting from managed care are probably one-time savings (61). In the year 2008, we may find that all that managed care has done is to have delayed the inevitable struggles about the fair allocation of resources. Consider the likely evolution of reimbursement for health care for seniors. In 1998, a 90-year-old with Medicare and secondary insurance can get a CABG if all parties believe it is appropriate. Similarly, in 1998, a 90-year-old in a managed care plan for seniors can get CABG, albeit with some hassles, if all parties believe it is appropriate. When the federal government pays the managed care company 95% of the average adjusted per capita cost (AAPCC), the care between traditional Medicare and managed care looks very similar. Granted, there are extra hassles in

obtaining appropriate interventions in managed care. In the end, however, the care should not look much different.

What is likely to happen in the year 2008? First, most seniors will have changed from traditional Medicare to managed care. Second, the reimbursement from the federal government to the managed care company may be 85% (or lower) of the AAPCC. This assumes that the federal government plans to reign in the costs of health care for seniors. If many managed care companies are seeing their profit margins diminish in 1998 when they receive 95% of the AAPCC, they will surely feel the pinch when they receive 85% of the AAPCC. Consider also that many of the healthy seniors who signed up with the managed care plans in 1994, for example, will have chronic diseases by the year 2008. The golden days of managed care will be history. At that point, advocating for a CABG for a 90-year-old will be much more difficult than it is in the managed care environment of 1998. In short, our free market solution will turn out to have been short-sighted. We will be left with the question of how to set limits in an aging society, particularly if our natural lifespan is actually decades more than anyone imagined just a few years ago (62). The debate on age-based rationing will boil over again.

PHYSICIAN-ASSISTED SUICIDE

Physician-assisted suicide has captured the attention of the public (63,64), of clinicians (65), and of the courts (66) in the last few years. If current trends continue, we can expect that physician-assisted suicide will become more prevalent, at least in some states. Most requests for physician-assisted suicide have come from patients with terminal diseases that are associated with significant pain and fairly predictable courses, such as metastatic cancer. Patients with end-stage cardiovascular disease may begin to seek this alternative if physicians cannot adequately control symptoms, such as dyspnea, and if states allow physician-assisted suicide without recriminations.

A couple of predictions seem safe. First, extensive debate on the pros and cons of physician-assisted suicide is unlikely to lead to a consensus, or even a strong majority opinion, about how our society should resolve this controversy. The physician-assisted suicide debate will follow a course very similar to that for abortion. As in the abortion debate, opposing groups are unlikely to waiver. We can expect much polarization after years, even decades, of debate.

Second, requests for physician-assisted suicide from patients with end-stage cardiovascular disease will likely remain infrequent if clinicians learn to use hospice more appropriately. Appropriate use of hospice will require changes at many levels in the health care profession. Medical students and residents will need more exposure to hospice in training if they are expected to use hospice more appropriately in practice. Patients and families will need to consider this option earlier in the final stages of disease. For example, a patient with advanced cardiomyopathy who is not a transplant candidate ought to consider hospice when her life expectancy is 2 to 3 years, not just when it is 6 months or less. Reimbursement for hospice will need to change so that patients and clinicians can consider hospice earlier than they do now.

CONCLUSION

Ethical dilemmas and quality-of-life considerations are prevalent across the spectrum of care for seniors with cardiovascular disease or risk factors. Balancing the four fundamental

ethical principles and many other factors is a constant challenge for clinicians and their patients. A decision to prescribe aspirin prophylactically for a 65-year-old may present as great an ethical challenge as a decision to place a pacemaker in a 95-year-old.

Solutions for the major controversies in medical ethics may be decades away. These controversies will play themselves out in outpatient clinics, long-term care facilities, hospital intensive care units, hospices, and every other setting where clinicians work to reduce cardiovascular risk factors and treat cardiovascular disease in older patients.

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