CORONARY CARE MEDICINE

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A Practical Approach

Elliott M. Antman
and
John D. Rutherford

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To our families

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FOREWORD

Attention to reducing the major risk factors associated with the development of arteriosclerosis has been widespread and appears to have lowered the incidence of coronary artery disease. Nevertheless, acute myocardial infarction and related ischemic syndromes represent the most common causes of death as well as one of the principal reasons for hospitalization in the industrialized world. In light of this, care of the patient with acute coronary disease remains a major medical challenge.

The approach to managing patients with acute myocardial infarction can be said to have evolved through three major phases. For the first half-century after Herrick's landmark paper describing this condition was published in 1912, management consisted primarily of placing the patient at rest in order to allow the myocardial scar to heal and to prevent cardiac rupture. In the second phase, beginning in the early 1960s, the focus was on the coronary care unit and on continuous monitoring of the heart's electrical activity, which allowed prophylaxis against and treatment of life-threatening cardiac arrhythmias. The third and current phase in the therapy of acute myocardial infarction and related syndromes is the subject of this book by Elliott Antman and John Rutherford, my colleagues at the Harvard Medical School and the Brigham and Women's Hospital.

Contemporary coronary care involves a multitude of measures: efforts to prevent the acute event; thrombolytic therapy to abort infarction; pharmacological measures to delay and reduce ischemic cell death; monitoring of the hemodynamic consequences of myocardial infarction; treatment of acute pump failure; use of modern electrical devices as well as a large number of new drugs to prevent and treat cardiac arrhythmias; and finally, identification prior to hospital discharge of patients who are at high risk for recurrent infarction or sudden death and the choice of the appropriate management approach.

This fine book provides comprehensive descriptions of these various aspects of contemporary coronary care. It is accurate, thorough, and easily readable. The authors have succeeded in weaving together both well-established practice and the most up-to-date information available in this rapidly changing field. Rather than offering a "cookbook" approach, they have developed a sound strategy for caring for patients with coronary disease.

For all those professionals responsible for the care of patients with these serious and important disorders—cardiologists, internists, and coronary care nurses, both those in training and those already practicing—*Coronary Care Medicine* will be of enormous value.

Eugene Braunwald, M.D.

PREFACE

The proliferation of specialized cardiac intensive care units over the last two decades has brought about significant advances in coronary care medicine. For patients suspected to be suffering from a serious cardiac disorder (usually acute myocardial infarction), the need for close monitoring and skilled nursing care is widely accepted. Staff members who care for these critically ill patients are now expected to become familiar with a multitude of new and potent cardiovascular pharmacotherapeutic agents, specialized invasive hemodynamic monitoring techniques, and means of mechanically supporting the failing cardiovascular system. Newcomers to the intensive care unit area — such as medical students, interns, medical residents, and cardiovascular trainees during the early phases of their fellowship as well as nursing students and recently graduated nurses — feel understandably anxious when called upon to implement life-saving therapeutic modalities in this setting and are often unfamiliar with the appropriate use of the latest drugs and specialized invasive techniques.

In this manual, we have tried to offer as concisely as possible a pragmatic approach to diagnosis and the problems of management for patients with severe heart disease. In addition, we have endeavored to provide the reader with practical information about differential diagnosis, drugs, arrhythmias, and means for interpreting hemodynamic data. It is our hope that this book will be useful not only for persons at various stages of training in this field but also for the practicing internist, cardiologist, and intensive care unit physician who encounter patients in the coronary care unit.

Acknowledgments

The authors gratefully acknowledge the invaluable editorial assistance of Diane Q. Forti. The authors also acknowledge the leadership and continued support of Eugene Braunwald, M.D.; Thomas W. Smith, M.D.; and John M. Neutze, M.D. Finally, our thanks to others who contributed to the completion of this project including Mary Gillan, Lisa McHale, and Kay Martin.

CORONARY CARE MEDICINE

1. PATHOGENESIS AND PATHOLOGY OF ISCHEMIC HEART DISEASE SYNDROMES

1. Atherosclerosis

1.1. DEFINITIONS

The terms "arteriosclerosis" and "atherosclerosis" are often confused in descriptions of experimental and clinical arterial lesions. *Arteriosclerosis* is a general term implying arterial hardening without respect to a specific etiology, examples being atherosclerosis, Mönckeberg's medial calcification, and arteriolosclerosis (small vessel disease) [1]. *Atherosclerosis* refers to a specific disease process characterized by the development of yellow, lipid-laden plaques. There are three pathological stages in such plaque development:

1. *The fatty streak*, which is a yellow, generally flat patch on the intima made up of accumulated lipid-containing smooth muscle cells. Commonly found in young individuals fatty streaks probably have no pathological significance in many cases.

2. *The fibrous plaque*, which is an intimal deposit of lipid-laden smooth muscle cells surrounded by collagen, elastic fibers, and extracellular lipid. Fibrous plaques may or may not arise from fatty streaks and can exist without causing significant obstruction of the vascular lumen.

3. *The complex plaque*, which is a fibrous plaque that has progressed to include calcification, hemorrhage, cell necrosis, an inflammatory reaction, and extension to the arterial media. Adventitial fibrosis and inflammation may be present.

1.2. PATHOGENESIS OF ATHEROSCLEROSIS

1.2.1. Classic theories. Historical concepts of the pathogenesis of atherosclerosis can be divided into two major schools of thought. One is the *encrustation* theory (proposed by Rokitansky), which states that small mural thrombi form in areas of endothelial injury. These become organized by smooth muscle cells, grow, and play a major role in the development of a mature plaque. The second theory is the *imbibition/insudation* theory (proposed by Virchow), which states that the infiltration of plasma constituents into the arterial intima is the principal factor in the development of atherosclerotic plaques. As summarized by Wissler [1], these two theories are now being combined into a more unified concept (figure 1–1). Abundant evidence has accumulated indicating that elevated serum cholesterol levels are strongly associated with progressive atherosclerosis. Although mural thrombi are not thought to play a major role in atherosclerotic plaque development, injury to the vascular endothelium (at least in part due to *insudation* of hyperlipidemic serum) causes *encrustation* of platelets and monocytes. Smooth muscle cells in the intima and media are subsequently stimulated to proliferate and form an advanced plaque.

1.2.2. New concepts in atherosclerosis. The study of the pathogenesis of atherosclerosis is a complex, rapidly evolving field that combines many disciplines, including cellular and molecular biology, biochemistry, and genetics.

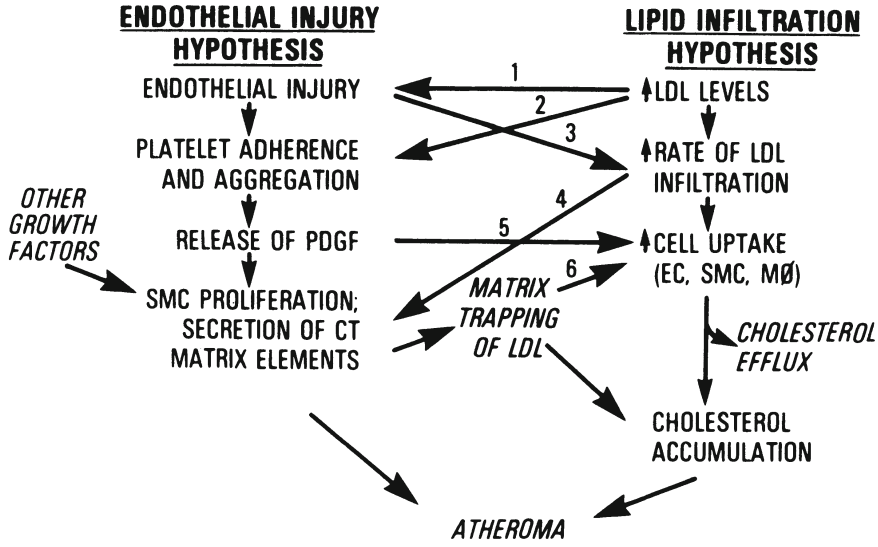

FIGURE 1–1. Proposed unification of the endothelial injury and lipid infiltration hypotheses. (1) Elevated LDL levels may damage endothelial cells (EC). If so, hyperlipidemia could simultaneously initiate the series of events characterizing the lipid infiltration hypothesis and those of the endothelial injury hypothesis. (2) Hyperlipoproteinemia has been reported to favor platelet aggregation, an effect that might initiate release of platelet-derived growth factor (PDGF) even when endothelial damage is modest. (3) Injury to the endothelium, by removing a transport barrier, will concurrently increase the rate of lipoprotein infiltration, cellular uptake, and degradation at any given plasma lipoprotein level. (4) LDL, particularly LDL from hypercholesterolemic animals, can stimulate the growth of smooth muscle cells (SMC). (5) PDGF (and probably other growth factors) increases the expression of LDL receptors on smooth muscle cells and thus increases their rate of uptake of lipid. (6) Stimulation of smooth muscle cell growth may cause deposition of larger amounts of certain intercellular matrix materials, such as glucosaminoglycans, that can trap LDL in the subintimal space. CT = connective tissue; MØ = macrophages. (From Steinberg D: Lipoproteins and atherosclerosis. A look back and a look ahead. *Arteriosclerosis* 3:283, 1983.)

Several excellent overviews have recently been published [1–5], and important interactions between some of the major pathogenetic mechanisms proposed for the development of atherosclerosis have been summarized (figure 1–1). Mention should be made of the intriguing suggestion made by Benditt and Benditt that foci of smooth muscle cells from atherosclerotic plaques may have a monoclonal origin [6]. Potential mitogenic factors might include such substances as the various growth factors derived from platelets, macrophages, and endothelium in the region of a developing plaque [7]. Another interesting idea is that, in addition to fibroblasts and arterial smooth muscle cells, blood-derived macrophages may act as "scavenger" cells and correspond to lipid-laden foam cells seen in complicated, advanced plaques [7,8].

Another new concept in the biology of coronary atherosclerosis is that, as a consequence of the development of an atherosclerotic plaque, a region of the coronary artery becomes hyperresponsive to circulating or locally generated/delivered vasoactive substances such as histamine or serotonin. (Supporting evidence for this theory can be found in isolated tissue studies of deendothelialized vascular strips [9].) Finally, Barger and coworkers have demonstrated an intense neovascular network of vasa vasorum in the area of atherosclerotic plaques in coronary arteries [10]. Such a network may constitute a fragile, unstable blood supply to the coronary vessel wall and may play a role in the local delivery of vasoactive compounds or conceivably could either rupture (hemorrhage into plaque) or promote thrombosis.

TABLE 1–1. Characteristics of the major classes of lipoproteins in human plasma

Lipoprotein class	Major core lipids	Major apoproteins	Density (g/ml)	Diameter (Å)	Electrophoretic mobility
Chylomicrons	Dietary triglycerides	AI, AII, B, CI, CII, CIII	<1.006	800 to 5000	Remains at origin
VLDL	Endogenous triglycerides	B, CI, CII, CIII, E	<1.006	300 to 800	Prebeta
Remnants	Cholesteryl esters, triglycerides	B, CIII, E	<1.019	250 to 350	Slow Prebeta
LDL	Cholesteryl esters	B	1.019 to 1.063	180 to 280	Beta
HDL	Cholesteryl esters	AI, AII	1.063 to 1.210	50 to 120	Alpha

(From Brown MS, Goldstein JL, in Petersdorf RG, et al (eds): *Harrison's Principles of Internal Medicine*. New York, McGraw-Hill Book Co., 1983, p. 548.)

1.2.3. Risk factors. While several factors, including age, sex, obesity, sedentary life style, personality type, and uric acid concentration, are thought to predispose an individual to atherosclerosis, the four risk factors discussed below are thought to be most important [11]. Reduction of primary risk factors should be a major goal in the long-term management of patients. It is important to initiate risk factor reduction programs during the initial contact with patients, whether in the hospital or in the family practice setting.

1.2.3.1. HYPERLIPIDEMIA. Abnormalities in the synthesis or degradation of plasma lipoproteins that result in disturbances of lipid transport and elevated plasma lipoprotein levels cause a condition known as *hyperlipoproteinemia*. Lipoproteins are globular particles of high molecular weight that transport monopolar lipids such as triglycerides and cholesterol through the plasma. There are five major classes of plasma lipoproteins, which contain a lipid core and transport proteins referred to as apoproteins (table 1–1).

Several different diseases cause elevations in one or more lipoprotein classes, resulting in a measurable increase in fasting cholesterol or triglyceride levels (referred to as *hyperlipidemia*). Since plasma lipid levels are influenced by diet and vary widely in the population, the definition of hyperlipidemia is somewhat arbitrary [12]. Statistically significant hyperlipidemia is said to be present when the following conditions pertain:

	Triglycerides	*Cholesterol*
Age < 20 years	140 mg/dl	200 mg/dl
Age > 20 years	200 mg/dl	240 mg/dl

The Lipid Research Clinics (LRC) Program Prevalence Study has provided age- and sex-adjusted guides for the normal ranges of plasma cholesterol and triglyceride values in the population (table 1–2) [13]. These guidelines are important, since there are now abundant experimental and clinical epidemiological data linking elevated serum cholesterol levels with increased risk of coronary heart disease (CHD). Furthermore, the recently published Lipid Research Clinics Coronary Primary Prevention Trial demonstrated that lowering low-density lipoprotein (LDL) cholesterol to reduce total cholesterol diminished the incidence of mortality and morbidity in men with elevated LDL cholesterol who are at risk for CHD [14,15].

In contrast to the data supporting elevated cholesterol levels as a risk factor for CHD, there appears to be only a weak association between elevated triglyceride levels and CHD [16]. However, elevated triglyceride levels may be associated with late graft atherosclerosis after coronary artery bypass surgery [17]. They may also be a clue to familial combined hyperlipidemia (the commonest monogenic lipid disorder in survivors of myocardial infarction) and, when markedly elevated, can predispose a patient to pancreatitis [1].

Additional important recent epidemiological findings relate to high-density lipoproteins (HDL). This lipoprotein class may facilitate cholesteryl ester and triglyceride metabolism and is inversely associated with risk of CHD. Thus, the prevalence of CHD at HDL levels of 30 mg/dl is twice that at HDL levels of 60 mg/dl [18]. Factors found to increase HDL levels include exercise and moderate ethanol use, while factors found to decrease these levels include smoking, use of progestin-containing oral contraceptives, obesity, and poorly controlled diabetes mellitus.

TABLE 1–2. Guides to plasma cholesterol and triglyceride values

A. Plasma Total Cholesterol (mg/dl) (Population Distribution)

Age (yr)	White males (percentiles)							White females (percentiles)						
	5	10	25	50	75	90	95	5	10	25	50	75	90	95
0 to 4	—	—	—	—	—	—	—	—	—	—	—	—	—	—
5 to 9	125	131	141	153	168	183	189	131	136	151	164	176	190	197
10 to 14	124	131	144	160	173	188	202	125	131	142	159	171	191	205
15 to 19	118	123	136	152	168	183	191	118	126	140	157	176	198	207
20 to 24	118	126	142	159	179	197	212	121	132	147	165	186	220	237
25 to 29	130	137	154	176	199	223	234	130	142	158	178	198	217	231
30 to 34	142	152	171	190	213	237	258	133	141	158	178	199	215	228
35 to 39	147	157	176	195	222	248	267	139	149	165	186	209	233	249
40 to 44	150	160	179	204	229	251	260	146	156	172	193	220	241	259
45 to 49	163	171	188	210	235	258	275	148	162	182	204	231	256	268
50 to 54	157	168	189	211	237	263	274	163	171	188	214	240	267	281
55 to 59	161	172	188	214	236	260	280	167	182	201	229	251	278	294
60 to 74	163	170	191	215	237	262	287	172	186	207	226	251	282	300
65 to 69	166	174	192	213	250	275	288	167	179	212	233	259	282	291
70+	144	160	185	214	236	253	265	173	181	196	226	249	268	280

B. Plasma VLDL-Cholesterol (mg/dl) (Population Distribution)

0 to 4	—	—	—	—	—	—	—	—	—	—	—	—	—	—
5 to 9	0	2	4	7	11	15	18	1	1	4	9	13	19	24
10 to 14	1	2	5	9	13	18	22	2	3	6	10	15	20	23
15 to 19	2	3	8	12	17	23	26	2	3	6	11	15	22	24
20 to 24	1	5	8	12	18	24	28	2	4	8	13	18	24	28
25 to 29	3	6	9	15	22	31	36	2	3	7	11	19	24	29
30 to 34	1	5	8	11	26	36	48	1	3	6	11	17	21	27
35 to 39	3	7	12	19	30	46	56	2	3	8	13	21	29	36
40 to 44	5	8	14	21	30	43	56	3	5	8	13	20	28	32
45 to 49	5	8	13	20	31	40	51	2	4	9	15	22	33	41
50 to 54	8	10	14	23	33	49	62	2	5	9	15	23	32	37
55 to 59	3	6	11	19	28	39	49	2	4	9	18	28	37	49
60 to 64	3	4	9	16	23	35	44	1	3	6	13	20	29	39
65 to 69	0	3	8	16	23	40	45	0	3	7	13	21	36	41
70+	0	3	7	15	23	31	38	0	1	6	13	19	32	48

C. Plasma LDL-Cholesterol (mg/dl) (Population Distribution)

0 to 4	—	—	—	—	—	—	—	—	—	—	—	—	—	—
5 to 9	63	69	80	90	103	117	129	68	73	88	98	115	125	140
10 to 14	64	72	81	94	109	122	132	68	73	81	94	110	126	136
15 to 19	62	68	80	93	109	123	130	59	65	78	93	111	129	137
20 to 24	66	73	85	101	118	138	147	57	65	82	102	118	141	159
25 to 29	70	75	96	116	138	157	165	71	77	90	108	126	148	164
30 to 34	78	88	107	124	144	166	185	70	77	91	109	128	147	156
35 to 39	81	92	110	131	154	176	189	75	81	96	116	139	161	172
40 to 44	87	98	115	135	157	173	186	74	84	104	122	146	165	174
45 to 49	98	106	120	141	163	186	202	79	89	105	127	150	173	186
50 to 54	89	102	118	143	162	185	197	88	94	111	134	160	186	201
55 to 59	88	103	123	145	168	191	203	89	97	120	145	168	199	210
60 to 64	83	106	121	143	165	188	210	100	105	126	149	168	191	224
65 to 69	98	104	125	146	170	199	210	92	99	125	151	184	205	221
70+	88	100	119	142	164	182	186	96	108	127	147	170	189	206

D. Plasma HDL-Cholesterol (mg/dl) (Population Distribution)

0 to 4	—	—	—	—	—	—	—	—	—	—	—	—	—	—
5 to 9	38	42	49	54	63	70	74	36	38	47	52	61	67	73
10 to 14	37	40	46	55	61	71	74	37	40	45	52	58	64	70
15 to 19	30	34	39	46	52	59	63	35	38	43	51	61	68	74
20 to 24	30	32	38	45	51	57	63	33	37	44	51	62	72	79
25 to 29	31	32	37	44	50	58	63	37	39	47	55	63	74	83
30 to 34	28	32	38	45	52	59	63	36	40	46	55	64	73	77
35 to 39	29	31	36	43	49	58	62	34	38	44	53	64	74	82
40 to 44	27	31	36	43	51	60	67	34	39	48	56	65	79	88
45 to 49	30	33	38	45	52	60	64	34	41	47	58	68	82	87
50 to 54	28	31	36	44	51	58	63	37	41	50	62	73	85	91
55 to 59	28	31	38	46	55	64	71	37	41	50	60	73	85	91
60 to 64	30	34	41	49	61	69	74	38	44	51	61	75	87	92
65 to 69	30	33	39	49	62	74	78	35	38	49	62	73	85	98
70+	31	33	40	48	56	70	75	33	38	48	60	71	82	92

*Adapted from the Lipid Research Clinics Population Studies Data Book [13].

The general approach to an evaluation of hyperlipidemia consists of measuring total cholesterol, HDL cholesterol, and total triglyceride levels on several occasions. Provided that the total triglyceride level is less than 400 mg/dl and no abnormal intermediate-density lipoproteins are present (e.g., type III hyperlipoproteinemia, as noted below), one may estimate LDL cholesterol levels (i.e., the cholesterol fraction most closely linked to CHD risk) as follows:

$$\text{LDL cholesterol} = \text{Total cholesterol} - \left(\text{HDL cholesterol} + \frac{\text{Triglyceride}}{5}\right)$$

By examining lipoprotein electrophoretic patterns, clinicians can categorize patients with hyperlipidemia into one of the hyperlipoproteinemic phenotypes described in the literature (table 1–3). Correlation with clinical observations helps confirm the patient's classification, and exclusion of the secondary causes of hyperlipoproteinemia points to the diagnosis of a primary hyperlipoproteinemia. The primary hyperlipoproteinemias may be the result of well-defined single-gene mutations or of poorly understood combinations of genetic, dietary, and environmental causes (table 1–4). The latter are currently considered to be of "unknown etiology." Clinical data on the primary hyperlipoproteinemias, including the estimated prevalence of single-gene mutations in the population and the frequency of specific hyperlipoproteinemias in survivors of myocardial infarction, may be more useful if we recognize three major groups:

Group A: Hypercholesterolemia only (Phenotype IIa)
Group B: Mild-moderate hypertriglyceridemia (Phenotypes IIb, III, and IV)
Group C: Severe hypertriglyceridemia (Phenotypes I and V)

Reference to these three simple groups, clinical examination of the patient, and observation of a plasma specimen after overnight refrigeration (table 1–3) should allow one to define the hyperlipoproteinemic pattern clearly without resorting to lipoprotein electrophoresis. It is important to remember that lipoprotein concentrations are "dynamic" and may change significantly immediately after an acute myocardial infarction and during the next 6 weeks. Although there can be a 60 per cent reduction in total plasma cholesterol and LDL cholesterol values within the first few days after infarction, it appears that cholesterol values obtained within 48 hours of the event are valid measurements on which to base long-term therapeutic decisions [19]. Plans should be made to follow up these patients with abnormal lipid values 2 to 3 months after discharge from the hospital. Patients with previously diagnosed hyperlipoproteinemias should be advised about dietary and drug therapy regimens appropriate for their form of hyperlipoproteinemia (as summarized in tables 1–5 and 1–6).

1.2.3.2. HYPERTENSION. Elevated systolic and/or diastolic blood pressure have each been shown to have predictive value for the development of CHD [20]. Blood pressure elevation shows a continuous unimodal distribution in the general population, and there is a direct correlation

TABLE 1–3. Lipoprotein electrophoretic patterns to distinguish hyperlipoproteinemia phenotypes

Hyperlipoproteinemia phenotypes and synonyms	Genetic form	Plasma cholesterol level	Plasma triglyceride level
I. *Exogenous hypertriglyceridemia* Familial hyperglyceridemia Familial chylomicronemia Fat-induced hyperlipidemia Hyperchylomicronemia	Autosomal recessive; *rare*	Normal or slightly increased	Very greatly increased
II. *Familial hypercholesterolemia* Familial hyperbetalipoproteinemia Familial hypercholesterolemic xanthomatosis	Autosomal dominant; *common*	Greatly increased	Normal or slightly increased
III. *Broad beta disease* Familial dysbetalipoproteinemia Floating betalipoproteinemia	Mode of inheritance unclear; *uncommon but not rare*	Greatly increased	Greatly increased
IV. *Endogenous hypertriglyceridemia* Familial hyperprebetalipoproteinemia Carbohydrate-induced triglyceridemia	*Common*, often sporadic when familial, genetically heterogeneous	Normal or slightly increased	Greatly increased
V. *Mixed hypertriglyceridemia* Combined exogenous and endogenous hypertriglyceridemia Mixed hyperlipemia	*Uncommon but not rare*; genetically heterogeneous	Normal or slightly increased	Very greatly increased

Appearance of chilled plasma	Risk factor in atherosclerosis	Major secondary causes	Clinical presentation	Treatment
Creamy layer over clear plasma	Risk not apparently increased	Dysglobulinemias Systemic lupus erythematosus	Pancreatitis Eruptive xanthomas Hepatosplenomegaly Lipemia retinalis	Dietary: low intake of fat, no alcohol, weight reduction
Clear or slightly cloudy	Very strong risk factor, especially for coronary atherosclerosis	Nephrotic syndrome Hypothyroidism Dysglobulinemias Cushing's syndrome Acute intermittent porphyria	Accelerated atherosclerosis Xanthelasma Tendon and tuberous xanthomas Juvenile corneal arcus	Dietary: Low cholesterol, low-fat diet consisting mainly of polyunsaturated fats Drugs: Cholestyramine, colestipol, niacin, probucol Possible surgery
Slightly cloudy to cloudy	Very strong risk factor for atherosclerosis, especially in peripheral circulation	Hypothyroidism Systemic lupus erythematosus Cholestasis (with LP-X) Hepatic failure (with lamellar HDL)	Accelerated atherosclerosis of coronary and peripheral vessels Planar xanthomas Tuboeruptive and tendon xanthomas	Dietary: Reduction to ideal weight, maintenance of low cholesterol, balanced diet Drugs: Clofibrate, niacin
Clear, cloudy, or milky	Probable risk factor, especially for coronary atherosclerosis	Diabetic hyperlipemia Glycogenosis, type I Lipodystrophies Dysglobulinemias Uremia Hypopituitarism Nephrotic syndrome (Diabetes mellitus) (Alcoholism) (Estrogen use) (Glucocorticoid use) (Stress-induced)	Possible accelerated atherosclerosis Glucose intolerance Hyperuricemia	Dietary: Weight reduction, low-carbohydrate diet, no alcohol Drugs: Niacin
Creamy layer over milky plasma	Risk of atherosclerosis not clearly increased	Diabetic hyperlipemia Glycogenosis, type I Lipodystrophies Dysglobulinemias Uremia Hypopituitarism Nephrotic syndrome (Diabetes mellitus) (Alcoholism) (Estrogen use) (Glucocorticoid use) (Stress-induced)	Pancreatitis Eruptive xanthomas Hepatosplenomegaly Sensory neuropathy Lipemia retinalis Hyperuricemia Glucose intolerance	Dietary: Weight reduction, low-fat diet, no alcohol Drugs: Niacin

between the degree of hypertension and excess risk of morbidity and mortality from CHD [20]. Recent epidemiological studies have demonstrated that even casual elevated blood pressure readings are predictive of the development of CHD. Hypertension in the elderly and in women is also a potent risk factor [21].

While it is important to identify conditions such as hypertension as risk factors for CHD it is also important to know whether modification of the risk factor will in fact reduce the risk. Until recently this last point has been difficult to demonstrate for hypertension and currently the benefits of standard therapy for "mild" hypertension are controversial (i.e., diastolic pressure = 90 to 99 mm Hg). These issues are reviewed in detail elsewhere [21–23], and only the important highlights will be mentioned here.

The Veterans Administration Cooperative Study Group on antihypertensive agents reported that although treatment of severe (diastolic pressure above 115 mm Hg) and moderate (defined in this study as diastolic pressure above 90 mm Hg) hypertension favorably affected the indices of stroke and congestive heart failure [5], no reduction in the incidence of CHD (acute myocardial infarction and sudden cardiac death) was demonstrated [24,25], perhaps owing to the small sample size. More recent studies have shown a diminution in morbidity and mortality due to CHD with antihypertensive therapy. These include the Göteborg Study [26], the Australian Therapeutic Trial in Mild Hypertension [25], and the Hypertension Detection and Follow-Up Program (HDFP) [28,29]. Opinion appears to be unanimous that treatment of severe or moderate

TABLE 1–4. Characteristics of primary hyperlipoproteinemias

Single-Gene Mutations

Genetic disorder	Primary biochemical defect	Plasma lipoprotein elevation	Lipoprotein pattern	Xanthomas
Familial lipoprotein lipase deficiency	Deficiency of lipoprotein lipase	Chylomicrons	I	Eruptive
Familial apoprotein CII deficiency	Deficiency of apoprotein CII	Chylomicrons and VLDL	I or V	
Familial dysbeta-lipoproteinemia	Abnormal apoprotein E of VLDL	Remnants	III	Xanthelasma; tuberous; palmar creases
Familial hypercholesterolemia	Deficiency of LDL receptor	LDL	IIa (rarely IIb)	Xanthelasma; tendon
Familial hypertriglyceridemia	Unknown	VLDL (rarely chylomicrons)	IV (rarely V)	(Eruptive)
Multiple lipoprotein-type hyperlipidemia (familial combined hyperlipidemia)	Unknown	LDL and VLDL	IIa, IIb, or IV (rarely V)	
Unknown Etiology				
Polygenic hypercholesterolemia	Unknown			Absent
Sporadic hypertriglyceridemia				

hypertension does reduce CHD morbidity and mortality; however, there is controversy over whether the treatment of mild hypertension is necessary and whether the benefits of treatment outweigh the side effects of the therapeutic agents used. The Multiple Risk Factor Intervention Trial (MRFIT) tested the value of treating mild-moderate hypertension and hypercholesterolemia and of limiting cigarette smoking using specially designed "stepped-care" clinics versus the usual care (i.e., by the community physician). While blood pressure was reduced in the special care group, it was *also* reduced in the usual-care group. Special care appeared to offer no advantage to individuals with diastolic pressure less than 100 mm Hg [30]. Of particular concern was the finding that mortality was increased in hypertensives with an entry diastolic pressure of 90 to 99 mm Hg and an abnormal baseline ECG (e.g., left ventricular hypertrophy with strain) who were treated in a stepped-care fashion, usually beginning with diuretics. It was hypothesized that diuretic-induced potassium depletion predisposed such patients to lethal ventricular arrhythmias.

Therefore some investigators feel that mild hypertension should *not* be treated unless the diastolic pressure is consistently above 100 mm Hg after 6 months on nondrug therapy or unless diastolic blood pressure is consistently between 90 and 100 mm Hg with other risk factors present. Based on the HDFP data, it appears that a cutoff of 90 mm Hg would impose antihypertensive therapy on 3,000 patients to prevent one death per year, whereas a cutoff of 100 mm Hg would require that only 140 persons be treated.

Pancreatitis	Premature atherosclerosis	Lipoprotein pattern in affected relatives	Estimated prevalence in population	Frequency of disorder in survivors of myocardial infarction: % Total MI survivors: Under age 60	Over age 60	Ratio
+		I	<1:100,000			
+		I or V	<1:1,000,000			
	+	IIa, IIb, III, or IV	1:100			
	+	IIa (rarely IIb)	1:500	4.1	0.7	6:1
(+)	+	IV (rarely V)	1:500	5.2	2.7	2:1
	+	IIa, IIb, or IV (rarely V)	1:300	11.3	4.1	3:1
		<10% of first-degree relatives show hyperlipidemia		5.5	5.5	1:1
		Absence of hyperlipidemic relatives		5.8	6.9	1:1

MI = Myocardial infarction.

TABLE 1–5. Diets for type I to V hyperlipoproteinemias

	Type I	Type IIa	Types IIb and III	Type IV	Type V
Diet prescription	Low fat, 25 to 35 gm	Low cholesterol, polyunsaturated fat increased	Low cholesterol Approximately: 20% cal Protein 40% cal Fat 40% cal CHO	Controlled CHO (approximately 45% of cal) Moderately restricted cholesterol	Restricted fat, 30% of cal Controlled CHO, 50% of cal Moderately restricted cholesterol
Calories	Not restricted	Not restricted	Achieve and maintain "ideal" weight, i.e., reduction diet if necessary	Achieve and maintain "ideal" weight, i.e., reduction diet if necessary	Achieve and maintain "ideal" weight, i.e., reduction diet if necessary
Protein	Total protein intake not limited	Total protein intake not limited	High protein	Not limited other than control of patient's weight	High protein
Fat	Restricted to 25 to 35 gm Kind of fat not important	Saturated fat intake limited Polyunsaturated fat intake increased	Controlled to 40% cal (polyunsaturated fats recommended in preference to unsaturated fats)	Not limited other than control of patient's weight (polyunsaturated fats recommended in preference to saturated fats)	Restricted to 30% of cal (polyunsaturated fats recommended in preference to saturated fats)
Cholesterol	Not restricted	As low as possible; the only source of cholesterol is the meat in the diet	Less than 300 mg; the only source of cholesterol is the meat in the diet	Moderately restricted to 300 to 500 mg	Moderately restricted to 300 to 500 mg
Carbohydrate	Not limited	Not limited	Controlled-concentration sweets are restricted	Controlled-concentrated sweets are restricted	Controlled-concentrated sweets are restricted
Alcohol	Not recommended	May be used with discretion	Limited to 2 servings (substituted for carbohydrate)	Limited to 2 servings (substituted for carbohydrate)	Not recommended

CHO = carbohydrate; cal = calories.

From Levy, RI, Feinleib M: Risk factors for coronary artery disease and their management. In: *Heart disease: a textbook of cardiovascular medicine*, 2nd ed, Braunwald E (ed), Philadelphia, WB Saunders Company, 1984.

Finally, because of concerns about diuretic-induced hypokalemia, it has been suggested that the initial drug in "stepped-care" therapy of hypertension should instead be a beta-adrenoceptor blocking agent. This is particularly true for young individuals with evidence of ECG abnormalities at rest. Some support for such an approach may be gleaned from the results of beta blocker secondary prevention trials after MI, such as the The Beta-Blocker Heart Attack Trial (BHAT) (propranolol) [31], the Norwegian Multicentre Study Group (timolol) [32], and Goteborg Metoprolol Trial in Acute Myocardial Infarction [33], since a substantial proportion of the patients entered into these trials had a past history of hypertension.

1.2.3.3. CIGARETTE SMOKING. Cigarette smoking is a well-recognized major risk factor for

TABLE 1–6. Approved hypolipidemic agents

	To decrease lipoprotein synthesis	Enhanced intravascular lipoprotein catabolism		To increase lipoprotein catabolism		
	Nicotinic acid	Clofibrate	Gemfibrozil	Colestipol, cholestyramine	D-Thyroxine	Probucol
Primary indication	↑ VLDL; ↑ IDL (Types III, IV, and V)	↑ IDL (Type III)	↑ VLDL (Types IV and V)	↑ LDL (Type II)	↑ LDL (Type II)	↑ LDL (Type II)
Other indications	↑ LDL (Type II)	↑ VLDL (Types IV? and V)	↑ IDL (Type III)		↑ IDL (Type III)	
Initial dose	100 mg t.i.d.	1 g b.i.d.		8 g b.i.d.	2 mg q.i.d.	250 mg b.i.d.
Maintenance dose	1 to 3 g t.i.d.	1 g b.i.d.	600 mg b.i.d.	8 to 16 g b.i.d.	4 to 8 mg q.d.	500 mg b.i.d.
Major side effects	Flushing Pruritus Nausea Diarrhea	Nausea Diarrhea	Nausea GI discomfort	Constipation Nausea	Mild hypermetabolism ↑ Angina and cardiac irritability in patients with heart disease	Diarrhea Nausea
Other side effects	Glucose intolerance Hyperuricemia Hepatotoxicity	Myositis Ventricular ectopy Abnormal liver function tests Cholelithiasis	? ↑ Glucose intolerance ? Cholelithiasis	Hyperchloremic acidosis Biliary tract calcification Steatorrhea	Glucose intolerance Neutropenia	?
Drug interactions	↑ Vasodilatation by ganglioplegic antihypertensive agents	↑ Hypoprothrombinemic effect of warfarin	Potentiates effect of anticoagulants	↓ Absorption of phenylbutazone, thiazides, tetracycline, phenobarbital, thyroid, digitalis, and warfarin sodium	↑ Hypoprothrombinemic effect of warfarin	?

From Levy, RI, Feinleib M: Risk factors for coronary artery disease and their management. In: *Heart disease: a textbook of cardiovascular medicine*, 2nd ed, Braunwald E (ed), Philadelphia, WB Saunders Company, 1984.

myocardial infarction and death due to CHD [34]. Extensive clinical experience in North America, Europe, and Scandinavia has led to the conclusion that the rates of total mortality, total cardiovascular mortality, and mortality due to CHD are 1.6 times higher among male cigarette smokers than among nonsmokers. For pipe and cigar smokers the rates of cardiovascular mortality and morbidity are only slightly increased [35,36]. Risk of developing CHD increases with the daily consumption of cigarettes; most importantly this risk is substantially reduced upon discontinuation of smoking, with the excess risk imposed by smoking apparently declining within 1 to 2 years of quitting.

Obviously patients who have had an acute myocardial infarction should stop smoking. In addition to the risks of smoking in the presence of an oxygen-enriched atmosphere, other adverse factors may exist such as increased

myocardial oxygen demand induced by nicotine, decreased oxygen availability to tissues by carboxyhemoglobin, increased incidence of ventricular arrhythmias, increased platelet adhesiveness, and possibly an increased tendency toward coronary artery spasm [35]. Infarct victims who continue to smoke after the acute event have a twofold increase in long-term mortality compared with those who stop smoking [35,36] as well as higher rates of nonfatal reinfarction and postinfarction angina. Thus, among the important secondary prevention measures that clinicians should consider are programs to help the postinfarction patient stop smoking and remain a nonsmoker thereafter.

1.2.3.4. GLUCOSE INTOLERANCE. Glucose intolerance and hyperglycemia are associated with an increased chance of developing CHD and suffering its consequences. This risk is one and one-half times higher for men and two times higher for women compared with individuals without glucose intolerance [37,38] and in adults applies to both insulin-dependent and noninsulin-dependent diabetes mellitus.

Fuchs and Scheidt have succinctly summarized other important relationships between diabetes and CHD [39]:

1. There is a striking prevalence of CHD in premenopausal diabetic women that is equal to or greater than that in diabetic men of the same age.
2. The incidence of painless myocardial infarction is increased in diabetics.
3. Early mortality rates are higher and long-term survival is decreased after an acute myocardial infarction in diabetic compared with nondiabetic patients.
4. There is an increased prevalence of other coronary risk factors, particularly hypertension, obesity, and hyperlipidemia, in diabetics.

Controversy surrounds the potential benefits and risks of various regimens to control hyperglycemia with respect to their effects on the atherosclerotic complications of diabetes. When the University Group Diabetes Program evaluated the effects of several oral hypoglycemic agents and two insulin regimens versus placebo in patients with adult-onset diabetes, they found that the drugs offered no benefit in controlling the vascular complications of diabetes [40,41]. Since there is some evidence that control of hyperglycemia may favorably affect the renal complications of diabetes, for this reason alone dietary and medical treatment regimens should be formulated in the hospital and implemented after discharge.

2. *Nonatherosclerotic coronary artery disease*

While atherosclerotic coronary artery disease is the most common of the pathophysiological mechanisms underlying CHD, several important nonatherosclerotic processes can cause myocardial ischemia. Clinicians should suspect the presence of nonatherosclerotic coronary artery disease in infarct victims who are young and who lack the traditional risk factors. Nonatherosclerotic disease may be due to a congenital or an acquired disorder of the coronary arteries or a hereditary connective tissue disorder with coronary artery involvement (table 1–7). Autopsy studies indicate that about 5 to 10 per cent of patients who have suffered an acute myocardial infarction do not have significant atherosclerotic narrowing in the coronary arterial bed [42]. The natural history of coronary artery lesions in nonatherosclerotic coronary artery disease is not well defined, but secondary myocardial infarction can occur, and in certain instances coronary artery bypass surgery is indicated for relief of angina (e.g., anomalous origin of left coronary artery from the pulmonary artery).

Finally, myocardial infarction can occur in the absence of significant coronary artery disease and coronary obstruction (possibly in about 5 to 10 per cent of cases), for which Likoff has proposed the following explanations [43]:

1. Limitations of coronary arteriography
2. Functional coronary vasoconstriction (e.g., spasm)
3. Small vessel disease
4. Platelet aggregation
5. Abnormal form of hemoglobin
6. Redistribution of coronary blood flow away from the subendocardium

3. *Pathology of Acute Myocardial Infarction*

Jennings et al have defined severe myocardial ischemia as a reduction in coronary arterial

TABLE 1–7. Nonatherosclerotic coronary artery diseases

I. Congenital disorders of coronary arteries
   A. Anomalous origin of coronary artery from pulmonary artery
   B. Aberrant coronary artery origin from aorta or other coronary artery
   C. Coronary arteriovenous fistula
   D. Coronary artery aneurysms
   E. Other types
II. Hereditary connective tissue disorders with coronary artery involvement
   A. Disease causing aortic dissection
   B. Pseudoxanthoma elasticum
   C. Gargoylism
   D. Homocystinuria
III. Acquired disorders of coronary arteries
   A. Embolism
   B. Dissection
   C. Syphilitic
   D. Infiltrative
      1. Tumors
      2. Amyloidosis
   E. Collagen-vascular diseases
      1. Polyarteritis nodosa
      2. Rheumatoid arthritis
      3. Systemic lupus erythematosus
   F. Miscellaneous disorders
      1. Irradiation
      2. Chest trauma
      3. Nitrate withdrawal
      4. Cardiomyopathy associated with progressive muscular dystrophy
      5. Generalized fibrous arterial disease of children
      6. Mucocutaneous lymph node syndrome (Kawasaki disease)

Adapted from Hillis and Cohn (67).

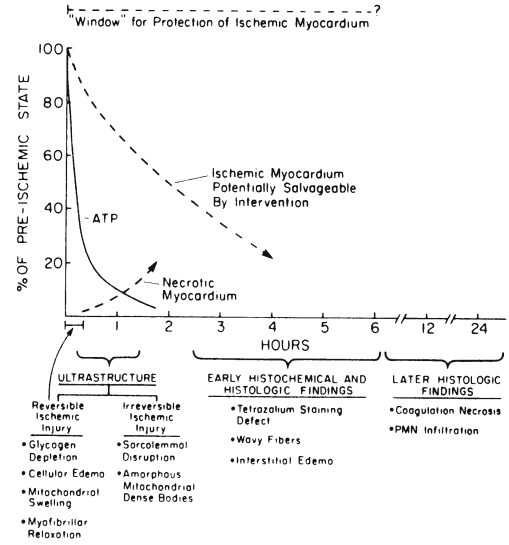

FIGURE 1–2. Temporal sequence of early biochemical, ultrastructural, histochemical, and histological findings after onset of myocardial infarction The "window" for protection of ischemic myocardium in humans is not firmly established. (See text for further discussion.) (Courtesy of Dr. Frederick Schoen.)

blood flow to less than 15 per cent of control levels in the affected myocardial zone [44]. With the onset of cellular ischemia, important metabolic alterations occur (i.e., a shift from aerobic to anaerobic metabolism) characterized by a reduction in ATP content, glycogen depletion, and the formation of lactic acid [45–47]. When such conditions persist for only a brief period, reversible myocardial injury occurs. The precise duration is unclear but is thought to be about 20 minutes based on available experimental data [45]. Recent studies have identified evidence of glycogen depletion, cellular edema, mitochondrial swelling, and myofibrillar relaxation as important ultrastructural hallmarks of reversible myocardial ischemic injury [5].

As time passes after the onset of irreversible cell death, certain early histochemical and histological findings become evident as the infarct evolves (figure 1–2). In association with leakage from the cell of such enzymes as the MB fraction of creatine kinase (MB-CK) the ability to reduce the histochemical stain triphenyl tetrazolium chloride is decreased, causing a paler or colorless section in the necrotic myocardial zone. On light microscopy, one might detect wavy myocardial fibers after only a few hours of ischemia [5]. These thin, undulating fibers probably represent stretching and shearing at the junction of contracting and noncontracting muscle. An additional histological feature of this stage is the development of eosinophilic contraction bands of fused sarcomeres, which are seen particularly at the edge of the infarcted zone but may form throughout the ischemic region if flow is restored. Somewhat later histological findings include coagulation necrosis in the center of the infarct and progressive infiltration by polymorphonuclear leukocytes.

Gross pathological changes due to myocardial infarction begin to become prominent at 18

to 24 hours, at which time the infarct appears cyanotic and swollen (figure 1–3). The area then begins to take on a tan or reddish-purple appearance followed by the development of a yellowish, thinned cardiac wall at 8 to 10 days. Over the course of 2 to 3 months, a shrunken, white scar develops that results in progressive endocardial thickening in the infarcted area.

3.1. INFARCT SIZE

In an anatomical sense, the ultimate size of a myocardial infarction in experimental animals (dogs) and probably in man is determined largely by the size of the occluded vascular bed and the intensity of collateral blood flow to the ischemic region. Thus, interventions to protect ischemic myocardium and limit infarct size by improving coronary blood flow include attempts to decrease the size of the occluded vascular bed (e.g., thrombolytic and/or mechanical reperfusion) and enhance collateral blood flow by increasing coronary perfusion pressure (e.g., preventing hypotension), decreasing extravascular compressive forces (e.g., nitrate-induced decrease in ventricular volume), and decreasing the resistance of collateral vessels (e.g., nitrates) (see chapter 13). Interventions that improve coronary blood flow such as thrombolysis are most successful if applied early during the critical "window" for protection of ischemic myocardium (figure 1–2). In man, the precise timing and duration of this "window" remains to be established but may be as short as 2 to 3 hours and is probably not longer than about 4 to 6 hours [48–51]. Alternative infarct size-limiting interventions such as the administration of various pharmacological agents (e.g., beta blockers) may be helpful by providing a longer period during which myocardial blood flow can be restored. It is important to emphasize that once coronary occlusion occurs, the myocardial zone does not undergo necrosis at a uniform rate. Instead, a wave of ischemic cell death spreads outward from the subendocardial region to the mid- and subepicardial regions [49,50], and myocardial salvage is directed at retarding and/or interrupting progression of this ischemic wavefront.

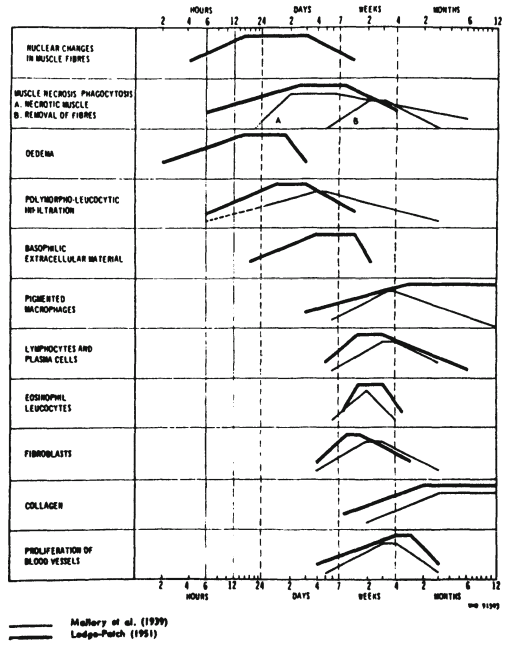

FIGURE 1–3. Early and late histological changes during evolution of myocardial infarction, summarized from observations by Mallory et al (1939) and Lodge-Patch (1951) and a working committee of the World Health Organization (1970). (From Willerson JT, Hillis LD, Buja LM: Pathogenesis and pathology of ischemic heart disease. In: *Ischemic heart disease. Clinical and pathophysiological aspects*, Braunwald E (ed). New York, Raven Press, 1982, pp 7–83.)

4. Relationship between Coronary Artery Occlusion and Acute Ischemic Heart Disease Syndromes

An early notion regarding the consequences of coronary artery occlusion held that once a coronary artery became obstructed, acute myocardial infarction ensued, and the pathological sequence described in the preceding sections was initiated. However, this concept was questioned when it was shown that coronary occlusion could occur without subsequent infarction and that infarction could occur in the absence of coronary occlusion. Even to this day the precise relationships among occlusion of a coronary artery and the various ischemic heart disease syndromes (i.e., acute myocardial infarction, unstable angina pectoris, and the related condition sudden cardiac death) are unclear. Several excellent reviews of this subject have appeared in the literature [5,52,53].

4.1. ACUTE MYOCARDIAL INFARCTION

Based on data collected from pathological studies [54], the clinical experience with coronary artery surgery and coronary angiography in acute myocardial infarction, and the results of thrombolysis during acute infarction, it is clear that coronary artery thrombosis is the cause of acute *transmural* myocardial infarction in 90 per cent of cases. Such thrombi usually complete occlusion of the vessel lumen already narrowed by an atherosclerotic plaque of significant size. The exact factors that "trigger" development of coronary thrombosis are not yet clear (and may vary from individual to individual), but likely possibilities include fissuring of the atherosclerotic plaque, coronary spasm, platelet aggregation, or some combination of these.

It has been proposed that when coronary artery occlusion does occur, transmural myocardial infarction will probably ensue unless a sufficient collateral arterial supply exists to compensate for the reduction in blood flow to the jeopardized zone. It is further hypothesized that it is the extent of coronary collateral flow (possibly combined with the degree of coexistent generalized coronary atherosclerosis) that determines whether infarction will occur at all or whether the infarct will be nontransmural (usually confined to the subendocardium). *Nontransmural* myocardial infarction appears to be caused by coronary thrombosis in a much smaller percentage of cases than is transmural infarction (i.e., 30 to 50 per cent of cases compared with 90 per cent [54].) Such nontransmural infarcts are more often associated with hemodynamic factors predisposing to reduced coronary artery perfusion and therefore result from alterations in the myocardial oxygen supply-demand ratio.

While *acute* coronary artery thrombi appear to play an important role in myocardial infarction, their detection by radionuclide tracer techniques [55,56], coronary angiography [57], direct inspection at operation [58] or postmortem examination [54] appears to depend on the time that has elapsed since the acute event. The natural history of occlusive coronary thrombi includes spontaneous lysis, retraction, and recanalization. Such "late" subtotal obstruction of coronary arteries supplying infarcted zones may have contributed to previous confusion about the incidence and pathophysiological role of coronary thrombi in acute myocardial infarction.

Finally, while coronary artery thrombosis appears to play a pivotal role in the development of acute myocardial infarction, nonthrombotic coronary artery occlusion may also cause infarction. Thus, some of the "trigger factors" for thrombosis mentioned above — i.e., coronary vasospasm, rupture and/or hemorrhage into a plaque, and platelet aggregation — may lead to complete coronary occlusion without thrombosis. It appears that malfunction of the platelet-vessel wall interaction in the form of an imbalance in the thromboxane A_2-prostacyclin system may contribute to coronary occlusion [52]. This may include situations in which thrombi serve to occlude the coronary lumen and those in which nonocclusive thrombi are present and coronary vasospasm is playing a more significant role.

4.2. UNSTABLE ANGINA PECTORIS

As emphasized in a recent review by Epstein and Palmeri, the transition from chronic stable angina to unstable angina occurs in a substantial number of patients without evidence of progressive worsening of underlying atherosclerosis [59]. Preliminary studies suggest that when coronary angiography is performed within the first week after the onset of unstable angina, coronary thrombosis may be seen with increasing frequency, In addition, two studies of antithrombolytic therapy for unstable angina have yielded positive results [60,61]. Additional coronary obstructive processes that may contribute to the transitory nature of unstable angina include epicardial coronary artery spasm (especially when ST-segment elevation is seen on the ECG) and platelet aggregation [59].

4.3. SUDDEN CARDIAC DEATH

Although the epidemiological risk factor profiles for coronary artery disease and sudden cardiac death overlap significantly, they are not identical. Current evidence indicates that in the majority of patients sudden cardiac death results from lethal ventricular tachyarrhythmias occurring on the substrate of occlusive coronary artery disease. However, in the majority of survivors of sudden cardiac death, evidence of acute myocardial infarction does not evolve. In a review of 17 studies that examined the frequency of *recent* occlusive coronary thrombi in sudden cardiac death due to ischemic heart disease, the incidence of thrombosis in 14 of the studies was 50 per cent (range = 4 to 64 per

cent) [62]. While the incidence of coronary thrombi in patients with sudden cardiac death is increased if one includes nonocclusive thrombi attached to the intima [63], it is not clear how significant thrombi or other findings, such as plaque fissuring, are in the genesis of ventricular tachycardia and fibrillation. The apparent protective effects of such agents as sulfinpyrazone and aspirin reported in some studies are intriguing; however, these results must be confirmed before use of these drugs can become accepted practice [64–66]. At present, research efforts in the field of sudden cardiac death due to ischemic heart disease are focusing on improving techniques for arrhythmia detection and treatment.

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2. CLINICAL PRESENTATION OF ISCHEMIC HEART DISEASE

American physicians refer to James B. Herrick as the first to describe the clinical presentation of a nonfatal myocardial infarction in 1912. In his description Herrick indicated his familiarity with an earlier report by Obraztsov and Strazhesko in a German translation in which they discussed five cases of myocardial infarction, three of which were confirmed by autopsy [1]. The description of the first case, which is recounted below, continues to serve as an excellent clinical description of a patient with acute myocardial infarction:

A 49-year-old artillery man was admitted to the medical division of the Aleksandrovsky Hospital on December 5, 1899. For 12 days prior to admission, he had experienced substernal pain radiating to the throat, head and left arm. The attacks lasted 2 to 4 hours and after a brief pause would begin again. During the attacks he experienced shortness of breath and the inability to breathe deeply. The chest pain was so severe that the intern on my service, who was young and inexperienced, in response to my question as to the patient's admitting diagnosis responded "rheumatism of the chest."

Objective Findings: He was well nourished and well developed. There was moderate cyanosis of the mucous membranes. His facial expression revealed distress from the substernal pain which radiated to the neck and head. No vessel motion was visible in the neck. The respiratory and abdominal organs were without abnormalities. The cardiac impulse was not visible, but was weakly palpable in the 5th intercostal space in the left mammary line. The heart sounds were distant and there were no murmurs. Direct auscultation revealed presystolic splitting of the first sound. Pulse 90 and barely palpable. Rhythm regular. After the initial examination the diagnosis of coronary thrombosis was made. The patient died 4 days later on December 9, 1899.

Autopsy Findings: On cross section of the left ventricle its entire thickness was of a muddy-gray yellowish color, as seen with necrosis. These changes occurred in almost the entire wall of the left ventricle and septum.

Near the origin of the right coronary artery there was 1 cm long yellowish projection from the wall of the vessel producing some luminal narrowing. The changes in the left coronary were more severe. The left anterior descending coronary artery was occluded by grayish-red thrombus 1 cm long and 1 mm in diameter. The left circumflex was occluded by a 3 cm long soft yellow thrombus.

Herrick also described the clinical features of sudden obstruction of the coronary arteries [2]. Although pathologists of the time had recognized the existence of coronary thrombi, Cohnheim, a prominent researcher, had occluded the coronary arteries in a group of dogs and all had died quickly thereafter. This experiment and Cohnheim's influence led to the view generally held, at that time that the only symptom of coronary occlusion was sudden death. Like the Russian physicians, Herrick was trying to refute the belief that occlusion of a major coronary artery would be immediately fatal and alluded to the existence of collateral vessels and the possibility of survival after such occlusion.

1. Clinical Presentation

1.1. SUDDEN DEATH

Prospective epidemiological studies have confirmed that sudden, unexpected, nontraumatic,

nonself-inflicted collapse leading to death within 6 hours ("sudden death") is the initial and terminal event in patients with coronary artery disease in over half the deaths. Most commonly this is due to ventricular tachycardia or ventricular fibrillation. Two-thirds of such patients have severe occlusive atherosclerotic disease of the major epicardial coronary vessels or evidence of old infarction. Approximately three-fourths are known to have prior hypertension, diabetes mellitus or heart disease. Acute coronary thrombosis is noted in only about 10 per cent of such patients, and in another 10 per cent no morphological abnormality can be found [3]. Of some importance is the fact that about 40 per cent of such patients are noted to have visited a doctor within 2 weeks of the fatal event.

1.2. CHEST PAIN

Patients who suffer myocardial infarction usually have prodromal symptoms that precede the event by at least one week. Pain is the most common symptom [4,5] and is similar in nature to angina pectoris but is usually more severe, persists despite nitroglycerin and is often associated with marked sweating almost from the onset, accompanied by nausea and vomiting. The pain may be in the central chest or near the epigastrium and may either radiate or be localized to the anterior neck, jaw, back, shoulder, or arms. Other symptoms occurring in the weeks prior to myocardial infarction are usually nonspecific, although many patients complain of unexplained fatigue.

1.3. ECG CHANGES

In the Framingham Study, almost one-fourth of myocardial infarctions that occurred during the 18-year followup went unrecognized clinically and were detected only upon the appearance of diagnostic Q waves on routine electrocardiograms [6]. Conversely, physicians evaluating patients suspected of having infarction should not dismiss the diagnosis on the basis of a normal ECG at presentation. ECG changes characterizing myocardial infarction may evolve at a rate that varies from one person to another.

1.4. MODIFIED PRESENTATION IN THE ELDERLY

In the elderly a classic presentation of myocardial infarction is the exception rather than the rule. More often, the patient has symptoms of sudden breathlessness or worsening heart failure. In addition, dizziness, confusion, fainting, or strokes may be the modes of presentation [7]. Indeed, in a prospective study of patients admitted to a geriatric unit within 72 hours of onset of an acute cerebrovascular accident, 13 per cent had acute myocardial infarction. The majority of those in whom the infarction was detected by serial ECGs and enzymes gave no history of chest pain [8].

1.5. INFARCTION ASSOCIATED WITH NONCARDIAC SURGERY

Noncardiac surgery may be the precipitating event in acute myocardial infarction. The incidence of perioperative myocardial infarction is 0.5 per cent in patients with no previous infarction but increases to 6 per cent in those who have previously suffered an infarct. While the mortality rate among patients who first suffer an infarct is similar to that of persons in the general population, who suffer a first infarction — i.e., 15 per cent during hospitalization and 10 per cent during the first year — mortality due to a second infarct during the perioperative period is higher — i.e., 50 to 70 per cent — and does not seem to be significantly reduced by intensive care management.

The type of surgery is an important determinant of the risk. Although mortality is minimal and equal for cardiac and noncardiac patients undergoing herniorrhaphy and transurethral resection, intraabdominal procedures such as cholecystectomy or bowel resection are associated with twice the mortality in cardiac patients. Other factors contributing to a higher death rate include age greater than 40 years, the presence of heart failure, and emergency rather than elective surgery.

Patients with coronary artery disease tolerate unexpected, sustained hypotension poorly, and the induction of general anesthesia within 3 to 6 months of a myocardial infarction carries a higher risk of reinfarction than does anesthesia delivered at a later time. After an acute infarct, the risk of reinfarction during anesthesia is 37 per cent during the first 3 months, 16 per cent between 3 and 6 months, and 5 to 6 per cent after 6 months [9]. The clinician should also be aware that 50 per cent of perioperative infarcts are painless, so that a high index of suspicion and careful evaluation of serial ECGs and cardiac enzyme levels are necessary for accurate diagnosis. Preoperatively, it is important to treat heart failure and hypertension, normalize

electrolytes, control arrhythmias, and correct anemia. Intraoperative monitoring of blood loss, fluid balance, and arrhythmias is mandatory. Recent studies suggest that in patients who have undergone aortocoronary bypass surgery the risk of infarction during major noncardiac surgery may be subsequently decreased.

1.6. UNSTABLE ANGINA

The term "unstable angina" applies to several patterns of angina encountered clinically including pain occurring at rest, pain that awakens the patient from sleep, effort angina of recent onset that has progressed, or a new and changing pattern of angina. Characteristically, along with episodes of pain there is evidence of ischemia on the ECG; however, the biochemical and ECG changes of myocardial infarction do not evolve in the majority of cases. Recently, evolution of infarction has been reported in less than 10% of patients and hospital mortality has been reduced to about 4% with medical treatment [10].

There has been recent, intense interest in the morphology of coronary artery lesions likely to be associated with unstable angina. "Active lesions" tend to be coronary artery narrowings of greater than 50% diameter loss (or greater than 75% cross-sectional area loss) which are asymmetric with a narrow neck and irregular border, have associated intraluminal lucencies (which may represent thrombus), and are eccentrically situated [11]. Such lesions are more likely to be associated with the pathologic features of plaque rupture, hemorrhage, and superimposed thrombus (figures 2–1 and 2–2). "Nonactive lesions" are more likely to be sym-

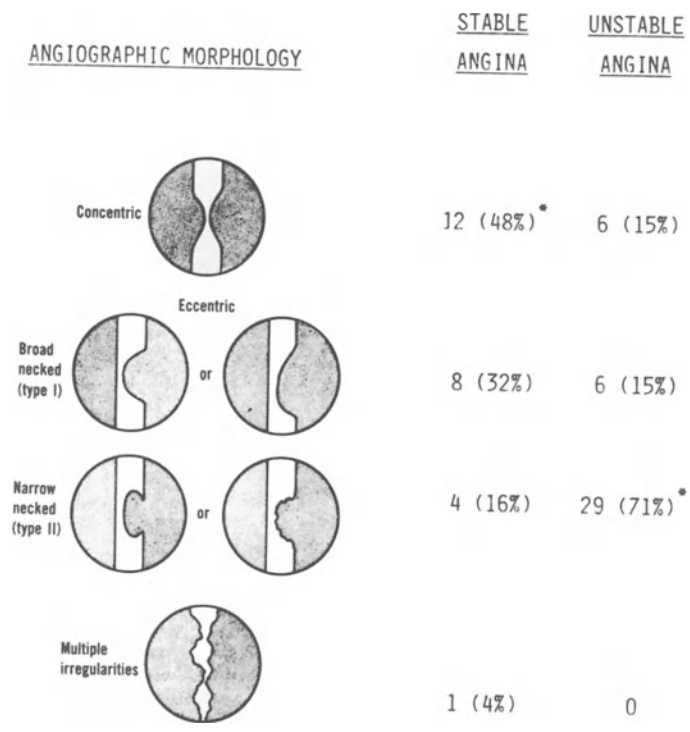


FIGURE 2–1. Frequency of morphologically different obstructions in angina-producing coronary arteries in 66 patients with angina. Arteriographic analyses were performed independently of the clinical data. It is noteworthy that stable angina pectoris is most often associated with concentric lesions whereas unstable angina is most often associated with narrow-necked (type II) lesions. *$p < 0.01$. (Reprinted with permission from Ambrose JA et al, *J Am Coll Cardiol* 5:609–616, 1985, The American College of Cardiology.)

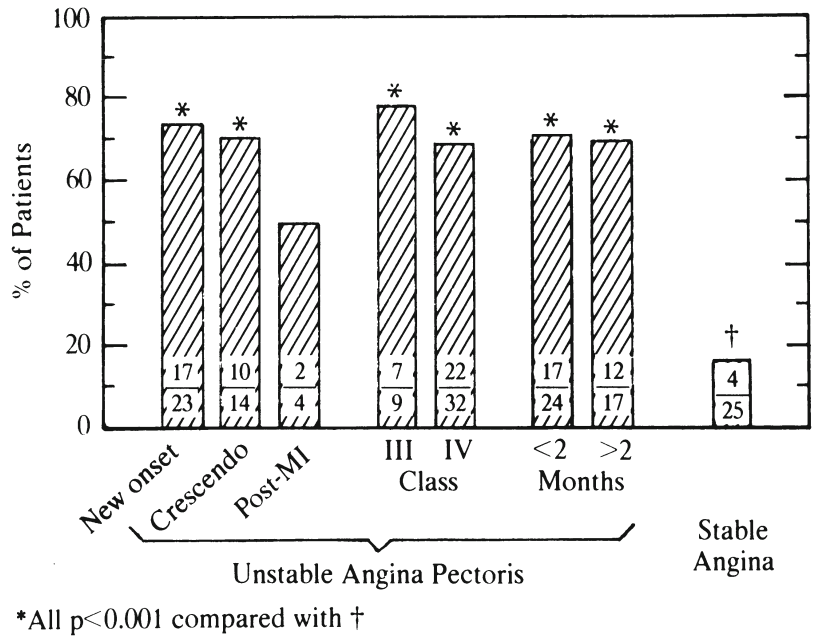


FIGURE 2–2. Distribution of type II eccentric lesions in different subgroups of patients with unstable angina. The numbers within the bars indicate the number of eccentric lesions and the number of patients in each subgroup. MI = myocardial infarction. (Reprinted with permission from Ambrose JA et al, *J Am Coll Cardiol* 5:609, 1985. The American College of Cardiology.)

metrical or concentric or asymmetric with smooth borders and a broad neck. The typical deformities are smooth with an "hourglass" configuration and absence of intraluminal lucencies during coronary angiography. Pathologically, the intima of such lesions is likely to be intact and have fatty or fibrous plaques without superimposed thrombus. Postmortem studies have shown that approximately 70% of specimens of diseased arterial segments with significant narrowings have an eccentric residual arterial lumen that is partially circumscribed by an arc of at least 60° of normal arterial walls. The presence of this pliable, muscular elastic arc of normal wall provides a mechanism whereby variations in intraluminal pressure and/or vasomotor tone may affect lumen caliber and thus flow resistance. It is not difficult to conceive that alterations in coronary artery tone at the site of irregular plaques may initiate and/or be exacerbated by local formation of platelet thrombi, with resultant angina.

Patients with unstable angina should be hospitalized. Bedrest should be initiated, and sedation with appropriate analgesia should be provided. Initially patients are treated with sublingual, oral, topical, or intravenous nitrates, beta-adrenergic blocking agents (if these are not contraindicated), and calcium-channel blocking agents. If appropriate, heart failure or hypertension should be corrected. Occasionally, intraaortic balloon counterpulsation may be required to stabilize the patient both symptomatically and hemodynamically. This last measure is instituted only if all other modes of therapy have failed and if the patient requires coronary arteriography with a view toward coronary artery surgery.

Large randomized studies have shown that patients with unstable angina can have normal coronary arteries (about 10% of patients), although triple-vessel coronary disease exists in the majority of instances (about 50% of patients) double-vessel disease in some (about 25%), and single-vessel disease in the remainder [12].

With vigorous medical therapy, particularly in patients who have never previously received antianginal medication, unstable angina may quickly settle. If, after mobilization, the situation remains stable, patients may be treated conservatively. At some later date, exercise testing may help define future management. If patients on an appropriate medical regimen complete stage III of the Bruce protocol (or its equivalent) without symptoms, evidence of widespread ischemia, or manifestations of global ischemia (such as a fall in blood pressure), conservative therapy can most likely be continued.

If the pattern of angina remains unstable or if, during episodes of pain, widespread ECG changes suggest global ischemia, then coronary angiography would be warranted. The presence of significant left main coronary artery disease will invariably lead to early surgery. An operation would also be recommended for many patients with triple-vessel disease, particularly when left ventricular function is impaired. Recommendations for surgery of double-vessel coronary artery disease are made on a case by case basis. It is becoming increasingly common for patients to undergo percutaneous transluminal coronary angioplasty with cardiac surgical backup, if symptoms or evidence of ischemia remain despite medical therapy.

In large, prospective randomized studies comparing medical and surgical therapy of unstable angina, surgical therapy has been shown to offer an advantage over medical therapy in improving the functional class of treated patients [13]. During hospitalization, the incidence of myocardial infarction and the mortality rate are reported to be higher among surgically treated patients. The total incidence of myocardial infarction has been reported to be 21% in medically treated patients and 28% in surgically treated patients during the first few years. Long-term survival appears to be similar in the two groups (figure 2–3).

Two recent, well-designed studies showed the effectiveness of aspirin administered to patients with unstable angina. The Veterans Administration Study [14] showed that buffered aspirin (324 mg/day) administered to patients with unstable angina for a period of 12 weeks reduced the occurrence of fatal or nonfatal acute myocardial infarctions and also reduced mortality. More recently, a Canadian Multicenter Trial of patients with unstable angina [15] followed 555 patients, within eight days of hospitalization, for a mean of 18 months. Patients were randomized in double-blind, placebo controlled fashion to regimens of aspirin 325 mg four times daily, sulfinpyrazone 200 mg four times daily, both treatments, or neither treatment. The endpoints were cardiac death and nonfatal infarction. The aspirin-treated groups had significant reductions in cardiac death and nonfatal myocardial infarction as well as all causes death compared with the other treatment groups (figures 2–4 and 2–5). These two studies provide strong evidence for a beneficial effect of aspirin, long-term, in patients with unstable angina.

Currently, we feel the prudent course for physicians to follow is to decide initially whether or not the individual patient should be a candidate for coronary artery surgery. If revascularization is deemed appropriate, it is important to consider whether or not the patient may be a candidate for percutaneous transluminal coronary angioplasty. At this time, the role of intravenous or intracoronary thrombolytic agents or antiplatelet agents in treating this condition remains ill defined although two large, recent studies suggest a long-term benefit of treatment with aspirin.

2. *Signs*

Physical examination may be unremarkable or may support the diagnosis of myocardial infarction. Sweating, pale cool skin, sinus tachycardia, a fourth heart sound, and basal crepitations are all seen reasonably commonly. In severely affected patients, cardiogenic shock may be present, extreme left ventricular failure with pulmonary edema may dominate the picture, or more rarely there may be murmurs suggestive of either acute severe mitral insufficiency or acute ventricular septal rupture. It is not uncommon, however, to detect a soft murmur of mitral regurgitation in the early phases of acute MI in the absence of acute disruption of a papillary muscle; the murmur in such instances probably is secondary to dysfunction of the mitral apparatus usually from loss of appropriate contraction of the segment of myocardium into which a papillary muscle inserts.

3. *ECG Evaluation*

The electrocardiographic diagnosis of myocardial infarction requires the fresh appearance of

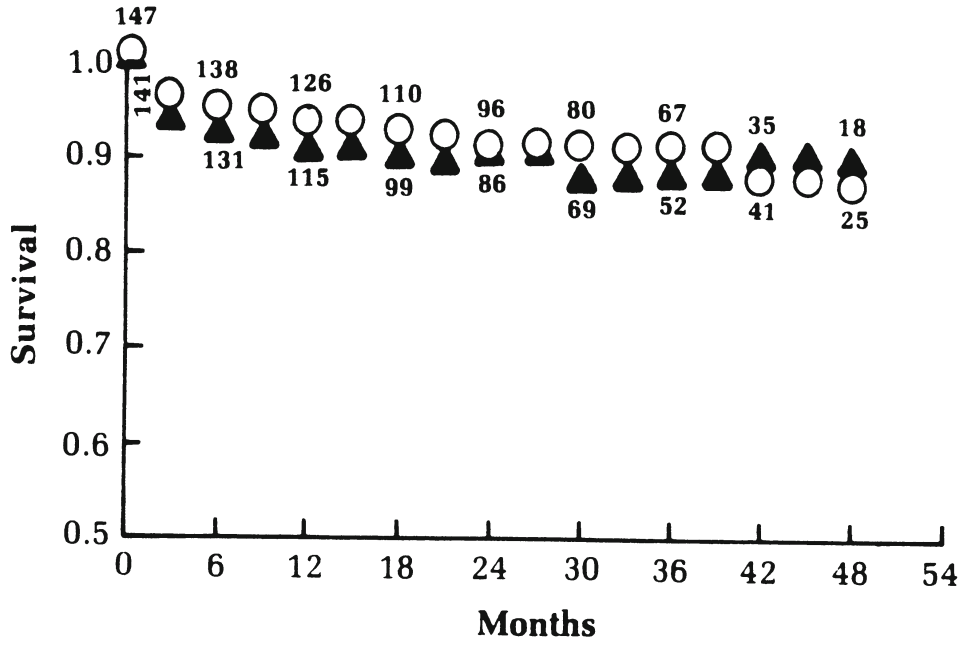


FIGURE 2–3. Survival of patients randomized to medical and surgical therapy in the National Cooperative Study of Unstable Angina Pectoris designed to compare surgical and medical therapy. The open circles represent all medical patients and the closed triangles represent all surgical patients. The survival curves for patients assigned to surgical and medical therapy did not differ statistically. The one-year survival rate was 93% for the medical and 92% for the surgical group, at two years the respective estimated survival rates were 91% and 90%. The numbers above and below the symbols indicate the number of patients at risk at each time point. (Adapted from National Cooperative Study Group: *Am J Cardiol* 42:839–848, 1978.)

Q waves (or increased prominence of existing Q waves) ST-segment elevations, and T-wave inversions. As noted earlier in the initial phase of myocardial infarction ECG changes may be within normal limits or nonspecific, and serial tracings taken every 8 to 12 hours should be examined.

When obtained at the time the patient presents to a doctor or the emergency room, the ECG should be a means of confirming the clinical impression and should not supersede it. If the patient is suspected clinically of having sustained a myocardial infarction, particularly based on the history, then he should be treated accordingly, even if the ECG tracing is completely normal. It is our view that all decisions regarding admission of a patient to a coronary care unit should be based on the patient's history alone. Valuable time is often wasted while physicians base their decisions on an examination of ECG appearances, which in the early phase of infarction can be misleading.

Early ECG features usually consist of repolarization abnormalities (e.g., peaked T waves, ST-segment deviation) that progress at a variable rate to abnormalities of the QRS complex indicative of necrosis of myocardial tissue (e.g., Q waves, slurring and notching of portions of the QRS, and loss of R-wave height). Most patients with previously normal electrocardiograms will show a series of changes during acute infarction.

According to the classic dipole theory of electrocardiography, a diastolic *current of injury* flows between ischemic and normal myocardial cells, resulting in a vector oriented away from the infarcted zone. Although this would be expected to cause ST-segment depression, the AC circuits in conventional ECG recorders compensate for this baseline shift and exhibit apparent ST-segment elevation in leads overlying the infarct. During electrical systole, the

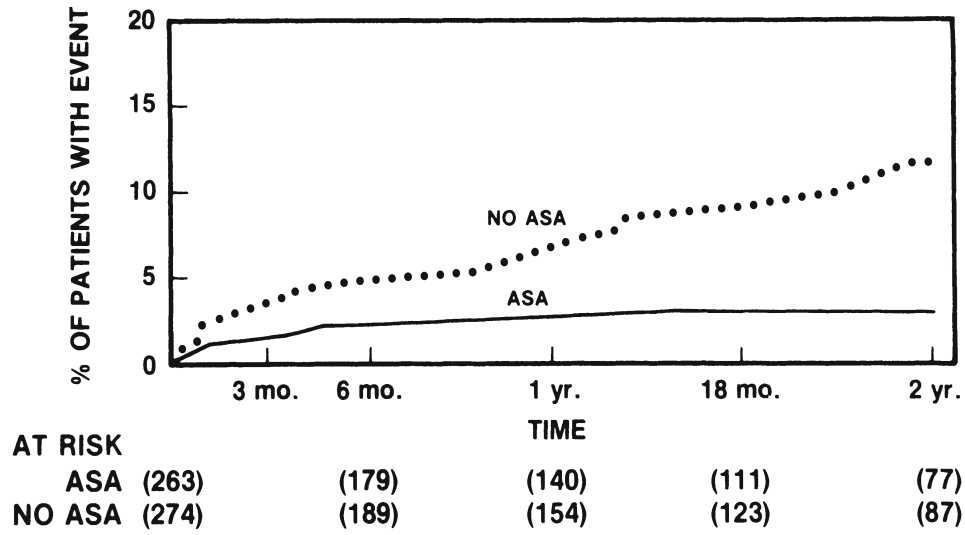


FIGURE 2–4. Occurrence of cardiac death or nonfatal myocardial infarction (MI) in the aspirin (ASA) and no-aspirin groups. The graph is a life-table depiction of the cumulative risk and time of the first occurrence of an outcome event, according to aspirin allocation. The numbers of patients at risk are noted below the graph. (Reprinted with permission from Cairns JA et al: *N Engl J Med* 313:1369–75, 1985.)

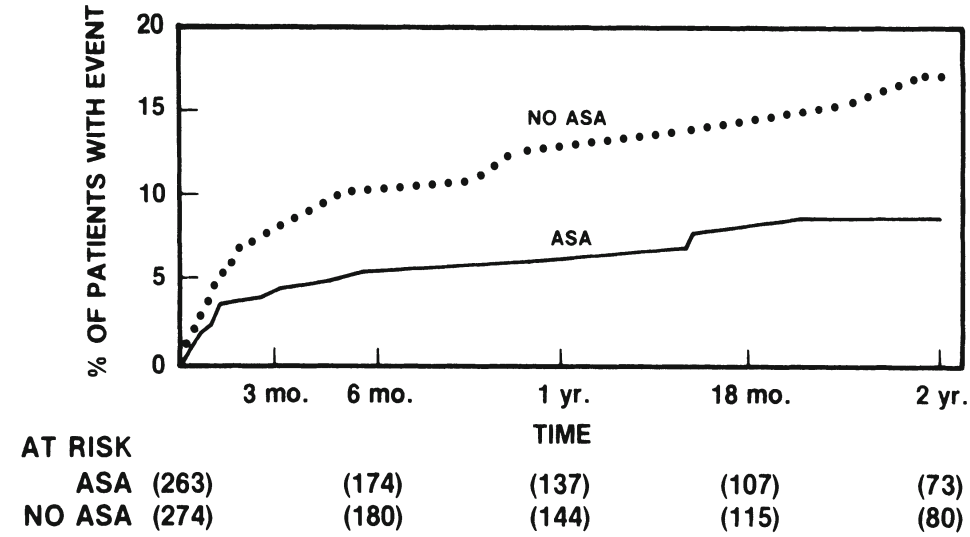


FIGURE 2–5. Occurrence of cardiac death in the aspirin (ASA) and no-aspirin groups. (Reprinted with permission from Cairns JA, et al: *N Engl J Med* 313:1369–75, 1985.)

current of injury flows in a direction opposite to that of the diastolic current of injury (i.e., toward the infarcted zone), causing primary ST-segment elevation and tall, positive, hyperacute T waves in leads overlying the infarct. The precise etiology of the systolic current of injury is controversial, but leading theories include disappearance of the diastolic current of injury and accelerated repolarization of the injured area (figure 2–6).

When these repolarization abnormalities are seen along with "pathological" Q waves of infarction (0.04 sec in width) in a particular combination of ECG leads, clinicians attempt to diagnose the location of an MI. Vectorcardiography (VCG) was used extensively as a diagnostic tool in the past but is less commonly applied today. The traditional ECG (and VCG) terminology of infarct location (table 2–1) is based in part upon classic ECG-pathological correlation studies, such as those carried out by Myers and associates (table 2–1). However, recent experimental and clinical data have emphasized the potential pitfalls and inaccuracies of the standard ECG classification of myocardial infarction. It is not surprising that ECG and pathological localization of the infarct may be discrepant, since a number of factors contribute to such inconsistencies. For example, ST-segment elevation on the ECG is a function not only of the transmembrane *voltage* gradient between normal and infarcted tissue, but also of several important *spatial* factors. Among these are the shape of the injured myocardial area (subepicardial, transmural, subendocardial, or intramural wedges); the size, number, and location of injured zones; wall thickness in the injured zone (e.g., right versus left ventricle, apex versus base); and the location of the recording electrode (precordial, epicardial, or intracavity). Many of the factors are accounted for in a modern approach to electrocardiography referred to as the *solid-angle theory* [16], which combines spatial and nonspatial influences on ECG waveforms.

Because of such complexities in ECG diagno-

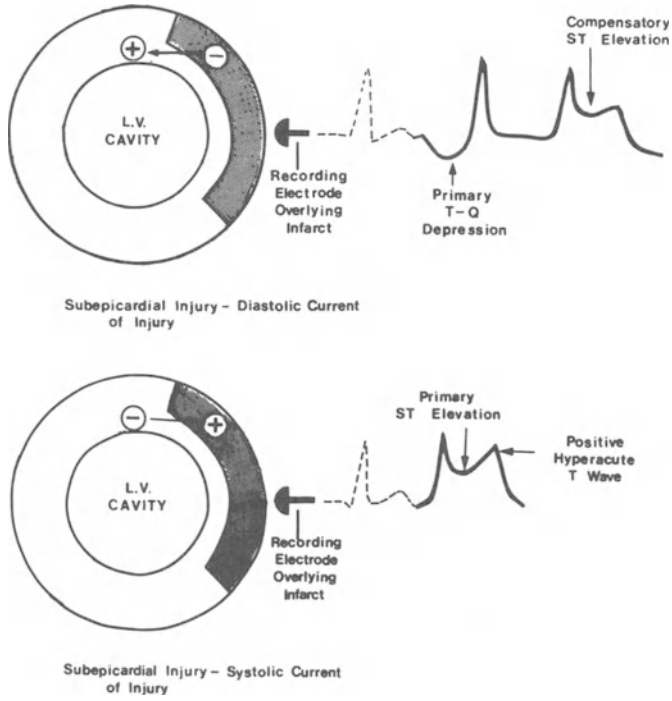


FIGURE 2–6. Theoretical basis for ST-segment deviation in acute myocardial infarction. (See text for details.)

TABLE 2–1. Electrical site of infarction, VA vectors affected, and QRS changes

Electrical site of infarction	Direction of infarction vector	Instantaneous VA vectors affected	Resulting abnormalities of QRS complex	Resulting abnormalities of QRS sE loop
Anteroseptal	Left, posterior	0.01-sec septal and 0.02-sec apicoanterior	QS deflections or abnormal Q waves in leads V_1, V_2, and sometimes V_3	Leftward and posterior inscription of initial deflection and early efferent limb
Anterior	Posterior	0.02- and 0.04-sec left ventricular	QS deflections or abnormal Q waves in leads V_2, V_3, and V_4	Posterior displacement of efferent limb and sometimes long axis of loop
Anterolateral	Right, posterior	0.02- to 0.04-sec	Abnormal Q waves leads I, V_5, and V_6	Posterior and rightward or medical displacement of efferent limb and long axis of loop
Extensive anterior	Right, posterior	0.01- to 0.06 sec	Abnormal Q waves in leads I and V_1 through V_6	Initial inscription of loop to right and posterior and rightward or medical displacement of both efferent and afferent limbs and long axis of loop
Inferior (diaphragmatic)	Superior	0.02- and 0.04-sec	Abnormal Q waves in leads II, III, and aVf	Superior displacement of efferent limb and sometimes long axis of loop
Posterolateral	Right, anterior	0.02- and 0.04-sec	Abnormally tall and/or wide R waves in lead V_1 and abnormal Q waves in leads I and V_6	Rightward and anterior displacement of early efferent limb and anterior displacement of later efferent limb and long axis of loop
Strictly posterior	Anterior	0.04- and 0.06-sec (or 0.08-sec)	Low, vibratory RR′ deflection of rSR′ deflection in leads V_{3R} and V_1	Anterior displacement of long axis and afferent limb of loop

From Cooksey JD, Dunn M, Massie: *Clinical vectorcardiography and electrocardiography*, 2nd ed. Chicago, Year Book Medical Publishers, 1977, p 376.

sis, clinicians should be circumspect about precise infarct localization and diagnosis of specific coronary artery occlusion, especially if the diagnosis is based on ECG leads. Inspection of the entire ECG pattern and the recording of supplemental leads (e.g., V_{4R} to search for right ventricular infarction) may be more helpful. Representative ECG examples of acute myocardial infarction in various locations and stages of evolution are shown in figures 2–7 to 2–15

If pathological Q waves do not develop the evolving changes in ST-segments and T waves can be nonspecific. Often, the detection of associated changes in serum enzyme values is needed to establish the diagnosis of myocardial infarction. It should be noted that the development of pathological Q waves is not necessarily synonymous with "transmural myocardial infarction." Such infarctions are probably more appropriately called Q-wave infarctions, since transmural necrosis of the myocardial wall can be seen with "non-Q-wave infarctions," while nontransmural infarcts pathologically can be associated with "Q-wave infarctions."

Although the development of left bundle branch block (LBBB) on the ECG may be caused by an acute myocardial infarction, in the absence of previous tracings it is usually wisest to base management decisions on the history, serial enzyme changes, and other noninvasive markers of infarction, such as technetium pyrophosphate scintigrams. There are, however, certain *primary* repolarization changes on the ECG in the presence of LBBB that may be taken as suggestive evidence of acute infarction. These are summarized in figure 2–16 and represent ST-segment and T-wave changes that differ in either direction or character (or both) from the expected *secondary* changes due to the abnormal depolarization sequence in LBBB (figures 2–17 and 2–18). Right bundle branch block, which does not ordinarily alter the initial QRS forces, allows the infarct vector and therefore Q waves diagnostic of infarction to be seen on the ECG (figure 2–13). This is an important

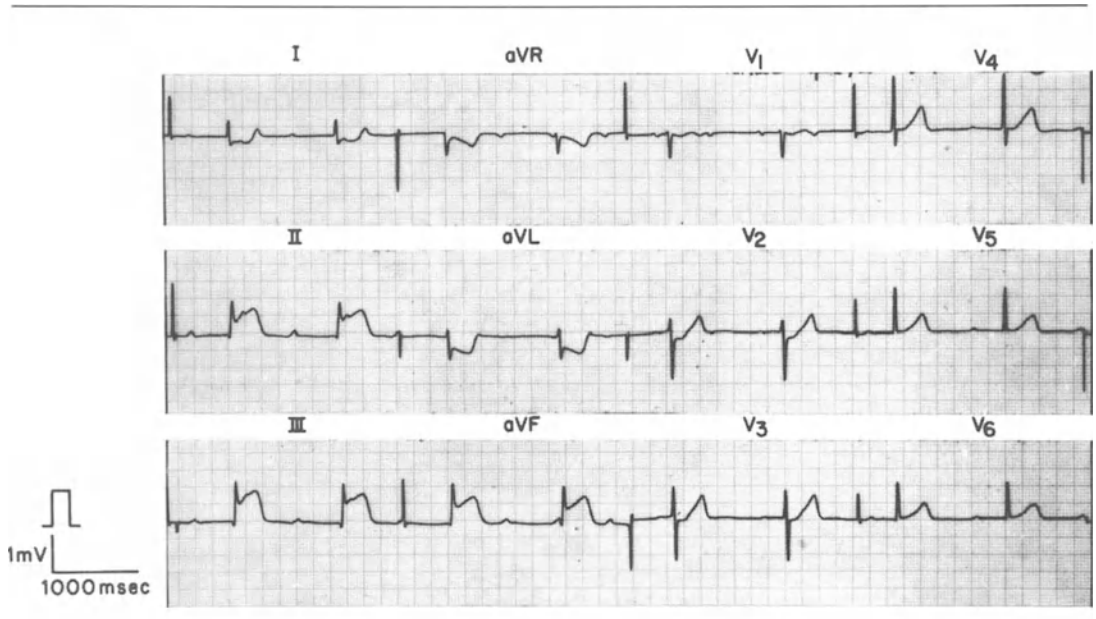


FIGURE 2–7. Acute inferior myocardial infarction with complete heart block. The Q waves and acute ST-segment elevation in leads II, III, and aVF (with reciprocal ST depression in I and aVL) are indicative of inferior wall infarction. The atrial rate (98 bpm) is faster than the ventricular rate (47 bpm), and there is no consistent pattern of AV conduction confirming the presence of complete heart block.

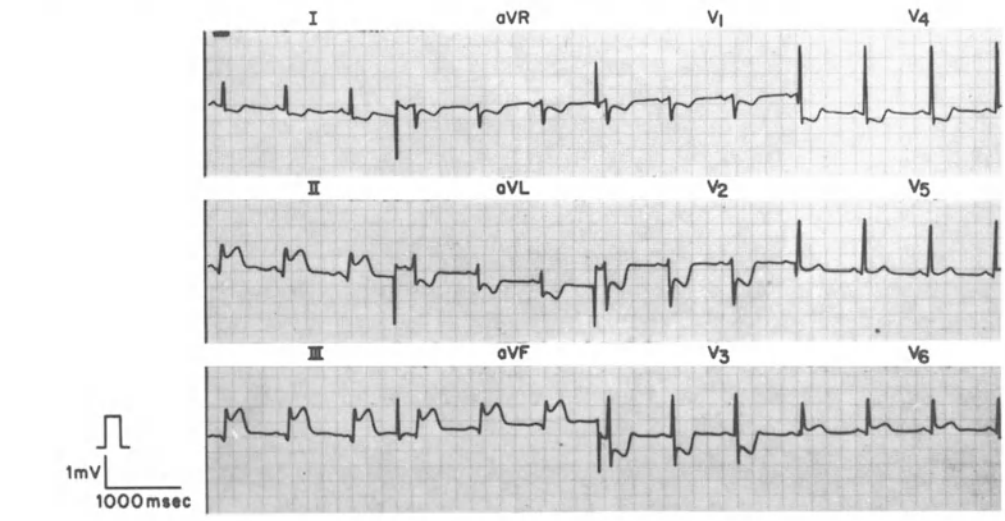


FIGURE 2–8. Acute inferior myocardial infarction with ST-segment depression in anterior precordial lead. The significance of this finding associated with acute inferior infarction is controversial. It may indicate anterior ischemia, posterior infarction, or "reciprocal" ECG changes. Some investigators feel it may signify more extensive left ventricular dysfunction and may be associated with a higher rate of in-hospital complications.

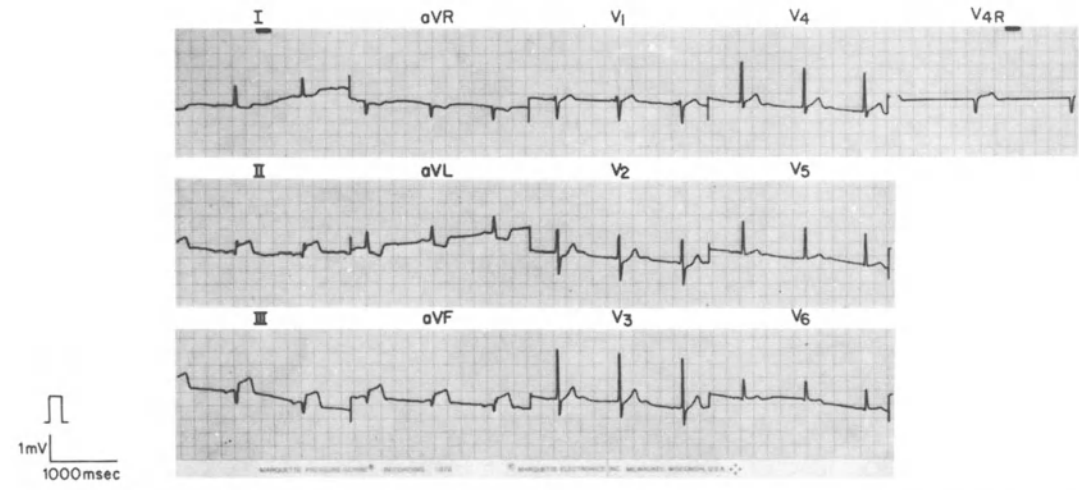
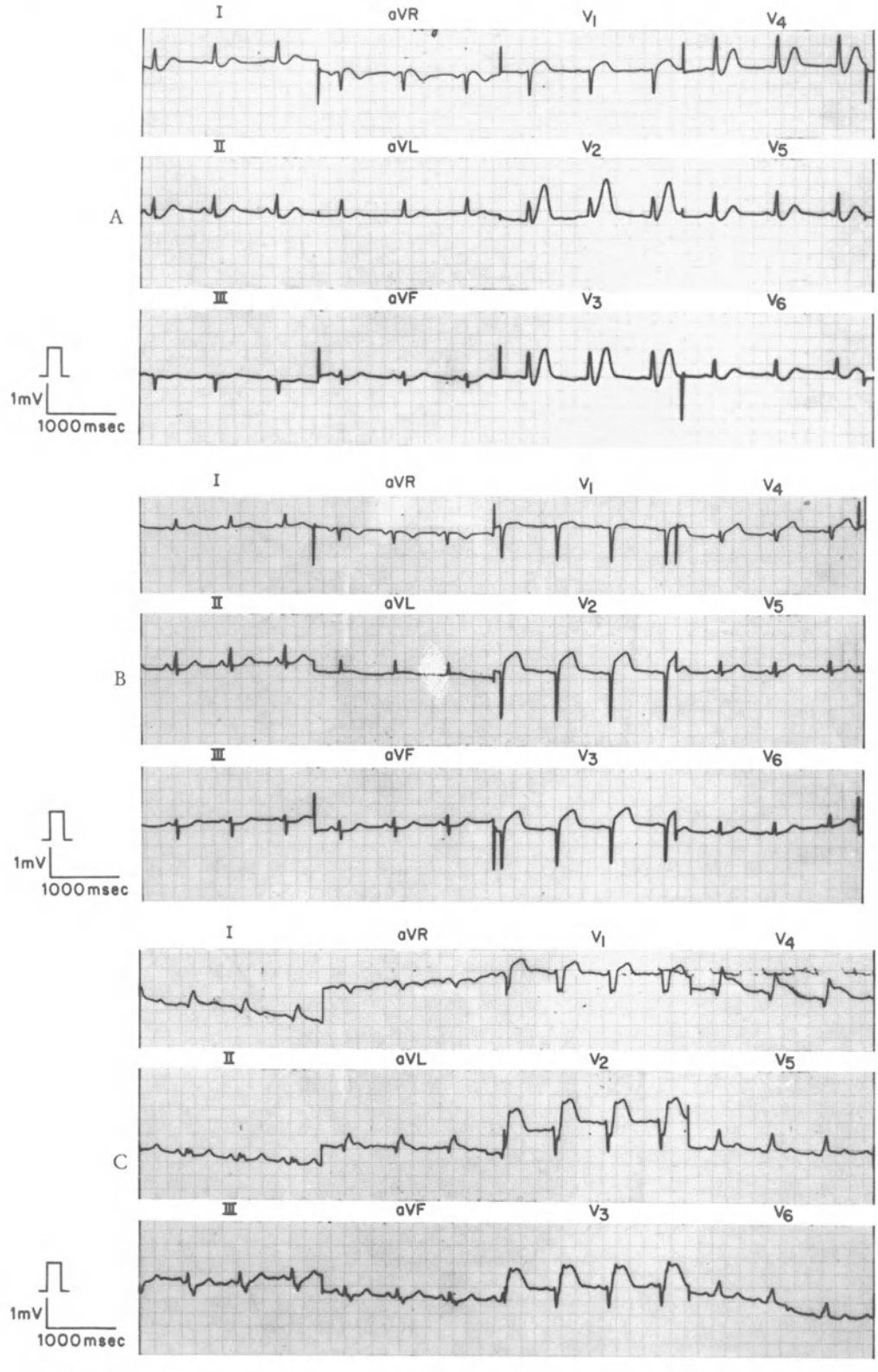


FIGURE 2–9. Acute inferior myocardial infarction with possible right ventricular infarction. ST-segment elevation of $\geq$0.1 mV in lead V_1 or V_{4R} in the setting of acute inferior infarction (i.e., within the first 24 hours) may indicate infarction of the right ventricle. (See also figure 2–10.)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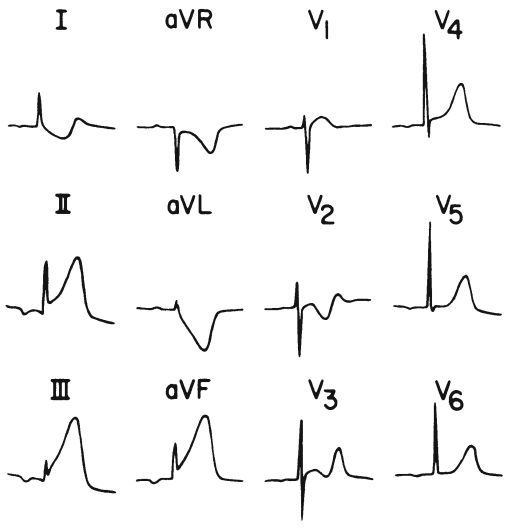


FIGURE 2–10. Acute inferior myocardial infarction, atrial infarction, and probable right ventricular infarction. The inverted P waves in the inferior leads suggest a nonsinus origin of atrial depolarization. This observation coupled with the development of a variety of supraventricular arrhythmias led to the clinical diagnosis of atrial infarction in association with inferior wall infarction. Note also the ST-segment elevation of 0.1 mV in V_1, raising the suspicion of right ventricular infarction.

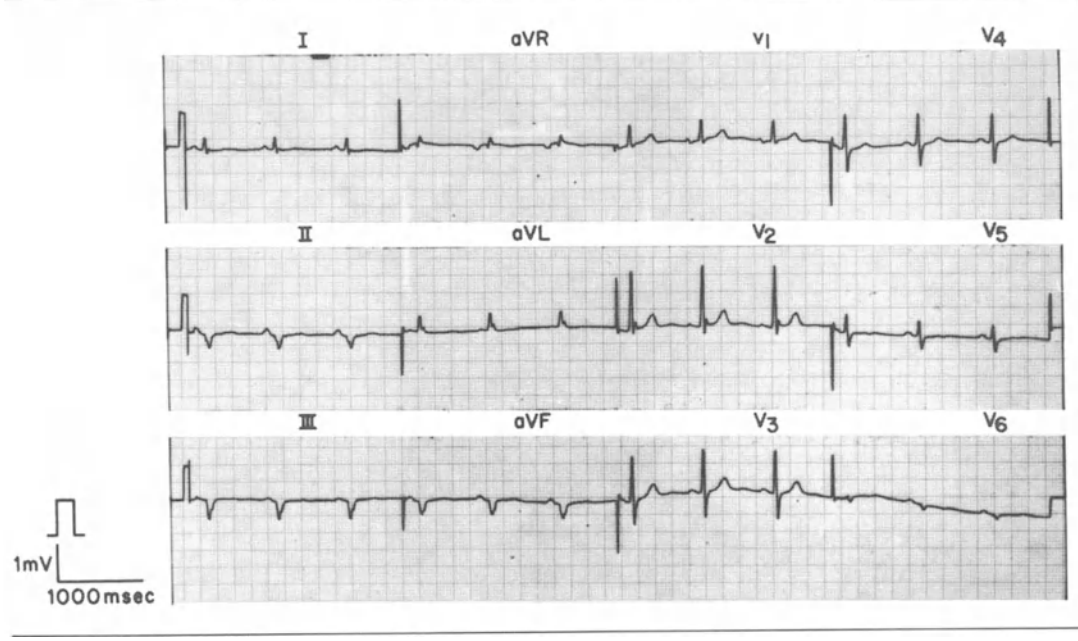
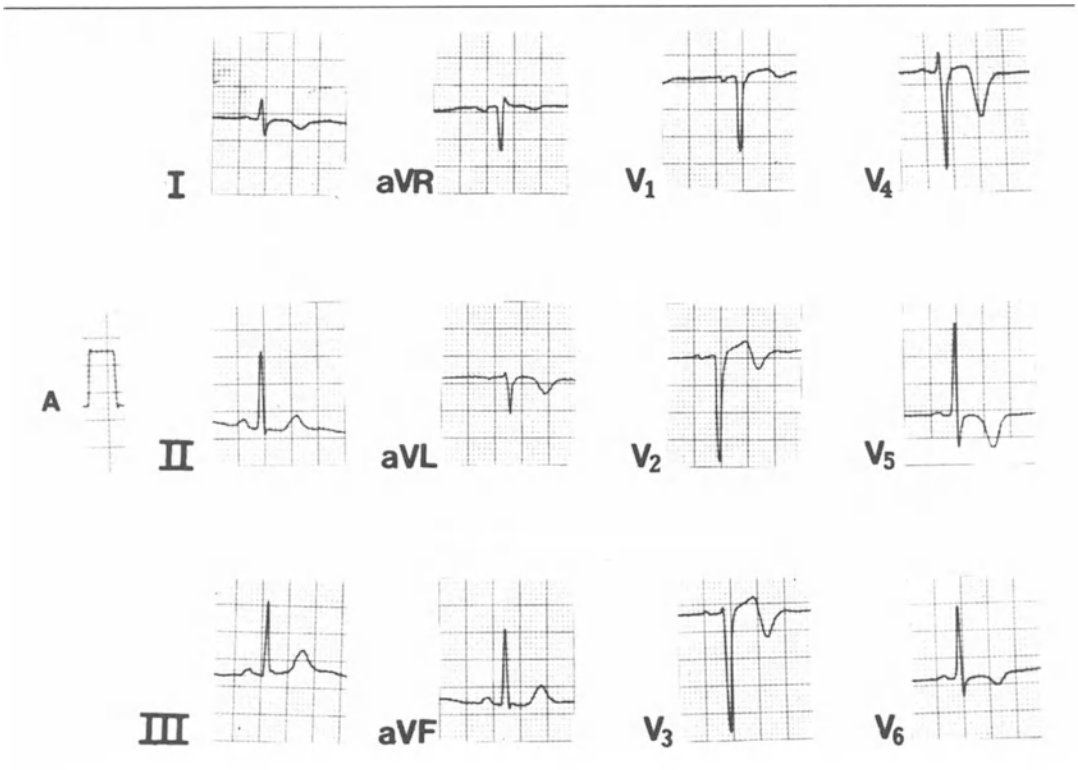


FIGURE 2–11. Inferoposterolateral myocardial infarction. The QS pattern in II, III, and aVF are consistent with inferior wall infarction while the unusually prominent R waves in V_1 and V_2 and the QS pattern in V_6 are consistent with true posterior and lateral wall infarction.

FIGURE 2–12. *A*, Acute anterior wall infarction with peaked "hyperacute" T waves in V_2 to V_5. *B*, Evolution of the infarct shown in *A* to an extensive anteroseptal and apical infarction. Note the development of deep Q waves V_1 to V_3, loss of lateral R-wave height, and marked anterior precordial ST-segment elevation. *C*, Left bundle branch block and extensive acute anterior infarction. The infarct shown in *A* and *B* has progressed and is now associated with an intraventricular conduction delay suggestive of left bundle branch block. However, the prominent Q waves in leads I and aVL and the small Q waves in V_5 to V_6 are not typically found in LBBB. In this clinical setting the most likely explanation is severe necrosis of the proximal interventricular septum so that laterally oriented leads such as I, aVL, and V_5 to V_6 "see" unopposed right ventricular forces moving away from the recording electrode and thereby creating a negative deflection.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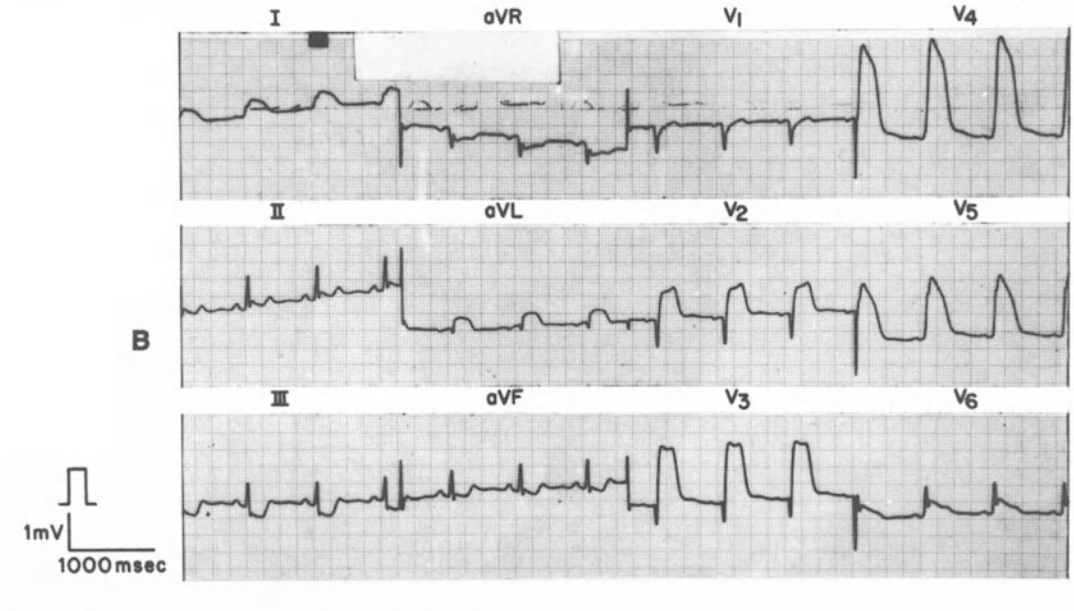
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B
III
aVF
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V6
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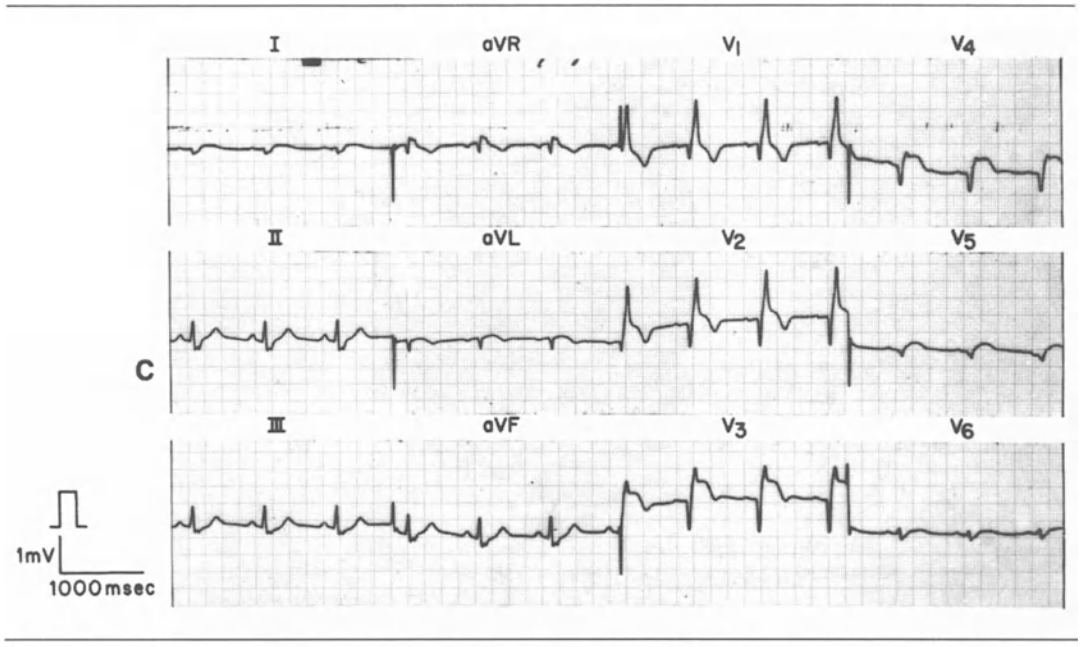


FIGURE 2–13. *A*, Anterior myocardial infarction. The pattern of "poor R-wave progression" in V_1 to V_4 is consistent with anterior wall infarction. The lack of Q waves in V_3 to V_4 and widespread inverted T waves suggest extensive subendocardial infarction. *B*, The infarct shown in *A* was complicated by recurrent ischemia and infarction as evidenced by the development of deep Q waves in V_1 to V_3 and marked ST-segment elevation in V_2 to V_5. The appearance of the QRS-ST-T wave complex in V_4 to V_5 has been likened to the shape of a "tombstone" — an apt analogy because of the high mortality rate associated with such extensive infarctions. *C*, Anterior myocardial infarction and right bundle branch block. The infarct shown in *A* and *B* is now complicated by the development of RBBB, as indicated by the QR pattern in V_1 to V_3.

pattern to recognize, since it has potential implications for temporary pacemaker therapy (chapters 8 & 9).

Myocardial infarction may cause intraventricular delays on the ECG that are either nonspecific or represent "incomplete" forms of classic conduction blocks. With further infarction, more severe conduction delays may be seen associated with enhanced ST-segment and T-wave abnormalities (figure 2–19).

Other conditions that limit the diagnostic value of the ECG because they may either mask or mimic acute infarction include the Wolff-Parkinson-White syndrome, hypertrophic obstructive cardiomyopathy, severe left ventricular hypertrophy, and central nervous system events such as subarachnoid hemorrhage (figure 2–20).

Finally, a careful review of ventricular ectopic depolarizations recorded on a 12-lead ECG may offer important clues to the presence of acute myocardial infarction (figure 2–21).

4. Elevation of Serum Enzymes

Myocardial cells release a number of enzymes into the circulation at different times after myocardial necrosis (figure 2–22).

Creatine kinase (CK) participates in a reversible reaction, transferring high-energy phosphate from ATP to creatine phosphate. Serum activity is a sensitive index of myocardial infarction; however, a false-positive result will be found in 15 per cent of cases owing to muscle disease or trauma, alcohol intoxication, or pulmonary embolism [17].

CK is a dimeric molecule consisting of two subunits of type B or M. Three isoenzymes of CK have been identified by electrophoresis: both MM and MB isoenzymes are present in

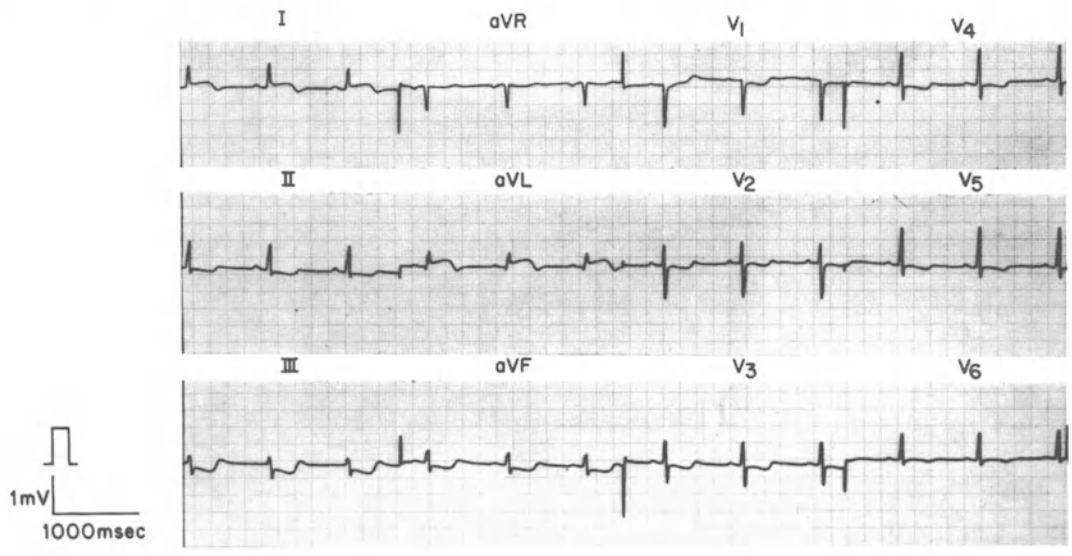


FIGURE 2–14. "High" lateral myocardial infarction. The ST-segment elevation I and aVL, the T wave inversion in V_4 to V_6 and the Q wave in aVL are consistent with "high" anterolateral wall infarction. When the lateral precordial leads are taken one interspace above the standard position, a more diagnostic pattern of infarction may sometimes be uncovered.

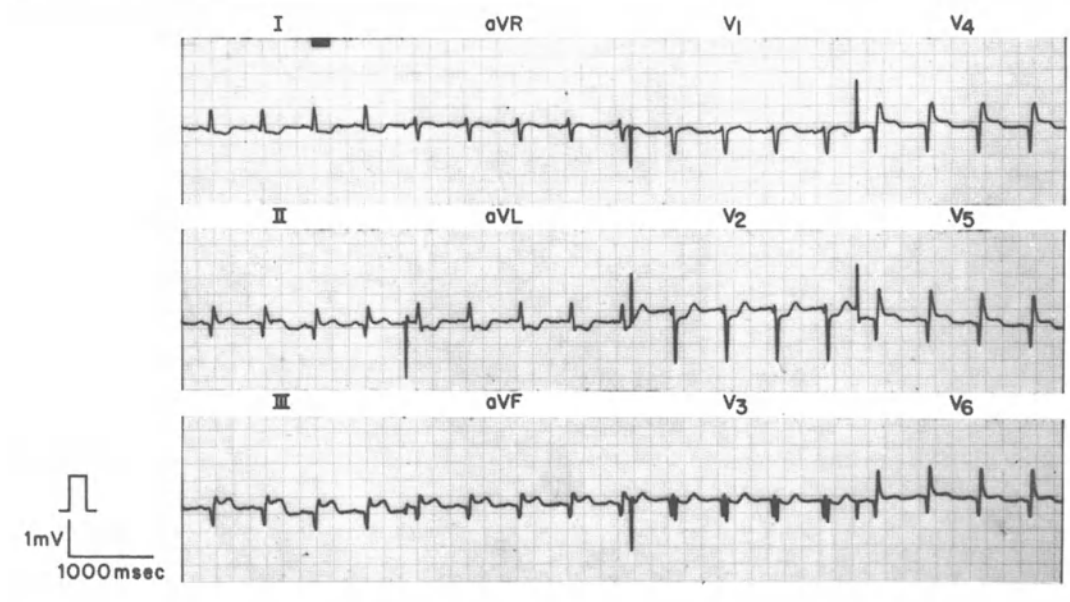


FIGURE 2–15. Q waves are seen in II, III, and aVF (inferior); V_2 to V_4 (anteroseptal and anteroapical); and V_5 and V_6 (anterolateral), indicating multiple zones of infarction in the myocardium.

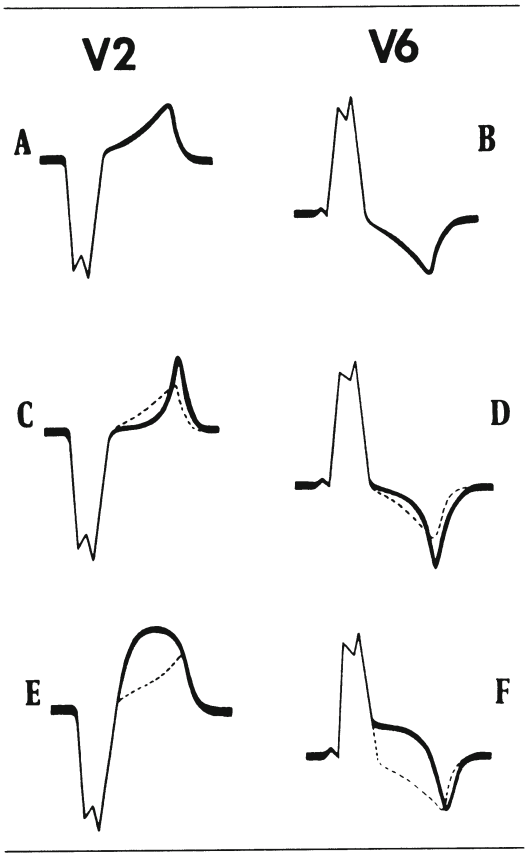


FIGURE 2–16. *A* and *B*, Normal QRST configuration in left bundle branch block. *C* and *D*, Effect of myocardial ischemia on ST segment and T wave in same condition. *E* and *F*, Effect of anterior wall infarction on ST segment and T wave. (From Schamroth L: *The electrocardiology of coronary artery disease*, 2nd ed. Oxford, Blackwell Scientific Publications, 1984, p 88.)

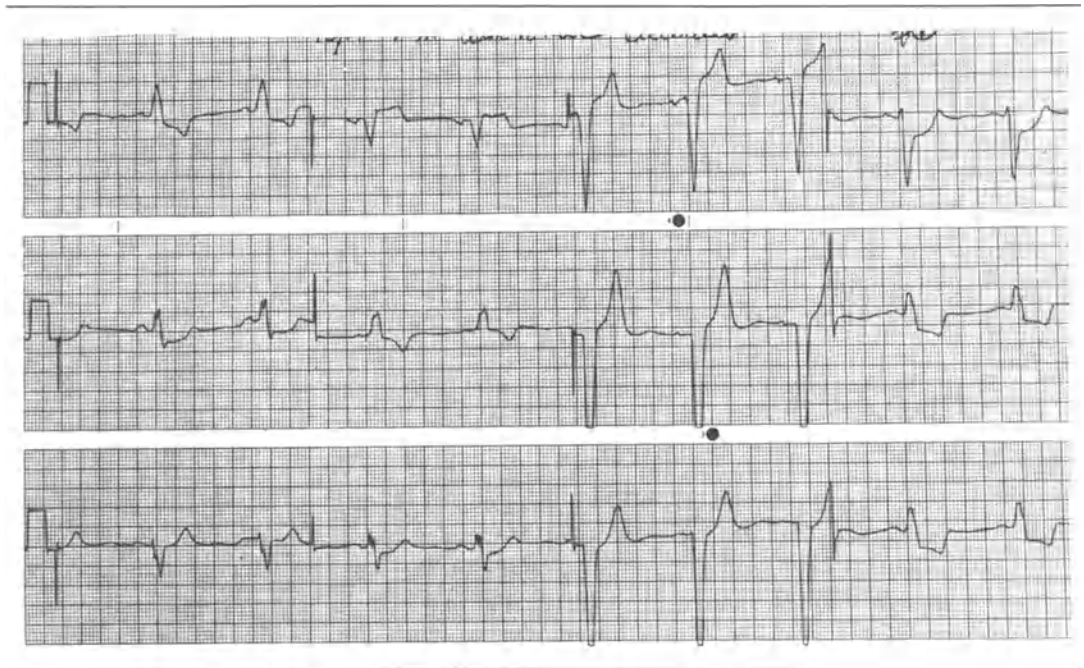


FIGURE 2–17. Left bundle branch block with primary repolarization abnormalities. The striking horizontally oriented ST-segment depression in V_4 to V_6 is not typical of uncomplicated LBBB and is consistent with acute infarction, probably of the anterolateral wall.

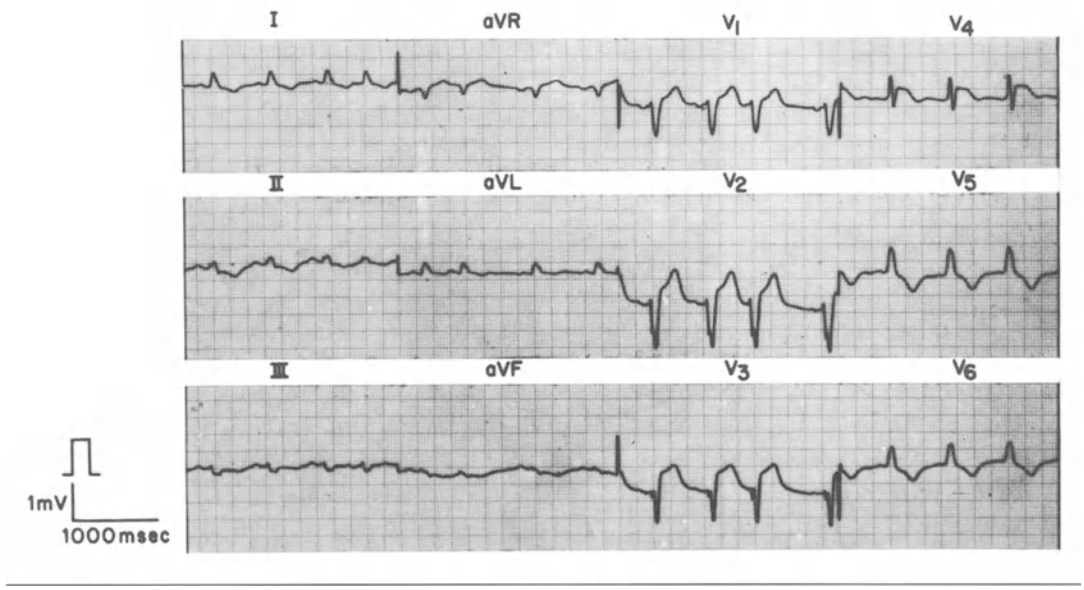
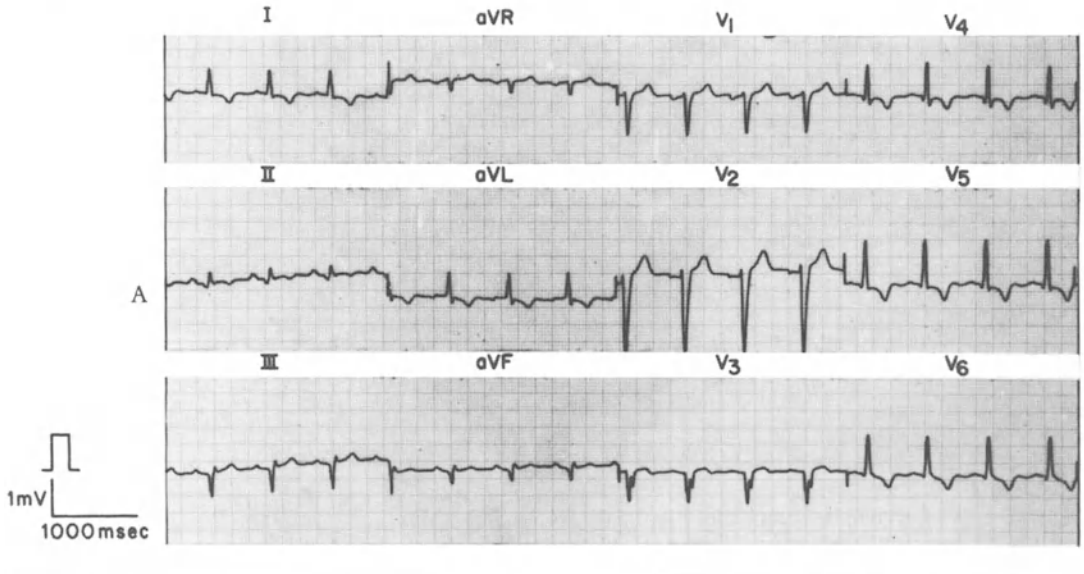


FIGURE 2–18. Left bundle branch block with primary repolarization abnormalities. The upward coving nature of the ST-segment elevation in V_4 to V_6 is consistent with acute anterior wall infarction complicating the long-standing LBBB pattern. Atrial premature depolarizations are also present.



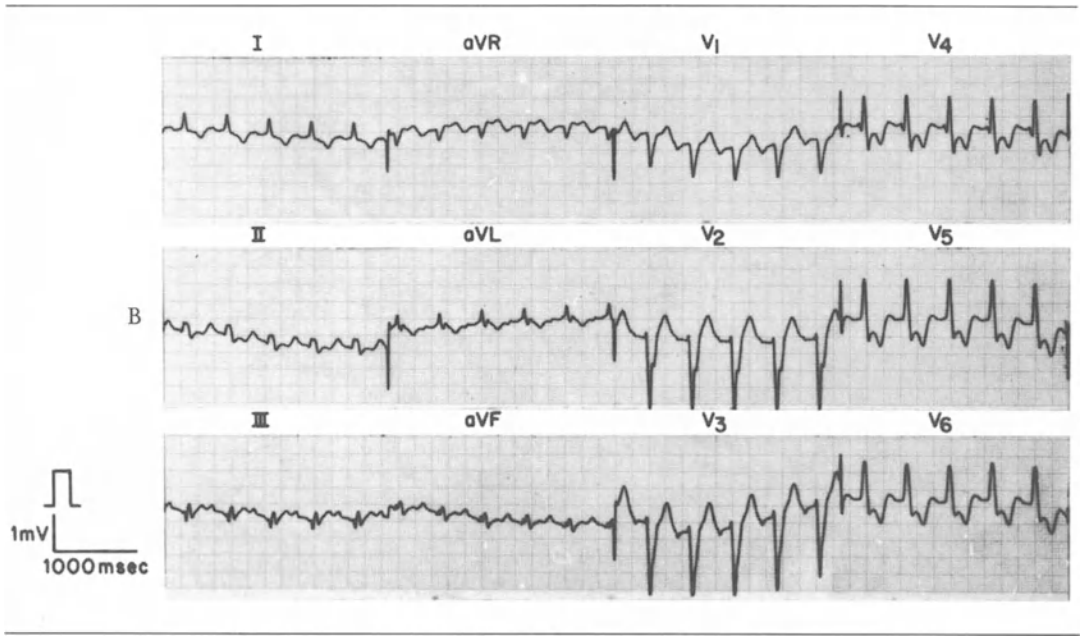


FIGURE 2–19. *A*, Anterior myocardial infarction with nonspecific intraventricular conduction delay. *B*, The patient whose ECG is shown in A developed recurrent ischemia, as shown by the marked ST-segment depression in V_2 to V_6.

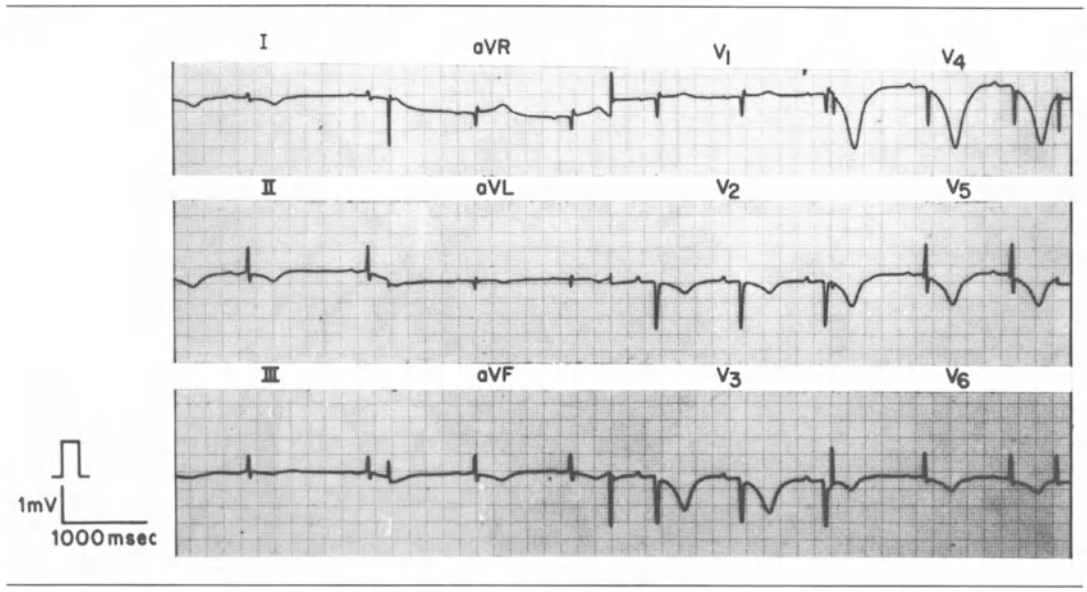


FIGURE 2–20. "Cerebral" T waves mimicking acute myocardial infarction. The deeply inverted, seemingly symmetrical T waves in V_3 to V_5 superficially suggest anterior subendocardial infarction. The symmetrical pattern of the T-wave inversion is somewhat atypical for subendocardial infarction and in this case was due to a subarachnoid hemorrhage. Central nervous system lesions may occasionally cause marked repolarization abnormalities on the ECG and mimic acute infarction. Clinical circumstances usually lead to the correct diagnosis.

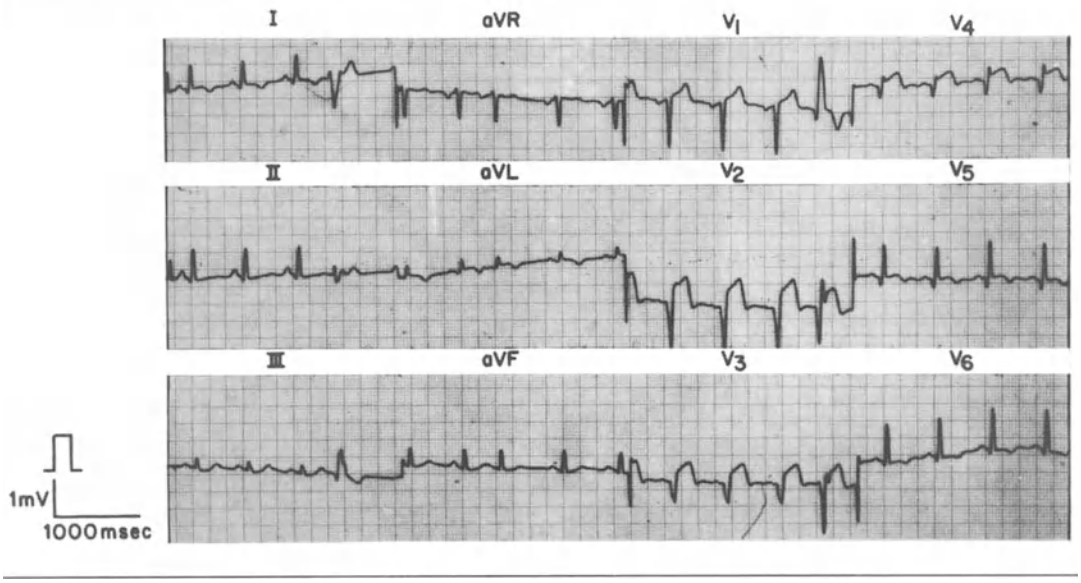


FIGURE 2–21. Anterior myocardial infarction with ventricular premature depolarizations. The ectopic ventricular beat seen in leads V_1 to V_3 shows a Q wave and repolarization abnormalities consistent with anterior wall infarction. Although the 12-lead ECG permitted the diagnosis of anterior infarction in this case, the findings here serve to emphasize the need to scrutinize ectopic ventricular depolarizations carefully for signs of infarction when the ECG is not as diagnostic.

cardiac muscle, while skeletal muscle contains mainly MM, and brain and kidney contain predominantly the BB isoenzyme. The MB isoenzyme may also be present in small quantities in the small intestine, tongue, and diaphragm. In 1976 a specific and highly sensitive radioimmunoassay for MB-CK was developed [18,19]. Table 2–2 compares some of the currently available CK isoenzyme assay techniques. Physicians should familiarize themselves with the normal range for CK isoenzyme values established in their individual laboratory. For practical purposes, MB-CK can be said to be released from the myocardium only when necrosis occurs. Normally, a trace of MB-CK can be present in the serum (i.e., less than 2 per cent); if levels greater than 2 per cent to 4 per cent of the total CK released are detected, myocardial necrosis is presumed to have occurred until proved otherwise. Only about one-third of the original CK content remains in situ after a myocardial infarction; the rest is largely inactivated locally (owing to a fall in pH or removal by the cardiac lymphatic system). Only 15 per cent of the original total CK released eventually reaches the plasma [20].

Myocarditis and cardiac surgery may also elevate MB-CK activity; however, intramuscular injections will not usually influence MB-CK release. (See table 2–3 for a list of pathological conditions in which CK isoenzymes are elevated.) MB-CK appears in the circulation 4 to 6 hours after the onset of infarction and peaks at about 16 to 22 hours.

Measurement of the catalytic activity of other enzymes may be helpful in deciding whether or not an evolving infarction is present. *Lactic dehydrogenase* (LDH), which is present in myocardium, lung, liver, and red blood cells, has five specific isoenzymes, each consisting of a tetramer composed of a combination of H and M subunits. The H polypeptide chain is so called because it has been isolated from the heart and the M chain has been found in skeletal muscle. Under ordinary circumstances, the concentration of LDH_1 (a tetramer consisting of

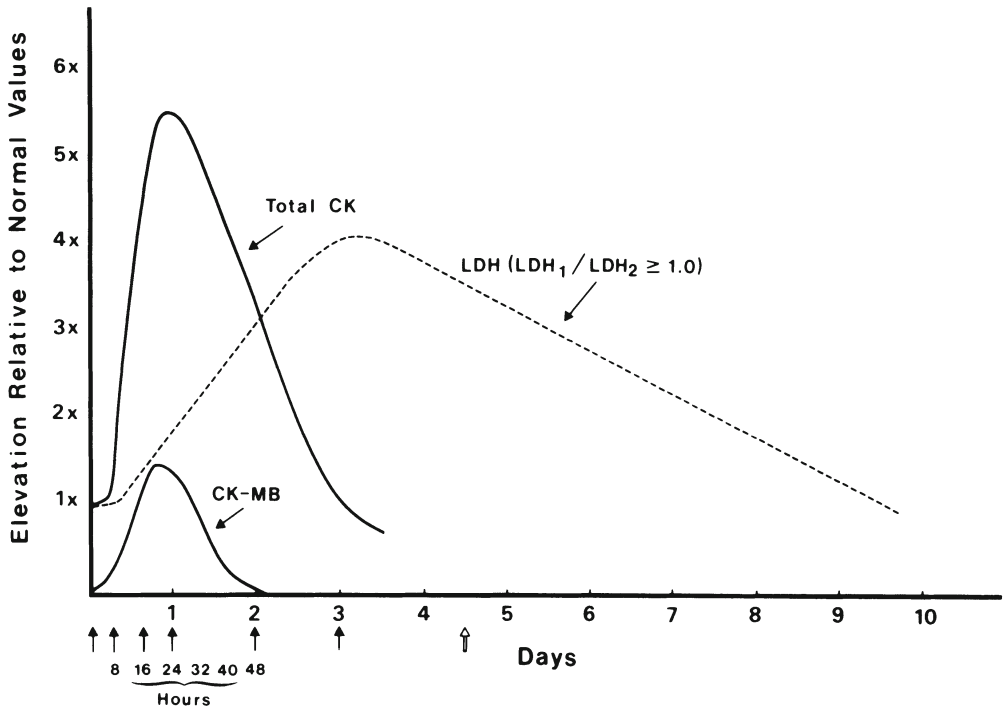


FIGURE 2–22. Time course of serum CK, MB–CK, and LDH elevations after acute myocardial infarction. After about a 6 hour delay, CK values rise above normal and achieve peak levels at 18 to 20 hours after onset of infarction. The MB isoenzyme of CK, ordinarily found in insignificant quantities in plasma, becomes elevated within 4 to 6 hours after chest pain and reaches a peak at 12 to 20 hours. Because of faster clearance, the level of MB isoenzyme falls back to normal faster than the MM isoenzyme level and may not be elevated after 48 to 72 hours. LDH activity is elevated within 6 to 10 hours after infarction, reaches a peak at 48 to 96 hours and may remain elevated for at least 10 days. The ratio of LDH_1/LDH_2 approaches or even exceeds 1.0 for most of the period of elevation of total LDH. Thus, a patient admitted 48 to 72 hours after a suspected myocardial infarction may have nondiagnostic CK elevations, but the situation can often be clarified by evaluating the isoenzymes of LDH since the LDH_1/LDH_2 "flip" (i.e., $LDH_1 \geq LDH_2$) is abnormal for a longer period.

Suggested times for blood sampling to detect a rise in cardiac enzymes are indicated by the solid arrows. Not all patients require such extensive blood testing (i.e., six specimens) if the diagnosis is more obvious; fewer specimens may be drawn but at the times indicated relative to the onset of chest pain. The open arrow emphasizes the utility of drawing a blood specimen for LDH isoenzymes in an individual who presents beyond the point where an elevated CK value would be obtained after a routine infarction. (Modified from Das Gupta DS (ed): *Principles and Practice of Acute Cardiac Care*. Chicago, Year Book Medical Publishers, 1984, p 393.)

four H subunits) is lower than that of LDH_2 (a tetramer consisting of three H subunits and one M subunit). When acute myocardial infarction occurs a "flipped" LDH pattern is seen, with the concentration of LDH_1 exceeding that of LDH_2. In the laboratory these various isoenzymes are easily separated by means of electrophoretic techniques. The LDH_1 isoenzyme (the fastest migrating isoenzyme) is relatively cardiospecific but can also be raised in the presence of hepatic disease or hemolysis of the blood sample. (See table 2–4 for a more detailed review of the differential diagnosis of elevated LDH isoenzyme values.) However, isoenzymes of LDH will preferentially reduce alpha-oxybutyrate if it is substituted for pyruvate (as it is reduced to lactate), and hydroxybutyrate dehydrogenase (HBD) is formed.

TABLE 2–2. CK isoenzyme assays

Technique	Sensitivity of detection	Disadvantages	Advantages
Qualitative			
1. Electrophoresis on agar, agarose, cellulose acetate, or polyacrylamide gel followed by fluorescence analysis	5 to 10 IU/liter	Nonspecific fluorescence (e.g., adenylate kinase) plus interfering substances (e.g., tetracycline, aspirin, chlorpromazine, diazepam, tricyclic compounds, chlordiazepoxide)*	
Quantitative			
1. Kinetic fluorometric method		Too cumbersome for routine clinical use	Serves as a standard for evaluating new techniques
2. Column chromatography (sephadex, cellulose DEAE)	5 to 10 IU/liter	Still has limited specificity*	Some procedures may be automated
3. Batch absorption to glycophase-coated glass beads	5 to 10 IU/liter	Difficult to automate	Simple, rapid, avoids cumbersome chromatographic methods
4. Immunoinhibition		Results too erroneous for routine clinical use	
5. Radio immunoassay for beta subunit	1 IU/liter	Requires laboratory capable of RIA techniques Provision for disposal of radioactive waste material	Measures concentration of enzyme protein and not enzyme activity and therefore not subject to enzyme lability. Detects MB-CK in circulation earlier than other techniques

*A variant CK consisting of IgG complexed to BB occurs in about 1 to 3 per cent of sera. It migrates as a band between MM + MB on electrophoresis and may be carried with the MB fraction on ion-exchange chromatography.

Unlike total LDH, HBD is less likely to be elevated in the presence of hepatic congestion or pulmonary infarction. It has a relatively long decay rate, with levels remaining elevated for up to a week after infarction, in contrast to CK and *aspartate aminotransferase* (Asp AT), which usually return to normal within 3 days of the onset of chest pain. (*Note:* The International Union of Biochemists recommended in 1964 that the name serum glutamic oxaloacetic transaminase (SGOT), be changed to aspartate aminotransferase.) Asp AT is present in liver and pancreas and is therefore affected by disease processes in these organs as well as in the heart. If a patient receives intramuscular injections, levels of CK may become elevated, but the activity of MB-CK or Asp AT should not be increased.

In order to determine the fastest, safest, and cheapest way of diagnosing acute myocardial infarction, a Danish group evaluated the predictive values of serum activities of MB-CK, Asp AT, and CK as well as the ECG in 401 patients consecutively admitted to the hospital for suspected acute infarction [21]. When these variables were assessed individually and in combination, MB-CK was found to be a better predictor than all the other tests, and this was true for both single and serial measurements. In all cases of acute myocardial infarction MB-CK

TABLE 2-3. Pathological conditions in which CK isoenzymes are elevated

MB-CK:
Myocardial infarct or injury (also subendocardial infarct or infarct extension)
Rhabdomyolysis
Polymyositis
Duchenne's muscular dystrophy (some from heart, most from muscle)
Early dermatomyositis
Rocky Mountain spotted fever
Reye's syndrome
BB-CK:
Biliary atresia
Malignancy
Severe shock syndrome
MM-CK:
Normal serum
Muscle injury
Brain injury
Myocardial injury

was positive within 17 hours of admission.

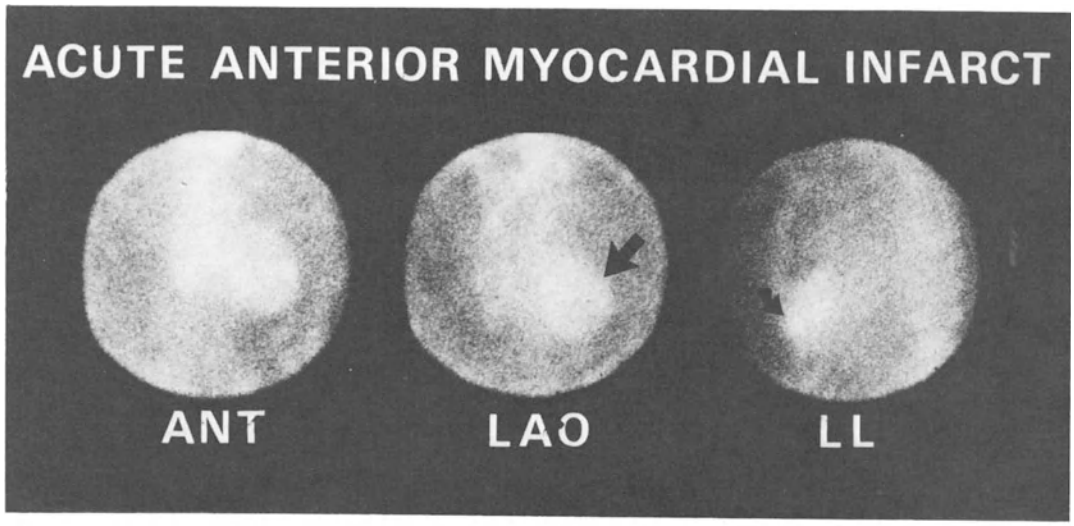
Most would agree that MB-CK is the most reliable single diagnostic test for acute infarction in patients admitted to the hospital within 24 hours of the onset of symptoms. The radioimmunoassay is specific for the B subunit and is the most sensitive test of CK. It can detect 0.01 IU/L of MB-CK, there is no cross-reactivity with MM-CK and it depends on binding of immunoreactive MB-CK protein by antibody so that the concentration of the enzyme protein is measured. This test can detect infarction within 3 hours of the onset of chest pain.

After cardiac surgery, MB-CK is invariably elevated as a result of even minor operative trauma to the heart. To make the diagnosis of infarction in this instance, physicians rely on serial ECGs and radionuclide scans and must be suspicious when SGOT values are unusually high (greater than 200 units/ml) [17].

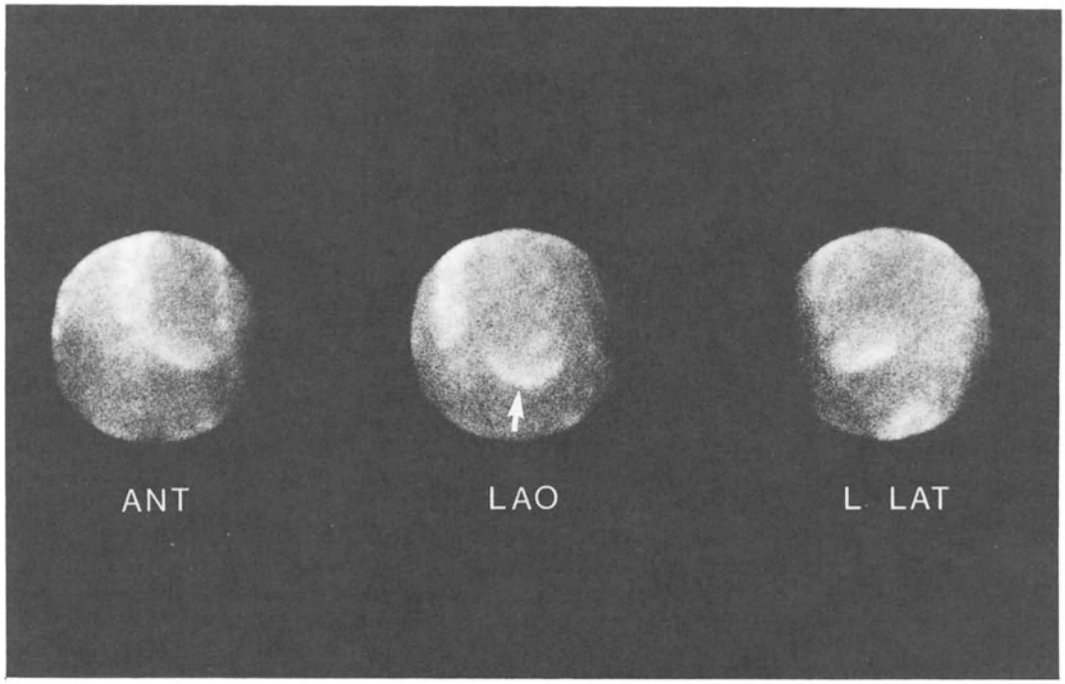
In marathon runners, elevated MB-CK levels have been detected in the presence of normal infarct-avid (hot-spot) scintigrams, suggesting that MB-CK arises from a noncardiac or skeletal muscle source under such extreme conditions [22].

TABLE 2-4. Differential diagnosis of elevated LDH isoenzyme values

ELEVATED LDH		
$LDH_1 > LDH_2$	LDH_4 and LDH_5 Elevated	All LDH isoenzymes increased but not relative
Myocardial injury	Hepatic injury	Thrombocytosis
Acute myocardial infarction	Hepatitis	Polycythemia rubra vera
Myocardiopathy	Drug	Tuberculosis
Pulmonary embolism	Pulmonary embolism	Primary
Renal cortical infarction	Tricuspid insufficiency	Neoplasm
Hemolytic anemias	Dermatomyositis	Myeloma
Pernicious	Muscle trauma	Hodgkin's disease
Folate deficiency	Surgery	Disseminated
Acquired	Cardioversion	Duchenne's and
Valvular disease	Cardiac massage	facioscapulohumeral
Valvular prosthesis		muscular dystrophy
This ratio is normally greater than 1 in young menstruating women and in men receiving oral diethylstilbestrol in the treatment of carcinoma of the prostate.		Hyperthyroidism
		Mixed connective tissue disease

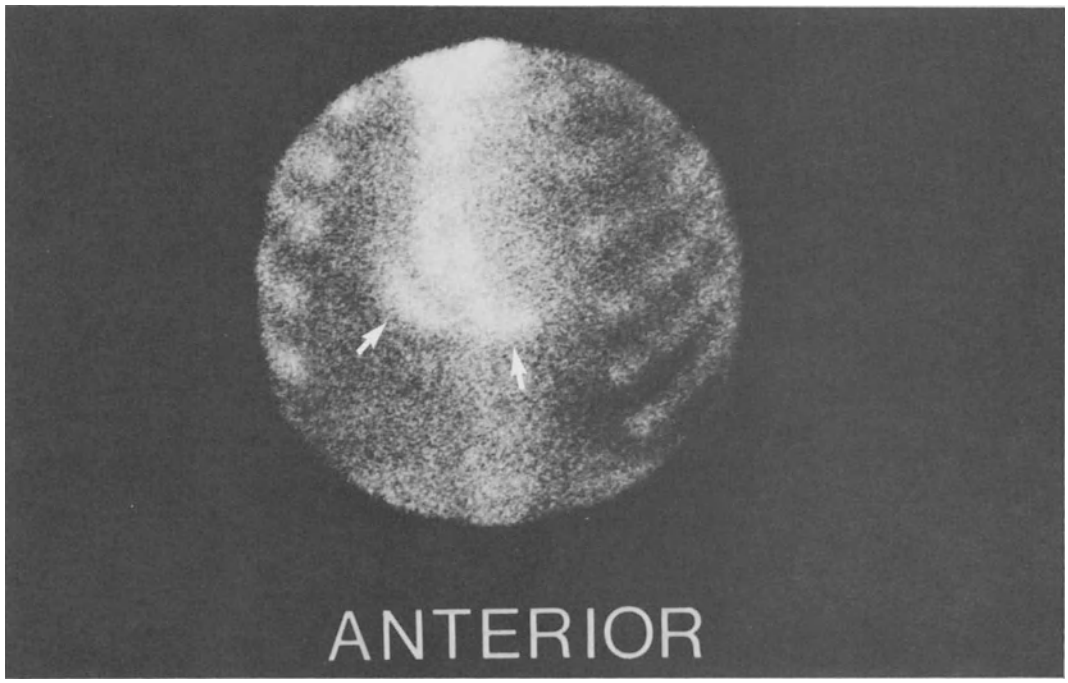


A



B

FIGURE 2–23. *A*, Myocardial scintigrams with ^{99m}Tc-pyrophosphate of a patient with a large acute anteroseptal infarct. There is extensive uptake involving the anterior left ventricular wall and septum. Uptake is seen best on the anterior view to the left of the sternum. Anterior wall uptake is seen on the edge of the left lateral view, directly behind the sternum. ANT = anterior; LAO = 45 degree left anterior oblique; LL = left lateral. *B*, Myocardial scintigrams with ^{99m}Tc-pyrophosphate of a patient with an acute inferoposterior infarct. Inferior wall activity is seen on the edge in all three conventional projections. ANT = anterior; LAO = 45 degree left anterior oblique; L LAT = left lateral. *C*, Myocardial scintigram with ^{99m}Tc-pyrophosphate of a patient with an acute inferior infarct (right arrow) with extension to the right ventricular wall (left arrow). (From Holman BL: Infarct-avid scintigraphy. In Freeman LM (ed): *Freeman and Johnson's clinical radionuclide imaging*, Vol 1, 3rd ed. New York, Grune and Stratton, 1984, pp 550–552.)



C

5. *Myocardial Infarction Imaging*

Another technique used to assess ischemic injury clinically is myocardial infarction imaging. Hot-spot radiotracers such as technetium 99m stannous pyrophosphate can detect infarcts as early as 12 to 16 hours after the onset of symptoms [23] (figure 2–23). It is likely that uptake by normal myocardium is not significant. The tracer probably has an affinity for calcium, denatured protein, or sulfhydryl groups that accumulate in areas of myocardial necrosis. Technetium requires some residual vascular supply to the infarcted region for delivery of the tracer and consequently uptake is maximal if flow is approximately 30 per cent to 40 per cent of normal. A doughnut pattern may be observed if the center of the infarct is not perfused. The method is highly sensitive for Q-wave infarctions but less so for non-Q-wave infarctions. Results may be falsely positive in the presence of rib fractures, valve calcification, and left ventricular aneurysms. This technique can be useful for determining whether myocardial necrosis has occurred in a patient who is hospitalized subsequent to the peak release of cardiac enzymes, since the maximal uptake abnormality becomes evident between 48 and 72 hours.

Thallium-201 perfusion scanning allows one to compare perfusion in different areas of the heart (figure 2–24). Nonperfused areas do not take up the isotope and are thus seen as "cold spots" on the scan. These may be due to either acute or old infarction. In the latter case, the perfusion defect will persist on repeat scanning 4 hours later. The initial accumulation of thallium-201 in myocardium occurs as a function of regional myocardial blood flow and the integrity of the sodium-potassium ATPase system. Clearance from the blood and accumulation within the heart occurs 5 to 10 minutes after intravenous injection. In the normal subject, the radionuclide is distributed homogeneously throughout the myocardium. An area that shows decreased thallium-201 accumulation may represent myocardial necrosis and/or ischemia. This method is more sensitive for large infarcts and in patients studied early (i.e., within 6 to 10 hours of the infarction).

Another form of nuclear medicine studied, radionuclide ventriculography, may provide useful information about regional wall motion abnormalities and the relative function of the left and right ventricles (figure 2–25).

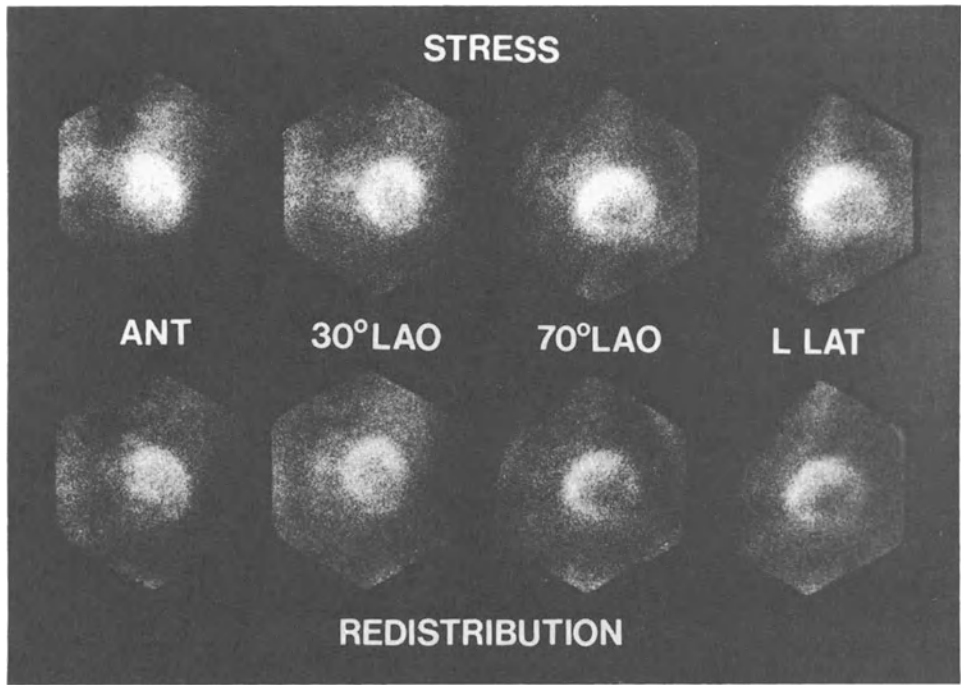


FIGURE 2–24. Normal myocardial perfusion scintigraphy with thallium-201 after stress in four different projections. Notice the uniform uptake of radiotracer throughout the left ventricular wall and the central defect due to the left ventricular cavity. ANT = anterior; 30° LAO = 30-degree left anterior oblique; 70° LAO = 70-degree left anterior oblique; LLAT = left lateral.

6. *Differential Diagnosis of Acute Myocardial Infarction*

6.1. AORTIC DISSECTION

Over the age of 50 years, aortic dissections are more common in men, although sex distribution is a virtually equal under age 40. In women about half the dissections occur during pregnancy. Virtually all patients (approximately 90 per cent) have a history of hypertension [24].

Pain, the most frequent symptom is often described as "ripping" or "tearing" rather than the tight, constrictive pain of acute infarction. It is sudden in onset, continuous and unremitting, and often radiates to the back and abdomen. About one-fourth of patients suffer transient or permanent paralysis. Physical examination reveals a pale, perspiring patient who is usually hypertensive. Unequal or absent pulses in the limbs, especially if this is a new finding, are highly suggestive of dissection. Half the patients have cardiomegaly secondary to hypertensive disease, and a diastolic murmur of aortic insufficiency is present in a minority (about 25 per cent).

Usually the ECG reveals evidence of left ventricular hypertrophy. The absence of changes typical of myocardial infarction, especially in equivocal cases, supports the diagnosis of dissecting aneurysm, although ischemic or infarction patterns are present in 10 per cent to 40 per cent of reported cases [24]. In pure aortic dissection, the chest x-ray may show superior mediastinal widening compared with previous films, a finding that is suggestive of the diagnosis. The chest x-ray may be normal. Aortography is the most widely available diagnostic test that defines the extent of dissection and allows one to plan management (figure 2–26).

Untreated acute aortic dissection is associated

with a high mortality rate. Without treatment, about 80 per cent of these patients die within one month of onset. Factors that make this prognosis worse are the location of the tear (with ascending aortic lesions carrying a high risk), significant hypertension, and advanced age. Dissections involving the aortic root and ascending aorta are now preferentially treated surgically, whereas more distal dissections are usually treated medically [25].

6.2. ACUTE PERICARDITIS

Acute pericarditis of unknown cause is usually assumed to result from viral infections. It tends to occur in a younger age group than those suffering acute myocardial infarction. Diagnosis depends on a triad of findings, including chest pain, pericardial friction rub, and specific ECG changes. Chest pain is usually fairly sudden in onset, severe and constant, and usually pleuritic in nature. It is often worse on inspiration, which helps distinguish it from acute myocardial infarction. Patients often find palpation of the trapezius ridge uncomfortable. The discomfort is usually worse with coughing, swallowing, or inspiration. Relief may be obtained by sitting up and leaning forward. A pericardial friction rub can be detected in most cases if listened for carefully at various times with the patient in different positions. Early widespread ST-segment elevation is seen in all leads where the positive electrode faces the ventricular cavity rather than the epicardial surface (i.e., aVR, III, and/or V_1). Reciprocal ST-segment changes are absent. Depression of the P-R segment is also seen in acute pericarditis and reflects inflammation of the atrial myocardium. CK and other myocardial enzyme levels are usually normal, and technetium pyrophosphate scans are usually negative.

6.3. PULMONARY EMBOLISM

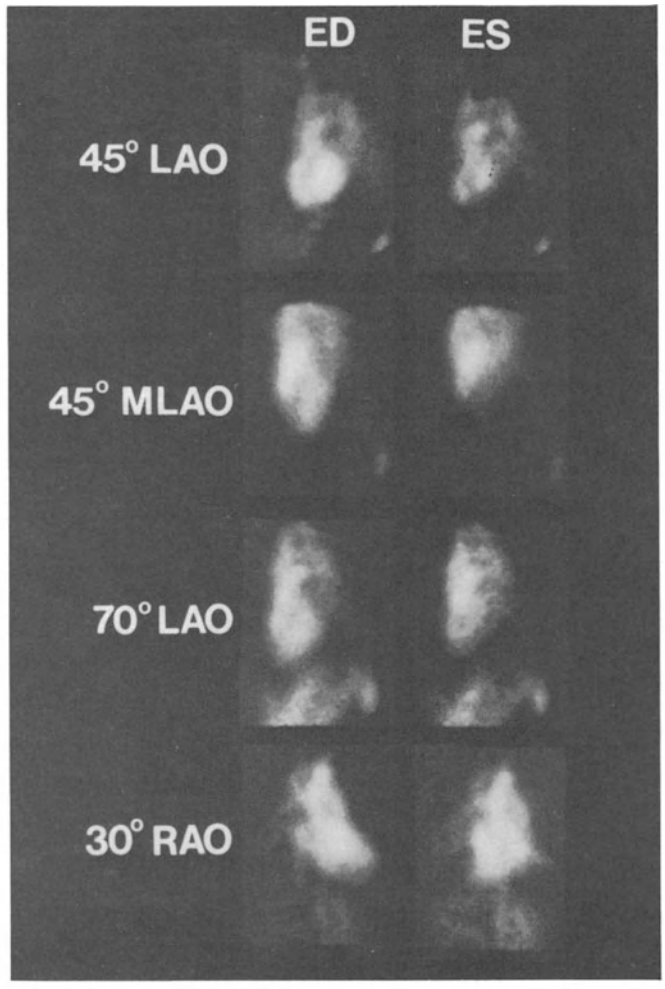
Dyspnea occurs in virtually all patients with pulmonary embolism and most have this symptom along with tachypnea and pleuritic pain. Sinus tachycardia is common; however, other findings such as cardiac gallop rhythms, accentuation of the pulmonic component of the second heart sound, rales in the chest, and pleuritic rubs are less common and nonspecific. In most patients with a pulmonary embolus, arterial oxygen tension is less than 90 mm Hg. A normal chest film does not exclude the diagnosis, and abnormalities such as pulmonary infiltrates or effusion, which are sometimes seen, are nonspecific.

There is a good correlation between normal radionuclide scans and the absence of emboli and between multiple segmental or larger abnormalities on the scan and the presence of emboli. Unfortunately, small emboli frequently cannot be confirmed or excluded using this technique. Pulmonary angiography is the most accurate way of diagnosing pulmonary emboli, since it is fairly sensitive and specific as well as reproducible [26]. Thrombi as small as 3 mm in diameter can be defined, and correlation with autopsy findings is excellent.

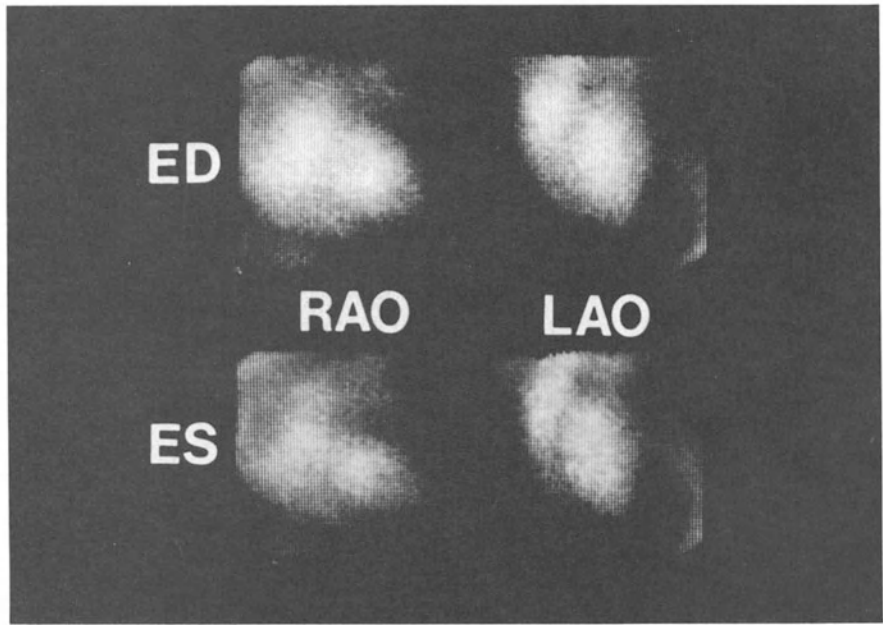
In considering ventilation and perfusion lung studies, one would wish to distinguish between areas that lack perfusion but show normal ventilation (as in pulmonary embolism) and areas that lack perfusion because of underlying parenchymal disease (such as asthma or chronic obstructive pulmonary disease). In patients with entirely normal perfusion scans, ventilation imaging would not be indicated, since this pattern excludes pulmonary embolism. Ventilation scans are generally not helpful in patients in whom single or multiple perfusion defects match abnormalities on the chest radiograph. The most definitive scan pattern for pulmonary embolism consists of single or multiple lobar or large perfusion defects without associated defects on the chest x-ray. If a ventilation scan shows no associated defects in the presence of a lobar or large perfusion defect, the likelihood of pulmonary embolism increases from 80 per cent to almost 100 per cent [27].

6.4. ESOPHAGEAL DISORDERS

6.4.1. Esophageal Reflux. Abnormal regurgitation of acid from the stomach to the esophagus is relatively common. This can cause inflammation of the esophageal mucosa and is often associated with a retrosternal burning — "heartburn," indigestion, or belching. Rarely the discomfort is felt in the shoulders, neck, or jaw. Acid regurgitation or acid-induced spasm as a cause of chest pain may be elucidated by alternate infusions of dilute acid and normal saline via a nasogastric catheter with the tip at the level of the mid-esophagus (Bernstein test). Hiatus hernia is found relatively frequently when looked for but is not often a cause of chest



A



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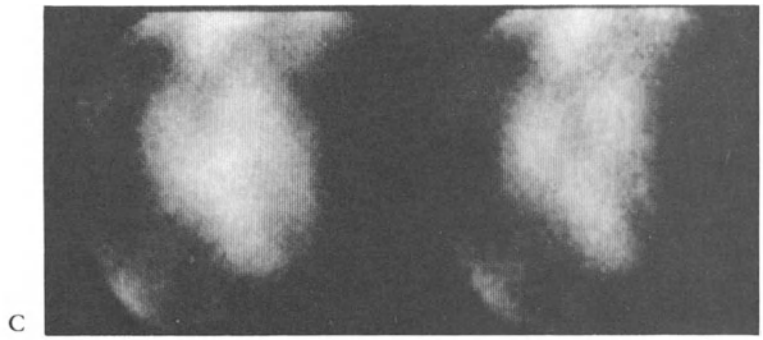

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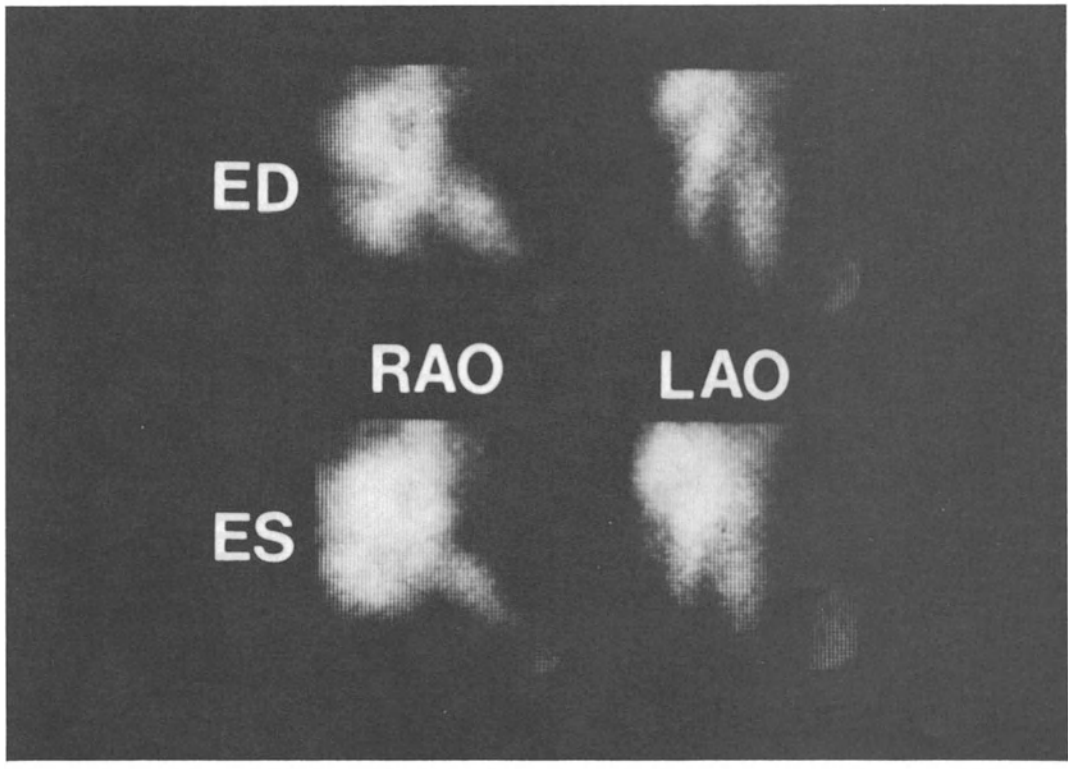

D

FIGURE 2–25. *A*, Normal equilibrium (gated) radionuclide angiocardiogram. LAO = left anterior oblique projection; MLAO = modified left anterior oblique; RAO = right anterior oblique; ED = end diastole; ES = end systole. *B*, Equilibrium (gated) radionuclide angiocardiogram of a patient with ischemic cardiomyopathy. There is global asynergy of the markedly enlarged left ventricle. Note the small difference in size and intensity of left ventricular activity between diastole and systole. The right ventricle is normal in size and performance. ED = end-diastolic frame; ES = end-systolic frame; RAO = 30-degree right anterior oblique projection; LAO = 45-degree modified left anterior oblique projection. *C*, Equilibrium (gated) radionuclide angiocardiogram of patient with extensive right ventricular infarction. *Left*, During diastole, the right ventricle is dilated. *Right*, During systole, the left ventricle is contracting normally, while the right ventricle remains hypokinetic and dilated. *D*, Equilibrium (gated) radionuclide angiocardiogram of a patient with an apical aneurysm. Note the apical dyskinesis seen best on the RAO projection. Performance is normal in the other ventricular segments. ED = end-diastolic frame; ES = end-systolic frame; RAO = 30-degree right anterior oblique projection; LAO = 45-degree modified left anterior oblique projection. (*A*, *B*, and *D* from Holman BL: Cardiac imaging. In Braunwald E (ed): *Heart Disease*. 2nd ed Philadelphia, W B Saunders Co, 1984.)

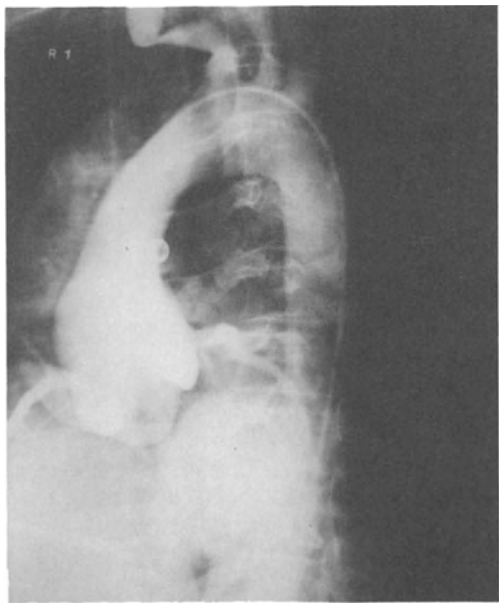

FIGURE 2–26. Aortogram taken in left anterior oblique projection of a 57-year-old man with hypertension who presented with severe "tearing" chest pain, unequal arm pulses, and a murmur of aortic regurgitation. A double lumen, outlined anteriorly, is consistent with aortic dissection commencing near the aortic valve. Some contrast is present in the left ventricle, indicating some degree of aortic insufficiency.

pain, although it may be associated with gastrointestinal bleeding, iron deficiency anemia, and possibly symptoms of acid reflux.

6.4.2. Esophageal Spasm. During or after swallowing patients may suffer constant retrosternal discomfort of uniform intensity or severe, spasmodic pain. The symptoms are intermittent and often accompanied by difficulty swallowing, although the pain may occur spontaneously at times. The condition is characterized by segmental nonperistaltic esophageal contractions. X-ray studies reveal spasm, narrowing, or irregular uncoordinated esophageal motility in the majority of patients. Intraesophageal pressure measurements may be high and consistent with uncoordinated peristalsis. Some patients may progress from diffuse spasm to typical achalasia. If a cardiac cause for such pain has been excluded, esophagoscopy must be performed to detect esophagitis or other disease. Barium studies during pain may reveal motility problems, and manometric studies can be diagnostic. Cold water may be difficult to swallow in patients with esophageal spasm and may provoke the typical manometric findings. Long-acting nitrates may provide some relief [28], and dilatation and myotomy may also be helpful at times.

6.5. GASTRIC PAIN

Pain arising from peptic ulceration is usually epigastric or substernal, is usually precipitated within an hour or two of ingesting food, and is often relieved by antacids or milk. Exercise is not a precipitating factor.

6.6. BILIARY COLIC

Biliary colic is caused by a rapid rise in biliary pressure due to obstruction of the cystic or bile duct. The pain is usually abrupt in onset and steady in nature, subsiding slowly over minutes or hours. It is usually felt in the right upper abdomen but can also be felt in the epigastrium, left abdomen, or precordium and may be referred to the scapula, may radiate around the costal margin to the back, or may rarely be felt in the shoulder, suggesting diaphragmatic irritation. Nausea and vomiting are common. Relationship to meals is variable, and a history of dyspepsia, fatty food tolerance, flatulence, and indigestion may be associated with gallstone disease but is also common among the general population. If symptoms are accompanied by signs of infection, acute cholecystitis may be present. Ultrasonic scanning will often help to confirm the diagnosis. Usually oral cholecystography will show if stones are present in the gallbladder; failure to opacify the gallbladder may indicate nonfunction due to disease. Cholangiography performed after episodes of acute cholangitis may demonstrate bile duct stones, which if radiopaque may be seen on plain x-ray. A careful history, examination of the ECG, and examination of serial serum enzyme values will all help distinguish patients with biliary colic from those with cardiac pain.

6.7. COSTOSTERNAL SYNDROME

A syndrome of local pain and tenderness, usually limited to the anterior chest wall, and swelling of the costal cartilages was first described by Tietze in 1921. This condition can coexist with typical angina pectoris and the pain can resem-

ble angina [29]. Because it is said that up to 10 per cent of patients evaluated for angina can have this syndrome, local pressure should be applied routinely to the anterior chest wall during examination of these patients. Usually the skin is not involved, and there are no characteristic x-ray changes; pathological changes have been noted in soft tissues rather than cartilage [30]. Treatment may consist of reassurance, antiinflammatory agents, and local steroids.

7. *Diagnosis of Acute Infarction*

Identification of patients with early or evolving acute myocardial infarction can be a difficult clinical problem. Out of fear of missing the high-risk patient with an evolving infarction, physicians in the community and in hospital admission wards tend to admit patients to coronary care units (CCUs) and as few as 30 per cent actually suffer acute myocardial infarctions [31]. Because of this, the practice of admitting all patients with either suspected or confirmed myocardial infarction to CCUs is being reexamined. Some advocate that home care of acute myocardial infarction may be appropriate in elderly patients who are first seen a day or more after the onset of an uncomplicated infarction and may avoid unnecessary expense [32].

Recently Fuchs and Scheidt [33] identified eight specific procedures unique to the CCU: administration of lidocaine, atropine sulfate, sodium nitroprusside, or vasopressors; Swan-Ganz or arterial catheterization; insertion of temporary pacemakers; and direct-current defibrillation. Working on the hypothesis that patients who do not require one or more of these interventions derive no particular benefit from their stay in a CCU, these investigators undertook to determine whether patients requiring these interventions could be identified prospectively. The study group consisted of 414 patients consecutively admitted to their CCU because of either unstable angina or suspected or confirmed acute myocardial infarction. Specialized interventions were required in patients who exhibited one or more of the following three signs:

1. Chest pain.
2. Pulmonary rales indicating congestive heart failure.
3. Premature ventricular contractions (PVCs).

Only 6 per cent of a total of 108 patients who had none of these criteria received specialized intervention, and none of these died in the CCU. The investigators concluded that if a patient does not have ongoing chest pain, congestive heart failure, or PVCs upon admission to the CCU, the risk of early complications is low and prolonged stay in the CCU is not required.

In order to determine whether the data available to physicians in the emergency room accurately identify which patients with acute chest pain are having a myocardial infarction, several investigators have developed decision-tree algorithms [35]. Goldman et al [36] constructed a decision protocol in the format of a simple flow chart using recursive partitioning analysis. Nine important clinical factors were identified (table 2–5), and they then prospectively tested the protocol at a second hospital. They found that integrating the protocol with physicians' judgments resulted in a classification system that preserved the sensitivity for detecting myocardial infarctions and improved the

TABLE 2–5. Nine clinical factors identified by recursive partitioning decision protocol

History of present illness:
1. How old is the patient?
2. How long ago did the present pain or episodes of recurrent pain begin?
3. Is the pain primarily in the chest but radiating to the shoulder, neck or arms?
4. Was the chest pain associated with diaphoresis?

Past medical history:
5. If the patient was ever told that this same pain was angina, is the present pain somehow worse? *or* Is the present pain the same as pain that was previously diagnosed as an acute myocardial infarction?
6. Was this pain called angina (and *not* a myocardial infarction) the last time the patient had it?

Physical examination:
7. Does local pressure reproduce the pain?

Electrocardiogram:
8. Does the emergency room ECG show ST-segment elevation or definite Q waves suggestive of acute infarction and not known to be old?
9. Does the emergency room ECG show ST-segment or T-wave changes suggestive of ischemia or strain and not known to be old?

From Goldman L, *et al*: A computer-derived protocol to aid in the diagnosis of emergency room patients with acute chest pain. *N Engl J Med* 307:588, 1982.

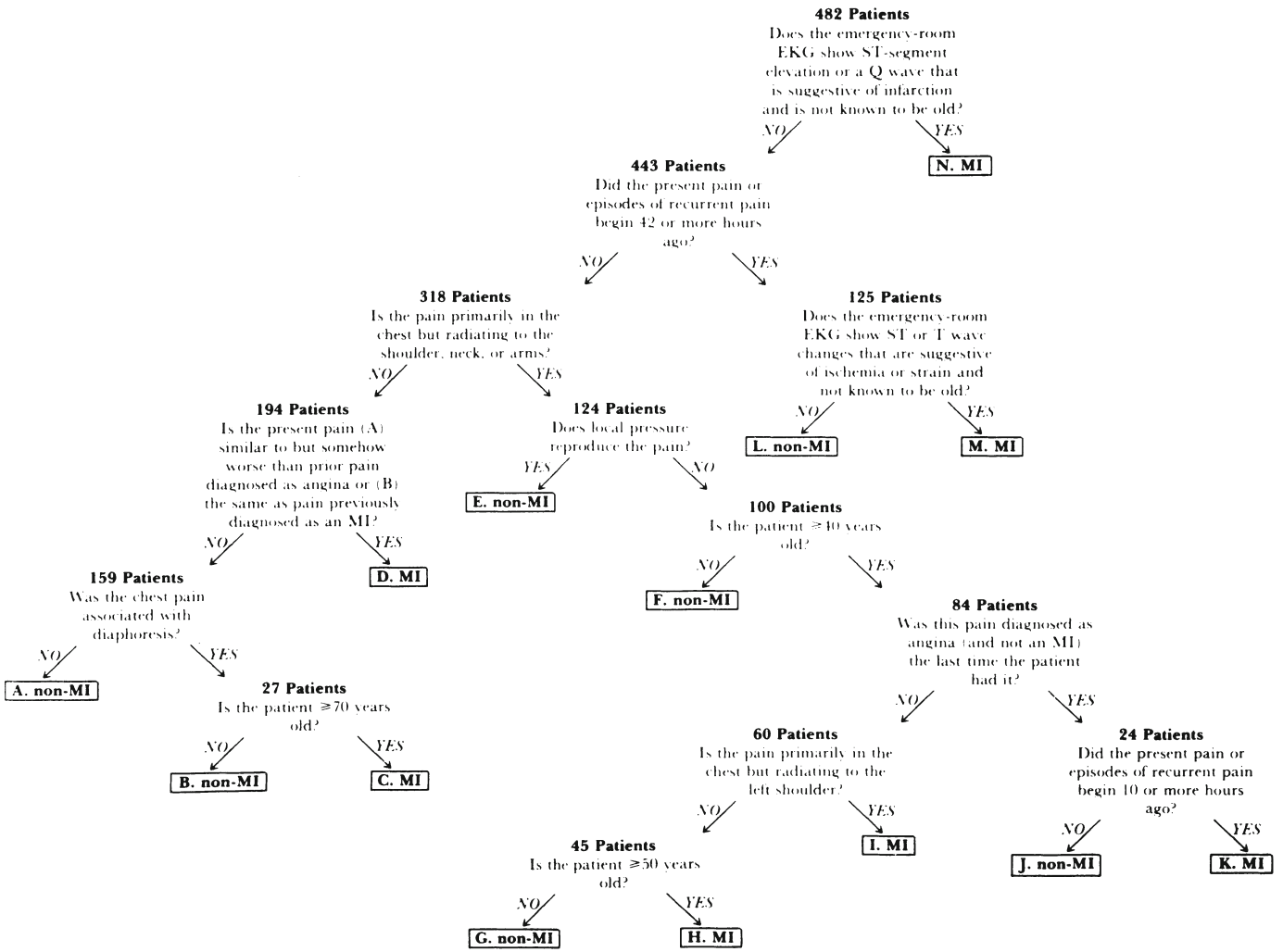
482 Patients
Does the emergency-room EKG show ST-segment elevation or a Q wave that is suggestive of infarction and is not known to be old?
NO
YES
N. MI
443 Patients
Did the present pain or episodes of recurrent pain begin 42 or more hours ago?
NO
YES
318 Patients
Is the pain primarily in the chest but radiating to the shoulder, neck, or arms?
NO
YES
125 Patients
Does the emergency-room EKG show ST or T wave changes that are suggestive of ischemia or strain and not known to be old?
NO
YES
L. non-MI
M. MI
194 Patients
Is the present pain (A) similar to but somehow worse than prior pain diagnosed as angina or (B) the same as pain previously diagnosed as an MI?
NO
YES
D. MI
124 Patients
Does local pressure reproduce the pain?
YES
NO
E. non-MI
100 Patients
Is the patient ≥40 years old?
NO
YES
F. non-MI
159 Patients
Was the chest pain associated with diaphoresis?
NO
YES
A. non-MI
27 Patients
Is the patient ≥70 years old?
NO
YES
B. non-MI
C. MI
84 Patients
Was this pain diagnosed as angina (and not an MI) the last time the patient had it?
NO
YES
60 Patients
Is the pain primarily in the chest but radiating to the left shoulder?
NO
YES
I. MI
24 Patients
Did the present pain or episodes of recurrent pain begin 10 or more hours ago?
NO
YES
J. non-MI
K. MI
45 Patients
Is the patient ≥50 years old?
NO
YES
G. non-MI
H. MI

TABLE 2–6. Classification of patients with acute chest pain

Terminal branch	No. of acute infarctions/ no. of patients in terminal subgroups			
	Yale training set	BWH validation set	BWH admission validation set	Total
A	0/132	2/84	0/13	2/229 (1)[+]
B	0/20	0/19	0/9	0/48
C*	2/7	1/3	0/1	3/11 (27)
D*	4/35	4/37	5/12	13/84 (15)
E	0/24	0/12	0/1	0/37
F	0/16	0/12	0/1	0/29
G	0/13	1/7	0/5	1/25 (4)
H*	9/32	4/10	4/16	17/58 (29)
I*	8/15	1/15	1/6	10/36 (28)
J	0/9	1/18	0/8	1/45 (2)
K*	2/5	1/9	0/3	3/17 (18)
L	0/115	1/64	0/6	1/185 (1)
M*	1/10	4/16	0/6	5/32 (16)
N*	34/39	35/51	20/24	89/114 (78)

Breakdown of patients in each of the 14 terminal branches of the computer-derived decision tree for the classification of patients with acute chest pain (see figure 2–27). * = All patients in this branch would be classified as having had an acute myocardial infarction using the decision tree.[+] Numbers in parentheses are percentages. BWH = Brigham and Women's Hospital; ER = emergency room.
From Goldman L, *et al*: A computer-derived protocol to aid in the diagnosis of emergency room patients with acute chest pain. *N Engl J Med* 307:588, 1982.

specificity from 67 per cent to 77 per cent and the positive predictive value from 34 per cent to 42 per cent of admissions to an intensive care area [36].

A computer-derived decision tree for classifying patients with acute chest pain was used to segregate patients with apparently new ST-segment elevations or Q waves into a high-probability terminal subgroup (figure 2–27). The computer protocol then classified the other patients using the presence or absence of new ischemic ST-segment or T-wave changes and seven other clinical factors. The breakdown of patients in each of the 14 terminal branches of the decision tree is documented in table 2–6. Integration of such a model with physicians' judgment may identify patients at low risk who do not need to be cared for in CCUs and may prevent the failure to admit patients who do require this specialized attention.

As an epidemiological tool to enable coronary registers to be set up in several countries, the World Health Organization established diagnostic criteria for myocardial infarction. These criteria were designed so that patients with myocardial infarction would not be missed. The three diagnostic categories were definite myocardial infarction, possible myocardial infarction, and no evidence of infarction (table 2–7). However, problems with these criteria have been discerned and are discussed elsewhere [37].

FIGURE 2–27. Computer-derived decision tree for the classifications of patients in the emergency room (ER) with acute chest pain. For a particular patient, start with the first question regarding ST-segment elevation and trace the patient through the appropriate subsequent questions until a permanent branch is reached. Each of the 14 letters (A through N) identifies a terminal branch of the tree. In the Yale-New Haven Hospital sample, seven terminal branches (C, D, H, I, K, M, and N) contained all 60 patients with acute myocardial infarction (MI) as well as 28 patients with unstable angina and 43 patients with other ultimate diagnoses. EKG = electrocardiogram. (From Goldman L, et al: A computer-derived protocol to aid in the diagnosis of emergency room patients with acute chest pain. *N Engl J Med* 307:588, 1982.)

TABLE 2–7. World Health Organization diagnostic criteria for myocardial infarction

Category	Criteria	Definitions
Definite myocardial infarction	ECG shows unequivocal serial changes	Unequivocal ECG changes are development of pathological Q waves and/or evolution of a current of injury that lasts more than one day; at least two ECGs are necessary for changes to be regarded as unequivocal
	History is typical or atypical with equivocal ECG and elevated cardiac enzymes	Equivocal ECG changes are evolution of a current of injury that disappears within 24 hours or when only one ECG is available; a stationary injury current; symmetrical inversion of the T wave; bundle branch block with additional Q waves; or pathological Q waves in a single ECG
	History is typical, cardiac enzymes are elevated, but ECG is negative or unavailable	
	Fatal cases, whether sudden or not, with naked-eye detection of fresh myocardial infarction and/or recent coronary occlusion	
Possible myocardial infarction	Living patients with typical pain whose ECG and enzyme findings do not put them in the first category and in whom there is no good evidence for another diagnosis	Typical pain is (1) diffuse through chest; may remain localized; or may radiate to the shoulder, arm, jaw or abdomen on one side or both; (2) is resistant to nitroglycerin if this is taken during the attack; (3) is of more than 20 minutes' duration; and/or (4) is usually severe and at times of agonizing intensity
		Atypical pain is "characterized by a sense of suffocation, indigestion, syncope, general malaise, or acute cardiac failure"
	Fatal cases, whether sudden or not, when there is no good evidence for another cause of death clinically or at autopsy when (1) the patient has a history of pain, typical or atypical; (2) there is no history of chest pain but there is autopsy evidence of coronary disease; or (3) there is clinical evidence of ischemic heart disease	
No myocardial infarction	Living patients with an equivocal ECG without a typical history or elevated cardiac enzymes	
	When the chest pain has been explained by another diagnosis	
	Fatal cases in which another diagnosis was made clinically or at autopsy	
	"Fatal cases with insufficient data" when the cause of death is completely unknown	

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3. ROUTINE MANAGEMENT OF MYOCARDIAL INFARCTION

Recent changes in the routine management of patients with uncomplicated myocardial infarction (MI) over a 10-year period have been highlighted in a publication that surveyed general and family practitioners, internists, and cardiologists in the United States [1]. This survey revealed that half the myocardial infarcts were regarded as uncomplicated. Because intensive or coronary care facilities were widely available in both metropolitan and rural areas, more than 90 per cent of physicians routinely hospitalized their patients. Between 1970 and 1979, the use of intensive care and coronary care facilities increased and the availability of progressive care facilities rose from 33 to 75 per cent.

Treatment of patients with acute MI can be conveniently divided into three phases: (1) the prehospital phase, (2) the hospital phase, and (3) the posthospital phase.

1. Prehospital Phase

With the development of coronary care units in the 1960s, hospital mortality due to acute MI was reduced from about 30 to 15 per cent. The prehospital phase of management logically evolved as it became apparent that death from acute myocardial ischemia or infarction occurs within an hour of the onset of symptoms in about 50 per cent (or more) of cases. Although the vast majority of these deaths occur seconds to minutes after the onset of acute symptoms owing to ventricular tachyarrhythmias generated by electrically unstable myocardium, the average interval between the onset of MI and admission to an acute cardiac care facility has been variously reported to be as long as 5 to 8 hours or even longer.

1.2. THE MOBILE CORONARY CARE UNIT

In 1966 Pantridge and Geddes developed the mobile coronary care unit [2–4], which was designed to reduce the delay between the first signs and symptoms of acute MI and the initiation of intensive monitoring and therapy. In one of their studies they found that most dysrhythmias occurred within one hour of the onset of symptoms of infarction. (See Table 1 in Chapter 4). In 73 per cent of the patients these dysrhythmias required therapy before the patient was transported to the hospital. They also emphasized the high early incidence of bradyarrhythmias (31 per cent) — a rhythm disorder that is significant if accompanied by a drop in blood pressure or if it represents a precipitating factor in the development of reentrant tachyarrhythmias. Although lidocaine had been reported to suppress ventricular ectopic beats in 88 to 95 per cent of patients studied in hospital coronary care units, these authors found lidocaine (100 mg given intravenously or infused over 10 minutes) to be ineffective in abolishing ventricular irritability in more than one-third of the patients in this study [4]. This was thought to be due to autonomic overactivity occurring soon after the onset of infarction.

Initial survival after a cardiac arrest is mainly determined by the rapidity with which cardiopulmonary resuscitation (CPR) is undertaken and achieved and defibrillation is initiated. *Preventing delay is most important.* Factors that contribute to delay include the time taken for the patient or bystanders to recognize the severity of the situation and to seek medical help, physicians' recommendation for an initial office or house visit, prescribing a trial of medication or a cardiovascular consultation rather than advising the patient to proceed

directly to the hospital, and transportation problems. Often upon the patient's arrival at the admitting area or emergency room of the hospital, effective monitoring and emergency care are not begun immediately.

Progress in the area of management has come about through extensive public education and the development of mobile coronary care units. Although physicians caring for patients with angina should educate them about the symptoms of acute MI in order to expedite the initiation of medical care, prodromal symptoms that appear in the days or weeks prior to collapse (and that occur in about two-thirds of sudden death victims) are often nonspecific in nature. Indeed, one study suggests that about one-fourth of patients with coronary artery disease who die suddenly have been seen by a physician within 7 days of the onset of the fatal event [5]. Inevitably, *sudden death* (i.e., death occurring within one hour of the onset of a major cardiac symptom), which is usually due to ventricular fibrillation and is secondary to coronary artery disease, will occur in the community without sufficient warning for the victim to seek help.

The concept of mobile coronary care units staffed by trained medical personnel, as was developed in Belfast, has evolved into the *mobile intensive care unit* manned by trained paramedics capable of carrying out emergency procedures and often in voice communication with physicians or nurses at a nearby base hospital. Furthermore, electrocardiograms may be transmitted telemetrically and observed at the base hospital so that appropriate instructions concerning resuscitation can be given. Such units usually operate through the ordinary emergency system using specially equipped ambulances or in conjunction with local fire departments. Items essential to these mobile units include a battery-operated direct-current (DC) defibrillator, apparatus for administering oxygen, endotracheal tubes and suction devices, and a variety of commonly used cardiovascular drugs (e.g., morphine sulfate, atropine, and lidocaine). Rapid initiation of resuscitative efforts by trained personnel can lead to successful defibrillation and recovery in one-third to two-thirds of patients, depending on the individual circumstances.

1.3. BYSTANDER PARTICIPATION

Of more recent interest is the concept that, in addition to a rapid-response emergency care system, administration of CPR by bystanders can have a salutary effect on outcome [6]. The Seattle Fire Department's Medic I program has provided comprehensive prehospital emergency care to a population of more than half a million people since 1970. Fire Department personnel reach the scene within an average of 3 minutes after dispatch and in the event of cardiac arrest initiate basic life support maneuvers. Secondary advanced life support units arrive an average of 3 minutes later. Advanced life support is carried out under standing orders and includes tracheal intubation, defibrillation, and commonly accepted drugs and fluids [7].

In an effort to educate the public about their possible role in this program, the Seattle Fire Department began to train citizens in CPR techniques in 1971; by 1979, about 200,000 Seattle area residents had been so instructed. Bystander-initiated CPR did not reduce the number of deaths at the scene of the collapse, but it did improve survival by reducing later hospital mortality. Fewer deaths were attributed to anoxic encephalopathy or shock. The proportion of patients who regained consciousness was greater and the duration of unconsciousness was shorter when bystanders had initiated CPR. A similar effect was described in another study in which ambulance response times were considerably longer (8 minutes) and delays in resuscitation efforts were common unless bystanders became involved [8]. Bystander participation in the management of cardiac arrest thus represents an important adjunct to a high-quality emergency care system and appears to reduce the incidence of neurological complications and to increase survival.

1.4. PROGNOSIS AND FOLLOWUP CARE

Prognosis and followup of patients successfully defibrillated in the prehospital phase of management are very important. Survival rates of 30 per cent or greater are now reported for patients initially found to be in ventricular fibrillation, whereas the outcome for those with initial asystole or electromechanical dissociation is extremely poor. Ventricular fibrillation or ventricular tachycardia recurs in up to 50 per cent of patients over a 48-hour period after initial prehospital defibrillation [9], and most inhospital deaths in this group occur within the first week of infarction. The size of the infarction probably determines the ultimate prognosis.

Recent reports have emphasized that patients whose condition is more serious or life-threatening are more likely to request assistance from emergency medical service systems [10,11]. In general, such patients may have a higher hospital mortality and more complications than those admitted to the hospital directly, without prior treatment. However, a review of the patients treated and transported by the Seattle emergency services system showed that when care was provided within one hour, mortality was lower among those receiving prehospital care than among those comparably ill patients transported by other means.

Since 50 to 60 per cent of deaths from acute MI occur within the first hour of the event, and since a large number of these patients collapse instantaneously or within a few minutes of the onset of symptoms [9], a community-based rapid-response emergency care system with minimal delays in performing CPR and defibrillation as well as widespread public education are worthwhile goals in the prehospital management of these patients.

2. *Hospital Phase*

With the onset of an acute MI, a healthy individual can be rapidly transformed into someone who is experiencing considerable pain, a sense of intimidation, and a fear of death. During transport to and arrival at the hospital, patient anxiety is universal. All personnel who come in contact with the patient and his or her family members must be sensitive to the traumatic and disruptive effects of this acute illness and should provide a calm, professional atmosphere in which help can be delivered in a concerned but efficient manner. Patients and their families can be reasonably reassured that extensive resources are available to ensure a successful outcome and that the purpose of intensive or coronary care is to provide continuous but unobtrusive monitoring so that problems can be dealt with quickly and effectively.

2.1. EMERGENCY ROOM TREATMENT

Upon the patient's arrival in the emergency room or at the acute admitting facility, a prompt decision must be made as to whether the event is in fact an MI. At this stage decisions about whether or not an infarction may be evolving should be based virtually on the patient's history alone. Lengthy interviews with the patient and protracted physical examinations should be avoided. The orderly transfer of the patient from the acute admitting area to the coronary care unit (CCU) should *not* be postponed while one obtains x-rays and blood tests.

It is important for the clinician who evaluates the electrocardiographic recording obtained upon arrival of the patient to consider the findings as evidence to *confirm* the clinical impression and not to supersede it. If the patient is suspected clinically of having sustained an MI, particularly on the basis of the history, the patient should be treated accordingly even if the ECG appears to be completely normal.

Therapeutic measures of the greatest importance at this stage include

1. Providing an adequately functioning intravenous line (5 per cent dextrose in water).
2. Administering effective analgesia (morphine sulfate, 2 to 4 mg every 5 minutes intravenously).
3. Providing supplemental oxygen (2 to 4 liters/minute by nasal prongs).
4. Rapid decisions on triage.

As soon as the decision has been made to admit the patient to the CCU, this move should be made promptly. A physician and nurse, or trained technician, should accompany the patient, and a portable ECG monitor and syringes loaded with lidocaine and atropine should be available en route. In many institutions nearly all patients receive prophylactic lidocaine upon arrival at the emergency room in order to provide effective prophylaxis during transportation of the patient. At a convenient time, blood samples should be obtained to determine complete blood count and serum electrolytes, blood urea nitrogen, serum glucose, serum creatinine, and cardiac enzyme levels (i.e., creatine kinase, serum glutamic oxaloacetic transaminase [SGOT], and lactate dehydrogenase [LD]).

2.2. MANAGEMENT IN THE CORONARY CARE UNIT

2.2.1. General Measures. Ideally, the CCU should be equipped for continuous centralized cardiac monitoring of all patients, with alarm systems and cardiomemory tape recordings of heart rhythms that are used to detect life-threatening arrhythmias and that can be re-

trieved for detailed analysis. Although computerized arrhythmia detection circuits are more reliable in recognizing the *presence* of cardiac arrhythmias than are human observers, such alarm systems can be triggered by artifactual materal and should not be considered a substitute for monitoring by trained personnel with a detailed knowledge of electrocardiography and rhythm disturbances.

All CCUs should be equipped for electrical cardioversion/defibrillation. Also, the capability to perform invasive hemodynamic monitoring with portable x-ray facilities is desirable. Many coronary care units now use portable gamma cameras for noninvasive nuclear imaging at the bedside to allow infarct-avid and gated blood pool scanning.

2.2.1.1. ANALGESIA AND SEDATION. Pain contributes to excessive overactivity of the autonomic nervous system, which tends to increase myocardial oxygen demands by increasing heart rate, arterial pressure, and cardiac contractility. Thus, administering an analgesic is a primary therapeutic strategy during the acute phase of MI. *Morphine sulfate* remains the drug of choice for the treatment of pain and can be administered intravenously at a rate of 2 to 4 mg every 5 minutes or 4 to 8 mg every 5 to 15 minutes, depending on the circumstances. Occasionally patients may require as much as 25 to 35 mg of morphine before pain is adequately controlled. Pain can thus be effectively relieved provided that respiratory depression does not preclude further administration of the drug. It should be noted, however, that respiratory depression is an unusual complication of morphine in the presence of severe pain or pulmonary edema. In normal subjects, only minimal and short-lived hemodynamic changes are noted after administration of intravenous morphine in the supine position, whereas in patients with acute MI, systemic arterial blood pressure has been observed to fall transiently after intravenous morphine is delivered at a rate of 1 mg/min up to a maximum dose of 10 mg [12]. In the almost supine position in which patients are nursed in the CCU, therapeutic doses of morphine usually have no adverse effects on heart rate, arterial pressure, or rhythm; however, as with other narcotics, when the supine patient sits up, or stands, orthostatic hypotension may result owing to peripheral vasodilation. This can be particularly important in patients with a decreased effective blood volume or hypovolemia or in the presence of other vasodilator drugs such as nitrates or nitroprusside.

Morphine is a primary depressant of respiration. In man, death from morphine poisoning is nearly always due to respiratory arrest. Respiratory depression peaks within about 7 minutes of intravenous administration but can be delayed for up to 1½ hours after subcutaneous administration. Directly related to the total dose administered, respiratory depression can persist for hours and appears to result from the drug's effects on pontine and medullary centers that control the rhythm of respiration and from a morphine-induced reduction in the responsiveness of the brain stem to elevations in PCO_2. In addition, small doses of morphine can produce striking and consistent depression of ventilatory responses to hypoxia and to hypercapnia, suggesting that morphine may affect peripheral chemoreceptor function [13]. Having the patient resume the supine posture with the legs elevated should correct hypotension that occurs after morphine administration, and naloxone (Narcan), 0.4 mg IV at up to 3-minute intervals to a maximum of three doses, may relieve respiratory depression. Volume expansion may also be necessary.

Intravenous meperidine or pentazocine can be used as alternative agents to morphine, however, because of their adverse hemodynamic effects we do not favor their use. In a randomized, double-blind study comparing morphine and pentazocine, cardiac work was reduced by morphine but was actually increased by pentazocine, owing largely to its peripheral vasoconstrictor effects [14].

Nitrous oxide was first used for the treatment of angina in Russia in 1881. In Britain, nitrous oxide has been used for treatment of coronary pain since 1966, and its use has been advocated in patients with MI in both the British and American literature [15–17]. In one double-blind study nitrous oxide (35 per cent mixed with oxygen) was found to be an effective and safe analgesic for patients with acute MI [17]. Pain was significantly reduced in 74 per cent of those patients who received nitrous oxide and was completely relieved in 39 per cent. In no case was complete pain relief achieved with 100 per cent oxygen. Although nitrous oxide was particularly useful for mild pain, its effects were less consistent in patients with more severe pain. Its main use appears to be as an adjunct to more potent analgesics. (Measurements of pulse rate

and blood pressure showed no significant change in any patients in the study just described.)

A mixture of 50 per cent nitrous oxide and oxygen delivered by a face mask to patients with heart disease appears to lower myocardial oxygen requirements, mainly by reducing heart rate and cardiac output, and also causes a small but detectable degree of left ventricular dysfunction [18]. In the CCU, nitrous oxide can be an important and effective analgesic agent when administered in combination with oxygen via a rebreathing mask. A nitrous oxide tank and blender are used in conjunction with a wall oxygen outlet to provide a variable atmosphere composed partly of nitrous oxide and partly of oxygen. The maintenance range of nitrous oxide is usually 30 to 40 per cent, with dosage increased in a stepwise fashion to a maximum of 70 per cent.

Side effects of prolonged high-dose nitrous oxide include nausea, vomiting, hyperexcitability, and obtundation. Bone marrow depression has been reported in patients who inhale nitrous oxide continuously for 48 hours or more; however, patients with myocardial ischemic pain rarely, if ever, require such prolonged administration. Once pain has been relieved, the inspired nitrous oxide concentration should be tapered to the maintenance range. If pain recurs, dosage may be transiently increased according to need. Once the patient has remained pain-free for about 6 hours on maintenance nitrous oxide, administration is usually discontinued and replaced by pure oxygen via nasal prongs.

In addition to being an effective analgesic agent for mild to moderate cardiac pain, nitrous oxide also provides adequate background sedation. For patients who do not require nitrous oxide for relief of pain, sedation can be provided with diazepam (2 to 10 mg orally every 6 to 8 hours). A hypnotic should routinely be made available in the coronary care setting. Flurazepam (30 mg orally) or chloral hydrate (500 mg orally) is often employed for this purpose.

2.2.1.2. SUPPLEMENTAL OXYGEN. Hypoxemia is common in acute MI and is usually secondary to ventilation-perfusion abnormalities that are proportional to the severity of left ventricular failure. As pulmonary diastolic pressure rises, arterial oxygen tension falls inversely in patients with acute infarction. Intrapulmonary shunting of blood has also been noted when left ventricular failure complicates infarction, and clinical studies have shown that lung water is increased in infarct patients.

Because of clinical and experimental evidence that increased levels of oxygen in the inspired air protects ischemic myocardium, it has been common practice to treat all patients hospitalized with acute infarction with 100 per cent oxygen, which is usually delivered via nasal prongs at a rate of 2 to 4 L/min for 24 to 48 hours. Augmentation of the fraction of oxygen in inspired air does *not* significantly elevate oxygen delivery to the tissues in patients who are not hypoxemic. However, if one suspects significant hypoxemia, a history of chronic obstructive lung disease, or anemia, arterial blood gases should be measured and the fraction of oxygen in inspired air can be altered appropriately. In patients with acute pulmonary edema, endotracheal intubation and controlled positive-pressure ventilation may be indicated. To enhance oxygen delivery (i.e., beyond that provided by nasal prongs), a face mask that delivers humidified air should replace prongs.

2.2.1.3. DIET (table 3–1). Usually during the first 4 to 12 hours after admission to the CCU the patient is given either nothing by mouth (NPO) or clear liquids only. Since heavy meals can precipitate bouts of angina and because of the risks of nausea (i.e., vomiting or cardiac arrest), a liquid diet for 24 hours is often reasonable. In general the CCU diet should be limited to 1,000 to 1,500 calories a day, and portions should not be unusually large or bulky. If possible, multiple small feedings should be given for several days.

Since the convalescent period after an acute MI is an opportune time to introduce the patient to the concept of dietary modification, a diet low in cholesterol and saturated fats is appropriate. In addition, the diet should contain 3 to 4 gm of sodium chloride per 24 hours (no added salt) and liberal amounts of foods containing glucose and potassium. To combat constipation, stool softeners may be given as dietary supplements.

2.2.1.4. PHYSICAL ACTIVITY. Patients with uncomplicated infarcts need not be confined to bed for more than 24 to 36 hours and may use a bedside commode from the time of admission. Early on, passive range-of-motion exercises are permissible, although the degree of physical strain and exertion should be minimized. For both physical and psychological reasons, we favor early ambulation for patients with uncom-

TABLE 3–1. Guidelines for diet therapy in the CCU

Specific Recommendations

1. NPO prior to evaluation by physician.
2. Dietary allowances for fluids, electrolytes, and calories and other adjustments are ordered by the house officer to meet the needs of each individual patient.

General Recommendations

1. *Kilocalories and Protein*: The diet should be planned to provide adequate kilocalories and protein consistent with individual needs. Caloric restrictions may be initiated for weight loss or control of maintenance weight.
2. *Fats*: The diet should be limited to 30 to 35 per cent total fat. Foods high in cholesterol and saturated fats should be avoided (no specific daily limit). Two or three eggs per week may be given if requested and/or to ensure adequate protein intake; egg substitutes should also be available.
3. *Carbohydrates*: Carbohydrates are not routinely excluded except for patients with documented familial hypertriglyceridemia or diabetes.
4. *Roughage*: The diet should contain roughage consistent with a balanced mixed diet, including fresh fruit and vegetable, whole-grain bread, and cereals. Foods that may cause gastrointestinal intolerance should be eliminated on an individual basis.
5. *Sodium*: A "no added salt" (NAS) diet (3 to 4 g Na^+) is recommended, with adjustment as indicated by clinical status. The NAS diet order excludes a salt shaker as well as foods high in sodium (greater than 300 mg/serving).
6. *Potassium*: Food high in potassium should be encouraged except for patients with renal insufficiency.
7. *Quantity*: Small, frequent feedings may be recommended on an individual basis.
8. *Beverages*: Caffeine intake should be limited to less than 250 mg/day, i.e., use of regular coffee should be moderated. Decaffeinated beverages and weak tea are suggested as substitutes.
9. *Education*: The principal goal of patient education and long-term planning is to achieve and maintain ideal body weight and to adhere to dietary adjustments as ordered by the physician.
10. *Patient Transfers*: The CCU dietitian will inform the unit dietitian about each patient to be transferred to ensure continuity of the diet prescription and educational program.

plicated infarctions. Patients are permitted to sit in a specially designed cardiac chair for 15 to 20 minutes once or twice a day within 48 hours of admission, with time spent in the chair extended daily unless complications intervene. By day 4 or 5, ambulation around the bed is permitted. Activities can be increased progressively according to the progress of the individual (table 3–2).

2.2.1.5. CONTINUATION OF MAINTENANCE MEDICATIONS. Often patients who have suffered an acute MI were taking cardioactive medications prior to admission. Thus, a common-sense approach would be to continue these medications unless there is a clear contraindication or evidence of toxicity. If the hemodynamic status of the patient changes dramatically during the evolution of the infarction, such medications should be carefully reviewed. Furthermore, careful clinical monitoring is essential since maintenance doses of such medications may need to be modified in the acute infarct setting.

Beta-adrenoceptor blocking agents taken regularly prior to the acute MI should be continued. The usual contraindications to these drugs apply, including bradycardia, hypotension, left ventricular failure, atrioventricular block, asthma, or episodes suggesting coronary artery spasm. Abrupt discontinuation of beta blockers may be associated with severe myocardial ischemia and possibly infarct extension and should therefore be avoided. Currently, parenteral beta blockers are being tested to determine whether or not they limit infarct size and have other beneficial or detrimental effects. Currently, this practice cannot be recommended on a widespread scale. On occasion it may be necessary to reduce the dose of beta blockers if bradycardia or mild congestive heart failure is present.

In the setting of acute infarction, excess tachycardia and hypotension due to a continuation of long-acting *nitrates* can be a problem owing to unstable hemodynamics. These agents are therefore generally not continued for the first 24 to 48 hours of a definite evolving infarction.

Maintenance *digitalis* is usually continued. The possible development of digitalis toxicity should be considered if the hemodynamic situation changes. Most authorities would agree that digitalis has beneficial effects in patients with MI in two important situations. The first is in the treatment of left ventricular failure not responsive to diuretic therapy. The second is the treatment of atrial tachyarrhythmias (such as fibrillation or flutter), which can be particularly harmful if a rapid ventricular response is not

TABLE 3–2. Progressive care

Interdisciplinary program for the myocardial infarction patient	Date Requested	Person Requesting	Physical Therapy Occupational Therapy Social Service Nutrition Counseling	Person Initiating	Date Began

Date and M.D. Initial	Physical (P) and Occupational (O) Therapy (T)			Cardiac Education	Nutrition Counseling	Social Service
Stage I Days 1–2	*Complete bed rest* • Use of bed pan • Feed self prepared tray with arm and back support • Wash face, brush teeth	P.T. • Supine exercise • Passive ROM to all extremities 5x • Active ankle motion • Emphasis on relaxation	O.T. As appropriate, begin to relate work simplification and energy conservation techniques to P.T. self-care activities	Assessment of patient and/or family; home and work environment manner of coping with stress and acute illness. Simple explanations of care and procedures	Initial assessment of nutrition needs; calories, protein Determine appropriate diet	Psychosocial assessment of patient and family; identification of strengths and weaknesses
Stage II Days 2–4	*Assisted Transfers/Attended Activity* • Bed to chair 15–20 mins 2x a day • Bed to commode • Feed self with arm and back support • Partial bath upper body with back support	• Supine exercise • Assisted to active ROM, all extremities 5x • Progress to 10x supine and sitting • Sitting exercises 5x	As appropriate, monitor self-care activities and assist patient in reducing energy expenditures	Assessment of patient and/or family, health beliefs and values, history of self-care and adherence to prescribed regimen. Knowledge of cardiac disease; activity/life-style	Introduction: • Visits on daily lunch rounds • Assessment of daily intake • Explanation of selective menu	Referral can be made at any point in patient's rehabilitation course
Stage III Days 4–6	*Supervised Ambulation in Room* • Bed to chair 30 mins 3x/day • Bathe, groom self-dress, sitting on bed with assist for lower extremities and back • Bed to bathroom in room	• Supine, sitting • Active exercise 10x • Standing exercise 10x • Ambulate in room with gradual increase supervised 2x	As appropriate, teaching of good body mechanics energy conservation, work simplification	• Begin teaching origin of cardiac disease, risk factors, rationale for restricted activity. • Discuss current medications, explore patient's attitude about taking meds. • Involve family in teaching.	• Initial diet instruction with patient, family, significant others. • Compare to diet prior to admission • Assess knowledge of therapeutic diet	
Stage IV Days 6–10	*Supervised Ambulation Outside Room* • Bed to chair ad lib • Bed to bathroom independent • Complete bath sitting • Dress in PJ or gown, robe and shoes	• Supine, sitting standing, active exercise 5x • Ambulate outside room supervised 50–300′ x1, 300′ x2, 600′ x2 • Ambulate ad lib in room	Continue body mechanics, energy conservation, work simplification	• Teaching short- and long-term activity/lifestyle changes • Patient sets short- and long-term goals for self. • Begin patient rehearsing potential problem situations	• Teach rationale for diet in relation to disease. • Modification of: Na, total fat, cholesterol, calories. • Develop meal plan	

Table 3.2 Continue

Stage V Days 8–12	*Independent Ambulation Outside Room* • Showers standing or bathes • May dress in own clothes • Supervised stairwalking	• Supine, sitting, standing and trunk exercise x10 • Ambulate 600 ft and independent • Stairs down one flight, up and down one flight	• Discuss any work or lifestyle modifications necessary • Explore alternatives.	• Begin review of teaching re activity in and out of hospital (also sexual) meds, diet, warning signs, complications, expected psychological problems	Cover in teaching: • Food labeling • Dining out • Attempt group class on diet in cardiac disease • Give written instructional material	• Plans finalized for followup counseling or support services if necessary
Stage VI Days 10–14	*Discharge* • Review of home activity and exercise instructions		• Review teaching if necessary	Answer questions of patient/family	Verbal review of diet modification utilizing rehearsal technique for given situations	

ROM = range of motion.

controlled, since this might intensify myocardial ischemia. Digitalis has been shown to increase contractility, oxygen consumption, and infarct size in the nonfailing heart. When heart failure is present, the diminution of heart size and wall tension with digitalis administration frequently causes a net reduction of myocardial oxygen demands.

Maintenance oral *antiarrhythmic therapy* taken prior to the infarction (e.g., for control of paroxysmal supraventricular tachyarrhythmias or recurrent ventricular tachycardia) is continued unless there is evidence of drug toxicity. Once again, careful monitoring of the patient's clinical status and serum concentrations of cardioactive medications is important, since drug clearance may be altered by an infarct-induced diminution in hepatic and/or renal blood flow.

2.2.2. *Specific Treatment Measures*

2.2.2.1. MANAGEMENT OF VENTRICULAR ARRHYTHMIAS. Virtually all patients with an MI exhibit arrhythmias in the CCU. The most common arrhythmia seen here is the ventricular premature beat (VPB), which can be documented in over 90 per cent of patients. Although isolated VPBs may be benign, rapid repetitive salvos, such as ventricular tachycardia, can lead to marked hemodynamic compromise. Since it is such a common problem and a serious concern, routine management of ventricular arrhythmias will be discussed briefly. More detailed discussion of specialized techniques for managing ventricular arrhythmias can be found in chapters 4 and 5 and for arrhythmias and conduction disturbances in chapter 8.

When CCUs first came into being, VPBs were treated when they occurred frequently; were very premature (i.e., exhibited the R-on-T phenomenon), multiform, or paired; or appeared in runs of three or more consecutive beats. These were considered "warning arrhythmias" signalling that the patient was at risk for ventricular fibrillation. However, several studies have shown that primary ventricular fibrillation (i.e., occurring in the absence of congestive heart failure, pulmonary edema, or cardiogenic shock) may occur without such "warning VPBs" in patients with acute infarction. In the past, there has been a tendency to prescribe widespread antiarrhythmic prophylaxis to prevent this life-threatening arrhythmia.

The drug studied most completely and for which we have the most evidence to support its effectiveness is *intravenous lidocaine* [19]. Some physicians feel that *all* patients with known or suspected acute MI should receive prophylactic lidocaine as a routine measure; others, including ourselves, favor a more selective use of this drug. Younger patients with no previous history of either acute MI or congestive heart

failure who present early after the onset of chest discomfort (within 4 to 6 hours) are at greatest risk for developing ventricular fibrillation and should receive lidocaine prophylaxis. For elderly patients, in whom the incidence of lidocaine toxicity is increased, the clinician should be more circumspect about such an approach, particularly if the patient presented late after the onset of chest discomfort. Finally, patients with congestive heart failure, cardiogenic shock, disease of the conduction system, acidosis, or hypokalemia in the setting of acute MI are at increased risk for both ventricular fibrillation and lidocaine toxicity; in such cases, it is far from clear whether or not lidocaine prophylaxis would be beneficial.

Lidocaine prophylaxis consists of an initial loading dose of 1 to 2 mg/kg intravenously followed immediately by a continuous infusion of 2 to 4 mg/min. During the early distribution phase, this drug has a half-life of approximately 10 minutes; 20 to 40 minutes after the loading dose is given, the serum level of lidocaine may transiently fall below the therapeutic range before the continuous infusion has allowed accumulation of drug. If arrhythmias occur at this time, the appropriate response is to administer a smaller supplemental intravenous bolus in a dose of 0.50 to 0.75 mg/kg rather than to increase the rate of the infusion. Saturation of the extravascular pool normally occurs after 3 hours of continuous infusions, and at this time it may be desirable to reduce the rate of delivery by about 25 per cent. Since the major site of metabolism of lidocaine is in the liver, the dose should be reduced in patients with hepatic congestion, decreased hepatic blood flow secondary to low cardiac output, or primary liver disease. The metabolites of lidocaine are excreted by the kidney, so that the dose may also need to be modified in patients with severe renal failure.

2.2.2.2. ANTICOAGULANT THERAPY. Five recent articles attest to the uncertainties and controversy surrounding the use of anticoagulants during and after MI [20–24]. Interestingly, routine prescription of anticoagulants during hospitalization decreased substantially between 1970 and 1979 in internal medicine, cardiology, and family practices (table 3–3). One provocative report has surveyed some of the problems associated with earlier anticoagulant trials and the interpretation of their results [24].

In the past sporadic reports have indicated that anticoagulants reduce mortality among patients hospitalized for acute MI. However, salutary effects on the underlying coronary disease, on the progression or recurrence of infarction, and on early death after MI have not been demonstrated. In patients with an evolving infarction, factors such as infarct size, pump failure, and arrhythmia are likely to influence

TABLE 3–3. Regimens routinely prescribed during hospitalization after myocardial infarction (Percent of 3,183 responding physicians)

	Family/general practice		Internal medicine		Cardiology	
	1970	1979	1970	1979	1970	1979
Anticoagulant drugs	70.3	39.8	68.5	40.5	72.8	48.6
Prophylactic antiarrhythmic agents	27.0	27.3	19.0	25.2	19.2	32.0
Calorie-restricted diet	75.0	68.0	77.0	71.2	78.7	62.6
Sodium-restricted diet	68.1	72.4	57.0	68.2	55.5	61.7
Fat-restricted diet	71.4	50.5	59.5	48.4	62.1	58.5
Cholesterol-restricted diet	—	59.8	—	57.8	—	67.5
Antihypertensive drugs (for hypertensive patients)	—	83.1	—	81.9	—	86.3
Tranquilizers	—	71.1	—	69.5	—	59.9
Nitrate drugs	—	59.9	—	57.0	—	56.9
Beta-adrenergic blocking drugs	—	31.5	—	33.7	—	37.7
Antidepressant drugs	—	9.6	—	4.7	—	1.8
Digitalis	—	6.7	—	3.0	—	1.0

From Wenger NK, et al: Physician practice in management of patients with uncomplicated myocardial infarction: Changes in the past decade. *Circulation* 65:421–427, 1982. With permission from The American Heart Association, Inc.

mortality to a much greater extent than is the contribution of anticoagulant therapy. Furthermore, it is highly unlikely that hospital mortality among MI patients is influenced by anticoagulation soon after admission, since death is a consequence of the initial infarction and its size rather than of new arterial thrombosis.

In 1977, Chalmers and coworkers assembled and reanalyzed the literature regarding the use of anticoagulants in the hospital phase of acute MI and reported a lower incidence of thromboembolism, lower case-fatality rates, and more hemorrhagic complications in the anticoagulated group. They concluded that "all patients who present no specific contraindication should receive anticoagulants during hospitalization for infarction" [20] — a viewpoint that has not been widely accepted. We must remember that conclusions based on data pooled from dissimilar trials can prove hazardous [22].

The role of anticoagulants in venous thromboembolism is widely accepted. Both full-dose heparin and warfarin therapy are effective in preventing the occurrence of pulmonary embolism and deep venous thrombosis. Full-dose intravenous heparin therapy (i.e., sufficient to prolong the partial thromboplastin time 1½ to 2 times control) is administered in the belief that doses sufficient to neutralize thrombin are required to prevent recurrence or extension of thrombus. For both deep venous thrombosis and pulmonary embolism the role of full-dose intravenous heparin therapy is unquestioned. Although major pulmonary embolism is uncommon, it can be catastrophic, so that such therapy is usually administered without delay. Furthermore, survivors of pulmonary embolus appear to be at substantially increased risk for a lethal recurrence, and full-dose heparin therapy may prevent this. Warfarin anticoagulation should be continued in patients who have experienced an episode of deep venous thrombosis or pulmonary embolism, since there is a persistent, although diminishing, risk of recurrence over a 6-month period.

It has become common (and reasonable) practice to administer short-term anticoagulants prophylactically to patients at high risk. Medical patients who have a high incidence of deep venous thrombosis include those who are markedly obese, have congestive heart failure or a low cardiac ouput state, are on prolonged bed rest, have a previous history of venous disease, have a ventricular aneurysm, or have had a myocardial infarction or stroke. In patients at risk but in whom thrombosis has not yet occurred, it is believed that a measure of protection against the development of deep venous thrombosis can be achieved with *low-dose heparin* (i.e., subcutaneous heparin, 5,000 units every 8 to 12 hours). Relatively low doses of heparin such as this usually do not interfere with systemic coagulation mechanisms and thus carry a minimal risk of bleeding. The principle underlying low-dose heparin therapy is that neutralizing thrombin precursors as they are generated (i.e., while they are still at low levels) will confer protection. Because of the necessity of bed rest during the early phase of an MI and the higher incidence of lower extremity venous thrombosis in such patients, we routinely utilize low-dose heparin therapy.

In patients at high risk for embolism, full-dose anticoagulation should be considered and administered on a case-by-case basis. Low-dose heparin therapy is not considered an acceptable alternative to full-dose heparin therapy if the patient is considered to be at risk for bleeding complications nor is there evidence to suggest that low-dose therapy will prevent pulmonary embolism in patients with established thrombophlebitis or that it will halt progression or propagation of thrombus distal to an arterial thrombus. Low-dose heparin therapy should be continued until the patient has been ambulatory for 48 to 72 hours. The value of antiplatelet drugs in the management of patients with acute MI has not yet been defined.

Formation of left ventricular thrombus is most common after Q-wave anterior infarction and much less common after inferior myocardial infarction or non-Q-wave infarction. Its incidence after anterior infarction is reported to be approximately 30 per cent. Severe depression of left ventricular ejection fraction is not a prerequisite; however, an apical wall motion abnormality is almost always present [25,26]. Although the incidence of clinically recognized systemic embolism in patients with left ventricular thrombus after acute infarction is relatively low, its effects can be devastating. Embolic events tend to occur within 4 to 6 months of acute myocardial infarction.

Since the advent of two-dimensional echocardiography, identification of left ventricular thrombus has become relatively easy in the 75 per cent of patients with acute infarction in whom imaging is satisfactory. The morphology

of the thrombus has been shown to be related to the likelihood of subsequent embolism. Thrombus that has a protruding configuration or is freely mobile is more likely to embolize [27]. When adequate two-dimensional echocardiograms are not possible, indium-111 platelet scintigraphy appears to be highly specific and can detect thrombi that are actively incorporating platelets into their surfaces [28]. Therefore, most patients with anterior infarction can be adequately screened for the development of left ventricular thrombus.

A study by Nordrehaug et al shows that intravenous heparin followed by oral warfarin within 12 hours of the onset of symptoms of acute myocardial infarction will prevent the formation of left ventricular thrombus as detected by two-dimensional echocardiography 3, 6, and 10 days after hospital admission. The patients were selected on the basis of electrocardiographic criteria, and thrombus was detected in one-third of surviving patients in the placebo group [29]. Interestingly, urokinase administered within one month of acute myocardial infarction was successful at lysing left ventricular thrombus, with no evidence of embolic events [30]. With the information now available, it would seem entirely reasonable to initiate early anticoagulation (intravenous heparin followed by oral warfarin) in patients with anterior myocardial infarction and associated wall motion abnormalities as identified by two-dimensional echocardiography. If left ventricular thrombus is found to be protuberant or mobile, there is probably a strong impetus to initiate anticoagulant therapy forthwith. It would not seem unreasonable to continue oral anticoagulants for at least 6 months after the acute event and then to reevaluate the situation. As always, when initiating anticoagulation, the probability of embolism should be carefully weighed against the danger of bleeding.

Warfarin therapy administered during the course of an acute MI has been found to result in a fourfold decrease in the incidence of stroke, presumably owing to systemic arterial emboli [31]. The advantages of long-term administration of warfarin after the acute episode of infarction are unclear. Theoretically, long-term anticoagulation is not likely to have an impact on the incidence of sudden death, since postmortem examinations do not typically reveal coronary thrombus in these patients, although significant coronary disease is often found.

Does long-term anticoagulation reduce the rate of reinfarction? In one multicenter, double-blind trial in Holland of elderly survivors of MI, long-term anticoagulant therapy led to a significant decrease in the 2-year mortality from "all causes" in patients who were still taking their allocated anticoagulant treatment or who were within 20 days of deviating from it [32]. In addition, the total number of deaths attributed to recurrent infarction — a more subjective end point than death — was reduced in the patients receiving anticoagulants. In this study the mean age of the patients was 62 years, and 85% were men with a mean interval since infarction of 5.9 years. As expected, the incidence of bleeding was higher in the anticoagulated group; however, the reduced incidence of nonhemorrhagic stroke more than balanced the excess number of hemorrhagic strokes in the anticoagulant-treated group. Interestingly, anticoagulation did not alter the incidence of sudden death in this group.

It would be unwise to extrapolate the apparent salutary effect of anticoagulants of "all causes death" and reinfarction rates in these elderly Dutch patients treated about 6 years after infarction. Except in high-risk groups, long-term warfarin anticoagulation in survivors of acute infarction does not seem justified at present. Relative selectivity of the use of anticoagulant drugs during hospitalization of patients with uncomplicated acute MI is reflected in the significant decline in the routine prescription of these drugs by physicians — from about 70 per cent in 1970 to about 50 per cent in 1979 (table, 3–3).

2.2.2.3. PSYCHOLOGICAL ASPECTS OF INFARCTION. Anxiety and depression are common after an MI [33]. Feelings of anxiety are greatest during the first 48 hours after admission to the hospital and then decline until shortly before discharge when anxiety recurs. Depression occurs early after admission, reaching a maximum on the third or fourth day and tends to regress during the hospital stay, with a rise prior to discharge. As Spicer has pointed out, the patient suffering an MI has been "confronted with his own vulnerability. Rightly or wrongly he often feels that he has been near to death" [33]. This feeling is accentuated by the usually sudden onset of infarction, often at an unexpected time in the patient's life. The threatening nature of the event is intensified by the uncertain prognosis and the fact that there is no way to guarantee

that the threat of death can be removed.

The CCU environment also emphasizes the patient's precarious state. As Spicer succinctly put it, "the coronary patient's predicament is characterized by the threatened close, or at least some diminution of the quality, of his life. These threats are made all the more potent by their sudden and often premature appearance, and by the sense of helplessness in the face of an uncertain future." A common defense mechanism adopted by the patient is denial, which may be complete (i.e., total rejection of the occurrence of a recent infarction) or selective (i.e., a smaller range of the consequences of myocardial infarction is denied). Attempts should therefore be made to reduce the patient's anxiety and depression directly, to provide social support, and to reduce future uncertainty by providing adequate information. The CCU staff should be alert to the problem of anxiety in the first few days after admission and of later depression. Therapeutic intervention should be carefully tailored to the individual patient, and support and reassurance should be given in this time of crisis. The patient should be provided with accurate, pertinent information, and misconceptions should be avoided or corrected. When major changes in the therapeutic strategy occur — e.g., transfer from intensive care monitoring to a stepdown area, the initial period of mobilization when the patient is no longer being monitored, or at the time of discharge — clear explanations and reassurance are vital.

It is important to realize the "successful deniers" tend to return to work more quickly, have fewer marital conflicts, report that infarction had little impact on their lives, and have significantly lower mortality and morbidity rates than do non-deniers in the first 2 years after the infarction [34]. Unfortunately, deniers also tend to comply less to their medical regimens, so that during the period of recovery denial behavior may be appropriately modified to prevent this possibility.

2.2.2.4. AMBULATION. In general, patients with an uncomplicated MI remain in the CCU for 3 or 4 days, after which they are transferred to an intermediate care or stepdown area. We prefer to keep patients here until the time of discharge, since the process of education and rehabilitation is greatly facilitated by a cohesive unit structure. The progressive activities of the patient can be individualized within the framework of the general scheme of progressive ambulation (table 3–2). As a general rule, patients are confined to bed for as brief a period as possible and are permitted to resume mild activity early during the hospital stay unless significant complications such as heart failure have developed.

Over the last 30 years, clinicians have realized that the capacity for energy expenditure of the postinfarction patients usually exceeds the energy demands of recreational activities and a typical job, even before the period of healing has been completed. Up to 85 per cent of survivors can resume working, since the energy costs of most jobs in urban society and industry are relatively small [35,36]. Observations in 62 subjects (36 with heart disease) during a normal working day in a manufacturing plant revealed that the average rate of energy expenditure during the working shift was on the order of 2 calories/minute. This low rate of energy expenditure was comparable to that observed during nonworking activities. The maximum rate of energy expenditure rarely exceeded twice that in the resting rate.

Another way of defining the physiologic cost of work is in METs (metabolic units), which are defined as "the oxygen uptake/kilogram of body weight/minute when the subject is sitting quietly in a chair or at supine rest." The capacity for energy expenditure above basal levels depends on both health status and previous physical conditioning. The aerobic capacity of a middle-aged man who has recovered from an uncomplicated MI is likely to be in the range of 7 to 9 METs. If less than ordinary activity produces signs or symptoms, the aerobic capacity is probably closer to 4 METs.

The rate of progression of physical activity in the intensive care and stepdown areas is usually based on clinical observations of the patient's tolerance for low-level activities. Curtailing this rate of progression or developing additional therapeutic strategies is in order if during ambulation the patient exhibits symptoms (chest pain, dizziness, or sweating), abnormal cardiovascular physical signs (new murmurs, gallop rhythms, dyspnea, or hypertension), tachycardia excessive for the level of effort (greater than 115 to 120 beats/minute at low levels of exercise), or dysrhythmias or marked ST-T changes on the electrocardiogram.

2.2.2.5. EXERCISE TESTING SOON AFTER ACUTE MYOCARDIAL INFARCTION. Early exercise testing after an uncomplicated acute MI, if adequately supervised and performed according to certain

TABLE 3–4. Exclusion criteria for early exercise testing after acute MI

1. Unstable angina or pain at rest within previous 3 to 5 days
2. Evidence of significant cardiac dysfunction (e.g., heart failure apparent on chest x-ray, pulmonary rales, or an S_3 gallop rhythm)
3. Complex ventricular ectopy (multiform complexes, burst or sustained runs of ventricular tachycardia, R-on-T complexes)
4. Arterial hypertension (systolic pressure >150 to 160 mm Hg, diastolic >90 to 100 mm Hg)

guidelines, may be considered safe [38–44]. Such testing should be performed only when there is no evidence of unstable angina or significant left ventricular dysfunction. (Exclusion criteria for early exercise testing are listed in table 3–4.) Mortality is increased during the first postinfarction year in survivors of acute MI who have significant left ventricular dysfunction or its sequelae. If such patients also exhibit ventricular ectopy, they constitute a subgroup at especially high risk for subsequent cardiac events.

Probably more than half the patients who survive an acute MI have an uncomplicated course, i.e., they do not appear to have significant left ventricular dysfunction or its sequelae. Nevertheless, among these survivors are subpopulations of patients who are at high risk, and, if possible, they should be identified, followed carefully, and given the benefit of appropriate medical or surgical therapy. Similarly, other subpopulations are at low risk and can thus be spared the anxiety of frequent followups, intensive studies, and restrictions upon their work and recreational activities.

Exercise testing soon after MI can help identify these high- and low-risk subpopulations by revealing:

1. Cardiovascular responses to exercise.
2. Prognostic information.
3. Diagnostic information (e.g., provocation of arrhythmias, detection of myocardial ischemia with or without warning symptoms, and detection of ventricular wall motion disorders).

Various exercise protocols have been used for postinfarction assessment, including treadmill exercise according to a combination of protocols described by Naughton et al [37], modified and unmodified Bruce protocols, and bicycle ergometer protocols (table 3–5). Low-level exercise tests are used to determine the patient's tolerance for activities comparable to those he or she will be performing during convalescence at home and are designed to impose workloads of about 3 to 4 METs.

Exercise protocols may have symptom-limited, sign-limited, or submaximal thresholds. In general, the criteria for stopping low-level exercise tests are more stringent than those used for peak or maximal performance exercise testing (table 3–6). *Symptom-limited tests* are terminated with the development of angina, shortness of breath, dizziness, or fatigue. *Sign-limited tests* are terminated owing to the development of ischemic ST-segment depression, serious ventricular arrhythmias, hypotension, or an unsteady gait. *Submaximal tests* aim for a target heart rate (around 60 per cent of the age-predicted maximal heart rate, which is usually in the range of 120 to 130 beats/minute) or performing the set task at a specified workload (e.g., 4 to 5 METs).

Three of these designated end points require explanation:

1. *ST-segment depression:* This ECG finding has certain prognostic implications after acute MI. In patients tested soon after the event who do not have unstable angina or overt heart failure, ischemic ST-segment depression is associated with a significantly increased incidence of subsequent coronary events [38,39]. Among patients who performed a limited treadmill exercise test prior to hospital discharge, the one-year mortality rate in those without ST-segment changes during exercise was 2.1 per cent and sudden death occurred in less than 1 per cent versus a 27 per cent mortality rate and a 16 per cent sudden death rate in those with ST-segment depression (≥1 mm) during exercise [39].

In another study that incorporated both heart rate-limited and symptom-limited protocols for patients tested 3 weeks after an uncomplicated MI, a stepwise multiple logistical regression program identified exercise-induced ST-segment depression (≥2 mm) and angina pectoris occurring at a maximal workload of less than 4 METs as risk factors predictive of subsequent MI, sudden death, cardiac arrest, or coronary artery bypass surgery over a 2-year

TABLE 3–5. Oxygen requirements for step, treadmill, and bicycle ergometer*

Functional class	METS	O_2 Requirements (ml O_2/kg/min)	Step test	Treadmill tests								Bicycle ergometer
			Nagle Balke Naughton 2-min stages 30 steps/min	Bruce 3-min stages		Kattus 3-min stages		Balke % grade at 3–4 mph	Balke % grade at 3 mph	DeBusk 3-min stages		
	16	56.0	(Step height					26				For 70 kg
Normal	15	52.5	increased					24				body weight
and	14	49.0	4 cm q 2 min)			mph	% gr	22				kgm/min
I	13	45.5	Height (cm)	mph	% gr	4	22	20				1500
	12	42.0	40	4.2	16			18	22.5	mph	% gr	1350
	11	38.5	36			4	18	16	20.0			1200
	10	35.0	32					14	17.5	3	17.5	1050
	9	31.5	28	3.4	14	4	14	12	15.0	3	15.0	1050
	8	28.0	24					10	12.5	3	12.5	900
	7	24.5	20			4	10	8	10.0	2	17.5	750
	6	21.0	16	2.5	12	3	10	6	7.5	2	14.0	600
II	5	17.5	12			2	10	4	5.0	2	10.5	450
	4	14.0	8					2	2.5	2	7.0	
III	3	10.5	4	1.7	10				0.0	2	3.5	300
	2	7.0								2	0	150
IV	1	3.5										

*Oxygen requirements increase with workloads from bottom of chart to top in various exercise tests of the step, treadmill, and bicycle ergometer types.
Modified from Ellestad MH, *et al*: Standards for adult exercise testing laboratories, American Heart Association Subcommittee on Rehabilitation, Target activity Group. *Circulation* 59:421A, 1979. With permission of American Heart Association, Inc.

period [40]. Other clinical characteristics such as age, magnitude of serum creatine kinase elevation, site of infarction, and previous history of angina or infarction did not permit prognostic stratification. A low maximal workload exercise performance (below 4 METs) alone was predictive of subsequent cardiac events, probably correlating with the extent of left ventricular dysfunction.

In another study of patients tested within 3 weeks of an acute MI, the risk of death or reinfarction over the next 2 years was greater in those patients who exhibited ST-segment depression at less than 60 per cent of the predicted maximal heart rate [41]. It is possible that the low incidence of exercise-induced ST-segment depression in some studies reflects premature termination of exercise. Nevertheless, in properly conducted exercise tests, the absence of ischemic ST-segment depression (≥2 mm) or ventricular ectopic activity does identify a group of patients with an excellent prognosis during the first and second years after the event, while the presence of ischemic ST-segment depression (≥2 mm) identifies those at high risk for early fatal coronary events. In the absence of significant ST-segment depression, the occurrence of angina pectoris alone is not associated with a greater likelihood of subsequent medical events [40].

2. *Anginal pain:* This occurs in about one-third of patients who undergo predischarge exercise tests. In the absence of a significant ST-segment abnormality, anginal pain does not appear to predict the occurrence of sudden death, nonfatal cardiac arrest, or MI, although the likelihood of later surgery is increased [40]. Furthermore, the predictive value of ST-segment abnormalities is not enhanced by concurrent angina. Angina that occurs during the exercise test may predict future stable angina during the first 12 months after infarction [39].

3. *Arrhythmias:* In patients with *chronic* ischemic heart disease there appears to be a close relationship between the extent of left ventricular dysfunction and the prevalence of ventricular premature beats. Schulze et al have shown that complex VPBs after an acute MI (recorded on ambulatory ECGs during the late hospital phase) are not associated with an increased risk for sudden death in the first year after infarction in patients with left ventricular ejection fractions exceeding 40 per cent. The exclusion of patients with significant ventricular dysfunction from early exercise testing protocols probably accounts for the variable results obtained regarding the prognostic importance of exercise-induced ectopy in the early weeks after infarction [43]. Some authors have found that the presence of ventricular ectopy on a single exercise test 3 weeks after infarction has no independent prognostic value, even in patients with complex configurations or a high frequency of VPBs [40]. Others have shown that exercise-induced ventricular ectopic activity or ischemic ST-segment depression 11 weeks after infarction identifies patients at increased risk for subsequent coronary events, whereas the absence of these two factors identifies a group of patients with an excellent prognosis [42]. In a relatively small population, ventricular arrhythmias occurring during exercise correlated with sudden death in the first year after acute MI [39], and an increased risk of subsequent cardiac events was noted in patients with exercise-induced VPBs 2 to 3 weeks after infarction [44].

Exercise-induced ventricular arrhythmias are almost certainly of greater prognostic significance if detected in patients with ventricular dysfunction. It is likely that therapeutic strategies will evolve only when arrhythmias detected during early postinfarction exercise testing and late hospital phase 24-hour ambulatory monitoring are coupled with information about cardiac function and anatomy. A prospective study of survivors of acute MI identified two variables — previous infarction and an ejection fraction below 40 per cent — as the best predictors of mortality. Complicated ventricular arrhythmias in the late hospital phase did not provide additional information about mortality once the information gleaned from the first two variables was considered [45].

At the time of hospital discharge, left ventricular function rather than acute ischemia appears to be the prime determinant of exercise performance [46]. When maximal symptom-limited treadmill exercise testing was performed (Bruce protocol) 6 to 8 weeks after myocardial infarction, the rate of reinfarction during a mean followup of 28 months was found to be only 2 per cent in patients with an exercise tolerance of 10 minutes or more compared with 9 per cent in patients with an exercise tolerance of less than 10 minutes [47]. Thus, at this stage, an exercise

tolerance criterion of 10 minutes or more identifies a group at very low risk for subsequent mortality and morbidity. An ejection fraction of less than 30 per cent or the presence of three-vessel disease identifies a high-risk group for subsequent mortality [47].

In summary, in patients surviving uncomplicated acute MI who do not have unstable angina or evidence of overt heart failure, exercise testing can provide prognostic information and identify a subgroup of patients at high risk for subsequent morbid or fatal events. Of equal importance, the absence of any abnormalities during predischarge exercise testing is an important psychological boost and is useful in reassuring both patient and physician that tasks performed during conditions of controlled exercise are safe. The patient may then be allowed to progress more rapidly to normal activity levels.

Symptom-limited serial treadmill testing performed during the first 12 months after infarction may have a role in predicting subsequent morbid events. Exercise-induced ventricular arrhythmias that occurred during multiple tests performed from 5 weeks to 1 year after MI were more prevalent in patients who later suffered recurrent MI (90 per cent) than in those without subsequent events (47 per cent) [42]. The occurrence of exercise-induced arrhythmias during a single test at 3 weeks was a less powerful predictor of subsequent cardiac events.

3. Posthospital phase

3.1. ROLE OF BETA BLOCKERS

Secondary prevention trials of beta blocker therapy in survivors of acute MI have indicated that prophylactic beta blockade reduces the incidence of sudden death and possibly reinfarction.

These postinfarction beta blocker trials have recently undergone rigorous statistical appraisal by Lewis and Ellis, who examined the 28 published trials in detail [48]. Figure 3–1 shows the effects of beta blockers on postinfarction mortality in 16 trials; the other 12 trials were excluded from analysis because (1) analysis of mortality by "intention to treat" was not available; (2) randomization and control groups were inadequate; and (3) the number of deaths in these trials was less than 20, thus reducing the precision and likelihood of accurate statistical analysis. The results are presented in terms of the per cent effect of treatment on the total mortality rate using the following formula:

$$\frac{(\text{Placebo mortality rate} - \text{Treated mortality rate}) \times 100}{\text{Placebo mortality rate}}$$

The horizontal bars correspond to 95 per cent confidence limits, so that the right end of the bars indicates an upper limit for a beneficial treatment effect and the left end or lower limit generally corresponds to a deleterious effect. The actual per cent of treatment is represented by the vertical line toward the center of the bars. For example, in the timolol trial, the observed effect of timolol on total mortality was a 36 per cent reduction (95 per cent confidence limits = 19 to 50 per cent reduction). In this particular study, these limits are likely to contain the true effect of treatment on mortality.

This analysis has several features of interest. First, the observed trial results tend to lie to the right of the zero line — i.e., to correspond with a reduction in mortality. Second, negative trials with observed results lying to the left of the zero line have wide confidence limits and are therefore less precise. Finally, all trials consistently show a beneficial effect of treatment of about a 20 per cent reduction in mortality, with confidence limits ranging from 12 to 28 per cent. Four of the studies have narrow confidence limits. In three of these (the practolol, BHAT, and timolol trials) treatment began at least 5 days after infarction. Thus, it is highly unlikely that the observed reduction in mortality was due to a reduction in infarct size. However, in the metoprolol trial 69 per cent of patients with definite or suspected infarction were treated within 12 hours (mean 11.3 ± 0.3 hours) and a 15 per cent reduction in enzyme-estimated infarct size was reported.

Although the mechanisms underlying the salutary effect of beta blockers in preventing sudden death is uncertain, improvements in ischemia or prevention of arrhythmias is possible. Despite these persuasive data, large percentage alterations in mortality may result from relatively small absolute numbers of patients being saved from sudden death. In other words, to prevent sudden death in three to six patients, one must provide continuous treatment to over 100 patients for 1 to 2 years.

Many clinicians favor the selection of a "high-risk" subgroup of infarct survivors for beta blocker therapy. Yet, even here it must be remembered that those at greatest risk for

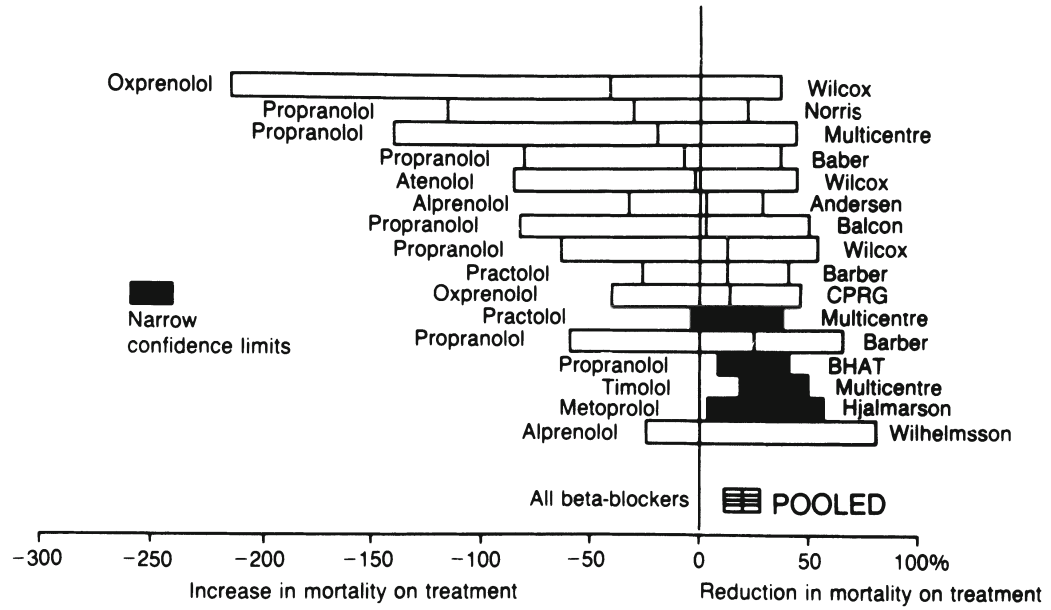

FIGURE 3–1. Postinfarction beta blocker trials. Analysis of total mortality rate in 16 trials. Horizontal bars correspond to 95% confidence limits for percentage effect of beta blockers on mortality. The pooled percentage effect of a reduction in mortality is significant (confidence limits = 12 to 28%). (From Lewis JA, Ellis SH: A statistical appraisal of postinfarction beta blocker trials. *Primary Cardiol Suppl* 1:31–37, 1982.)

sudden death are those who have low ejection fractions or are suffering from cumulative effects of significant myocardial damage. Such patients often cannot tolerate beta blockers. Thus, it might be reasonable to give beta blockers to survivors of infarction who have hypertension, positive exercise tests, or ischemia during convalescence and those otherwise at "high risk," whoever they eventually prove to be.

3.2. PROPHYLAXIS AGAINST PLATELET AGGREGATION AND THROMBOSIS

Since there is considerable evidence that platelet aggregation and platelet-induced thrombosis may play a role in the pathogenesis of MI, several trials have been undertaken to evaluate the efficacy of antiplatelet agents in preventing recurrence. Based on the results of randomized, controlled trials, it is still difficult to conclude that aspirin, dipyridamole, or sulfinpyrazone will lower mortality in patients who have survived an MI.

In the Aspirin Myocardial Infarction Study (AMIS), regular administration of aspirin in a dose of 1 gm/day did not reduce 3-year mortality rates in survivors of an MI, and was therefore not recommended for use in such patients. In the Persantine-Aspirin Reinfarction Study, patients were randomized to therapy with Persantine (dipyridamole) plus aspirin, aspirin alone, or placebo. The results suggested that total mortality appeared lower in the treated than in the placebo group over a 41-month followup period, but these differences were not statistically significant according to the study criteria. Patients who entered into the study within 6 months of the qualifying MI and were thus randomized to active treatment earlier showed the most favorable trends.

The results of the Anturane Reinfarction Trial have been vigorously debated in the medical literature. This randomized double-blind multicenter trial compared sulfinpyrazone (200 mg four times a day) and placebo in the prevention of cardiac mortality over a 16-month

followup period. Therapy was begun within 25 to 35 days after a documented MI, and the initial report indicated that sulfinpyrazone reduced the incidence of sudden cardiac death by 43 per cent in post infarction patients at 2 years and by 74 per cent in the 2 to 7 months after infarction. When samples of the case records were reviewed by the FDA, the reviewers questioned assignment of the causes of death, stating that the effect on total cardiac mortality was not convincing because it depended heavily on retrospective exclusion from analysis of certain patients who died while receiving the drug.

Currently, the available evidence is inconclusive as to whether aspirin, sulfinpyrazone, or dipyridamole (with or without aspirin) reduce mortality after MI. One possible flaw in these studies is the delay in treatment after the initial episode of acute infarction.

3.3. POST-DISCHARGE EXERCISE

Early exercise test evaluation provides (1) prognostic information on subgroups of patients, (2) an assessment of cardiovascular capacity, (3) reassurance to the patient, and (4) a basis for prescribing exercise after hospital discharge. The energy costs of various activities the patient may perform are shown in table 3–7 and the exercise prescription based on exercise testing is presented in table 3–8. Subpopulations at high and low risk for subsequent morbid events can be identified based on the presence or absence of significant left ventricular dysfunction, the presence or absence of unstable symptoms, and results of the early exercise test.

Patients should be advised to warm up adequately prior to partaking in postdischarge exercise, exercise regularly and slowly increase the amount of activity without setting rigid goals, adjust their exercise intensity and duration to the prevailing climatic conditions, and avoid exercising after a recent meal. Although cardiac rehabilitation programs provide hemodynamic and symptomatic benefits, controlled studies have demonstrated no decrease in morbidity and mortality in patients who adhere to such exercise programs. Nevertheless, many patients feel that they derive psychological and physical benefits from a supervised rehabilitation program that includes exercise and helps them avoid adverse risk factors, such as recommencement of smoking, excessive weight gain, or inappropriate invalidism.

Specific counseling about future sexual activity prior to discharge from hospital can allay anxiety in the patient and spouse. The energy expenditure of sexual intercourse is about 4 METs. If problems are encountered, sexual activity less physically demanding than coitus may be a prelude to later resumption of a normal sexual relationship.

Most patients can return to work 6 to 8 weeks after infarction, although this depends on the patient's clinical progress and type of employment. By 3 months, most patients who have had an uncomplicated MI return to a functional capacity similar to that which they enjoyed prior to the event.

TABLE 3–6. Criteria for stopping exercise tests during early postinfarction assessment

1. Chest discomfort or pain
2. Excess fatigue or dyspnea
3. Decrease in systolic blood pressure of at least 20 mm Hg (or confusion, ataxia, incoordination, faintness, or dizziness)
4. ECG changes:
   a. ST-segment displacement >2 mm from preexercise baseline level
   b. Salvos of ventricular ectopic impulses, R-on-T phenomenon, sustained ventricular tachycardia
   c. Paroxysmal supraventricular tachycardia or atrial fibrillation
   d. Second- or third-degree AV block
   e. Excess sinus tachycardia (heart rate >130 to 150 bpm)

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TABLE 3–7. Energy cost of various occupational and recreational activities

	Occupational	Recreational
1 to 2 METs	Desk work, auto driving, typing	Standing, walking (1 mph), playing cards, sewing, knitting
2 to 3 METs	Auto repair, radio, janitorial work, bartending	Level walking (2 mph), level bicycling (5 mph), riding lawn mower, billiards, bowling, shuffleboard, woodworking (light), powerboat driving, golf (power cart), canoeing (2½ mph), horseback riding (walk), playing piano and other musical instruments.
3 to 4 METs	Bricklaying, plastering, wheelbarrow (100-lb load), machine assembly, trailer truck in traffic, welding, (moderate load), cleaning windows	Walking (3½ mph), cycling (8 mph), table tennis, golf (carrying clubs), dancing, badminton (singles), tennis (doubles), raking leaves, hoeing, many calisthenics
5 to 6 METs	Digging garden, shoveling light earth	Walking (4 mph), cycling (10 mph), canoeing (4 mph), horseback riding, stream fishing, ice or roller skating (9 mph)
6 to 7 METs	Shoveling (10 lb)	Walking (5 mph), cycling (11 mph), badminton (competitive), tennis (singles), splitting wood, snow shoveling, hand lawn mowing, folkdancing, light downhill skiing, ski touring (2½ mph), waterskiing
7 to 8 METs	Digging ditches, carrying 80 lb, sawing hardwood	Jogging (5 mph), cycling (12 mph), horseback riding (gallop), vigorous downhill skiing, basketball, mountain climbing, ice hockey, canoeing (5 mph), touch football, paddleball
8 to 9 METs	Shoveling (14 lb)	Running (5½ mph), cycling (13 mph), ski touring (4 mph, loose snow), squash (social), handball (social), fencing, basketball (vigorous)
10^{+} METs	Shoveling (16 lb)	Running: 6 mph = 10 METs; 7 mph = 11½ METs; 8 mph = 13½ METs; 9 mph = 15 METs; 10 mph = 17 METs; ski touring (5^{+} mph), handball (competitive), squash (competitive)

METs = multiples of resting energy expenditure. From Goldschlager N: Treadmill exercise testing soon after myocardial infarction. *Cardiovasc Rev Rep* 1:397–402, 1980.

TABLE 3–8. Exercise prescription based on results of low-level exercise testing

	Treadmill time (METs)	
≤3 minutes (≤2.3)	≤6 minutes (≤3.5)	≤9 minutes (≤4.6)
Dining (1.4)	Self-grooming at sink, standing (2.5)	Beating carpets (4.0)
Sweeping floor (1.5)	Level walking at 2.5 mph (2.5)	Making beds (4.6)
Polishing furniture (1.8)	Ironing (2.7)	Bowling (3.5)
Washing dishes seated (2.0)	Sewing (2.9)	Golfing (4.0)
Dressing (2.3)	Showering (3.5)	Gardening (4.5)
	Bedside commode (3.6)	Walking downstairs (4.5)
		Table tennis (4.0)

Numbers in parentheses = METs (multiples of resting energy expenditure.) From Weld F.M., De Turk WE: *Primary Cardiology* 9:126, 1983.

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4. CARDIAC ARRHYTHMIAS DURING ACUTE MYOCARDIAL INFARCTION

In the patient with acute myocardial infarction (MI), the clinician may encounter a variety of abnormal cardiac rhythms and conduction disturbances. The incidence of specific arrhythmias varies, depending on the time from onset of infarction (table 4–1). In order to catalog these rhythm disturbances, several classification schemes have been proposed. According to a modified version of the scheme developed by Lown in 1969, arrhythmias in patients with acute MI may be divided into three broad categories [1]:

1. Arrhythmias due to electrical instability.
2. Arrhythmias due to pump failure/excessive sympathetic stimulation.
3. Bradyarrhythmias and conduction disturbances.

It should be recognized that, by necessity, any classification scheme is arbitrary, and overlap between categories is possible. Nevertheless, the approach to be discussed here should provide a useful guide to the management of infarction-related arrhythmias. Table 4–2 outlines the objectives of treatment as well as therapeutic options for the various arrhythmias.

1. Arrhythmias Due to Electrical Instability

Laboratory studies of animals with experimental MI and observations in the mobile coronary care unit setting have added greatly to our understanding of arrhythmias due to electrical instability [2]. Acute cellular effects of ischemia include inhibition of active ion transport, an increase in the extracellular concentration of K+, local liberation of catecholamines, and a fall in extracellular pH due to release of intracellular enzymes. These events cause depolarization of ischemic cells and slow conduction, thus facilitating *reentry*. This pathogenic mechanism probably accounts for the majority of ventricular arrhythmias seen within the first few hours of infarction (i.e., the *prehospital phase* or very *early CCU phase* of acute MI). Prolonged ischemia leads to cell death and loss

TABLE 4–1. Incidence of arrhythmias within 4 hours among 294 patients after acute myocardial infarction

Arrhythmia	During 1st hour	During 2nd hour	During 3rd and 4th hours	Total within 4 hours
Bradyarrhythmias	34%	3.5%	2.5%	40%
Ventricular premature beats	58%	27%	8%	93%
Ventricular fibrillation	9.5%	4.5%	1.5%	15.5%
Ventricular tachycardia	2%	1.5%	0.5%	4%
Supraventricular dysrhythmias	1.5%	2.5%	2%	6%

Modified from Adgey AAJ, et al: Acute phase of myocardial infarction. Prehospital management of the coronary patient. *Minnesota Med* 59:347, 1976.

TABLE 4–2. Cardiac arrhythmias during acute myocardial infarction

Category	Arrhythmia	Objective of treatment	Therapeutic options
I. *Electrical instability*	Ventricular premature beats	Prophylaxis against ventricular fibrillation	Antiarrhythmic agents (lidocaine, procainamide)
	Ventricular tachycardia	Prophylaxis against ventricular fibrillation; restoration of hemodynamic stability	Antiarrhythmic agents; cardioversion/ defibrillation
	Ventricular fibrillation	Urgent reversion to sinus rhythm	Defibrillation; bretylium tosylate
	Accelerated idioventricular rhythm	Observation unless hemodynamic function is compromised	Increase sinus rate (atropine, atrial pacing); antiarrhythmic agents
	Nonparoxysmal AV junctional tachycardia	Search for precipitating causes (e.g., digitalis intoxication); suppress arrhythmia only if hemodynamic function is compromised	Atrial overdrive pacing; antiarrhythmic agents; cardioversion relatively contraindicated if digitalis intoxication present
II. *Pump failure/ Excessive sympathetic stimulation*	Sinus tachycardia	Reduce heart rate to diminish myocardial oxygen demands	Antipyretics; analgesics; evaluate level of PCW pressure and treat accordingly
	Atrial fibrillation and/or atrial flutter	Reduce ventricular rate; restore sinus rhythm	Verapamil, digitalis glycosides; anticongestive measures (diuretics, afterload reduction); cardioversion; rapid atrial pacing (for atrial flutter)
	Paroxysmal supraventricular tachycardia	Reduce ventricular rate; restore sinus rhythm	Vagal maneuvers; verapamil, cardiac glycosides, beta-adrenergic blockers; cardioversion; rapid atrial pacing
III. *Bradyarrhythmias and conduction disturbances*	Sinus bradycardia	Acceleration of heart rate only if hemodynamic function is compromised	Atropine; atrial pacing
	Junctional escape rhythm	Acceleration of sinus rate only if loss of atrial "kick" causes hemodynamic compromise	Atropine; atrial pacing
	Atrioventricular block and intraventricular block		(see chapters 8 and 9)

of electrical activity in infarcted cells. However, surviving subendocardial Purkinje fibers and ventricular muscle fibers on the periphery of the infarct may exhibit *enhanced automaticity* as well as participate in *reentrant* circuits, leading to the *CCU* and *late hospital phases* of ventricular arrhythmias. In addition, MI and chronic ischemic heart disease may place a patient at risk for sudden cardiac death. This important area bears detailed discussion and will be reviewed in Chapter 5.

1.1. VENTRICULAR PREMATURE BEATS (VPBS)

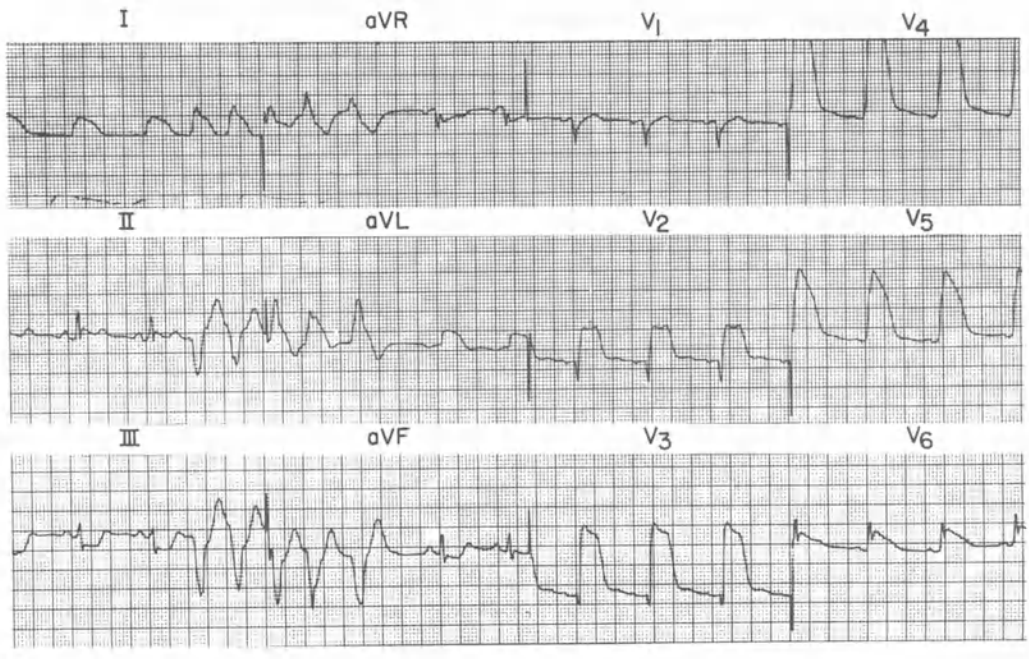
The most common arrhythmia seen in acute MI is the *ventricular premature beat* (VPB), which can be documented in at least 90 per cent of patients. Isolated VPBs may be benign, but when they degenerate into rapid repetitive salvos, such as ventricular tachycardia, hemodynamic function is compromised, with a fall in cardiac output, left ventricular failure, and angina pectoris (figure 4–1). Controversy continues regarding the potential relationship between isolated VPBs and ventricular tachyarrhythmias.

Early studies suggested that the appearance of certain *warning arrhythmias* might serve to identify VPBs with malignant potential. Thus, VPBs that were frequent (more than 5 per minute), multiform, repetitive, and early in the cardiac cycle (or "R on T" [figure 4–1*B*]) were initially designated as those to be suppressed [3]. More recent investigations have shown that as many as 50 per cent of patients with ventricular fibrillation during acute infarction may *not* exhibit such "warning" VPBs [4,5]. Also, warning arrhythmias may occur relatively infrequently in a given patient or may occur only seconds before fibrillation is seen. Conversely, warning arrhythmias may develop in as many as 50 per cent of patients who do not go on to have ventricular fibrillation. Finally, even the technique of real-time arrhythmia detection carried out by skilled nurses may be inadequate to uncover warning arrhythmias in sufficient time to intervene with drug therapy [6], hence the introduction in many coronary care units of on-line computer arrhythmia detection systems.

1.1.1. Lidocaine prophylaxis. In view of these clinical considerations, widespread prophylaxis against ventricular fibrillation has been suggested. Although a variety of drugs has been used as prophylactic agents, the one that has been studied most completely and for which there is the most supporting evidence is intravenous lidocaine [2,7–10].

Although some CCU physicians routinely prescribe prophylactic lidocaine for all patients carrying the diagnosis of known or suspected acute MI, it is best to administer the drug selectively. Analysis of pooled data from several studies suggests that certain patients may benefit more than others [8–10]. Younger patients (e.g., ages 40 to 50) with no prior history of congestive heart failure or acute MI who are admitted early after the onset of chest pain (within 4 to 6 hours) are at high risk for ventricular fibrillation and should therefore receive lidocaine prophylaxis. In elderly patients (e.g., age 70 or over), the risk of ventricular fibrillation appears to be reduced, whereas the risk of lidocaine toxicity appears to be increased. Thus, one should be circumspect about administering lidocaine to elderly patients admitted to the CCU late after the onset of chest pain. Finally, it should be realized that patients with congestive heart failure, shock, conduction system disease, acidosis, or hypokalemia are at high risk for *both* ventricular fibrillation and lidocaine toxicity; it is not yet clear whether lidocaine prophylaxis is of benefit in such individuals.

Patients considered to be appropriate candidates for lidocaine prophylaxis are given an initial loading dose of 1.5 to 2.0 mg/kg intravenously followed by a continuous infusion of 2 to 4 mg/min. The infusion is maintained for 48 hours in patients with an uncomplicated MI. Between 15 and 40 minutes after the initial loading dose, the patient's serum lidocaine concentration may transiently fall below a therapeutic level before the continuous infusion has begun to accumulate. The appropriate response at this time is to administer a smaller supplemental intravenous bolus of 0.50 to 0.75 mg/kg rather than to increase the rate of the continuous infusion. Since the major site of metabolism of lidocaine is the liver, the dose should be reduced in patients with hepatic congestion secondary to congestive heart failure, decreased hepatic blood flow from low cardiac output, or primary hepatic failure [11]. Since lidocaine's metabolites are excreted via the kidney, the dose may also need to be reduced in severe renal failure. During prolonged infusion of lidocaine (greater than 24 to 48 hours), the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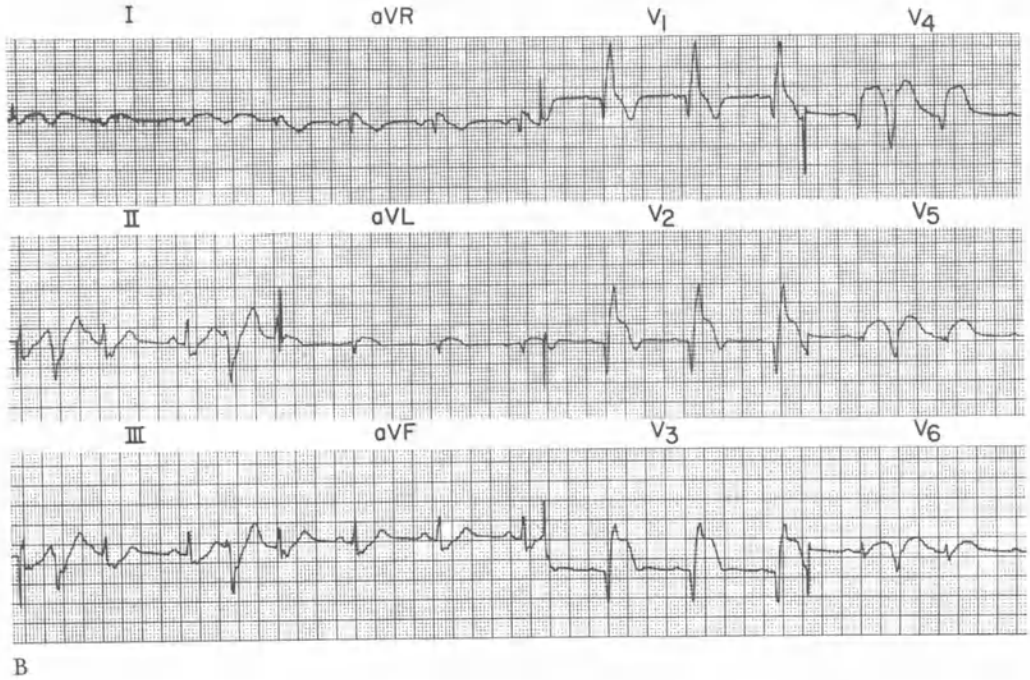
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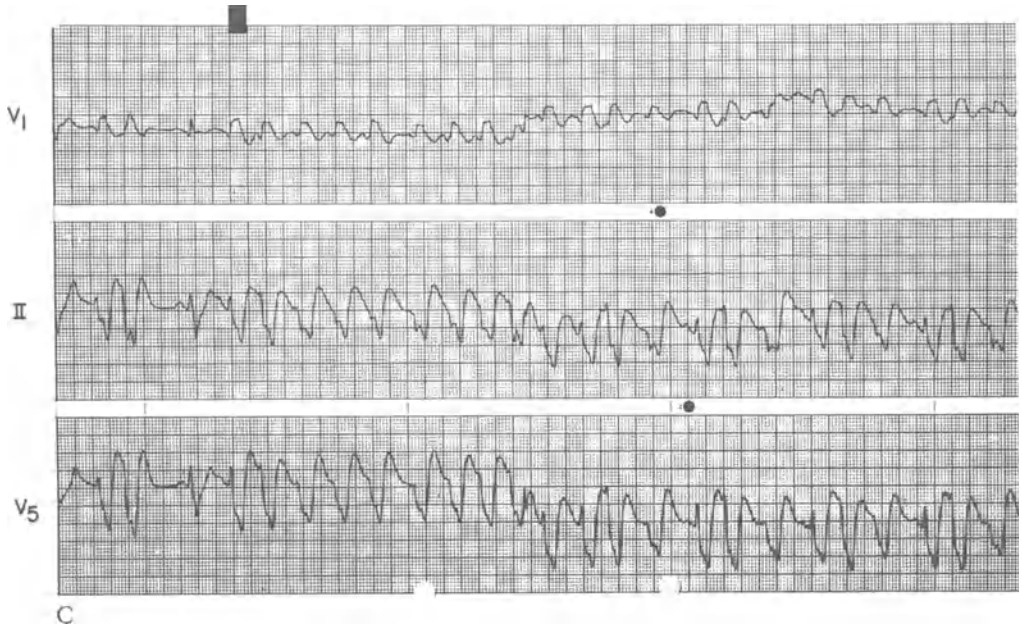

FIGURE 4–1. *A*, This 12-lead ECG was obtained from a middle-aged man admitted with an extensive acute anterior MI. (Note pathological Q waves in the precordial leads and marked repolarization abnormalities in the anterior and lateral leads.) A five-beat salvo of ventricular tachycardia is seen extending over the transition between leads III and aV_f. *B*, Several hours after admission, this patient developed right bundle branch block. He continued to exhibit frequent VPBs that encroached on the repolarization phase of the preceding QRS complex (R-on-T phenomenon), as can be seen in leads V_4 to V_6. *C*, Early-cycle VPBs, such as those seen in *B*, may degenerate into salvos of ventricular tachycardia, as shown in this long, three-lead rhythm strip from another patient.

$t_{1/2}$ of elimination may increase, necessitating a reduction in dose. *Cimetidine* has been reported to decrease both the systemic clearance and the volume of distribution of lidocaine, suggesting a need to reduce the rate of lidocaine infusion when these two drugs are given together [12].

1.1.2. Other antiarrhythmic drugs. Occasionally, repetitive ventricular ectopic activity (couplets, ventricular tachycardia) early after MI may not be adequately suppressed with lidocaine. In such instances, intravenous *procainamide* should be administered utilizing a loading dose of 750 to 1,000 mg followed by an infusion of 1 to 4 mg/min. While blood pressure is being closely monitored, the loading dose of procainamide should be given as 100-mg intravenous boluses every 5 minutes until the arrhythmia is suppressed, a total of 1,000 mg has been administered, or electrocardiographic evidence of toxicity (QRS and Q-T widening beyond 50 per cent of control) is noted. Procainamide may also be administered in oral doses of 250 to 750 mg every 3 to 4 hours following an initial oral loading dose of 500 to 750 mg. Sustained-release preparations of procainamide (e.g., Procan-SR) are now available that allow dosing every 6 hours.

Quinidine is less useful in the acute setting, since it is usually administered orally. Intravenous quinidine is generally not used because of its potential hypotensive effect and deleterious consequences in a patient with acute infarction. Intramuscular quinidine may also cause hypotension and can elevate creatine kinase levels in response to muscle trauma. The usual oral dose for quinidine is 200 to 400 mg every 6 hours. An initial loading dose of 400 mg

orally may reduce the time required to develop a satisfactory blood level.

Although *phenytoin* is usually not considered a first-line antiarrhythmic agent, it is especially useful in the setting of digitalis toxicity. A loading dose of 1,000 mg is administered as 100-mg increments intravenously every 5 to 10 minutes under careful clinical monitoring for CNS toxicity (e.g., nystagmus, seizures). This is followed by a daily maintenance dose of 300 to 500 mg orally.

Beta-adrenergic blocking agents used alone or in combination with other antiarrhythmics are occasionally helpful for control of ventricular ectopic activity. Propranolol may be administered intravenously and/or orally. After an initial intravenous test dose of 0.5 to 1.0 mg, the patient is given a full intravenous loading dose consisting of 1 to 2 mg every 5 minutes up to 0.1 mg/kg (not to exceed 10 mg for a 70-kg person). Because of a prominent first-pass effect in the liver, the oral dose of propranolol is considerably higher than the intravenous dose and ranges from 40 to 480 mg/day divided into four equal doses.

Disopyramide phosphate (Norpace) has recently been made available as an oral antiarrhythmic agent. It is administered in a dose of 100 to 150 mg every 6 hours. The drug should be used with caution in patients with acute MI, particularly those with a history of left ventricular decompensation, because of the drug's negative inotropic potential.

A number of investigational antiarrhythmics (see chapter 6) have also been used in patients with acute infarction, but their efficacy and safety have not been clearly established. At this time, they are not recommended for routine use in the CCU. However, these potent new drugs have an important place in the management of patients with refractory cardiac arrhythmias and patients resuscitated from sudden cardiac death (see chapters 7 and 8).

1.2. VENTRICULAR TACHYCARDIA

Ventricular tachycardia is a potentially lethal rhythm disturbance seen frequently in patients with acute MI. A recent study suggests that ventricular tachycardia early after the onset of infarction is more prevalent in patients with a prolonged Q–Tc (>0.48 sec) [13].

Management of this disorder depends on the degree of hemodynamic compromise associated with the arrhythmia. If the patient has no effective perfusion during an episode of ventricular tachycardia, *urgent electrical reversion* of the rhythm is indicated. If the rate of the tachycardia is below 150 to 180 bpm and the QRS morphology allows synchronization, a cardioversion discharge is employed (see chapter 7). This arrhythmia is often quite sensitive to electrical energy in that many cases can be reverted to sinus rhythm with a discharge of only 5 to 10 watt-seconds or less. This sensitivity explains the occasional reversion to sinus rhythm following a "chest thump" (which delivers approximately 0.5 to 1.0 watt-second). More rapid paroxysms of ventricular tachycardia (e.g., rates >160 to 180 bpm) or those which cannot be adequately synchronized for cardioversion are treated with a defibrillatory impulse (unsynchronized shock) of 100 to 200 watt-seconds (figure 4–2). Extremely rapid ventricular tachycardia is characteristically seen in acutely ischemic or infarcted ventricles and has been labeled "ventricular tachycardia of the vulnerable period" by Lown and coworkers [1] (see figure 7–12 in chapter 7).

Ventricular tachycardia that is tolerated hemodynamically should be treated with *intravenous antiarrhythmic drugs*. Lidocaine may be administered in a dose of 50 to 150 mg as single or multiple boluses, or procainamide may be delivered as a series of 100-mg intravenous boluses to a total of 1,000 mg. Following acute management of the tachycardia, the patient is begun on a maintenance antiarrhythmic program consisting of either continuous infusion of an intravenous drug or an oral antiarrhythmic. A diligent search should be made for reversible causes of ventricular irritability such as congestive heart failure, hypoxemia, hypokalemia, or an intracardiac catheter that could be irritating the endocardial surface of the ventricle.

Refractory or recurrent cases of ventricular tachycardia may occasionally respond to intravenous bretylium tosylate (5 mg/kg). This drug may be administered as a maintenance infusion of 1 to 2 mg/min; however, continuous infusion of bretylium often results in hypotension. The degree of hypotension may be reduced if the drug is given in intermittent boluses of 500 to 750 mg every 4 to 6 hours as required to control the rhythm disturbance. A transient worsening of ventricular ectopic activity may be seen shortly after each dose.

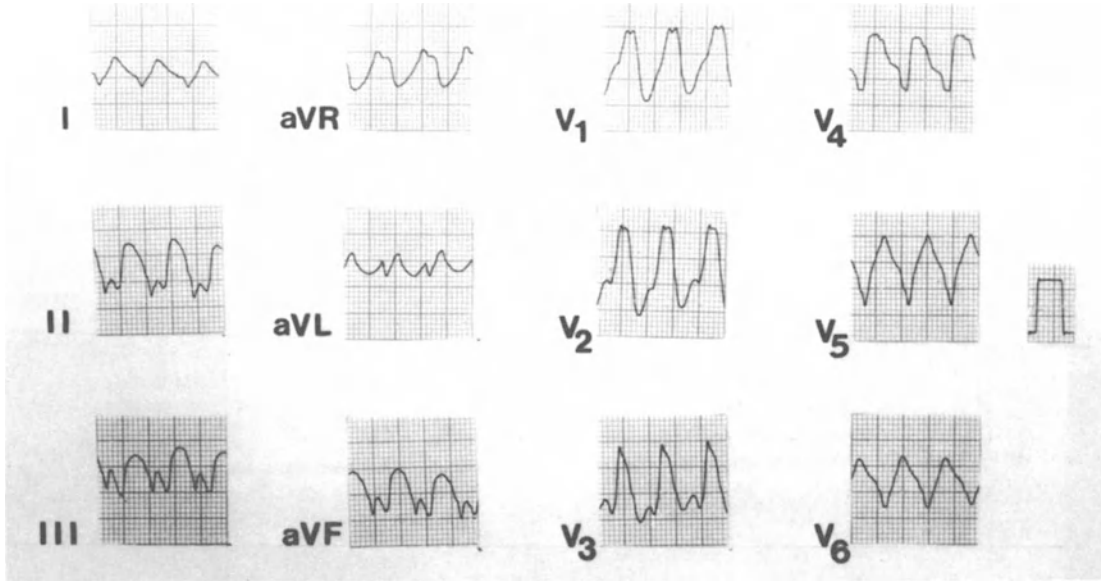

FIGURE 4–2. This 12-lead ECG was recorded from a patient with an acute anterior MI. The QRS pattern is typical of ventricular tachycardia. In view of the rapid rate (180 to 190 bpm) and difficulty with synchronization, a defibrillatory shock of 100 watt-seconds was utilized to restore sinus rhythm.

1.3. VENTRICULAR FIBRILLATION (FIGURE 4 –3)

Ventricular fibrillation is a lethal arrhythmia and is the most common cause of death within the first few hours of an MI. The concept of prophylaxis against this arrhythmia has been discussed above. When no prophylactic antiarrhythmic agents are used, the incidence of ventricular fibrillation has been found to range from 5 to 10 per cent in patients with acute infarctions [9].

Primary ventricular fibrillation in association with MI refers to fibrillation occurring during acute infarction without associated severe pump dysfunction, whereas *secondary ventricular fibrillation* is associated with advanced congestive failure and/or cardiogenic shock [2]. (It is also important to distinguish cases of primary ventricular fibrillation that are *not* associated with acute infarction but lead to sudden cardiac death. This refers to sudden cardiac death due to ventricular fibrillation in the noninfarction patient. Even if the patient is successfully resuscitated from ventricular fibrillation in the absence of an acute MI, there is a high recurrence rate if the patient is untreated; this situation has important therapeutic implications, which will be addressed in chapter 5.)

Primary ventricular fibrillation in the setting of acute infarction, if treated promptly, carries a good prognosis. Individuals who have secondary ventricular fibrillation have a poor clinical prognosis; the rhythm disorder tends to recur unless pump dysfunction can be reversed, which is often not possible.

Treatment of ventricular fibrillation requires a well-rehearsed, orderly, rapid resuscitation effort. Immediate *electrical defibrillation* with a nonsynchronized discharge should be employed. Energy settings of 300 to 400 watt-seconds are routinely recommended. Lower energy settings should be used only by experienced resuscitation teams until studies confirm the recent suggestion that 100 to 200 watt-seconds is appropriate for routine use; higher energy levels do not appear to be necessary, even for very obese individuals.

Correct technique is a prime factor in the

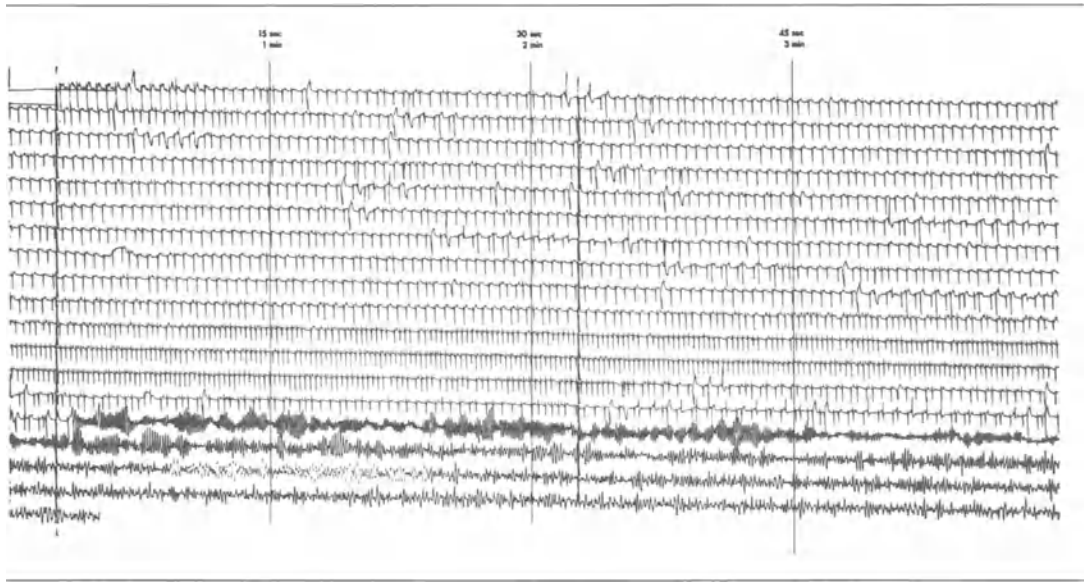

FIGURE 4–3. This slow-speed "trendscription" recording covers 30 minutes of time (1 min/line). Acceleration of the sinus rate can be seen, followed by the development of ventricular fibrillation (fifth line from bottom). Typical high-amplitude oscillations in QRS height are seen; these gradually become smaller as the patient progresses from a "coarse" to a "fine" form of fibrillation.

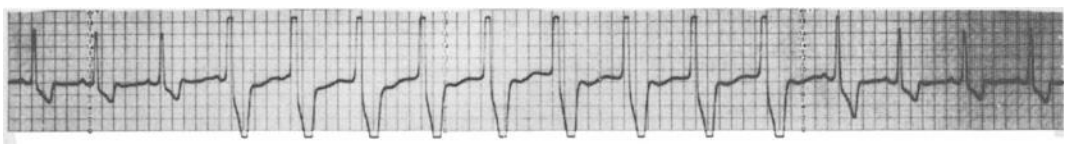

FIGURE 4–4. Sinus rhythm at the left is followed by a wide complex rhythm of ventricular origin. The fusion complexes (fourth beat from the right), QRS morphology, and rate of the arrhythmia are characteristic of accelerated idioventricular rhythm.

success of reversion of ventricular fibrillation. (For a complete description of this technique, see chapter 7.) The time between the appearance of ventricular fibrillation and attempted defibrillation should be minimized. Appropriately sized paddles should be heavily coated with electrode paste and held firmly against the thorax in either an anterior-posterior or an anteriorlateral position.

Ventricular fibrillation tends to recur unless the associated hypoxemia, acid-base disorders, and electrolyte disturbances are promptly reversed. Refractory or recurrent ventricular fibrillation can sometimes be treated with *bretylium tosylate*, 5 mg/kg intravenously, either alone or in conjunction with electrical defibrillation.

1.4. ACCELERATED IDIOVENTRICULAR RHYTHM (AIVR) (FIGURE 4–4)

This arrhythmia, also referred to as "slow ventricular tachycardia" [2], often appears transiently during the first 48 hours after infarctions in any anatomical zone. It is usually benign and seldom requires treatment. AIVR is believed to develop as a result of increased automaticity of a ventricular focus and emerges in association with sinus slowing. Characteristic rates of

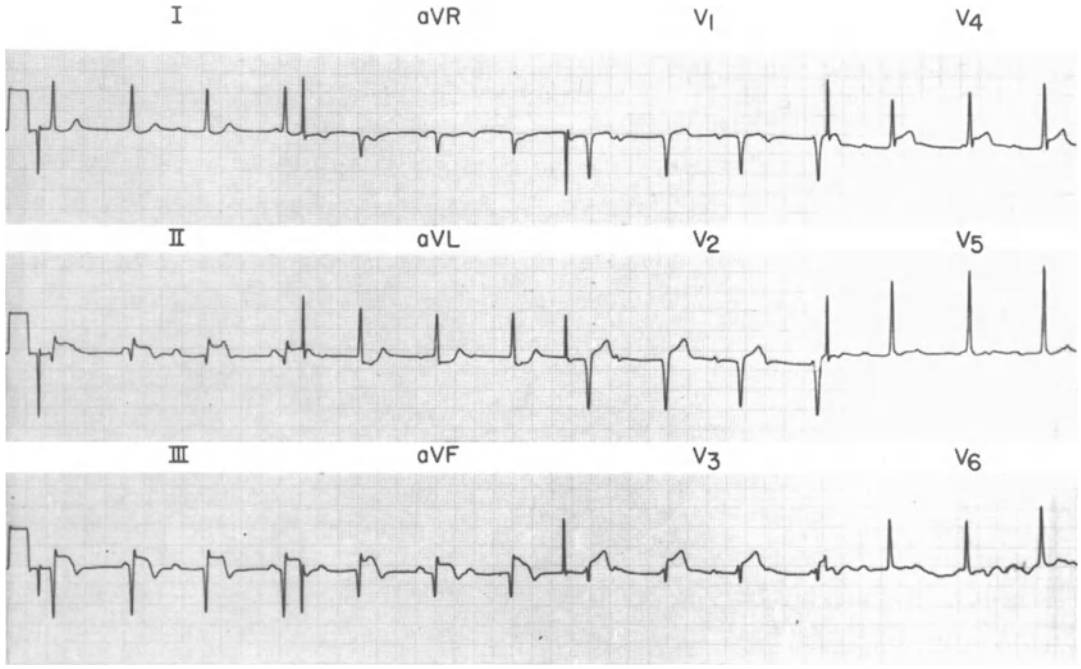

FIGURE 4–5. This patient with an acute inferior MI (and previous anterior MI) developed complete AV block and an escape rhythm with a QRS morphology similar to that seen during sinus rhythm. The escape rhythm rate and morphology shown in this 12-lead ECG in conjunction with the clinical setting are typical of nonparoxysmal AV junctional tachycardia.

AIVR are 80 to 100 bpm. If the patient suffers no hemodynamic compromise from loss of synchronized atrial contraction, the rhythm disorder may simply be observed. When hypotension or angina pectoris develops, therapy includes accelerating the sinus rate with atropine and, on rare occasions, suppressing ventricular ectopy with an antiarrhythmic agent. Atrial pacing may be used to control the heart rate more precisely and avoid possible sinus tachycardia in response to atropine administration.

1.5. NONPAROXYSMAL AV JUNCTIONAL TACHYCARDIA (FIGURE 4–5)

This rhythm disturbance is characterized by enhanced automaticity of the AV junction (see section 1.5. in chapter 4). In most cases, nonparoxysmal junctional tachycardia suggests a serious disorder such as acute inferoposterior MI, digitalis intoxication, or acute myocarditis, although it can be seen on an idiopathic basis [14].

2. Arrhythmias Due to Pump Failure/Excessive Sympathetic Stimulation

Rhythm disturbances in this category consist largely of *supraventricular tachyarrhythmias* [15–17]. Any circumstances that lead to excessive sympathetic stimulation may result in supraventricular tachyarrhythmias. A variety of conditions may increase sympathetic tone, including congestive heart failure, pain, fear, anxiety, fever, anemia, hypoxia, hypovolemia, pericarditis, pulmonary emboli, and the response to administration of atropine. When left ventricular (LV) failure occurs, LV end-diastolic pres-

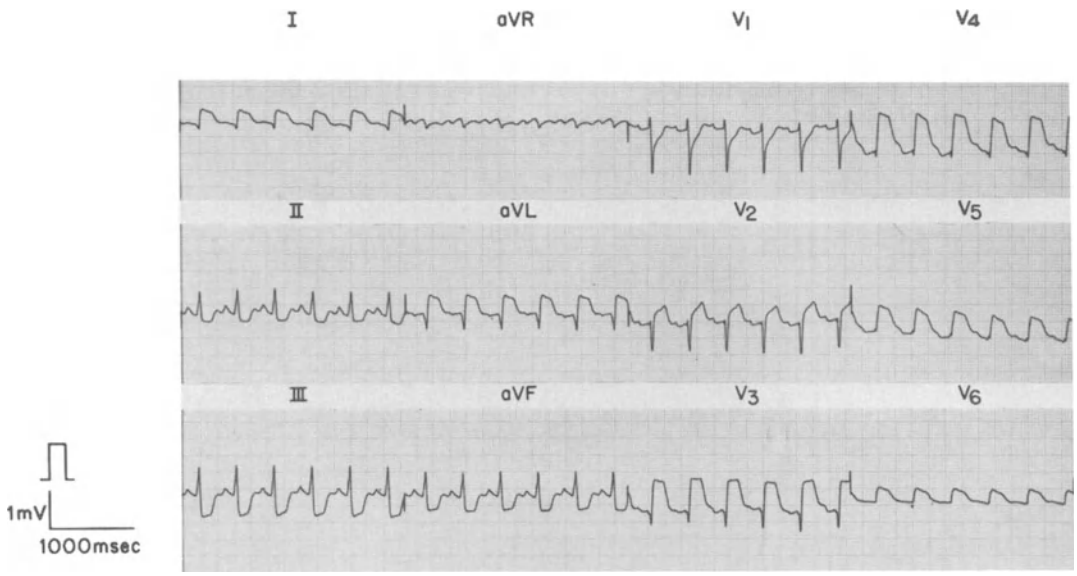

FIGURE 4–6. This patient presented to the emergency ward during the early phases of an extensive acute inferior MI. Such infarcts are often accompanied by sinus tachycardia, as shown in this 12-lead ECG.

sure rises, resulting in left atrial hypertension and distention. Ectopic atrial impulses develop and ultimately may degenerate into supraventricular tachyarrhythmias. Management of such rhythm disorders requires a diligent search for possible precipitating causes of LV failure and an aggressive attempt to control the ventricular response during acceleration of the atrial rate.

2.1. SINUS TACHYCARDIA (FIGURE 4–6)

Sinus tachycardia in the setting of acute MI may be caused by ongoing ischemia, intravascular volume depletion, pain, fever, pericarditis, or hypoxia [16]. It may also be a manifestation of LV dysfunction. Persistent sinus tachycardia is deleterious because of the increased oxygen demands imposed by acceleration of the heart rate. Refractory sinus tachycardia, despite anticongestive therapy in patients with no other precipitating causes, usually carries a poor prognosis, since it is associated with a large area of infarction.

Treatment of sinus tachycardia includes a search for and correction of precipitating factors. Fever should be suppressed with antipyretic agents such as acetylsalicylic acid, 650 mg orally every 4 to 6 hours, or acetaminophen in a similar dose. Anxiety and chest discomfort may be relieved with sedation and intravenous morphine. Careful examination of the patient and chest roentgenogram are necessary, to distinguish LV dysfunction and pulmonary venous hypertension from intravascular hypovolemia. Often it is necessary to measure LV filling pressure (mean pulmonary capillary wedge pressure) using a balloon flotation catheter. The mean pulmonary capillary wedge pressure should be kept in the range of 16 to 20 mm Hg by means of volume expanders, if necessary (see chapter 11). Anticongestive therapy is required if LV filling pressure exceeds 22 to 24 mm Hg. This consists of one or more of the following measures, as dictated by the clinical situation: diuresis, digitalization, intravenous pressor therapy, and/or afterload reduction.

2.2. ATRIAL FLUTTER OR FIBRILLATION

Atrial flutter or fibrillation occurs in about 10 to 15 per cent of patients during acute MI [15–17]. Atrial flutter and atrial fibrillation should be considered part of a spectrum of intraatrial

reentrant arrhythmias. A shift from atrial flutter to fibrillation takes place as the flutter wave breaks down into multiple smaller wavelets. In general, atrial flutter and fibrillation are seen under the same conditions as sinus tachycardia; however, pericarditis, atrial infarction, and pulmonary emboli in particular should be considered.

Acceleration of the ventricular rate with the onset of atrial flutter or fibrillation increases myocardial oxygen demands and shortens diastolic filling of the coronary arteries (figures 4–7 and 4–8). With loss of the contribution of atrial contraction to LV filling, cardiac output may decrease. As with sinus tachycardia, these rhythm disturbances usually have an identifiable underlying cause, may progress if not identified and treated correctly, and may cause further deterioration and enlargement of the infarct.

Atrial premature beats are a common premonitory feature. Although atrial premature beats themselves are rarely of hemodynamic consequence, they serve as markers that pathogenetic mechanisms inducing supraventricular tachyarrhythmias may be present. Atrial fibrillation is seen in a significantly higher proportion of patients with mild heart failure than those without heart failure [18] and is associated with an increased hospital mortality. This higher mortality rate may be explained in part by the fact that atrial fibrillation is more common in older patients and individuals with large infarcts.

Specific measures used to treat atrial flutter or fibrillation depend upon the degree of hemodynamic compromise present in association with the arrhythmia. The presence of atrial fibrillation and mild heart failure on initial presentation carries a high risk and requires prompt therapy. If hypotension develops or angina pectoris becomes more severe, urgent *electrical cardioversion* is required (see chapter 7). The patient should be sedated with diazepam (5 mg intravenously every 3 to 5 minutes until light anesthesia is achieved). A synchronized electrical discharge (cardioversion) is used. A low-energy shock is delivered initially, with subsequent shocks titrated to a higher energy level as required. The mean energy requirement for conversion of atrial fibrillation is about 100 watt-seconds, while that for atrial flutter is about 20 to 25 watt-seconds. Successful cardioversion may then be followed by an oral antiarrhythmic regimen such as quinidine sulfate, 200 to 300 mg every 6 hours. Digitalization is indicated for control of LV decompensation and for slowing of the ventricular response should the arrhythmia recur.

Antiarrhythmic therapy is the initial treatment of choice in patients who do not develop a rapid ventricular response and are hemodynamically compensated when the arrhythmia first occurs. Digitalis glycosides are given to slow the ventricular response and possibly convert the arrhythmia to sinus rhythm. Drugs most commonly used for this purpose include ouabain, 0.2 mg intravenously at first and then 0.1 mg every 30 minutes to a total dose of 0.8 mg, and digoxin, 0.25 mg intravenously followed by 0.25 mg every 4-8 hours to a total dose of 1.00 to 1.25 mg.

The calcium channel blocking agent *verapamil* has recently been approved as an intravenous antiarrhythmic agent for control of the ventricular response in supraventricular tachyarrhythmias. The initial or loading dose is 0.075 to 0.150 mg/kg (about 5 mg in the average adult). An additional 5 mg may be administered every 5 minutes for a total of 15 mg in an attempt to achieve rapid control of the ventricular response. A continuous intravenous infusion of 2.5 to 5.0 μg/kg/min may then be used. However, caution must be observed with the administration of verapamil, which may have a negative inotropic effect and may even block conduction in the AV node. In addition, verapamil may exacerbate latent or manifest sick sinus syndrome. The oral form of verapamil has recently been approved as an antianginal agent but is still considered investigational in the United States as an antiarrhythmic.

Beta-adrenergic blocking agents may have a similar salutary effect on the ventricular response by causing block of AV nodal conduction. However, one must be cautious when these drugs are given because of the presence of or precipitation of LV failure. As for patients treated with electrical cardioversion, those with atrial flutter or fibrillation who are hemodynamically stable initially should receive maintenance antiarrhythmic therapy with a drug such as quinidine.

Atrial flutter may often be terminated by

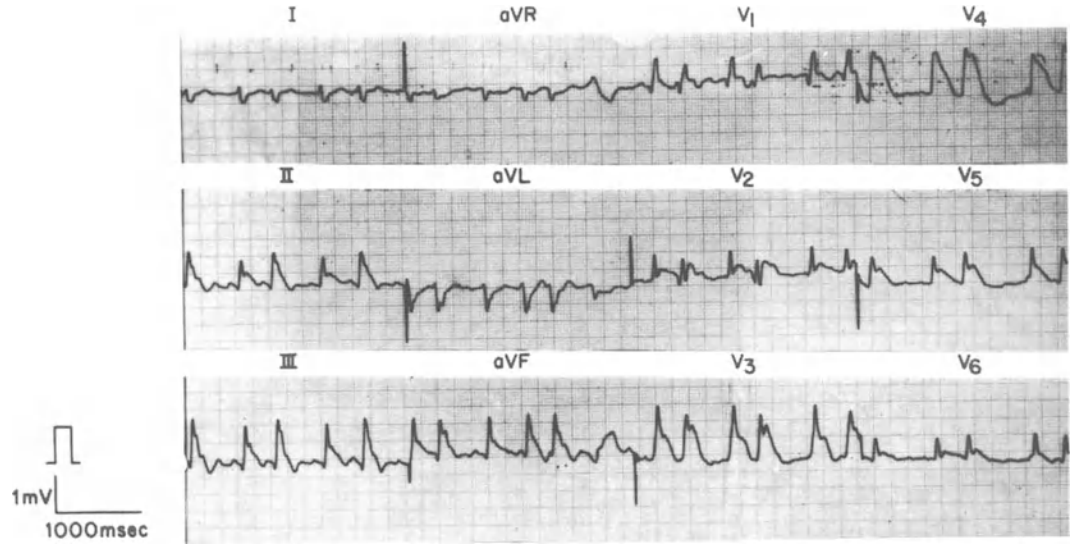

FIGURE 4–7. This individual sustained combined extensive infarction of the inferior and anterior walls of the left ventricle. Pulmonary edema and atrial fibrillation developed rapidly, followed shortly thereafter by the patient's demise.

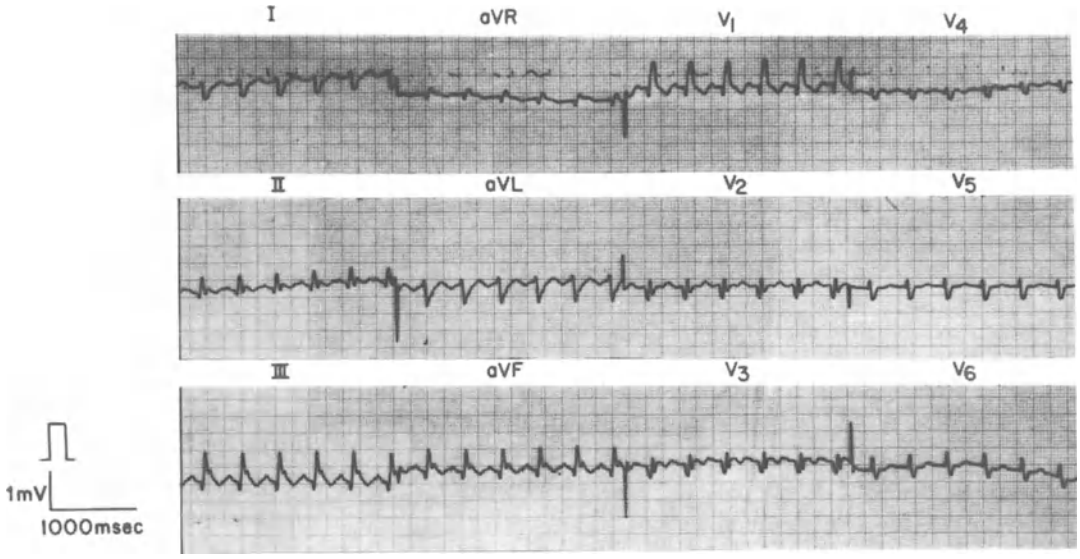

FIGURE 4–8. This patient developed an acute anterior MI complicated by right bundle branch block. Although the rhythm appears at first to be sinus, careful examination of the inferior leads reveals the characteristic sawtooth pattern of atrial flutter (with 2:1 AV conduction).

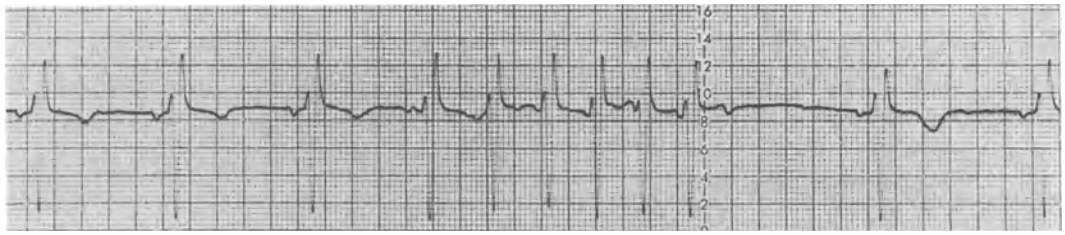

FIGURE 4–9. Paroxysmal supraventricular tachycardia (PSVT). Sinus rhythm is seen in the first four beats followed by a brief paroxysm of PSVT and then resumption of sinus rhythm. The narrow QRS morphology and similarity to the QRS pattern seen during sinus rhythm with interposed PSVT is characteristic of this disorder. The absence of clear P waves during PSVT suggests AV nodal reentry (see chapter 5).

bipolar rapid atrial pacing if the rate of pacing is rapid enough (up to 140 per cent of the spontaneous atrial rate), the duration of pacing is sufficient (10 to 30 sec), and the strength of the stimulus is adequate (5 to 20 ma) (see chapters 5 and 9). To achieve rapid atrial pacing, a standard bipolar pacing catheter is positioned in the right atrium under either electrocardiographic or fluoroscopic guidance, and a special external pulse generator capable of high rates of stimulation is used (chapter 9).

Finally, consideration should be given to the need for long-term maintenance oral antiarrhythmic therapy and anticoagulation if atrial flutter or fibrillation recur or if conditions likely to precipitate these arrhythmias persist. Although such a decision must be individualized, a conservative approach involving antiarrhythmic therapy, often in conjunction with anticoagulation for at least 3 to 6 months after the acute infarction, is appropriate.

2.3. PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA (PSVT) (FIGURE 4–9)

When the atrial mechanism is rapid (between 150 and 250 bpm), the diagnosis of paroxysmal supraventricular tachycardia (PSVT) should be entertained. This is an uncommon rhythm disturbance during acute MI; however, when it does occur, it is often both transient and recurrent [16]. LV failure and increased sympathetic tone may be precipitating factors, but this has not been firmly established.

Therapy for PSVT involves vagal maneuvers such as carotid sinus massage or the intravenous administration of verapamil, cardiac glycosides, or beta-adrenergic blocking agents. Vasopressors should be avoided in MI because of their potential for peripheral and coronary vasoconstriction. Synchronized electrical cardioversion and rapid atrial pacing are additional therapeutic options. To prevent recurrences, maintenance therapy with digitalis or beta blockers may be required.

Automatic atrial tachycardias are uncommon and suggest the presence of atrial infarction or digitalis intoxication. A characteristic atrial tachycardia encountered in digitalis intoxication is *paroxysmal atrial tachycardia (PAT) with block* (see figure 5–9 in chapter 5). This is a hybrid disorder that exhibits features of both atrial flutter and atrial tachycardia.

3. Bradyarrhythmias and Conduction Disturbances

Sinus bradycardia is especially frequent within the first hour of the infarction process (figure 4–10). It has been estimated to occur in 10 to 41 per cent of cases of acute infarction [19–22]. Sinus bradycardia is more common with inferior infarction and appears to occur more frequently in males with a first infarction [18]. Commonly, autonomic imbalance (particularly excessive parasympathetic activity) causes isolated sinus bradycardia or sinus bradycardia with hypotension. Cardiac vagal afferent receptors are more numerous in the inferoposterior than in the anterior portion of the left ventricle, resulting in efferent cholinergic stimulation of the heart in patients with inferoposterior MI. Experimental and clinical evidence suggests that vagal stimulation within the first few hours of infarction may enhance electrical stability in the

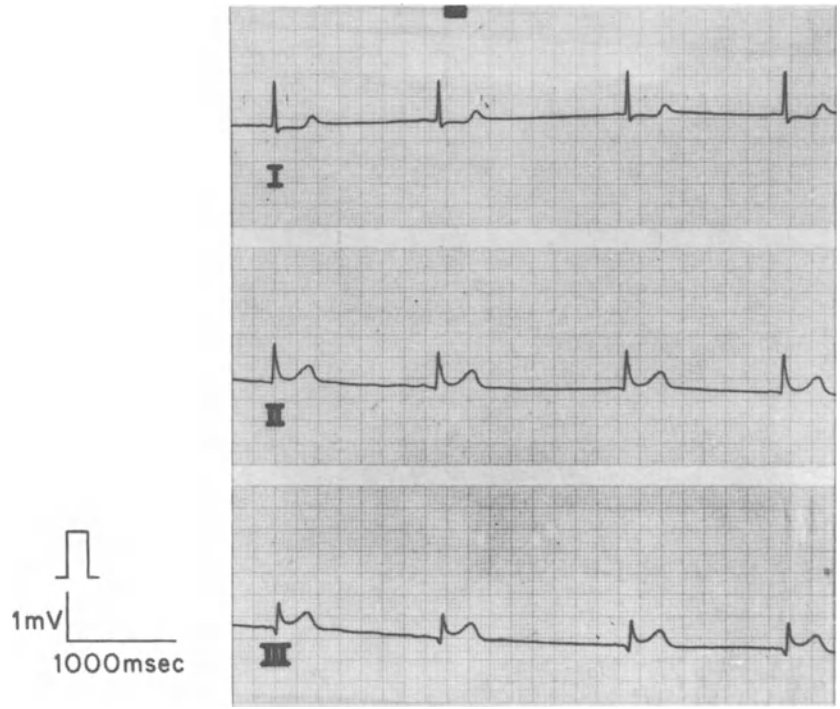

FIGURE 4–10. This patient presented during the early stage of an acute inferior MI (note ST-segment elevation in leads II and III) complicated by sinus bradycardia (rate = 35 bpm).

absence of concomitant hypotension. Sinus bradycardia may on occasion develop as a result of ischemia or infarction of the sinus node.

Management of sinus bradycardia depends upon the timing of the arrhythmia and whether hypotension accompanies the reduced heart rate. Isolated sinus bradycardia *without* hemodynamic compromise should simply be observed, since the prognosis is generally good and is not affected by atropine [18,23]. Sinus bradycardia associated with hypotension probably represents a form of the complex syndrome of *vasovagal* or *vasodepressor syncope*. Pain and medications commonly used in the management of MI, such as morphine and nitroglycerin, have been shown to cause vasovagal-type decreases in blood pressure and heart rate. Therefore, careful monitoring is advised in the routine administration of both morphine and nitroglycerin during acute MI.

When sinus bradycardia is associated with hemodynamic compromise, atropine should be administered intravenously, initially in small doses (0.3 mg). Sequential intravenous boluses may then be given to a total dose of 2.0 mg. If administered in the first 4 to 6 hours after infarction, atropine is likely to restore the heart rate and blood pressure to more acceptable levels, particularly if excessive parasympathetic tone is one of the pathogenetic mechanisms. Sinus bradycardia occurring more than 6 hours after the onset of chest pain is often transitory. It may be caused by sinus node dysfunction, infarction, or ischemia rather than vagal hyperactivity and tends not to be as responsive to atropine. If atropine is unsuccessful in abolishing bradycardia, a temporary transvenous pacemaker may be inserted into the right atrium or right ventricle to accelerate the heart rate. Newly developed multipurpose balloon flotation catheters have both atrial and ventricular pacing electrodes, which may be used to pace either chamber and provide AV sequential pacing (see chapter 9). Isoproterenol, which is a positive chronotropic and inotropic agent, should be avoided except under extreme circumstances, since this agent markedly augments myocardial oxygen demands.

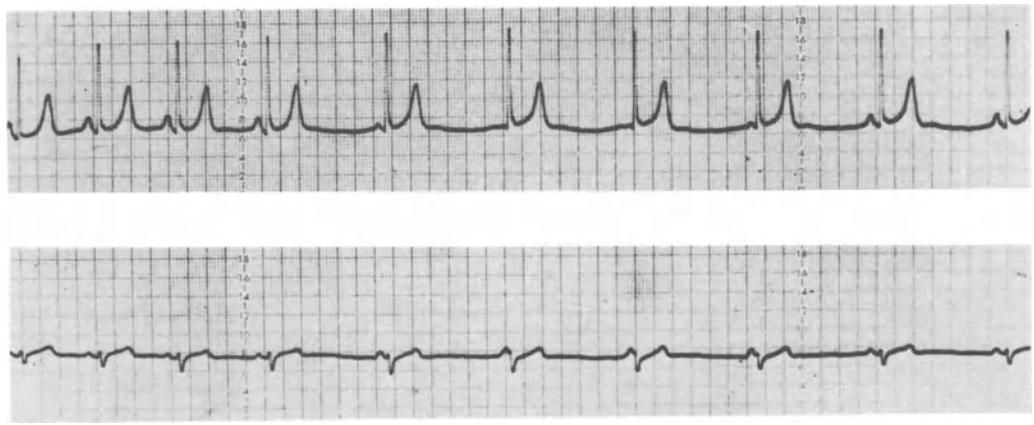

FIGURE 4–11. Junctional escape rhythm. This two-channel ECG recording shows sinus rhythm at the left followed by a period of sinus slowing and emergence of a junctional escape rhythm with a QRS morphology identical to that seen during sinus rhythm. When atrial activity speeds up (right-hand portion of strip), sinus rhythm resumes.

Junctional escape rhythms (figure 4–11) represent a normal escape mechanism when automaticity of the sinus node falls below that of the AV junction, as may occur in inferoposterior MI. The sinus rate should be increased with atropine or atrial pacing only if loss of the atrial "kick" causes hemodynamic compromise.

Since *atrioventricular and intraventricular conduction defects* and *pacemaker therapy* are broad topics worthy of detailed discussion, coverage of the electrophysiology of proximal and distal conduction defects and the indications for and techniques of temporary and permanent pacemaker therapy can be found in chapters 8 and 9.

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5. MANAGEMENT OF CARDIAC ARRHYTHMIAS NOT ASSOCIATED WITH ACUTE MYOCARDIAL INFARCTION

1. General Considerations

Modern *coronary care units*, particularly those in large university medical centers, usually serve as *cardiac intensive care units*. Of course, patients with acute myocardial infarction (MI) are admitted to such units, but so are patients with a variety of cardiac arrhythmias that are not the result of acute MI. Clinicians caring for patients in cardiac intensive care units *must* be prepared to deal with disorders of sinus node function, supraventricular arrhythmias (including those associated with preexcitation syndromes), and recurrent ventricular arrhythmias. Often the patient has been resuscitated from one or more bouts of sudden cardiac death; to prevent recurrences, a therapeutic program of antiarrhythmic drugs at times combined with sophisticated pacemaker and cardiac surgical techniques may be needed.

In this chapter, we will review noninfarction-related arrhythmias and describe the available therapeutic options. A detailed discussion of antiarrhythmic drugs can be found in Chapter 6, while techniques of cardioversion/defibrillation and pacemaker therapy are described in Chapters 7 and 9, respectively.

The authors wish to acknowledge HealthScan Inc., Upper Montclair, New Jersey, for allowing us to borrow both text and illustrations from Antman EM: *Supraventricular arrhythmias*. HealthScan Inc., 1981, for inclusion in this chapter.

2. Mechanisms of Arrhythmia

Hoffman and Rosen [1] have recently summarized the cellular electrophysiological mechanisms involved in cardiac rhythm disorders (table 5–1). Although a working knowledge of these basic electrophysiological concepts is important for understanding arrhythmias, it is often impossible to identify which specific cellular mechanism(s) is (are) responsible for a given derangement of rhythm in a particular clinical setting.

2.1. ABNORMAL IMPULSE GENERATION

This refers to accelerated depolarization during electrical diastole. It may result from *normal automatic mechanisms* (figure 5–1*A*) arising from alterations in sympathetic tone or in circulating catecholamine levels or from metabolic or acid-base derangements; *abnormal automatic mechanisms* (figure 5–1*B*), as might result from ischemia, infarction, or diseased myocardium occurring in the setting of chronic pressure and/or volume overload; or *triggered activity* (figure 5–1*C*). Triggered activity refers to repetitive activity arising from afterdepolarizations. It differs from spontaneous rhythmic activity in that the first beat or impulse must be initiated by an external drive stimulus (e.g., pacemaker). In the electrophysiology laboratory, experimental conditions that have resulted in triggered activity include hypokalemia, high concentrations of catecholamines, and digitalis intoxication. The precise role that triggered

TABLE 5–1. Mechanisms for arrhythmias

Abnormal impulse generation	Abnormal impulse conduction	Simultaneous abnormalities of impulse generation and conduction
A. Normal automatic mechanism 1. Abnormal rate a. Tachycardia b. Bradycardia 2. Abnormal rhythm a. Premature impulses b. Delayed impulses c. Absent impulses B. Abnormal automatic mechanism 1. Phase 4 depolarization at low membrane potential 2. Oscillatory depolarizations at low membrane potential preceding upstroke C. Triggered activity 1. Early afterdepolarizations 2. Delayed afterdepolarizations 3. Oscillatory depolarizations at low membrane potentials following action potential upstroke	A. Slowing and block 1. Sinoatrial block 2. Atrioventricular block 3. His bundle block 4. Bundle branch block B. Unidirectional block and reentry 1. Random reentry a. Atrial muscle b. Ventricular muscle 2. Ordered reentry a. Sinoatrial node and junction b. AV node and junction c. His-Purkinje system d. Purkinje fiber-muscle junction e. Abnormal AV connection (WPW) 3. Summation and inhibition C. Conduction block and reflection	A. Phase 4 depolarization and impaired conduction 1. Specialized cardiac fibers B. Parasystole

From Hoffman BF, Rosen MR: Cellular mechanisms for cardiac arrhythmias. *Circ Res* 49:2, 1981, by permission of the American Heart Association, Inc.

activity plays in arrhythmias encountered clinically is still not completely understood [2].

2.2. ABNORMAL IMPULSE CONDUCTION

This may occur as a result of *slowing and block, unidirectional block and reentry*, or *conduction block and reflection*. Reentry requires slowed conduction, an area of unidirectional impulse block, and an appropriate functional electrophysiological substrate (e.g., atrioventricular [AV] bypass tract in Wolff-Parkinson-White syndrome or longitudinal dissociation within the AV node). The concepts of reentry, summation and inhibition, and reflection are schematically summarized in figure 5–1*D* and 5–1*E*.

2.3. COMBINED ABNORMALITIES OF IMPULSE GENERATION AND CONDUCTION

Such abnormalities may interact to yield unusual examples of arrhythmias, such as parasystole (which demonstrates automatic firing along with entrance and exit block) (figure 5–1*F*).

3. *Supraventricular Arrhythmias*

3.1. NONCARDIAC CAUSES OF SUPRAVENTRICULAR ARRHYTHMIAS

3.1.1. Acid-base Imbalance [3–5]. Arrhythmias may be caused by a number of noncardiac conditions. Acute respiratory failure (e.g., due to decompensation from chronic pulmonary disease) can precipitate an array of supraventricular rhythm disturbances. Although supraventricular arrhythmias such as atrial flutter or fibrillation are more common than ventricular arrhythmias in acute respiratory failure, the latter carry a more ominous prognosis. Proper treatment is therefore essential and consists of correcting the hypoxemia and acidosis.

Improper use of mechanical respirators may

TABLE 5–2. Differential diagnosis of multifocal atrial tachycardia (MAT)

Mechanism	Atrial rate (bpm)	P-P interval	P-wave morphology	Ventricular response
Atrial rate < MAT				
Wandering atrial pacemaker	≤100	Random variation	Random variation (P wave may be absent if AV junctional rhythm arises)	1:1
Sinus arrhythmia	≤100	Phasic change with respiration (may not correlate with respiration in elderly patients)	Unvarying	1:1
Atrial rate > MAT				
Sinus tachycardia with multifocal atrial premature beats (APBs)	>100	Regular with short cycles caused by APBs	Constant morphology except for APBs	1:1 (except for nonconducted early APBs)
Atrial tachycardia with block	130 to 250	Ventriculophasic variation may result in slight irregularities	Constant morphology but different from sinus; isoelectric baseline	Usually 1:1
Atrial flutter	250 to 400	Regular	Regular "sawtooth" morphology	Usually 2:1
Atrial fibrillation	350	Random variation	Indistinct morphology of atrial activity; undulatory baseline	Variable; may be as high as 190/min in untreated cases
MAT	>100	Random variation	Random variation of at least 3 separate P-wave morphologies; isoelectric baseline	Usually 1:1 (except when rate increases and/or AV block occurs)

lead to hypoxemia combined with respiratory acidosis or alkalosis and, ultimately, rhythm disturbances. By adjusting the ventilator settings, one can achieve a more normal carbon dioxide tension (PCO_2) and pH of the blood to prevent this complication.

Another noncardiac cause of supraventricular arrhythmias is metabolic alkalosis due to excessive use of diuretics, infusion of lactated Ringer's solution, citrated blood (from blood bank storage), sodium bicarbonate therapy, or nasogastric suction. Hypokalemia and hypomagnesemia — frequently concurrent derangements — may result from diabetic coma, alcoholic cirrhosis, congestive heart failure, intestinal malabsorption, chronic diarrhea, the postoperative state, acute tubular necrosis, hypoparathyroidism, primary hyperaldosteronism, or acute pancreatitis.

3.1.2. Multifocal Atrial Tachycardia (MAT) [6]. This common supraventricular rhythm disturbance is often seen in elderly, severely ill patients with ventilatory and metabolic derangements. The atrial rate is greater than 100 beats per minute (bpm). There are well-organized, discrete P waves having at least three distinct morphologies; irregular variations are seen in the P-P interval, and an isoelectric baseline is present between the P waves. Since MAT is associated with a high mortality rate, it is important to distinguish this arrhythmia from other supraventricular rhythm disturbances.

Table 5–2 gives the differential diagnosis of

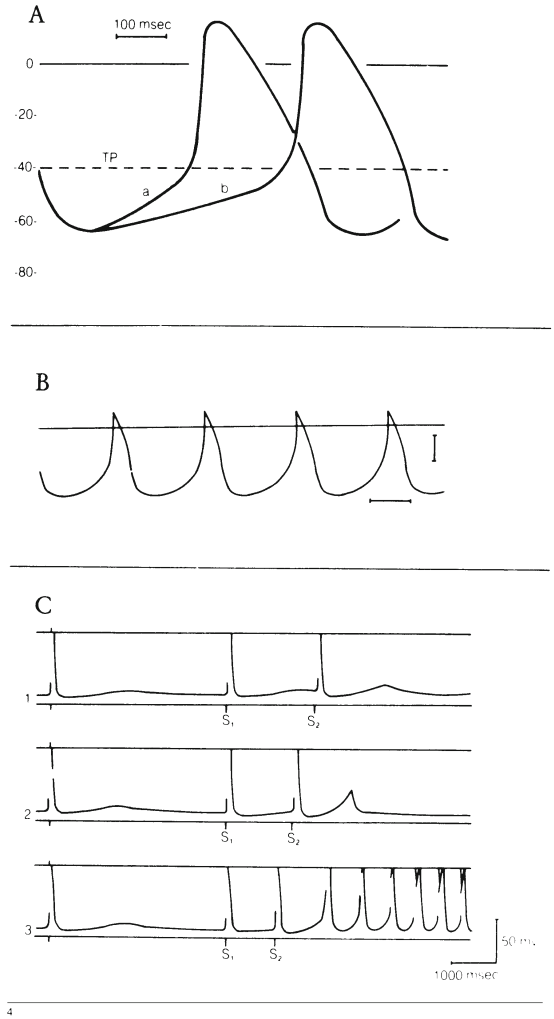


FIGURE 5–1. *A*, Normal automatic mechanism. An increase in rate caused by an increase in the slope of phase 4 from b to a and thus a decrease in the time required for the transmembrane potential to reach the threshold potential (TP) can be seen. (Modified from Hoffman BF, Cranefield PF: *Electrophysiology of the heart.* Mt Kisco, New York, Futura Publishing Co, 1976, p 109.)

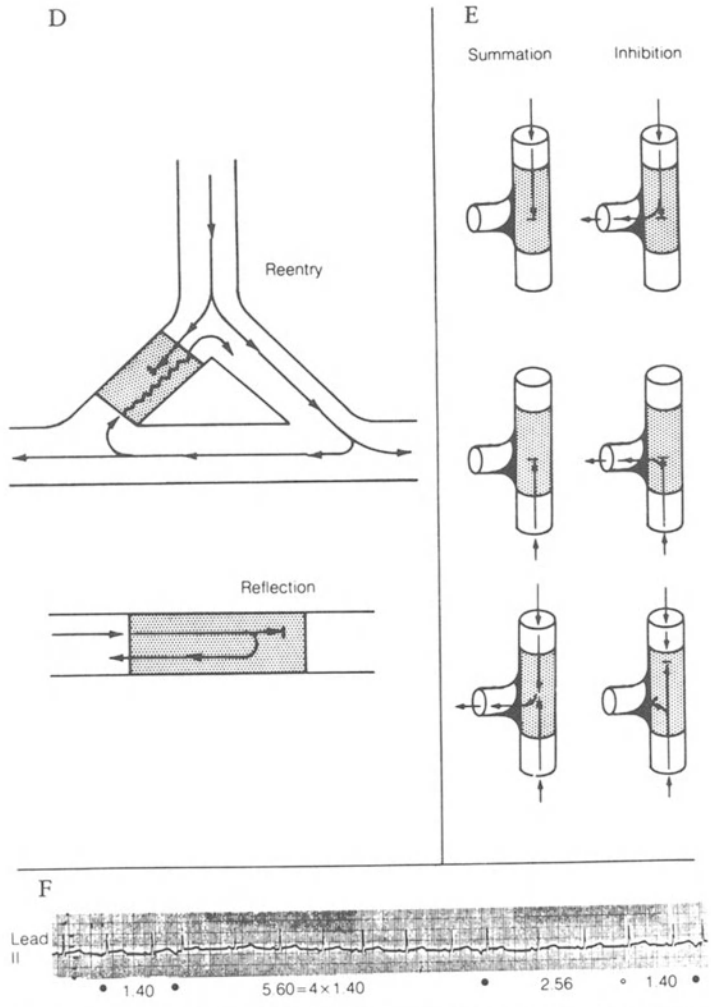
B, Abnormal automatic mechanism recorded from left atrial fiber in isolated preparation from failed canine heart. The left atrium was markedly dilated, and atrial cell resting potentials were generally very low. (From Mandel WJ: *Cardiac arrhythmias.* Philadelphia, JB Lippincott Co, 1980, p 71.)

C, Afterdepolarizations and triggered activity in canine coronary sinus cell. The fiber is stimulated at a cycle length of 4000 msec for 10 cycles and then stimulated prematurely; in each panel, the last cycle of the basic drive train is shown followed by a premature stimulus (S_2), delivered at increasing maturity from 1 to 3.

(*1*) S_1–S_2 =2,000 msec. The afterdepolarization is 11 mv in amplitude and occurs long after the premature response.

(*2*) S_1–S_2 = 1,400 msec. The afterdepolarization is 31 mv in amplitude and peaks relatively soon after the premature response.

(*3*) S_1–S_2 = 1,000 msec. Triggered activity arises from the peak of the afterdepolarization and is sustained. (From Wit SL, Cranefield PF: Triggered and automatic activity in the canine coronary sinus. *Circ Res* 41:435, 1977, by permission of the American Heart Association, Inc.)



D, Models of reentry as described by Schmitt and Erlanger. Top diagram shows a loop of cardiac fibers that could represent either a terminal branch of a Purkinje fiber ending on ventricular muscle or a loop of the Purkinje syncytium. In this case, one-way block and slow conduction permit reentry. Bottom diagram shows a linear strand of cardiac muscle with a depolarized zone in cross section. One-way block occurs in this zone, allowing the propagating impulse to be reflected toward the direction from which it came.

E, Summation and inhibition of impulses. In summation, only when impulses arrive at the T junction from both branches simultaneously is the impulse propagated out the side branch. Impulses arriving from either branch alone are too weak to pass out the side branch. In inhibition, impulses arriving from either branch at different times will be propagated out the side branch. When impulses arrive from both branches at once, propagation to the side branch fails. (*D* and *E* from Bigger JT: Mechanisms and diagnosis of arrhythmias. In: *Heart disease*. Braunwald E (ed). Philadelphia, WB Saunders Co, 1980, p 643.)

F, Intermittent atrial parasystole. The regular sequence of upright P waves in lead II is on six occasions disturbed by P waves of different shapes. On four occasions, this is due to an atrial parasystole with a common denominator interval of 1.4 sec (dark circles). The parasystolic focus is protected from sinus impulses but is reset by ectopic atrial impulse (open circle). (From Pick A, Langendorf R: *Interpretation of complex arrhythmias*. Philadelphia, Lea and Febiger, 1979, p 66.)

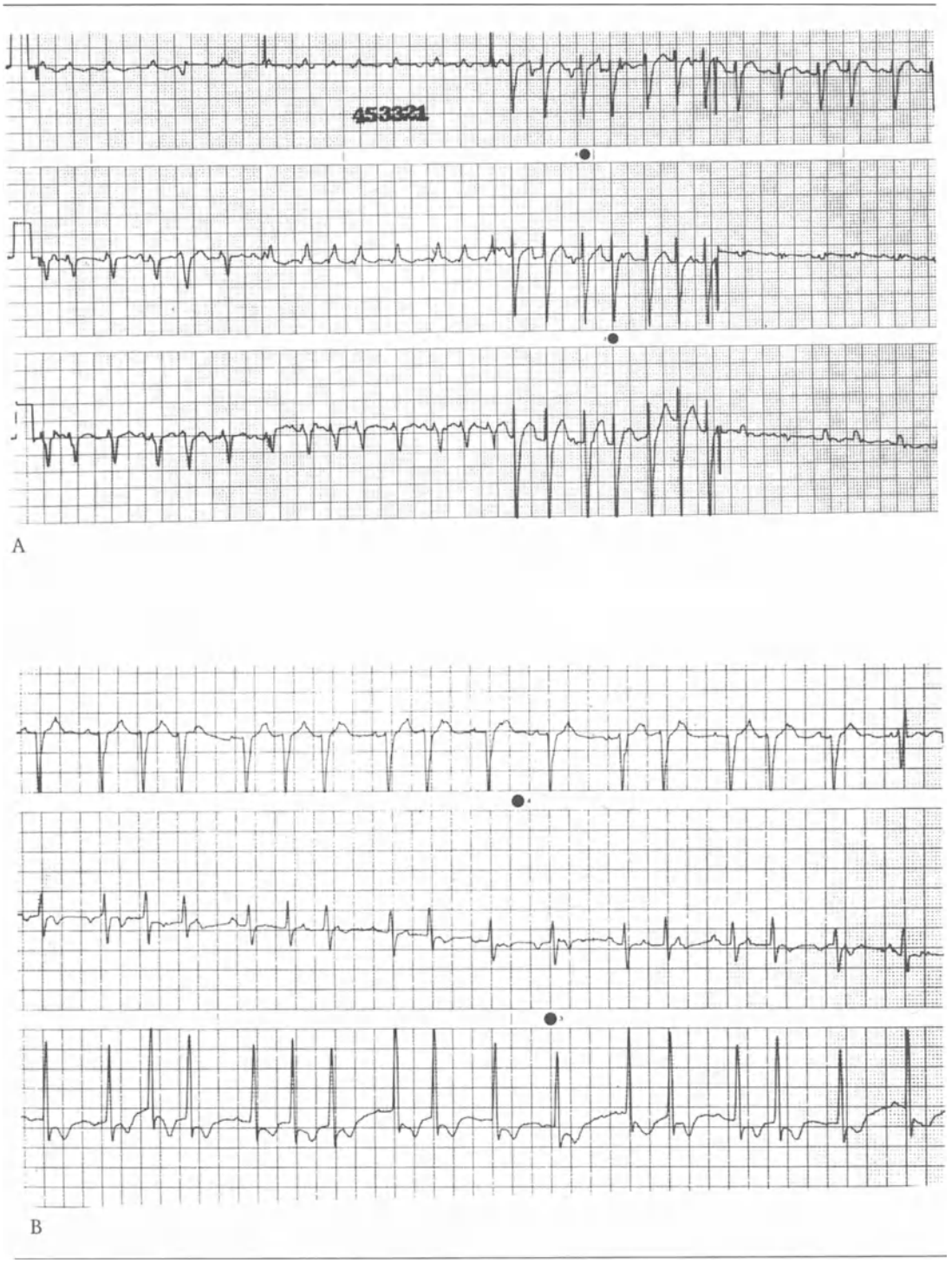


FIGURE 5–2. *A*, Multifocal atrial tachycardia (MAT) seen on 12-lead ECG. *B*, MAT with block seen in simultaneous recording of leads V_1, II, and V_5.

MAT. Most critical is the differentiation between MAT and atrial fibrillation. The indistinct morphology of atrial activity and undulatory baseline seen with atrial fibrillation stand in contrast to the discrete P waves and isoelectric baseline seen in MAT (figure 5–2*A*). Although carotid sinus pressure can be used transiently to decrease the rate of atrial activity in MAT, this rate quickly returns to control levels upon release of pressure.

Maintenance digitalis therapy may on occasion be well tolerated; however, incremental doses of digitalis given to decrease the ventricular rate for presumed atrial fibrillation often cause additional serious rhythm disturbances, such as MAT with block (figure 5–2*B*), AV junctional escape rhythm, and high-grade ventricular arrhythmias. On the other hand, digitalis therapy is acceptable in congestive heart failure associated with MAT. Quinidine therapy may be useful for controlling the degree of atrial ectopy seen in MAT.

3.2. SINUS RHYTHM AND ITS VARIANTS

3.2.1. Physiologic Variations in Atrial Rate [7]. *Sinus tachycardia*, arbitrarily defined as a sinus rate greater than 100 bpm, is usually the result of physiologic stress — exertion, fever, thyrotoxicosis, anemia, or elevated levels of circulating catecholamines. No attempt should be made to slow the atrial rate in sinus tachycardia. Instead, a thorough search for the precipitating physiologic event(s) should be undertaken and treatment initiated, if appropriate.

Sinus bradycardia is arbitrarily defined as a sinus mechanism producing less than 50 to 60 bpm. During sleep or in young, well-conditioned athletes, the heart rate may normally slow to as low as 30 to 40 bpm with pauses in sinus activity of several seconds. Thus, one should not consider a specific sinus rate abnormal without first evaluating the patient's age, the extent of heart disease, and the hemodynamic response to the reduced heart rate.

3.2.2. Changes in Pacemaker Site. Sinus arrhythmia is a slightly irregular sinus rhythm in which P-P intervals vary by 10 per cent or more. The arrhythmia is usually phasic, increasing in rate during inspiration and decreasing during expiration. Unless AV block is present, each P wave has a normal duration and is followed, after a normal P-R interval, by a QRS complex [7].

Relocation of the primary pacemaking site far from the sinoatrial (SA) node may cause marked alterations in the P wave and hence *ectopic atrial rhythms* [8]. Two such disturbances widely discussed in the classic electrocardiographic literature are *left atrial rhythm* (the "dome-and-dart" P-wave configuration in lead V_1 and negative P waves in leads I and V_6) and *coronary sinus rhythm* (inverted P waves in leads II, III, and aV_f but a normal P-R interval). However, since discrete lesions in the interatrial tracts can significantly alter P-wave morphology on the surface ECG, making precise diagnosis of the pacemaker focus difficult, *ectopic atrial rhythm* is a more suitable term for such changes.

3.2.3. Conduction Block. When regular sinus rhythm is interrupted by pauses devoid of P-wave activity, the possibility of *sinoatrial block* should be considered. When the P-P interval is suddenly prolonged, and the length of the pause is a multiple of the basic sinus cycle length, type II second-degree SA block can be diagnosed by analogy to type II AV block (see Chapter 8). Progressive shortening of the P-P intervals followed by a long pause constitutes type I SA block, analogous to Mobitz I or Wenckebach type AV block. In contrast to SA exit block, *sinus arrest* occurs when the length of the pauses is *not* some multiple of the basic cycle length.

3.2.4. Sick Sinus Syndrome [9–11]. The term sick sinus syndrome is used to characterize a defect in the elaboration or conduction of sinus impulses. This may be recognized on the ECG as an unstable P-wave focus, frequent ectopic atrial beats, and extremely variable P-P intervals. An array of atrial arrhythmias and abnormalities may be seen in this syndrome, including (a) sinus arrest and atrial standstill (an example of which is seen in figure 5–3); (b) sinoatrial block; (c) failure to restore sinus rhythm promptly after electroconversion of atrial arrhythmias; (d) marked sinus bradycardia, with or without atrial premature systoles; (e) chronic atrial fibrillation with a slow ventricular rate that is not drug-induced; (f) sinus bradycardia with recurring paroxysmal atrial fibrillation; (g) the bradycardia/tachycardia syndrome; and (h) the tachycardia/bradycardia syndrome [11].

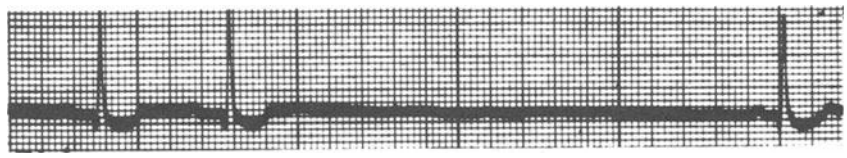


FIGURE 5–3. Sinus arrest and atrial standstill shown in lead II. (From Antman EM, Young E: Interpretation of P wave abnormalities on the electrocardiogram. *Pract Cardiol*, December, 1978, p 113.)

More than one arrhythmia may be observed at different times in the same patient.

Patients with the sick sinus syndrome may present initially with sinus bradycardia and then progress at variable rates to one of the more severe forms of sinus node dysfunction listed above [9]. Symptomatology usually consists of lightheadedness (with or without palpitations) or frank syncope due to cerebral hypoperfusion.

The sick sinus syndrome does not have a single etiology but rather represents a group of conditions in which the ECG indicates sinus node dysfunction [10]. Correct diagnosis requires careful correlation of ECG findings with symptomatology. Ambulatory monitoring is helpful in detecting infrequent instances of sinus node dysfunction. Additional diagnostic techniques include assessment of autonomic tone and programed electrical stimulation of the atrium to measure sinus node recovery time and SA conduction time (table 5–3).

When symptoms are severe, therapy consists of implantation of a permanent pacemaker [10]. Since a significant number of patients with sinus node dysfunction have abnormalities of AV conduction, use of atrial pacing may be precluded. Although pacemakers have provided dramatic relief of symptoms in patients who experience profound pauses in sinus activity, antiarrhythmic therapy should be considered for episodic atrial tachyarrhythmias, which cause overdrive suppression of the sinus node and result in the tachycardia/bradycardia sequence so often seen in these patients.

3.2.5. Sinoventricular Rhythm. Cells of the specialized atrial internodal tracts are relatively resistant to increases in extracellular potassium concentration to levels that inhibit depolarization of ordinary atrial cells [7]. Action potential generation persists in these specialized portions of the atrial tissue when hyperkalemia has rendered the remainder of the atrium quiescent. Sinus node impulses are delivered via these intact specialized atrial conduction tracts to the AV node. Because most of the atrial tissue is electrically silent in this situation, no P waves are seen in this unusual form of sinus rhythm, known as *sinoventricular rhythm*. The heart rate can be altered by any maneuver that ordinarily increases or decreases the normal sinus rate. A useful technique for differentiating sinoventricular rhythm from idioventricular rhythm is the intravenous administration of sodium bicarbonate. Emergence of a P wave before each QRS complex (at an unaltered rate) suggests retrospectively that the rhythm was sinoventricular (figure 5–4*A* and 4*B*).

4. Atrial Premature Beats and Atrial Parasystole

4.1. ATRIAL PREMATURE BEATS (APBS) [12,13]

Ectopic depolarizations in the atria occur frequently in individuals both with and without heart disease. On the ECG the P-wave morphology differs from that of the sinus P wave; this P wave arrives earlier than expected in regular sinus rhythm and is usually followed by a lengthened P-R interval. APBs may occur at any time during the atrial cycle and on occasion are incorporated in the T wave of the preceding ventricular complex. When the effective refractory period of the atrium is prolonged (beyond 160 to 200 msec), ectopic depolarizations may not capture a sufficient portion of the atrium to register a P wave on the ECG. Finally, APBs early in the cycle may find the AV node refractory. If such early-cycle APBs are not accurately identified, a mistaken diagnosis of sinus arrest or SA block may be made.

TABLE 5-3. Electrophysiological evaluation of patients with sinus node dysfunction

A. Clinical tests for evaluation of sinus node function

Test	Criteria of abnormal response	Comments
Atropine (0.04 mg/kg IV)	<20 to 50% increase in sinus rate or increase to <90 bpm	Relatively easy, safe test; helpful only if positive
Isoproterenol (1 to 3 μg/min IV)	<25% increase in sinus rate	Helpful if positive; may be dangerous in ventricular arrhythmia and ischemic heart disease
Sinus node recovery time	(i) SNRT > 1400 to 1600 msec or > 1.3 (SCL) + 101 (ii) $SNRT_c$ > 525 to 550 msec (Note: $SNRT_c$ = SNRT–SCL) (iii) SNRT/SCL > 130 to 150% (iv) TRT > 5 sec or 4 to 6 beats (Note: TRT = return to baseline SCL)	Highly specific, moderately sensitive invasive procedure
Sinoatrial conduction time	SACT > 120 msec	Moderately specific; highly sensitive invasive procedure
Ambulatory electrocardiographic monitoring	Sinus bradycardia, sinus arrest, sinoatrial block, brady/tachyarrhythmias	Excellent test; can correlate symptoms with arrhythmias
Treadmill testing	<90% of predicted maximum heart rate for age and sex; development of exercise-induced sinus bradycardia	Difficult to assess in the elderly and debilitated patient
Intrinsic heart rate	>10% decrease in age predicted rate; IHR = 117.2 bpm − (0.53 × age)	Wide experience unavailable

B. Chronotropic response from common cardiac drugs

Drug	Normal	Sinus node dysfunction
Atropine (0.04 mg/kg intravenously)	>20 to 50% ↑ in SCL	<20 to 50% ↑ in SCL
Isoproterenol (3 μg/min intravenously)	>25% ↑ in SCL	<25% ↑ in SCL
Digitalis (therapeutic dose)	<20% ↓ in SCL	↓ SCL, ↑ SEB, can ↑ ER
Propranolol (0.05 mg/kg intravenously)	<20% ↓ in SCL	Marked ↓ in SCL and ER*
Quinidine sulfate (0.2 to 0.3 gm orally)	Mild ↓ in SCL	Slight ↓ in SCL, marked ↓ in ER

$SNRT_c$ = sinus node recovery time, corrected; SNRT = observed sinus node recovery time; SACT = sinoatrial conduction time; IHR = intrinsic heart rate; TRT = total recovery time; SND = sinus node dysfunction, SCL = sinus cycle length, SEB = sinus exit block; ER = ectopic atrial pacemaker rate; * = contraindicated.

Modified from Talano JV et al: Sinus node dysfunction: an overview with emphasis on autonomic and pharmacologic considerations, *Am J Med* 64:773, 1978; Josephson ME, Seides SF: *Clinical cardiac electrophysiology: techniques and interpretations*. Philadelphia, Lea and Febiger, 1979, pp 61–78.

4.2. ATRIAL PARASYSTOLE [12,13]

A parasystolic focus fires automatically in an independent fashion from the dominant pacemaker of the heart. Interectopic intervals can be demonstrated to be a multiple of the shortest measured interectopic interval or can all be reduced to a "common-denominator" interval, which represents the intrinsic cycle length of the

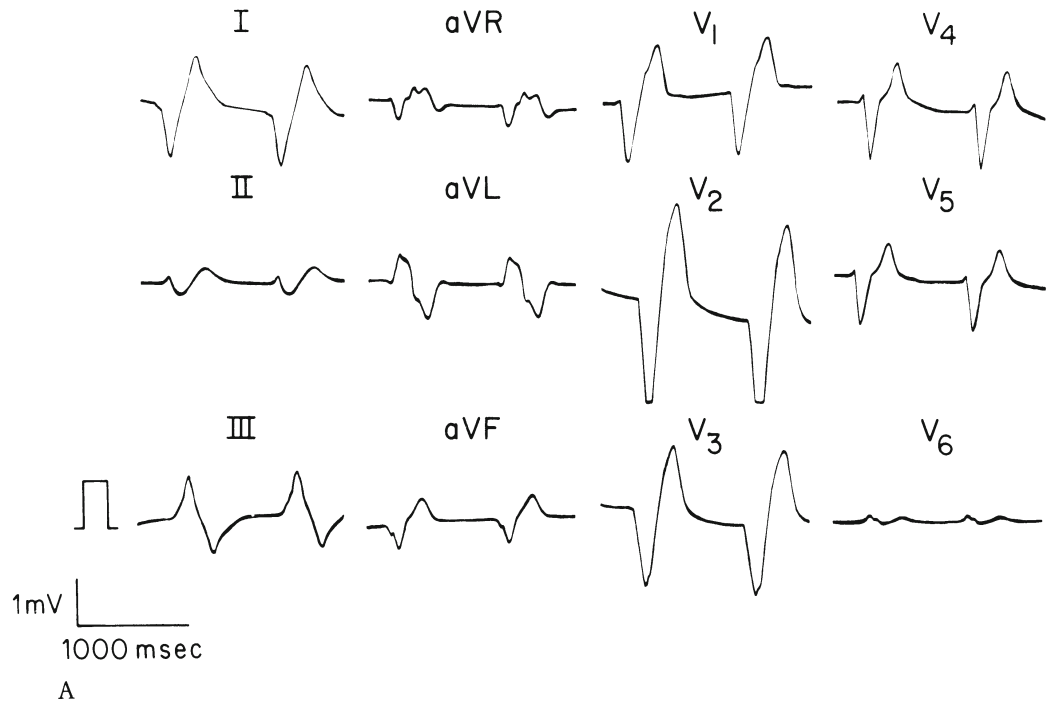


FIGURE 5–4. *A*, Regular rhythm with wide QRS complexes and peaked T waves typical of hyperkalemia (K^+ = 7.1). *B*, After administration of intravenous glucose, insulin, and sodium bicarbonate, the QRS complexes are narrower, appear at essentially the same rate as in panel *A*, and are now preceded by low-amplitude atrial deflections (with first-degree AV block). This sequence of tracings allows one to make the diagnosis of sinoventricular rhythm in panel *A*.

parasystolic focus. Parasystolic foci exhibit "entrance block," which protects them from invasion by impulses in other portions of the myocardium. Emergence of parasystolic beats is prevented by "exit block" out of the ectopic focus. When such exit block breaks down, parasystolic beats appear with inconstant or variable coupling intervals relative to the intrinsic sinus beats.

Atrial parasystole is a rare arrhythmia but can occur during sinus rhythm. It has also been reported during AV junctional rhythm. Parasystolic firing may be of no clinical significance to the patient, often exists for years, and may be relatively resistant to antiarrhythmic therapy.

5. Paroxysmal Supraventricular Tachycardia (PSVT) [14–19]

The diagnosis of PSVT should be entertained when the atrial mechanism is rapid, between 150 and 250 bpm. Intracardiac recording techniques have improved our understanding of the pathophysiological mechanisms responsible for PSVT. For clinical purposes the two basic mechanisms are considered to be *reentry* and *enhanced automaticity* [15] (table 5–4). When our understanding, of *triggered automaticity* improves, this classification may be revised.

5.1. REENTRY

Reentrant rhythms involve a complex mechanism, the substrate of which is electrophysiological inhomogeneity of adjacent cardiac tissue.

5.1.1. AV Nodal Reentrant Tachycardias. These account for about 60 per cent of cases of PSVT. Functionally distinct "dual" AV nodal pathways can be demonstrated in the electrophysiology laboratory in about three-fourths of patients with this type of tachycardia. The alpha pathway conducts impulses more slowly, but its refractory period is shorter than that of the beta pathway, which has more rapid conduction. APBs that block in the beta pathway will be conducted slowly in the antegrade direction down the alpha pathway. This renders the beta pathway available for retrograde conduction, thus establishing the appropriate substrate for reentrant tachycardia. Either an atrial or a ventricular premature beat can initiate AV nodal reentrant tachycardias (figure 5–5) [14].

Rarely, a patient with AV nodal reentrant tachycardia will have an alpha pathway that has a longer refractory period than that of the beta pathway during antegrade stimulation. Patients with this unusual characteristic manifest an uncommon and frequently incessant form of AV nodal reentrant supraventricular tachycardia that is more difficult to control.

Vagal maneuvers such as carotid sinus pressure or application of ice water to the face will usually slow and abruptly terminate AV nodal reentrant tachycardia, as will digitalis, propranolol, verapamil, procainamide, or edrophonium (Tensilon) — all agents that slow conduction and prolong the effective refractory period of AV nodal conduction tissue.

Approximately 15 to 30 per cent of patients with PSVT utilize a concealed accessory tract capable of conduction only in the retrograde direction. Most episodes of PSVT at rates exceeding 200 bpm involve a concealed bypass tract — a helpful clinical finding. Another indication of *concealed bypass tract reentry* is the effect of bundle branch block on the tachycardia cycle length [14]. As shown in the left panel of figure 5–6, the tachycardia involves antegrade invasion of a left sided bypass pathway. The right panel of figure 5–6 depicts the situation when left bundle branch block develops; the impulse continues to conduct normally down the right bundle branch and then, more slowly, conducts retrograde through the ventricular myocardium, eventually arriving at the ventricular end of a left-sided bypass tract. Thus, although the tachycardia may continue after a bundle branch block develops, the cycle length will decrease because of delayed conduction in the ventricular myocardium. This occurs only when bundle branch block occurs on the same side as the concealed bypass tract.

The response to vagal maneuvers varies in this form of PSVT, and the effects of pharmacological agents are somewhat unpredictable, since most of the drugs commonly available have different actions on the bypass tract and AV node. Propranolol and verapamil, which may cause complete conduction block in the AV node, can interrupt a paroxysm of supraventricular tachycardia due to a concealed bypass tract.

Reentry may occur less commonly within the sinus node or atrial myocardium. *Sinus node reentry tachycardia* usually occurs at a slower rate (usually about 130 bpm) than either AV

TABLE 5–4. Paroxysmal supraventricular tachycardia (PSVT)

Mechanism	Rate (bpm)	% PSVT caused by mechanism	Mode of *initiation*		Effect of BBB on tachycardia cycle
			APB	VPB	
Reentrant AV nodal reentry	150 to 180	60	+	+	No change
Concealed bypass tract (CBT)	150 to 200+	15 to 30	+	+	Decreased*
Sinus node reentry**	130	4	+	+	No change
Intraatrial reentry**		5	+	–	No change
Automatic Automatic atrial tachycardia**	<175	4	– (Warmup phenomenon)	–	No change

*If BBB is ipsilateral to bypass tract.
**AV block with maintenance of PSVT means source of arrhythmia is above AV node.
APB = atrial premature beats; AV = atrioventricular; BBB = bundle branch block; COPD = chronic obstructive pulmonary disease; CSP = carotid sinus pressure; MI = myocardial infarction; VPB = ventricular premature beats.

nodal reentry or concealed bypass tract reentry tachycardias (figure 5–7). Carotid sinus pressure and other vagal maneuvers may slow and terminate sinus node reentry, as do propranolol and verapamil. As would be expected, bundle branch block has no effect on the tachycardia cycle length in sinus node reentry.

If the atrial mechanisms should persist despite the appearance of AV block when carotid sinus pressure is applied during SVT, one can conclude that the source of the arrhythmia is above the AV node and represents sinus node reentry, intraatrial reentry, or an automatic atrial tachycardia.

Response to vagal maneuver	Agents that may slow or terminate tachycardia	Comments
Slows and abruptly terminates	Digitalis, propranolol, verapamil, procainamide 30 to 50 mg/min, edrophonium (Tensilon)	No predilection based on age, sex, or preexisting heart disease. Dual AV nodal pathways demonstrable in 75% of patients.
Variable	Propranolol, verapamil	No predilection based on sex. More common in younger patients. Most episodes of PSVT at rates >200 involve a CBT capable of only retrograde conduction.
CSP slows and terminates rhythm	Propranolol, verapamil	No predilection based on sex. Tends to occur in patients with organic heart disease and sinus node dysfunction.
AV block without terminating PSVT		P-R interval related to rate of PSVT. Tends to occur in patients with organic heart disease.
AV block without terminating PSVT		Occurs in setting of acute MI, COPD, alcohol ingestion, metabolic derangements. Precipitated by catecholamines, hypoxia, digitalis, and amphetamines. P-R interval related to rate of PSVT (faster rate has longer interval).

5.2 ABNORMAL AUTOMATICITY

Automatic atrial tachycardias (figure 5–8) usually have a rate less than 175 bpm, occur infrequently, and exhibit a warmup phenomenon (i.e., acceleration of the rate after the first few beats of the tachycardia). Characteristically, they are not initiated by an atrial or ventricular premature beat. These tachycardias occur in patients suffering from acute MI, chronic obstructive pulmonary disease, and various metabolic derangements. In addition, elevated catecholamine levels, hypoxia, amphetamines, and alcohol ingestion may precipitate this rhythm disturbance.

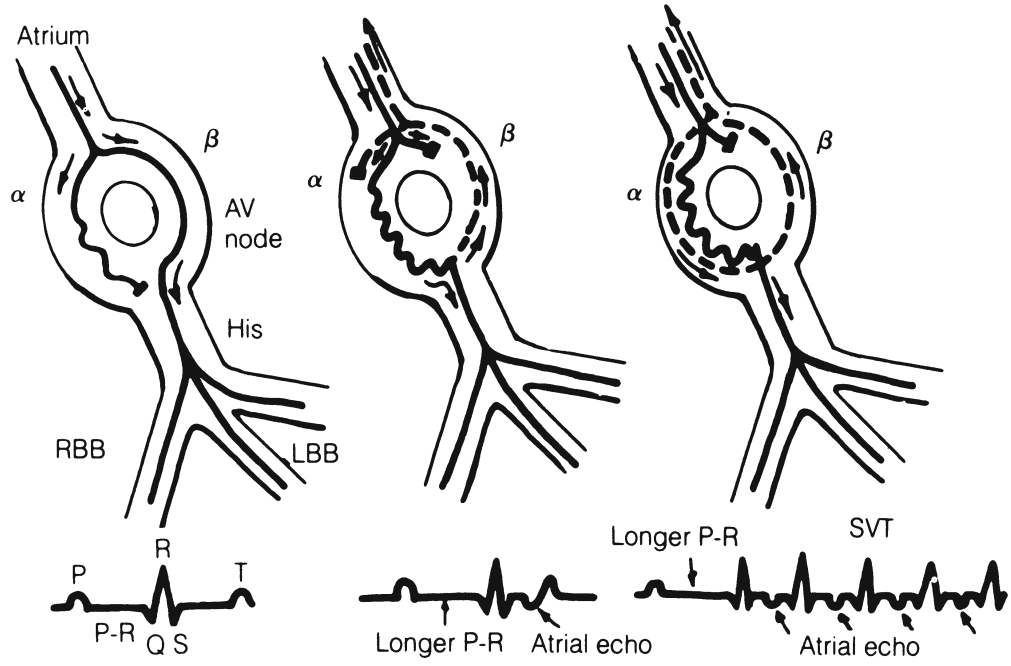


FIGURE 5–5. Mechanism of AV nodal reentrant tachycardia. Each diagram represents an atrium with its AV node (including both the alpha and beta pathways), the His bundle, and right and left bundle branches. The left panel shows sinus rhythm; the center panel depicts the AV nodal response to a single APB with a single atrial echo. The right panel shows initiation of supraventricular tachycardia with an APB. (From Josephson ME, Kastor JA: Supraventricular tachycardia: mechanisms and management. *Ann Intern Med* 87:350, 1977.)

A typical automatic atrial tachycardia encountered in digitalis intoxication is referred to as *paroxysmal atrial tachycardia (PAT) with block*. As noted in chapter 4, this hybrid disorder demonstrates features of both atrial flutter and atrial tachycardia. During the various phases of its development and recession, PAT with block may simulate any of the atrial arrhythmias (figure 5–9). In digitalized patients, potassium depletion favors the provocation of PAT with block; however, the serum potassium level need not always be abnormal. A sinus mechanism can be restored by discontinuing digitalis, withholding diuretics, and instituting supplemental potassium therapy. At times, PAT with block is difficult to distinguish from atrial flutter, and important features that differentiate the two are summarized in table 5–5.

Figure 5–10 presents a schematic summary of the various types of PSVT discussed above, and figure 5–11 reviews important ECG clues to the mechanism underlying PSVT.

5.3 THERAPY FOR PSVT

A distinction should be made between the need to treat acute attacks and the need for chronic prophylaxis to prevent recurrent PSVT. *Acute attacks* may be terminated by vagal maneuvers or intravenous administration of verapamil, digitalis, propranolol, procainamide, and edrophonium. When *chronic prophylaxis* of PSVT is being considered, a careful history must be taken. If the patient has infrequent attacks of PSVT that are clearly related to an identifiable precipitating event, chronic prophylaxis may be unnecessary. Avoidance of precipitating causes (e.g., alcohol or caffeine-containing beverages) in conjunction with "cocktail therapy" for acute attacks, should they occur, may suffice. Such a

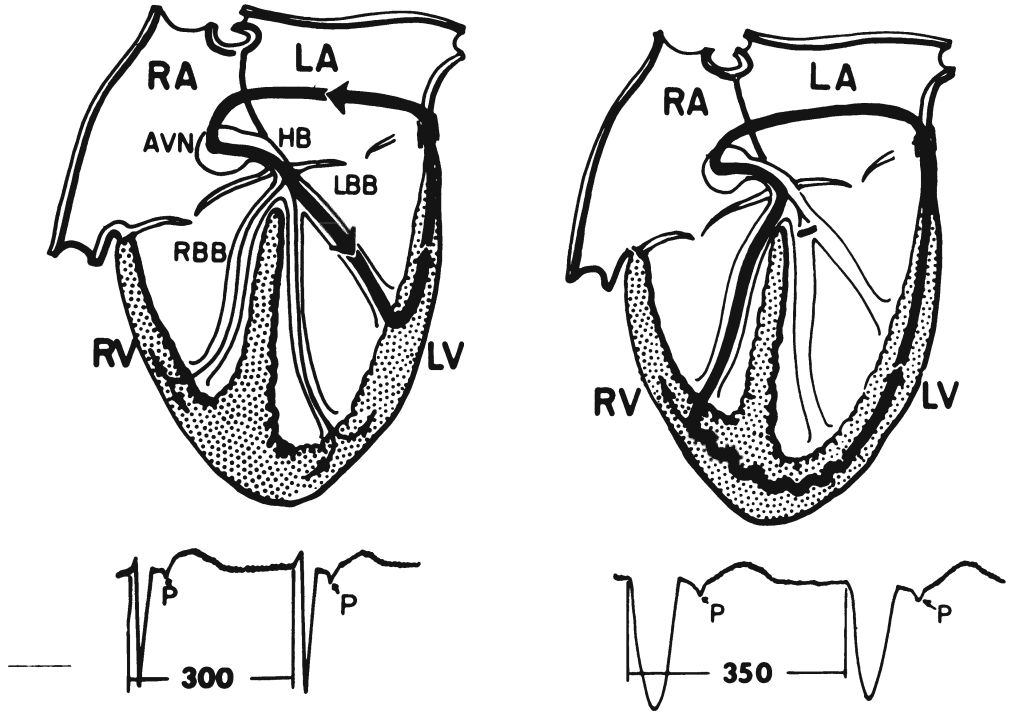


FIGURE 5–6. Effect of bundle branch block on supraventricular tachycardia in WPW syndrome. Both panels show reentrant circuit. Cycle length and retrograde P waves can be seen. *Left*, Tachycardia occurs as usual, down the normal pathway and up the accessory pathway to complete the reentrant circuit. QRS is normal, with retrograde P waves closely following it; cycle length is 300 msec. *Right*, Bundle branch block. The impulse must conduct down the right bundle branch and slowly through the ventricular myocardium until it completes the circuit at the distal end of the accessory pathway. This produces a longer cycle length (350 msec) with LBBB and a longer interval between the QRS and P wave. (From Josephson ME, Seides SF: *Clinical Cardiac Electrophysiology: Techniques and Interpretations*. Philadelphia, Lea and Febiger, 1979, pp. 147–190.)

TABLE 5–5. ECG features of digitalis-induced PAT with block compared with atrial flutter

	PAT with block*	Atrial flutter*
Usual atrial rate	150 to 250	Over 200
P-P baseline	Isoelectric	Mobile
AV response	1:1, 2:1, variable	Usually 2:1
P wave (limb leads)	Upright and diminutive	Inverted leads II and III ("common" flutter)
P-P interval	Regular or irregular	Regular
Ventricular premature beats	In 40%	In 20%
Carotid sinus pressure	AV block increased; atrial rate unchanged	AV block increased; atrial rate unchanged or accelerated
Onset and offset	Gradual change in rate; abrupt change in P wave	Abrupt
Potassium administration	Characteristic response (slowing of tachycardia and eventual reversion to sinus rhythm)	No effect

*Digitalis is a causative factor in approximately 66 per cent of cases of PAT with block but probably less than 1 per cent of cases of atrial flutter.
Modified from Lown B, Levine HD: *Atrial arrhythmias, digitalis, and potassium*. New York, Landsberger Medical Books, 1958

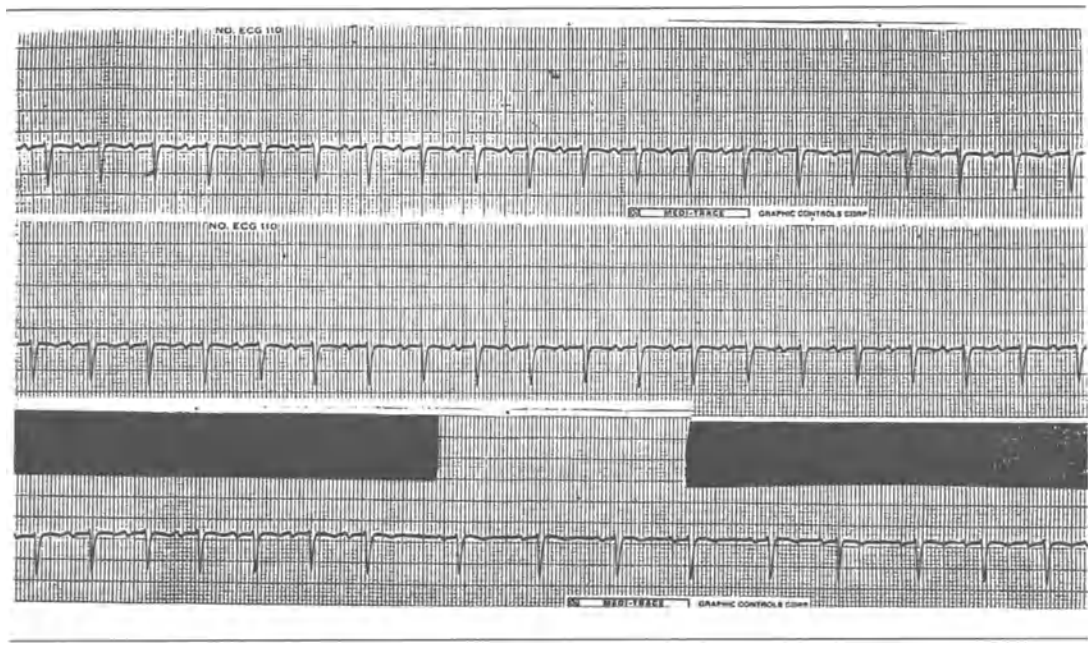


FIGURE 5–7. Sinoatrial reentry tachycardia. The initial appearance of the tachycardia at a rate of 115 bpm at first suggests sinus tachycardia (*top and center panels*). The abrupt offset of the tachycardia after the seventh beat (bottom panel) is followed by sinus rhythm with a P-wave morphology similar to that noted during the tachycardia. When offset is abrupt without an altered P-wave morphology, the tachycardia is most likely due to sinoatrial reentry.

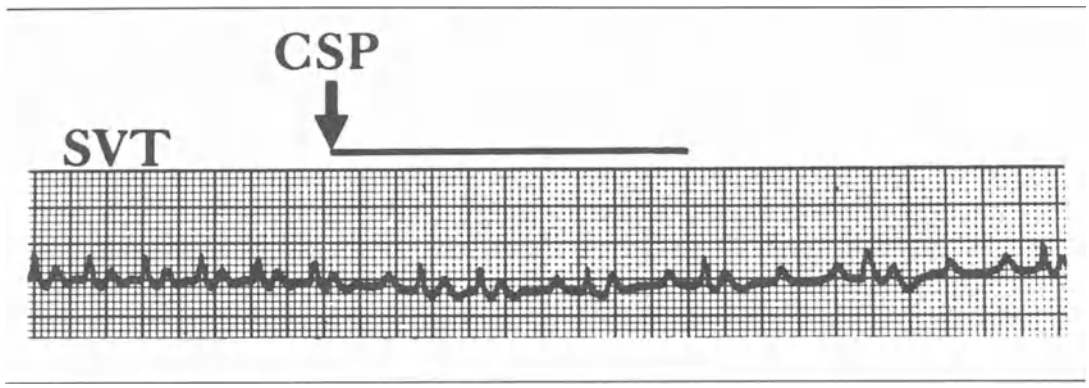
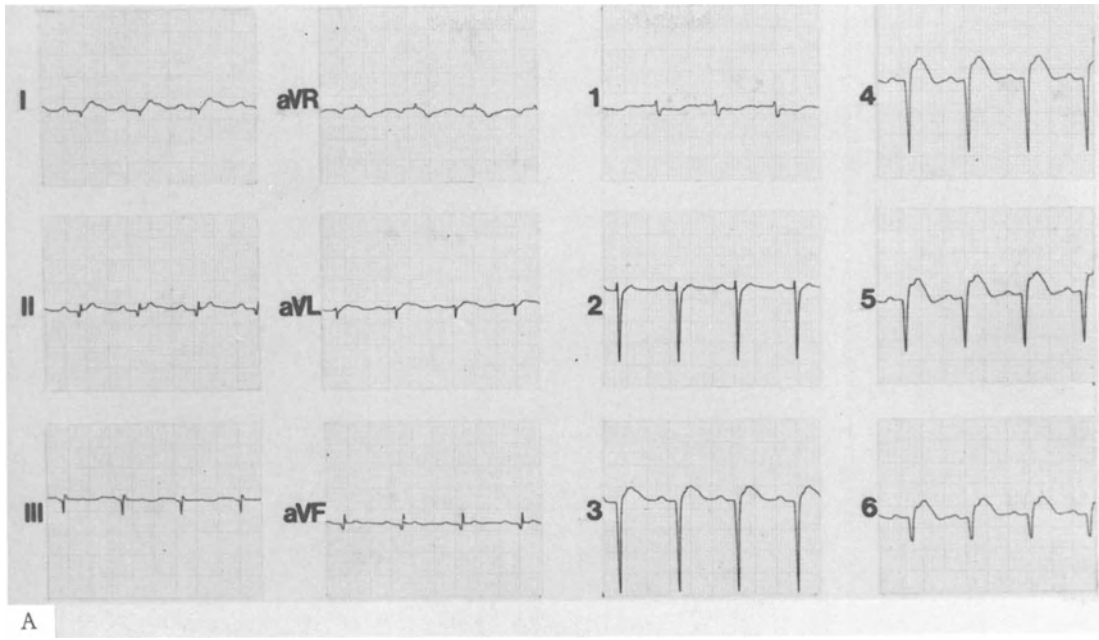
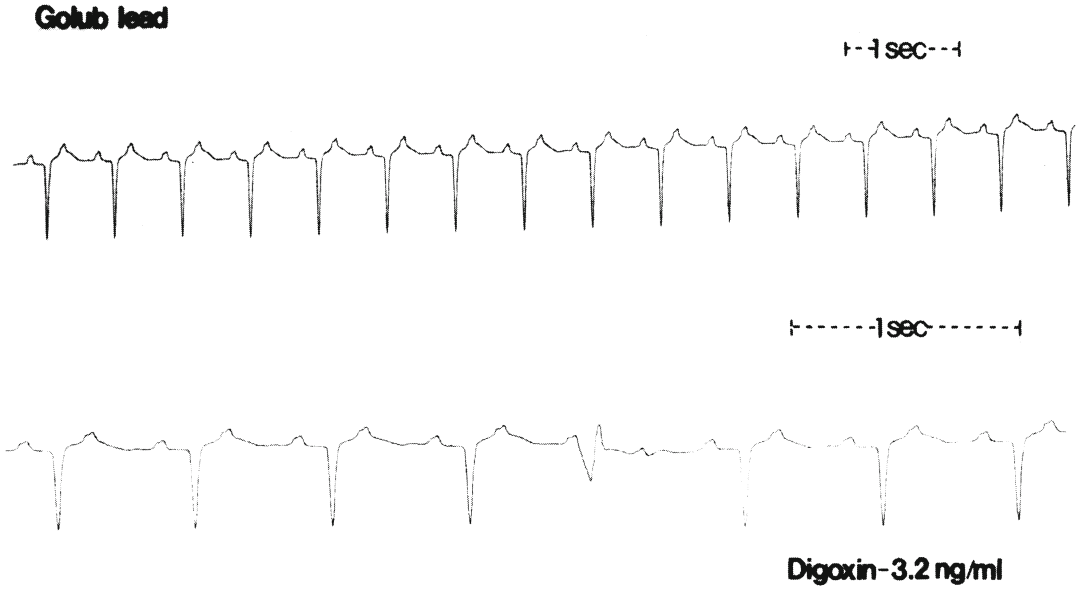


FIGURE 5–8. Automatic atrial tachycardia. During supraventricular tachycardia (SVT) of uncertain mechanism, carotid sinus pressure (CSP) is applied. The presence of this arrhythmia is revealed as AV nodal block appears, and the P waves continue at a rate of 160 bpm. (From Josephson ME, Kastor JA: Supraventricular tachycardia: mechanisms and management. *Ann Intern Med* 87:356, 1977.)

"cocktail" may be employed on an individual basis for each patient and might typically consist of a combination of oral digoxin, propranolol (Inderal), and diazepam (Valium) to be taken at the time of the attack.

On the other hand, the patient who experiences hemodynamic compromise or myocardial ischemia associated with PSVT should be treated more aggressively. In general, two aproaches may be tried: (1) suppression of





B

FIGURE 5–9. *A*, 12-lead ECG showing PAT with 2:1 atrioventricular conduction. The nature of the atrial mechanism is not clearly discernible in this tracing; alternate P waves are obscured by T-waves. *B*, A Golub lead recording on the same patient showing atrial tachycardia in the upper strip. A recording at 50 mm/sec is shown in the lower strip, where a ventricular premature beat further exposes the atrial tachycardia. (From Friedman PL, Antman EM: Electrocardiographic Manifestations of Digitalis Toxicity. In Smith TW, et al (eds): *Digitalis glycosides*, 1985, Orlando, Florida, Grune and Stratton, p 241.)

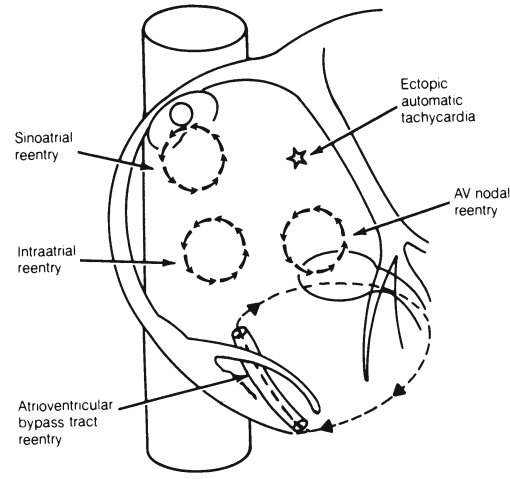


FIGURE 5–10. Various mechanisms and reentrant circuits responsible for paroxysmal supraventricular tachycardia. (Modified from Mandel WJ: *Cardiac arrhythmias*. Philadelphia, JB Lippincott Co, 1980, p 170.)

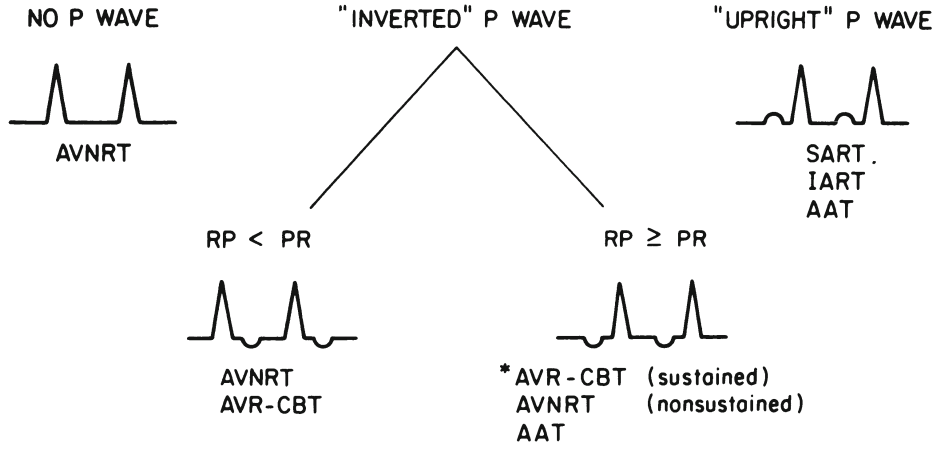


FIGURE 5–11. ECG clues in diagnosis of paroxysmal supraventricular tachycardia (PSVT). Analysis of the P-wave morphology and position relative to the QRS complex may be helpful in suggesting likely mechanisms for PSVT. When no P wave is present, PSVT is likely to be due to AVNRT. In the case of inverted P waves it is necessary to scrutinize the RP and PR relationships to differentiate the usual form of AVNRT and AVR-CBT from *AVR-CBT and AVNRT utilizing a slow retrograde pathway; less frequently, the PSVT with RP ≥ PR is due to AAT. Finally, an upright P wave may be due to reentry above the AV node (i.e., SART, IART) or on occasion AAT. (Courtesy of Dr. Peter L. Friedman, Director, Clinical Electrophysiology Laboratory, Brigham and Women's Hospital, Boston, Mass.)

extrasystoles that might initiate reentry, and (2) alteration in the conduction properties of the circuit to render it less hospitable to such mechanisms. Agents such as quinidine and disopyramide (Norpace) have been helpful in suppressing extrasystoles, while long-term alteration of the conduction circuit may be achieved through high-dose digitalis therapy and various combinations of propranolol or verapamil.

Incessant or more permanent reciprocating AV nodal reentrant tachycardia, most frequently seen in childhood, can be extremely difficult to treat. Characteristically this rhythm is constantly reinitiated as the sinus cycle length shortens. Initial experience indicates that patients do well when given quinidine combined with a drug that blocks AV conduction, such as digitalis, verapamil, or propranolol.

Sophisticated antitachycardia pacemakers have been used successfully in patients with refractory PSVT (see discussion in chapter 9). Before selecting such a pacing device, the clinician should consult those who are experienced in its use to obtain a complete electrophysiological evaluation.

Synchronized electrocardioversion (chapter 7) can be employed when PSVT responds poorly to medical measures and hemodynamic function is compromised. A synchronized discharge of 100 to 200 watt-seconds should be used. The response rate varies from 75 to 80 per cent, depending on the underlying cause. However, cardioversion is relatively contraindicated when supraventricular arrhythmias are thought to be due to digitalis intoxication.

6. *Atrial Fibrillation*

Atrial fibrillation is characterized on the ECG by chaotic, small-amplitude fibrillatory waves. Cases of simultaneous atrial flutter and fibrillation in distinct portions of the atria have been documented. Borderline or transitional situations may be described as "impure" atrial flutter or atrial flutter/fibrillation. Because of the extremely high rate of discharge of the fibrillating atria (500 to 600 cycles/min), impulses arriving in the AV node present a disorganized wavefront with insufficient potency to be conducted consistently to the ventricular specialized conduction system. Therefore, many fibrillatory impulses fail to propagate through the AV node because of *concealed conduction.*

Although atrial fibrillation may at times be paroxysmal, it is more often a chronic, stable rhythm. The critical determinant of the clinical response to atrial fibrillation is the rapidity of the ventricular rate. In patients with serious myocardial or valvular disease, such as mitral stenosis, a rapid ventricular rate may precipitate acute pulmonary edema. Prompt control of the ventricular rate may be achieved by drugs such as digitalis, propranolol, and verapamil (table 5–6).

Synchronized electrical cardioversion is often used to terminate atrial fibrillation and is usually appropriate when the arrhythmia has persisted for less than one year. However, one must decide whether atrial fibrillation or sinus rhythm is preferable for an individual patient. Experience has shown that certain patients with chronic atrial fibrillation are not suitable candidates for cardioversion (table 5–7).

Although the average energy needed to revert atrial fibrillation to sinus rhythm is about 100 watt-seconds, this requirement may vary and depends on multiple factors. In general, higher energies are necessary for (a) long-standing atrial fibrillation (1 to 3 years), (b) small (<1 mm) fibrillatory waves in lead V_1, (c) alcoholics and patients with cardiomyopathy, (d) Wolff-Parkinson-White syndrome, (e) severe coronary heart disease, (f) acute MI or (g) uncontrolled congestive heart failure with a rapid ventricular response.

Anticoagulation therapy for 3 weeks prior to attempting cardioversion is suggested to reduce the incidence of systemic and pulmonary embolism. After cardioversion, coumadin is given for an additional 4 weeks as a protective measure, since recurrence of atrial fibrillation is most likely during this time.

Oral antiarrhythmic therapy to prevent atrial fibrillation involves drugs such as quinidine, which can be administered in a large loading dose for acute attacks (e.g., quinidine sulfate, 400 to 600 mg) followed by chronic maintenance therapy as needed (see chapter 6).

Coexistent arrhythmias are often seen in conjunction with atrial fibrillation. Emergence of a regularized AV junctional rhythm in a patient receiving digitalis to control the rate of ventricular response in atrial fibrillation should

TABLE 5–6. Response to drug therapy for atrial fibrillation

Determinants of ventricular rate in AF	Drug effects on ventricular rate		
	Digoxin	Verapamil	Beta-adrenoceptor blockers
Atrial electrical input 400 to 800 impulses/min Rate increased by increase in vagal tone	↑ (vagal)	± ↑	0
AV nodal transmission of impulses High incidence of block in slow channel-dependent fibers Concealed conduction	↓	↓	↓
Modulating factors: Autonomic nervous system tone responses to exercise Vagal ↓ Sympathetic ↑	↓ (the direct actions of digitalis are weak and its rate-reducing potential decreases during withdrawal of vagal tone)	↓ ↓ (direct electrophysiologic effects of verapamil on AV nodal cells are independent of autonomic nervous system tone *and* are more pronounced at high rates)	↓ ↓ (blunts effects of increased sympathetic tone)

From Antman EM, Friedman PL: Use of digitalis glycosides in the management of cardiac arrhythmias. In Smith TW (ed): *Digitalis glycosides*, 1985 Orlando, Grune and Stratton, 1986, p 127.

cause one to suspect digitalis intoxication. Such regularization may be premonitory of impending high-grade ventricular ectopic activity if digitalis administration continues.

Aberrant ventricular conduction may appear along with atrial fibrillation, since supraventricular impulses may be rapidly conducted through the AV node to the conduction system while the latter is still refractory. Although rules have been devised to help differentiate between supraventricular beats with aberrancy and ventricular ectopic beats, none of these is definitive, and at best, one can make only an educated guess (table 5–8) [20–22].

7. *Atrial Flutter*

Atrial flutter is characterized on the ECG by coarse, regular, "sawtooth" undulations of the baseline (F waves) that appear at a rate of about 250 to 350 per minute. The bulk of available evidence suggests that atrial flutter probably has a focal origin but is perpetuated via a reentrant mechanism. Figure 5–12 summarizes important differences between two proposed mechanisms for circus movement in atrial flutter [23].

In "common" atrial flutter, the flutter waves in the inferior leads show a predominantly negative deflection. "Uncommon" atrial flutter involves a reentrant circuit in which impulses travel in the opposite direction in such a way that the flutter waves are predominantly positive in the inferior leads. Flutter waves may also appear in a low-amplitude sinusoidal pattern or may be entirely indistinct in the standard ECG leads, necessitating special recording techniques (e.g., right-sided chest leads, esophageal leads, or a right atrial lead).

When the atrial rate is as low as 250 bpm, it must be differentiated from supraventricular tachycardia, whereas at higher frequencies, such as 400 bpm, atrial flutter must be differentiated from atrial fibrillation. To this end, vagal maneuvers may be employed to increase AV block and separate the F waves from the QRS complex and T waves.

The various antiarrhythmic agents available are of limited benefit in patients with atrial

flutter. Verapamil and digitalis increase the degree of AV block but are unlikely to restore sinus rhythm. Recently, rapid atrial pacing has been shown to "entrain" the atrial flutter focus, interrupt the reentrant circuit, and terminate the arrhythmia. However, when the atrial flutter rate is particularly rapid (e.g., above 400 bpm), this technique may precipitate atrial fibrillation. Since conduction of atrial flutter with a 1:1 AV response may at times prove disabling or life-threatening, and since atrial flutter is often difficult to terminate by means of antiarrhythmic agents, synchronized electrical cardioversion is a useful therapeutic modality in this condition. Cardioversion successfully restores sinus rhythm in over 90 per cent of patients, with an average energy requirement of 25 watt-seconds [24,25]. Usually only a single discharge is required.

Atrial fibrillation is often easier to control medically than is atrial flutter, so that in certain instances one may elect to convert atrial flutter to atrial fibrillation by means of cardioversion. This can be accomplished by administering a low-energy shock (5 to 10 watt-seconds) at any time during the cardiac cycle except when the ventricle is vulnerable.

TABLE 5–7. Poor candidates for cardioversion from atrial fibrillation

1. Elderly patients with a slow ventricular response or the sick sinus syndrome.
2. Patients with advanced mitral valve disease or an enlarged left atrium or who have undergone mitral valve replacement.
3. Certain "lone fibrillators," especially those with a small heart and a slow ventricular rate, in whom atrial fibrillation represents a well-tolerated "electrical accident" of the heart.
4. Patients with a history of frequently recurring atrial tachyarrhythmias in whom atrial fibrillation has lately developed.
5. Patients who are able to maintain sinus rhythm for only a brief period despite adequate antiarrhythmic therapy.
6. Patients who suffer adverse reactions to maintenance doses of antiarrhythmic agents.

8. Atrioventricular Junctional Arrhythmias [26,27]

8.1. JUNCTIONAL ESCAPE RHYTHMS

These represent a normal escape mechanism in settings in which the automaticity of the SA node falls below that of the AV junction. The normal escape rate for these rhythms is 40 to 60 per minute. On the ECG, the rhythms are manifest as a QRS complex having a normal configuration and P waves having a variable relationship to the QRS complex.

8.2. NONPAROXYSMAL AV JUNCTIONAL TACHYCARDIA

This term refers to rhythm disturbances characterized by enhanced automaticity at the AV junction [26]. By convention, junctional rhythms occurring at a rate above 70 beats/min are considered abnormal and indicate acceleration of activity of the AV junction. The rate is usually between 75 and 110 (or 120) beats/min, with evidence of AV dissociation.

Although rarely a patient may have an idiopathic form of nonparoxysmal junctional tachycardia, as noted in chapter 4, this arrhythmia usually suggests a serious disorder, such as acute inferoposterior MI, digitalis intoxication, or acute myocarditis. It may also be seen in the early postoperative period after mitral valve replacement. For this reason its recognition is most important.

When nonparoxysmal AV junctional tachycardia coexists with another supraventricular tachycardia, such as atrial tachycardia, the phenomenon is known as *double atrial tachycardia*. This may occur in digitalis intoxication and warrants careful ECG monitoring.

Management consists of recognizing the rhythm and searching for the precipitating cause. Atrial pacing is needed only if the loss of atrial contraction results in low cardiac output. Because of its common association with conditions that may seriously compromise cardiovascular function and cause potentially malignant cardiac arrhythmias, direct-current cardioversion is relatively contraindicated in nonparoxysmal AV junctional tachycardia.

Finally, *paroxysmal AV junctional tachycardia* is an old term used by some authors to describe a rhythm identical to that referred to as paroxysmal supraventricular tachycardia due to reentry within the AV node.

TABLE 5–8. Features favoring supraventricular beats with aberrancy vs ventricular ectopic beats*

	Aberrancy	Ventricular ectopy
General findings		
Short interval following long	+ (Ashman phenomenon)	+ (rule of bigeminy)
Fixed coupling	–	+ if VPB – if parasystole
Rate	Often > 200	
Fusion beats	–	+
AV dissociation	–	+
QRS width	<140 msec	>140 msec
Onset	APB with wide QRS	VPB
Carotid sinus pressure	+ (? 30%)	–
Form		
With right bundle branch block appearance:		
In lead V_1	Triphasic	Monophasic or biphasic
Initial deflection (V_1)	Similar to sinus	Different from sinus
Taller deflection (V_1)	Second deflection, RsR′	First deflection
S wave (V_6)	Smaller than R wave	Larger than R wave
Axis	Usually to right of −30°	Often to left of −30°
With left bundle branch block appearance:		
Axis deviation	Rarely rightward	May be rightward
Negative deflection in left precordial leads	Less deep than in V_1	Deeper than in V_1
R wave in V_1	Narrow or absent	Wide, >40 msec

*In addition to the clues listed here, one should note the value of "concordance" or similarity in the form of the QRS in leads V_1 to V_6, which strongly favors a ventricular origin.
Adapted from Kastor JA, et al: Clinical electrophysiology of ventricular tachycardia. *N Engl J Med* 304:1004, 1981.

Circus Movement

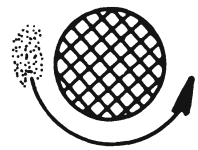
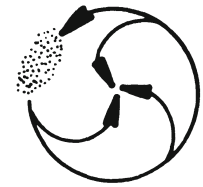
	Anatomic obstacle (Mines, 1913)	Leading circle (Allessie, 1977)
		
Pathway length	Fixed: Determined by perimeter of obstacle	Variable: Determined by electrophysiologic properties of circuit
Fully excitable gap	Yes	No
Shortcut possible	No	Yes
Revolution time	Related inversely to conduction velocity	Related directly to refractory period

FIGURE 5–12. Comparison of circus movement mechanisms proposed for atrial flutter. (Modified from Josephson ME, Seides SF: *Clinical cardiac electrophysiology: Techniques and interpretations.* Philadelphia, Lea and Febiger, 1979, p 197.)

9. *Syndromes Characterized by Frequent Supraventricular Tachyarrhythmias*

A number of clinical syndromes have been described that have in common a high incidence of supraventricular tachyarrhythmias. In these cases, careful clinical assessment is needed to define the appropriate therapy.

9.1. THE PARKINSON-PAPP SYNDROME

In 1947, Parkinson and Papp described a syndrome of repetitive paroxysmal tachycardia characterized by short bursts of supraventricular arrhythmias separated by sinus beats occurring in a repetitive pattern over a period of months or years [28]. The usual symptom is palpitations; evidence of hemodynamic compromise is infrequently seen. When it occurs in childhood or youth, this disorder usually represents a benign process. However, in adults it is commonly associated with organic heart disease and may not be entirely benign [29].

In their original definition, Parkinson and Papp stated that no more than two sinus beats would occur in a row without an intervening paroxysm of supraventricular tachycardia. This pattern may consist of frequent atrial premature beats, atrial flutter, or paroxysmal supraventricular tachycardias.

Attempts at suppression with antiarrhythmic medications appear to be unwarranted, since these agents are not usually successful. In addition, patients with the Parkinson-Papp syndrome should not undergo direct-current cardioversion owing to the repetitive and recurrent nature of this arrhythmia.

9.2. THE PREEXCITATION SYNDROME [30–36]

In this syndrome, impulses originating in the atrium activate the ventricles earlier than would be expected if they traversed their normal route from the AV node to the bundle of His. This short-circuiting of the normal conduction pathway may take place via a number of extranodal or accessory pathways. Anatomical substrates involved in ventricular preexcitation are shown in figure 5–13.

Depending on the precise pathway that the impulse travels between the atrium and the ventricle, a variety of ECG patterns may be observed [30]. The availability of a pathway that lacks a site at which conduction is slowed — as would normally occur at the AV node — allows rapid, repetitive ventricular stimulation. Profound tachycardias result, often displayed as a bizarre QRS complex.

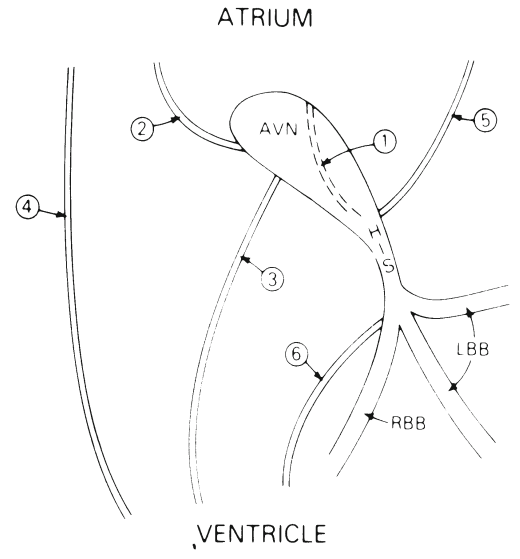


FIGURE 5–13. Anatomical substrates for preexcitation. ① Preferential intranodal pathway, ② Posterior internodal tract, ③ Nodo-ventricular pathway, ④ Atrioventricular pathway, ⑤ Atrio His pathway, ⑥ Fasciculo ventricular pathway. (From Josephson ME, Seides SF: *Clinical cardiac electrophysiology: Techniques and interpretations.* Philadelphia, Lea and Febiger, 1979, p 212.)

9.2.1. The Wolff-Parkinson-White (WPW) Syndrome. If a lateral AV bypass tract or Kent bundle is utilized, one sees the classic pattern described by Wolff, Parkinson, and White in 1930. This consists of a short P-R interval; slurring of the initial segment of the QRS complex, referred to as a *delta wave*; and a wide QRS complex (figure 5–14). Because of marked anatomical variations, one might see patients who exhibit a normal P-R interval but a wide QRS complex with a delta wave [30].

In the WPW syndrome, impulses may be conducted from the atrium to the ventricle (a)

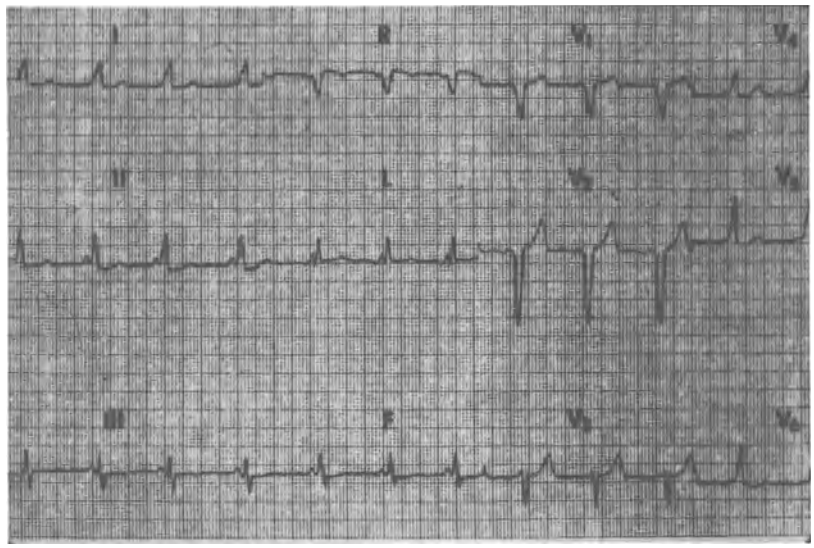


FIGURE 5–14. Short P-R interval and slurred, wide QRS with delta waves typical of the WPW syndrome. (From Stokes JP: *ECG management and diagnosis*. Self-Assessment Test in postgraduate course, San Francisco, March 16–19, 1981, published by American College of Cardiology Publishers.)

solely via the normal AV conduction pathway; (b) via some combination of normal and accessory AV conduction, resulting in ventricular "fusion" on the ECG; or (c) solely via the accessory pathway, resulting in a markedly distorted QRS complex. Because of the abnormal pattern of ventricular excitation in WPW, ECG changes in these patients frequently mimic those seen in acute MI, bundle branch block, or left ventricular hypertrophy [33]. This is especially so because abnormal repolarization often accompanies the bizarre QRS pattern and limits the ability to diagnose MI or ischemic responses on exercise testing.

Although many patients with the WPW syndrome are asymptomatic, those who present with palpitations and tachycardia usually have paroxysmal supraventricular tachycardia or atrial flutter/fibrillation with a rapid ventricular response [31,32,34,36]. When conduction through the bypass tract is only retrograde, paroxysmal supraventricular tachycardia due to a concealed bypass tract will be seen on the ECG (see Paroxysmal Supraventricular Tachycardia above). Alternatively, a reciprocating supraventricular tachycardia may involve antegrade conduction through the accessory tract and retrograde conduction through the AV node. Paroxysms of supraventricular tachycardia in the WPW syndrome usually involve retrograde conduction through the bypass tract; however, one should be alert to the possibility that a wide QRS complex in the setting of a regular tachycardia may represent antegrade accessory pathway conduction in this condition [31].

Atrial fibrillation or atrial flutter can be particularly distressing in patients with WPW, since extremely rapid conduction over the accessory pathway is possible. A rapid ventricular rate may cause symptoms, and in patients with extremely rapid ventricular stimulation, there is risk of ventricular fibrillation [35]. Atrial flutter with 1:1 conduction over the accessory pathway, as shown in figure 5–15, may result in a regular tachycardia that is difficult to distinguish from ventricular tachycardia.

9.2.2. The Lown-Ganong-Levine (LGL) Syndrome. In 1952, Lown, Ganong, and Levine described a syndrome characterized by a short P-R interval, a normal QRS complex, and frequent paroxysmal arrhythmias [33]. A precise anatomical substrate has not yet been described for this syndrome; in fact, a single

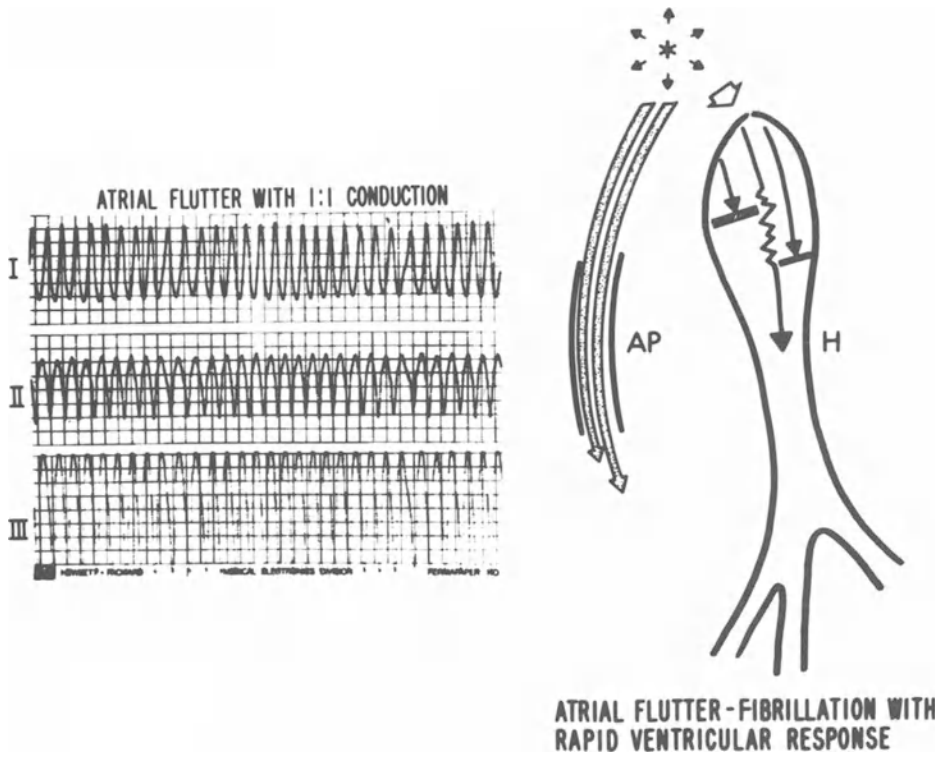


FIGURE 5–15. Atrial flutter-fibrillation associated with WPW syndrome. *Left*, Atrial flutter with 1:1 anomalous AV conduction of the accessory pathway (AP). *Right*, Atrial impulses undergo conduction delay and block in the AV node-His system with 1:1 conduction over the accessory pathway. (From Gallagher JJ, et al: The Wolff-Parkinson-White syndrome and the preexcitation dysrhythmias. *Med Clin N Am* 60:108, 1976.)

pathological pathway may not exist. The prevalence of the ECG abnormality seen in this syndrome is not known, but the pattern is often seen in asymptomatic patients with normal hearts. Before making the diagnosis of LGL syndrome, one should exclude other conditions associated with short P-R intervals due to elevated levels of circulating catecholamines or a hypermetabolic state, such as thyrotoxicosis, pregnancy, Paget's disease, and Cushing's syndrome. Atrial arrhythmias commonly seen in the LGL syndrome include paroxysmal supraventricular tachycardia and atrial fibrillation, at times with a rapid ventricular response.

9.2.3. Clinical Management of the Preexcitation Syndrome. First, a careful history should be taken to establish the frequency of tachycardias, and a diligent search should be made for precipitating causes. In the patient with infrequent episodes of symptomatic tachycardia, only acute therapy with *antiarrhythmic agents* — either intravenous or oral — is necessary. A particularly promising agent is verapamil, which slows AV conduction and may interrupt the reentrant pathway. In patients known to have an accessory pathway of the Kent-bundle type, the use of digitalis glycosides or verapamil may present a perplexing problem. In a number of cases, digitalis has been shown to shorten the effective refractory period of the accessory tract, thus increasing the propensity for rapid conduction of atrial fibrillatory impulses to the ventricles, with the attendant risk

of ventricular fibrillation. Preliminary investigations suggest that verapamil may have a similar deleterious effect in some WPW patients with rapid conduction over the accessory tract during atrial fibrillation and that this drug may be contraindicated in patients with a short effective refractory period of the bypass tract.

Some investigators feel that patients with the WPW syndrome who have symptomatic reentrant PSVT or atrial flutter should undergo electrophysiological testing to determine the effective refractory period of the accessory tract and assess the maximum ventricular response in atrial fibrillation. In addition, an electrophysiology study should include evaluation of the safety of digitalis or verapamil in an individual patient. When the effective refractory period of the accessory tract is short (≤200 msec) or is shortened significantly by the administration of cardiac glycosides or verapamil, those drugs are contraindicated. Conversely, if digitalis or verapamil has no adverse effects, it may be used as a valuable adjunct in a chronic antiarrhythmic drug program.

Chronic suppression of recurrent tachycardias can often be achieved with a combination of antiarrhythmic agents, such as quinidine and propranolol or procainamide and propranolol. The investigational antiarrhythmics — encainide and amiodarone — effectively reduce the frequency of tachycardias in the preexcitation syndrome.

For patients refractory to antiarrhythmic therapy, one may consider installing a *radiofrequency-triggered programmable pacemaker.* This mode of therapy is effective only if one can demonstrate a reentrant pathway that can be interrupted by a brief burst of atrial or ventricular pacing, critically timed extrastimuli, or sophisticated AV sequential pacing.

Finally, *surgical therapy* has been employed to interrupt accessory extranodal pathways involved in the tachycardia. Surgical division of the aberrant pathway may eliminate PSVT or prevent extremely rapid ventricular rates in atrial flutter/fibrillation. Alternatively, surgical division of the normal AV conduction pathway may be chosen and has been carried out in a few cases. Since the patient then becomes dependent on the accessory pathway for conduction, a standby permanent ventricular demand pacemaker may be required. Before surgical therapy is contemplated, careful electrophysiological mapping must be performed by experienced personnel.

10. Ventricular Arrhythmias

Ventricular arrhythmias are disturbances of cardiac rhythm that originate distal to the subdivision of the bundle of His. They may result from rapid discharge of an ectopic focus or reentry involving the bundle branches or fascicles or at the Purkinje fiber-myocardial interface. A more detailed summary of the mechanisms of arrhythmia is provided earlier in this chapter (see section 2).

10.1. VENTRICULAR PREMATURE BEATS (VPBS)

Electrocardiographically, ventricular premature beats (VPBs) may be distinguished by a QRS complex that is premature, often bizarre in appearance, and usually wide (>120 msec). Multiple-lead recordings (preferably obtained simultaneously) are helpful in detecting those VPBs which may be partially isoelectric in a single lead and which are likely to be diagnosed as supraventricular complexes. Adjunctive criteria that aid in the recognition of VPBs are ST-T abnormalities, a T wave directed opposite to the QRS complex, and lack of a premature P wave preceding the QRS. VPBs may produce a variety of patterns on the ECG; some of the more common ones are defined in table 5–9. A grading system commonly used to classify VPBs is shown in table 5–10 [37].

10.2. ACCELERATED IDIOVENTRICULAR RHYTHM AND VENTRICULAR PARASYSTOLE

10.2.1. Accelerated Idioventricular Rhythm (AIVR). AIVR is defined as an independent ventricular rhythm having a rate between 50 and 100 bpm [38]. It oftens occurs during sinus slowing and usually has an intrinsic rate faster than the sinus mechanism (see figure 4–4 in chapter 4). AIVR may become the dominant cardiac rhythm for varying periods of time (ranging from a few seconds to several hours). The rate of AIVR is usually slow enough to permit accurate measurement of the basic sinus rate and is often close enough to the basic sinus rate so that the ventricles are driven alternately by sinus rhythm and AIVR. Fusion beats and

TABLE 5–9. ECG patterns of ventricular premature beats

Pattern	Comment
1. R-on-T	Extremely premature VPB abutting T wave of preceding beat.
2. Late cycle (late diastolic)	Fusion with sinus conducted impulse yielding QRS with features of both normal beats and VPBs.
3. Compensatory pause	VPB conducts retrograde through AV node but does not invade sinus node, so that R-V interval plus V-R intervals equals two R-R interval in sinus rhythm. If VPB invades and resets sinus node, the pause following VPB may be less than compensatory.
4. Interpolated	A decidedly premature VPB occurring during slow sinus rhythm blocks on ventricular aspect of AV node. Retrograde conduction into AV node may cause refractoriness, so that the subsequent sinus complex is conducted with a long P-R interval.
5. Repetitive	
a. Bigeminy	Every other QRS is a VPB
Trigeminy	Every third QRS is a VPB
Quadrigeminy	Every fourth QRS is a VPB
b. Couplet (pair)	Two successive VPBs
c. Tachycardia	Often arbitrarily defined as 3 to 5 successive VPBs with a rate greater than 100 bpm.
d. Accelerated idioventricular rhythm	Often defined as 3 successive VPBs with a rate between 50 and 100 bpm.

TABLE 5–10. VPB characteristics [37]

Grade 0	No ventricular beats
1A	Occasional, isolated VPBs (<30/hr, <1/min)
1B	Occasional, isolated VPBs (<30/hr, >1/min)
2	Frequent VPBs (>30/hr)
3	Multiform VPBs
4A	Repetitive VPBs (couplets)
4B	Repetitive VPBs (salvos)
5	Early VPBs (i.e., abutting or interrupting the T wave).

AV dissociation are common findings. AIVR is frequently seen during the early phase of acute MI [39] (when it is sometimes referred to as *slow ventricular tachycardia*) but has been reported in healthy individuals with no heart disease who are undergoing ambulatory ECG monitoring.

Although some authors suggest that AIVR is associated with more rapid ventricular tachycardia when it occurs in patients with acute infarction, no such relationship has been suggested when AIVR is seen in the noninfarction setting. However, an intriguing hypothesis concerning AIVR holds that it may really be a faster rhythm with exit block (see Ventricular Parasystole below) and may at times interact with surrounding abnormal ventricular tissue to yield faster ventricular tachyarrhythmias [38]. Such a possibility has been demonstrated in animals in which infarction has been produced, but the clinical significance of this observation in humans either with or without infarction is uncertain. For general purposes, AIVR seen in the noninfarction setting should be considered a benign arrhythmia that does not require treatment. In the rare individual in whom AV dissociation causes a fall in blood pressure, acceleration of the sinus rate (by means of atropine or atrial pacing) is all that is required.

10.2.2. Ventricular Parasystole. Ventricular parasystole is an ectopic automatic ventricular rhythm classically described as having variable coupling of VPBs to sinus beats and a "common-denominator" interectopic interval [40]. The electrophysiological concepts of

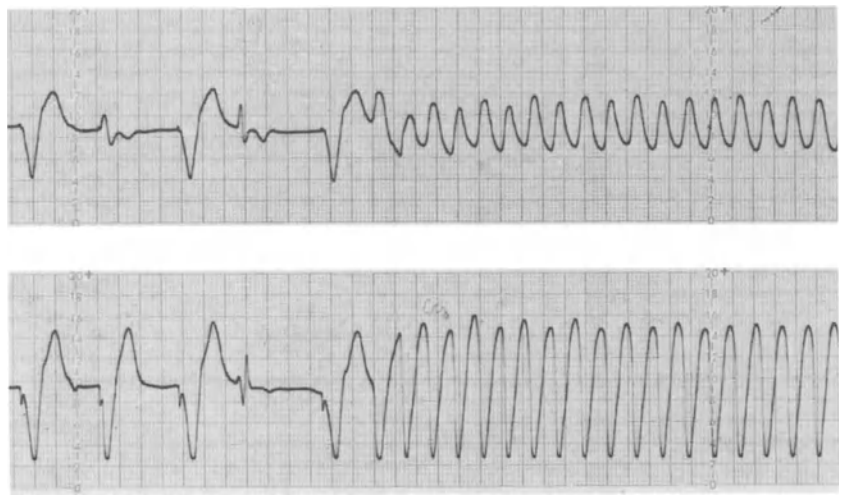


FIGURE 5–16. Sinus beats alternating with demand ventricular paced beats are seen at the left. Following the fifth beat from the left, an episode of *ventricular flutter* (240 bpm with sinusoidal waveform) begins. This paroxysm lasted 5 seconds and then terminated spontaneously.

entrance block (preventing invasion of the parasystolic focus by sinus beats) and *exit block* (preventing invasion of the surrounding ventricular myocardium by the parasystolic focus) have been invoked to explain the episodic emergence of ventricular parasystolic rhythms. The diagnosis of ventricular parasystole usually requires analysis of long rhythm strips, with careful measurement of interectopic intervals to search for the "parasystolic firing rate." This may be difficult if variable exit block (e.g., Wenckebach) out of the ectopic focus is present. In addition, it is possible that the parasystolic firing rate (which has been reported to range from 20 to 400 bpm!) may show intrinsic variation over time in that sinus impulses may cause an electrotonic interaction across the margin of the parasystolic focus, producing a variation in the rate of exit characteristics [41]. The exact incidence and clinical significance of ventricular parasystole are poorly defined, but the available literature suggests that it is a relatively benign disorder that may be resistant to antiarrhythmic drug therapy and can persist for years.

It should be mentioned that digitalis glycoside toxicity may occasionally present as rhythms having features suggestive of AIVR or ventricular parasystole. In such instances suppressive antiarrhythmic therapy with a drug such as lidocaine is indicated.

10.3. VENTRICULAR TACHYCARDIA. Definitions of *ventricular tachycardia* (VT) vary in both the rate range (usually 100 to 200 bpm) and the number of successive VPBs in a run (3 to 5 VPBs). It is clear that VT may occur at rates in excess of 200 bpm, and it seems arbitrary to call such rhythms *ventricular flutter* merely on the basis of rate [38]. Ventricular flutter should be reserved for very fast ventricular rhythms (rates usually in excess of 200 bpm) and a sinusoidal ventricular depolarization pattern (figure 5–16).

VT may occur in both a paroxysmal and a sustained fashion. Although it is almost always seen in the setting of organic heart disease VT can occur in normal individuals. A list of common etiologies of VT is given in table 5–11. The electrocardiographic diagnosis may be difficult, since many other arrhythmias can mimic VT. When the tachycardia morphology is similar to isolated VPBs, the likelihood of the tachycardia being VT increases, especially if *ventricular capture* (by sinus beats) and *fusion beats* (com-

TABLE 5–11. Etiologies of ventricular tachycardia

I. Ischemic Heart Disease
  A. Acute myocardial infarction
  B. Variant angina
  C. Chronic ischemic heart disease
    1. Myocardial scarring
    2. Ventricular aneurysm
II. Non ischemic Cardiac Disorders
  A. Valvular
    1. Mitral valve prolapse
    2. Rheumatic heart disease
  B. Myocardial
    1. Cardiomyopathy
    2. Myocarditis
    3. Tumor
  C. Q-T prolongation
    1. Inherited syndromes
      a. Jervell and Lange-Nielsen (autosomal recessive with accompanying deafness)
      b. Romano-Ward (autosomal dominant without deafness)
    2. Acquired conditions
      a. Drugs
        (1) Antiarrhythmic agents — quinidine, procainamide, disopyramide, aprindine, amiodarone
        (2) Tricyclic antidepressants
        (3) Phenothiazines
        (4) Calcium channel blocking agents — prenylamine, lidoflazine
      b. Electrolyte disorders
        (1) Hypokalemia
        (2) Hypocalcemia
        (3) Hypomagnesemia
      c. Hypothermia
      d. Cerebrovascular accident
      e. Neck surgery
      f. Liquid protein diets
  D. Drug- or Toxin-induced
    1. Catecholamines
    2. Digitalis glycosides
    3. Carbon monoxide
  E. Idiopathic

plexes intermediate between sinus beats and VPBs) are observed [38]. ECG features of supraventricular beats with aberrant conduction are contrasted with those of ventricular ectopy in table 5–8.

It may be necessary to record special leads to detect atrial activation in an attempt to classify the etiology of a tachycardia (see 13.3.2.). When multiple-lead intracardiac recordings are made, criteria that strongly favor VT are as follows [38]:

1. Dissociation of His spike and ventricular electrogram.
2. His-ventricular electrogram association but with H-V interval *shorter* than in sinus rhythm *and* dissociation of atrial and ventricular electrograms.
3. Initiation of the tachycardia with *loss* of the His spike *and* dissociation of atrial and ventricular electrograms.

Management of VT may present a clinical challenge because of the episodic nature of the arrhythmia, coexisting heart disease, and the multiple treatment modalities available (drugs, pacemakers, surgical techniques). Epidemiological studies of VT have been carried out most extensively in patients with ischemic heart disease [42–43]. Most episodes of VT in such individuals are brief and repetitive, but even such abbreviated salvos appear to carry a risk of more sustained arrhythmias and cardiovascular collapse. Sustained VT is a relatively rare disorder but may cause symptoms based upon the rate and underlying myocardial function. For example, a young athletic individual with idiopathic VT may be able to tolerate VT at a rate of 180 bpm without symptoms, whereas a middle-aged individual with a cardiomyopathy may not tolerate VT at a rate of 140 bpm, owing to the increased rate and loss of atrial contribution to cardiac output. General guidelines for approaching a patient with ventricular arrhythmias are discussed subsequently (see section 11).

10.4. VENTRICULAR FIBRILLATION AND TORSADES DE POINTES

Ventricular fibrillation (VF) is diagnosed on the ECG by the absence of discrete QRS complexes and disorganized undulatory waves of variable amplitude oscillating around the isoelectric baseline (see figure 4–3 in chapter 4). It is almost always a fatal rhythm disorder unless prompt defibrillation is performed (see chapter 7) although occasional cases of spontaneous defibrillation have been reported.

VF may be seen in:

1. Myocardial infarction/ischemia
2. Extreme electrolyte disorders
3. Electrocution
4. Hypothermia
5. Drug toxicity

Torsades de pointes is a rapid ventricular arrhythmia believed by many authors to repre-

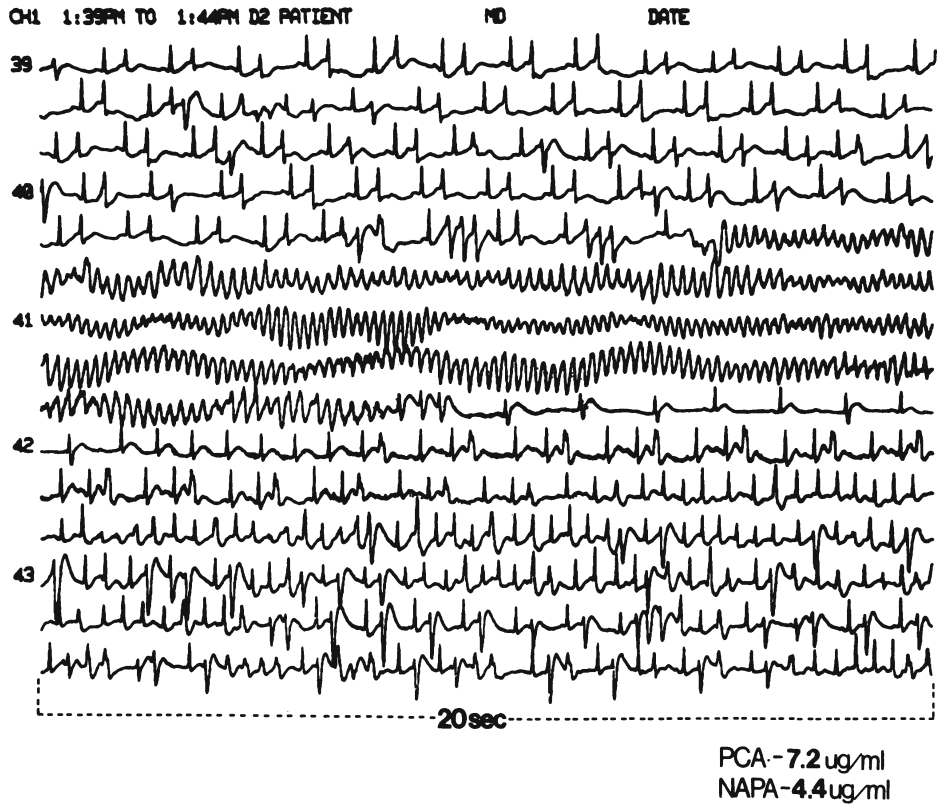


FIGURE 5–17. Torsades de pointes. This 5–7 minute strip from a 24-hour ECG recording shows Q-T prolongation, isolated VPBs, and several short paroxysms of VT followed by a long, self-terminating episode of the torsades de pointes type of VT. The characteristic oscillation of the major QRS axis is clearly evident. The patient was being treated with procainamide (note drug levels at bottom right), a drug known to cause this type of arrhythmia (along with other membrane-active antiarrhythmic agents). PCA = procainamide; NAPA = Nacetyl procainamide.

sent a disorder intermediate between the more organized circulating wavefront of VT and the multiple, disorganized wavefronts of VF [44]. It is characteristically seen in the setting of Q-T prolongation (table 5–11) and is usually repetitive and self-terminating (figure 5–17). The dangers of torsades de pointes relate to the occurrence of syncope during the paroxysm and the occasional paroxysm that degenerates into VF. It is important to recognize torsades de pointes, since most ventricular antiarrhythmic drugs will prolong the Q-T interval further and perpetuate the disturbance. Appropriate therapeutic measures include discontinuation of any potential offending agents (table 5–11), correction of electrolyte disturbances, and overdrive atrial or ventricular pacing to shorten the Q-T interval [44].

11. Sudden Cardiac Death

Between 450,000 and 500,000 individuals succumb to sudden cardiac death in the United States annually [45]. Definitions of the *suddenness* of death vary among investigators and range from several minutes to up to 24 hours from the onset of symptoms (provided the patient was in a usual state of health prior to the onset of symptoms) [46]. This entire field is being investigated extensively and evokes considerable controversy. The majority of sudden deaths result from VF, and it appears that the

prognosis varies depending on whether VF occurred in the setting of acute myocardial infarction [47]. Patients resuscitated from out-of-hospital VF who do not evolve an acute MI are at greater risk for a recurrence of cardiac arrest and sudden death than are patients who sustain an infarction. Although a number of clinical variables such as hypertension, cigarette smoking, elevated serum cholesterol, and overt chronic myocardial disease (especially ischemic heart disease) have been shown to represent potential risk factors for sudden cardiac death, accurate identification of those individuals with a potentially electrically unstable myocardium from within the large pool of patients with heart disease is still not possible [45,48]. Because of the high rate of recurrence of VF when the catastrophic arrhythmia occurs in the absence of infarction, aggressive attempts must be made to document the presence or absence of an MI.

The management of sudden death victims is a controversial area with emotionally charged overtones because of the unpredictable and often lethal consequences of misjudgment. In addition, many new therapies are becoming available, and it is not yet clear how they rank in terms of efficacy *and* ease of implementation. Table 5–12 outlines the therapeutic options that have been proposed for management of malignant ventricular arrhythmias (e.g., recurrent ventricular tachycardia or ventricular fibrillation that leads to hemodynamic compromise.) Each of these will now be discussed briefly.

TABLE 5–12. Therapeutic options for malignant ventricular arrhythmias

1. Empirical choice of antiarrhythmic agent with maintenance of therapeutic serum levels
2. Selection of one or more antiarrhythmic agents utilizing a combination of ambulatory ECG monitoring and exercise testing
3. Invasive electrophysiological testing for initiation of tachyarrhythmias and selection of antiarrhythmic agent
4. Intraoperative mapping with surgical excision/interruption of arrhythmogenic zones or circuits
5. Insertion of sophisticated pacemakers capable of detecting and terminating tachyarrhythmia

11.1. MANAGEMENT OF MALIGNANT VENTRICULAR ARRHYTHMIAS

11.1.1. Antiarrhythmic Prophylaxis. The concept of mass prophylaxis against malignant ventricular arrhythmias seems a logical approach not only for those individuals who have survived an episode of sudden cardiac death but also for persons at high risk, such as those with overt ischemic heart disease, particularly within the first year after MI. This approach would involve the empirical choice of an antiarrhythmic agent and the maintenance of therapeutic serum levels [49].

Although several recent reports have indicated that beta-adrenergic blocking agents [50] or sulfinpyrazone [51] will reduce the incidence of sudden cardiac death, it is important to realize that the target population in these studies comprised postinfarction patients. No large-scale studies have been performed to indicate that such agents are helpful in cases of primary electrical failure (i.e., VF not in the setting of acute MI). Furthermore, data from the Seattle Heart Watch Program indicate that many patients resuscitated from out-of-hospital cardiac arrest were receiving chronic antiarrhythmic therapy [52]. Unfortunately none of the antiarrhythmic drugs currently available has a sufficiently low risk: benefit ratio to substantiate its widespread use as a prophylactic agent, so that this option is untenable as a first-line approach at the present time.

Finally, it has been suggested that in those individuals resuscitated from sudden cardiac death due to VF in whom it is not possible to reduce ventricular arrhythmias or suppress chronic VPBs, treatment with one or more antiarrhythmic agents along with monitoring to assure that adequate plasma drug levels are maintained appears to be of some value in protecting against recurrent cardiac arrest [49]. However, such patients probably represent a minority of the victims of sudden cardiac death, and the validity of the data needs to be confirmed by other investigators.

11.1.2. Monitoring and Exercise Testing. In this approach, one or more antiarrhythmic agents are selected on the basis of results of ambulatory ECG monitoring combined with exercise testing [37,45,53]. Although the techniques of ambulatory ECG monitoring and exercise testing are established methods for evaluating a patient for the *presence* of ventricular arrhythmias, their use as tools for assessing the efficacy of an antiarrhythmic drug program to protect a patient against sudden cardiac death

TABLE 5–13. Protocol for ambulatory ECG monitoring and exercise testing

This protocol is designed to select one or more antiarrhythmic agents using a combination of ambulatory ECG monitoring and exercise testing. This method was proposed by Lown and coworkers for the management of patients with malignant ventricular arrhythmias*.

Phase 0: Control phase.
Control ambulatory ECG monitoring (for 48 hours) and treadmill exercise testing (Bruce protocol) are carried out. Patient is *taken off* all antiarrhythmic agents in order to establish baseline arrhythmia frequency and reproducibility.

Phase 1: Antiarrhythmic drug testing.
A single large oral dose of an antiarrhythmic drug is administered after a period of suitable control monitoring. The amount of drug administered generally consists of half the commonly employed daily maintenance dose of the given agent. This is designed to achieve therapeutic blood levels of the drug rapidly.

Continuous ECG monitoring using trendscription is performed along with hourly bicycle exercise procedures for 3 to 5 hours. Blood levels are obtained hourly as well as at the onset of action, peak drug effect, and appearance of any adverse effects.

The criteria for drug efficacy are broadly defined as a greater than 50% reduction in total VPBs, 90% reduction in ventricular couplets, and total elimination of ventricular tachycardia salvos as compared with control.

Phase 2: Short duration maintenance therapy.
During this phase (which lasts 48 to 96 hours for each drug), drugs that appear to be efficacious during Phase 1 testing are examined for efficacy as well as patient tolerance. The efficacy criteria are the same as in Phase 1 and must be met on *both* ambulatory monitoring and maximal exercise stress testing. In addition, during Phase 2 the efficacy of digitalis glycosides for arrhythmia suppression are tested using the ultrashort-acting compound acetylstrophanthidin.

Phase 3: Selection of final drug program.
Efficacious and well-tolerated drugs as discerned from Phase 2 testing are given in various combinations to provide a "fail-safe" program of drug protection. During this phase, potential drug interactions are sought and dose modifications are made.

Because of strong experimental and clinical evidence linking psychological stress to the precipitation of malignant ventricular arrhythmias, supportive psychotherapy and meditation techniques are utilized in conjunction with the above drug program.

*See references 37, 45, and 53.

is controversial. There is inherent spontaneous variability in the frequency of ventricular arrhythmias using ambulatory ECG recorders. This has led to a number of sophisticated statistical approaches to cataloguing the frequency of a patient's arrhythmia [54,55]; unfortunately, such complex approaches limit the broad application of ambulatory ECG monitoring in general clinical practice.

Because a variety of monitoring and exercise protocols are in practice, it is difficult to compare the success of one method versus another. Lown and coworkers have developed the protocol outlined in table 5–13. Results of an uncontrolled, nonrandomized study utilizing the criteria broadly outlined in table 5–13 have recently been reported [56]. Therapy with multiple antiarrhythmic agents individually selected to abolish advanced grades of VPBs enhances long-term survival among patients with malignant ventricular arrhythmias. The advantages of such an approach include its noninvasive nature and potential for general application; however, it is time-consuming (often requiring hospital stays of at least 17 to 21 days). Furthermore, about 20 per cent of patients do not exhibit frequent or reproducible ventricular arrhythmias with monitoring or exercise testing, so that invasive electrophysiological testing is required to define a drug program.

11.1.3. Electrophysiological Testing with Induction of Tachyarrhythmias. Invasive electrophysiological testing can also be used to initiate tachyarrhythmias and select the appropriate antiarrhythmic agent(s) [57,58]. This technique consists of an invasive multicatheter study designed to provide a comprehensive

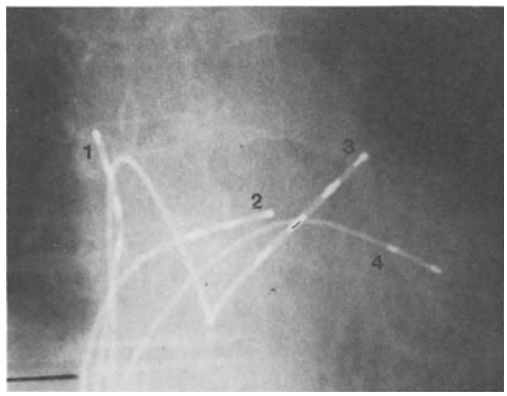


FIGURE 5–18. Standard postioning of electrode catheters in the high right atrium ①, His bundle region ②, coronary sinus ③, and right ventricular apex ④ during a diagnostic electrophysiology study (Courtesy of Dr. Peter L. Friedman, Director, Clinical Electrophysiology Laboratory, Brigham and Women's Hospital, Boston, Mass.)

electrophysiological evaluation of the patient's heart function and the effects of various drugs. The standard catheter positions are shown in figure 5–18. (On occasion, ventricular stimulation is performed at sites other than the right ventricular apex, e.g., the outflow region of the right or left ventricle.) Such studies can be used both diagnostically and therapeutically, since in many cases tachypardias may be terminated by critically timed electrical stimuli.

As with ambulatory monitoring and exercise testing, a variety of study protocols are in practice. The sensitivity and specificity of the various protocols have not been established nor have there been adequate scientific investigations comparing electrophysiological testing with the ambulatory monitoring/exercise testing method. Testing protocols vary with respect to such items as the number of premature stimuli delivered, number of sites stimulated, pulse width of each stimulus (in milliseconds), and amount of current (in milliamperes) delivered with each stimulus. A full description of electrophysiological testing techniques is beyond the scope of this chapter but can be found in several literature sources [57–59]. The broad outlines of a typical stimulation protocol for inducing VT are given in table 5–14. Examples of the use of electrophysiological testing to evaluate antiarrhythmic efficacy are shown in figures 5–19 and 5–20.

TABLE 5–14. Example of electrophysiological testing stimulation protocol to induce ventricular tachycardia in a patient with a history of sudden cardiac death or recurrent VT/VF

1. Incremental (100 to 300 bpm) rapid right atrial pacing to AV Wenckebach block.
2. Premature atrial stimulation during atrial pacing.
3. Premature right ventricular apical stimulation during spontaneous rhythm.*
4. Incremental ventricular pacing (60 to 150 bpm) at moderate rates.
5. Premature right ventricular apical stimulation during ventricular pacing at various rates.*
6. Brief bursts of rapid ventricular pacing (150 to 280 bpm).
7. Repetition of above protocol during (a) isoproterenol infusion of 1 to 5 μg/min or (b) premature stimulation of additional sites in right or left ventricle if VT not induced.

*Premature ventricular stimuli are usually initially applied late in diastole, after which the coupling interval is decreased by 10-msec decrements until ventricular refractoriness. Depending on the protocol, one, two, or three premature stimuli are delivered. During ventricular pacing at an S_1-S_1 interval, the premature stimuli are usually referred to as S_2, S_3, S_4 or V_2, V_3, V_4. During spontaneous rhythm, they are usually referred to as S_1, S_2, S_3 or V_1, V_2, V_3.

One particular advantage of this method is that it provides comprehensive electrophysiological data. Wide QRS tachycardias initially thought to be VT may on rare occasion prove to be antidromic circus movement tachycardias involving an accessory pathway. With the aid of multiple intracardiac recordings, short bursts of nonsustained VT due to microreentry (intramyocardial reentry) can be differentiated from macroreentry involving the bundle branches. The effects of antiarrhythmic agents and the intraventricular conduction system can be assessed (e.g., prolongation of the H-V interval and the possible need for pacemaker therapy). Partial response to a drug can be readily assessed (e.g., slowing of the rate of VT but not elimination of the inducibility of VT). Finally, the patient's hemodynamic response to the arrhythmia can be evaluated in both the control and the drug treatment phases. Serial studies allow one to select effective agents within a shorter period of time than do ambulatory monitoring and exercise testing.

The disadvantages of this method include complications as a result of cardiac catheterization and the need for expensive, sophisticated equipment. Because of its complex nature, electrophysiological testing can be readily carried

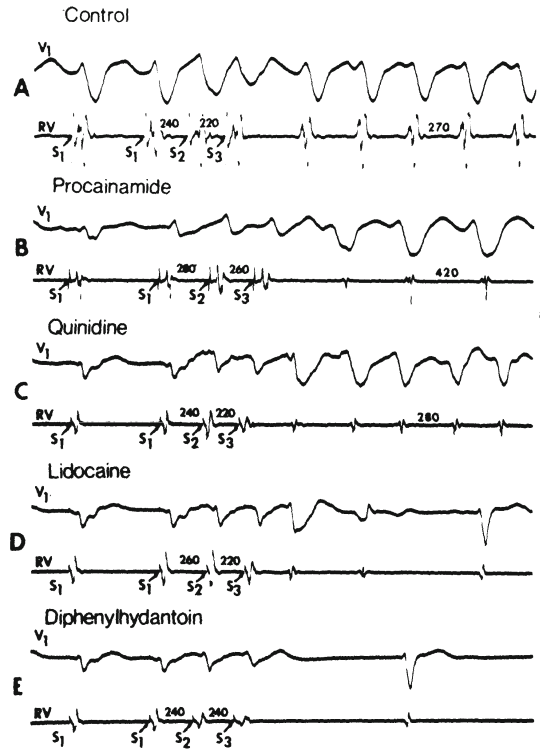


FIGURE 5–19. Prediction of drug efficacy for recurrent ventricular tachycardia (VT). In each panel, ECG lead V_1 and a right ventricular electrogram (RV) are shown. Stimuli during ventricular pacing (S_1) and programmed extrastimuli (S_2 and S_3) are indicated. The coupling intervals of the extrastimuli are shown on the left between S_1–S_1 and S_2–S_3. The tachycardia cycle length is indicated on the right. In *A*, the control study, VT was initiated by two extrastimuli and the cycle length was 270 msec.

In *B*, after the intravenous administration of 1,500 mg of procainamide (18.7 μg/ml), VT was still inducible at slightly longer coupling intervals; however, the tachycardia cycle length was markedly prolonged. The QRS complex was also widened to 215 msec (165 msec in the control study).

In *C*, after oral administration of 2,000 mg of quinidine (3.4 μg/ml), VT was inducible at the control coupling intervals and the cycle length was not significantly different from that in the control study.

In *D*, after intravenous administration of 175 mg of lidocaine, nonsustained VT (one complex) was induced.

In *E*, after intravenous administration of 1,000 mg of diphenylhydantoin (9.75 μg/ml), two ventricular extrastimuli resulted in no VT complexes. No other coupling intervals or stimulation protocol produced VT after diphenylhydantoin. Identical results were obtained 3 days later during chronic oral administration of diphenylhydantoin (10.5 μg/ml). (From Horowitz LN, et al: Recurrent sustained ventricular tachycardia. 3. Role of the electrophysiologic study in selection of antiarrhythmic regimens. *Circulation* 58:986, 1978, used by permission of the American Heart Association, Inc.)

out only at large medical centers where experienced personnel are available. Furthermore, with this approach the patient is exposed to the risks of cardiac arrest and myocardial ischemia.

Two well-designed studies have been reported that demonstrate the utility of electrophysiological testing for managing patients with recurrent VT or out-of-hospital cardiac arrest [57,58]. Therapy with antiarrhythmic agents that suppress the inducibility of ventricular tachyarrhythmias are associated with enhanced survival.

11.1.4. Surgical Approaches. Intraoperative mapping can be performed to detect arrhythmogenic zones or circuits for the purpose of

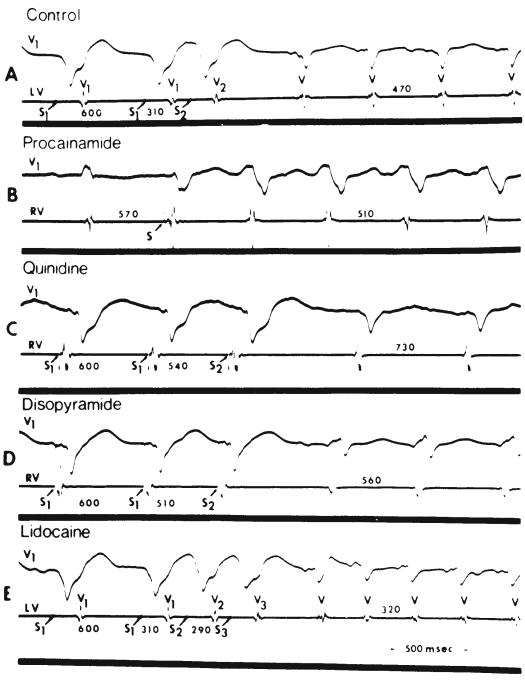


FIGURE 5–20. Failure of drugs to prevent the initiation of ventricular tachycardia (VT). In each panel, ECG lead V_1 and a right ventricular (RV) or left ventricular (LV) electrogram are shown.

In *A*, during the control study, VT is induced by a single extrastimulus during ventricular pacing.

In *B*, after intravenous administration of 1,250 mg of procainamide (11.3 μg/ml), VT is induced by a single extrastimulus during sinus rhythm and the cycle length is longer than control. The difference in QRS morphology in panel B is due primarily to a change in gain and QRS complex prolongation.

In *C*, after oral administration of 2,000 mg of quinidine (3.4 μg/ml), VT is initiated by a single extrastimulus during ventricular pacing, and the cycle length was 730 msec.

In *D*, after oral administration of disopyramide (200 mg loading dose and 400 mg daily), VT (cycle length = 560 msec) was induced by a single extrastimulus during ventricular pacing.

In *E*, after intravenous administration of 150 mg of lidocaine, VT was more difficult to induce, requiring two extrastimuli; however, the tachycardia cycle length is shortened to 320 msec from a control of 470 msec. No drug at tolerated plasma concentrations prevented the initiation of VT. (From Horowitz LN, et al: Recurrent sustained ventricular tachycardia. 3. Role of the electrophysiologic study in selection of antiarrhythmic regimens. *Circulation* 58:986, 1978, used by permission of the American Heart Association, Inc.)

TABLE 5–15. Surgical therapy of tachyarrhythmias

I. *Supraventricular Tachycardia*
  A. Interruption of accessory pathway
    1. Surgical sectioning of tract
    2. Cryoablation
  B. Interruption of AV node-His bundle junction
    1. Surgical incision
    2. Cryoablation
    3. Direct-current shock through catheter positioned in His bundle area
  C. Resection of localized arrhythmogenic atrial focus

II. *Ventricular Tachycardia*
  A. Patients with ischemic heart disease
    1. Coronary artery bypass grafting
    2. Simple aneurysmectomy
    3. Ventriculotomy
    4. Cryoablation
    5. Electrophysiologically directed endocardial resection
    6. Encircling ventriculotomy
  B. Patients without ischemic heart disease
    1. Ventriculotomy (e.g. arrhythmogenic right ventricular dysplasia, following repair of tetralogy of Fallot)
    2. Left stellate ganglionectomy (e.g., long Q-T syndrome)
    3. Valve replacement (e.g., mitral valve replacement for ruptured chordae tendineae)

surgical excisional interruption [60–62]. The objectives of a surgical approach to tachyarrhythmias are to excise the origin of a tachycardia, to interrupt reentrant pathways necessary for maintaining the tachycardia, and, in the case of supraventricular tachycardias, to slow the ventricular response by interruption of either an accessory pathway or the AV node-His bundle junction (table 5–15). Although coronary artery bypass grafting and "blind" or simple aneurysmectomy may afford hemodynamic benefit in a patient with ischemic heart disease, they are only moderately successful in controlling recurrent VT. *Mapping* of the heart is a complex procedure in which electrical potentials are recorded at multiple sites to ascertain the origin of a tachycardia and/or the pathway(s) it follows in the heart [61]. The procedure may be performed crudely with catheters in the electrophysiology laboratory or more precisely us-

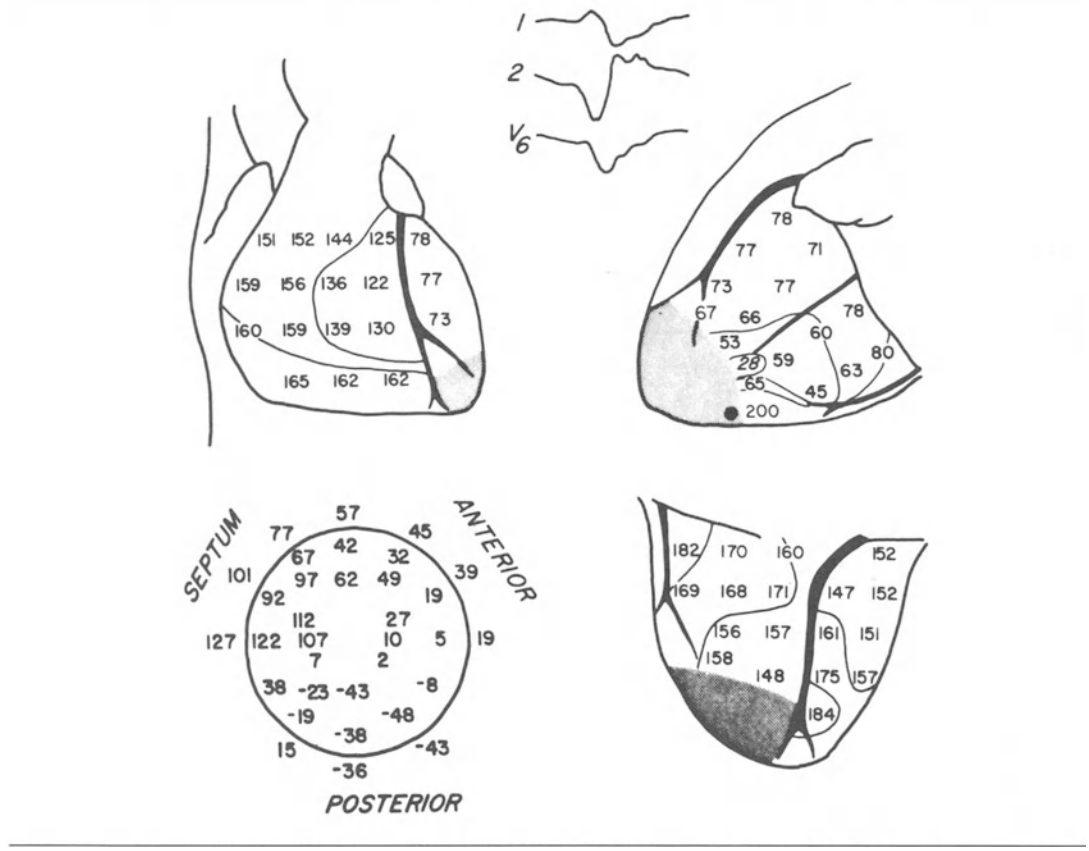


FIGURE 5–21. Epicardial and endocardial mapping data during VT with a right bundle branch block morphology. A schematic representation of the epicardial surface is shown in the anterior, left lateral, and inferior projections (clockwise from upper left). The aneurysm is stippled. Activation times at selected epicardial sites are shown with 20-msec isochrones. A representation of the endocardial surface of the aneurysm is shown at the lower left. The solid line indicates the border of the aneurysm. Epicardial breakthrough occurred 28 msec after the onset of the QRS complex on the anterolateral left ventricle along the border of the aneurysm. The earliest endocardial electrogram occurred 48 msec before the QRS complex on the lateral endocardial border. This site is indicated on the epicardial map by the solid circle. The site of epicardial breakthrough was 3 cm from the endocardial origin. From Horowitz LN, et al: Epicardial and endocardial activation during sustained ventricular tachycardia in man. *Circulation* 61:1227, 1980, used by permission of the American Heart Association, Inc.)

ing handheld probes applied to the epicardium and endocardium in the operating room [62]. The available surgical techniques include a simple ventriculotomy or cryoablation of suspected arrhythmic foci. Recently, considerable success has been reported with electrophysiologically directed (i.e., mapped) endocardial resection combined with aneurysmectomy and encircling ventriculotomy (which does not require mapping) [63] (figures 5–21 and 5–22).

Problems encountered in performing an intraoperative map include difficulty recording and interpreting recordings due to low-amplitude signals or hemodynamic instability, difficulty in inducing VT under general anesthesia and at normothermia, prolonged bypass time, the presence of multiple arrhythmogenic foci, and location of an arrhythmogenic focus in a "sensitive" area such as a papillary muscle [62]. When VT cannot be induced in the operating

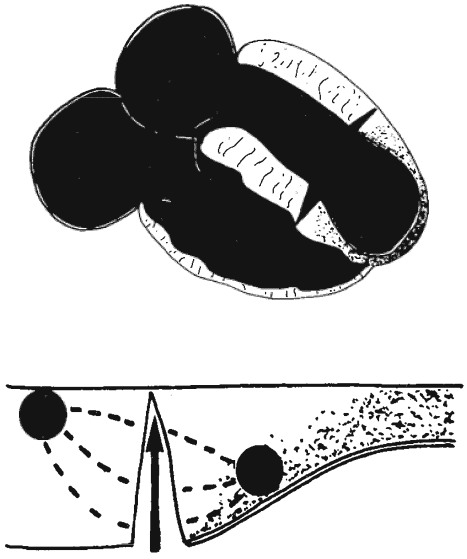


FIGURE 5–22. Encircling endocardial ventriculotomy (EEV), shown schematically as a transmyocardial incision at the border of infarcted tissue. *Top*, Heart in horizontal section showing three areas of myocardium after healing of an infarct as well as the site and depth of the EEV. *Bottom*, Closeup of the site of EEV. Circles localize two points on the reentry circuits, one in the border zone and the other in healthy myocardium. The EEV sections the reentry pathway between the healthy and diseased zones. (From Guiraudon G, et al: Encircling endocardial ventriculotomy: A new surgical management of ventricular tachycardia related to myocardial infarction. In: *Management of ventricular tachycardia — Role of mexiletine*. Sandoe E, Julian DG, Bell JW (eds), Amsterdam, Excerpta Medica, 1978, p 635.)

room, a technique known as "pace-mapping" is performed. The heart is paced from an area suspected to be the focus of a tachycardia in an attempt to produce an arrhythmia morphologically similar to the patient's spontaneously occurring one [61].

Lessons learned from endocardial mapping are that the area of earliest endocardial electrical activation (presumably the focus of the tachycardia) may be several centimeters distant from the earliest epicardial "breakthrough" of activation, limiting the utility of epicardial maps [62]. In addition, a single ventricular focus may have two morphologically distinct tachycardias depending on the path of exit from the focus and route of activation of the ventricle. Thus, a focus in the posterior interventricular septum may be the source of VT with either a right or a left bundle branch block pattern (figure 5–23).

The advantages of sophisticated electrosurgery are that it is highly successful in preventing recurrences of VT, often reduces or eliminates the need for medical therapy, and offers the opportunity to improve the patient hemodynamically as well. However, it is an extremely time-consuming and expensive endeavor that for now should be reserved for life-threatening and drug-refractory cases of malignant ventricular arrhythmias. (The success attained with surgical interruption of accessory pathways is a separate clinical question, and its use may spare young patients many years of drug therapy.) Such surgical procedures are performed in a limited number of medical centers and certainly cannot be viewed as the therapy of choice for the vast number of patients who suffer from malignant ventricular arrhythmias.

For patients who do not have ischemic heart disease, map-guided ventriculotomy may be successful (table 5–15). Some individuals with a long Q-T syndrome have benefited from left stellate ganglionectomy, which presumably reduces the asymmetry of sympathetic neural traffic to the heart.

11.1.5. Pacemaker Therapy. Another option is insertion of sophisticated pacemakers capable of detecting and terminating tachyarrhythmias [64–65]. Implantable devices to control VT are limited by the hemodynamic status of the patient during this arrhythmia. Available pacing techniques include tachycardia recognition with automatic antitachycardic pacing using bursts of stimuli or critically timed stimuli and patient-activated devices which perform antitachycardia pacing. Before such a device is implanted in a patient, a thorough electrophysiological and hemodynamic evaluation is necessary. It must be shown conclusively that the patient tolerates the tachycardia long enough for antitachycardia pacing to occur *and* that pacing does not accelerate the rate of the arrhythmia (figure 5–24). Further discussion of antitachycardia pacing for ventricular arrhythmias may be found in the next section.

An implantable automatic defibrillator has been developed and was recently marketed. An analysis of its advantages and disadvantages can

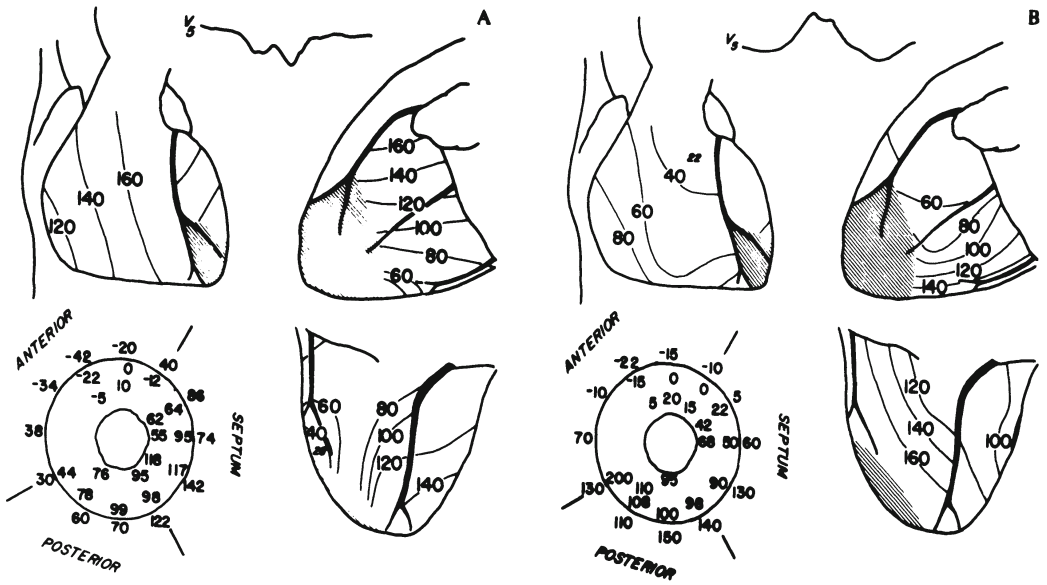


FIGURE 5–23. Ventricular tachycardia (VT) with right bundle branch block and left bundle branch block (RBBB and LBBB) morphologies in a patient with an anteroseptal aneurysm. In both *A* and *B*, epicardial maps with the site of epicardial breakthrough indicated by the italicized numeral and 20-msec isochrones are shown with ECG lead V_5 and endocardial activation data (*lower left*). In *A*, during VT-RBBB, epicardial breakthrough (EBT) occurred 28 msec after the onset of the QRS complex on the lateral left ventricle, the site of origin was located on the anterior endocardial border of the aneurysm (−42 on the endocardial map). In *B*, during VT-LBBB, EBT occurred on the anterior right ventricle 22 msec after the onset of the QRS; however, the site of origin was located at the same anterior endocardial site (−22 on the endocardial map). The pattern of endocardial activation explains the different QRS morphologies. During VT-RBBB, septal endocardial activation is relatively late; however, during VT-LBBB, conduction is slow toward the lateral wall and the septum is activated earlier, leading to early right ventricular activation. (From Horowitz et al: Epicardial and endocardial activation during sustained ventricular tachycardia in man. *Circulation* 61:1227, 1980, used by permission from the American Heart Association, Inc.)

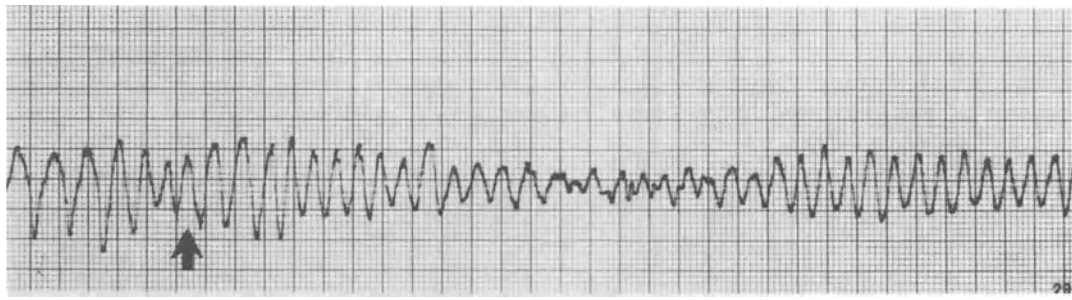


FIGURE 5–24. During an electrophysiology study in this patient with an anterior wall left ventricular aneurysm following myocardial infarction, a sustained episode of rapid VT was initiated (extreme left-hand portion of strip). At the arrow two closely coupled electrical stimuli are applied via an intracardiac catheter in the right ventricle in an attempt to terminate the arrhythmia. However, the stimuli accelerated of the rate of VT and produced a more unstable rhythm (middle to right-hand end of strip) that degenerated to ventricular fibrillation.

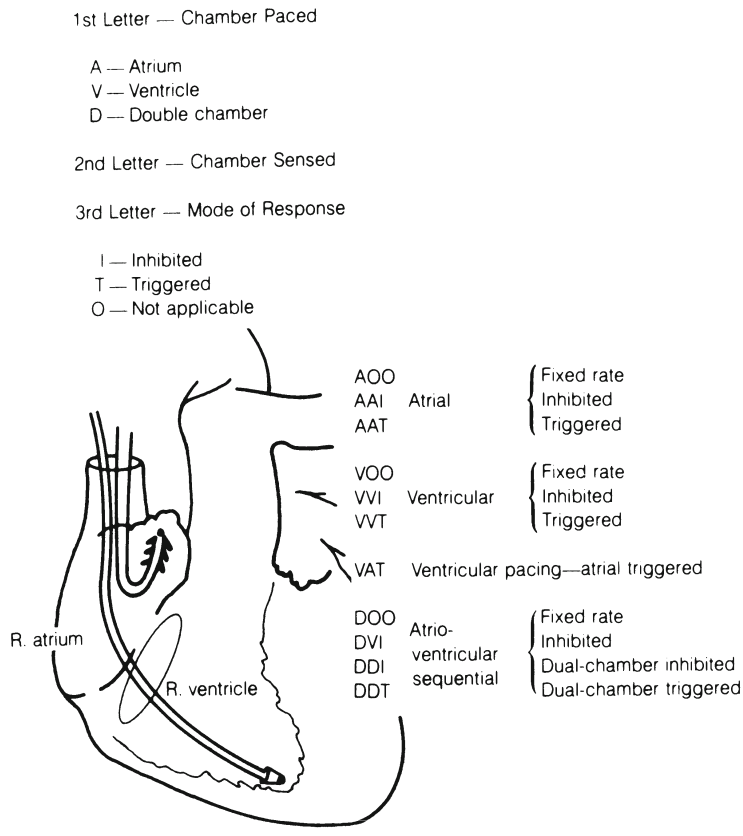


FIGURE 5–25. International code to describe modes of pacing. The dual-lead system shown emphasizes that either one or both may be employed by the clinician. As an alternative, the electrodes may be placed on the epicardium or the atrial lead can be in the coronary sinus. (From Harthorne JW: Indications for pacemaker insertion: Types and modes of pacing. *Progr Cardiovasc Dis* 23:395, 1981, by permission of Grune and Stratton.) See also table 9–6.

be found in chapter 9. At present, the device is limited to cases of severe life-threatening ventricular arrhythmias that have proved difficult to manage by other means [65].

12. Pacemaker Therapy for Supraventricular and Ventricular Arrhythmias

12.1 GENERAL CONSIDERATIONS

Because of the increasing complexity of cardiac pacemakers, a short-hand code has been devised for describing the essential features of each device (table 9–6 in chapter 9). At present, a five-position code has been adopted, and this will be used throughout this section. The important features of the first three letters of the code are listed in figure 5–25; the fourth and fifth letters of the code correspond to sophisticated pacing features that will be discussed only briefly below.

12.2. PACING TO PREVENT BRADYCARDIA

Symptomatic patients with an absent or inappropriately slow sinus mechanism are candidates for cardiac pacing, as are those who have an inappropriately slow ventricular rate during atrial fibrillation. Pacing may be needed when a required antiarrhythmic drug program pro-

duces bradycardia. Generally, such individuals do well with a standard ventricular demand pacemaker (VVI), with the rate adjusted to alleviate symptoms. On occasion — provided that no competing atrial rhythm is present — "physiologic" pacing may improve cardiac performance by synchronizing atrial and ventricular contractions by means of devices capable of sensing and/or pacing the atrium followed by sequential ventricular pacing (e.g., VAT, DVI, DDD). If atrioventricular conduction is intact, atrial demand pacing (AAI) may be used.

In some patients, preserving the atrial contribution to ventricular filling offers hemodynamic improvement. Evidence for the "pacemaker syndrome" (i.e., a fall in systolic pressure of more than 25 mm Hg during ventricular pacing, which may be accompanied by "cannon" waves in the jugular venous pulse) should alert clinicians to the possible need for "physiologic" pacing [66].

12.3. PACING TO PREVENT SUPRAVENTRICULAR TACHYCARDIAS

Permanent pacing techniques have a limited role in *preventing* supraventricular arrhythmias. However, selected patients with troublesome circus movement tachycardias involving the AV node and/or bypass tracts can derive benefit from various forms of sequential or simultaneous AV pacing.

As summarized by Weiner [67], the ventricular impulse must be appropriately timed to collide with the atrial impulse in the antegrade limb of the circuit and must find the retrograde limb of the circuit refractory [67]. Pacing modalities that have been employed include

1. Continuous AV sequential pacing (DVI).

2. Continuous AV sequential pacing (DVI) with programmable options to stimulate the atrium and ventricle sequentially (DVO) or simultaneously (DOO). (Since this pacemaker is capable of sensing ventricular events in the DVI and DVO modes, it has been referred to as a "dual-demand pacemaker.")

3. Dual-chamber sensing with simultaneous atrial and ventricular stimulation in response to tachycardia (DDT).

Additional pacing modes that have been used, although with limited success, include competitive underdrive and overdrive suppression. These modes are designed to keep the reentrant pathway constantly depolarized.

12.4. PACING TO TERMINATE SUPRAVENTRICULAR TACHYCARDIAS

The supraventricular tachycardias susceptible to acute termination by pacing techniques consist of rhythm disturbances that are sustained via a reentrant mechanism (e.g., atrial flutter and reentrant SVT). When applied close enough to the reentrant circuit, stimuli of sufficient magnitude and appropriate timing may depolarize a portion of the activation pathway and thus interrupt the tachycardia. Although some supraventricular tachycardias can be terminated by single stimuli, others require multiple stimuli (e.g., atrial flutter).

Ectopic automatic atrial tachycardias and chaotic atrial rhythm disturbances such as MAT or atrial fibrillation are *not* amenable to termination by pacemakers.

12.4.1. Temporary Pacing Techniques. Pacing electrodes positioned transvenously or sewn onto the atrial epicardium during cardiac surgery can be used both for recording purposes (to document the arrhythmia) and for acute termination of tachycardias. Reentrant supraventricular tachycardias — those due to AV nodal reentry or to reentry involving an AV bypass tract — can be terminated by fixed-rate rapid atrial pacing (figure 5–26*A*) or by the introduction of critically timed atrial premature beats. Atrial flutter may often be terminated by bipolar rapid atrial pacing when one uses sufficiently rapid rates (up to 140 per cent of spontaneous atrial rate), a sufficient duration of pacing (10 to 30 sec), and adequate stimulus strength (5 to 20 ma) (figure 5–26*B*).

Difficulties in terminating atrial flutter may be encountered when the spontaneous atrial rate is rapid (e.g., >350 bpm) and when pacing stimuli are applied at a great distance from the focus initiating the arrhythmias.

12.4.2. Permanent Pacing Techniques. Clinical experience with permanent pacemakers has almost exclusively involved patients with forms of reentrant SVT. Available devices include patient-activated units that utilize radiofrequency signals (figure 5–27) and "scanning" units that continuously monitor the patient for the presence of tachycardia and can activate special antitachyarrhythmia functions (e.g.,

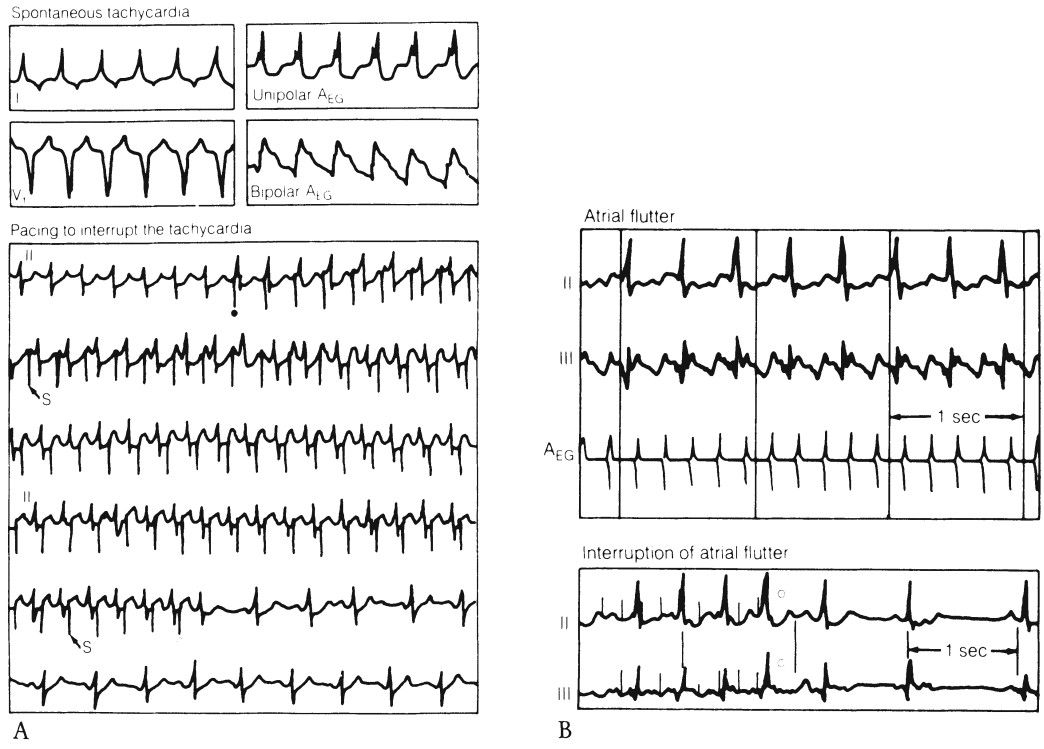


FIGURE 5–26. *A*, Rapid atrial pacing to interrupt paroxysmal atrial tachycardia. *Top*, Sequential tracings show regular tachycardia with narrow QRS complex and 1:1 AV relationship. Surface ECG leads show regular, narrow QRS complexes at 150 bpm, but no atrial activity can be identified. Bipolar and unipolar atrial electrograms (A_{EG}) demonstrate a 1:1 AV relationship in which the atrial and ventricular events occur simultaneously. *Bottom*, Continuous lead II recording during and after overdrive atrial pacing of the tachycardia. Pacing at 160 bpm is initiated (solid circle) and capture of the atria is achieved by the end of the second ECG strip. After cessation of pacing (open circle), sinus rhythm resumes. (S = pacemaker stimulus artifact.)

B, Rapid atrial pacing to interrupt atrial flutter. *Top*, Simultaneous tracings at 50 mm/sec reveal flutter (300 bpm) with 2:1 AV conduction. Lead III shows typical sawtooth pattern of the flutter waves. Bipolar A_{EG} shows highly regular morphology and beat-to-beat interval characteristic of atrial flutter. *Bottom*, Lead II and III recordings (same patient) during rapid atrial pacing at 350 bpm, which interrupts the atrial flutter. On cessation of atrial pacing (open circle), sinus rhythm resumes. (Recording speed = 50 mm/sec.) (From MacLean WAH, Cooper TB, Waldo AL: Use of cardiac electrodes in diagnosis and treatment of tachyarrhythmias. *J Cardiovasc Med*, September, 1978, pp 968 and 973.)

rapid "burst" atrial pacing, sequential or simultaneous AV pacing). External programmers may be used to initiate burst atrial pacing (figure 5–28) or critically timed extrastimuli (figure 5–29).

Permanent pacing modalities used to *terminate* supraventricular tachycardias include

1. Patient-triggered fixed-rate ventricular pacing (VOO).
2. DVI-DVO, DOO (see above).
3. DDT (see above).
4. Rapid atrial pacing.
5. Critically timed extrastimuli.

When contemplating the use of permanent pacemaker techniques for patients with supraventricular arrhythmias, the clinician should consider the following important factors:

1. The need to perform detailed intracardiac studies to define the precise arrhythmia

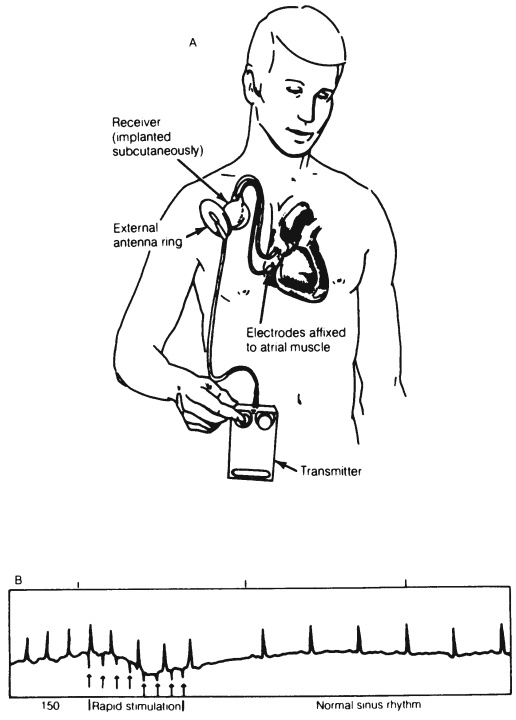


FIGURE 5–27. *A*, Schematic representation of patient-activated radiofrequency pacemaker. *B*, Tracing showing episode of tachycardia at a rate of 150 bpm reverted to sinus rhythm by brief rapid atrial stimulation. (From Kahn AR, Citron P: Patient initiated rapid atrial pacing to manage supraventricular tachycardia. In Lüderitz B (ed): *Cardiac pacing: diagnostic and therapeutic tools*. Berlin, Springer-Verlag, 1976, pp 206 and 207.)

mechanism and to establish the response of the arrhythmia to proposed pacing modalities.

2. The need for a stable, reliable atrial lead that can adequately sense atrial events and capture the atrium during tachycardia. Fortunately, the newly designed atrial "J" shaped leads and permanent coronary sinus leads have led to cumulative survival rates similar to those obtained with standard ventricular leads. On occasion, a thoracotomy is necessary for implantation of a permanent electrode.

3. The possible need to continue medical therapy, which may become a more viable option when used in a complementary fashion with pacing.

4. The fact that pacing techniques may be inappropriate for patients unable to recognize the onset of a tachycardia or to tolerate rapid heart action for prolonged periods of time. Rapid atrial pacing should be avoided in patients with accessory pathways having a short effective refractory period and a propensity for rapid ventricular rates.

12.5. PACING TO PREVENT VENTRICULAR TACHYCARDIA

Individuals with bradycardia-dependent ventricular arrhythmias or those with paroxysmal ventricular arrhythmias due to prolonged Q-T intervals (particularly those secondary to drugs) may benefit from pacing. In the latter case, pacing may be the only means to stabilize the patient until the offending drug is removed. The proposed beneficial effects of pacing in these settings is a decrease in the dispersion of ventricular refractoriness from acceleration of the heart rate. The availability of a large number of antiarrhythmic drugs has quenched earlier enthusiasm for maintenance overdrive pacing in patients with paroxysmal VT.

Since the pacing site may be critical for preventing tachycardia, the various modes listed below should be tried on a temporary basis before committing the patient to a permanent device:

1. Overdrive atrial pacing.
2. Overdrive ventricular pacing.
3. Overdrive AV sequential pacing.

12.6. PACING TO TERMINATE VENTRICULAR TACHYCARDIA

The success rate of cardiac pacing for terminating VT depends on a number of factors, including the setting in which the tachycardia occurs, the rate of tachycardia, and the pacing technique.

12.6.1. Temporary Pacing Techniques. Experience derived from clinical electrophysiological laboratory studies has indicated that the following pacing methods may terminate VT:

1. Single or double premature ventricular stimuli applied at progressively premature coupling intervals. These stimuli are triggered by an endocardial electrogram or surface ECG recording. Multiple pacing sites may be required.

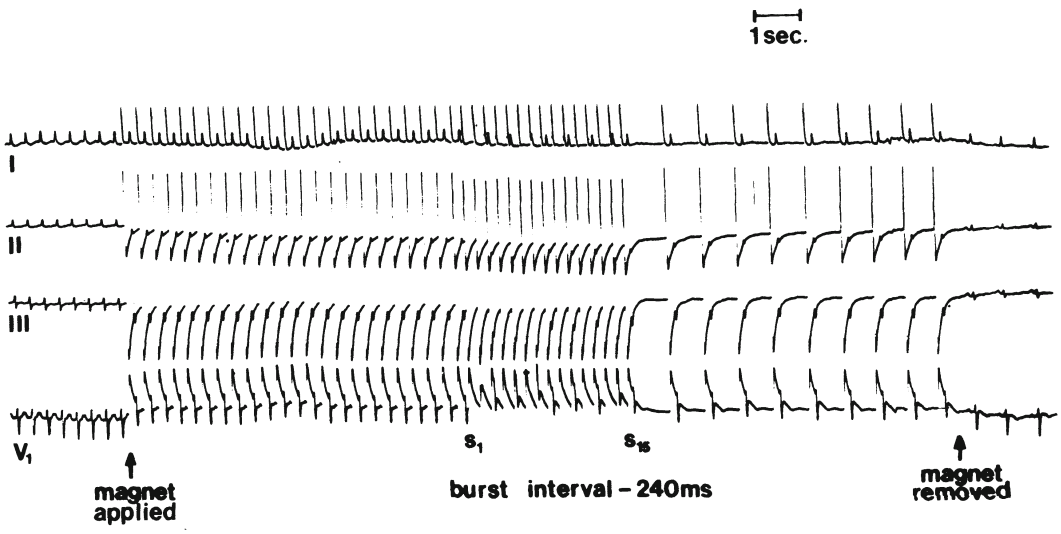


FIGURE 5–28. Burst atrial pacing to terminate SVT shown in a continuous tracing of leads I, II, III, and V_1. Application of a magnet synchronizes the pacer with the atrial electrogram. This is followed by a 15-beat "burst" of atrial pacing at 240-msec intervals, successfully terminating SVT, as evidenced by the onset of normal sinus rhythm when the magnet is removed. (Courtesy of Julio A. Danoviz, M.D., and John F. Moran, M.D., Loyola University Medical Center, Chicago, IL.)

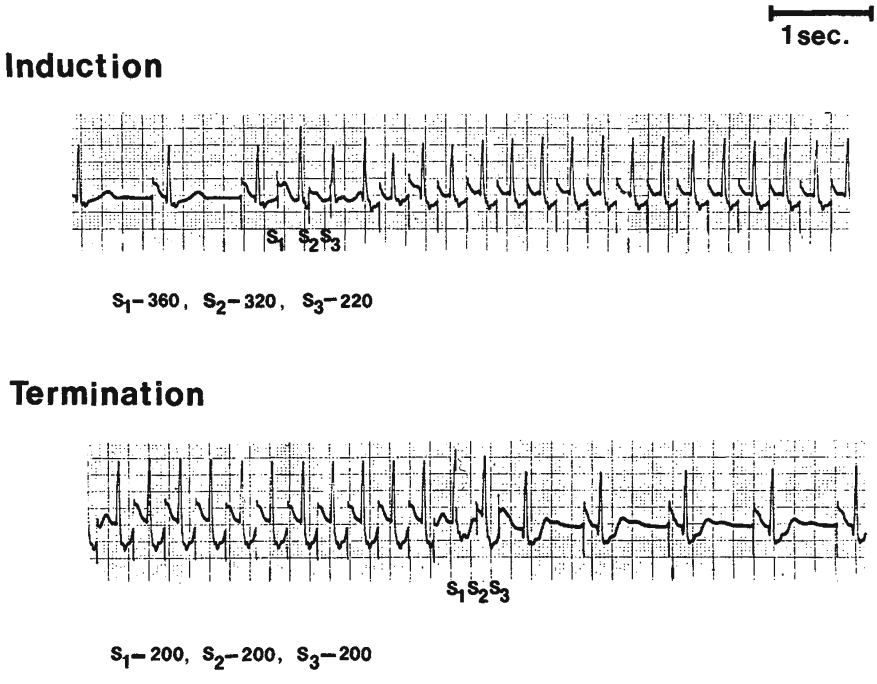


FIGURE 5–29. Critically timed extrastimuli to terminate SVT. *Upper tracing*, Induction of SVT in an atrially paced patient by three critically timed pulses followed by synchronization with the tachycardia while the magnet is in place. *Lower tracing*, Termination of SVT by three additional critically timed pulses, with a return to atrial synchronous pacing at 71 bpm. (Courtesy of Barry L. Albert, M.D., University of Pittsburgh School of Medicine, Pittsburgh, PA.)

2. Brief bursts of rapid ventricular pacing. If these fail to terminate the tachycardia but it can be stopped by single or double ventricular premature stimuli, it is possible that the tachycardia is actually terminated but is rapidly reinitiated by pacing. In such a case, a slower rate of ventricular pacing should be tried.

The above techniques are limited by the fact that therapy often must be initiated rapidly; cardioversion is the preferred technique outside the clinical electrophysiology laboratory. Furthermore, pacing during VT carries the risk of accelerating the rate with degeneration to a more malignant rhythm (figure 5–24).

12.6.2. Permanent pacing techniques. This therapeutic option is used only rarely because of the risk of accelerating the tachycardia rate and the increasing availability of potent antiarrhythmic agents. Furthermore, only patients who are hemodynamically stable during the arrhythmia are appropriate candidates. Pacing modes that have been employed include:

1. Patient-triggered slow-rate asynchronous ventricular pacing (VOO).
2. Patient-triggered "burst" ventricular pacing.
3. A "scanning" pacemaker with automatic antitachycardia pacing using either critically timed premature stimuli or burst pacing.

13. A Practical Approach to the Evaluation and Management of Arrhythmias

13.1. GENERAL CONSIDERATIONS

Before embarking on any therapeutic program for a rhythm disturbance, the clinician should confirm that an arrhythmia is in fact present and should ascertain both its mechanism (if possible) and its functional significance to the patient. Since not all arrhythmias require therapy, the safest and most effective therapy for the patient should be chosen, with careful consideration given to both acute and possibly chronic phases of treatment.

13.2. DIAGNOSIS

13.2.1. History. A complete history includes an investigation of the possible factors that triggered the arrhythmia, such as food or drink, drugs, activities, emotional state, and medical illnesses. A profile of the patient's past response to drug therapy should also be carefully catalogued.

Cyclical variation of the arrhythmia over time may provide important clues as to the mechanism. Asking the patient to tap out the cadence of the arrhythmia on a table top may provide the alert clinician with a surprisingly accurate representation of the rhythm abnormality.

Because the hemodynamic consequences of an arrhythmia are determined largely by myocardial and valvular function, it is *incorrect* to assume that hemodynamic decompensation indicates a rhythm disturbance of ventricular origin. For example, in a patient with moderate mitral stenosis, atrial fibrillation with a rapid ventricular response might precipitate pulmonary congestion and compromise the systemic circulation.

13.2.2. Physical Examination. Inspection of the jugular venous impulses should be performed in an attempt to estimate the pattern and rate of atrial contraction and to determine its relationship to ventricular contraction. Unfortunately, both ventricular tachycardia and supraventricular tachycardia may be associated with regular VA or AV conduction ratios. Therefore, evidence of AV dissociation in the form of "cannon" waves is more helpful and is suggestive — but not diagnostic — of a tachycardia with a junctional or ventricular origin.

On *auscultation*, the first heart sound will be accentuated, with short P-R intervals, and may be a clue to the presence of the preexcitation syndrome. Repeated auscultation during alterations of heart rate and AV conduction (either spontaneous or induced by carotid sinus pressure) may indicate a change in the intensity of the first heart sound as conduction of the impulse shifts back and forth from the bypass tract to the normal AV conduction system. Complete AV block results in a variable relationship between S_4 and S_1, but this may be difficult to detect clinically.

13.3. SPECIALIZED ELECTROCARDIOGRAPHIC PROCEDURES

13.3.1. Carotid Sinus Pressure. This invaluable maneuver should be employed often to aid in the diagnosis of arrhythmias. If no significant bruits are present over the carotid arteries, the

TABLE 5–16. Effect of carotid sinus pressure on tachyarrhythmias

Arrhythmia	Possible responses to CSP				
	No effect	Gradual slowing	Abrupt conversion to sinus rhythm	AV block and decreased ventricular rate	Other
1. Sinus tachycardia		+			
2. PSVT-AV nodal reentry	+		+		
3. PSVT-Concealed bypass tract	+		+		Slight slowing
4. Automatic atrial tachycardia	+			+	
5. Atrial flutter	+			+	Atrial fibrillation
6. Atrial fibrillation	+			+	
7. Ventricular tachycardia	+				AV dissociation

Modified from Bigger JT: Supraventricular tachycardia. *Hosp Pract*, August, 1980, p 51.

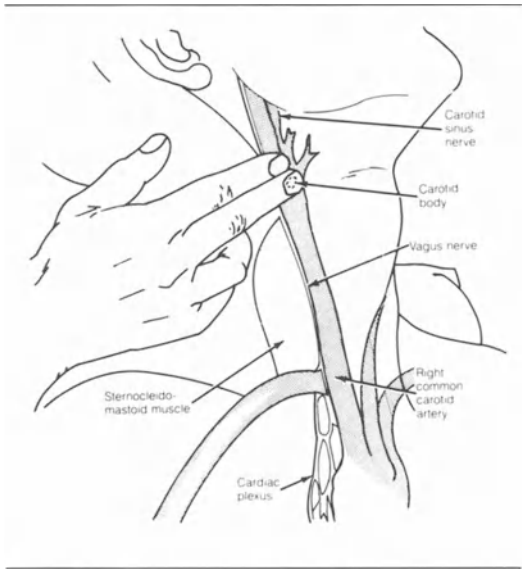


FIGURE 5–30. As an aid to diagnosis of a cardiac arrhythmia, external pressure can be applied using a gentle massaging motion on the carotid sinus in conjunction with ECG recording. This pressure stimulates baroreceptors, activating a reflex that results in vagal inhibition of the heart. The most important application of the technique is in differentiating causes of regular tachycardia when no P waves are apparent. (From Bigger JT: Supraventricular tachycardia. *Hosp Pract*, August, 1980, p 51; illustration by Carol Donner.)

patient should be placed in the recumbent position, and continuous ECG monitoring should be carried out (if at all possible).

Figure 5–30 shows the anatomical location of the carotid sinus. Continuous external pressure is applied in a circular motion to massage the right and left carotid sinuses *sequentially* for 3 to 5 seconds. Because of the obvious risk of cerebral hypoperfusion, simultaneous massage of both carotid sinuses is contraindicated.

In this manner, stimulation of baroreceptors activates a reflex that results in vagal discharge. Pressure applied to the right carotid sinus usually leads to sinoatrial slowing and/or block, while pressure on the left usually results in AV block; however, in some patients, the opposite pattern or a mixed response may be encountered. The effect of carotid sinus pressure on various tachyarrhythmias is summarized in table 5–16.

13.3.2. Recording Procedures to Detect Atrial Activation. On occasion, the traditional ECG leads do not record distinct atrial depolarizations, making diagnosis of an arrhythmia difficult. Specialized leads can be employed to enhance the amplitude of atrial deflections and to elucidate the relationship between atrial and ventricular events. In general, these specialized leads are placed in close proximity to the atrium and may be manipulated to achieve the optimal

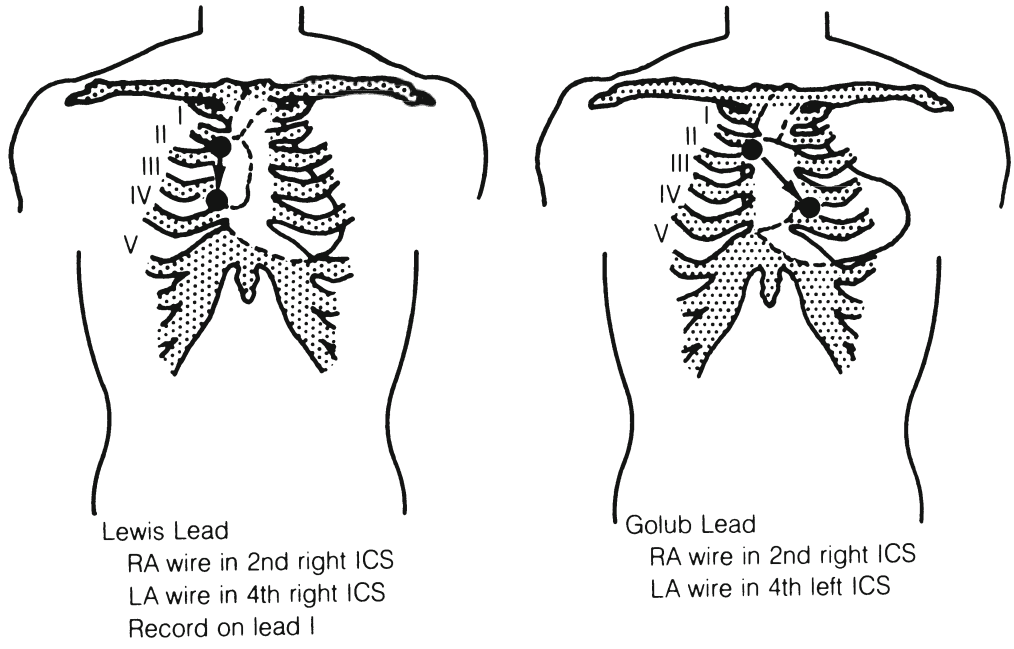


FIGURE 5–31. Lewis and Golub leads. The axis of the parasternal lead closely overlies the right atrium, picking up its excitation (P) wave. When the right atrium is enlarged, the diagonal Golub lead parallels the axis of atrial excitation when a Lewis lead might be too far to the right. The recording is made from lead I. (ICS = intercostal space.) (From Ferrer MI: *Electrocardiographic notebook*. Mt Kisco, New York, Futura Publishing Co, 1973.)

vectorial orientation in order to record the atrial mechanism. The available specialized lead systems include (1) the Lewis and Golub leads (figure 5–31), (2) an esophageal lead (figure 5–32), and (3) a right atrial lead (figure 5–33).

14. Management of Cardiac Arrhythmias

Disturbances of cardiac rhythm can be classified simply into those in which the heart rate is excessively slow or excessively fast and those requiring urgent intervention to prevent hemodynamic compromise. Figures 5–34 and 5–35 provide general guidelines for the management of supraventricular and ventricular arrhythmias.

15. Syncope

Patients are often admitted to a cardiac intensive care unit for the evaluation of syncope. While a cardiac arrhythmia that is excessively slow or excessively fast and causes cerebral hypoperfusion may cause transient loss of consciousness, a number of other conditions should be considered (figure 5–36).

FIGURE 5–33. *A*, Regular rapid repetitive atrial activity (250 bpm) can be seen in the bipolar atrial lead (*center strip*). Simultaneously recorded surface ECG leads V_1 and V_5 aid in distinguishing atrial and ventricular events. This recording is suggestive of atrial flutter (slowed by antiarrhythmic therapy). (A_{EG} = atrial electrogram.) *B*, Sinus rhythm can be seen in simultaneously recorded leads (as in A) in a different patient. The sharp bipolar deflection in the center panel corresponds to the P waves recorded on the body surface leads.

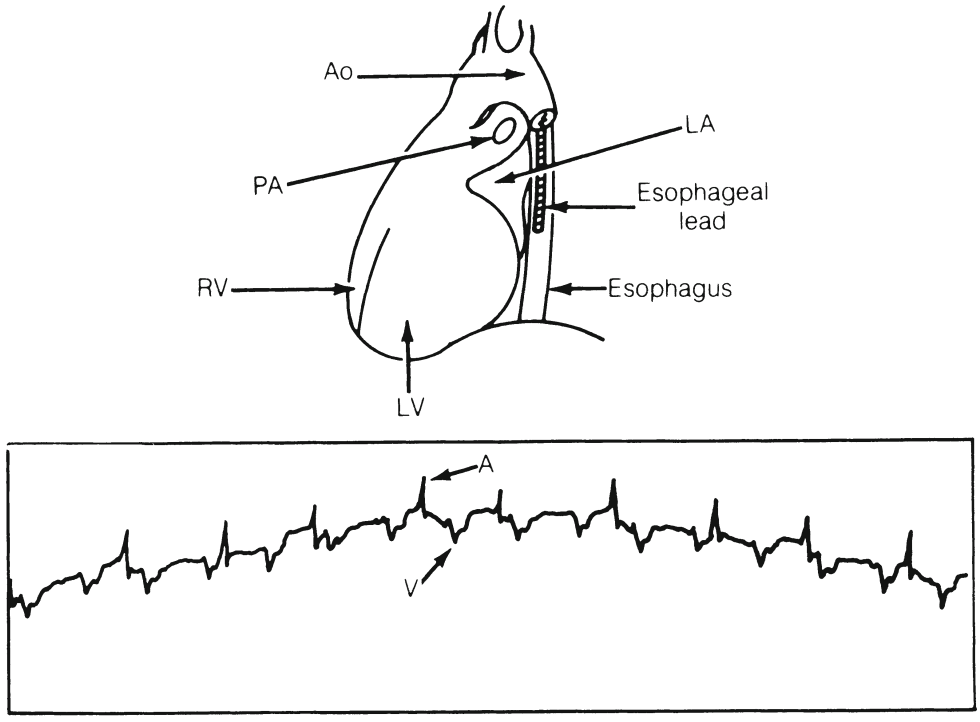
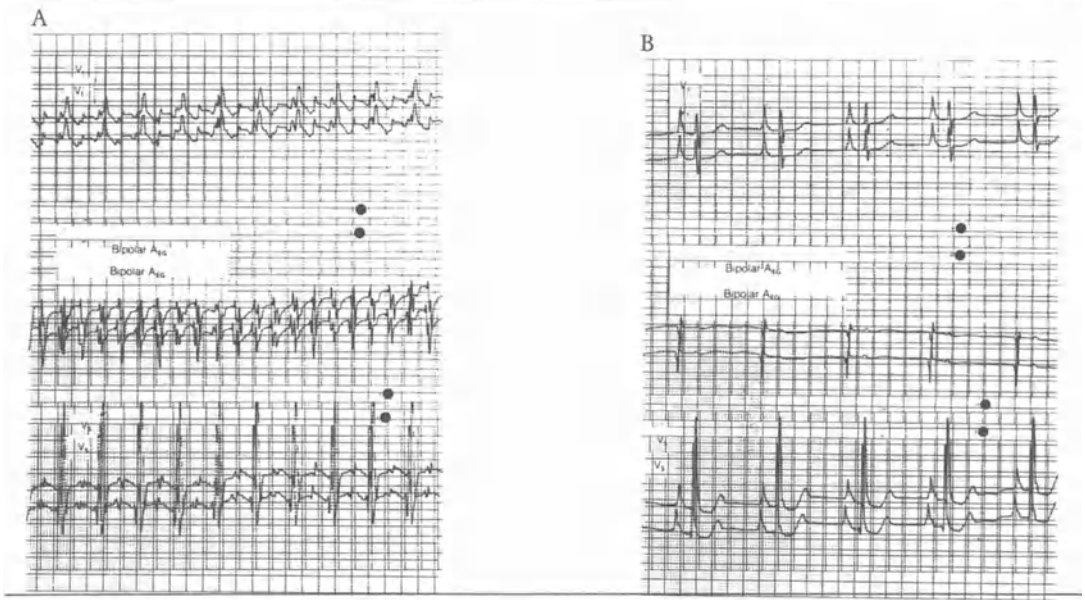


FIGURE 5–32. Esophageal lead. This lead wire is enclosed in a rubber tube and is swallowed down to the level of the left atrium (LA). Often, it reveals hidden P waves. (Ao = aorta; PA = pulmonary artery; RV = right ventricle; LV = left ventricle.) (From Ferrer MI: *Electrocardiographic notebook*. Mt Kisco, New York, Futura Publishing, 1973.) In the recording shown here, the narrow upright complexes correspond to atrial activity and the broad inverted complexes correspond to ventricular activity. AV dissociation is present, indicating that the rhythm is ventricular tachycardia. (A = atrial event; V = ventricular event.) (From Antman EM: *Supraventricular Arrhythmias*, 1981, Upper Montclair, NJ, Health Scan, Inc., p 46.)



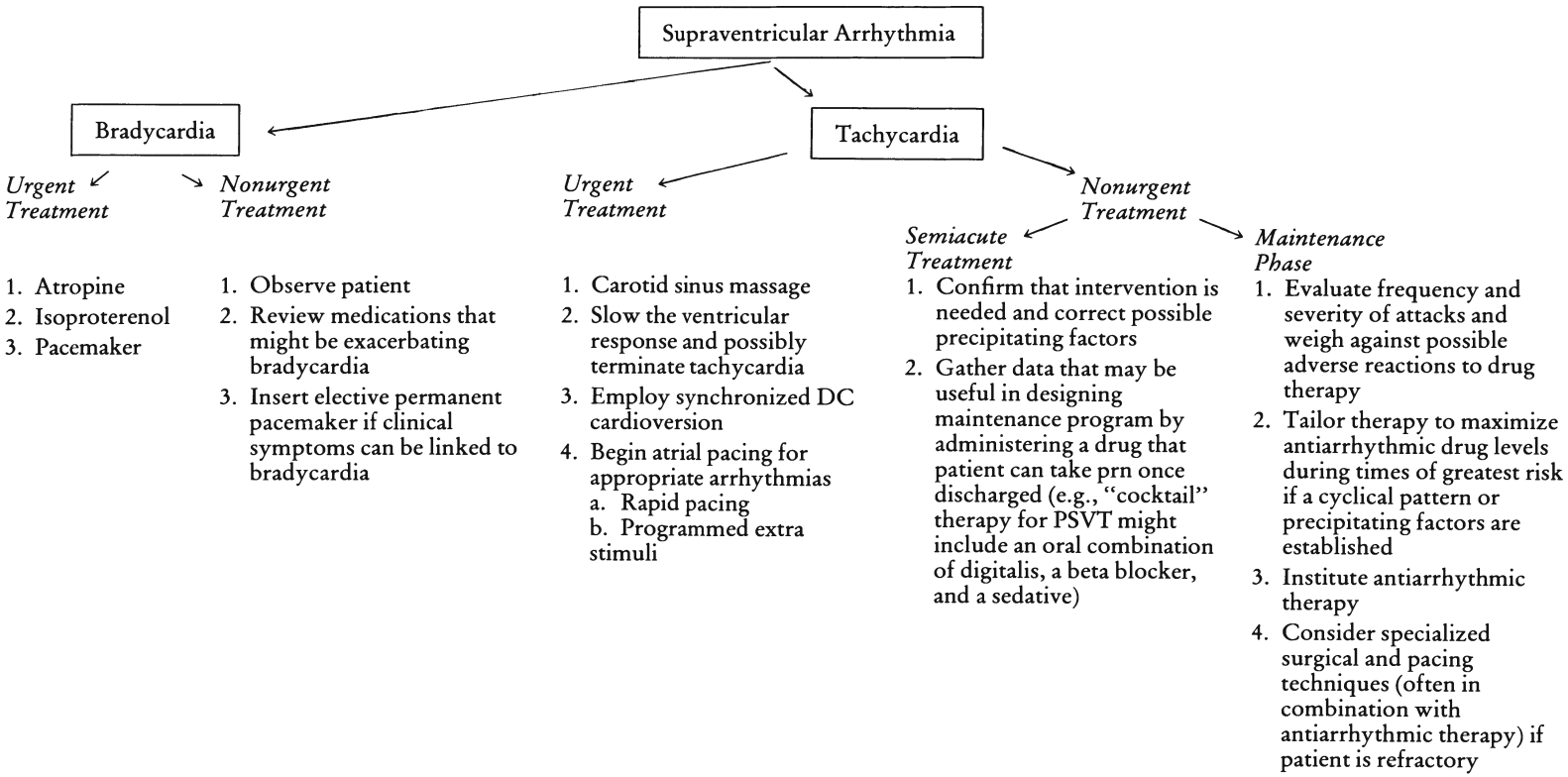


FIGURE 5–34. Guidelines for urgent and nonurgent management of supraventricular arrhythmias.

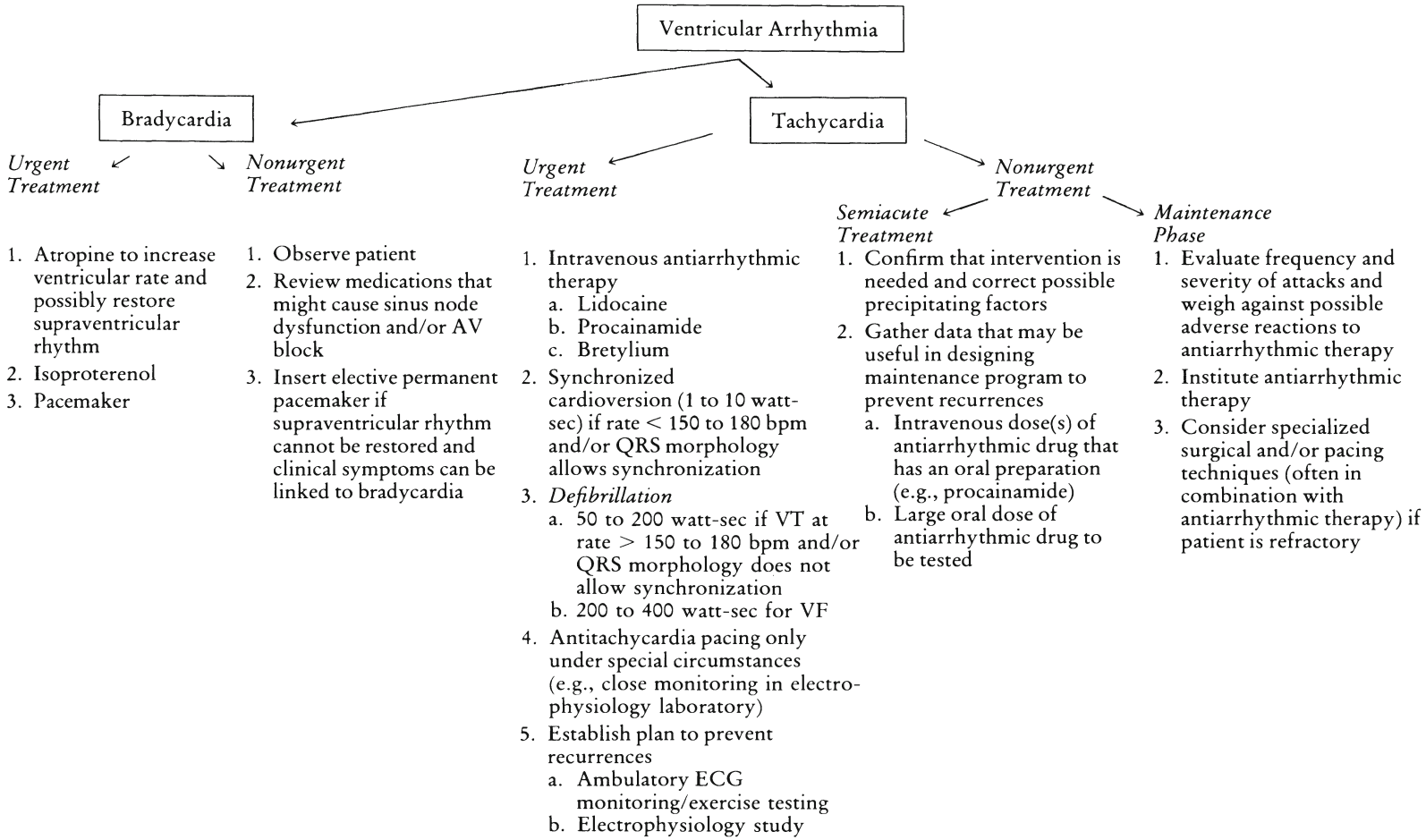


FIGURE 5–35. Guidelines for urgent and nonurgent management of ventricular arrhythmias.

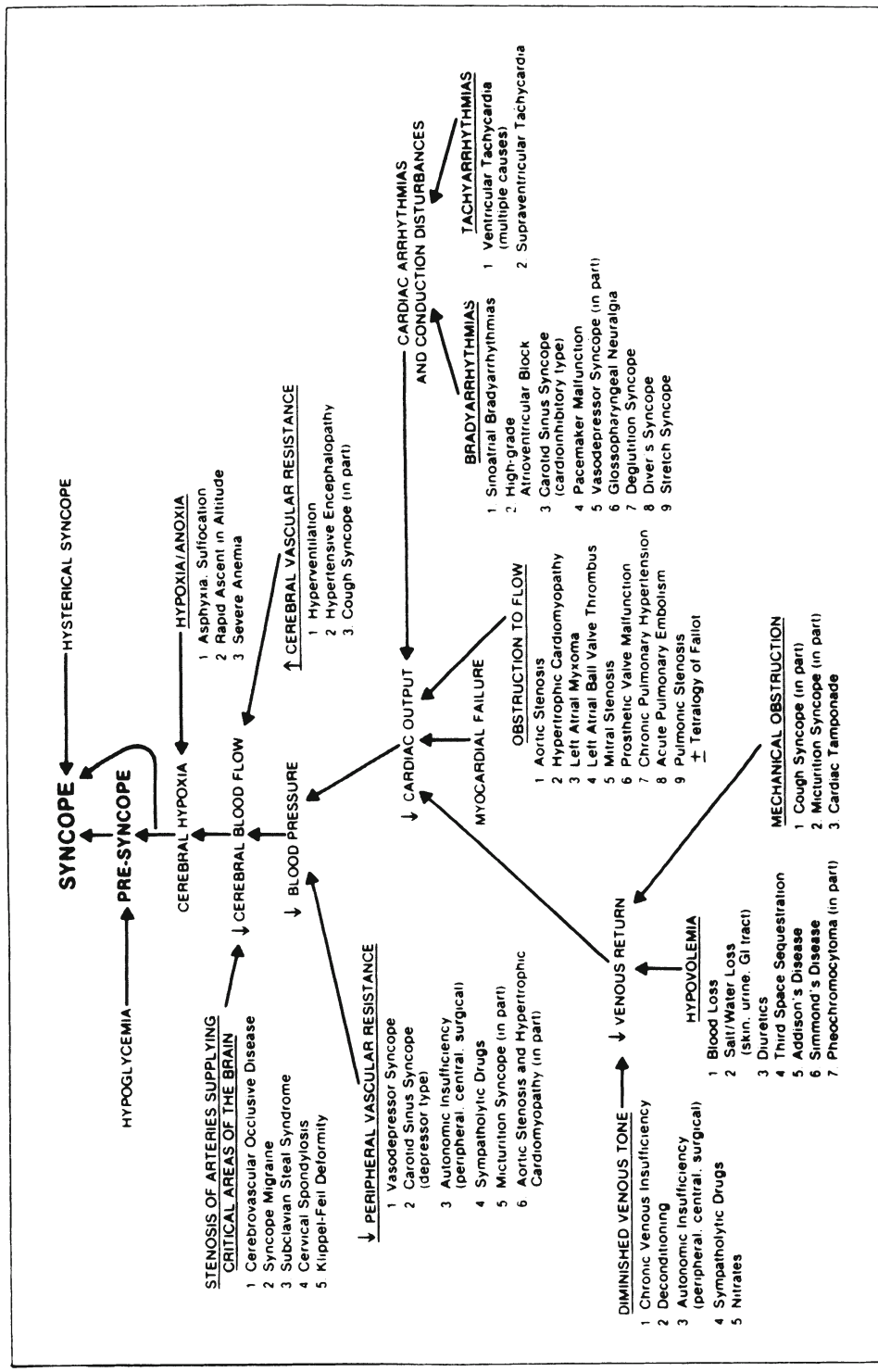


FIGURE 5–36. Pathophysiological mechanisms associated with the various courses of syncope. Arrows indicate increase (↑) or decrease (↓). (From Alpert MA: Syncope: Clinical, pathophysiologic, and therapeutic considerations (Part II). *Cardiovasc Rev Rep* 4 [10]:1378, 1983.)

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6. PHARMACOLOGICAL THERAPY OF CARDIAC ARRHYTHMIAS: ANTIARRHYTHMIC AGENTS, BETA ADRENOCEPTOR BLOCKING AGENTS, AND DIGITALIS GLYCOSIDES

1. General Principles

The ideal approach to the management of cardiac rhythm disorders depends on the following:

1. Proper identification of the arrhythmia.
2. An understanding of the natural history of the arrhythmia in a particular patient.
3. An understanding of the multiple factors that may precipitate and maintain a cardiac rhythm disturbance in a particular patient.
4. An understanding of the pharmacology of the numerous antiarrhythmic drugs available.
5. An appropriate clinical assessment of the risk to the patient due to the cardiac arrhythmia versus the side effects that might ensue upon initiation of treatment with an antiarrhythmic drug.

In this chapter we will concentrate on the last two items through a discussion of the clinical pharmacology of standard and investigational antiarrhythmic agents, beta-adrenoceptor blocking agents, and digitalis glycosides. These drugs are used alone or in combination to treat cardiac arrhythmias. The therapeutic goal is to achieve an effective, well-tolerated plasma drug concentration. For serious, hemodynamically compromising, or life-threatening arrhythmias, this goal must be achieved rapidly. In many instances the steady-state plasma concentration of the drug correlates with its antiarrhythmic effect, so that monitoring of plasma drug levels can be used to assess the adequacy of drug dosing. It should be realized that despite the extensive development of new cardiovascular pharmacological agents for the treatment of arrhythmias, the "ideal" antiarrhythmic compound has not yet been produced. When reading through the discussion regarding individual drugs, the reader should bear in mind that drugs most suitable for managing cardiac arrhythmias should possess the following qualities [1]:

1. A wide therapeutic margin
2. Minimal side effects
3. A broad antiarrhythmic profile
4. Favorable hemodynamic effects
5. Intravenous and oral preparations
6. Few drug interactions but favorable drug synergism
7. Minimal effects on normal tissue
8. Prolonged action and/or cumulative effect

1.1. DRUG INTERACTIONS

Unless clinicians are aware of potential drug interactions and take preventive or corrective measures when indicated, such interactions can present appreciable risks to the patients. The first is a *pharmaceutical interaction* which consists of a chemical reaction between drugs that occurs in vitro, and that changes the physical-chemical nature of at least one of the drugs. An

TABLE 6–1. Comparative mechanisms of action of antiarrhythmic drugs*

Class	Agent	Depression of phase 0 and fast response	Effect on action potential duration	Sympatholytic effect	Depression of the slow response	Extracardiac actions
I	Quinidine	++++	Lengthen+	+(Noncompetitive antagonism)	0	Anticholinergic; peripheral vasodilator
	Procainamide	++++	Lengthen+	0	0	
	Lidocaine	++++	Shorten+	0	0	Local anesthetic
	Diphenylhydantoin	++++	Shorten+	0	0	Anticonvulsant
	Disopyramide	++++	Lengthen+	0	0	Anticholinergic
	Aprindine	++++	0	0	+	Anticonvulsant
	Mexiletine	++++	0	0	0	Anticonvulsant
	Tocainide	++++	0	0	0	Local anesthetic
II (B-adrenoceptor blocking drugs)	Propranolol	+	Shorten+	++++(Competitive inhibition)	0	Insignificant
	Oxprenolol	+	Shorten+	++++(Competitive inhibition)	0	Insignificant
	Alprenolol	+	Shorten+	++++(Competitive inhibition)	0	Insignificant
	Pindolol	Phase 4 only	0	++++(Competitive inhibition)	0	Insignificant
	Practolol	Phase 4 only	0	++++(Competitive inhibition)	0	
III	Bretylium	Increases phase 4	Lengthen ++++	Neuron blockade+	0	Hypotensive
	Amiodarone	Decreases phase 4 only	Lengthen ++++	Noncompetive blockade+	0	Coronary vasodilator
IV	Verapamil	Phase 4 only	Lengthen phases 1 and 2	Noncompetitive blockade+	++++	Coronary vasodilator

*Classification based on electrophysiological actions. ++++ = principal electrophysiological action; + = subsidiary effect; 0 = no effect in presumed therapeutic plasma concentrations. From Singh BN, Mandel WJ: Antiarrhythmic drugs: Basic concepts of their actions, pharmacokinetic characteristics and clinical applications. IN: *Cardiac arrhythmias: Their mechanisms, diagnosis and management*. Mandel WJ (ed). Philadelphia, JB Lippincott Co, 1980, p 555.

example would be the precipitation of calcium carbonate crystals when solutions of calcium chloride and sodium bicarbonate are mixed in the same intravenous line. The second type of drug interaction is a *pharmacokinetic interaction*, in which one drug effects the action or effective concentration of a second drug at the site of action. Examples of pharmacokinetic drug interactions include absorption interference, protein-binding alterations, and stimulation or inhibition of drug metabolism or of drug excretion. The third type of interaction is a *pharmacodynamic interaction*, which occurs when the pharmacological effect of one drug influences the response to another. For example, diuretic-induced hypokalemia may predispose to digitalis toxicity.

2. *Antiarrhythmic Agents*

2.1. CLASSIFICATION OF ANTIARRHYTHMIC AGENTS

Analysis and categorization of the fundamental mode of action of these drugs continues to be subject of considerable controversy. A recently published version of a popular classification scheme is shown in table 6–1 and is based on the assumption that antiarrhythmic compounds have a single, predominant electrophysiological

TABLE 6–2. In vivo electrophysiological characteristics

	Electrocardiographic intervals						Electrophysiological intervals				
Drug	Sinus rate	P-R	QRS	Q-T	A-H	H-V	ERP AVN	ERP HPS	ERP A	ERP V	ERP AP
Lidocaine	0	0	0	0	0↓	0↑	0↓	0↑	0	0	0
Quinidine	0↑	↓0↑	↑	↑	↓0↑	0↑	↓0↑	0↑	↑	↑	↑
Procainamide	0	0↑	↑	↑	0↑	0↑	0↑	0↑	↑	↑	↑
Disopyramide	0↑	0	0↑	0↑	0	0↑	0↓	↑	↑	↑	↑
Phenytoin	0	0	0	0↓	0↓	0	0↓	↓	0	0	0
Propranolol	↓	0↑	0	0↓	0↑	0	↑	0	0	0	0
Bretylium	0↓	0↑	0	0↑							0
Verapamil	0↓	↑	0	0	↑	0	↑	0	0	0	0
Amiodarone	↓	0↑	0	↑	↑	0	↑	↑ ↑	↑	↑	↑
Aprindine	↓	↑	↑	0↑	↑	↑	↑	↑	↑	↑	↑
Encainide	0	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Mexiletine	0	0	0	0	0↑	0↑	0↑	0↑	0	0	0
Tocainide	0↓	0	0	0↓	0↑	0	↓	0	0↓	0↓	0
Ethmozine	0↓	0↑	0↑	0					↑	↑	
Flecainide		↑	↑	↑	↑	↑	↑		↑	↑	↑
Lorcainide		0↑	↑	↑	0	↑	0		0	0	↑
Propafenone	0↓	↑	↑	0↑	↑	↑	0↑		0↑	↑	↑
Bethanidine	0↓	0	0	0↑							0
Cibenzoline	↑	↑	↑	0↑	0	↑	0		0	↑	

Results presented may vary according to tissue type, experimental conditions, and drug concentration. ↑ = increase; ↓ = decrease; 0 = no change; 0↑ = or 0↓ = slight inconsistent increase or decrease. A = atrium; AVN = AV node; HPS – His Purkinje system; V = ventricle; AP = accessory pathway (WPW); ERP = effective refractory period — longest $S_1 = S_2$ interval at which S_2 fails to produce a response.
From Zipes DP: Management of cardiac arrhythmias. In: *Heart disease*, 2nd ed, Braunwald E (ed), Philadelphia, WB Saunders, 1984, p 653.

action on the myocardial cell. However, as summarized by Zipes [2], "such classification schemes suffer from several inadequacies:

1. All drugs assigned to a single group do not exhibit entirely similar actions, and some drugs exert more than one type of action.

2. Classifications are based primarily on the electrophysiological properties exerted by the drugs on normal Purkinje fibers, yet these drugs may exert different effects on muscle, in different species, on acutely or chronically damaged tissue, or when the electrolyte milieu is abnormal; in vitro studies of healthy fibers usually establish the properties of antiarrhythmic agents rather than their antiarrhythmic properites.

3. Many antiarrhythmic agents produce their effects in vivo not by direct electrophysiological actions on cardiac cells but indirectly by metabolic or antiischemic actions, by effects on the central or peripheral autonomic nervous system, by improving circulatory hemodynamics, or by active metabolites.

4. Some drugs do not fit neatly into one class, leading to formulation of a variety of classifications.

5. Insights into the mechanisms by which antiarrhythmic agents may affect ion transfer are only recently being gained, and this new knowledge will undoubtedly influence concepts about how antiarrhythmic agents function.

Based upon animal studies and human clinical investigation the in vivo electrophysiological characteristics of standard and investigational antiarrhythmic drugs have been established. These are outlined in table 6–2.

2.2 PHARMACOKINETIC CONSIDERATIONS: DRUG DISTRIBUTION AND ELIMINATION

Antiarrhythmic agents as a class have a relatively narrow therapeutic/toxic ratio; the toxic concentration exceeds the effective level by only two- or threefold. Therefore, plasma levels of antiarrhythmic drugs can be an invaluable aid for monitoring therapy, but it is essential that the results be interpreted appropriately. In addition, the clinician must have a working knowledge of pharmacokinetic principles for optimal use of antiarrhythmic agents [3].

Once a drug has been *absorbed* or *injected*

into the body, two basic processes — *distribution* and *elimination* — determine its concentration at any given time. The term *clearance* (CL), defined as the volume of plasma or blood cleared of drug in a unit of time, is used to express the body's ability to eliminate a given drug. Since clearance is measured in terms of units of flow, it can be assessed relative to organ blood flow to determine the efficiency of elimination. Thus, if a drug is cleared at a rate of 750 ml/min by the liver, which has a blood flow of 1500 ml/min, then 50 per cent of the drug delivered to the liver is removed in a single pass, so that the extraction ratio is 0.5.

At steady state, the concentration of a drug that has been infused depends only on drug clearance and the infusion rate. Unfortunately, pharmacokinetic principles are not as simple as the above statement would imply. Various compartmental models are useful for describing and predicting the time course of antiarrhythmic drug concentrations in plasma [3]. After oral administration, the body generally behaves as a single compartment, where only drug clearance and the terminal half-life of elimination need be considered in designing dosage regimens. On the other hand, many drugs administered intravenously can be fit to a two-compartment pharmacokinetic model, in which the body is assumed to consist of: a *central* compartment composed of the plasma and extracellular fluid of highly perfused tissues (heart, lungs, liver, and kidneys) and a *peripheral* compartment composed of muscle, skin, and fat into which an administered drug perfuses more slowly. Drugs enter and leave via the central compartment; reversible transfer occurs between the two compartments, with the peripheral compartment acting as a "reservoir" connected to the central compartment (figure 6–1).

Following sudden intravenous injection of a drug, one can define an *early* phase, during which plasma drug concentration falls rapidly, and a *later* phase of slower decline in concentration. The early phase is dominated by distribution of the drug between the volume in compartment 1 (central) and the volume in compartment 2 (peripheral). The dominant process occurring during the later phase is elimination of drug from the central compartment. Various terms are used to describe the parameters of the two-compartment model (table 6–3) and are discussed below [3].

The volume of distribution (V_d) is not a real space but is rather an estimate of the extent of drug distribution through the body fluid compartments. It is, in effect, the relationship between the amount of drug in the body and the plasma drug concentration after absorption and distribution. Drug *half-life* ($t_{1/2}$) refers to the

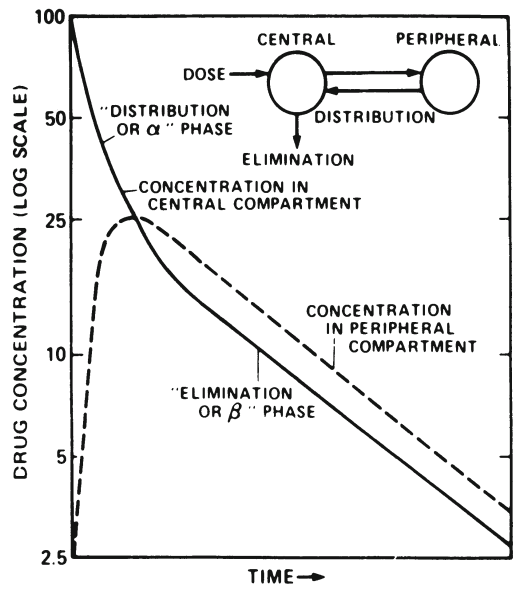

FIGURE 6–1. Conceptual representation of a two-compartment model showing reversible distribution between a rapidly equilibrating peripheral compartment and the central compartment. Also shown are the concentrations of drug at various times, in both the central and the peripheral compartments, following an intravenous bolus into the central compartment. (From Harrison DC, Meffin PJ, Winkle RA: Clinical pharmacokinetics of antiarrhythmic drugs. *Progr Cardiovasc Dis* 20:217–242, 1977.)

TABLE 6–3. Relationships between pharmacokinetic parameters

Equation 1	$t_{1/2_\beta} = \frac{V_d \times 0.693}{CL}$
Equation 2	$\bar{C}_{ss} \cong \frac{D \times t_{1/2_\beta}}{V_d \times \tau}$
	D = Dose
	τ = Dosage interval

Key: $t_{1/2_\beta}$ = elimination half-life; V_d = volume of distribution; CL = clearance; $\bar{C}_{ss}$ = drug concentration in plasma at steady state.

time required for the drug concentration to decrease by 50 per cent; it is important when considering intravenous drug dosing to differentiate a $t_{1/2}$ of distribution ($t_{1/2\alpha}$) from the $t_{1/2}$ of elimination ($t_{1/2\beta}$). For the commonly employed drugs lidocaine and procainamide, an understanding of this concept is important to proper drug dosing in the acute management of cardiac arrhythmias.

Certain caveats are worth noting: Strict reliance on listed values for $t_{1/2\beta}$ may be misleading since $t_{1/2\beta}$ is a hybrid term that is heavily dependent on V_d and CL, as can be seen in Equation 1 in table 6–3. Abnormalities of renal and hepatic function can significantly alter $t_{1/2\beta}$ so that serum levels must be monitored frequently. Since it takes a finite time after starting a patient on a given dose for plasma drug concentrations to reach their eventual steady-state level, one should not order a serum antiarrhythmic drug level until a stable equilibrium has been achieved. At least three to four half-lives must elapse for the drug to attain greater than 90 per cent of its steady-state concentration ($\bar{C}_{ss}$).

2.3. ORAL DRUG ADMINISTRATION AND BIOAVAILABILITY

After oral administration of an antiarrhythmic drug, only a fraction of the dose actually reaches the systemic circulation. This fraction (F) represents the systemic availability or *bioavailability* of a given drug. For agents that can be administered intravenously as well as orally, F can be estimated by comparing the area under the serum concentration curve (AUC) for an oral dose (AUC_{PO}) with that for an intravenous dose (AUC_{IV}):

$$F = \frac{AUC_{PO}}{AUC_{IV}}$$

Bioavailability of orally administered antiarrhythmic agents is less than 100 per cent because of incomplete gastrointestinal absorption (in the small intestine) and presystemic metabolism (in the liver). The completeness of gastrointestinal absorption (which may vary from 50 to over 90 per cent) depends on the physical-chemical characteristics of the tablet (especially its dissolution rate), the integrity of the gut mucosa, and the rate of gut motility. Disease states such as malabsorption syndromes or concomitant use of drugs that alter gut motility may impair the degree and rate of absorption of orally administered antiarrhythmic agents. When maintenane of therapeutic blood levels is critical, such as in the management of life-threatening ventricular tachyarrhythmias, the intravenous route is the preferred method of drug.

TABLE 6–4. Factors influencing drug disposition

1. Activity of basic removal process (intrinsic clearance) (*Example*: First-pass hepatic metabolism)
2. Organ blood flow (*Example*: Diminished hepatic blood flow in congestive heart failure)
3. Drug binding in blood and tissues (*Example*: Amount of *protein-bound* drug will greatly affect *free* drug in serum)

2.4. DRUG DISPOSITION AND DISEASE STATES

For several important antiarrhythmic drugs, notably lidocaine, propranolol, and verapamil — a significant proportion of the parent compound is converted to inactive metabolites in the liver before reaching the systemic circulation. This presystemic metabolism is also referred to as *first-pass hepatic metabolism*, and it explains for the most part the striking difference between the intravenous and oral doses of drugs such as propranolol or verapamil.

Additional factors are known to alter *drug disposition* by modifying CL and V_d of antiarrhythmic compounds in both health and disease. These are outlined in table 6–4. Although such factors may be anticipated by the clinician, their precise quantitative effect on drug concentration may be difficult to calculate, necessitating frequent monitoring of serum drug levels until a steady state is achieved.

2.5. MODES OF DRUG ADMINISTRATION AND CALCULATION OF DOSE [4]

The above considerations on drug disposition notwithstanding, clinicians may arrive at a rough guess of the appropriate oral dosing regimen for an individual patient by remembering that the *loading dose* = V_d × desired concentration and that the *daily maintenance* dose = daily drug clearance × desired plasma concentration. Thus, for a 75-kg man to be treated with quinidine sulfate, the following assumptions would be made [4]:

V_d = 2 liters/kg, $t_{1/2\beta}$ = 6 hr
Desired concentration = 4 mg/liter
Loading dose = 150 liters × 4 mg/liter = 600 mg
Daily maintenance dose = 415 liters/day × 4 mg/liter
= 1660 mg/day

A convenient dosing schedule that usually does not permit peak and trough levels to vary by more than a factor of 2 or 3 is to administer the drug each time it reaches its half-life. Thus, in the example above, a schedule of 400 mg every 6 hours could be used.

For the majority of antiarrhythmic drugs commonly administered orally one may assume that the enzyme systems that degrade the parent compound are not exceeded and that a *constant fraction* of the body stores will be eliminated per unit of time — i.e., *linear first-order kinetics.* An important exception is phenytoin, which exhibits *nonlinear zero-order kinetics.* This refers to the fact that when drug concentrations are high or the capacity of the enzyme system is limited, a constant amount of the drug is removed per unit of time as the enzyme system becomes saturated. If this is not recognized, a disproportionate increase in plasma drug concentration may occur if the maintenance dose is not adjusted accordingly.

For intravenous dosing, if the patient is at steady state, the concentration of the drug is related to the rate of infusion divided by the total plasma clearance. Thus, to achieve a 2 μg/ml concentration of lidocaine, assuming that the patient has a normal hepatic blood flow of 1 liter/min, the infusion rate should be maintained at 2 mg/min. Since patients with myocardial infarction often have reduced cardiac output and therefore reduced hepatic blood flow, the infusion rate should be lowered to avoid lidocaine toxicity.

Another example of intravenous dosing would be the use of 100-mg boluses of procainamide intravenously every 5 minutes to treat a persistent ventricular arrhythmia. Giardina and colleagues published the following empirical formula to allow bedside estimation of the procainamide concentration based on cumulative dose administered [5]: plasma procainamide concentration (mg/ml) = 0.84 + 0.73X, where X is the cumulative procainamide dose (mg/kg of body weight).

Because the time taken to reach a steady state may be too long in patients requiring urgent treatment, the use of loading and maintenance intravenous doses are often required. There are several ways to achieve the desired effect relatively rapidly [3,4] (table 6–5). The first involves use of a *single loading dose.* In the case of antiarrhythmic drugs given intravenously, this is usually satisfactory, because the peak levels attained are often associated with adverse effects. A second method involves administering a *loading dose followed by a maintenance infusion.* This is typically used in many clinical instances when intravenous lidocaine is given. Recall that, when this second method is employed, plasma concentrations of lidocaine may transiently become subtherapeutic about 15 to 40 minutes after the initial loading dose, with a resultant breakthrough of arrhythmia. The appropriate response at that point would be to administer a second, smaller loading dose rather than to increase the rate of the maintenance infusion, which would not have any effect for several hours. The third and final method is a *double infusion technique* in which, a rapid infusion is followed by the maintenance infusion. Although this type of regimen is available for all antiarrhythmic drugs, safety is achieved at the expense of the time taken for the drug to reach its therapeutic range.

By utilizing the pharmacokinetic and dosing information provided in tables 6–6 and 6–7 as a guide, clinicians can optimally administer the standard antiarrhythmic agents. Manufacturers of antiarrhythmic compounds have developed preparations that exhibit delayed absorption from the gut or are enclosed in a special vehicle (such as a wax matrix) that will delay release of the drug. Both these modifications make possible dosage forms that obviate frequent administration with the hopes of improving patient compliance (table 6–8).

TABLE 6–5. Common techniques of drug administration

1. *Oral*
   a. Single large loading dose
   b. Maintenance dosing
2. *Intravenous*
   a. Single intravenous loading dose
   b. Loading dose followed by maintenance infusion
   c. Double infusion technique
3. *Intravenous loading maintenance followed by conversion to oral maintenance*

TABLE 6–6. Pharmacokinetics of standard antiarrhythmic agents

	Bioavailability (%)	Half-time for absorption (hr)	Volume of central compartment (V_c) (liters/kg)	Volume of distribution at steady state (V_{dss}) (liters/kg)	Plasma protein binding (%)	Effective Plasma Concentration (μg/ml)	Half-time for distribution ($t_{1/2\alpha}$) (min)	Half-time for elimination ($t_{1/2\beta}$) (hr)	Total body clearance (ml/min)	Excretion of unchanged drug (%)
Quinidine	60 to 80	0.5	0.9	2 to 4	80	2 to 6		5 to 9	200 to 300	10 to 40*
Procainamide†	70 to 85	0.5	0.1	1.5 to 2.5	15 to 25	3 to 8	5	3 to 7	300 to 700	30 to 60
Disopyramide	85	0.5		0.5 to 1.5	5 to 65‡	2 to 5		6 to 9	100 to 200	40 to 50
Lidocaine	35	0.3	0.5	1.0 to 2.0	20 to 40	1 to 5	8	1 to 2§	400 to 1600	10
Phenytoin	50 to 70	0.5 to 3.0		0.5 to 1.0	90	6 to 20		18 to 36	12 to 48	5
Propranolol	20 to 50	0.5		2.5 to 3.5	85 to 95	0.02 to 0.90		3 to 6	400 to 1000	5
Bretylium	Erratic PO									High
Tocainide	>90	0.5	0.8	1.6 to 3.2	10 to 20	6 to 12	10	11 to 15	115 to 140	40

* Varies with pH of urine.

† A clinically important active metabolite called NAPA exists. It has similar but not identical antiarrhythmic properties, $t_{1/2B}$ = 6.9 hours, and with almost total renal excretion. Because of variations in acetylator phenotype and renal function, the clinical relevance of NAPA levels (which may run as high as 30 μg/ml) has yet to be determined.

‡ Concentration-dependent.

§ May be longer than listed values in patients with reduced hepatic blood flow or infusions lasting >24 hours. From Bigger JT, Jr: Management of arrhythmias. In: *Heart Disease*. Braunwald E (ed). Philadelphia, WB Saunders Co, 1980, p 701, and Gillis AM, Kates RE: Clinical pharmacokinetics of the newer antiarrhythmic agents. *Clin Pharmacokinetics* 9:375–403, 1984.

TABLE 6–7. Dosage Information for Standard Antiarrhythmic Agents

	Oral dosage				Intermittent intravenous injection				Constant-rate intravenous infusion		
	Total daily dose (mg)	Dosing interval (hr)	Time to peak plasma level (hr)	Time to steady state (days)	Loading dose (mg)	Maximum total dose (mg)	Unit dose (mg)	Dosing interval (min)	(mg/min)	Rate (μg/kg/min)	Time to 90% of plateau (hr)*
Quinidine†	1200 to 2400	6 to 8	1.5 to 2.0	1 to 2	600	200–300	100–200	20	1 to 2	10 to 30	20
Procainamide†	2000 to 8000	4 to 6	1.0 to 1.5	1	1000	1000	100	5	1.5 to 5.5	20 to 80	12
Disopyramide	400 to 1200	6 to 8	1.5 to 2.0	1 to 2	300	—	—	—	—	—	—
Lidocaine	—	—	—	—	—	300	75	5	1.0 to 3.5	10 to 50	5
Phenytoin	300 to 800	12 to 24	4.0 to 12.0	3 to 5	1000	1000	100	5	—	—	—
Propranolol	40 to 1000	6 to 8	2.0 to 4.0	1	—	10	1	5	0.1 to 0.3	1.5 to 5.0	10
Bretylium	—	—	—	—	1000	1000	500	5 to 15	1 to 2‡	—	—
Tocainide	1200 to 1400	8 to 12	1.0 to 2.0	2 to 3							

* Steady-state plasma concentration should be evaluated only after sufficient time has elapsed for a steady state to be reached.
‡ May cause orthostatic hypotension when administered by continuous infusion. This often can be corrected by infusing 500 to 1,000 mg over 20 min every 4 to 6 hr.
† Sustained-release formulations are available (Quinaglute, Procan SR), but bioavailability may vary considerably, requiring individual assessment of drug levels.
From Bigger JT, Jr: Management of arrhythmias. In: *Heart Disease*. Braunwald E (ed). Philadelphia, WB Saunders Co, 1980, p 708, and references 2, 6, 7, and 8.

TABLE 6–8. Comparison of some immediate-release and controlled-release/delayed-absorption preparations of standard antiarrhythmic agents

	Immediate-Release Preparations				Controlled-Release/Delayed-Absorption Preparations			
Antiarrhythmic Agent	Formulation	Available Strengths	Manufacturer's Suggested Dosing Interval (hr)	Comment	Formulation	Available Strengths	Manufacturer's Suggested Dosing Interval (hr)	Comment
Quinidine	Quinora (Quinidine sulfate tablets)	200 or 300 mg	4 to 8		Duraquin (Quinidine gluconate tablets)	330 mg	6 to 8	Each 330-mg tablet contains 206 mg of quinidine base and is equivalent to 248 mg of quinidine sulfate
	Quinidine sulfate	200 mg	4 to 8	Available as capsules or tablets	Quinaglute Duratabs (Quinidine gluconate tablets)	324 mg	6 to 8	Equivalent to about 244 mg of quinidine sulfate
					Cardioquin (Quinidine polygalacturonate tablets)	275 mg	8 to 12	Equivalent to 200 mg of quinidine sulfate
					Quinidex Extentabs (Quinidine sulfate tablets)	300 mg	8 to 12	
Procainamide	Pronestyl	250, 375, or 500 mg	4 to 6	Available as capsules or tablets (tablet contains tartrazine)	Procan SR	250, 500, or 750 mg	6	Wax matrix may appear in stool
					Pronestyl-SR	500 mg		
Disopyramide	Norpace	100 or 150 mg	6		Norpace-CR	100 or 150 mg	12	

TABLE 6–9. Indications for monitoring serum levels of antiarrhythmic drugs

1. To establish therapeutic level for prophylaxis against arrhythmias.
2. To evaluate apparent failure to respond (i.e., "resistant" arrhythmias).
3. To evaluate symptoms suggestive of drug toxicity.
4. To evaluate effects of changing physiological state (e.g., alterations in circulatory, hepatic, or renal function) that may alter systemic availability.
5. To establish drug compliance or drug abuse.
6. To detect drug interactions.

2.6. MONITORING SERUM DRUG LEVELS

Because $t_{1/2}$ and V_d may be altered in an unpredictable fashion, it is useful to monitor serum levels. Listed in table 6–9 are the appropriate indications for determining the serum level of an antiarrhythmic agent.

When the result of a serum level determination of one of the antiarrhythmic drugs is reported, one should first determine whether it is in the therapeutic range. If it is, and the patient is doing well clinically, nothing further need be done. If the level is in the normal range, but the patient shows signs of toxicity, consider the possible problem of decreased protein binding leading to a normal total drug level but an increase in the free drug concentration. Should the value be outside the therapeutic range, first confirm that the specimen was drawn at an appropriate interval after drug dosing (preferably a "trough" level immediately prior to the next dose). Next, evaluate the patient clinically; if no toxicity is present and the arrhythmia is well controlled, the patient may simply be observed despite the laboratory result. However, if toxicity is present and/or the arrhythmia is not well controlled, evaluate the dosage schedule and search for possible drug interactions and conditions that alter drug clearance.

2.7. NEW OR INVESTIGATIONAL ANTIARRHYTHMIC AGENTS

As emphasized earlier in this chapter, the ideal antiarrhythmic agent has not been developed. Many patients suffer from arrhythmias that are refractory to the standard antiarrhythmic drugs already reviewed. New compounds have been produced for clinical use, some which are reviewed in tables 6–10 and 6–11. Although several of these drugs have already been incorporated into clinical practice in various countries, at present they remain investigational in the United States. The available information regarding pharmacokinetics and optimal dosing for some of the new antiarrhythmic agents is incomplete and indeed may be modified in the future as more clinical experience is gained [2,6,7,8]. Tables 6–10 and 6–11 present *preliminary* data on these new drugs.

TABLE 6–10. Pharmacokinetic properties of new and investigational antiarrhythmic agents

	Bioavailability (%)	Plasma protein binding (%)	Half-time of elimination (hr)	Major route of excretion
Mexiletine	90	70	10 to 15	Liver
Aprindine	80 to 90	85 to 95	15 to 30	Liver
Amiodarone	?		25 to 50 days	Liver
Ethmozine	High		8	Liver
Lorcainide	Low (first pass)		5 to 20	Liver
Encainide	40		3 to 8	Liver
Flecainide	High	35 to 45	14 to 20	Liver
Propafenone	Moderate		3 to 4	Liver
Ajmaline				
Bethanidine	Moderate		14	Kidney
Acecainide (NAPA)	High	11	6 to 10	
Cibenzoline	High		7 to 20	Kidney

Data compiled from references 2, 6, 7 and 8.

TABLE 6–11. Dosage information for new and investigational antiarrhythmic agents

	Oral dosage			Intermittent intravenous injection					Constant-rate intravenous infusion
	Total Daily Dose (mg)	Dosing Interval (hr)	Time to Peak Plasma Level (hr)	Loading Dose (mg)	Loading Dose (mg/kg)	Maximum Total Dose (mg)	Unit Dose (mg)	Dosing interval (min)	Rate (mg/min)
Mexiletine	600 to 1000	6 to 8	2 to 4	500					0.35 to 0.70
Aprindine	50 to 200	12	2	300		300	25	5	2
Amiodarone	200 to 800	24	4		5 to 10	300			0.1
Ethmozine	(600 to 900 8 to 12 mg/kg)	8 to 12	2						
Lorcainide	200 to 400	8 to 12		100 to 200	1 to 2	200	50 to 100	10 to 20	
Encainide	75 to 250	6 to 8	1 to 2		0.6 to 0.9				
Flecainide	?160 to 360	12	1.5 to 3.0		2				
Propafenone	300 to 900	8	1 to 3		1 to 2				2
Ajmaline							50		
Bethanidine	15 to 30 mg/kg	8	1 to 4	5 to 20					
Acecainide (NAPA)	?2000 to 4000				1 to 1.2				
Cibenzoline	?240 to 320	6							

Data compiled from references 2, 6, 7 and 8.

2.8. DOSING OF ANTIARRHYTHMIC AGENTS UNDER SPECIAL CIRCUMSTANCES

2.8.1. Renal failure. Since the incidence of cardiovascular disease is high in patients with end-stage renal disease, one must be aware of the adjustments that need to be made in antiarrhythmic dosing schedules in such cases. Data are available regarding dose adjustments for some of the standard antiarrhythmic agents (table 6–12), but these must be considered guidelines only, and measurement of individual plasma concentrations is required for finer adjustments.

2.8.2. Pregnancy and Nursing Mothers. The increases in blood volume cardiac output, and renal blood flow that occur during pregnancy make a prior estimate of plasma concentrations of antiarrhythmic drugs difficult and underscore the need for individual measurements. Of additional concern are the potential adverse effects on the fetus or nursing infant. Table 6–13 summarizes information related to potential teratogenic effects of antiarrhythmic drugs and their ability to cross the placenta or enter breast milk.

2.9. ADVERSE CONSEQUENCES OF ANTIARRHYTHMIC DRUG THERAPY

As emphasized in recent studies, virtually all antiarrhythmic agents have the potential to *exacerbate* cardiac arrhythmias [9]. In addition, specific side effects may be encountered that are unique to individual agents. Table 6–14 summarizes important adverse reactions to both standard and investigational antiarrhythmics. It should be noted that hematological dyscrasias are potentially life-threatening but often reversible side effects (table 6–15 and 6–16 and figure 6–2).

2.10. DRUG INTERACTIONS INVOLVING ANTIARRHYTHMIC AGENTS

Since antiarrhythmic agents are prescribed to control potentially hemodynamically harmful or life-threatening cardiac arrhythmias, it is important to be aware of drug interactions that may affect the serum concentration or duration of action of these agents. Commonly encountered and/or more carefully investigated interactions are summarized in table 6–17.

3. Beta-Adrenoceptor Blocking Agents [10,11]

Current concepts about the basic mechanism of beta-adrenoceptor agonists propose that catecholamines interact with a "beta" receptor on the cell membrane to form a hormone-receptor complex. This results in stimulation of the enzyme adenylate cyclase and ultimately provides more cyclic AMP for activation of protein kinases. Protein phosphorylation then occurs followed by a particular hemodynamic, electrophysiological, or metabolic event. Beta receptors have been subclassified into two major subtypes. Although both subtypes may be present in the same organ, one type generally predominates according to the following scheme:

β_1 = cardiac stimulation, renin release, lipolysis
β_2 = bronchodilation, vasodilation, glycogenolysis

Beta-adrenoceptor blocking agents (or *antagonists*) are competitive inhibitors of catecholamine binding at beta-adrenoceptor sites. They serve to blunt the effect of a given concentration of beta-adrenoceptor *agonist* on sensitive tissue by causing a shift to the right in the dose-response curve.

Eleven beta-adrenoceptor blocking agents are now available for clinical use; however, not all are currently marketed for use in the United States. A list of cardiovascular indications reported (but not necessarily currently approved by regulatory agencies) for beta-adrenoceptor blocking agents is shown in table 6–18.

The basic pharmacological differences among the various drugs have been analyzed along several lines, resulting in multiple classification schemes. To simplify our discussion, the major points of pharmacological diversity have been presented in general form below; the reader is referred to tables 6–19 through 6–22 for specific data relating to individual compounds.

3.1. CARDIOSELECTIVITY

The beta blockers have been classified according to their relative abilities to antagonize various catecholamine actions in some tissues at lower doses than those required in other tissues. For example, $beta_1$ selective blocking agents inhibit cardiac $beta_1$ receptors to a much greater degree than they do bronchial or vascular $beta_2$ receptors [12]. This is often an advantage clinically in patients with a history of bronchoconstriction

TABLE 6–12. Effect of renal failure on elimination rate of cardiovascular drugs*

Drug	Half-life (t 1/2) in ESRD (hr)	% Excreted in urine unchanged	Extrarenal elimination	Plasma protein binding (%, NRF)	*Dosage interval (hr) with Creatinine clearance of:* ≥80 ml/min	50 to 79 ml/min	30 to 49 ml/min	<30 ml/min	Dialyzability
Disopyramide	43	50 to 60	Hepatic	60	6	6	6 to 8	12 to 24	HD
Lidocaine	0.75 to 2.00	2 to 3	Hepatic	60 to 65			IV INFUSION		
Phenytoin	6 to 10	65	Hepatic	89 to 91†	8 to 24	8 to 24	8 to 24	8 to 24	HD slow
Procainamide	9 to 16	45 to 65	Hepatic	15	3	3	4 to 6	AVOID	HD
Quinidine	3 to 16	10 to 50	Hepatic	80	6 to 12	6 to 12	6 to 12	6 to 12	
Bretylium	31.5	80				Individualized based upon response			HD

* This is only a guideline. Individual plasma concentration must be correlated with therapeutic effect for ideal monitoring.
ESRD = end-stage renal disease; NRF = normal renal function; HD = hemodialysis.
† Decreased binding in abnormal renal function.
From Lowenthal DT, Affrime MB: Clinical pharmacology of cardiovascular drugs. In *Mangement of Cardiac Patient with Renal Failure*, Lowenthal DT, Pennock RS, Likoff W, Onesti G (eds), Philadelphia, FA Davis Co., 1981, p 36.

TABLE 6–13. Guide to the use of antiarrhythmic drugs in pregnancy

Drug	Placental transfer*	Excretion into breast milk†	Use in pregnancy	Comments
Digoxin	1.0	~1.0	Safe	Adult dosage when quinidine or verapamil is given concomitantly
Quinidine	1.0	~1.0	Relatively safe	Excessive doses may lead to premature labor
Procainamide	0.25	?	Relatively safe	High incidence of maternal antinuclear antibodies and lupus-like syndrome with chronic use
Disopyramide	0.4	~1.0	Probably safe‡	One report documents uterine contractions
Beta-adrenoceptor blocking agents	~1.0	~4.0 to 5.0	Relatively safe	Chronic administration may be associated with intrauterine growth retardation
Phenytoin	0.8 to 1.0	<0.5	Not recommended for chronic use §	High risk of malformations ("fetal hydantoin syndrome")
Verapamil	~0.4	?	Probably safe‡	Rapid intravenous injection may occasionally cause maternal hypotension and fetal distress
Lidocaine	0.5 to 0.6	~1.0	Safe	Toxic doses and fetal acidosis may cause central nervous system and cardiovascular depression in newborns

* Umbilical venous/maternal venous concentration ratio.
† Breast milk/maternal plasma concentration ratio.
‡ These drugs have not been studied extensively enough in pregnant patients to establish safety, but no serious adverse effects to the fetus have been reported.
§ Probably safe as acute therapy for digitalis-induced arrhythmia.
Adapted from Rotmensch HH, et al: Antiarrhythmic drug therapy during pregnancy. *Ann Intern Med* 98:487, 1983.

for whom selective inhibition of cardiac stimulation is desired so as to prevent an asthmatic attack. It should be remembered that some drugs are *nonselective* blockers and that selectivity of beta-adrenoceptor blockade becomes less evident with increasing doses of beta adrenoceptor blocking agents.

3.2. PARTIAL AGONIST ACTIVITY (INTRINSIC SYMPATHOMIMETIC ACTIVITY [ISA])

This property of beta blockers is identified as slight cardiac stimulation which can be blocked by propranolol [13]. Drugs with ISA are less likely to cause resting bradycardia and to reduce cardiac output and are associated with a flatter dose-response curve [11]. The relative clinical benefits (e.g., less bradycardia and slowing of atrioventricular conduction) of ISA have yet to be elucidated by careful large-scale clinical studies.

3.3. MEMBRANE STABILIZING ACTIVITY

This refers to the local anesthetic-like properties of some beta-adrenoceptor blockers that cause inhibition of phase 0 of the cardiac action

potential. Such effects are usually seen when the drug is present in high concentrations, well above the therapeutic level. Furthermore, beta blockers without membrane-stabilizing activity may also be antiarrhythmic, thus diminishing the clinical relevance of this pharmacological property.

3.4. POTENCY

The standard drug against which the beta-adrenoceptor blocking potentials of other drugs are measured is propranolol. In tables 6–19 and 6–21 all drugs are considered in reference to propranolol, which is given a value of 1 (one).

3.5. STRUCTURE ACTIVITY RELATIONSHIPS

While most of the available drugs are marketed as racemic mixtures, almost all the beta-adrenoceptor blocking activity resides in the negative (−) levorotatory stereoisomer [14].

3.6. LIPOPHILICITY

Beta blockers vary in their lipid solubility and this can influence their distribution in certain tissues in the body. Recently, attention has been directed toward the fact that more water-soluble agents are less concentrated in the brain. It should be noted, however, that even drugs that accumulate in brain fat may not be available to act on cell surface receptors. It appears that the ratio of cerebrospinal fluid to plasma water concentration rather than lipophilicity alone may be more important in determining whether a particular drug causes fewer central nervous system side effects.

3.7. ALPHA-ADRENOCEPTOR BLOCKING ACTIVITY

The only available beta-adrenoceptor blocking agent that possesses alpha-adrenoceptor blocking activity is labetalol [15]. The alpha-adrenoceptor blocking potency of labetalol is four to 16 times less than its beta-blocking potency. It remains to be determined whether concomitant alpha-adrenoceptor blocking activity offers important clinical advantages.

3.8. PHARMACOKINETIC PROPERTIES

The beta-adrenoceptor blockers can be grouped into 2 broad categories based on the solubility in lipids or water. The lipid-soluble drugs (acebutolol, alprenolol, metoprolol, oxprenolol, pindolol, propranolol, timolol) are metabolized and have a short half-life (2 to 6 hours). The water-soluble drugs (atenolol, nadolol, practolol, sotalol) are excreted by the kidney and have a long half-life (7 to 20 hours).

3.9. DRUG INTERACTIONS INVOLVING BETA-ADRENOCEPTOR BLOCKING AGENTS

Two main types of drug interactions involving beta blockers have been reported: pharmacokinetic and pharmacodynamic (table 6–22). A major portion of the available information relates to propranolol, but detailed information on other beta blockers is available in specialized reference texts [16]. It appears that pharmacodynamic drug interactions are more important clinically and are particularly relevant to patients with respiratory disease, diabetes mellitus, hypertension, and cardiac arrhythmias.

4. Digitalis Glycosides [17]

4.1. PHARMACOKINETICS AND BIOAVAILABILITY

Each cardiac glycoside is made up of a combination of an *aglycone* (or *genin*) and one to four glycoside moieties. While water solubility and pharmacokinetic properties are influenced by the particular sugars attached to the aglycone [18], pharmacological activity resides in the aglycone [18].

The derivation of clinically relevant digitalis preparations is shown in figure 6–3. Review of these figures in conjunction with table 6–23 should facilitate understanding of the confusing and awkward terminology often used to refer to these agents in the literature. Manifestations of toxicity due to the digitalis glycosides have similar clinical profiles but dissimilar time courses, reflecting pharmacokinetic differences among the drugs.

The individual cardiac glycosides are discussed briefly below, with clinically relevant data summarized in table 6–24.

4.2. DIGOXIN

Digoxin is the cardiac glycoside used most frequently in the United States in both hospital and office practice [19]. The drug may be administered orally (in tablet or elixir form), intravenously, or intramuscularly. The intramuscular preparation is painful and causes signif-

TABLE 6–14. Undesirable effects of antiarrhythmic drugs

Drug	Effects on cardiac rhythm				Hypotension	Central nervous system effects	Other effects
	Asystole	Disturbances of sinus node function	AV block	Exacerbation of ventricular arrhythmias			
Quinidine	+	+	+	+	+++	Cinchonism	GI distress, granulomatous hepatitis, fever, thrombocytopenia
Procainamide	+	+	+	+	++	Psychosis, giddiness, depression, sleep disturbances	Lupus-like syndrome, fever, agranulocytosis, nausea
Disopyramide	+	+	+	+	++		Dry mouth, blurred vision, urinary retention, cardiac decompensation
Lidocaine		+	+		+	Paresthesias, disorientation, convulsions	
Phenytoin		+			++	Nystagmus, ataxia lethargy, coma	Megaloblastic anemia, lymphoma-like syndrome, rash
Propranolol	+	+	+		+	Sleep disturbances, decreased alertness	Bronchospasm, fatigue, hypoglycemia, GI distress, sexual dysfunction, Raynaud's phenomenon
Bretylium	+	+		+(initially)	++++		Nausea and vomiting, painful

							parotid glands, increased sensitivity to catecholamines
Verapamil	+	+	+		+		Constipation, peripheral edema
Mexiletine				+	+	Ataxia	GI distress (drug should be administered with food)
Tocainide				+	+	Similar to lidocaine	GI distress
Aprindine	+	+	+	+	++	Cerebellar toxicity, psychosis, dizziness	Agranulocytosis, congestive heart failure, cholestatic jaundice
Amiodarone	+	+	+	+	+(IV)		Photosensitivity, bluish skin discoloration, thyroid dysfunction, corneal microdeposits, pulmonary infiltrates, nausea
Ethmozine				?		Lightheadedness, dizziness, numbness, headache	
Lorcainide	+	+	+	+	+	Insomnia	
Encainide		+	+	+	+	Dizziness, diplopia, vertigo, paresthesias	Metallic taste, leg cramps
Flecainide		+	+	+	+	Blurred vision, lightheadedness, headache	

TABLE 6–15. Blood dyscrasias caused by antiarrhythmic agents

Anemias:
  Aplastic — Phenytoin
  Megaloblastic — Phenytoin
  Hemolytic — Quinidine
Neutropenia — Ajmaline, aprindine, phenytoin, procainamide, propranolol, quinidine
Thrombocytopenia — Digitoxin, phenytoin, quinidine
Lupus-like syndrome — Procainamide
Lymphoma-like syndrome — Phenytoin
Porphyria — Phenytoin

TABLE 6–16. Mechanisms of drug-induced hemolytic anemias

Type of mechanism	Drug	Role of drug	Coombs' reagent reaction	Method of cell destruction
Innocent bystander	Quinidine	Antigenic: Leads to antigen-antibody complex	Complement	Complement lysis
"Classic" immune	Methyldopa	Forms anti-Rh red cell antibody	IgG	Agglutination, splenic sequestration
Hapten	Penicillin	As hapten, binds to red cell	IgG	Agglutination

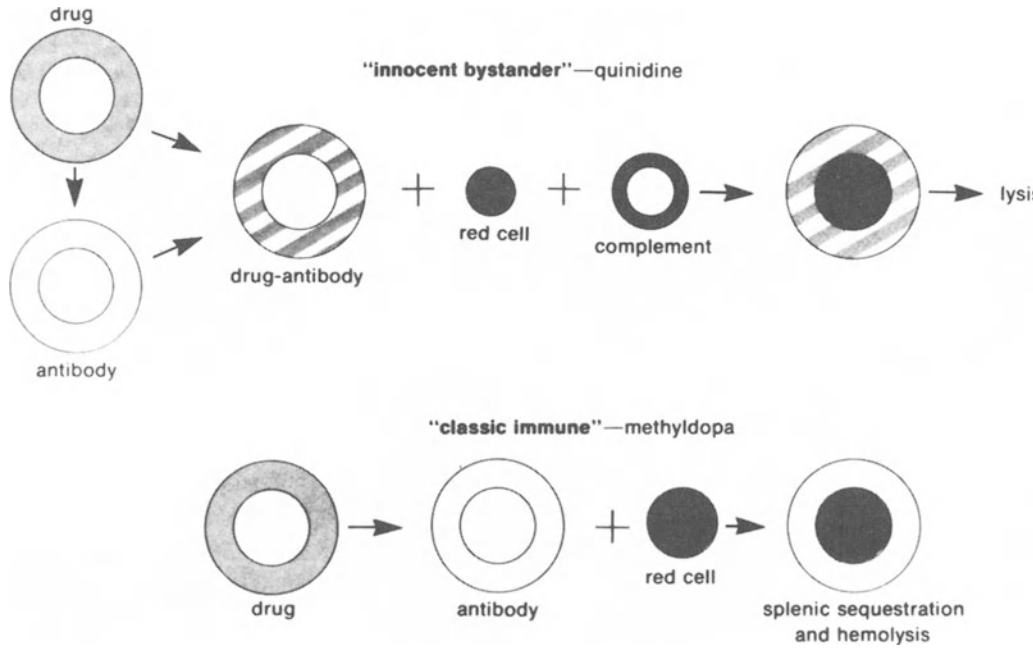

FIGURE 6–2. The "innocent bystander" type of drug-induced hemolysis, as occurs with quinidine, involves binding of a drug-antibody complex to the red cell membrane. In the presence of complement, hemolysis occurs. The "classic immune" hemolysis that occurs with, for example, methyldopa is precipitated by a drug-induced antibody directed against the Rh locus of red cells. Red cells coated with antibody are removed by the spleen. (From Rosenthal DS: Blood disorders induced by cardiovascular drugs. *J Cardiovasc Med*, January, 1980, pp 91–100.)

TABLE 6–17. Drug interactions with antiarrhythmic agents

Drug	Interactions	Comment
Quinidine	Phenobarbital, phenytoin	Induction of drug-metabolizing enzymes in liver enhances elimination of quinidine and shortens duration of action.
	Digoxin	Quinidine reduces clearance of digoxin, raises serum digoxin level, and may precipitate digitalis toxicity.
	Anticoagulants	Quinidine enhances hypoprothrombinemic effect of coumarin-type drugs.
	Muscle relaxants	Quinidine potentiates neuromuscular blockade by depolarizing muscle relaxants.
	Propranolol	Synergistic antiarrhythmic actions, quinidine levels may be higher than in absence of propranolol.
	Potassium	Hyperkalemia may enhance development of quinidine toxicity.
	Alkali, acetazolamide, some oral antacids	Increase in urinary pH decreases renal clearance of quinidine (a weak base).
	Vasodilators; blood volume depletion	Quinidine's hypotensive effect (alpha adrenoceptor blockade) is enhanced.
	Neostigmine, edrophonium	Anticholinergic properties of quinidine may antagonize vagal-stimulating effects of these drugs.
Lidocaine	Propranolol, halothane, cyclopropane	Arterial lidocaine concentration increased (possibly owing to reduced hepatic blood flow).
Phenytoin	Quinidine	(See Quinidine above).
	Barbiturates, carbamazepine	Induction of drug-metabolizing enzymes in liver enhances rate of phenytoin metabolism.
	Chloramphenicol, coumarins, disulfiram, isoniazid, sulfonamides, diazepam, chlordiazepoxide	Increase in phenytoin plasma levels due to inhibition of inactivation.
	Sulfisoxazole, phenylbutazone, salicylates	May increase effective phenytoin plasma concentrations by competing for plasma protein-binding sites.
	Cholestyramine	May slightly decrease absorption of phenytoin.
Bretylium	Vasodilator, diuretics	Augmentation of bretylium's hypotensive effect.
Verapamil	Beta-adrenoceptor blocking agents	Additive negative inotropic, chronotropic and dromotropic (AV block) effects.
	Digoxin	Serum digoxin levels increase during verapamil administration.
Amiodarone	Warfarin	Enhancement of hypoprothrombinemic effect (may be marked).
	Digoxin	Serum digoxin levels increase.
	Quinidine, procainamide	Amiodarone may decrease clearance of quinidine and procainamide.
Beta-adrenoceptor blocking agents	(See Table 6–22)	

TABLE 6–18. Reported cardiovascular indications for beta-adrenoceptor blocking drugs

Systemic hypertension
Angina pectoris
Arrhythmias
Acute myocardial infarction
Secondary prophylaxis in survivors of an acute myocardial infarction
Dissection of the aorta
Hypertrophic cardiomyopathy
Digitalis intoxication
Mitral valve prolapse
"Q-T interval" prolongation syndromes
Mitral stenosis
Congestive cardiomyopathy
Fetal tachycardia
Neurocirculatory asthenia

From Frishman WH: The beta-adrenoceptor blocking drugs. *Int J Cardiol* 2:165, 1982.

TABLE 6–19. Pharmacodynamic properties of beta-adrenoceptor blocking drugs [11]

Generic name	Proprietary name (s)	Cardio-selectivity	Intrinsic sympathomimetic activity	Membrane-stabilizing activity	Potency (propranolol = 1)
Acebutol	Sectral	+	+	+	0.3
Atenolol	Tenormin	+	0	0	1.0
Labetalol	Trandate, Normodyne	0	0	0	0.3
Metoprolol	Lopressor	+	0	0	1.0
Nadolol	Corgard	0	0	0	1.0
Oxprenolol	Trasicor	0	++	+	0.5 to 1.0
Pindolol	Visken	0	+++	+	6.0
Practolol	Eralden	+	++	0	0.3
Propranolol	Inderal	0	0	++	1.0
Sotalol	Sotacor, Betacardone	0	0	0	0.3
Timolol	Blocadren	0	0	0	6.0 to 8.0

icant increases in serum creatine kinase levels [20] and is characterized by greater pharmacokinetic variability than the oral or intravenous forms of digoxin.

Renal excretion of digoxin is usually independent of the rate of urine flow when renal function is normal, since it is proportional to the glomerular filtration rate (and hence to creatinine clearance) [17]. Renal tubular reabsorption of digoxin may increase with low urinary flow rates, while tubular secretion of digoxin, may be increased by acute vasodilator therapy in patients with congestive heart failure [21]. Digoxin is predominantly excreted in unchanged form, although occasional patients may excrete measurable quantities of relatively inactive metabolites. Some degree of metabolism to digoxin reduction products (DRPs), such as dihydrodigoxin and dihydrodigoxigenin, occurs. DRPs are formed in the gut by the gastrointestinal tract bacterial flora. Antibiotic therapy that alters gut flora reverses the body's tendency to metabolize digoxin to cardioinactive products and can result in significant alterations in the state of digitalization [22].

When daily maintenance therapy is begun in patients not previously digitalized, steady-state plateau concentrations occur after four to five

TABLE 6–20. Pharmacokinetic properties and elimination characteristics of beta-adrenoceptor blocking drugs [11]

Generic name	Lipophilicity	Extent of absorption (%)	Protein binding (%)	Oral bioavailability (%)	Elimination half-life (hr)	Predominant route of elimination	Active metabolites
Acebutol	Low	70	30–40	50	3 to 4	Renal	+
Atenolol	Low	50	5	40	6 to 9	Renal	–
Labetalol	Low	90	50	33	3 to 4	Hepatic	–
Metoprolol	Mod	90	12	50	3 to 4	Hepatic	–
Nadolol	Low	30	30	30	14 to 24	Renal	–
Oxprenolol	Mod	90	80	40	2 to 3	Hepatic	–
Pindolol	Mod	90	57	90	3 to 4	Renal (40%) Hepatic	–
Practolol	Low	90	40	100	6 to 8	Renal	–
Propranolol	High	90	93	30	3 to 4	Hepatic	+
Sotalol	Low	70	0	60	8 to 10	Renal	–
Timolol	Low	90	10	75	4 to 5	Renal (20%) Hepatic	–

TABLE 6–21. Dosage information for beta-adrenoceptor blocking drugs

Generic name	Potency (propranolol = 1)	Average dose		Onset of action	
		Intravenous (mg/kg BW)	Oral maintenance (mg/day)	Intravenous (min)	Oral (hr)
Acebutol	0.3	0.4	600 to 1200		
Atenolol	1.0	—	50 to 200		
Labetalol	0.3		100 to 800		
Metoprolol	1.0	0.1 to 0.15	100 to 400	5	1 to 2
Nadolol	1.0		40 to 320		3 to 4
Oxprenolol	0.5 to 1.0	0.2	160 to 300		
Pindolol	6.0	0.15	20 to 40		1
Practolol	0.3	0.4	400 to 1200		
Propranolol*	1.0	0.15	40 to 480	5	1 to 2
Sotalol	0.3		80 to 320		
Timolol	6.0 to 8.0	—	20 to 60		

*A long-acting preparation (Inderal LA [Ayerst]) is available allowing bid dosing. However, doses are not equivalent to conventional propranolol, since the area under the curve (AUC) for LA capsules is 60 to 65% of that for comparable doses of propranolol tablets.

half-lives, corresponding to about 7 days in subjects with normal renal function [17]. Digoxin pharmacokinetics are essentially the same before and after loss of large amounts of adipose tissue in massively obese patients, suggesting that lean body mass should be used when dosage is being calculated.

A nomogram for calculating the total oral loading dose and daily maintenance dose of digoxin based upon body weight and renal function has been devised (figure 6–4) and may be helpful for obtaining an initial clinical estimate of digoxin dosage requirements; however, clinicians should recall that a number of factors influence an individual's sensitivity to digitalis. Electrolyte derangements may exert clinically significant effects on the myocardial uptake and distribution of cardiac glycosides [17,19]. Hyperkalemia and hyponatremia reduce myocardial binding of digoxin and probably of other glycosides as well. Hypomagnesemia may contribute to digitalis toxicity. Finally, an important interaction between digoxin and quinidine exists [23]. On average, an approximately twofold increase in serum digoxin concentration will occur when conventional quinidine doses are added to a standard digoxin maintenance regimen. In studies of this interaction, total body clearance, renal clearance, and volume of distribution of digoxin were found to be significantly reduced.

4.3. DIGITOXIN

Since it is the least polar of the cardiac glycosides in common use, digitoxin binds to serum proteins and is excreted most slowly [17]. Since it constitutes the principal active component of digitalis leaf, the two agents may be considered together. The half-time of elimination of digitoxin is usually in the range of 4 to 6 days, irrespective of renal function [19]. Thus, initiation of a daily maintenance program of digitoxin without a prior loading dose will result in steady-state plateau levels after 3 to 4 weeks of oral administration.

Renal clearance of unchanged digitoxin is relatively slight compared with that of digoxin; digitoxin is extensively metabolized presumably in the liver [17,19].

Enterohepatic recycling of digitoxin (averaging about 6 per cent) can be interrupted, at least partially, by nonabsorbable resins such as cholestyramine that bind digitoxin in the gut lumen [17]. However, administration of cholestyramine to patients suffering from digitoxin intoxication will only modestly enhance the clearance rate, and its clinical efficacy remains to be proved.

The major route of elimination of digitoxin is via metabolic change to a number of poorly characterized products. In some patients, drugs such as phenobarbital and phenylbutazone can accelerate the metabolism of digitoxin.

4.4. DESLANOSIDE (DESACETYL LANATOSIDE C; CEDILANID D)

This digitalis principle is structurally similar to digoxin except for the presence of an additional terminal glucose residue [17]. Because of this additional glycoside moiety, deslanoside is poorly absorbed from the gastrointestinal tract and is recommended for parenteral use only. Its half-life has been shown to be similar to that of digoxin. Deslanoside is excreted predominantly in the urine, mostly as metabolites, including digoxin. This drug offers no substantial advantages over parenteral digoxin except that its onset of action is somewhat more rapid. If rapidity of onset is critical, ouabain may be a preferable choice.

4.5. OUABAIN AND ACETYLSTROPHANTHIDIN

These two cardiac glycosides are derived from seeds of the *Strophanthus* species (figure 6–3). Ouabain is the most polar of the commonly used cardiac glycosides and is administered parenterally for rapid digitalization [17]. Because it is poorly absorbed from the gastrointestinal tract it is *not available* for oral use. Its excretion from the body follows first-order pharmacokinetics, with a fixed proportion of the residual drug in the body being excreted daily. The mean serum half-life in patients with normal renal function is 21 hours. Disturbances of renal function can prolong the half-life of ouabain and thus extend the period during which accumulation will continue.

Acetylstrophanthidin is a rapid acting semisynthetic C_3 acetyl ester of the aglycone strophanthidin. It has been used extensively in both experimental and clinical investigations; but its clinical use at present remains largely investigational. In man, the principal exponential decline of plasma acetylstrophanthidin commences 10 to 30 minutes after intravenous infusion, and the mean half-life of this drug in plasma is 2.3 hours.

4.6. LANATOSIDE C (CEDILANID) AND ACETYLDIGITOXIN (ACYLANID)

Cedilanid is a precursor glycoside obtained from *D. lanata*. Although marketed for oral administration, it is poorly absorbed and therefore not recommended. Acetyldigitoxin has features similar to those of digitoxin, but it is not known to offer any advantage over the latter drug. The usual loading dose of acetyldigitoxin is 2.0 mg and the maintenance dose is 0.1 to 0.2 mg daily.

4.7. BIOAVAILABILITY

Formulations of a drug that meet chemical and physical standards established by governmental or regulatory agencies are termed *chemically equivalent*. They are termed *biologically equivalent* if they result in similar concentrations of drug in the blood and tissues and are considered *therapeutically equivalent* if they show equal therapeutic benefit in a clinical trial. Preparations that are chemically equivalent but lack biological or therapeutic equivalence are said to differ in *bioavailability*. Although tablets may contain chemically equivalent amounts of digoxin, careful studies have indicated a wide range of dissolution rates among the available digoxin tablets marketed by several manufacturers [24]. Such inconsistency can result in considerable variation in the bioavailability of digoxin. Patients with malabsorption syndromes sometimes absorb digoxin poorly and erratically; however, patients with maldigestion due to pancreatic insufficiency usually continue to absorb the drug normally. Administration of digoxin with or shortly after meals may result in lower peak serum levels, but total absorption is usually not affected to any significant degree [17]. For patients receiving ion-exchange resins concurrently with either digoxin or digitoxin, it is advisable to ingest the cardiac glycoside 2 hours before the resin to minimize interference with intestinal absorption.

Clinicians must constantly be alert to alterations in the patient's total medication program, since the addition or discontinuation of substances such as antibiotics or ion-exchange resins can alter digoxin bioavailability and/or impact on the extent of conversion to inactive metabolites possibly precipitating digitalis toxicity or underdigitalization if the maintenance dose is not adjusted appropriately.

4.8. DRUG INTERACTIONS WITH CARDIAC GLYCOSIDES

Drug interactions can present appreciable risks to patients receiving digitalis glycosides unless clinicians are aware of potential interactions and take preventive or corrective measures when indicated. Interactions involving digitalis glycosides are of either the pharmacokinetic or pharmacodynamic type and are summarized in table 6–25.

TABLE 6–22. Examples of drug interactions involving beta-adrenoceptor blocking agents

Drug	Pharmacological effect	Mechanism of interaction	Clinical significance	Patient management
I. Pharmacokinetic Interactions				
A. Aluminium hydroxide gel	Decreased therapeutic effect of propranolol	Decreased bioavailability of propranolol	Unknown	Avoid concurrent administration or increase dose of propranolol
B. Lidocaine	Diminished clearance in presence of propranolol	Reduced hepatic clearance of lidocaine as hepatic blood flow is reduced	Potential for lidocaine toxicity increased	Monitor plasma lidocaine concentration and adjust dose
C. Glucagon	Diminished beta blockade	Increased hepatic blood flow induced by glucagon causes increased metabolism of beta blockers with high extraction ratios	Individuals on beta blockers will have decreased hyperglycemic response to glucagon (additional pharmacodynamic interaction)	
D. Barbiturates	Reduction of plasma levels of beta blockers	Enchanced hepatic metabolism of beta blockers	Unknown	
E. Cimetidine	Increased plasma levels of beta blockers	Reduced hepatic blood flow by cimetidine causes reduced metabolism of beta blockers	Additive bradycardic effects (pharmacodynamic) and prolonged serum half-life of drugs such as propranolol	Careful ECG monitoring and possible reduction of dose of one or both drugs
II. Pharmacodynamic Interactions				
A. Isoproterenol	Inhibition of beta-adrenoceptor stimulatory effect	Agonist-antagonist competitive interaction	Bronchodilation, tachycardia, and positive inotropic effect of isoproterenol will be blunted	Avoid propranolol in asthmatic patients; choose a cardio-selective agent; withdraw beta blockers gradually, particularly in preoperative patients
B. Aminophylline	Concurrent use with beta blockers may result in inhibition of effects of both agents	Aminophylline inhibits phosphodiesterase resulting in beta-adrenoceptor stimulation; this may be inhibited by beta blocker	Drug interaction may be especially pertinent in patients with chronic lung disease	Use cardioselective blocker in patients with lung disease
C. Epinephrine	Hypertension	Blockade of beta receptors leaves alpha receptors unopposed, resulting in vasoconstriction	May be harmful in patients with coronary artery disease	Avoid concurrent use of beta blocker and epinephrine; choose cardioselective beta blocker if deemed necessary
D. Antidiabetics	May cause hypoglycemia or hyperglycemia and hypotension	Propranolol interferes with catecholamine-induced glycogenolysis causing hypoglycemia and may also inhibit	Hypoglycemic episodes that occur may fail to be recognized because of blunting of tachycardia	Avoid beta blockers of choose a cardioselective agent in diabetic patients

TABLE 6–22. (continued)

Drug	Pharmacological effect	Mechanism of interaction	Clinical significance	Patient management
		pancreatic release of insulin; hypertension may result from release of endogenous epinephrine and blockade of beta effect of epinephrine by propranolol		
E. Verapamil	Hypotension, congestive heart failure, bradycardia, AV block, asystole	Verapamil has additive effects on cardiovascular system causing a great potential for negative inotropic and cardiodepressant state	Pulmonary edema, hypotension, and conduction disorders may occur in patients with depressed LV function	Avoid concurrent use of verapamil and beta blockers; monitor patient extremely carefully if combination is deemed necessary
F. Clonidine	Severe hypertension upon sudden withdrawal of clonidine	Norepinephrine release occurs on clonidine withdrawal; excessive alpha-adrenoceptor action results in the presence of beta blockade		Withdraw beta blockers gradually before discontinuing clonidine
G. Digitalis	Excessive bradycardia	Combined effects of drugs may cause slowing or block of AV conduction	May be encountered clinically in patient with preexisting conduction disease	Reduce dose of beta blocker or insert pacemaker if combination deemed necessary
H. Cyclopropane	Depression of cardiac output	Combined effects of cyclopropane and beta blockers cause depression of LV function	Extent of interaction depends on depth of anesthesia	
I. Nitrates	Enhanced antianginal efficacy	Beta blockers blunt reflex tachycardia associated with nitrates; nitrates diminish tendency toward increased end-diastolic volume from bradycardia associated with beta blockers	Potency of antianginal regimen may be augmented by combination of drugs	
J. Procainamide, Quinidine	Enhanced antiarrhythmic effect in atrial fibrillation and ventricular ectopic activity	Different electrophysiological mechanisms of action have beneficial synergistic effects	May help maintain sinus rhythm in patient with history of atrial fibrillation or exercise-induced ventricular arrhythmia	
III. Additional Pharmacodynamic Interactions of Uncertain Clinical Significance				
A. Indomethacin	Inhibition of antihypertensive effect of beta blockers			
B. Tubocurarine, pancuronium, succinylcholine	Potentiation of neuromuscular blockade			

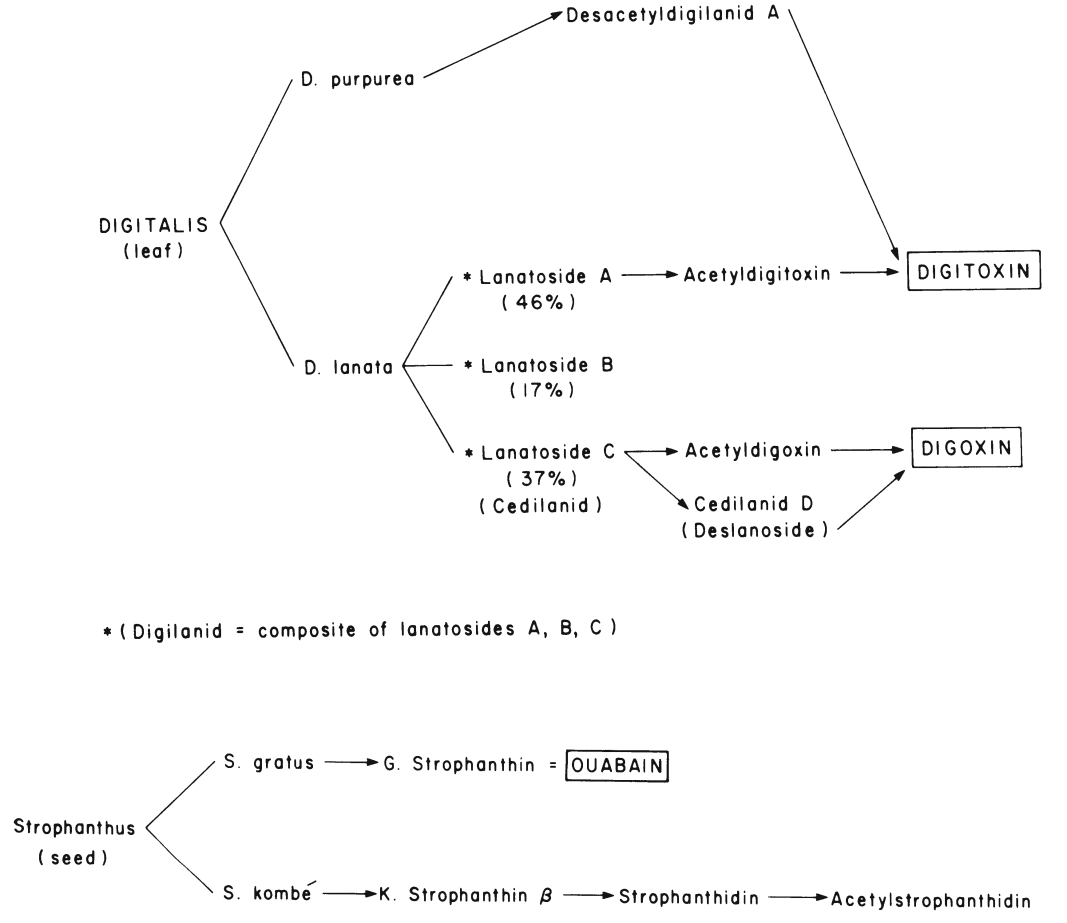

FIGURE 6–3. Derivation of clinically relevant digitalis preparations. (From Smith TW, et al: Digitalis glycosides: Mechanisms and manifestations of toxicity. *Progr Cardiovasc Dis* 26:415, 1984.)

4.9. DIGITALIS TOXICITY: MANAGEMENT

The major manifestations of digitalis toxicity include central nervous system and gastrointestinal symptoms and disturbances of cardiac rhythm. Cardiac toxicity manifested by arrhythmias may take the form of virtually every known rhythm disturbance. These may be categorized as disturbances due to *failure of impulse conduction* (sinoatrial and atrioventricular [AV] nodal block), disturbances due to *enhanced automaticity* (ventricular premature beats, ventricular tachycardia, nonparoxysmal AV junctional tachycardia), and disturbances due to a *combination of enhanced automaticity and failure of impulse conduction* (paroxysmal atrial tachycardia with AV block, nonparoxysmal AV junctional tachycardia with exit block). The rhythms noted above although representative of digitalis-toxic rhythms, are not be taken as an exclusive list. No distinct electrocardiographic features distinguish digitalis-toxic rhythms from arrhythmias of other causes, although rhythms demonstrating increased automaticity of ectopic pacemakers and failure of impulse conduction (such as paroxysmal atrial tachycardia with AV dissociation and an accelerated AV junctional pacemaker) are quite suggestive of digitalis toxicity.

Early recognition of a digitalis-toxic arrhythmia is germane to successful management Appropriate therapeutic measures to be taken are as follows [17]:

TABLE 6–23. Sources of cardiac glycosides of clinical importance

	Plant source	Precursor glycoside	Split off by enzymatic and mild alkaline hydrolysis*	Glycoside	Split Off by acid hydrolysis	Aglycone or genin
Digitalis	*D. purpurea* (leaf)	Purpurea-glycoside A (desacetyl-digilanid A)	Glucose	Digitoxin	Digitoxose(3)*	Digitoxigenin
	D. lanata (leaf)	Lanatoside A (digilanid A) Lanatoside B (digilanid B)	Glucose + acetic acid	Digitoxin	Digitoxose(3)	Digitoxigenin
		Lanatoside C (digilanid C; Cedilanid)		Digoxin	Digitoxose(3)	Digoxigenin
Strophanthus	*S. kombé* (seed)	K-strophanthin-B	Glucose	Cymarin	Cymarose	Strophanthidin
	S. gratus (seed)			Ouabain (G-strophanthin)	Rhamnose	Ouabagenin (G-strophanthidin)

*One mole of sugar or acetic acid is split off, unless the number of moles is otherwise indicated in parentheses. From Smith TW, et al: Digitalis glycosides: Mechanisms and manifestations of toxicity. *Progr Cardiovasc Dis* 26:416, 1984.

TABLE 6–24. Cardiac glycoside preparations

Agent	Gastrointestinal absorption	Onset of action* (min)	Peak effect (hr)	Average half-life†	Principal metabolic route (excretory pathway)	Average digitalizing dose		Usual daily oral maintenance dose@
						Oral‡	Intravenous §	
Ouabain	Unreliable	5–10	1/2–2	21 hr	Renal; some gastro-intestinal excretion	—	0.30–0.50 mg	—
Deslanoside	Unreliable	10–30	1–2	33 hr	Renal	—	0.80 mg	—
Digoxin	55%–75%¶ (Lanoxicaps 90–100%)	15–30	1 1/2–5	36–48 hr	Renal; some gastro-intestinal excretion	1.25–1.50 mg	0.75–1.00 mg	0.25–0.50††
Digitoxin	90%–100%	25–120	4–12	4–6 days	Hepatic#; renal excretion of metabolites	0.70–1.20 mg	1.00 mg	0.10 mg
Digitalis leaf	About 40%	—	—	4–6 days	Similar to digitoxin	0.80–1.20 g	—	0.10 g
Lanatoside C	10%–40%	—	—	Similar to digoxin	Renal	10 mg	—	0.5–1.5 mg
Gitalin**		—	—	4–6 days	Similar to digitoxin	6 mg	—	0.25–1.25 mg
Acetyldigitoxin	About 70%	20–30	8–10	Similar to digitoxin	Similar to digitoxin	2.0–3.0 mg	1.4–1.6 mg	0.1–0.2 mg

* For intravenous dose.
† For normal subjects (prolonged by renal impairment with digoxin, ouabain, and deslanoside and probably by severe hepatic disease with digoxin and digitalis leaf).
‡ Divided doses over 12 to 24 hours at intervals of six to eight hours.
§ Given in increments for initial subcomplete digitalization, to be supplemented by further small increments as necessary.
@ Average for adult patients without renal or hepatic impairment; varies widely among individual patients and requires close medical supervision.
¶ For tablet form of administration (may be less in malabsorption syndromes and in formulations with poor bioavailability). A recently marketed preparation (Lanoxicaps, [Burroughs Wellcome Co.]) contains digoxin solution in capsules and has a bioavailability of 90 to 100%. If such a preparation is used, the daily oral maintenance dose should be reduced by about 20% (e.g., Lanoxin Tablets of 0.250-mg and 0.125-mg strengths are approximately equivalent to Lanoxicaps of 0.2-mg and 0.1-mg strengths, respectively).
# Enterohepatic cycle exists.
** Gitalin is a mixture of cardiac glycosides, the principal one of which is digitoxin.
†† Approximately 20% lower maintenance doses are required if gel solution in capsules (Lanoxicaps) is used.
From Smith TW, et al: Digitalis glycosides: Mechanisms and manifestations of toxicity. *Progr Cardiovasc Dis* 26:417, 1984.

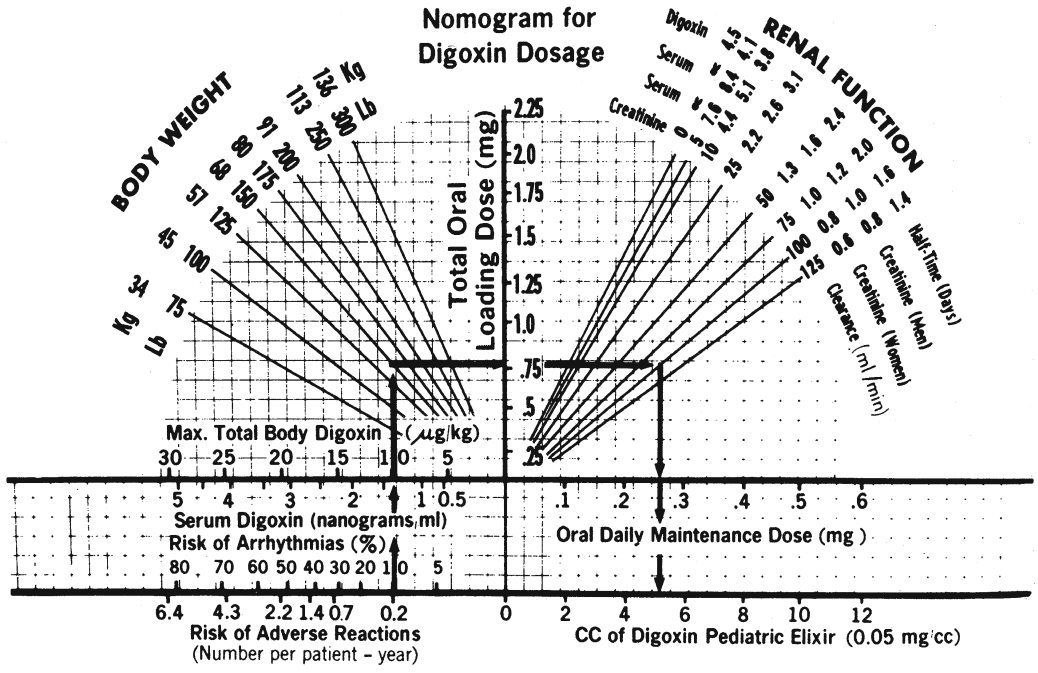

FIGURE 6–4. Nomogram for digoxin dosage. The central vertical scale represents the total oral loading dose. The fan-shaped group of lines on the left, leading from body weight and converging at zero, represents the effect of body weight upon this loading dose, adjusted for oral absorption. The fan of lines thus yields the lower left scale of maximum total body digoxin [Max. Total Body Digoxin (ng/kg)] showing the dilutional relationships that both the 85% effectiveness of oral digoxin (assumed to occur) and the body weight of the patient exert upon the oral loading dose and providing a computed overall peak total body concentration of glycoside, expressed in micrograms of glycoside per kilogram of body weight. To use the nomogram for adult euthyroid patients with reasonably normal hepatic function, who have a normal electrolyte balance, normal gastrointestinal absorption, and have received no previous digitalis therapy of any type, the physician must first decide what risk of arrhythmias or risk of adverse reactions per patient-year are acceptable for that patient, depending upon the urgency of the patient's clinical situation and an estimate of his or her possible sensitivity to digoxin. (In general, most patients with normal sinus rhythm have done well with a maximum total body digoxin concentration of 10 μg/kg.) If hypokalemia is present, the selected level should be revised somewhat downward.

The series of arrows shown in the nomogram represent the determination of a dosage regimen for the hypothetical example of 1 150-lb (68-kg) patient whose C_{Cr} is 100 mL/min, for whom a therapeutic goal corresponding to a maximal total body digoxin concentration of 10 μg/kg was selected, corresponding to a risk of adverse reactions of 0.2 episodes per patient-year, as shown in the lower left scale at the start of the upward vertical series of arrows. The user then looks upward vertically from the chosen maximum total body digoxin concentration, as shown by the sample ventical arrow, until the line corresponding to the patient's body weight is encountered. Once that point is found, the user proceeds horizontally rightward to obtain the suggested total oral loading dose. Here, as shown by the arrow, a loading dose of 0.8 mg is found. This total dose is divided into two or three parts to be given six hours apart, checking carefully for toxicity before giving each new increment. Once the increments of loading dose have been administered, and the patient has been shown to tolerate them, the maintenance dose is determined by continuing horizontally rightward from the point of the loading dose to the line corresponding to the patient's measured or estimated C_{Cr}, or to the patient's serum creatinine level, on the nomogram. In this example, C_{Cr} is assumed to be 100 mL/min. From this point, the user continues vertically downward to find the appropriate suggested single oral daily maintenance dose, which in this case is 0.27 mg. If the amount shown is difficult to achieve with tablets, the user may continue downward to find the appropriate corresponding dose of digoxin pediatric elixir (0.05 mg/mL). (Reprinted from Jelliffe RW, Brooker G: A nomogram for digoxin therapy, *Am J Med* 57:64, 1974.)

TABLE 6–25. Interactions involving cardiac glycosides

Mechanism of interaction	Interacting drugs/conditions	Digoxin	Digitoxin
Pharmacokinetic			
GI absorption			
Decreased			
	Cathartics	+	?
	Antacids	+	+
	Neomycin	+	?
	Cholestyramine	+	+
	Colestipol	+	+
	Activated charcoal	+	?
	Tablets with low bioavailability	+	
	Metoclopramide	+	
	Phenytoin	+	
Increased	Propantheline, Atropine	+	
Trapping of glycosides in entero-hepatic circulation (increased fecal excretion)	Cholestyramine		+
	Colestipol		+
Metabolism of glycoside			
Increased	Phenobarbital		+
	Phenytoin		+
	Phenylbutazone		+
	Isoniazid		+
	Ethambutol		+
	Rifampin		+
	Spironolactone		+
	Hyperthyroidism		+
Decreased	Antibiotic therapy	+	
Protein Binding			
Decreased	Phenylbutazone		+
	Sulfadimethoxine		+
	Phenobarbital		+
	Clofibrate		+
	Tolbutamine		+
Renal excretion			
Increased GFR	Hyperthyroidism	+	
Decreased GFR	Hydralazine	+	
	Guanethidine	+	
	Alpha-methyldopa	+	
	Debrisoquine	+	
	Thiazide diuretics	+	
	Ethacrynic acid	+	
	Furosemide	+	
Increased urine flow	Saline		+
	Ethacrynic acid		+
	Furosemide		+
Binding to cardiac tissues			
Decreased	Reserpine	+	?
	Hyperkalemia	+	?
Increased	Hypokalemia	+	?
Volume of distribution			
Decreased	Quinidine	+	?
	Quinine	+	?
	Verapamil	?	?
	Amiodarone	?	?

TABLE 6–25. Continued

Mechanism of interaction	Interacting drugs/conditions	Digoxin	Digitoxin
Clearance			
Decreased	Quinidine	+	?
	Spironolactone	+	?
Pharmacodynamic			
Alteration of serum electrolytes			
Hypokalemia	Diet	+	+
	Desoxycorticosterone	+	+
	Insulin/glucose	+	+
	Diuretics	+	+
Hyperkalemia	Potassium salts	+	+
Alteration of cardiac sympathetic tone			
Increased	Beta adrenergic agonists	+	+
	Reserpine	+	+
	Theophylline	+	+
	Cyclopropane	+	+
	Succinylcholine	+	+
Decreased	Beta adrenergic blockers	+	+
	Halothane	+	?
	Reserpine	+	?
	Bretylium	?	?
	Guanethidine	?	?

Modified from Bigger JT Jr, Strauss HC: Digitalis toxicity: Drug interactions promoting toxicity and the management of toxicity. *Semin Drug Treatment* 2:147–177, 1972.

1. Evaluate the rhythm disturbance and assess its potential risk to the patient. For high-risk rhythm disturbances, such as complex ventricular arrhythmias (e.g., ventricular tachycardia), the patient should be admitted to an intensive care unit. Other less ominous arrhythmias may be managed on a general hospital ward provided that some form of electrocardiographic monitoring is available.

2. Discontinue further glycoside administration.

3. Potassium repletion is in order *unless* (a) the serum potassium level is elevated (i.e., ≥5.0 mEq/liter) when the patient is seen initially, (b) severe renal insufficiency is present, (c) AV conduction is markedly delayed, or (d) the patient has taken a massive overdose (e.g., suicidal) of digitalis (in which case the serum potassium level may be expected to rise to high levels).

4. For disturbances of impulse conduction that compromise hemodynamic function, a brief trial of atropine (0.5 to 2.0 mg intravenously) should be attempted. If the situation is not corrected promptly, a temporary demand pacemaker should be inserted. Infusion of catecholamines such as isoproterenol should be *avoided* because of the risk of precipitating more serious ectopic arrhythmias. In cases of combined disturbances of automaticity and impulse conduction, a temporary pacemaker may be needed in conjunction with suppressive antiarrhythmic therapy.

5. For disturbances due to enhanced automaticity, lidocaine (100 to 300 mg IV) and phenytoin (200 to 400 mg IV) are the preferred drugs. Quinidine, procainamide, and beta-adrenoceptor agents may occasionally be helpful but are often associated with severe side effects in patients who are already hemodynamically compromised. Supplemental potassium should be given in conjunction with antiarrhythmic drugs, since these two therapeutic measures may act synergistically to suppress digitalis-toxic arrhythmias.

6. In cases of massive glycoside ingestion with advanced and potentially life-threatening rhythm disturbances and/or hyperkalemia not readily responsive to conventional measures, the patient should be considered a candidate for digoxin-specific antibody therapy [25].

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7. CARDIOVERSION AND DEFIBRILLATION

Although the application of electrical energy to the heart had been investigated in the 18th century, it was not until the first half of the 20th century that reference was made to the clinical use of electrical shocks to revert abnormal cardiac rhythms. Several recent reviews have summarized historical milestones in the development of devices capable of delivering specified electrical charges to the heart [1–4]. Early studies utilized alternating current (AC), employing 60-cycle AC of 1.5 to 2.0 amperes and 120 to 130 volts. Although AC discharges are capable of transthoracic defibrillation of the human heart, they are not suitable for correcting arrhythmias in man because they may lead to substantial deterioration in ventricular function and expose the patient to the risk of ventricular fibrillation [5]. The development of capacitors capable of delivering single-pulse discharges set the stage for the production of the cardioversion/defibrillation apparatus in use today (figure 7–1).

1. *Definitions*

Accurate use of terminology regarding the discharge of electrical impulses facilitates clinical discussion and is essential for an appropriate review of the literature. The application of synchronized electrical shocks for terminating cardiac arrhythmias is referred to as *cardioversion*, whereas application of nonsynchronized electrical shocks for this purpose is referred to as *defibrillation*. As shown in figure 7–1, the operator must manually select the appropriate mode of discharge. Many devices will automatically be in the defibrillate mode when the power is turned on.

2. *Technique*

A checklist of important items for elective procedures is shown in table 7–1, and these will be discussed in detail in the sections below.

The physiological principles involved in cardioversion [1,4] and defibrillation may be summarized as follows: (a) the abnormal mechanisms initiating cardiac arrhythmias (e.g., enhanced or abnormal automaticity) may be self sustaining when reentry of wave fronts occurs over a fixed or variable pathway; (b) an electrical discharge that succeeds in reverting an abnormal cardiac rhythm depolarizes a sufficient portion of the heart muscle instantaneously and simultaneously and extinguishes the ectopic mechanism [1,4]; and (c) this momentary depolarization of the heart permits the sinoatrial (SA) node, which has the highest degree of automaticity, to resume its function as the dominant pacemaker.

2.1. WAVEFORMS

Direct current (DC) discharge is utilized as opposed to AC to reduce the risk of ventricular fibrillation, atrial fibrillation, and myocardial injury during the procedure [5]. A variety of waveforms of capacitor discharges can be employed. As summarized by Lown [1], it appears that tissue damage, potassium release from skeletal muscle, and the provocation of arrhythmias are related to four variables: (a) A "rise time" of the wavefront of 500 microseconds or less; (b) a voltage greater than 3,000; (c) a discharge energy exceeding 400 watt-seconds; and (d) the absence of oscillatory recovery or "ringing" in the tail-end of the wave. By including an inductance in the discharge circuit of the

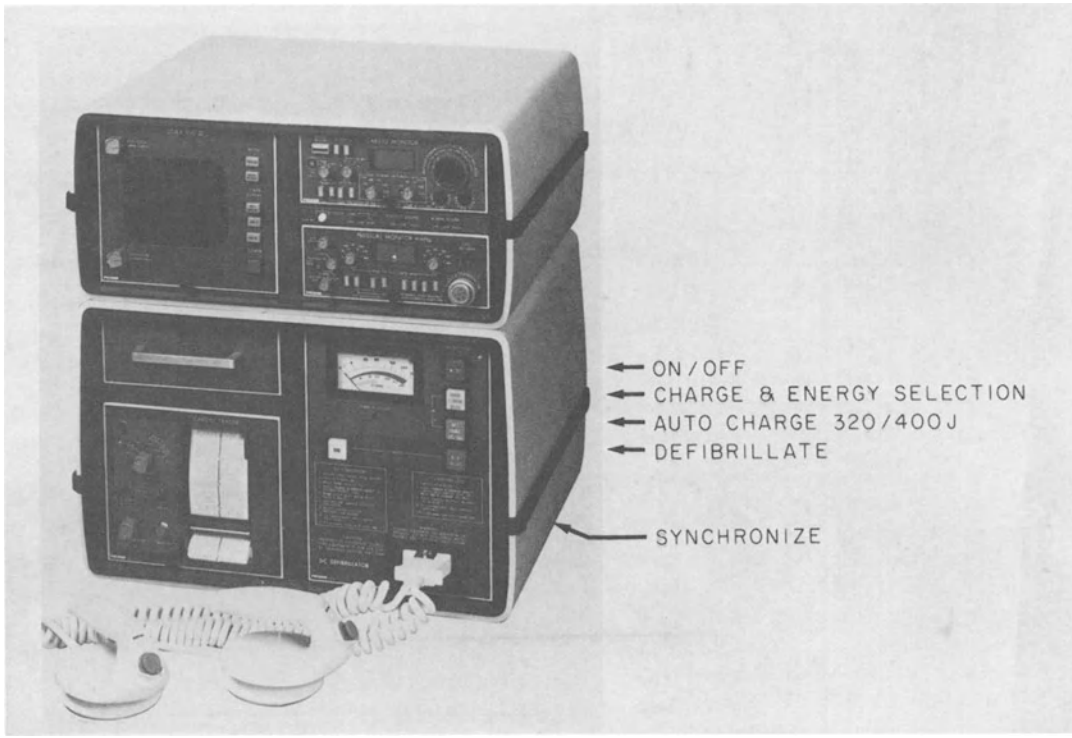


FIGURE 7–1. Contemporary device capable of defibrillation and synchronized discharge cardioversion.

capacitor it is possible to decrease peak voltage and current and lengthen the duration of the discharge. Initial clinical studies performed by Lown and coworkers utilized an underdamped half-sinusoidal waveform with a duration of 5.0 msec released from a 16-microfarad capacitor through a 100-millihenry inductance. The rise time was more than 500 microseconds to a peak value of less than 3,000 volts. In addition, at its termination, the waveform incorporated a momentary undershoot of the opposite polarity to aid in restoring the heart's electrolyte balance (figure 7–2).

Similar damped sinusoidal waveforms were developed by Edmark [6,7] and Pantridge [8]. Recently, truncated exponential waveforms have been employed, including square and trapezoidal waveforms. Trapezoidal waveforms may be of either high or low tilt, which refers to the percentage of decrease in current during the pulse duration [7] (figure 7–3).

The majority of devices currently in clinical use employ a damped sine wave impulse, although occasionally commercially available defibrillators provide trapezoidal waveforms. Clinical studies examining the relative efficacy and energy requirements utilizing the various waveforms are lacking, so that it is unclear whether trapezoidal waveforms offer any particular advantage. Unless otherwise specified, information contained in the remainder of this chapter and the suggested energy settings for reversion of various cardiac arrhythmias will assume use of a damped sinusoidal waveform.

2.2. SYNCHRONIZATION

In order to avoid the risk of ventricular fibrillation when one is delivering a synchronized cardioversion impulse, it is necessary to avoid the ventricular vulnerable period (30 to 50 msec in duration and *just preceding the apex of the T wave*) (figure 7–4*A*). One should confirm that the synchronizing circuit is correctly timed to fire *during the R wave of the QRS complex*. This can be facilitated by choosing a lead with a tall QRS complex and small T wave (figure

TABLE 7–1. Checklist for elective cardioversion

1. Confirm that patient is an appropriate candidate for cardioversion (see text)
2. Confirm that patient is adequately prepared for procedure
   a. Review anticoagulation status
   b. Review antiarrhythmic therapy
      i. Review status of digitalis glycoside therapy
      ii. Begin quinidine prior to electroversion of atrial fibrillation
   c. Obtain full 12-lead ECG prior to delivering shock
   d. Secure IV line in place
   e. Be sure that a reliable lead reflecting atrial activity is available on oscilloscope (V_1 or II)
   f. Provide sedation, with careful observation of vital signs
3. Confirm that emergency equipment is readily available
   a. Airway
   b. Ambu bag
   c. Medication
      i. Atropine
      ii. Lidocaine
      iii. Isoproterenol
   d. Temporary pacemaker
4. Confirm that device is adequately prepared for procedure
   a. Synchronization test
   b. Paddle preparation
      i. Select size
      ii. Select position
      iii. Apply electrode paste
   c. Appropriate energy selected in capacitor
5. Discharge capacitor
   a. Hold paddles with firm pressure
   b. Allow time for synchronization to occur after button(s) is (are) depressed.
   c. Anticipate generalized muscle twitch
6. Immediately after shock,
   a. Check vital signs
   b. Repeat 12-lead ECG
   c. Monitor patient as clinically indicated

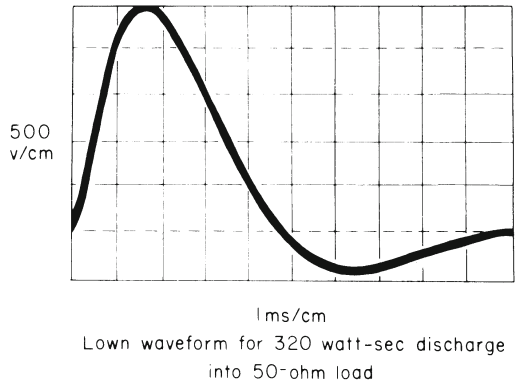


FIGURE 7–2. Underdamped half-sinusoidal waveform devised by Lown. This waveform has a peak value of less than 3,000 volts with a rise time of more than 500 microseconds. Its duration is 5.0 msec and it terminally incorporates an undershoot of opposite polarity to aid in restoring the heart's electrolyte balance. Assuming an electrical discharge of 400 watt-seconds persisting for 3 msec the delivered current would be 19 amperes and the power 133,000 watts. [1,3]

7–4*B*). The synchronizing circuit is designed to deliver the shock following a short delay (usually 20 to 50 msec) after the sensed R wave. The operator should be familiar with the synchronization test procedure for the particular machine in use. This usually incorporates a flashing light or "highlighting" marker (with or without an accompanying audio signal) synchronized with the QRS (figure 7–4*B*). Ideally one should determine which portion of the QRS is being sensed if a superimposable synchronization marker is available.

2.3. PREPARATION OF THE PATIENT

Before performing elective cardioversion, it is important to confirm that the patient is an appropriate candidate for the procedure (see considerations listed in section 4). Sample precardioversion orders are shown in figure 7–5, and are provided as general guidelines. Anticoagulation status should be reviewed, if pertinent (see 5.3.). To allay anxiety and facilitate reversion, clinicians should discuss the procedure with the patient in detail well in advance of the appointed time. In addition, it is important to ensure a full night's sleep prior to the procedure by prescribing an adequate dose of a hypnotic such as chloral hydrate, 500 to 1,000 mg orally.

Prior to sedation for elective cardioversion, one should confirm that the abnormal rhythm is still present by means of a brief ECG rhythm strip. As with all medical procedures that may precipitate patient anxiety or induce discomfort, adequate *sedation* is essential. One to two hours

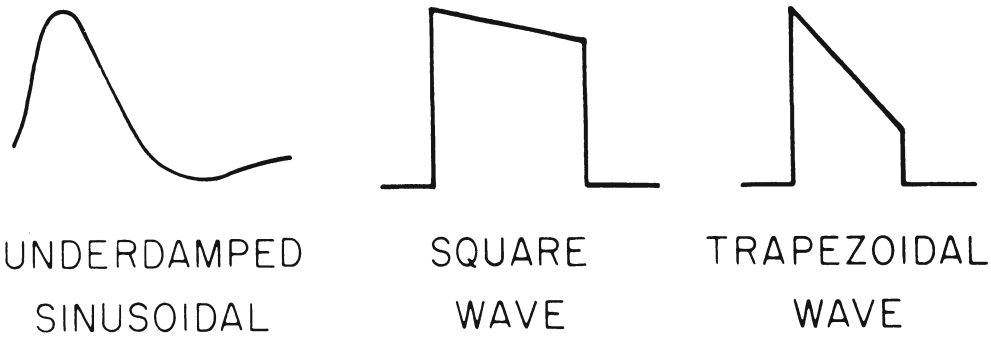


FIGURE 7–3. Commonly employed waveforms in commercially available cardioversion/defibrillation devices.

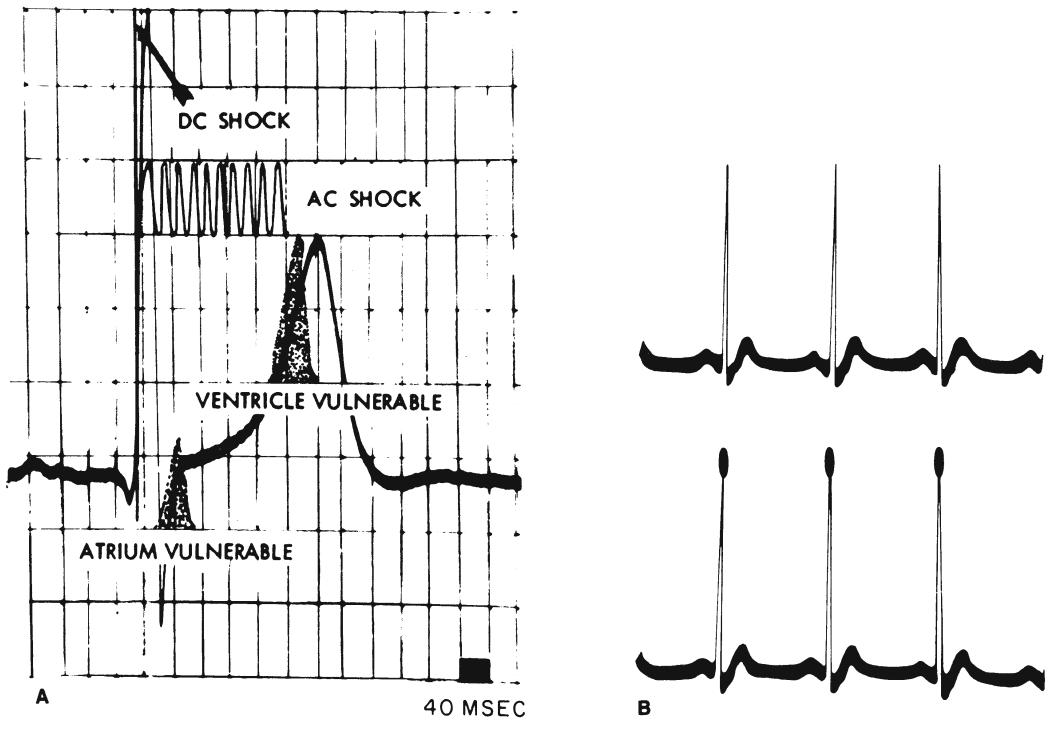
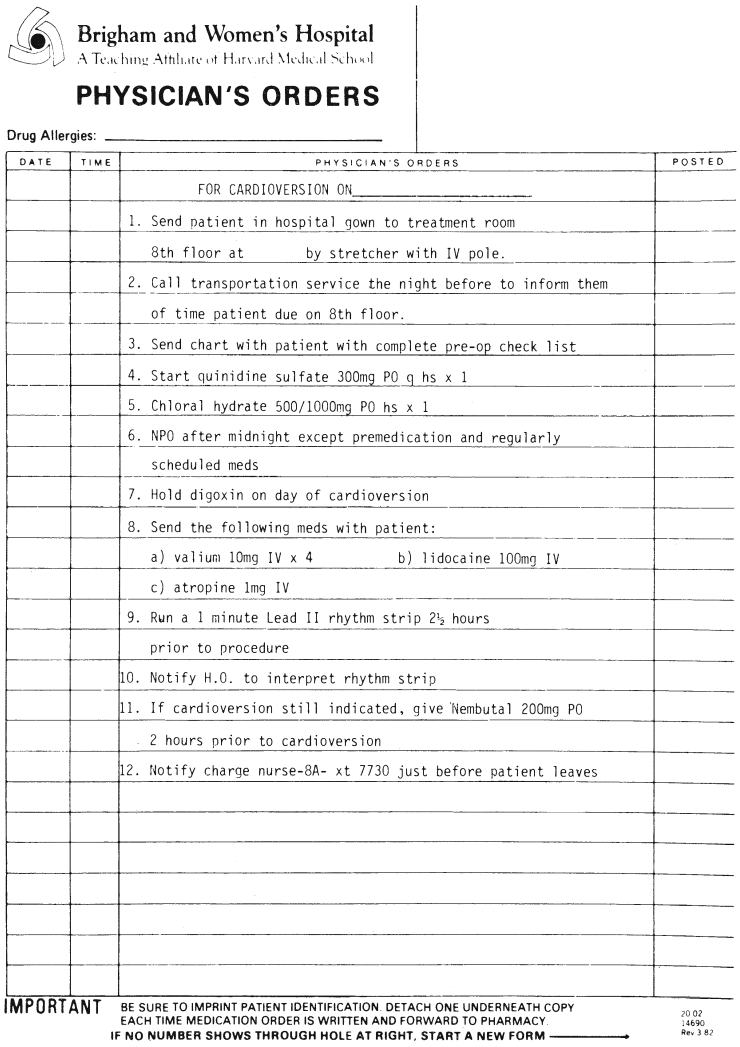


FIGURE 7–4. *A*, Phases of vulnerability for atrium and ventricle (stippled areas). The DC shock is synchronized to the R wave of the QRS complex and has a total duration of 5 msec. A 200-msec AC shock synchronized to the R wave may still encroach upon the ventricular vulnerable period. (From Resnekov L: Theory and practice of electroversion of cardiac dysrhythmias. *Med Clin N Am* 60:329, 1976.)

B, Synchronization test. Note the synchronization marker (*lower tracing*) coincident with the R wave (*upper tracing*). This indicates proper synchronization of the discharge and may be accompanied by an audio signal and/or a flashing light. Such a synchronization test should be performed before discharging the capacitor in the cardioversion mode.



Brigham and Women's Hospital
A Teaching Affiliate of Harvard Medical School

PHYSICIAN'S ORDERS

Drug Allergies: _____

DATE	TIME	PHYSICIAN'S ORDERS	POSTED
		FOR CARDIOVERSION ON_____	
		1. Send patient in hospital gown to treatment room	
		8th floor at by stretcher with IV pole.	
		2. Call transportation service the night before to inform them	
		of time patient due on 8th floor.	
		3. Send chart with patient with complete pre-op check list	
		4. Start quinidine sulfate 300mg PO q hs x 1	
		5. Chloral hydrate 500/1000mg PO hs x 1	
		6. NPO after midnight except premedication and regularly	
		scheduled meds	
		7. Hold digoxin on day of cardioversion	
		8. Send the following meds with patient:	
		a) valium 10mg IV x 4 b) lidocaine 100mg IV	
		c) atropine 1mg IV	
		9. Run a 1 minute Lead II rhythm strip 2½ hours	
		prior to procedure	
		10. Notify H.O. to interpret rhythm strip	
		11. If cardioversion still indicated, give Nembutal 200mg PO	
		2 hours prior to cardioversion	
		12. Notify charge nurse-8A- xt 7730 just before patient leaves	

IMPORTANT BE SURE TO IMPRINT PATIENT IDENTIFICATION. DETACH ONE UNDERNEATH COPY EACH TIME MEDICATION ORDER IS WRITTEN AND FORWARD TO PHARMACY.
IF NO NUMBER SHOWS THROUGH HOLE AT RIGHT, START A NEW FORM →

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FIGURE 7–5. Suggested orders for physician prior to cardioversion.

before the procedure, a dose of Nembutal should be administered. In preparation for the procedure a secure IV line should be placed and a full 12-lead ECG obtained. Immediately prior to the procedure, 5 mg of intravenous diazepam is given initially followed by 2-mg increments every 2 minutes to induce amnesia rather than anesthesia or unconsciousness [3,4]. Where there is a history of alcohol abuse, adequate sedation can often be safely obtained by administering diazepam, 5 mg every 2 minutes. Occasional patients may require administration of a rapidly acting barbiturate, delivery of which should be supervised by an anesthesiologist.

In general, muscle relaxants and endotracheal intubation are not necessary. Personnel involved in the procedure should maintain a calm, quiet, professional atmosphere with limited, low-volume conversation and subdued lighting. To evaluate the patient's cardiac rhythm adequately immediately before and after electrical

discharge, one should confirm that a reliable lead reflecting atrial activity is available. Lead V_1 is best, but lead II is usually acceptable. Skin impedance over the anticipated paddle position can be reduced by means of mild abrasion and swabbing with alcohol.

2.4. ANTIARRHYTHMIC DRUGS

For patients receiving maintenance doses of digoxin, it is usually sufficient merely to omit the morning dose of the glycoside on the day of the procedure. However, one should withhold digoxin for one or more days (longer for digitoxin) before the procedure if regularization of the ventricular response in atrial fibrillation is noted [4], since this may indicate digitalis toxicity. Twenty-four to 48 hours prior to elective cardioversion for patients with atrial fibrillation, it is useful to initiate quinidine sulfate, 300 mg orally every 6 hours [1,9]. The objectives of this approach are:

1. To build up an adequate tissue level of the drug to prevent recurrence of the arrhythmia.
2. To determine whether quinidine is well tolerated.
3. To obtain a small dividend of reversion, which occurs in about 10 per cent of cases of chronic atrial fibrillation.

Although its effects are not entirely agreed upon, pretreatment with quinidine has been suggested to improve the chances of the patient remaining in normal sinus rhythm after cardioversion [10], to reduce the number of shocks necessary for reversion, to decrease by about 40 per cent the energy required to restore normal sinus rhythm, and probably to diminish the incidence of postcardioversion arrhythmias (9).

2.5. PREPARATION AND USE OF THE PADDLES

Selection of the appropriate paddle position for elective procedures (figures 7–6*A* to 7–6*C*) is still controversial [11]. Some authors favor an anteroposterior paddle position because of the shorter pathway the current must traverse in depolarizing the myocardium [1,12,13]. Other investigators favor one anterior paddle placed at the upper right sternal border and a second anterior paddle placed at the ventricular apex [2,11]. The latter paddle arrangement may encounter lower myocardial resistivity during the discharge [14]. Additional considerations relative to paddle position include impedance to the current flow imposed by the air-filled lungs and shunting of the current via intercostal muscles and pleural effusions. Clearly, one should also avoid the bony manubrium, sternum, and ribs, which impede the flow of current.

It is essential to coat both paddles with thick layers of conductive paste all the way out to the edges of the electrode plates to avoid a spark gap and possible severe skin burns (figure 7–7*A*). When utilizing the posterior paddle, it should be placed at the angle of the left scapula, with the patient supine. The anterior paddle should be positioned over the upper right parasternal region at the level of the second and third intercostal spaces, and should be maintained in that position with firm hand pressure.

To discharge the capacitor, the operator should depress and hold down the discharge buttons (either one or two buttons are necessary, depending upon the particular device) until the discharge is completed (figure 7–7*B*). A generalized skeletal muscle twitch and movement of the patient's arms should be anticipated. During the discharge it is essential that all personnel *not* be in contact with the patient or bed to avoid accidental electrical shock.

Of incidental note is the recent development of an automated external defibrillator designed for emergency medical technicians. This device uses electrodes on the tongue and on the skin of the epigastrium, which apparently provides a low-impedance pathway for defibrillation [15].

2.6. ENERGY TITRATION

To minimize myocardial damage, *it is important to use the least amount of energy required to terminate the arrhythmia.* Low-energy shocks should be delivered initially, with subsequent increases of energy in successive shocks until sinus rhythm is restored. A suggested schedule for energy titration is 5, 10, 25, 50, 100, 200, 300, and 400 watt-seconds. Specific sections below detail the usual energy ranges employed for individual cardiac arrhythmias. If adverse cardiac arrhythmias develop before reversion to sinus rhythm is achieved, one should either (a) administer the appropriate antiarrhythmic drugs (e.g., lidocaine, 50 mg intravenously) or (b) discontinue the procedure.

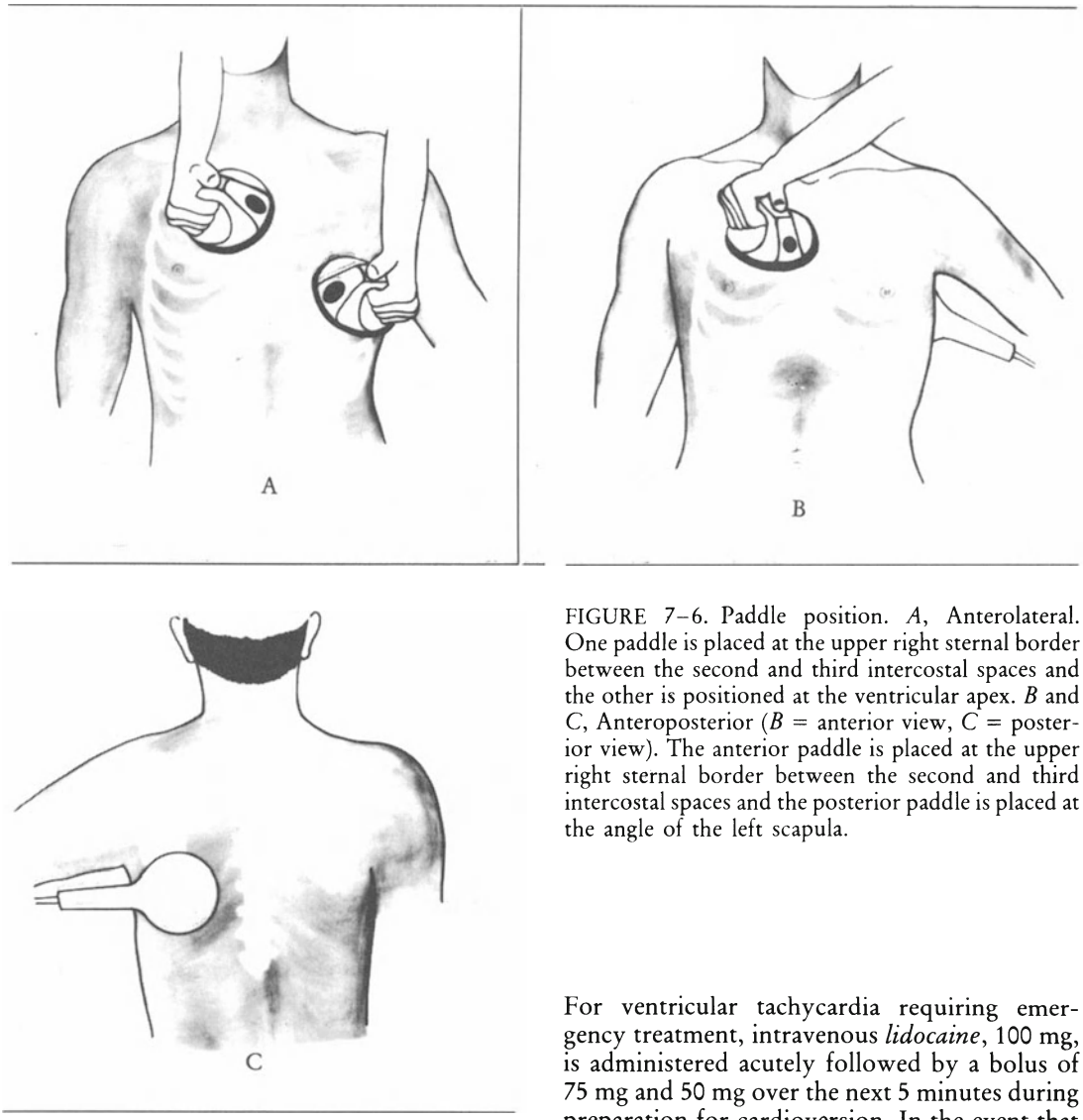

FIGURE 7–6. Paddle position. *A*, Anterolateral. One paddle is placed at the upper right sternal border between the second and third intercostal spaces and the other is positioned at the ventricular apex. *B* and *C*, Anteroposterior (*B* = anterior view, *C* = posterior view). The anterior paddle is placed at the upper right sternal border between the second and third intercostal spaces and the posterior paddle is placed at the angle of the left scapula.

3. Emergency Procedure for Ventricular Arrhythmias Causing Hemodynamic Decompensation

For life-threatening ventricular arrhythmias, omit the patient preparation described above, except for the administration of *diazepam* intravenously if the patient is still conscious. This is an important step, since defibrillation of an awake patient is painful and may induce severe psychological trauma that may last for years.

For ventricular tachycardia requiring emergency treatment, intravenous *lidocaine*, 100 mg, is administered acutely followed by a bolus of 75 mg and 50 mg over the next 5 minutes during preparation for cardioversion. In the event that lidocaine induces CNS toxicity or that further hemodynamic decompensation occurs as a result of the arrhythmia, no further lidocaine should be administered, and prompt electrical reversion of the rhythm disturbance should be performed.

In patients with ventricular fibrillation, it is important to proceed with prompt, nonsynchronized, high-energy shocks of 300 to 400 watt-seconds. Lower energy shocks are employed in children and may also be successful in certain adults when a defibrillating impulse is applied promptly before significant metabolic and electrolyte derangements have occurred.

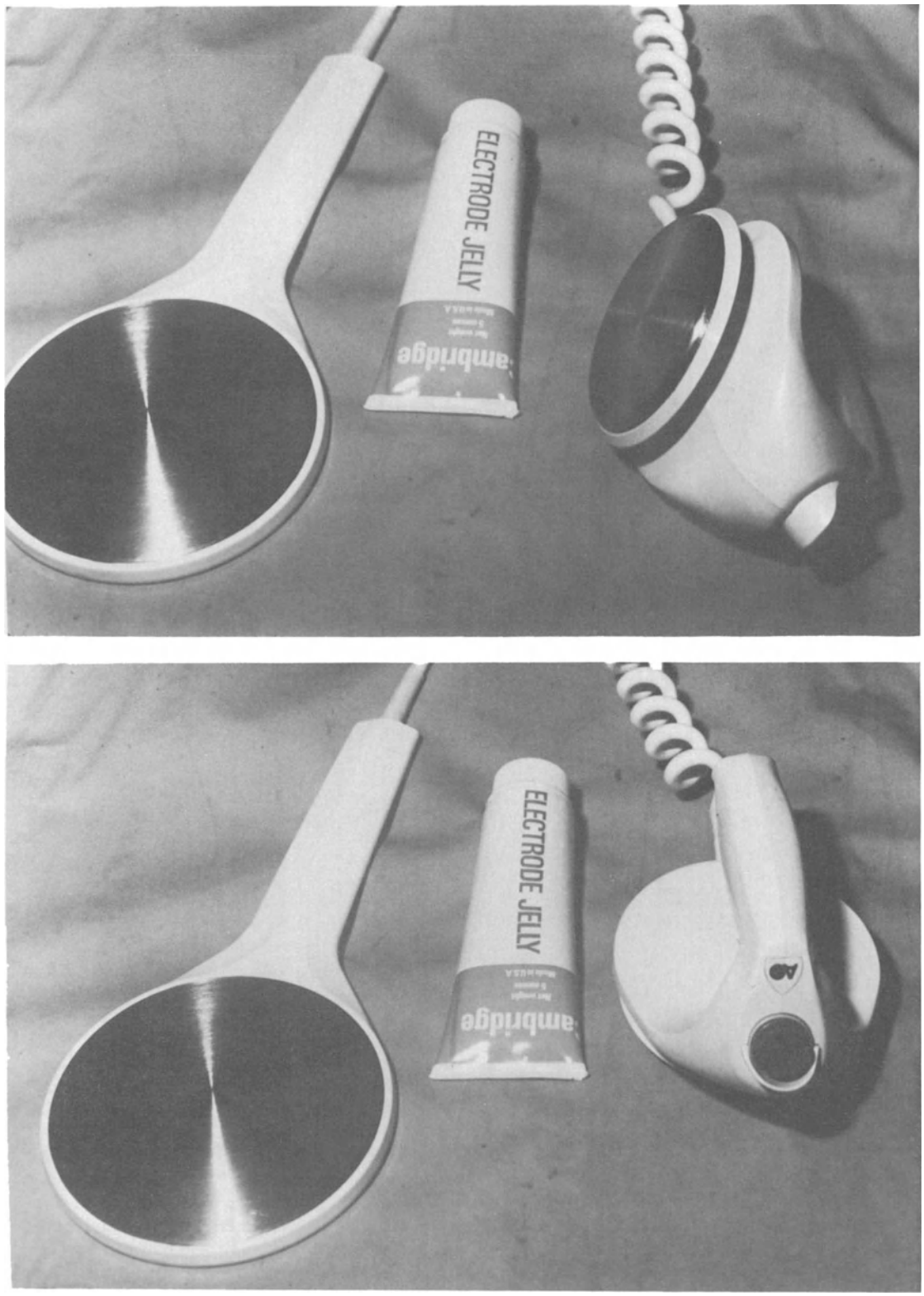

FIGURE 7–7. *A*, Paddle preparation. Liberal quantities of electrode paste should be applied to all exposed metal surfaces on the paddle. This important step should be carried out with meticulous care to avoid severe burns. *B*, Note single discharge button in this anteroposterior paddle arrangement.

TABLE 7–2. Energy considerations for specific cardiac arrhythmias [1,4]

Arrhythmia	Average energy	Synchronization	% Success
Atrial fibrillation	100	Yes	90%
Atrial flutter	25	Yes	98%
Supraventricular tachycardia	100 to 200	Yes	70%
Ventricular tachycardia (VT)	1 to 10	Yes*	98%
VT_{VP} (Ventricular flutter)	100 to 200	No	? 90%
Ventricular fibrillation	300 to 400	No	? 90%

*Use nonsynchronized shock for very rapid VT (e.g., 200 bpm) or when synchronization with the QRS is questionable.
VT_{VP} = ventricular tachycardia of the vulnerable period.

4. *Specific Arrhythmias Requiring Electrical Therapy*

Summarized in table 7–2 are the energy considerations for specific cardiac arrhythmias.

4.1. ATRIAL FIBRILLATION (AF)

In considering when to attempt elective cardioversion from atrial fibrillation, it is important to assess whether sinus rhythm is likely to be maintained. Poor candidates for elective cardioversion of atrial fibrillation are individuals for whom the chance of reversion to sinus rhythm is low and/or the risk of recurrence of atrial fibrillation after successful reversion to sinus rhythm is high [3,4,16] (table 7–3). Figure 7–8 depicts the relationship between success of reversion of atrial fibrillation and duration of that rhythm disorder.

Although the average energy required for reversion of atrial fibrillation is about 100 watt-seconds, this requirement is variable and depends on multiple factors (table 7–2). Although randomized controlled studies in *large* numbers of patients are lacking, clinical experience has indicated that higher energies are required for reversion from atrial fibrillation in certain patient groups (table 7–4).

The essential criteria that determine whether cardioversion should be undertaken are likelihood of reversion and anticipation of maintenance of sinus rhythm. As noted by Lown, "a number of electrocardiographic features at the time of reversion have been associated with rapid resumption of atrial fibrillation. These include a P-R interval greater than 0.28 second,

TABLE 7–3. Categories of patients with chronic atrial fibrillation who are not suitable candidates for cardioversion [3,4,16]

a. Atrial fibrillation of prolonged duration — i.e., greater than 1 year (figure 7–8).
b. Elderly patients with a slow ventricular response or the sick sinus syndrome.
c. Patients with advanced mitral valvular disease, giant left atrium, or mitral valve replacement.
d. Certain "lone fibrillators," especially those with a small heart and a slow ventricular rate.
e. Patients with a history of frequently recurring atrial tachyarrhythmias (Parkinson-Papp syndrome) in whom atrial fibrillation has developed.
f. Patients able to maintain sinus rhythm for only a brief period despite adequate antiarrhythmic drug therapy or who experience adverse reactions to maintenance doses of currently used antiarrhythmic agents.
g. Patients about to undergo a valvular operation.

TABLE 7–4. Circumstances requiring higher energy for cardioversion from atrial fibrillation [1,4]

a. Long-standing atrial fibrillation (1 to 3 years)
b. Small fibrillatory wave in lead V_1 (<1 mm)
c. Outpatients
d. Lone fibrillators
e. Alcoholics
f. Wolff-Parkinson-White syndrome
g. Cardiomyopathy
h. Severe coronary heart disease or acute myocardial infarction
i. Uncontrolled congestive heart failure with a rapid ventricular response

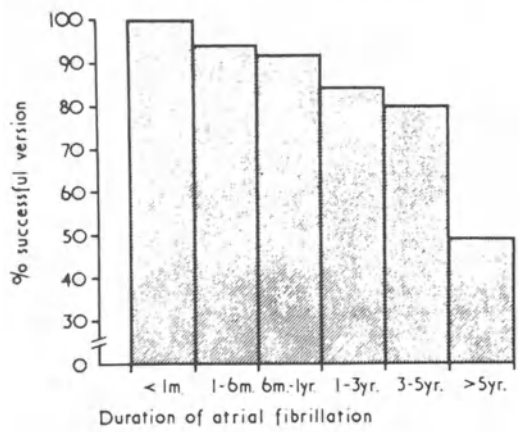

FIGURE 7–8. Influence of duration of atrial fibrillation on success of cardioversion. The chance of successful reversion of atrial fibrillation to sinus rhythm during a cardioversion procedure is inversely related to the duration of atrial fibrillation. In general patients with atrial fibrillation of prolonged duration (i.e., greater than one year) are poor candidates for elective cardioversion. (From Resnekov L: Theory and practice of electroversion of cardiac dysrhythmias. *Med Clin N Am* 60:332, 1976.)

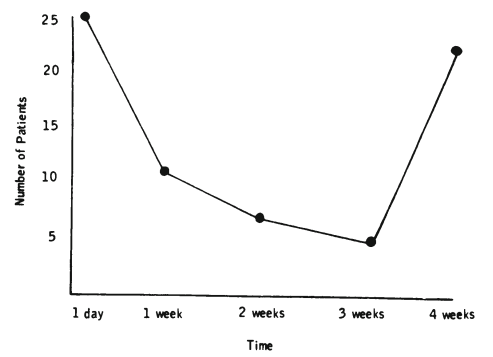

FIGURE 7–9. Timing of reversion to atrial fibrillation after successful cardioversion. Patients are at risk for recurrent atrial fibrillation during the first month after the procedure; the arrhythmia is particularly likely to recur during the first 1 to 7 days after the procedure. (From Resnekov L: Theory and practice of electroversion of cardiac dysrhythmias. *Med Clin N Am* 60:336, 1976.)

numerous and persistent atrial premature beats, atrial premature beats occurring early in the cardiac cycle, failure of the sinus node to generate a consistent impulse within several minutes following reversion, and the development of sinus tachycardia" [1].

In elderly patients with long-standing atrial fibrillation, one must be alert to the possibility of sick sinus syndrome. This refers to a defect in generation and/or conduction of sinus impulses after sinus rhythm has been restored. The syndrome is generally characterized by chaotic atrial activity, changing P-wave contour, and bradycardia interspersed with runs of supraventricular tachyarrhythmias. Patients who are unlikely to maintain sinus rhythm after cardioversion from atrial fibrillation will usually relapse within the first two weeks after the procedure, sometimes within 24 hours of cardioversion (figure 7–9). Failure to maintain sinus rhythm may be related to persistence of the abnormal mechanisms that originally precipitated the arrhythmia, a severely injured sinus node, or improper patient selection. Anticoagulation procedures in patients with atrial fibrillation deserve further discussion and will be reviewed subsequently (see 5.3.).

4.2. ATRIAL FLUTTER

Because atrial flutter is often difficult to terminate with antiarrhythmic agents, electrical procedures are employed clinically. These include cardioversion and rapid atrial pacing. Conduction of atrial flutter with a 1:1 atrioventricular (AV) response may prove disabling and, at times, life-threatening. Cardioversion is successful in restoring sinus rhythm in 98 per cent of patients with an average energy requirement of 25 watt-seconds (table 7–2 and figure 7–10). Usually only a single discharge is required.

Since atrial fibrillation is often easier to control medically than is atrial flutter, one may elect in certain instances to convert atrial flutter to atrial fibrillation by means of cardioversion. This can be accomplished by administering a low-energy shock of 5 to 10 watt-seconds delivered anywhere in the cardiac cycle except during the ventricular vulnerable period (see figure 7–4*A*). This latter point should be kept in mind, since an energy choice of less than 25 watt-seconds may convert atrial flutter to atrial fibrillation when sinus rhythm would have been a more preferable rhythm [17].

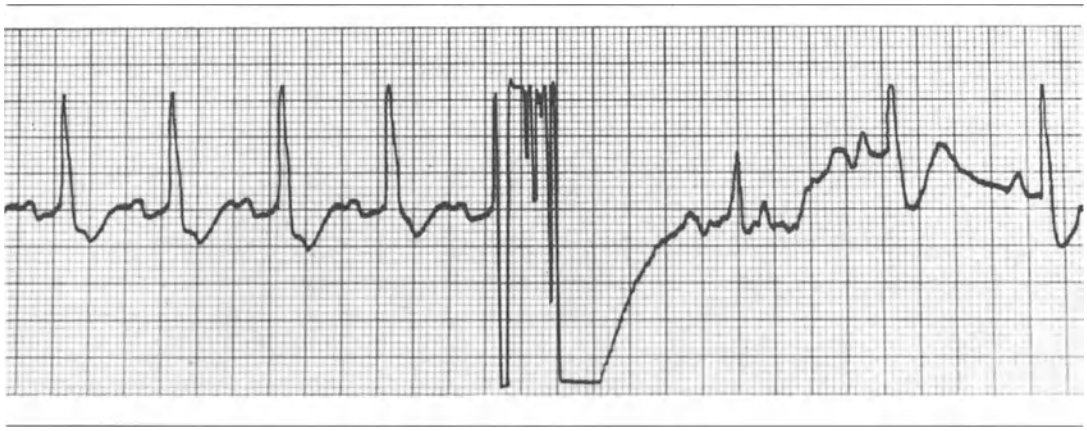

FIGURE 7–10. Cardioversion of atrial flutter. Atrial flutter with 2:1 AV conduction is seen at the left of the rhythm strip. The nonconducted flutter wave can be detected in the terminal portion of the ST segment. After a single 25-watt-second discharge synchronized to the R wave, sinus rhythm is restored.

4.3. SUPRAVENTRICULAR TACHYCARDIA (SVT)

The vast majority of patients with SVT do not require cardioversion, since they almost always respond to vagal maneuvers or antiarrhythmic therapy. Thus, cardioversion from SVT is usually required for more refractory patients among whom the rate of successful conversion to sinus rhythm is lower.

It is relatively contraindicated to perform cardioversion in cases of supraventricular arrhythmias believed to be the result of *digitalis toxicity* unless urgent clinical matters prevail. However, if digitalis intoxication is considered unlikely, cardioversion should be employed (table 7–2). Often, such refractory SVT is seen in patients with substantial organic heart disease, with ventricular decompensation and a rapid ventricular rate.

4.4. VENTRICULAR TACHYCARDIA (VT)

VT may occur in patients with significant organic heart disease, such as acute myocardial infarction, and in such instances can constitute a medical emergency. Energy requirements for reversion of VT are almost always less than 100 watt-seconds, and in the majority of cases 10 watt-seconds or less is successful (table 7–2). Such low energies can often be achieved by mechanical elecerical transduction as a result of striking the precordium with the first (thump-version) (figure 7–11) or inducing the patient to cough [15,18].

If an intravenous injection of an antiarrhythmic agent such as lidocaine fails to restore sinus rhythm, cardioversion using a low-energy discharge (table 7–2) is the treatment of choice, particularly if hemodynamic compromise becomes evident. The success of reversion of VT to sinus rhythm is greater than 95 per cent in most cases [4].

Lown and coworkers described a malignant form of VT in ischemic experimental animals. This is referred to as *ventricular tachycardia of the vulnerable period* (VT_{VP}) or *ventricular flutter* and is a prefibrillatory arrhythmia (figure 7–12). Although VT_{VP} may be reverted to sinus rhythm in animals with a shock as low as 1 watt-second, the waveform of the arrhythmia does not routinely permit proper synchronization of the discharge. Thus, when the QRS complex is wide and bizarre and cannot be readily distinguished from the T wave, there is a 50 per cent chance that synchronization will occur at the apex of the T wave, possibly provoking ventricular fibrillation. *In the presence of VT that is extremely rapid or associated with a wide bizarre QRS complex, a nonsynchronized shock of 100 to 200 watt-seconds is preferred* (table 7–2 and figure 7–12). This is designed to avoid inducing ventricular fibrillation, which might occur with a low-energy shock discharged during the vulnerable period.

4.5. VENTRICULAR FIBRILLATION (VF)

VF is defined as chaotic, asynchronous frac-

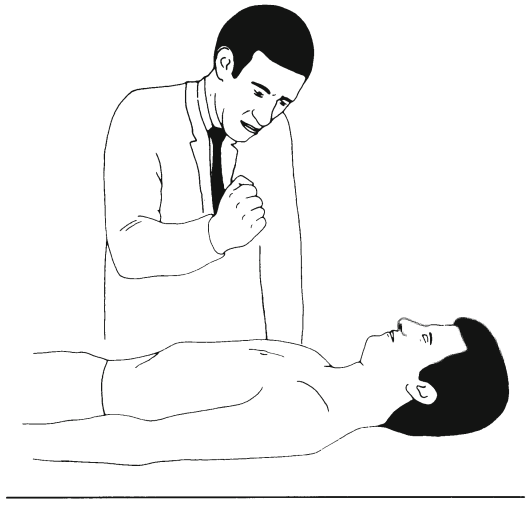

FIGURE 7–11. Technique of thumpversion. A sharp blow with the fist or heel of the hand should be delivered to the mid sternum from a distance of 8 to 12 inches above the chest.

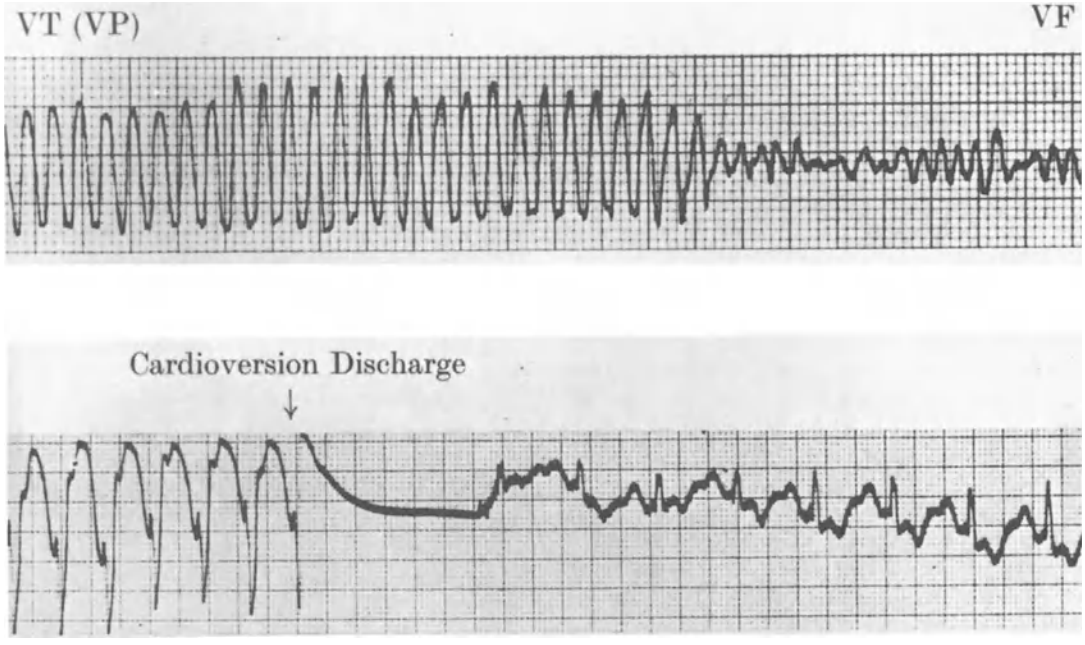

FIGURE 7–12. Ventricular tachycardia of the vulnerable period (VT[VP]). This is an extremely rapid prefibrillatory arrhythmia characteristically seen in states of myocardial ischemia (top strip). It must be recognized promptly, since rapid delivery of an external discharge has a good chance of reverting the rhythm to sinus. In view of the difficulties with adequate synchronization when the QRS waveform is bizarre or the rate is rapid (*top strip*), an unsynchronized discharge of 100 to 200 watt-seconds should be employed. When the QRS morphology allows R-wave synchronization and the rate is less than 180 to 200 bpm, a low-energy (5 to 10 watt-sec), synchronized discharge should be employed (*bottom strip*). (From Lown B: The philosophy of coronary care. *Arch Klin Med* 216:214 and 216, 1969.)

TABLE 7–5. Factors that may influence the success of defibrillation

1. Duration of ventricular fibrillation (a major factor inversely related to success of reversion to sinus rhythm)
2. Underlying cardiac disease, including heart size and weight
3. Metabolic/electrolyte derangements and drug effects
4. Technique of defibrillation
   a. Paddle position
   b. Paddle contact pressure with thorax
   c. Paddle size
   d. Energy delivered
   e. Manner of discharge (i.e., single vs multiple shocks)
5. Transthoracic resistance

tionated electrical activity of the heart. The excitation wavefront propagates in a random and irregular fashion, arriving at portions of the ventricular myocardium that have varying degrees of refractoriness and excitability. Electrophysiological factors that increase vulnerability to VF include (a) increased automaticity, (b) currents resulting from differences in membrane potential between adjacent cells during electrical activity and at rest, (c) an imbalance between conduction velocity and refractoriness, and (d) nonhomogeneous refractoriness (19). Animal studies have shown that a certain critical mass of myocardium is necessary to sustain VF [7,20]. Although the mass of excitable tissue can be reduced by surgical excision (20) or by selective chemical depolarization [21], the only practical means of defibrillation when the chest is closed consists of passage of an electrical current of sufficient magnitude to depolarize most of the excitable cells.

A number of factors may influence the success of ventricular defibrillation (table 7–5). Since the physician can control many of these factors, every effort should be made to optimize all these conditions rather than concentrating primarily on a single item, such as energy requirements.

The defibrillation procedure should be a well-practiced routine, capable of being performed by all personnel involved in critical care areas. After VF is recognized, the defibrillatory discharge should be delivered as promptly as possible. Recent noncontrolled studies suggest that survival rates can be increased by "blind" defibrillation rather than allowing a critical time to elapse while awaiting definitive electrocardiographic monitoring [22]. (Some types of commercially available defibrillators provide paddles that can serve as leads for such monitoring, thus obviating this difficulty.)

The only acceptable positions for paddle placement are the anterolateral electrodes or anterior-posterior electrodes (see earlier, figure 7–6). No definitive clinical study clearly demonstrates that one electrode position is superior to the other for ventricular defibrillation. Circular paddles having a minimum diameter of 8 to 9 cm (in adults) should be employed; the posterior paddle is larger with a diameter of 11 to 13 cm. These paddles should be applied to the thorax with firm pressure and held in position during the discharge.

Some controversy still exists in the literature regarding the optimal choice of energy and method of discharge [15]. Since the rapidity with which resuscitation efforts are performed is of paramount importance, theoretical considerations are secondary to establishment of a well-rehearsed, coordinated resuscitation procedure. Initial defibrillation in adults should be performed with the energy setting between 300 and 400 watt-seconds as a single large discharge (table 7–2).*

Lower energy settings delivered as rapid sequential discharges have been suggested by some workers; however, such a novel technique should be employed only by a highly experienced resuscitation team. Recommendations by Tacker, Geddes, and their coworkers that a dose of up to 6.6 watt seconds/kg is required for successful defibrillation in heavy individuals (based in large part on animal experimentation) have not been borne out by prospective clinical studies of defibrillation in humans [15]. Thus, devices storing 400 watt-seconds or less are capable of reverting over 95 per cent of patients with VF [15]. Furthermore, delivery of higher

*A recent study by Weaver et al [23] of patients experiencing out-of-hospital VF suggests that an initial shock of 175 watt-seconds was equally effective in initially terminating the arrhythmia compared with 320 watt-seconds. Survival was unrelated to the energy level used for defibrillation but was related to the rhythm identified after the first shock, i.e., survival rates were highest among patients with a supraventricular rhythm and lowest in those with asystole. If these findings are confirmed in a large number of patients, perhaps future recommendations for defibrillation in adults will include lower energy settings (less than 300 to 400 watt-seconds).

energy discharges is more likely to induce myocardial injury. As succinctly summarized by Crampton [15], it appears that (a) high-energy defibrillatory discharges (in excess of 400 watt-seconds) do not significantly improve the long-term survival of patients with VF and (b) the failure of the myocardium to defibrillate does not necessarily indicate failure of the device but rather that a particular patient's heart is not defibrillatable at a safe energy level in a given clinical situation.

Since it is the current flowing through the heart that actually depolarizes the critical portion of myocardium and serves to terminate VF, ideally one should measure intracardiac current flow and density. While this is possible in animals [24], it is difficult in humans. However, investigators have examined the determinants of *transthoracic resistance* to current flow in man [25]. The maximum energy delivered across a 50-ohm test load by most of the devices commercially available ranges from 270 to 330 watt-seconds. In human defibrillation, the wide variations in transthoracic resistance are difficult to predict clinically, making prescription of an energy dose at the bedside a difficult matter. The transthoracic resistance to current flow appears to correlate better with chest width than with total body weight and can be reduced somewhat when large paddles are used and held firmly against the chest [24]. Since only minimal reduction in transthoracic resistance occurs with double shocks at the same energy level, it is suggested that titrating each shock to a higher energy level will improve the chances for successful defibrillation.

It should be noted that the above recommendations relate to adult defibrillation. *Pediatric subjects* should be defibrillated with lower energies. A rough guideline of 2 watt-sec/kg ± 10 watt-sec appears to be useful in terminating 91 per cent of cases of VF in children [26]. Furthermore, open chest defibrillation should be performed with vastly lower energies than those recommended above because of the risk of severe burn of the myocardium if appropriate precautions are not taken. By convention, the internal defibrillating paddles are placed on each ventricle with optimal efficiency if the electrodes are positioned at the base of the right ventricle and apex of the left ventricle [15]. Discharges in the range of 5 to 15 watt-seconds are appropriate.

Recurrent or *prolonged* VF may be resistant to electric shock unless metabolic and electrolyte imbalances are corrected (i.e., administration of intravenous bicarbonate to reverse acidosis). Bretylium tosylate, 500 mg, should be administered intravenously and repeated for one or two doses with intermittent repeated attempts at defibrillation for resistant cases.

Mention should be made of a recently developed *implantable automatic defibrillator* [27,28]. This device defibrillates the heart via an electrode located on an intravascular catheter placed in the superior vena cava near the right atrial junction and a second electrode placed extrapericardially over the cardiac apex. This device is designed to detect the development of VF or VT by sensing the absence of an isoelectric segment in the electrocardiographic signal or by heart rate criteria using the electrodes described above and, more recently, a third bipolar electrode positioned in the right ventricular apex [27,30]. When VT or VF occurs, the unit delivers a 25 watt-second internal defibrillatory impulse. It can recycle three times during a single episode and will automatically increase the defibrillatory charge to 30 watt-seconds. Lithium batteries provide a projected monitoring life of three years, or the capacity to deliver 100 discharges. Several problems limit the clinical applicability of this implantable automatic defibrillator at this time. The first problem relates to whether the unit will consistently detect the occurrence of VT or VF and differentiate it from less malignant arrhythmias. Initial clinical studies raised concerns about appropriate sensing of ECG signals reported to be related to a problem with polarization of the electrodes. Newly assembled units incorporate electrodes with less potential for polarization and a new bipolar right ventricular apical sensing electrode catheter. Additional concerns relate to the possibility of internal myocardial damage due to repeated shocks and constraint of the device due to an arbitrarily fixed charge. More importantly, although there is an external monitoring system available for assessing battery depletion, it is not possible at this time to assess the integrity of the sensing or pulsing functions fully and therefore evaluate the device's capacity *actually* to defibrillate a *given* patient under changing conditions, such as fluctuating electrolyte levels and drug concentrations.

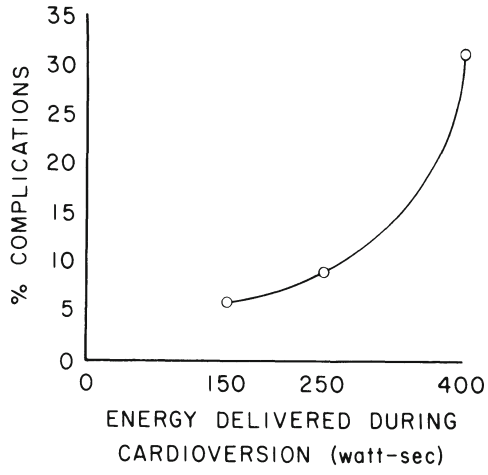

FIGURE 7–13. The incidence of serious complications during cardioversion is directly related to the maximal energy setting used, so that energy titration is essential. The minimum amount of energy required to revert the abnormal rhythm should be employed. In cases of known or suspected digitalis toxicity, the energy employed should be significantly reduced. (From Resnekov L: Theory and practice of electroversion of cardiac dysrhythmias. *Med Clin N Am* 60:335, 1976.)

TABLE 7–6. Incidence of various complications encountered in 220 patients undergoing cardioversion

Elevated levels of serum enzymes	10%
Hypotension	3.2%
Electrocardiographic evidence of myocardial damage	2.7%
Pulmonary and systemic embolism	1.4%
Increase in heart size and pulmonary edema (figure 7–14)	3.2%

From Resnekov L, McDonald L: Complications in 220 patients with cardiac dysrhythmias treated by phased direct current shock, and indications for electroconversion. *Br Heart J* 29:926–936, 1967.

5. *Complications of Cardioversion*

Serious disorders resulting from cardioversion can be prevented by careful attention to electrolyte balance before the procedure, energy titration, and appropriate synchronization; avoiding its use in digitalis-intoxicated patients; and the prompt administration of lidocaine at the first appearance of ventricular extrasystoles. In a review of 220 patients treated with DC shock for electrical cardioversion, Resnekov and McDonald found an incidence of complications of 14.5 per cent, excluding minor complications such as superficial burns from poor preparation of the skin [31]. Furthermore, these researchers indicated that complications were related to the energy settings used (figure 7–13). There was a 6 per cent incidence of complications when 150 watt-seconds were employed, but this incidence rose to 30 per cent when 400 watt-seconds were used. Since myocardial injury and arrhythmias resulting from cardioversion are related more to the energy content of the discharge than to the number of shocks, it is preferable to employ more frequent low-energy shocks and infrequent high-energy shocks. The incidence of various complications following cardioversion as summarized by Resnekov and McDonald is shown in table 7–6. An example of an unusual complication, increase in heart size and development of pulmonary edema, is shown in figure 7–14.

5.1. MYOCARDIAL DAMAGE

A large number of studies have demonstrated both morphological and functional derangements of the myocardium following electrical shocks [4]. This is evidenced by release of myocardial creatine phosphokinase; abnormal technetium pyrophosphate scintigrams [32]; gross and microscopic evidence of myocardial derangements; and release of substances such as potassium, which may be found in elevated concentrations in coronary sinus blood following transthoracic shocks.

5.2. CARDIAC ARRHYTHMIAS

A variety of ventricular arrhythmias including isolated ventricular premature beats, VT, and even VF have been noted following attempts at cardioversion. While ventricular fibrillation most often occurs as a result of malsynchronization, it should be recalled that digitalis glycosides (and possibly quinidine) appear to "sensitize" the heart to serious ventricular arrhythmias following transthoracic shocks, particularly if high energies are employed. Release of potassium during electrical shocks and the development of postcardioversion arrhythmias appear to be enhanced in the presence of digitalis glycosides [33]. For this reason it is wise to avoid cardioversion in patients suspected of having digitalis toxicity

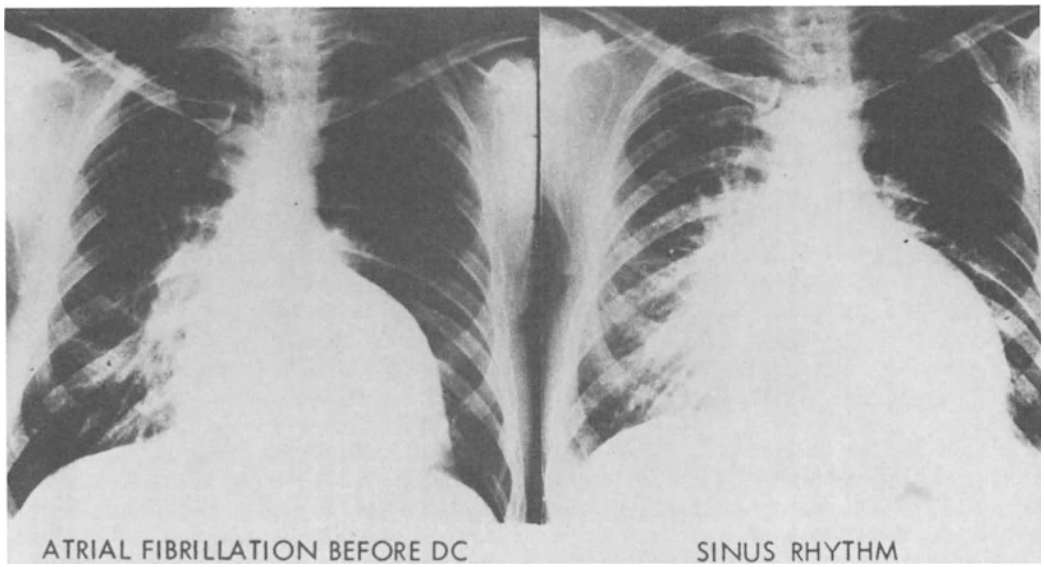

FIGURE 7–14. Increase in heart size and development of pulmonary edema after cardioversion of atrial fibrillation. With reversion to sinus rhythm and return of mechanical performance of the atria, there is an increase in cardiac output. In the presence of obstruction to blood flow across the mitral valve or associated left ventricular dysfunction, pulmonary edema may develop. (From Resnekov L, McDonald L: Complications in 220 patients with cardiac dysrhythmias treated by phased direct current shock, and indications for electroconversion. *Br Heart J* 29:927, 1967.)

(e.g., regularization of ventricular response in atrial fibrillation or vastly reduce the initial shock energies if the procedure is performed [1,4].

5.3. EMBOLISM AND THE NEED FOR ANTI-COAGULATION

The incidence of pulmonary and systemic emboli following electrical cardioversion of atrial fibrillation without the benefit of routine anticoagulation is about 1.5 per cent [1]. This is similar to the incidence seen after pharmacological reversion with quinidine [34]. Several studies have indicated that electrical mechanical dissociation may temporarily occur in the left or right atrium (or both atria), indicating a need for anticoagulation *both prior to and following* cardioversion from atrial fibrillation [35–37]. The incidence of embolism is increased immediately following cardioversion [4], is especially striking when atrial fibrillation recurs, and is clearly reduced by appropriate anticoagulation [38]. It is preferable to anticoagulate patients for three weeks prior to attempting cardioversion from atrial fibrillation and to continue anticoagulation for one to four weeks after the procedure. Table 7–7 summarizes those conditions in which anticoagulation is strongly favored prior to cardioversion owing to an increased risk of embolism [39]. This can be achieved by using a coumarin derivative or heparin if the situation is more urgent [39].

TABLE 7–7. Conditions in which anticoagulation is strongly favored prior to cardioversion

Atrial fibrillation
Recent myocardial infarction
Mitral valve disease
Cardiomyopathy
Prosthetic heart valve
Previous history of embolism

From Resnekov L: High energy eleltrical current in the management of cardiac dysrhythmias. In *Cardiac Arrhythmias: Their Mechanisms, Diagnosis and Management*, Mandel WJ (ed), Philadelphia, JB Lippincott, 1980, pp 589–604.

6. *Special Considerations [1,40]*

6.1. GERIATRIC PATIENTS

With aging there is an enhancement of vagal tone and a propensity for ineffective generation of sinus impulses. Thus the elderly asymptomatic patient with atrial fibrillation and a slow ventricular response who is not receiving digitalis seems an unsuitable candidate for cardioversion.

6.2. BETA-ADRENOCEPTOR BLOCKING DRUGS

Patients receiving beta blockers may exhibit arrhythmias following cardioversion owing to the depressant effect of the drugs on sinus node activity. Appropriate precautions should be taken, including readily available atropine, isoproterenol, and a temporary pacemaker.

6.3. PATIENTS WITH AN ARTIFICIAL PACEMAKER

Individuals with a permanent cardiac pacemaker present no difficulties, since their units are usually isolated from the cardioversion discharge. However, temporary pacemaker wires should be transiently disconnected from the generator pack during the period of reversion.

6.4. ATRIAL FIBRILLATION/FLUTTER OCCURRING AFTER OPEN-HEART SURGERY

Sinus rhythm is usually not well maintained in the immediate postoperative period if initial attempts at cardioversion are unsuccessful. For such patients, it is preferable to wait 10 to 14 days before attempting repeat cardioversion [1]. Recent application of the rapid atrial pacing technique for terminating atrial flutter has met with considerable success.

6.5. USE OF CARDIOVERSION AS A DIAGNOSTIC TOOL

Low-energy cardioversion may be used to determine whether an arrhythmia is the result of digitalis intoxication. If the arrhythmia is readily reverted, digitalis is probably *not* the cause of the rhythm disturbance. However, if cardioversion increases the atrial or junctional rate and provokes ventricular premature beats, digitalis may be implicated. Atrial flutter or nondigitalis-induced atrial tachycardia with block can be reverted to atrial fibrillation and normal sinus rhythm following low-energy cardioversion. Electrical treatment of digitalis-induced atrial tachycardia with block usually increases the atrial rate, provokes ventricular premature beats, and infrequently restores sinus rhythm.

The patient with an acute myocardial infarction and a wide-complex tachycardia that is compromising cardiac function often presents a diagnostic dilemma. Restoration of sinus rhythm by low-energy cardioversion retrospectively indicates that VT was the mechanism and usually produces sinus rhythm. If the rhythm was sinus with bundle branch block, a vagal discharge provoked by cardioversion promotes slowing of the rate, with emergence of P waves, and identifies the sinus mechanism.

Retrospective analysis of arrhythmias treated by cardioversion is often helpful. In general, if low energies terminated a tachyarrhythmia, it was probably ventricular rather than supraventricular with aberrancy or bundle branch block. Conversely, much higher energies (100 to 400 watt-sec) are usually required to terminate supraventricular arrhythmias.

6.6. CARDIOVERSION DURING PREGNANCY

Elective and emergency cardioversion for treatment of cardiac arrhythmias during pregnancy has been performed safely during all stages of gestation. Disturbance of fetal heart rhythm is only a remote possibility because of the insulating effect of amniotic fluid and the difficulty of fibrillating a heart that does not have a critical myocardial mass. However, if possible, fetal heart rhythm should be monitored during cardioversion. Induction of premature labor during cardioversion does not appear to be a significant clinical problem.

6.7. CLINICAL TRANSVENOUS CARDIOVERSION

Zipes and coworkers recently reported the efficacy of low-energy synchronized cardioversion of ventricular tachycardia and asynchronous termination of ventricular fibrillation in patients using a catheter electrode [41]. The system consists of a specially designed catheter with two bipolar pairs of stainless-steel electrodes coupled to a cardioverter instrument to deliver a truncated exponential waveform, 6 msec in duration, at 12 energy levels (0.0075 to 3.0 watt-sec). Initial success with this investigational apparatus suggests its possible therapeutic application during electrophysiological studies.

It has now been used in seven patients as a self-contained implantable device [42].

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8. ATRIOVENTRICULAR AND INTRAVENTRICULAR CONDUCTION DEFECTS

1. Anatomy of the Conduction System

For proper diagnosis and management of conduction defects it is important to understand the anatomy and vascular supply of the specialized conduction system of the heart (figure 8–1).

1.1. THE SINOATRIAL NODE

Excitation of the heart is initiated in the sinoatrial (SA) node, a cylindrical structure surrounding the central sinus node artery. In 60 per cent of patients the sinus node artery is a vessel that branches off the proximal 3 centimeters of the right coronary artery and in 40 per cent it is a branch of the left circumflex coronary artery [1].

The pacemaker impulse, which originates in specialized muscle cells of the SA node (P or pale cells), is transmitted via other specialized muscle cells (T or transitional cells) to the anterior, middle, and posterior *internodal tracts*. These tracts contain large cells that resemble the Purkinje cells in the ventricles and are interspersed with contracting atrial cells. These internodal tracts connect the SA node and the atrioventricular (AV) node (figure 8–1).

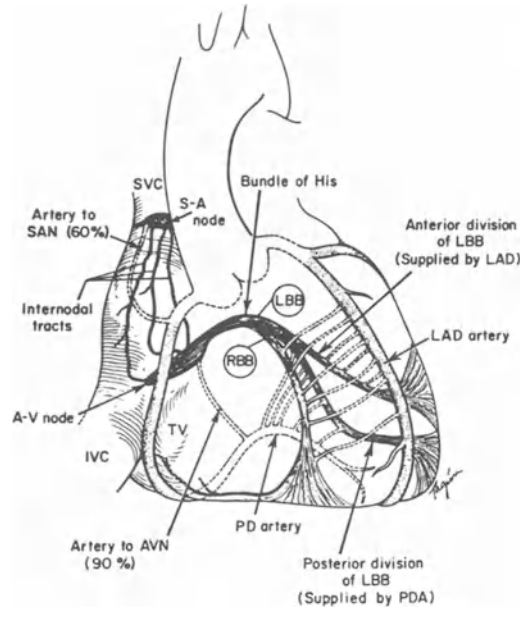


FIGURE 8–1. Anatomy and vascular supply of the conduction system of the heart. (From Harthorne JW, Pohost GM: Electrical therapy of cardiac dysrhythmias. In *Clinical Cardiovascular Physiology*, Levine H (ed), New York, Grune and Stratton, 1976.)

1.2. THE ATRIOVENTRICULAR NODE AND BUNDLE OF HIS

The AV node is situated below the endocardium of the right atrium, anterior to the orifice of the coronary sinus on the annulus of the tricuspid valve. Although most fibers of the internodal tracts terminate along the superior and posterior margins of the AV node, a few fibers in the posterior internodal tract bypass the bulk of AV nodal tissue and insert near the junction of the AV node and His bundle. Based on electrophysiological studies, the AV node may be

subdivided into three areas AN, N, and NH regions, each of which has distinct electrophysiological characteristics. Cells of the N or central region have the slowest rising action potential and represent the major source of delay in AV conduction, while cells in the AN and NH regions have more rapidly rising action potentials.

The blood supply of the AV node derives from the AV nodal artery located at the crux of the heart (figure 8–1). This vessel is a branch of the right coronary artery in 80 per cent of males and 93 per cent of females [3]; in the remaining patients, the AV nodal artery arises from the circumflex coronary artery (left dominant system). The right coronary artery may also supply blood to the common bundle of His and proximal right bundle branch.

After leaving the AV node, the impulse enters the common bundle of His, located in the endocardial cushion, between the annuli of the atrioventricular valves and beneath the noncoronary sinus of the aortic valve (figures 8–1 and 8–2). Because of its proximity to surrounding structures, the His bundle is susceptible to conduction block resulting from disease states that cause fibrosis or calcification of neighboring tissues. It may also exhibit abnormal conduction after surgical procedures involving the annuli of calcified valves, valve replacement, or repair of endocardial cushion defects [2].

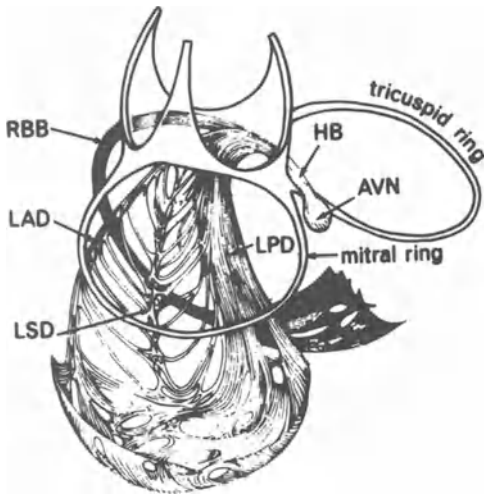


FIGURE 8–2. Anatomy of the specialized conduction system. (From Scheinman MM, Peters RW: Clinical and electropharmacologic characteristics of patients with bundle branch block. In *Cardiac Pacing*, 2nd ed, Samet P, El-Sherif N (eds), New York, Grune and Stratton, 1980, pp. 529–549.)

1.3. INTRAVENTRICULAR CONDUCTION SYSTEM

In the upper portion of the interventricular septum, the common bundle of His divides into a posterior nonbranching division, which becomes the *right bundle branch* and a more anterior branching portion that passes beneath the endocardium over to the left ventricular side of the septum. Although originally it was proposed that the left bundle divided further into discrete fascicles, this has not been borne out by careful anatomical investigations. However, from a functional standpoint, it is useful to divide the *branches of the left bundle* into the centroseptal, anterior, and posterior fascicles (figure 8–2). The centroseptal fascicle is responsible for early activation of the interventricular septum in a left-to-right direction.

The perforating septal branches of the anterior descending coronary artery provide blood to both the right bundle branch and the anterior fascicle of the left bundle. The anterior fascicle is more susceptible to block than is the posterior fascicle because of its single blood supply, thinner and longer anatomical structure, and location in the left ventricular outflow tract. In contrast, the posterior fascicle receives blood from both the left anterior descending and the posterior descending coronary arteries arising from either the left circumflex or right coronary artery. Thus, the posterior fascicle, with its dual blood supply and location in the left ventricular inflow area, is less susceptible to block.

1.4. CLINICAL CORRELATIONS

Because of the proximal origin of the sinus node artery, occlusion of this vessel is often associated with extensive infarction, atrial arrhythmias, and a high mortality rate. Furthermore, endarterectomy of the proximal right coronary artery may compromise the blood supply to the SA node.

Inferior rather than anterior myocardial infarction (MI) is more likely to be associated with disorders of conduction in the AV node (and, occasionally, in the common His bundle) in the absence of power failure of the left

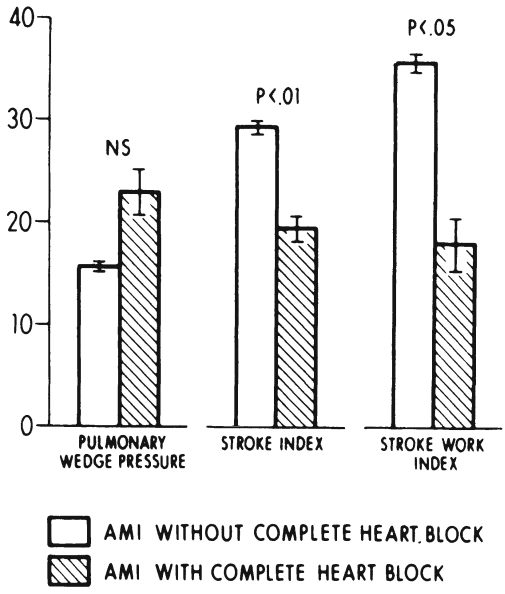


FIGURE 8–3. Relation of complete heart block to left ventricular dysfunction in patients with anterior myocardial infarction (AMI). The percentage of patients (vertical axis) developing complete heart block during AMI is higher with larger infarcts complicated by severe power failure. (From Biddle TL, et al: Relation of heart block and left ventricular dysfunction in acute myocardial infarction. *Am J Cardiol* 39:961, 1977.)

ventricle. Left or right bundle branch block with associated fascicular blocks in anterior MI is usually associated with extensive loss of myocardium and hemodynamic derangements. Complete AV block associated with anterior MI occurs with larger infarcts, as reflected in a significant reduction in cardiac work and elevations in mean pulmonary capillary wedge pressure [3] (figure 8–3).

Knowledge of the blood supply of the ventricular conduction system permits clinicians to postulate mechanisms that underlie the conduction defects observed on the electrocardiogram [ECG]. However, because of the variability in arterial supply, one cannot precisely determine which vessel is primarily responsible for the defect by inspecting the ECG alone. For example, about 25 per cent of patients with acute MI and right bundle branch block on the ECG have inferior wall infarction that would suggest right coronary artery occlusion [4]. Should AV block occur in these patients, it may be at the level of the AV node and associated with a stable proximal escape rhythm that does not require positioning of a temporary pacemaker. However, as noted above, infarction of the inferior wall may result in ischemia and/or infarction of the His bundle, leading to the development of complete AV block with an unstable distal escape focus and the need for pacemaker support [5].

2. *Conduction Defects Associated with Acute Myocardial Infarction*

Conduction defects are likely to occur at any level of the conduction system during myocardial ischemia or infarction. Thus, blocks may occur in the SA node, AV node, or specialized intraventricular conduction fibers described above. Blocks may occur singly or in combination, producing characteristic ECG patterns (figure 8–4). On occasion, scalar ECG recordings may be confusing (figure 8–5), in which case vectorcardiography may be employed to assist in the diagnosis of combined conduction blocks (figure 8–6).

Complete AV block may occur at several different levels, including the AV node, main bundle, main left bundle and right bundle, or combined defects in the right bundle and left anterior and posterior fascicles of the left bundle. Patients who develop AV block in the setting of acute MI can usually be grouped into two broad categories according to the site of the block, i.e., proximal or distal. Table 8–1 summarizes important features of these two groups. Recent histopathological studies have shown that many patients who develop transient AV block do not have actual necrosis of the conduction system, but rather demonstrate hydropic cell swelling that presumably resolves as the conduction defect disappears [6].

2.1. PROXIMAL CONDUCTION DEFECTS

Proximal conduction defects are more common during the prehospital phase, particularly during inferoposterior infarction. In part, these probably result from stimulation of cardiac vagal afferent receptors in the inferoposterior left ventricle [7]. Uncomplicated proximal conduction blocks are easy to manage clinically; one premonitory feature of high-grade AV block is progression from first- to second-degree AV block in a Mobitz I pattern (Wencke-

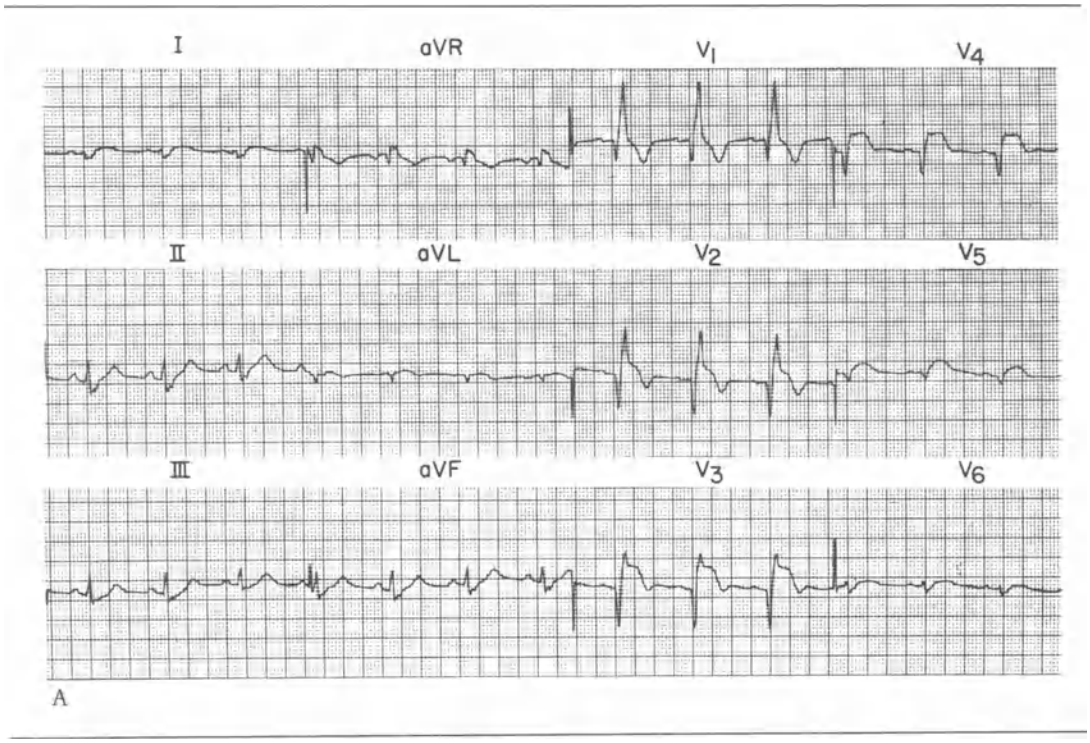


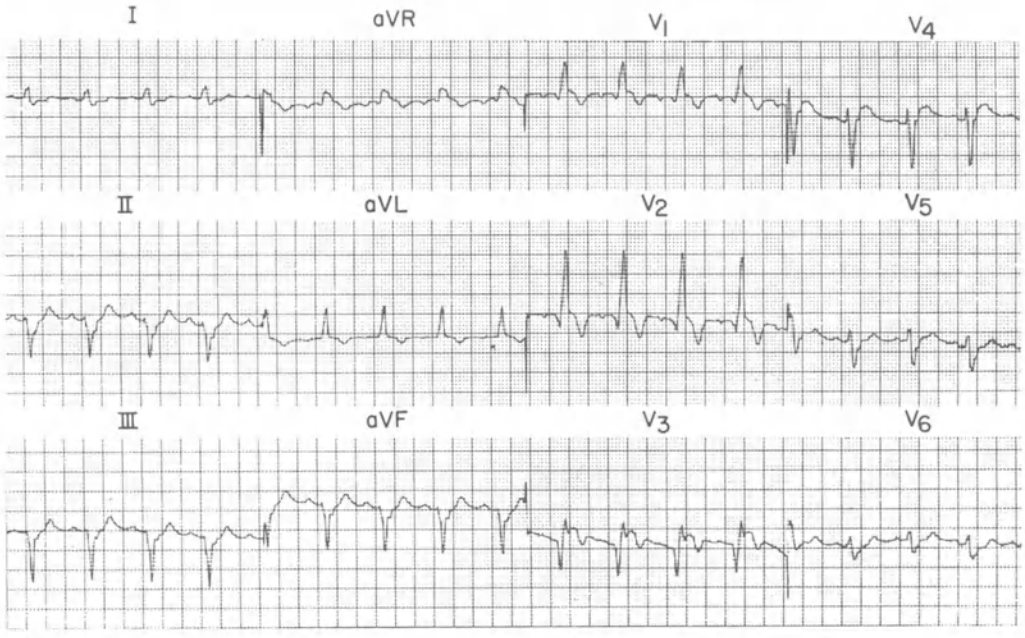
FIGURE 8–4. *A*, Acute anterior myocardial infarction (MI) complicated by right bundle branch block (RBBB). Note the pathologic Q waves in leads V_1 to V_4 indicative of an anterior MI and the terminal rightward forces (R_1) in leads V_1 to V_2 indicative of RBBB. The axis of the "unblocked" forces (i.e, first 40 to 60 msec of the QRS) in the frontal plane is normal.

B, Acute anterior MI complicated by RBBB and left anterior fascicular block (LAFB). The anterior precordial leads show the same changes as in anterior MI and RBBB, but now there is a marked left axis deviation of the unblocked forces in the frontal plane indicative of LAFB.

C, Acute anterior MI complicated by RBBB, LAFB, and 2:1 AV block. The tracing shows the changes described in panel *B* of an anterior MI with RBBB and LAFB, but now only every other P wave is followed by a QRS complex indicative of 2:1 AV block. The nonconducted P waves are buried in the ST segment and can be seen best in leads II, V_1, and V_5 by marching at an interval exactly one-half that of the conducted P waves. There is also first-degree AV block in those P waves which are conducted.

D, Anterior MI complicated by first-degree AV block, RBBB, and probable left posterior fascicular block (LPFB). The pathologic anterior Q waves indicate anterior MI and the terminal rightward forces in leads V_1 to V_2 and V_5 to V_6 are characteristic of RBBB. The PR interval is prolonged (first-degree AV block). The unblocked QRS forces in the frontal plane are deviated markedly to the right suggestive of LPFB. However, a similar deviation of the frontal plane forces could be caused by extensive high lateral MI, severe pulmonary disease, or right ventricular hypertrophy. This patient did not have pulmonary disease clinically, and the ECG does not show evidence typical of right ventricular hypertrophy. An echocardiogram showed preserved wall motion in the high anterolateral segments of the left ventricle and suggested that high lateral MI had not occurred and that this probably represents LPFB.

E, Chronic left bundle branch block (LBBB) complicated by acute anterolateral MI. The QRS is wide and there is poor R wave progression in V_1 to V_3 and a delayed intrinsicoid deflection in V_5 to V_6 — all suggestive of LBBB (which was a chronic ECG finding in this patient. Strikingly abnormal repolarization changes are seen in leads I, a V_1, and V_5 to V_6 indicative of myocardial ischemia/infarction. The deep horizontal ST-segment depression in I, V_5 to V_6, and upward-coving ST segment in a V_1 are *atypical* of LBBB and are an example of *primary* repolarization changes of MI as opposed to *secondary* changes due to LBBB. Ordinarily LBBB cause ST-segment elevation in V_1 to V_3 and slight ST-segment depression in V_5 to V_6 but of less magnitude than seen in this tracing. Note also that LBBB is characteristically associated with upright T waves in V_1 to V_3 and inverted T waves in V_5 to V_6. Although not illustrated in this ECG, T-wave inversion in V_1 to V_3 when the QRS shows LBBB also represents a *primary* repolarization abnormality and is suggestive of anteroseptal MI.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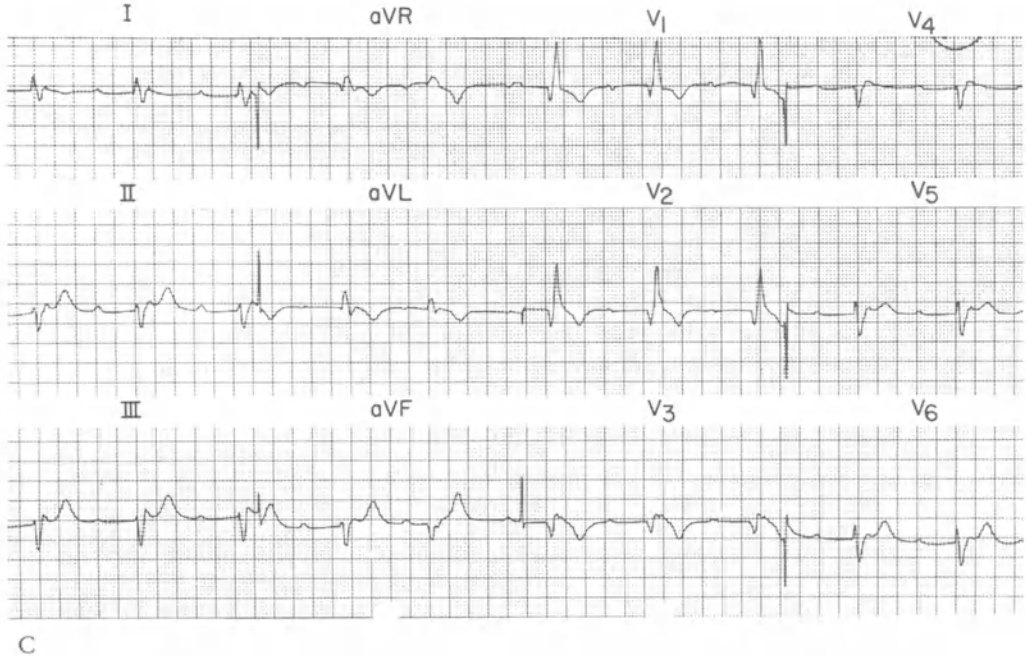
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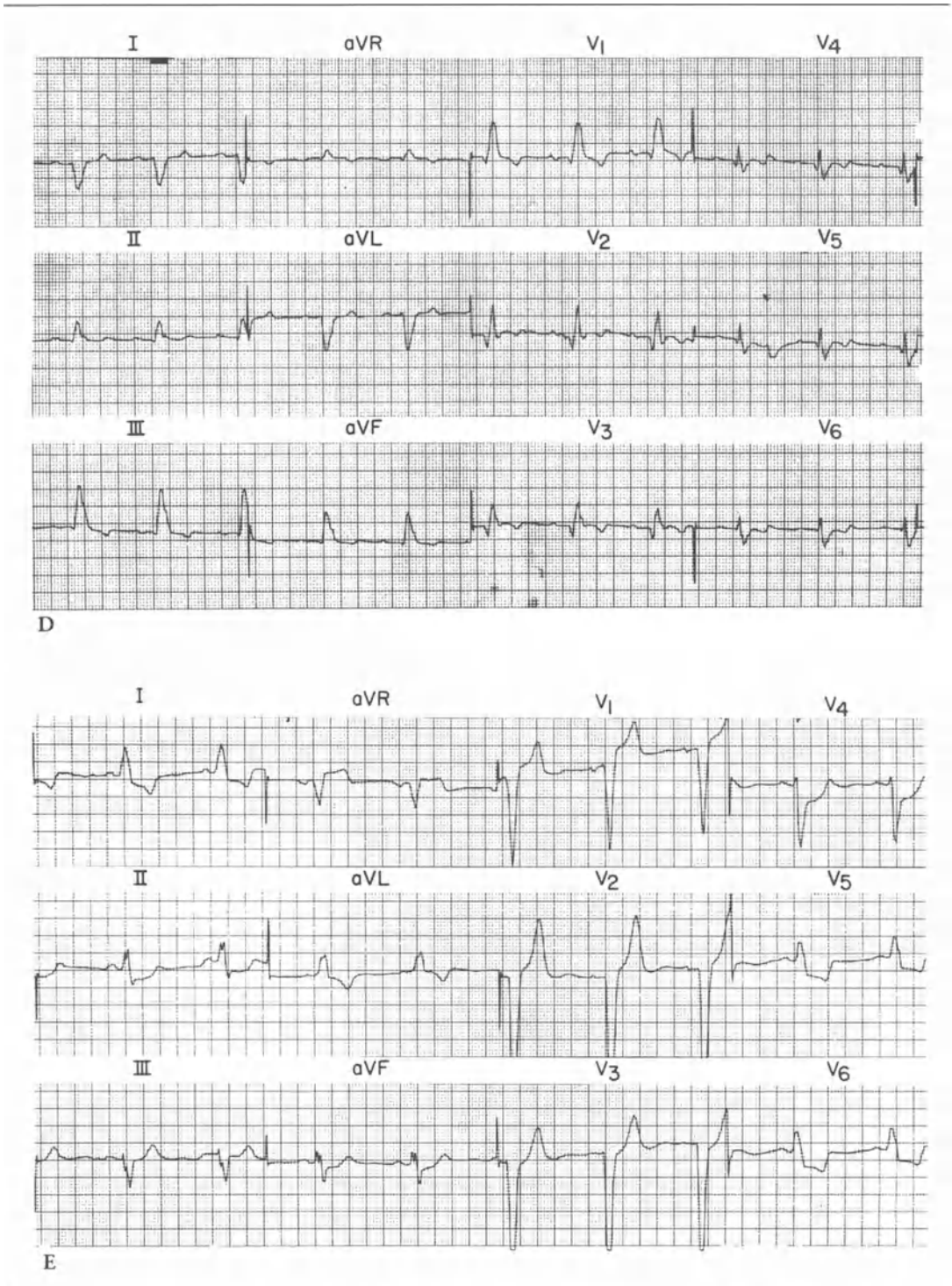


FIGURE 8–4. Continued

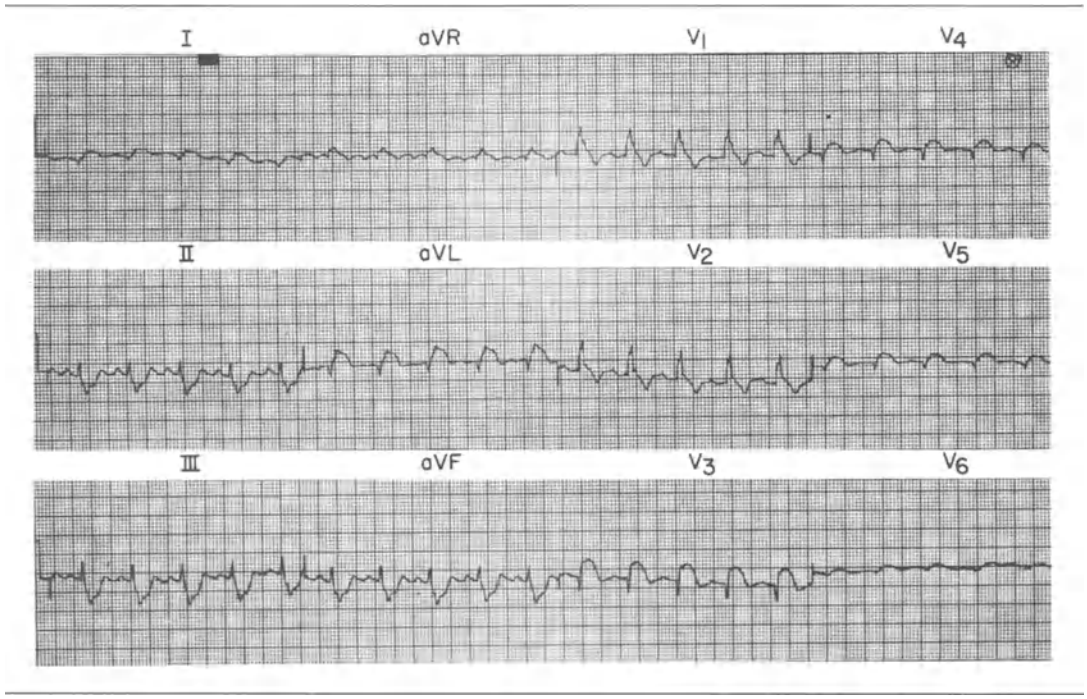


FIGURE 8–5. Acute extensive anterior MI with first-degree AV/block and wide QRS complex. This ECG shows evidence of acute anterior MI (best seen in leads V_3 to V_5) that is extensive, since virtually all the precordial leads are affected as well as leads I and aV_1. The QRS is wide and is directed toward the right in V_1 to V_2 indicative of RBBB. However, the frontal plane axis of the unblocked forces is somewhat difficult to calculate, making it unclear whether there is a coexistent fascicular block. A vectorcardiogram might be useful to confirm the RBBB in the horizontal plane and define the axis and presence or absence of a coexistent fascicular block.

bach type block*) (figure 8–7). When complete AV block occurs, the QRS complex is usually less than 0.12 second and the proximally located escape focus is usually reliable and fires at an acceptable rate.

Lie and Durrer have reported a group of patients with a slower, unstable, distally located escape mechanism characterized on ECG by a right bundle branch block configuration [8,9]. Furthermore, these authors noted that patients who demonstrated a left bundle branch block escape rhythm had bradycardia-dependent left bundle branch block in the presence of an AV junctional escape focus. Prognosis appears to be poor for patients with proximal conduction blocks associated with bradycardia, hypotension, and congestive heart failure [10]. Indications for temporary pacemaker therapy in proximal AV conduction blocks are outlined in table 8–2.

*The term Mobitz type I will be used throughout to refer to this type of block.

2.2. DISTAL CONDUCTION DEFECTS

The in hospital mortality is high among patients who develop bundle branch block during an acute MI (30 to 60 per cent) as is their risk of sudden death during the post hospitalization period [5,10,11]. Several reports suggest that this high incidence of sudden death in the period after discharge results from extensive infarction with left ventricular failure or ventricular arrhythmias, including ventricular fibrillation [5,10,11]. However, it is probably true that a finite population of patients who exhibit high-grade conduction defects during the acute phase of MI later die suddenly due to

TABLE 8–1. Features of AV conduction disturbances in acute myocardial infarction

	Location of AV conduction disturbance Proximal	Distal
1. Site of block in majority of cases	Intranodal	Infranodal
2. Site of infarction	Inferoposterior	Anteroseptal
3. Compromised arterial supply	RCA (90%) LCX (10%)	Septal perforators of LAD
4. Pathogenetic mechanisms of block	Ischemia, necrosis, hydropic cell swelling, excess parasympathetic activity	Ischemia, necrosis, hydropic cell swelling
5. Incidence during prehospital phase	11%	1%
6. Time of onset of high-grade AV block (second- and third-degree AV block)	Within 72 hours of infarction	Within 72 hours of infarction
7. Common premonitory features of third-degree AV block	a. First- to second- degree AV block b. Mobitz I pattern	a. Intraventricular conduction block b. Mobitz II pattern
8. Common features of escape rhythm following third-degree AV block		
a. Location	a. Proximal conduction system (e.g., His bundle)	a. Distal conduction system (e.g., bundle branches)
b. QRS width	b. <0.12 sec*	b. <0.12 sec*
c. Rate	c. 45 to 60/min but may be as low as 30/min	c. Often < 30/min
d. Stability of escape rhythm (i.e., risk of deceleration of rate or ventricular asystole)	d. Rate usually stable; asystole uncommon	d. Rate often unstable with moderate to high risk of ventricular asystole
9. Duration of high-grade AV block	Usually transient (2 to 3 days)	Usually transient, but some form of AV conduction disturbance +/− intraventricular conduction defect may persist
10. Associated mortality rate	<30% unless associated with hypotension and/or congestive heart failure*	30 to 60% because of extensive infarction associated with power failure or ventricular arrhythmias

*Some studies suggest that a wide QRS escape rhythm (<0.12 sec) following high-grade AV block in inferior infarction is associated with a worse prognosis.

complete heart block (distal AV block). Unfortunately, at this time it is impossible to identify this subset of patients accurately in the clinical setting, and this has led to a variety of recommendations for selecting candidates for permanent pacemaker implantation.

About 6 per cent of patients with MI and no ventricular conduction defects develop complete AV block, usually resulting from ischemia of the AV node. Intraventricular conduction blocks occur in 18 to 21 per cent of patients with MI. Mullins and Atkins have summarized the results of several studies on the incidence and prognosis of various types of conduction blocks in acute MI, as shown in table 8–3, but it is important to note that the relatively high risk of progression to complete AV block indicated in the table may be due to the fact that patients in cardiogenic shock were not excluded [11]; complete AV block may have occurred as a terminal event.

As shown in table 8–1, distal AV block is usually preceded by intraventricular block and a Mobitz type II pattern. The distal escape focus results in a slow rhythm with a wide QRS complex (figure 8–8) and may provide an unreliable cardiac pacemaker. Based on the statistical likelihood of the development of distal complete AV block, a number of authors have suggested a variety of conditions that require a

TABLE 8–2. Management of AV conduction disturbances in acute myocardial infarction

	Proximal	Distal*
Acute Therapy		
Indications for treatment	1. Bradycardia associated with left ventricular power failure, syncope, or angina	1. a. Isolated new or old left anterior hemi-block with normal P-R interval b. Isolated new or old left posterior hemi-block with normal P-R interval c. Right bundle branch block antedating acute MI (Very low risk, i.e., prophylactic pacing not indicated)
	2. Bradycardia-dependent ventricular arrhythmias	2. a. New unifascicular block and prolonged P-R interval b. Preexisting bifascicular block and normal P-R interval (Low risk, i.e., prophylactic pacing not indicated in units with readily accessible equipment and personnel for emergency pacemaker insertion)
	3. Unstable escape mechanism (RBBB)**	3. Any 2 of 3 a. First-degree AV block b. Bifascicular block c. Newly acquired bundle branch block (Moderate to high risk, i.e., prophylactic pacemaker insertion indicated)
Therapeutic options	1. Drug therapy — atropine, isoproterenol (results in less morbidity but may cause excessive tachycardia) 2. Temporary pacemaker	1. Temporary pacemaker; pharmacological maneuvers either ineffective or potentially harmful
Chronic Therapy		
Indications for permanent	1. Almost never indicated, since conduction defect is usually transient	1. Pacemaker indicated a. Development of high-degree AV block during hospitalization 2. Pacemaker not indicated (assuming no high-degree AV block during hospitalization) a. All inferoposterior MIs b. Anterior MI *without* prior MI, pulmonary edema, or shock 3. Role of permanent pacing unknown a. Anterior MI *with* prior MI, pulmonary edema, or shock

*Indications for pacemaker therapy in this group remain controversial (e.g., some authors feel prophylactic pacing is not indicated when the conduction disturbance is of late onset [<24 hours] or of short duration [<6 hours]). General guidelines are provided here; see text for more complete discussion.

**Some investigators have shown that escape beats with a right bundle branch block morphology are usually of fascicular or ventricular origin and have a slow rate.

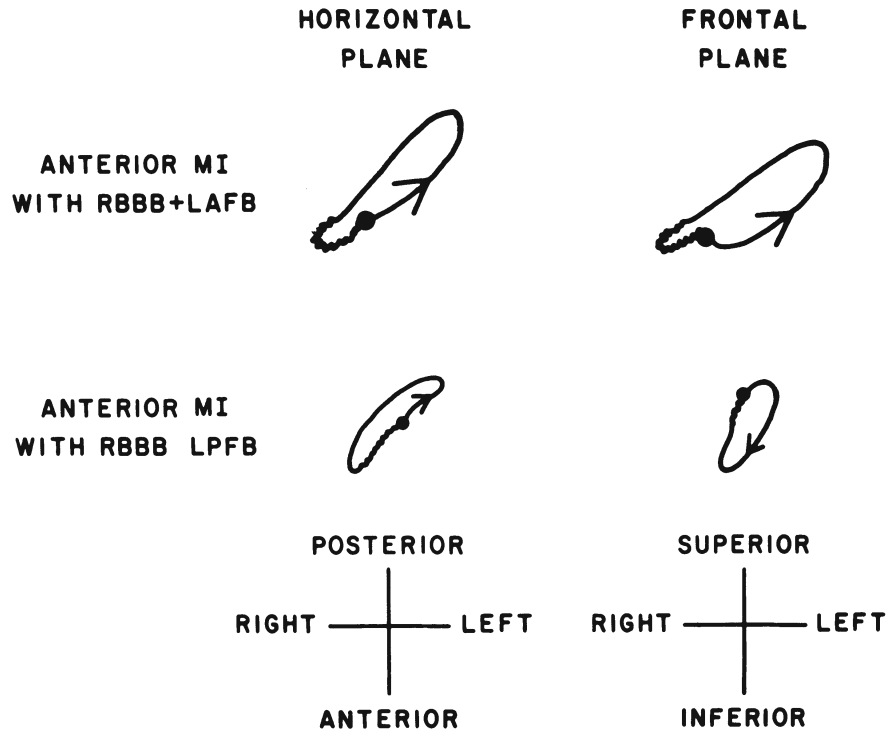


FIGURE 8–6. Vectorcardiograms (VCG) showing combined conduction defects complicting anterior MI. *A*, An anterior MI with RBBB and LAFB. *B*, An anterior MI with RBBB and LPFB. C, Orientation of the horizontal and frontal plane VCG loops. The direction of inscription of the loop is indicated by arrows. In both cases the horizontal plane loop shows loss of anterior forces and slowly inscribed terminal forces directed anteriorly and rightward indicative of anterior MI and RBBB, respectively. The frontal plane loop in LAFB is inscribed in a counterclockwise direction and is oriented toward the left upper quadrant. Conversely, the frontal plane loop is LPFB is inscribed in a clockwise direction and is oriented toward the right lower quadrant. (From Lemberg L, Castellanos A, Jr: *Vectorcardiography: A programmed introduction*, 2nd ed. New York, Appleton-Century-Crofts, 1975, pp. 166 and 169.)

TABLE 8–3. Incidence and prognosis of various conduction blocks in acute myocardial infarction*

Type of conduction block	Incidence of conduction block (%)	Complete AV block (%)	Mortality
None		6	15
Left anterior hemiblock	5	3	27
Left posterior hemiblock	1	0	42
Right bundle branch block	2	43	46
+ left anterior hemiblock	5	46	45
+ left posterior hemiblock	1	43	57
Left bundle branch block	5	20	44

*Summary of data available in the literature. [11].

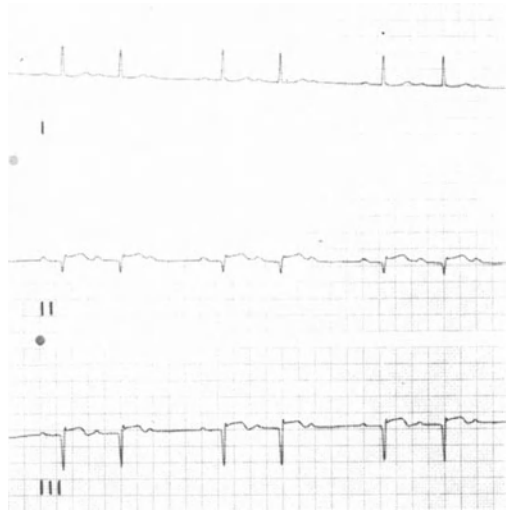


FIGURE 8–7. Inferior MI complicated by Mobitz type I second-degree AV block. The P-R interval is progressively prolonged after the first two P waves; the third P wave is not followed by a QRS complex in this example of 3:2 Mobitz type I (Wenckebach) second-degree AV block. The pattern repeats itself in a characteristic fashion for this type of proximal AV block.

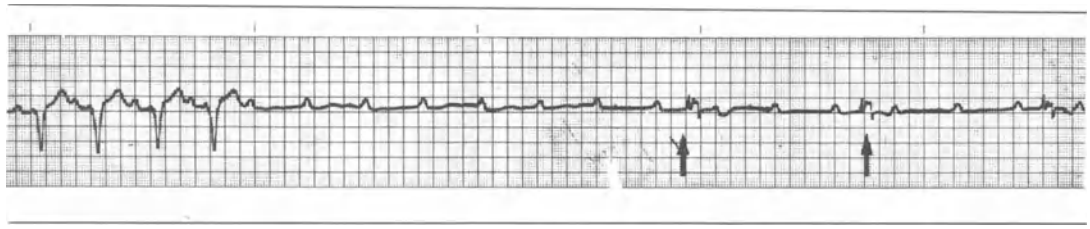


FIGURE 8–8. Acute anterior MI with Mobitz type II AV block. This ECG strip is from a monitor lead (modified chest lead) and shows sinus rhythm with first-degree AV block. The full 12-lead ECG revealed a large anterior MI and intraventricular conduction delay. The first four P waves are followed by QRS complexes, and then complete AV block occurs. All subsequent P waves are not followed by a conducted QRS complex. There is no premonitary progressive increase in P-R intervals before complete AV block occurs, indicative of Mobitz type II AV block. An idioventricular escape rhythm emerges after nearly 6 seconds of ventricular asystole (arrows) and shows evidence of deceleration (compare interval between first two idioventricular beats and the second and third beats). The entire pattern is typical of a *distal* AV conduction disturbance.

temporary pacemaker [13–16]. To date, no large-scale *prospective* studies are available to indicate whether temporary acute pacemaker therapy improves survival. On the other hand, a large-scale, multicenter *retrospective* study has recently been completed in which 432 patients with acute MI and bundle branch block were evaluated [17,18]. During hospitalization, 95 patients (22 per cent) developed high-grade AV block, defined in this study as Mobitz type II second-degree AV block, or complete AV block, in the absence of preexisting cardiogenic shock. Despite the fact that a large number of patients who usually develop highgrade AV block in the setting of an acute MI have significant left ventricular power failure, 35 of these 95 patients (40 per cent) developed high-degree AV block in the absence of significant left ventricular failure. Review of multiple factors in this study led to the development of a risk stratification scheme that divided these patients into a very low-risk group and a moderately high-risk group. On the basis of these findings, certain indications for prophylactic pacing of patients with acute MI and bundle branch block have been devised, and these are presented in table 8–2 [5,17,18]. Thus, emphasis is placed upon the time when bundle branch block develops, the number of fascicles involved, and the presence or absence of first-degree AV block. Whether patients with preexisting intraventricular conduction defects have the same risk of developing complete heart block as those who acquire a conduction defect during the acute infarction is still controversial [18–20].

2.3. PACEMAKER THERAPY

As indicated by Scheinman and Peters, reports addressing the issue of conduction defects with acute MI have presented varying conclusions [5]. The differences may relate to specific characteristics of the population of patients studied (e.g., the presence or absence of cardiogenic shock) and timing of the bundle branch block pattern (chronic or acquired acutely). Further controversy attends the question of whether to employ permanent prophylactic pacing for patients who have developed conduction system defects in the setting of acute MI — a complex problem, since a number of factors influence the likelihood of sudden death following discharge after MI, including the presence or absence of multivessel disease, left ventricular dysfunction, anterior (vs. inferoposterior) MI, complex ventricular arrhythmias, and intraventricular conduction abnormalities. Indeed, Lie and coworkers, in a prospective study, showed that more than one-third of CCU survivors with bundle branch block and anteroseptal infarctions developed late, inhospital, ventricular fibrillation one to six weeks after acute infarction [12]. It is suggested that such patients undergo prolonged monitoring in the hospital prior to discharge. Permanent pacemaker therapy would not be expected to prevent episodes of ventricular fibrillation or left ventricular power failure but rather is designed to prevent complete heart block in a select subset of patients. Once again, we are at a loss clinically to define the specific subset of patients who will receive the greatest benefit from permanent pacemaker implantation. Review of the available studies, especially the recently completed multicenter retrospective study by Hindman et al, has led to the following general recommendations (table 8–2) [5,18].

1. Permanent pacemaker therapy appears to be indicated when progression to high-degree AV block is likely after discharge from the hospital. This includes patients with anterior or indeterminant location infarcts associated with bundle branch block and left ventricular power failure. In addition, patients who develop bundle branch block and transient high-degree AV block during acute MI appear to be at considerable risk for recurrent high-degree AV block after discharge and should therefore receive a prophylactic permanent pacemaker. Some authors feel that individuals who develop right bundle branch and left anterior fascicle blocks with transient high-degree AV block in the setting of acute MI are at particularly high risk.

2. Permanent pacemaker therapy is *not* indicated when progression to high-degree AV block is unlikely following discharge. This applies to patients with posterior or inferior MI and those with anterior or indeterminant location MI with no prior history of MI pulmonary edema, or cardiogenic shock.

3. The role of permanent pacemaker therapy remains unclear in patients who have not experienced progression to high-degree AV block during the acute MI and those with anterior or indeterminant location infarctions with left ventricular power failure but no bundle branch

block. Since serious ventricular arrhythmias and power failure are quite likely in these patients, it is not clear whether permanent pacemaker therapy will prevent sudden cardiac death.

As can be seen from the preceding statements, the conclusions of these studies must be regarded as tentative and are likely to be modified as those patients at greatest risk are better defined.

2.4. HIS BUNDLE ELECTROCARDIOGRAPHY

Before leaving the subject of conduction defects developing in the setting of acute MI, mention should be made of the role and applicability of His bundle electrogram recordings. Relatively few data are available for interpretation, and it is difficult to compare existing reports because of differences in patient populations and the incidence of the various types of conduction defects. A number of investigators have confirmed the fact that AV block occurring in the setting of inferior wall MI is almost always located within the AV node, while in cases of anteroseptal MI, the AV block is almost always infranodal [8,21,22]. Because of the high specificity of this finding, routine performance of His bundle recordings for location of the block in uncomplicated cases is not indicated. On the other hand, His bundle recordings are particularly helpful when unusual types of block or escape mechanisms are encountered [5] as for patients with an inferior MI who develop high-grade AV block and a wide QRS complex as an escape rhythm (figure 8–9). Mobitz type I AV block, although commonly occurring in the AV node, can definitely be observed in the infranodal conduction system. This cannot be determined from the surface ECG.

Some authors suggest that His bundle recordings be used in patients with acute anteroseptal MI complicated by bifascicular block to detect prolongation of the H-V interval [23]. Although there appears to be an association between the presence of a prolonged H-V interval and the development of high-degree AV block when bundle branch block occurs in the setting of acute MI it is not clear that His bundle recordings should be routinely obtained in such cases [24]. The procedure is not without risk, and it would be premature to recommend its routine use until more data are available involving larger numbers of patients.

Finally, the question arises as to whether to administer antiarrhythmic drugs to patients with bundle branch block in the setting of acute MI. Several studies have indicated that the antiarrhythmic drugs now available can usually be given with safety to patients with chronic bundle branch block who are not suffering acute myocardial ischemia [5]. However, isolated reports of high-degree AV block developing after lidocaine administration in the setting of acute MI have appeared in the literature [25–27]. Investigations by Scheinman and coworkers suggest that although most patients with infarction can receive commonly administered antiarrhythmic agents without deterioration of AV conduction, those patients who acutely acquire a bundle branch block in the setting of acute MI are at increased risk for development of high-grade AV block [28]. Thus, for such individuals, antiarrhythmic agents must be administered with caution, and clinicians should seriously consider inserting a temporary pacemaker.

3. Conduction Defects in Settings Other Than Acute MI

In man, abnormalities of conduction may occur transiently or chronically, at all sites in the conduction system, and one may see varieties of combined conduction defects. As noted above, the surface ECG is of only limited value in localizing abnormalities of AV conduction (figures 8–9 and 8–10). Although it was hoped that the intracardiac electrophysiological recording techniques introduced by Scherlag et al, in 1969 and illustrated in figures 8–9 and 8–10 would help identify those patients with conduction system disease who would benefit from implantation of a permanent pacemaker [29], a number of areas remain controversial.

With the exception of the newer more sophisticated specialized antiarrhythmic devices, permanent electrical generators should be inserted only to prevent bradycardia, i.e., either ventricular asystole or an unacceptably slow ventricular rate. Besides the traditional ventricular demand pacemakers, new devices are available that provide "physiologic" pacing by coordinating the sequence between atrial and ventricular mechanical events.

Recent prospective epidemiological studies reported by Schneider and coworkers summarized data gathered in the Framingham Heart Study [30,31]. *Newly acquired complete right*

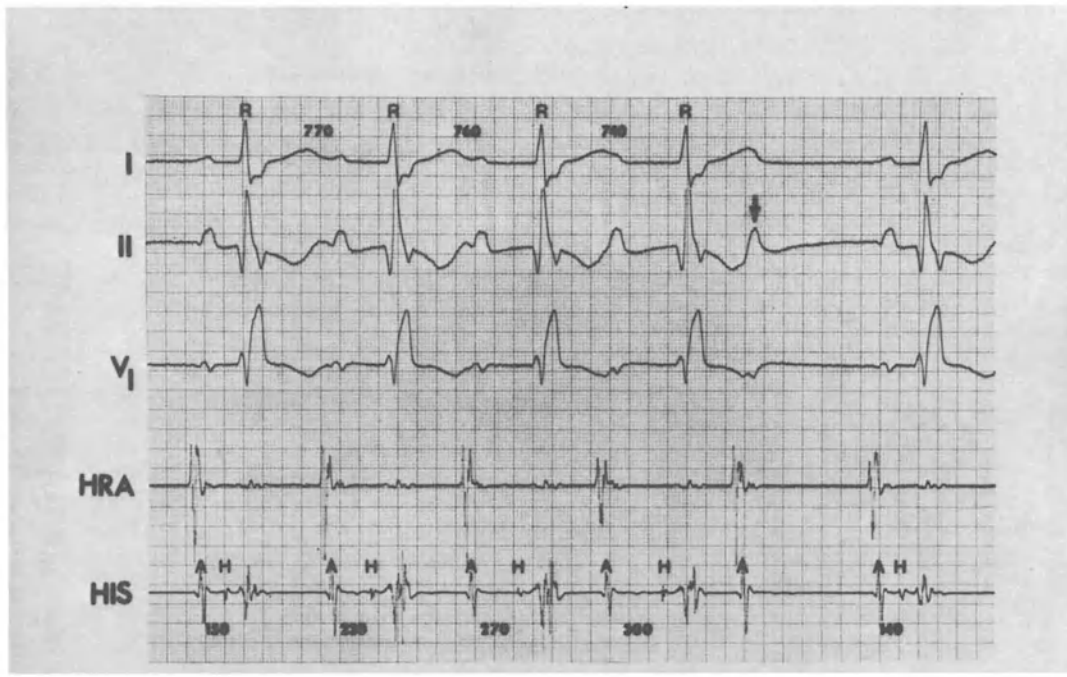
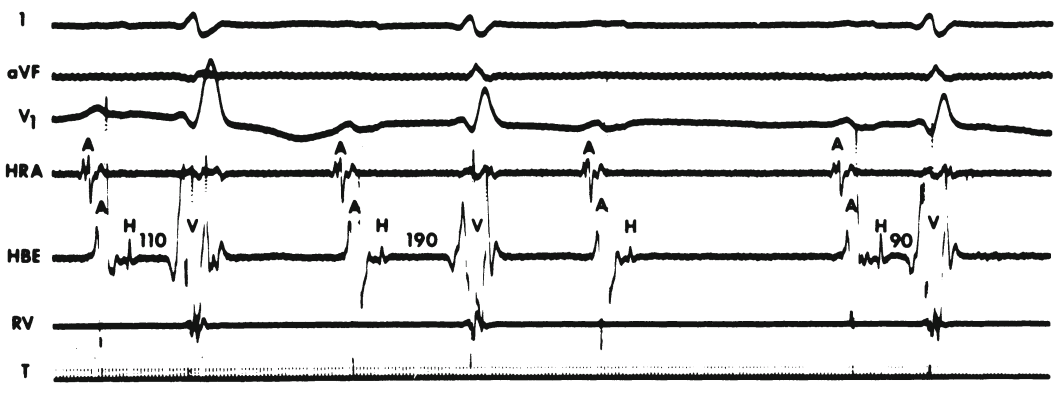


FIGURE 8–9. Simultaneous tracings of surface ECG leads I and II, and V_1 as well as bipolar electrograms from the high right atrium (HRA) and His bundle region (HIS) recorded during spontaneous 5:4 type I second-degree AV nodal block. Note progressive lengthening of the A-H interval and shortening of the H-V interval prior to the blocked P wave (arrow). The H-V interval remains unchanged throughout. (From Friedman PL: AV block in a patient with acute inferior myocardial infarction. *Clinical Dilemmas in Cardiology*, Vol 1, No. 1, June, 1983, p 11.)

FIGURE 8–10. *A*, Type I second-degree infra-His block. Note progressive prolongation of the H-V interval. The third A-H complex is not followed by a ventricular depolarization. The H-V interval shortens after the blocked impulse. *B*, Spontaneous Type II second-degree infra-His block. The A-H and H-V intervals remain constant during conducted impulses at 85 msec and 95 msec, respectively. The third A-H complex, however, is suddenly and unexpectedly *not* followed by a ventricular depolarization. The complex after the blocked impulse shows *no* alteration in conduction intervals. *C*, Second-degree block (intermittent conduction) in mid-His bundle induced by atrial pacing. Alternate A-H (proximal) complexes are not followed by H′ (distal)-V complexes with the impulse blocked within the His bundle distal to the H (proximal) recording site. (From Josephson ME, Seides SF: Clinical cardiac electrophysiology: Techniques and interpretations. Philadelphia, Lea and Febiger, 1979, pp 92, 95, and 96.)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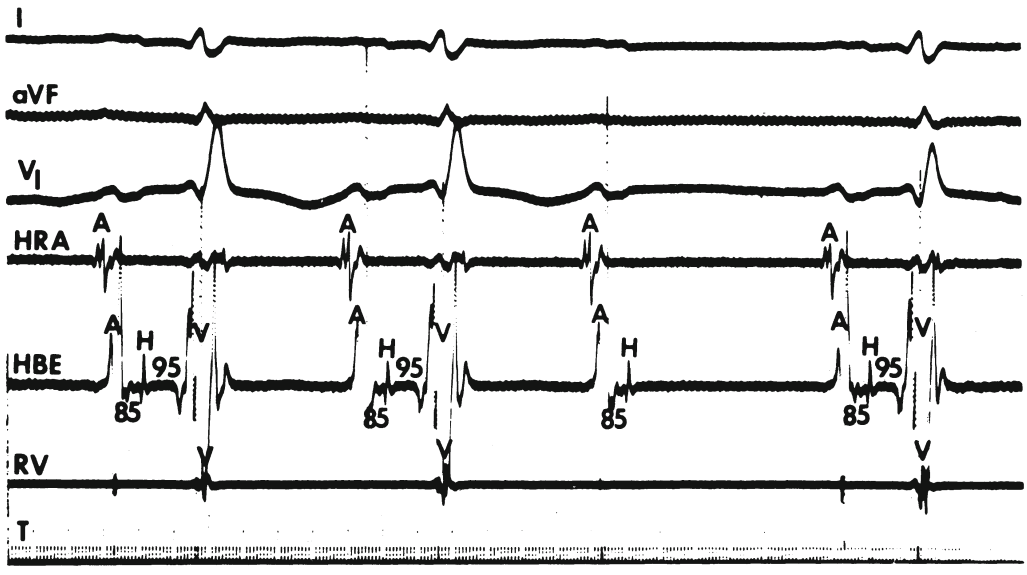
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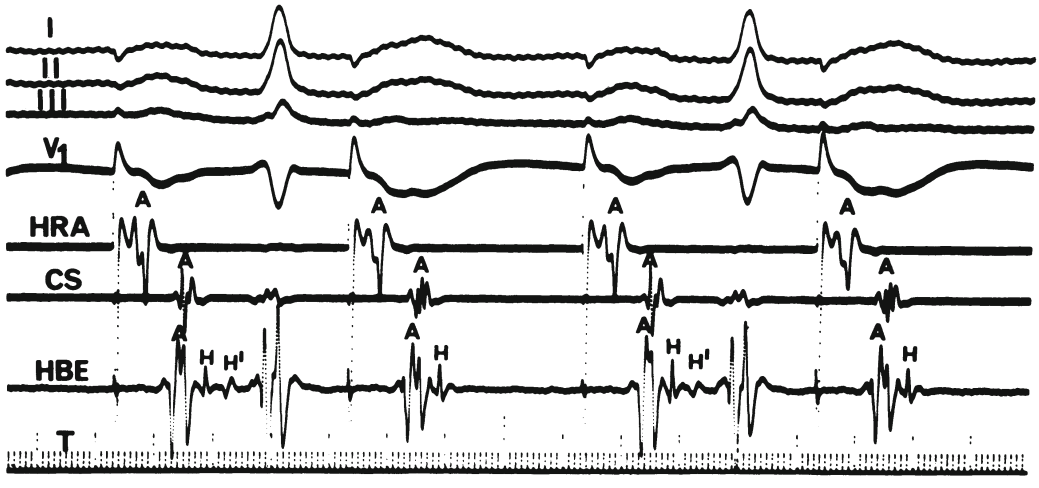
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and left bundle branch block, although occasionally occurring in otherwise healthy, young individuals, usually indicated the presence of advanced underlying cardiac abnormalities (hypertension, congestive heart failure, or coronary heart disease). During the 18-year followup only 11 per cent of patients with newly acquired left bundle branch block and 21 per cent with newly acquired right bundle branch block remained free of clinically apparent cardiovascular abnormalities. However, cardiovascular morbidity and mortality in such patients were related to the severity of the underlying cardiac disease rather than to the relentless progression of conduction system abnormalities leading to complete heart block and sudden cardiac asystole.

Chronic bifascicular block is associated with increased mortality, but available data do not consistently demonstrate that such conduction abnormalities are the cause of death. Chronic bifascicular disease is relatively common, affecting almost 1 per cent of one large hospital population [32]. Although occasionally found in the young, it presents a significant clinical dilemma when seen in the elderly patient. A large retrospective study revealed that as many as 20 per cent of patients with bifascicular disease have no other heart disease, and it is felt that these patients have primary degenerative disease of the conduction system [32]. McAnulty and coworkers reported a prospective study of sudden death in high-risk bundle branch block patients with bifascicular or trifascicular conduction system disease and intact AV conduction [33]. Clinical symptoms (including syncope), ECG findings, and/or electrophysiological data did not identify patients at high risk of sudden death. Sudden death due to bradyarrhythmias was uncommon in such patients, and the authors felt that routine prophylactic use of permanent pacemakers would be inappropriate.

Whether or not the finding of a prolonged H-V interval is of value in predicting a patient's risk of sudden cardiac death is still a subject of controversy. (The H-V interval represents cardiac conduction time below the AV node). It has been suggested that a greatly prolonged H-V interval (more than 75 msec) may identify a group of patients at greater risk of sudden death or syncope. On the basis of these findings, some investigators have recommended prophylactic long-term permanent pacemaker therapy for patients who have chronic bifascicular block with prolonged infranodal conduction times, while others believe that prolongation of the H-V interval has limited predictive value. Conceivably, differences in the results of studies examining this predictor may in part relate to variations in the length of followup and the age of the subjects studied. Scheinman and Peters originally suggested that since both coronary artery disease and conduction system disease are progressive disorders, it is possible that longer followup of greater numbers of individuals with prolonged H-V intervals will confirm preliminary reports of a close association between prolonged infranodal conduction and risk of sudden cardiac death [5].

Indeed, such a long-term followup study has recently been published (34) in which 313 patients with chronic bundle branch block were followed for a mean of almost 3 years. Based upon infranodal conduction divided into 3 groups: H-V $<$ 55 msec, H-V = 55 to 69 msec, and H-V $\geq$ 70 msec. Mortality and the incidence of sudden death were similar among the three groups, but patients in the third group had a greater incidence of progressive to high-grade AV block (particularly if the H-V interval was $>$100 msec). Most importantly, although transient neurological symptoms were relieved by pacing, there was no evidence to suggest that this intervention prolonged life, since the incidence of total and sudden cardiac deaths was not significantly different between paced and unpaced patients. The ultimate prognosis appears to be related to the severity of the underlying cardiac disease and not the specific details of the conduction disorder [34].

Recent studies of patients with *chronic second-degree AV block* provide further evidence that conduction system disease may be seen both with and without organic heart disease but that the clinical course is more clearly related to the severity of the underlying disease than to the presence of AV block [35]. Permanent pacemakers should be reserved for patients with heart disease who require augmentation of the ventricular rate for managing congestive heart failure or for those individuals suffering from recurrent syncope, especially when this can be documented as due to bradyarrhythmias.

TABLE 8–4. Criteria for permanent pacing in chronic conduction disease without acute MI

	Bifascicular block	Second- or third-degree AV block
Pacemaker indicated	— Symptomatic patients with documented bradyarrhythmia — Recurrent syncope of unknown cause after complete medical and neurological workup — AV block distal to His bundle, spontaneously or on pacing, in symptomatic patients	— Symptomatic patients (e.g., congestive heart failure) with block at any site — Asymptomatic patients with block in or distal to His bundle
Pacemaker not needed	— Asymptomatic patients with or without prolonged P-R interval	— Asymptomatic patients with block proximal to His bundle
Controversial	— Symptomatic patients with prolonged H-V interval without documented bradyarrhythmia	

Modified from Dhingra RC, et al: *J. Cardiovasc. Med*, May, 1978, p 493.

4. *Surgery and Antiarrhythmic Agents for Conduction Defects*

One must also consider the asymptomatic patient with chronic right bundle branch block and left anterior fascicular block who is about to undergo an operation. Since the risk of *intraoperative complete heart block* in such individuals is low, a temporary pacemaker prior to surgery does not appear to be needed [36]. Rather, one need only recommend to the anesthesiologist that atropine and a standby isoproterenol drip be available.

The use of *antiarrhythmic agents* in patients with intraventricular conduction system defects has been addressed by several investigators. Slight prolongation of infranodal conduction times has been reported, particularly with rapid infusions of antiarrhythmic drugs [5]. Nevertheless, episodes of high-degree AV block are uncommon. Thus, the commonly employed antiarrhythmic agents can probably be used safely in hemodynamically stable patients with chronic bundle branch block. However, individuals with sinus node dysfunction, those with episodic AV block in the setting of chronic bifascicular block, and critically ill patients suffering from acute MI or electrolyte/metabolic derangements should receive modified doses of antiarrhythmic agents with careful electrocardiographic and hemodynamic monitoring and provisions for pacemaker therapy available if needed.

Table 8–4 summarizes the current recommendations for permanent pacing in patients with chronic conduction disease without acute MI.

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9. TEMPORARY AND PERMANENT PACEMAKER THERAPY

1. Technique of Temporary Pacemaker Therapy

Temporary cardiac pacing can be achieved by four basic techniques: thump pacing, external transthoracic electrical pacing, percutaneous transthoracic pacing, and transvenous endocardial pacing.

1.1. THUMP PACING

This is performed by repetitive striking of the sternum with a clenched fist from a height of 8 to 12 inches at a rate of once per second. (See "Thumpversion" and figure 7–11 in chapter 7.)

1.2. EXTERNAL TRANSTHORACIC ELECTRICAL PACING

This technique utilizes a modified version of a system originally designed by Zoll and coworkers [1]. Pacemaker stimuli are delivered to the precordium through externally positioned electrodes, and sufficient energy is transmitted to the heart to capture the myocardium. However, this technique has certain disadvantages. Intercostal muscle depolarization may cause patient discomfort, cardiac capture may be unreliable, and electrical interference may make analysis of the ECG recording difficult. In an attempt to circumvent the problems noted above, an updated model of the device utilizes large sponge electrode pads, a widened pulse width, and special monitoring circuitry (to facilitate viewing of the ECG in the presence of a large stimulus).

1.3. PERCUTANEOUS TRANSTHORACIC PACING

Access to the pericardial space is achieved using a subxiphoid or low left lateral parasternal approach (figure 9–1). Once entry into a cardiac chamber is confirmed by observing the presence of ST-segment elevation on an exploring precordial V lead connected to the puncture needle by means of alligator clips, the needle is advanced until free flowing blood is aspirated. A bipolar wire electrode with a sharply angled J tip is then passed through the lumen of the needle and connected to a temporary generator (figure 9–1).

Some manipulation of this wire electrode may be necessary to assure adequate myocardial capture. Although, occasionally it is possible to pace the heart solely via the puncture needle, this method risks cardiac lacerations. A new transthoracic pacing kit has recently become available that allows the operator to pass a wire electrode through a 21 gauge needle at the time of entry into the myocardium (USCI, Billerica, MA). This offers two advantages: (1) shortened insertion time (since the electrodes, which are already in position, may be connected to the generator during initial needle insertion) and (2) rapid conversion to a unipolar pacing arrangement if desired.

The patient's ECG should be monitored continuously during insertion so that myocardial capture by the pacemaker can be recognized promptly. Complications of this technique include pleural bleeding; pneumothorax; cardiac tamponade; and laceration of the myocardium, a great vessel, or a coronary artery. It should be reserved for emergency situations, when immediate cardiac pacing is required. Unfortunately, it is rarely successful, since cardiac decompensation is usually far advanced by the time it is attempted.

1.4. TEMPORARY TRANSVENOUS ENDOCARDIAL PACING

Because it is most commonly employed, this

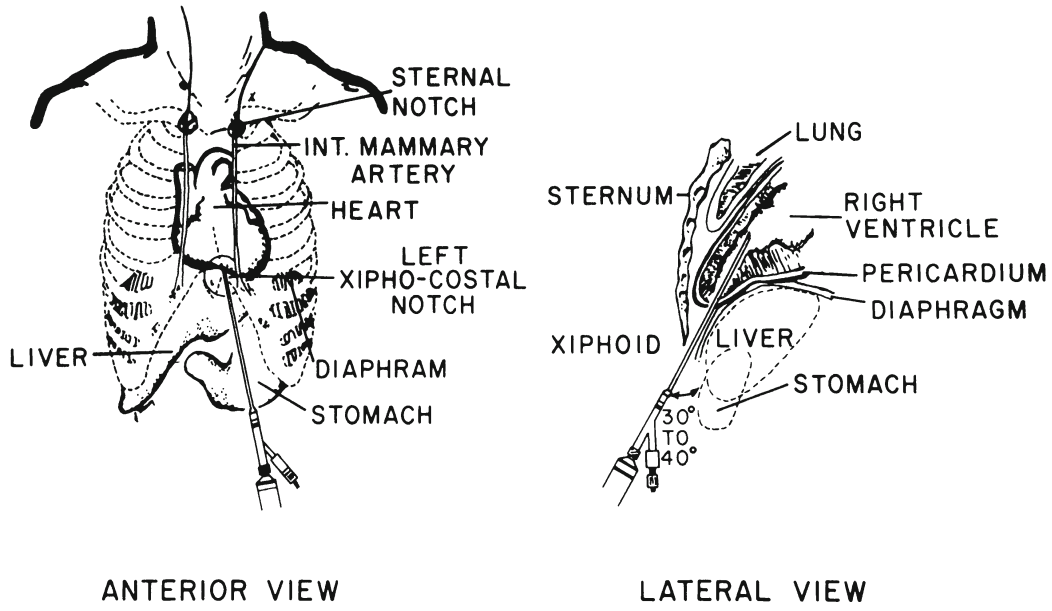


FIGURE 9–1. Percutaneous transthoracic pacing. The proper subxiphoid approach to the right ventricle is shown. The particular device illustrated allows the operator the opportunity to pace immediately via a preloaded pacing wire and to administer intracardiac medications via the side-arm connector. (Courtesy of Pace-Jector, Electro-Catheter Corp, Rahway, NJ.)

TABLE 9–1. Considerations when selecting a venous entry site for temporary transvenous endocardial pacing*

	Entry site			
	Internal jugular	Subclavian	Femoral	Brachial
1. Allows more rapid access via percutaneous route	+	+	+	
2. Usually allows positioning of electrode without fluoroscopy in emergency	+	+		+
3. May be associated with more serious *acute* complications	+	+		
4. May be associated with higher incidence of loss of ventricular capture or complications with increasing duration of pacemaker therapy				+
5. Patient mobility				
a. Restricted			+	+
b. Unrestricted	+	+		

*The clinical course of 1,022 consecutive patients who received a temporary transvenous pacemaker in the coronary care unit during a 5-year period (1976 to 1981) was recently reviewed (Hynes JK, Holmes DR, Harrison CE. Five-Year Experience with temporary pacemaker therapy in the coronary care unit. *Mayo Clin Proc* 58:122, 1983). Loss of ventricular capture occurred in 183 patients (17.9%) and a total of 140 complications (13.7%) without associated mortality was noted. The route with the highest incidence of loss of capture and pacemaker-related complications was via the brachial vein. Hynes *et al* concluded that the preferred routes of insertion were internal jugular and subclavian veins, provided that the operator is familiar with the relevant anatomical landmarks.

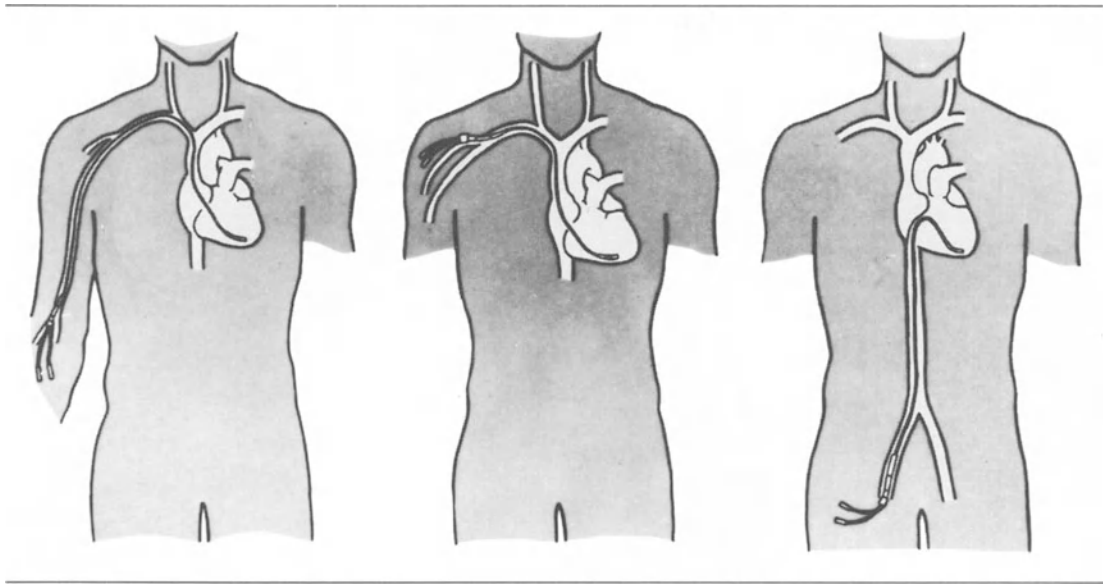


FIGURE 9–2. Approaches for temporary transvenous endocardial pacing. Shown from left to right are the brachial, subclavian, and femoral venous approaches.

technique will be considered in greatest detail. Unless otherwise specified, comments in this section will refer to ventricular rather than atrial pacing.

1.4.1. Entry Site. Adequate approach to the right heart can be achieved via percutaneous venous access through the internal or external jugular veins, subclavian veins, or femoral veins or via direct brachial venous cutdown (figure 9–2). Choice of the entry site depends on the severity of the clinical situation and the clinical expertise of the operator. Table 9–1 outlines important considerations when one is selecting an entry site.

1.4.2. Electrode System. A variety of temporary electrodes are now available for both atrial and venticular pacing. The characteristics of some commonly employed catheters are presented in table 9–2. These include small, soft, semifloating devices (with a primary 60-degree bend about 4 cm from the tip); large, more rigid nonfloating catheters; and flow-directed balloon-tipped catheters (figure 9–3). All types of systems are designed to facilitate positioning of the device in the right ventricular apex. Although semifloating and balloon-tipped devices may be positioned under ECG guidance, the more rigid nonfloating catheters are ideally positioned using fluoroscopic monitoring.

Bipolar pacing is most commonly employed. Since cathodal pacing thresholds are somewhat lower than anodal thresholds, the negative terminal (cathode) of the generator is connected to the distal pole of the electrode catheter and the positive terminal (anode) is connected to the proximal pole. Should difficulties develop with pacing or sensing functions, the polarity may be reversed or the system may be unipolarized. *Unipolar pacing* has the disadvantages of potential abnormalities of the sensing function in the demand mode and requires an indifferent skin electrode (figure 9–4). This results in a large pacing artifact on the ECG and on occasion causes skin twitching.

1.4.3. Positioning the Electrode. Two basic methods may be used, either singly or in combination. "*Blind*," or *nonfluoroscopic*, *guidance* of the electrode catheter can be accomplished by constant ECG monitoring using the distal pole as an exploring electrode. Unipolar ECG signals obtained when the electrode is in the various positions within the right heart are shown in figure 9–5. Once a right ventricular electrogram

TABLE 9–2. Examples of commonly employed temporary transvenous endocardial electrodes*

Electrodes	Available sizes (French)	Distance between electrodes (mm)	Length (cm)	Flotation balloon for positioning
Cordis				
1. Bipolar	4 to 6	10	100	–
2. Unipolar — remote anode	4	200	100	–
3. Temporary atrial J	5	10	100	–
4. Temporary atrial J with orienting "wings"	6	10	110	–
USCI				
1. Bipolar	4 to 7	10	100 to 125	–
2. Bipolar with balloon	4 to 5		110	+
3. Hexapolar for atrial and AV sequential pacing	7		125	
Hancock				
1. Bipolar	5	25	105	–
2. Bipolar with Stylet	5 to 6	10 to 25	110	–
Edwards Labs				
1. Swan-Ganz multipurpose catheter with atrial and ventricular electrodes	7		110	+
Medtronic				
1. Bipolar	5	28	125	–

*See also figures 9–3 and 9–8.

showing evidence of an "injury" potential (i.e., ST-segment elevation) is obtained, the electrode catheter should be connected to the generator and the pacing threshold should be evaluated (see below). *Fluoroscopic guidance* is the preferred method and may be combined with ECG monitoring. Blind passage from the *brachial vein* is acceptable until the catheter tip is estimated to be within the thorax, but manipulation from a sheath within a *femoral vein* should be continuously monitored fluoroscopically. Once the catheter enters the right atrium, a loop is formed, and the catheter is manipulated across the tricuspid valve and directed toward the right ventricular apex. In the anteroposterior projection, the catheter tip should be located about 2 to 3 cm leftward from the left side of the vertebral bodies (figure 9–6). The catheter should curve gently as it crosses the tricuspid valve; excessive angulation or "slack" may result in catheter dislodgment or perforation.

The operator should be aware of two other fluoroscopic positions that a temporary pacing catheter may assume: catheterization of the coronary sinus (figure 9–7) and misdirection of the catheter into the right ventricular outflow tract. Although coronary sinus pacing is acceptable as a temporary measure, right ventricular outflow tract pacing is unreliable and may even be hazardous.

To perform temporary *atrial* or *AV sequential pacing*, one must position an electrode catheter in the right atrium. Although a standard bipolar catheter can be used, it lacks stability and at times requires a high threshold for capture. To circumvent this problem, five types of temporary atrial electrode catheters have been developed (figure 9–8): (1) a hexapolar catheter, with a distal pair of electrodes for ventricular pacing and two pairs of proximal electrodes for atrial pacing: (2) a multipolar balloon-tipped catheter, with atrial and ventricular electrodes; (3) a ball-tip J-shaped bipolar catheter, with orienting "wings" that offer the potential for blind pervenous insertion; (4) a hexagonal spring electrode; and (5) an atrial flare electrode (figure 9–8*B*).

When employing any of the catheters described above, one should consider which type of pulse generator would be most appropriate.

1.4.4. Temporary Pulse Generators. The

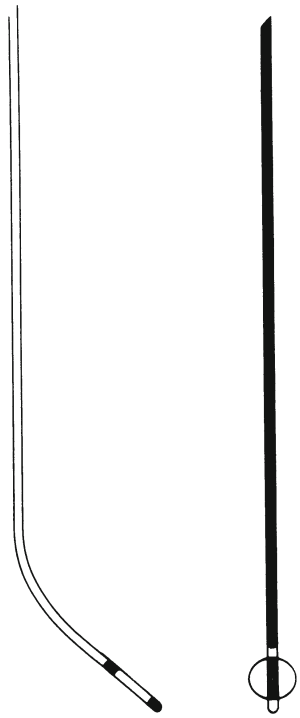


FIGURE 9–3. Examples of temporary bipolar pacing catheters with and without balloon tip for guidance.

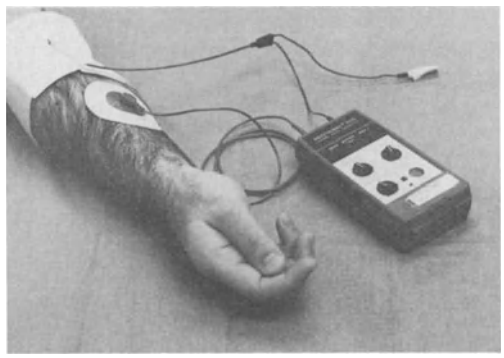


FIGURE 9–4. Unipolar temporary transvenous endocardial pacing. The lead on the bipolar pacing wire that shows the optimum combination of pacing and sensing is chosen as the active lead and is connected to the negative (−) terminal of the generator. The other lead is insulated and left unattached as shown. A new indifferent lead is created via direct attachment to the patient's skin through a paste-on ECG electrode (as shown) or superficial transcutaneous needle. The indifferent lead is then connected to the positive (+) terminal of the generator.

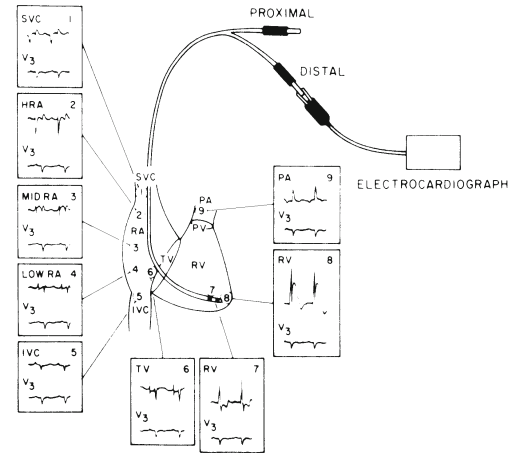


FIGURE 9–5. Electrocardiographic positioning of an endocardial pacing lead. This non fluoroscopic method requires careful analysis of endocardial ECG signals from the distal electrode in comparison with a surface ECG lead, as shown). As the electrode tip is advanced from the superior vena cava (SVC) to the right atrium (RA) (positions 1 to 4) and enters the right ventricle (RV) (positions 7 and 8), the atrial complex goes from a large negative and later biphasic or net positive potential to a smaller potential; simultaneously, the ventricular complex becomes larger (compare positions 4 and 7). When ST-segment elevation is encountered (position 8), the electrode tip is in contact with the endocardial surface and pacing can begin. The patterns at positions 5 and 9 indicate malpositioning of the electrode within the inferior vena cava (IVC) and pulmonary artery (PA), respectively.

temporary external pulse generators available today operate either in the *fixed-rate* or *demand modes* (table 9–3). In the fixed-rate mode, an electrical impulse is delivered at regular intervals, irrespective of the patient's intrinsic competitive rhythm. This may periodically result in a pacing impulse during the ventricular vulnerable period (R-on-T phenomenon). Because the level of energy required to capture the myocardium is relatively low compared with the much higher levels needed to produce fibrillation, ventricular fibrillation is not likely to be induced. Nevertheless, the presence of acute myocardial ischemia or infarction lowers the threshold for VF, so that the fixed-rate mode is dangerous in these clinical settings. It is acceptable, however, when pacing is instituted for complete ventricular standstill and no competing native rhythm is present.

TABLE 9–3. Commonly employed temporary pulse generators

	Medtronic	Cordis	Intermedics
Model	5375	Chronocor III (156B)	240–01
Available pacing modes	Fixed rate (VOO) Demand (VVI)	Fixed rate (VOO) Demand (VVI)	Fixed rate (VOO) Demand (VVI)
Rate range (ppm)	30 to 180	30 to 150	30 to 180
Output current (ma)	0.1 to 20.0	0.1 to 20.0	0.1 to 20.0
Maximum sensitivity (mv)	1.5 mv	1.0 mv	1.0 mv
Pulse duration (msec)	1.8 ± 0.2	1.5 ± 0.2	1.8 ± 0.2
Refractory period (msec)	250	240	250
Power source	Battery	Battery	Battery

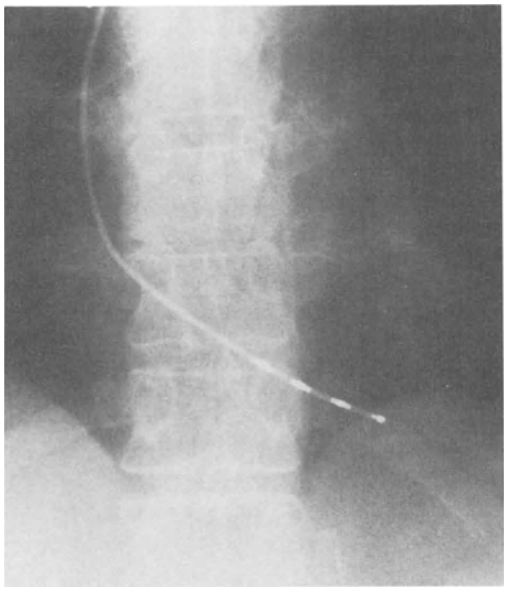


FIGURE 9–6. Anteroposterior view of quadripolar temporary pacing catheter introduced via right internal jugular vein and terminating in the right ventricular apex.

To prevent the possible precipitation of VF temporary pulse generators should be left in the demand mode (figure 9–9). In this mode the generator will be inhibited by a sensed electrical potential, provided such a potential is of sufficient magnitude in millivolts (mv). Hence, an important aspect of temporary pacemaker therapy is assessment of the ventricular electrogram obtained by a direct endocardial recording, which can be accomplished using a standard electrocardiograph machine (figure 9–10). It is important to obtain endocardial recordings from both distal and proximal poles of the electrode catheter individually as well as a direct endocardial bipolar recording. As noted in table 9–3, when the generator is set in the maximal demand mode the device is capable of sensing an electrical potential between 1.0 and 1.5 mv. However, one must ensure an adequate safety margin for sensing by positioning the electrode appropriately so that the bipolar electrogram displays a signal of at least 5 to 7 mv in amplitude (figure 9–10). Comparison should be made with the unipolar electrograms obtained from the distal and proximal poles of the electrode catheter in the event that unipolar pacing will be required subsequently.

The sensitivity adjustment control on the face of the generator is a variable resistor through which the endocardial signal must pass before it reaches the sensing circuit. To convert the generator to a fixed-rate mode, the knob should be rotated to the "asynchronous" position, which disables the sensing amplifiers. In the rare instance when "oversensing" occurs because of unusually large P or T waves, the sensitivity of the device should be adjusted based on careful ECG monitoring to maximize its sensing capability.

In order to capture the myocardium, a sufficient electrical charge must be delivered to the ventricular surface, which is in contact with the poles of the electrode catheter. The voltage output and pulse duration of the generator (table 9–3) are fixed. The operator may adjust the output current in milliamperes (ma) (figure 9–9), defining the threshold for capture. Not more than 0.7 to 1.0 ma should be required to capture the myocardium in a fresh implant if the electrode is appropriately positioned. The generator should have in reserve an adequate safety margin of at least three times the initial

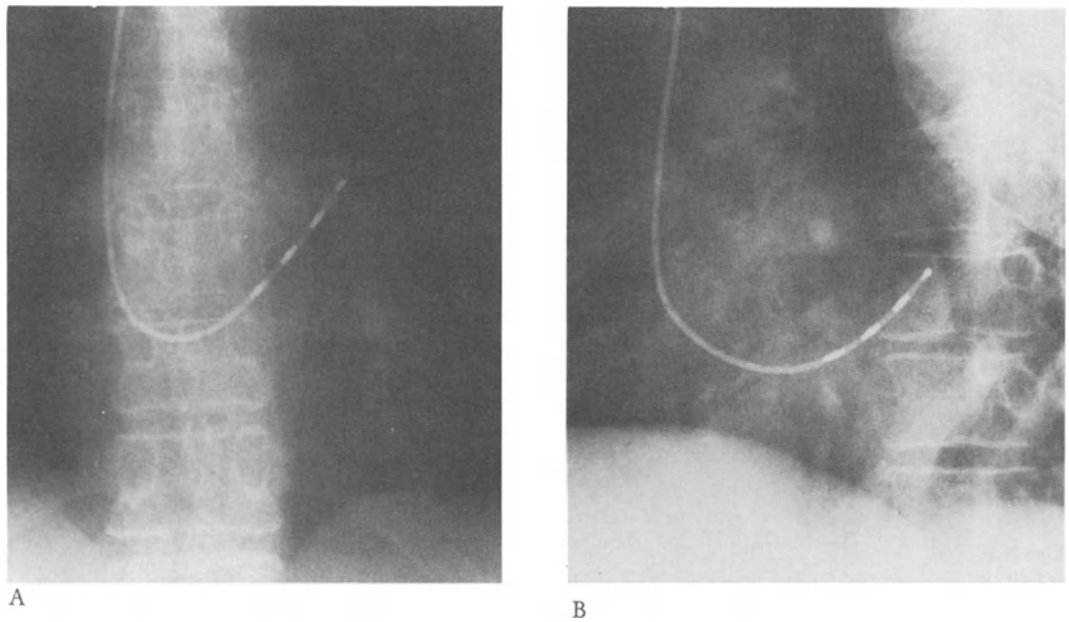


FIGURE 9–7. *A*, Anteroposterior view of quadripolar temporary pacing catheter introduced via right internal jugular vein and terminating in the coronary sinus. Note more superior orientation of catheter tip compared with that in Figure 9–6.

B, Lateral view of catheter position as described in *A*. Note posterior orientation of catheter, confirming its location in the coronary sinus. If the catheter shown in *A* were actually directed toward the right ventricular outflow tract instead of the coronary sinus, one could advance the tip beyond the cardiac silhouette (more distally in the pulmonary vasculature) and its orientation would not be as posterior as shown here.

threshold output current, since it is expected that the threshold will rise over the first week while the catheter is in position.

The *escape rate* of the generator (figure 9–9) should be adjusted according to the clinical situation. For example, a setting of 70 to 80 pulses per minute (bpm) might be appropriate for a patient whose intrinsic rhythm is only 40 to 50 bpm. However, for a patient whose native rhythm is already between 70 and 80 bpm for whom the temporary pacemaker is being placed prophylactically in the event of high-grade AV block, an escape rate of 50 pulses per minute might be appropriate. The operator should be alert for the development of angina pectoris or hypotension as the rate of ventricular pacing is increased.

For atrial pacing in the demand mode, the standard pulse generator described above would be adequate if a large enough atrial endocardial signal can be generated. More rapid atrial pacing to interrupt tachyarrhythmias requires a specific generator capable of emitting trains of high-frequency stimuli. (This technique is discussed in detail in chapter 7.) The device shown in figure 9–11 is an example of a hand-held rapid atrial pacer that operates solely in the fixed-rate mode.

Temporary AV sequential pacing can be accomplished with an external temporary AV sequential generator (figure 9–12). Once the electrode catheter poles have been carefully attached to the generator in the specified positions for atrial and ventricular electrodes, the atrial and ventricular output current threshold in milliamperes should be established independently for both atrial and ventricular electrodes. The output is then set at three times threshold to insure a safety margin for capture at both sites. The operator must also specify the AV interval in milliseconds (ms), as shown on the left-hand side of the face of the generator (figure 9–12). Note that the temporary AV sequential generators now available are inhibited only by

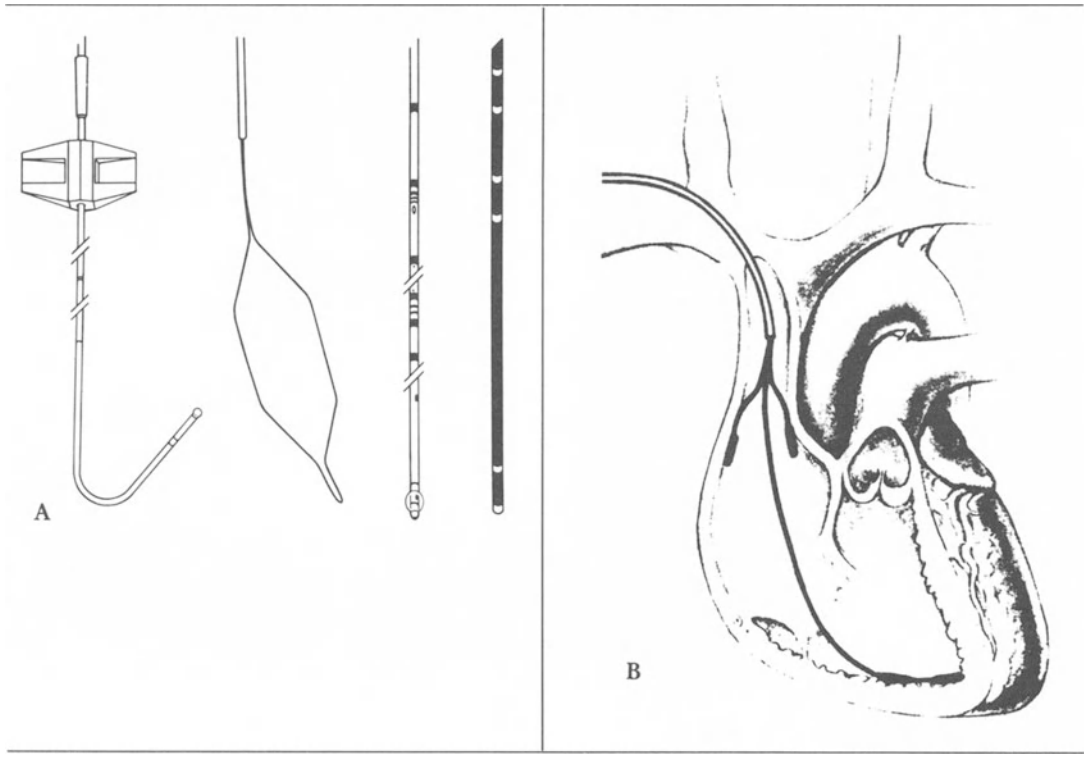


FIGURE 9–8. Examples of temporary atrial pacing catheters. *A*, From left to right, atrial "J" ball tip bipolar electrode with orienting skin "wings," hexagonal spring electrode, Swan-Ganz catheter with three atrial and two ventricular electrodes (farthest from balloon), and hexapolar AV sequential pacing catheter. *B*, This catheter is a recently developed device that allows greater independence in positioning atrial and ventricular electrodes and thus enhances the long-term stability of pacing.

sensed ventricular signals, so that the considerations about sensitivity setting discussed above must be kept in mind.

One important additional point is the potential for "*crosstalk*" between the atrial output and ventricular sensing circuits. If atrial output is of sufficient magnitude and vectorial orientation, it may be sensed by the ventricular electrode. To eliminate crosstalk, it may be necessary to reduce the current output on the atrial electrode or even reposition the atrial wire.

1.4.5. Maintenance of the Temporary Pacing System. A suggested protocol for maintenance of temporary pacing systems is outlined in table 9–4. To insure a secure temporary pacing system, it is important that the catheter be adequately sutured to the skin line after it has been formed into a loop at the entry site. Appropriately placed skin sutures (e.g., 2–0 silk), are required to prevent inadvertent withdrawal of the catheter. The skin surface should be carefully cleansed and, after initial insertion of the catheter, dressed with a dry, sterile bandage. Bandages should be changed every 24 to 48 hours, and some physicians favor application of antibiotic ointment to the entry site. Since the temporary pacing system may be required for extended periods of time, it is imperative that meticulous sterile technique be employed to prevent infections.

In addition, serial determination of the threshold for capture should be made in order to maintain an adequate safety margin. Serial recording of the endocardial signals is also important to insure that the device will continue to operate normally in the demand mode. Continuous oscilloscopic monitoring will detect episodes of failure to pace or failure to sense appropriately. It is good clinical practice to

TABLE 9–4. Protocol for maintenance of temporary pacing systems

A. Patient/Electode Catheter
   1. Examine dressing and entry site daily
   2. Evaluate patient for signs of skeletal muscle stimulation, pericarditis, tamponade daily
   3. Confirm that pacemaker terminals are securely tightened to make contact with wire
   4. Confirm that pulse generator and exposed electrodes are insulated adequately in rubber glove
   5. Monitor cardiac rhythm carefully using a lead that adequately distinguishes pacing spikes and paced QRS complexes

B. Pulse Generator
   1. Determine threshold and assess safety margin daily (a threshold of 5 to 7 indicates a need to reposition the catheter, insert a new catheter, and/or correct abnormal metabolic/electrolyte circumstances)
   2. Measure unipolar (proximal and distal) and bipolar endocardial signals to avert any potential sensing malfunction
   3. Confirm that generator is operating in desired mode
   4. Replace weak batteries (new units have a "battery test" light that signals the need for replacement)

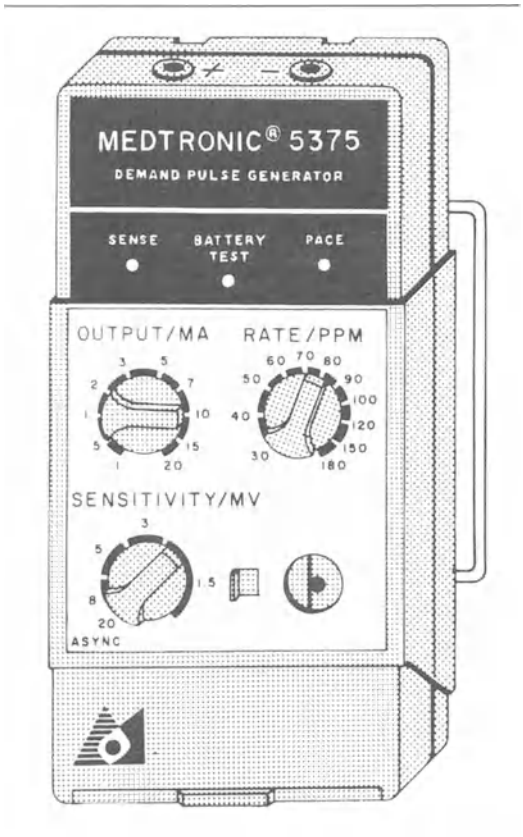


FIGURE 9–9. Temporary external pacing generator. Example of external demand pulse generator commonly used for temporary ventricular pacing. It is also capable of pacing the atrium, although this application is less common.

choose a lead that shows a small but detectable pacing artifact and left bundle branch block (LBBB) QRS morphology (which is to be expected with right ventricular apical pacing).

The full 12-lead ECG should be examined periodically (usually at least once every 24 to 36 hours) to evaluate the electrical axis and QRS morphology of paced beats and to enable the clinician to diagnose migration of the pacemaker electrode tip. Unipolar stimulation results in a large stimulus artifact (figure 9–13), which alters the paced QRS morphology. Unipolar pacing spikes are usually at least 10 mm in amplitude. Bipolar pacing stimuli may be diminutive and difficult to detect in a single ECG lead; however, usually at least one lead will demonstrate a bipolar pacemaker spike.

Right ventricular apical pacing produces QRS complexes with LBBB morphology and is usually associated with marked left-axis duration (figure 9–14). If the electrical axis becomes normal but the LBBB morphology persists, migration of the electrode tip from the right ventricular apex to the right ventricular outflow region should be suspected, with early activation of the septal wall of the right ventricular outflow tract (figure 9–15). Left ventricular pacing results in a right bundle branch block QRS morphology with right-axis deviation (figure 9–16).

Proper insulation of temporary pacemaker generators is essential to prevent electrical accidents. Since stray electrical currents in the patient's room may gain access to the heart via the temporary pacing electrode catheter, the tem-

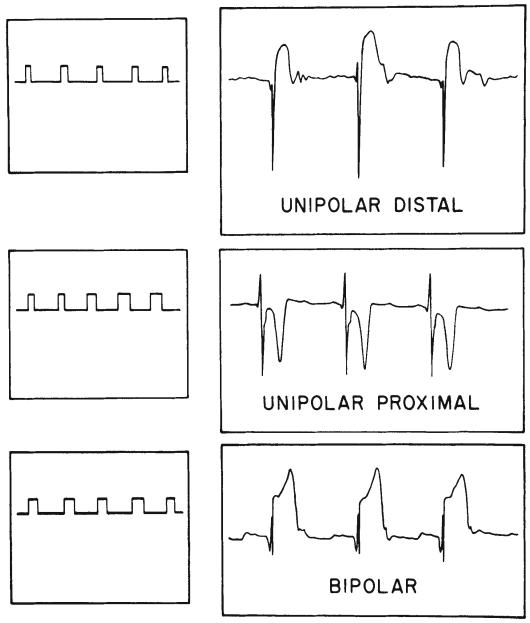


FIGURE 9–10. Endocardial ECG signals recorded from temporary pacing wire. The *unipolar distal and proximal recordings* were obtained by connecting the appropriate lead terminal to the unipolar V (chest) lead of a standard ECG machine using an alligator clip. Note the net negative QRS forces created by depolarization of the endocardium toward the epicardium (i.e., away from the recording electrode). The *bipolar recording* was obtained by connecting *both* lead terminals to a bipolar lead system on a standard ECG machine via two alligator clips (e.g., distal lead to right arm and proximal lead to left arm, recorded on ECG lead I). A series of 1-millivolt calibration pulses is shown to the left. In this particular case the bipolar signal was large enough for sensing, although the unipolar distal provided a larger electrogram. Should unipolar pacing become necessary the distal lead would be chosen.

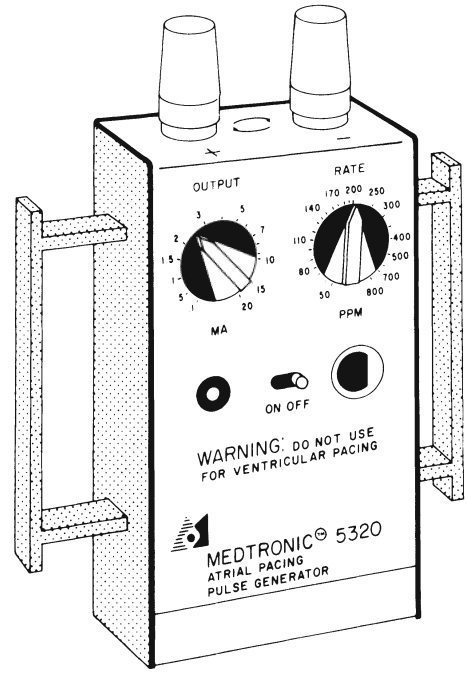


FIGURE 9–11. Temporary external atrial pulse generator. This device operates only in the asynchronous mode and is capable of extremely rapid pacing (up to 800 bpm). It is commonly used for atrial pacing, particularly when overdrive burst pacing is desired to terminate a supraventricular tachyarrhythmia (e.g., atrial flutter).

porary pacemaker generator should be covered with a rubber glove or plastic bag, as shown in figure 9–17. Sources of such stray currents may be an improperly grounded ECG machine, an electronic bed, or the oscilloscope used to monitor the patient's heart rhythm.

1.4.6. Complications of Temporary Pacing. Although a variety of potential complications may occur during temporary cardiac pacing, most are relatively minor and can be kept to a minimum with proper technique.

Local or systemic infection or phlebitis may occur as a result of improper sterile technique. Rare instances of endocarditis developing at the site of electrode implantation in the right ventricular myocardium have been reported. The electrode catheter must be removed and antibiotic therapy instituted to eradicate the infection.

Specific complications related to the various venous entry sites include hemo/pneumothorax or laceration of the subclavian artery during attempted subclavian vein puncture and a hematoma or arteriovenous fistula arising in the femoral region during attempted femoral vein catheterization (see table 9–1).

More serious cardiac complications include perforation of the right ventricular myocardium, with the development of hemopericardium and cardiac tamponade. In addition, both atrial and ventricular arrhythmias may develop after insertion of a temporary pacing catheter. Particular caution must be exercised during the initial implantation procedure, especially if

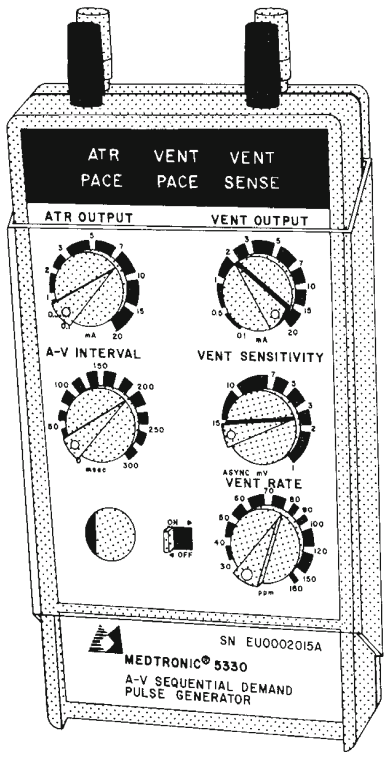


FIGURE 9–12. Temporary external AV sequential pacemaker. The right-hand portion of this pulse generator is similar to the device shown in Figure 9–9. Important differences include the selector knobs for atrial output and AV interval (no atrial sensing channel is available; the generator operates in the DVI mode.) Note the two sets of connector terminals for the pairs of atrial and ventricular leads. Proper connection and adherence to polarity is needed for proper performance of the generator. By convention, the distal lead is attached to the negative terminal.

myocardial ischemia is present.

Malpositioning of the catheter during blind insertion may inadvertently stimulate the skeletal musculature of the upper extremity if the tip of the catheter has not completely entered the thorax. More commonly, inadvertent diaphragmatic pacing may occur if the electrode tip is close to the diaphragm or perforates the right ventricular chamber. To eliminate diaphragmatic pacing, it may be necessary to reposition the electrode or reduce the output current.

The period of highest risk for serious cardiac complications appears to include the initial insertion procedure and the subsequent 24 hours, and appropriate ECG monitoring and observation for potential complications should therefore be carried out during this period.

1.4.7. Malfunction of Temporary Pacemakers. If one excludes pacemaker-induced cardiac arrhythmias and morphological changes on the ECG, pacemaker malfunction can be considered to take two forms: failure to sense and failure to pace (table 9–5). In this discussion, the malfunctioning device will be assumed to be a temporary ventricular pacemaker. Similar principles may be employed in analyzing temporary atrial pacemakers and permanent pacemakers.

Failure to sense may result from delivery of an inadequate ventricular depolarization to a normally functioning pacemaker. An inadequate signal may result from insufficient amplitude, poor rise time (slew rate), or fractured signals. Thus, an adequate signal must be of sufficient amplitude and slew rate and nonfragmented (figure 9–18). Clinical conditions associated with generation of inadequate ventricular depolarization include acute myocardial infarction, severe drug toxicity, hyperkalemia, preterminal states, and displacement of the electrode. A less common cause of failure to sense is delivery of an adequate depolarization to a malfunctioning pulse generator (e.g., battery depletion).

Clinicians should also be aware of the possibility of *apparent* failure to sense, which results from late occurring ventricular depolarizations that fail to achieve adequate voltage and slew rate at the site of the sensing electrode (e.g., right bundle branch block in a right ventricular apical pacemaker). Under these circumstances, the pacemaker generator will not be reset and a spike will be delivered prematurely. Electrocardiographic examples of sensing malfunctions are shown in figure 9–19.

To correct problems with failure to sense involving temporary pacemakers, one should first confirm that the generator has not been inappropriately set in a fixed-rate mode. The 12-lead ECG should be examined to search for clues indicating catheter migration (see 1.4.5). In addition, analysis of unipolar and bipolar endocardial electrograms can be helpful in determining the best endocardial signal for sensing (figure 9–10). Possible therapeutic maneuvers one might consider include repositioning of the catheter or conversion to unipolar pacing (if the

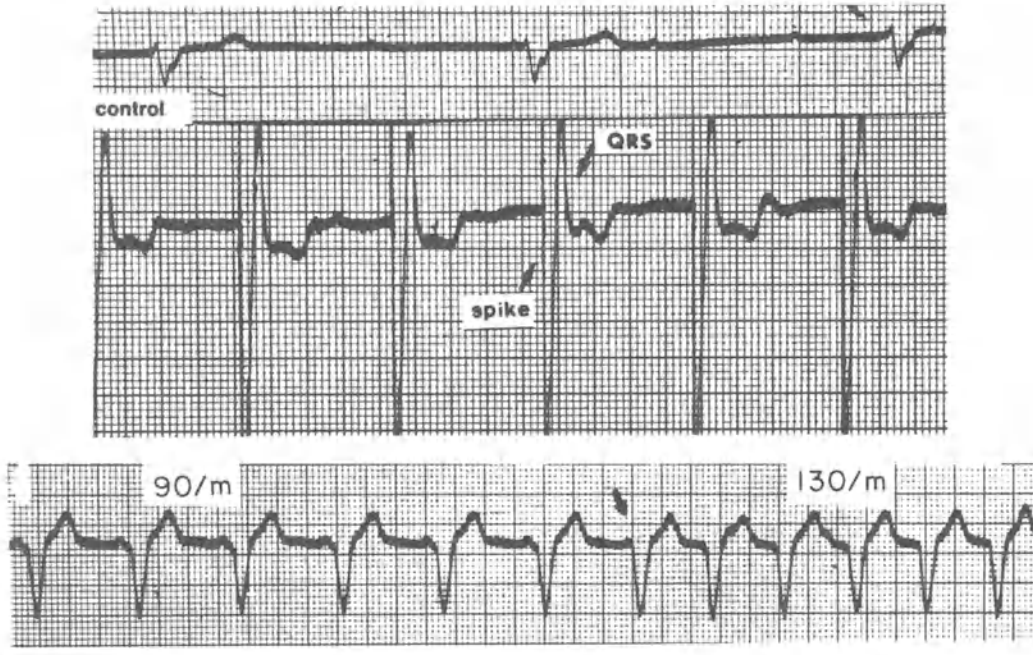


FIGURE 9–13. *Top*, In *unipolar* pacing, the high-amplitude, biphasic stimulus artifact (spike) alters the pacemaker QRS morphology. *Bottom*, In *bipolar* pacing, the increase in heart rate from 90 to 130 bpm is intentionally produced by increasing the artifical stimulation. Note the lack of pacemaker spikes in lead II (arrow), while the QRS morphology is clear. (Adapted from Pupillo JA: *The ECG of artificial pacemakers*. Parma, Ohio, Vismar Publishers, 1979, p 2.)

TABLE 9–5. Pacemaker malfunction.

I. *Sensing*
   A. Failure to sense
      1. Inadequate ventricular depolarization delivered to a normally functioning pacemaker. (An inadequate signal may result from poor amplitude, poor slew rate, or fractured signals.)
      2. Adequate signal delivered to a malfunctioning pulse generator.
   B. Apparent failure to sense

II. *Pacing*
   A. Discharges absent
      1. Loss of continuity (e.g., wire fracture)
      2. Sudden generator failure
      3. Abnormal sensing
         a. Extrinsic signals
         b. Intrinsic signals (e.g., Pw, Tw)
         c. Musculoskeletal potentials
         d. Partial lead fracture
         e. Second pacemaker
            (Note: This may be used therapeutically in the chest wall stimulation test)
   B. Discharges present, no capture
      1. Elevated threshold
      2. Displaced electrode
      3. Refractory myocardium
   C. Pacemaker exit block

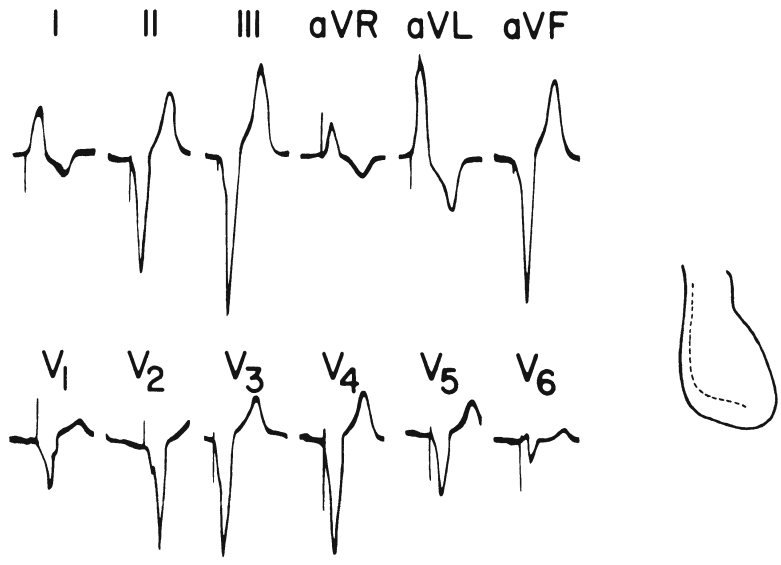


FIGURE 9–14. Right ventricular apical pacing. The catheter tip is located at the apex, and the electrical axis is deviated to the left. (Adapted from Pupillo JA: *The ECG of artificial pacemakers.* Parma, Ohio, Vismar Publishers, 1979, p 8.)

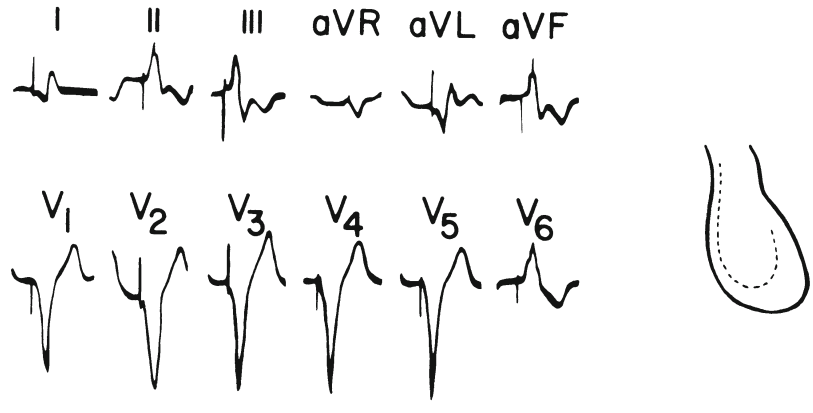


FIGURE 9–15. Right ventricular outflow tract pacing. Ventricular pacing starts in the septal wall of the pulmonary outflow tract. Notice the normalization of the electrical axis in the presence of QRS complexes of the left bundle branch block type. (Adapted from Pupillo JA: *The ECG of artificial pacemakers.* Parma, Ohio, Vismar Publishers, 1979, p 8.)

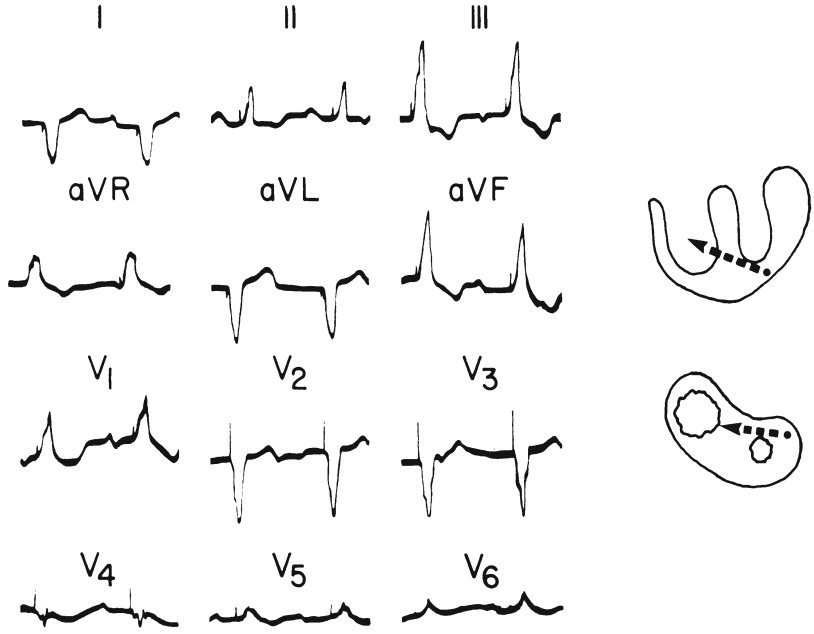


FIGURE 9–16. Left ventricular pacing. Control tracting shows second-degree AV block. Postimplant ECG shows an electrical axis deviated to the right and QRS complexes with a right bundle branch block configuration (V_1). The QRS loop is oriented to the right, anteriorly, and inferiorly. (Adapted from Pupillo JA: *The ECG of artificial pacemakers.* Parma, Ohio, Vismar Publishers, 1979, p 10.)

bipolar endocardial signal is of insufficient magnitude). Until the sensing failure has been corrected, consideration should be given to decreasing competition between the patient's native rhythm and the paced beats. This can usually be accomplished by increasing the pacing rate above the patient's native rate, which may suppress ventricular ectopy. It is important to evaluate sensing malfunction carefully, since it often represents "a" premonitory signal of impending failure to pace.

Failure to pace can be a serious and urgent clinical matter, particularly for the patient who is pacemaker-dependent. Should an emergency situation arise, the initial step should be to increase the output current of the pacemaker in an attempt to recapture the myocardium. Pharmacological support with isoproterenol and atropine should be available and preparations to provide alternative pacing modes should be initiated (see 1.1 to 1.3). A systematic approach should rapidly divulge the cause of the problem.

Failure to pace may be divided simply into those situations in which pacemaker discharges are absent and in which discharges are present. Absence of pacemaker discharges may be due to loss of continuity (e.g., disconnection of one or both terminals of the temporary generator or wire fracture), sudden generator failure, or abnormal sensing. Abnormal or "false" sensing may be the result of extrinsic and/or intrinsic signals. False sensing due to *extrinsic* signals usually applies to permanent pacemaker generators and is less often seen today in view of improved generator shielding. *Intrinsic* signals include unusually large P or T waves and musculoskeletal potentials.

Failure of generated pacemaker discharges to capture the myocardium is indicative of an abnormality at the catheter-myocardial interface. Physiological alterations such as acute infarction, antiarrhythmic drug administration, hyperkalemia, and preterminal states may elevate the threshold for capture of the myocardium (figure 9–20). Displacement of the electrode into the right ventricular outflow tract or pericardial space may also cause loss of capture. Finally, the myocardium may be refractory at the time of delivery of a pacemaker impulse. Thus, "a" ventricular premature beat that is not

FIGURE 9–17. Insulation of temporary pacing generator. To avoid the hazard stray electrical currents gaining access to the exposed lead terminals, the entire assembly should be surrounded by a nonconductive material (e.g., enclosed in a plastic bag or glove).

oriented appropriately to be sensed by the generator may be followed by a pacemaker spike that falls within its repolarization phase. Since the myocardium is refractory, the pacemaker impulse is ineffective.

Pacemaker exit block may occur as a result of ischemia, drug therapy, electrolyte changes, or the "dying heart syndrome." It refers to failure of a normal pacemaker impulse that falls outside the refractory period of the surrounding tissue to elicit a propagated response. On rare occasions, it may show a characteristic ECG pattern, such as Wenckebach periodicity.

2. *Technique of Permanent Pacemaker Therapy*

2.1. ENTRY SITE

Transvenous implantation of permanent electrode systems is usually accomplished with access through the cephalic (figure 9–21), external or internal jugular vein or subclavian vein. A pacemaker "pocket" is formed, and both the generator and the permanent lead are secured in their final positions (figure 9–22). Some instances of implantation of permanent leads via the femoral vein have been reported.

When transvenous lead systems prove unsuccessful (usually owing to unstable catheter positioning) or the decision is made to implant a permanent lead during open-heart surgery, permanent *epicardial* leads can be employed. Examination of the entry site in the acute setting should include search for hematoma, while subacute and chronic entry sites should be evaluated for any evidence of infection or erosion of the generator or pacemaker lead through to the skin surface.

2.2. ELECTRODE SYSTEM

A variety of permanent atrial and ventricular transvenous and epicardial leads are available. A variety of electrode tips can be utilized to anchor transvenous leads to the right ventricular endocardial surface, including a flanged, a multiple-tined, or screw-in mode of attachment. Permanent epicardial electrodes are screwed into the myocardial surface and sutured in position.

2.3. PERMANENT PULSE GENERATORS

Because of the increasing complexity of cardiac pacemakers, a short-hand *code* has been devised for describing the essential features of each device (table 9–6). At present, a five-position code has been adopted and is in common use. Important features are designated by the first three letters of the code, as described in figure 9–23; the fourth and fifth letters of the code correspond to sophisticated pacing features, including program ability and antitachycardia potential.

Symptomatic patients with an absent or inappropriately slow sinus mechanism are *candidates* for permanent cardiac pacing, as are those with an inappropriately slow ventricular rate during atrial fibrillation or high-grade AV block due to myocardial infarction or progressive conduction system disease (see Chapter 10). Generally such patients are best served by a standard ventricular demand pacemaker (VVI), with the rate adjusted to alleviate symptoms.

On occasion, when no competing atrial rhythm is present, *physiologic pacing* may improve cardiac performance. Atrial and ventricu-

TABLE 9–6. Five position pacemaker code (ICHD)

Position	I	II	III	IV	V
Category	Chamber(s) paced	Chambers(s) sensed	Mode of response(s)	Programmable functions	Special tachyarrhythmia functions
Letters used	V- Ventricle	V- Ventricle	T- Triggered	P- Programmable (rate and/or output)	B- Bursts
	A- Atrium	A- Atrium	I- Inhibited	M- Multiprogrammable	N- Normal rate competition
	D- Double	D- Double	D- Double* O- None	C- Multiprogrammable with telemetry	S- Scanning
		O- None	R- Reverse+	O- None	E- External
Manufacturer's designation only	S- Single chamber‡	S- Single chamber‡		, [Comma optional here]	

*Atrial triggered and ventricular inhibited.
+*Activated* by tachycardia and (usually) bradycardia.
‡Can be used for atrial *or* ventricular pacing; a manufacturer's designation.

lar contractions can be synchronized by means of devices capable of sensing and/or pacing the atrium, followed by sequential ventricular pacing (e.g., VAT, DVI, DDD). If AV conduction is intact, atrial demand pacing (AAI) may be used. The indications for the available pacing modes are succinctly summarized in table 9–7. For optimal clinical performance, one can "program" many of the currently available pacemakers as the patient's needs change.

When interpreting the ECG, the observer should be aware of the mode of operation and current program settings in the particular patient being studied. Examples of commonly employed pacing modes can be found in figure 9–24.

In some patients, preserving the atrial contribution to ventricular filling through physiologic pacing affords short-term hemodynamic improvement. Although long-term hemodynamic improvement may be possible in certain patients [2], there are as yet no consistent guidelines for identifying those patients who would achieve long-term hemodynamic improvement with physiologic pacing. Evidence of the "pacemaker syndrome" — i.e., a fall in systolic pressure of more than 25 mm Hg during ventricular pacing, often accompanied by cannon waves in the jugular venous pulse — should alert the clinician to the possible need for physiologic pacing.

Because of the large number of pacemaker manufacturers and their increasing inventories, the clinician may find it difficult to keep abreast of the many devices that become available and should refer to recently published reference texts [3].

Programming of permanent generators should be performed only by physicians experienced with the technique. Each pacemaker manufacturer provides a programmer uniquely designed for their devices. These programmers may be hand-held with varying programming capabilities or desk-top models for more sophisticated programming (figure 9–25). In the event of inadvertent misprogramming or deterioration of the patient's clinical status during programming setups, a "nominal" key on the programmer can be depressed to revert the generator to its original factory specification.

As seen in figure 9–26, the *threshold of capture* of the myocardium may be related to

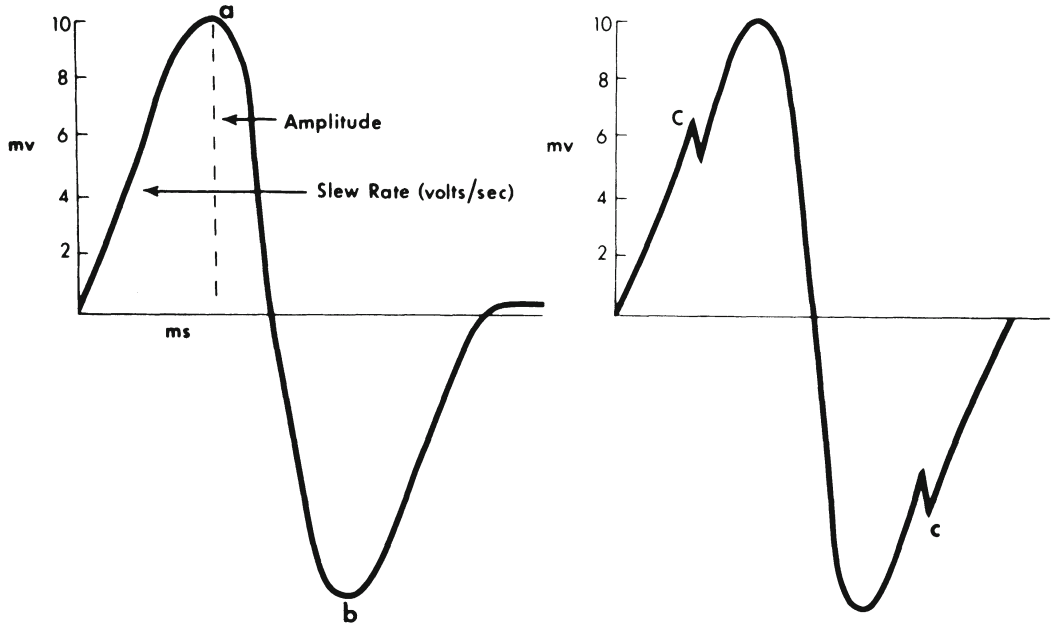


FIGURE 9–18. Endocardial waveform analysis. This waveform consists of deflection above and below the baseline on an electrogram. The pacemaker sensing circuit samples only a small portion of the waveform to determine the slew rate (rate of change in amplitude with respect to time) and the amplitude of the defection, defined as the maximal uninterrupted excursion of the wave deflection at a constant slew rate (points a and b). A change in the slew rate, such as a notch on the wave deflection (point c), will be interpreted as the point of maximal excursion (amplitude or peak). Modern sensing circuits can determine not only the peak deflections from the baseline (points a, b, and c) but also the peak-to-peak deflections across the baseline (point a to point b). The slew rate obtained from either of these two types of deflections can be extrapolated into a frequency measurement, assuming that the entire waveform has that slew rate. (From Byrd C: Permanent pacemaker implantation techniques. In: *Cardiac pacing*, 2nd ed, Samet P, El-Sherif N (eds), New York, Grune and Stratton, 1980, p 250, by permission of the publisher.)

the pulse width of the pacemaker stimulus (in ms) and the output of the generator (in either volts or ma). Certain manufacturers produce constant-voltage generators (e.g., Medtronic) while others produce constant-current generators (e.g., Cordis). In either case, manipulation of the pulse width or output enables the clinician to convert a system that is only marginally capable of capturing the myocardium to one capable of pacing with a sufficient safety margin. Note that increasing the pulse width from the usual setting of 0.5 ms will deplete the battery somewhat more with each discharge, ultimately reducing the total battery life. In addition to programming the pulse width, rate, and generator output, one can adjust the sensitivity and the refractory period for pacing or sensing and introduce rate hysteresis by means of certain devices (figure 9–27).

2.4. MAINTENANCE OF THE PERMANENT PACING SYSTEM

The key to successful maintenance of a permanent pacing system is a well-organized pacemaker follow-up clinic. Serial numbers and specific characteristics of both the generator and the implanted leads should be carefully recorded and kept with the patient's records. In the event of recall of a defective product, these records are essential to identifying patients who require replacement of part of their pacing system.

Serial determinations of the pacing spike interval and pulse width should be made at increasingly frequent intervals the longer the generator has been in place. This can be accomplished noninvasively using the programmer devices described above (figure 9–25) or simple hand-held accurate interval counters (figure

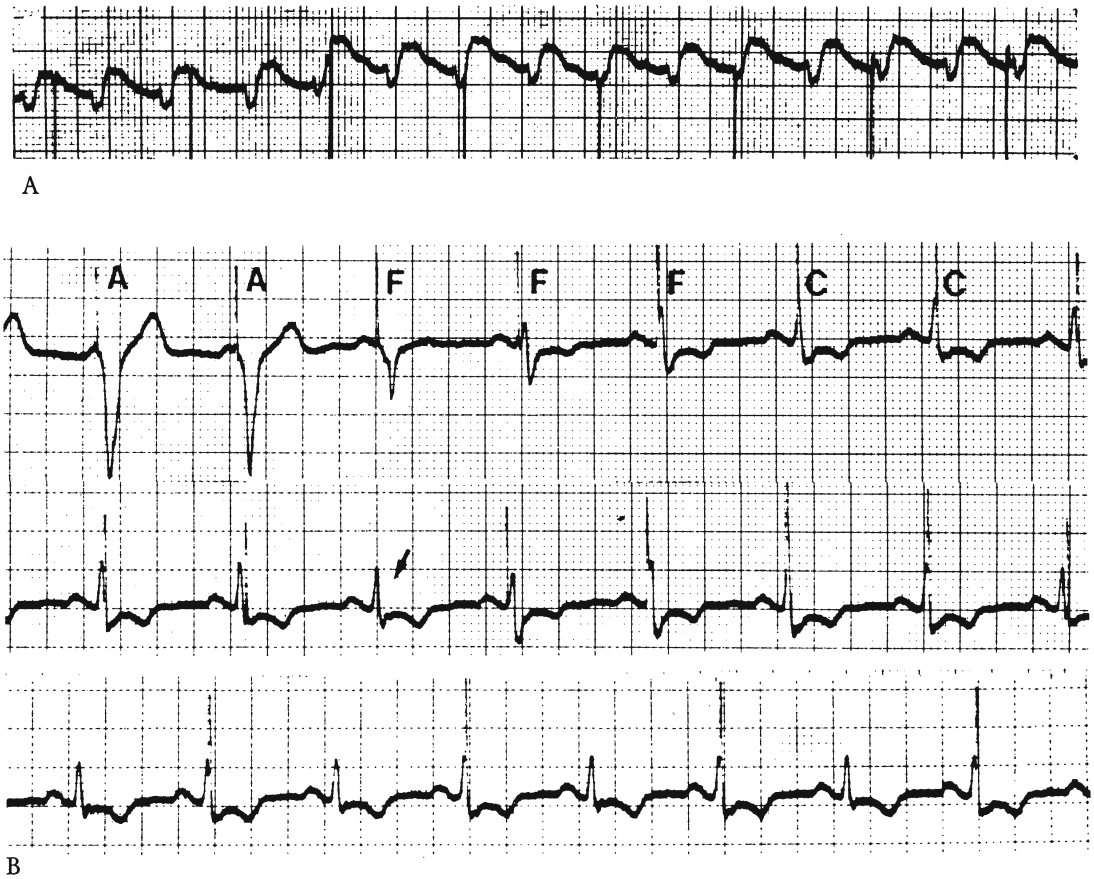


FIGURE 9–19. *A*, The QRS complexes during this paroxysm of ventricular tachycardia have a low-amplitude signal and are not sensed, resulting in inappropriate ventricular stimulation by the generator.

B, The QRS-inhibited pacemaker malfunctions as the catheter tip pentrates the pericardial sac and the pacemaker senses the cardiac potential only late during ventricular depolarization (arrow, middle) tracing. The pacing function is intact. *Top tracings*, automatic rhythm (A) is followed by ventricular fusion beats (F) and then by normal AV conduction (C). *Bottom tracing*, Recording made several days later. (From Pupillo JA: *The ECG of artificial pacemakers*. Parma, Ohio, Vismar Publ Co, 1979.)

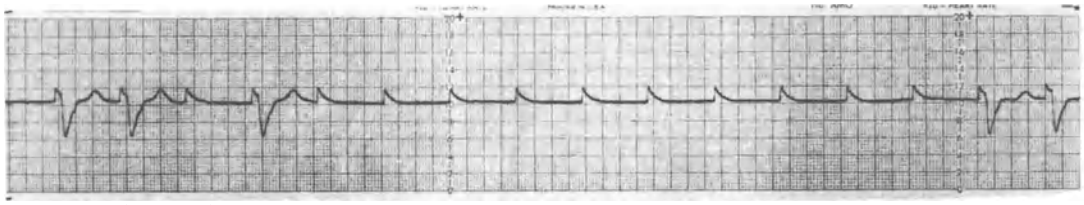


FIGURE 9–20. Two ventricular paced beats are seen at left, followed by a single spike that does not capture and later a series of 10 pacemaker spikes at a rate of 70 bpm, which fail to capture the myocardium. Such a finding may be associated with hyperkalemia and/or antiarrhythmic drug toxicity. (From Antman EM, Cohn PF: Ambulatory electrocardiographic monitoring. In: *Diagnostic methods in clinical cardiology*. Cohn PR, Wynne J (eds), Boston, Little, Brown and Co, 1982, p 47.)

TABLE 9–7. Indications for available pacing modes

AV conduction	Atrial rhythm		
	Normal	Bradycardia	Bradycardia-tachycardia
1. Normal	0	AAI	AAI
2. AV block without prolonged retrograde conduction time	VDD,DDD	DDD,DVI	DVI,VVI
3. AV block with prolonged retrograde conduction time	DVI	DVI	DVI

From Zipes DP, Duffin EG: Cardiac pacemakers. In: *Heart disease*, 2nd ed. Braunwald E (ed) Philadelphia, WB Saunders Co, 1984, p 755.

9–28). At each clinic visit, the generator should be evaluated for the appearance of any "end-of-life" indicator suggesting battery depletion.

In addition, some physicians favor a detailed display of the pacemaker discharge waveform, which often provides clues to the cause of failure of the electrode to sense or pace and and offers the alert clinician an opportunity to detect progressive battery depletion (figure 9–29).

The routine clinic evaluation should include analysis of the 12-lead ECG, application of a magnet over the generator to observe the "magnet rate," and assessment of the generator's demand function when appropriate. This last point is discussed below (see 11.2.6).

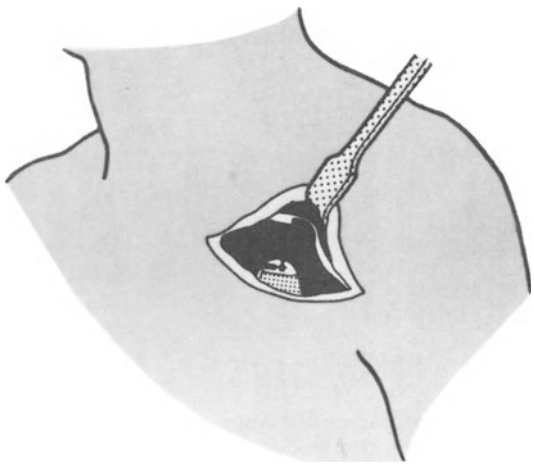


FIGURE 9–21. Placement of permanent generator in pocket with insertion of permanent endocardial lead in cephalic vein.

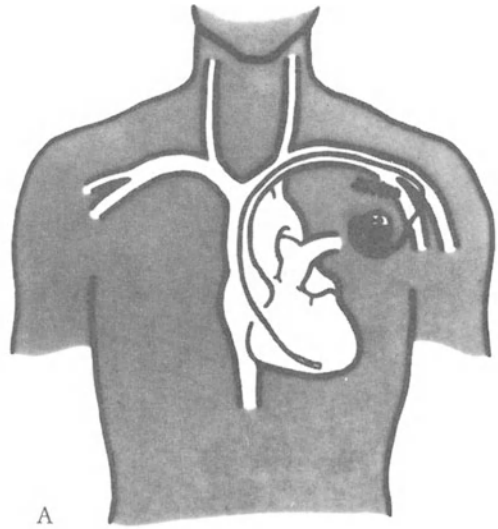
2.5 COMPLICATIONS OF PERMANENT PACING

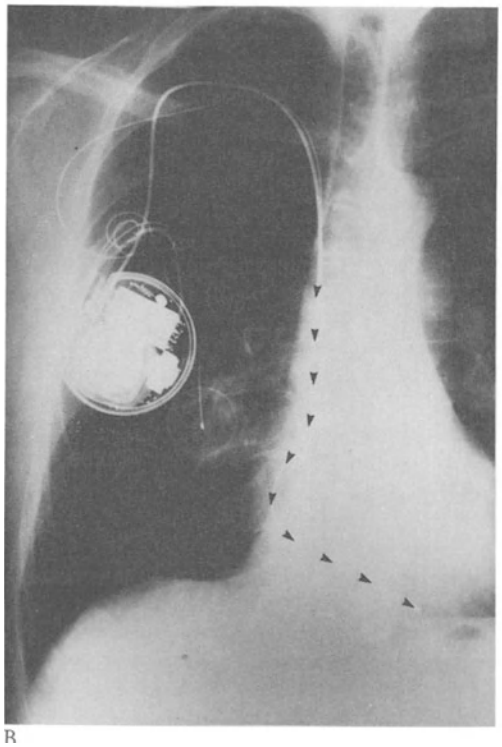
Complications are similar to those seen with temporary pacing and include infections and thrombotic/thromboembolic phenomena (figure 9–30). In addition, perforation with pericarditis, pericardial effusion, or cardiac tamponade may occur. Appearance of a right bundle branch block, although strongly suggestive of left ventricular perforation with stimulation of this chamber, may be seen normally during coronary sinus pacing with early activation of the inferoposterior aspect of the left ventricle.

Intercostal muscle or diaphragmatic contraction suggests cardiac perforation as does the appearance of a new heart murmur or friction rub. A pacemaker "click" occurring about 6 ms after the pacing spike appears to be related to intercostal or diaphragmatic stimulation by the pacing electrode and usually is a benign auscultatory finding. However, the *new* appearance of a pacemaker click should prompt a search for possible myocardial perforation. Finally, a variety of cardiac arrhythmias may be induced by normally functioning and malfunctioning permanent generators. The term "runaway pacemaker" refers to acceleration of the generator pacing rate so as to induce ventricular tachycardia. When the pacing rate is extremely rapid, failure to capture can occur and may result in bradycardia or VF. Appearance of a runaway pacemaker is a medical emergency that requires prompt removal of the generator.

2.6 MALFUNCTION OF PERMANENT PACEMAKERS

A detailed discussion of malfunction of permanent pacemakers is beyond the scope of this





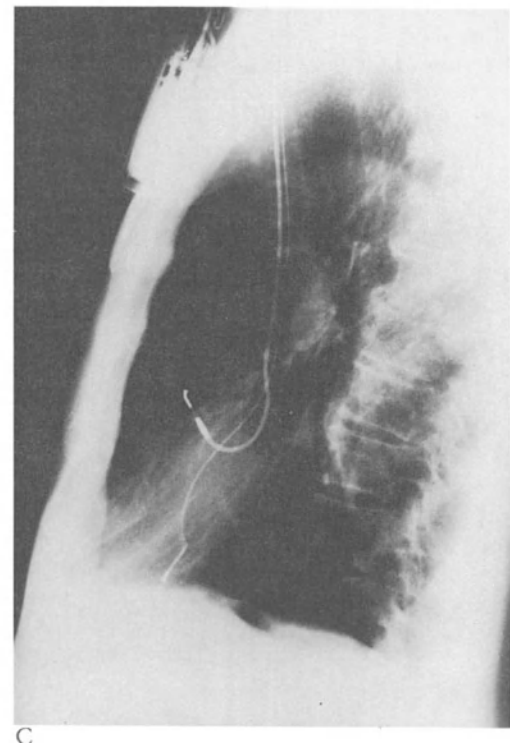


FIGURE 9–22. *A*, Final positioning of generator in pocket and tip of lead on RV Apex.

B, PA chest x-ray showing a dual-chamber (AV sequential) generator and proper positioning of permanent atrial and ventricular leads. In addition, a round permanent indifferent lead is seen inferomedial to the generator. The indifferent lead was required because the patient previously had a unipolar ventricular lead implanted, but the new generator (shown here) required a bipolar ventricular lead system.

C, Lateral chest x-ray of patient.

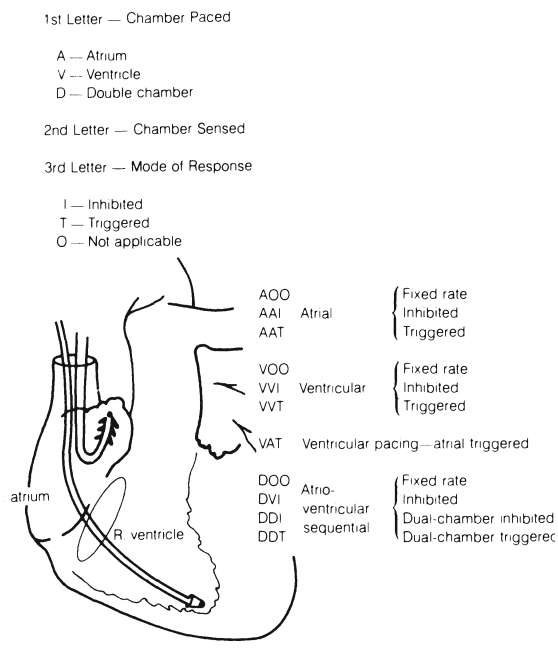


FIGURE 9–23. International code to describe modes of pacing. The dual-lead system shown emphasizes that either one or both may be employed by the clinician. As an alternative, the electrodes may be placed on the epicardium or the atrial lead can be in the coronary sinus. (From Harthorne JW: Indications for pacemaker insertion: Types and modes of pacing. *Progr Cardiovasc Dis* 23:395, 1981, by permission of Grune and Stratton.)

chapter; the reader is referred to the many excellent texts on this topic [4,5]. Many of the aspects discussed above for malfunction of temporary pacemakers apply to permanent pacemakers as well. Here, we will discuss additional specific considerations relating to permanent pacemakers. *Failure to sense* may be caused by inadequate signal generation, generator malfunction, or a mismatch between the intracardiac signal generated by the myocardium and then received by the pulse generator. This last cause may be due to an impedance mismatch between the permanent endocardial electrode and the generator or an insulation leak in the generator. In physiologic pacing systems it is necessary to evaluate atrial sensing in addition to ventricular sensing (figure 9–31). Mention should also be make of *partial sensing*. Usually VVI pacemakers sense in all-or-none fashion; certain models, however, exhibit partial sensing

TABLE 9–8. Evaluation of demand function

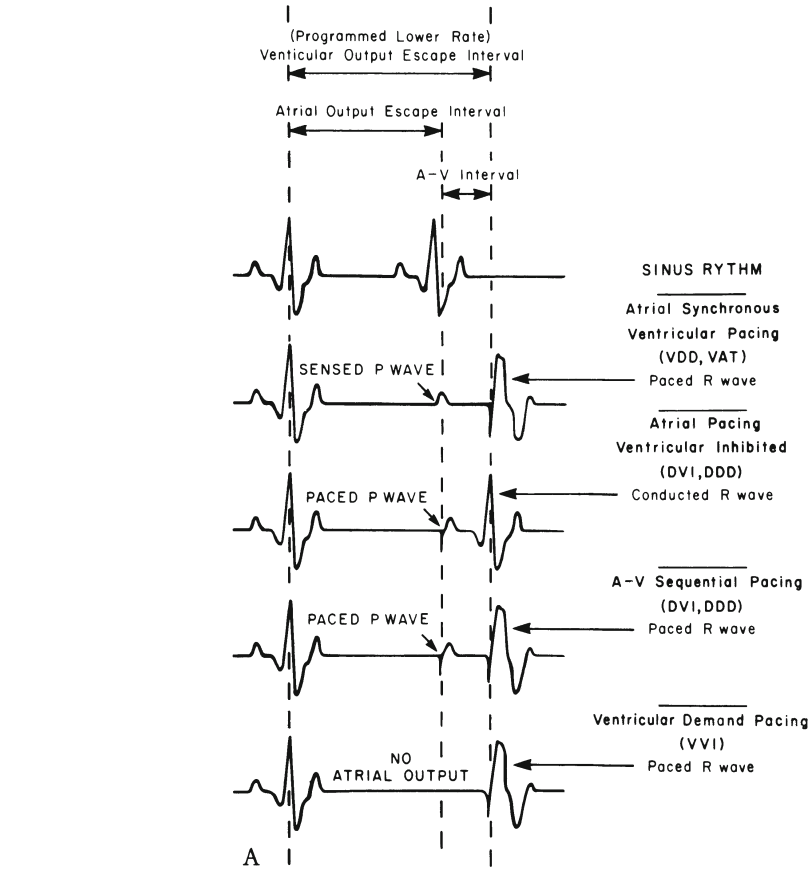
1. ECG
2. Magnet
3. Carotid sinus pressure (CSP)
4. Pharmacological interventions
5. Chest wall stimulation
6. Direct recordings from electrodes

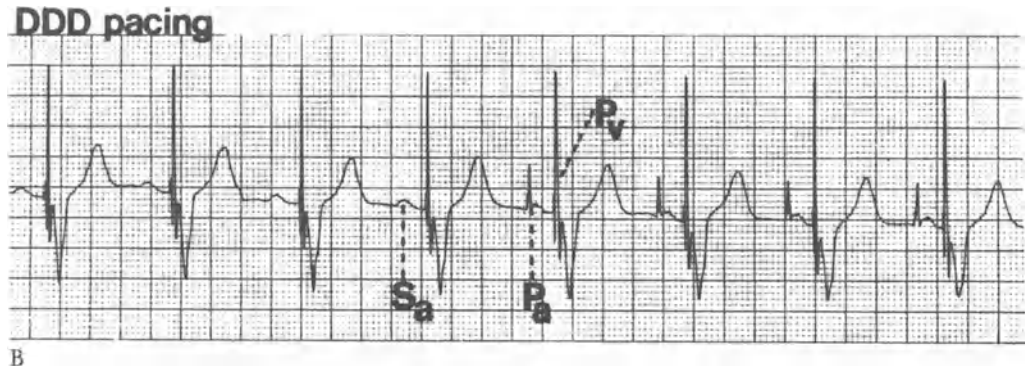
in response to borderline signals outside the refractory period. In these cases the ECG will show an abbreviated escape cycle.

Evaluation of the demand function of a permanent generator includes atrial sensing in addition to ventricular sensing (figure 9–31). A list of procedures to be performed is outlined in table 9–8. Simple observation of the ECG may not be adequate if the patient's native rhythm is continuously suppressing the device, in which case no pacemaker spikes will be seen. However, if alterations of the intrinsic rate occur or VPBs are present, the physician may have sufficient evidence to evaluate demand function. It should be recalled that demand pacemakers have a built-in refractory period following a paced or sensed beat. During this refractory period the device will not sense electrial signals to prevent the generator from being disturbed by its own QRS complexes or high-amplitude P or T waves. The usual refractory period is about 325 msec but may range from 220 to 400 msec and is programmable in more recent devices. When interpreting demand function, the clinician must keep this refractory period in mind so as to avoid mistakenly diagnosing failure to sense.

Application of a magnet over demand generators closes a reed switch and converts the device to a fixed-rate generator, enabling the clinician to observe myocardial capture and providing a clue to battery strength. Pacemaker manufacturers usually include a change in the specified magnet rate as an end-of-life indicator of battery depletion. In addition, some generators exhibit an electrocardiographic "signature" following application of a magnet. This not only helps to identify the generator but may provide information on battery depletion and the safety margin for myocardial capture (figure 9–32).

In order to slow the patient's heart rate and allow pacemaker impulses to emerge, *carotid sinus massage* and various pharmacological

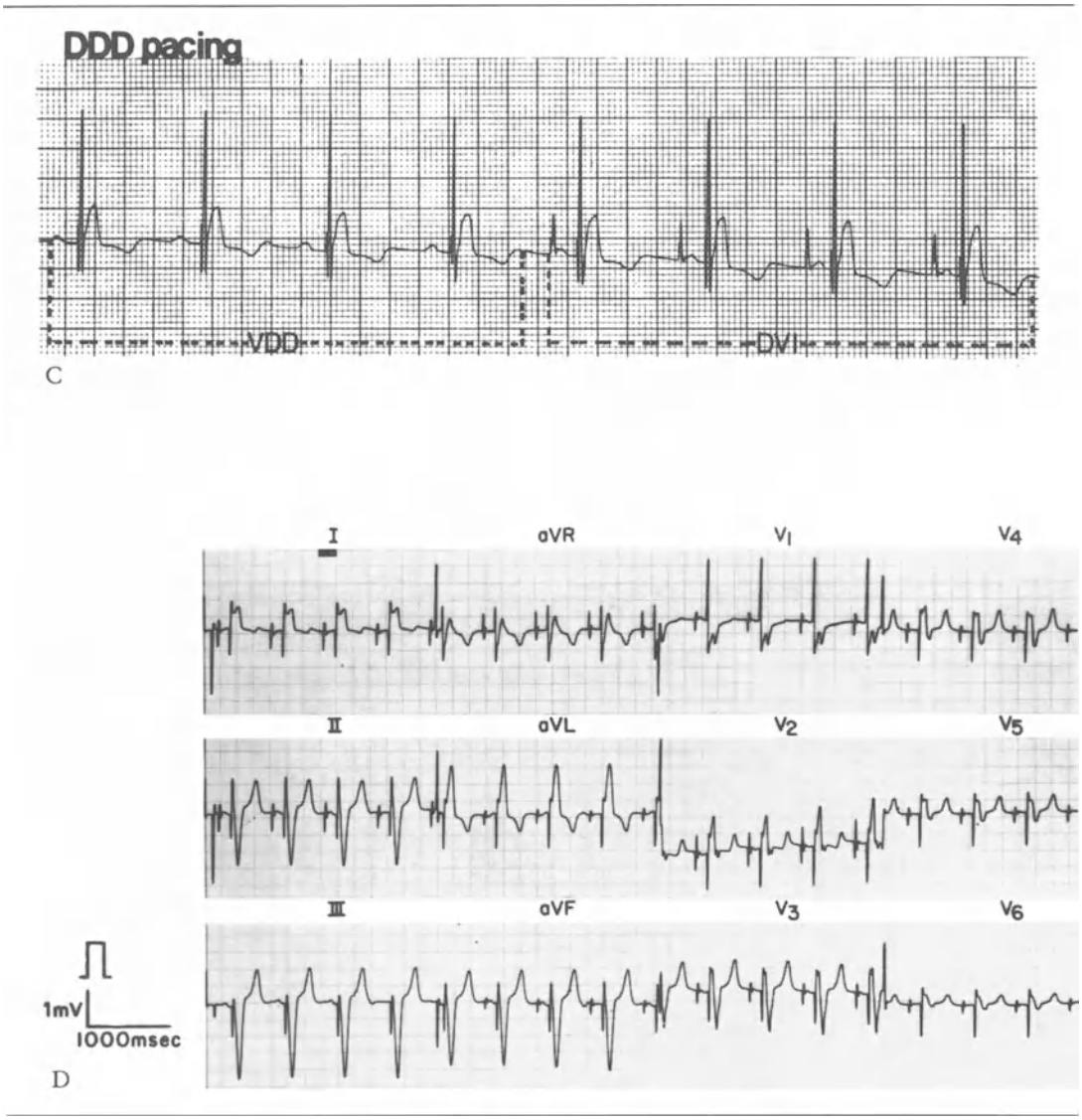




B

FIGURE 9–24. *A*, Basic operation of the AV universal (DDD) mode. The system is designed so that sensing and pacing can occur on both atrial and ventricular leads. If no spontaneous depolarization occurs before the end of the appropriate atrial or ventricular time-out interval, a stimulus will be emitted. In *committed systems*, once an atrial spike occurs, a ventricular spike will automatically occur at a set AV interval. However, most generators use a *partially committed system* that will allow a sensed ventricular depolarization to inhibit ventricular output from the generator provided that the sensed ventricular depolarization falls outside a brief *blanking period* (during which the ventricular sensing amplifier is nonfunctional) following the atrial stimulus. The purpose of the blanking period is to prevent crosstalk between atrial output and the ventricular sensing circuit.

B, ECG example of DDD pacing. At the left, the native atrial complexes (sensed atrial event = S_a) arrive at a fast enough rate to inhibit the output of atrial pacing spikes from the generator. In addition, these S_a events trigger a ventricular paced event (P_v) after a programmed AV delay. The P_v event appears since no spontaneous ventricular depolarization occurred before the end of the AV internal. When the native atrial rate slows below the programmed lower rate of the generator, a paced atrial event (P_a) occurs, maintaining the patient's heart rate at a present minimum rate.



C, Similar to the situation in *B*, the left-hand portion of the step shows atrial triggered ventricular pacing. Since this device is also capable of sensing ventricular events, it is operating functionally in a VDD fashion. When the spontaneous atrial rate slows, 100% AV sequential pacing occurs with the device operating functionally in the DVI mode. The programmed mode that allows the generator to adjust automatically from one form of pacing to another is the AV universal or DDD mode.

D, Example of 100% DVI (AV sequential) pacing. This 12-lead ECG illustrates the need to examine multiple leads to diagnose the presence of pacing spikes and to determine whether myocardial capture has occurred. In lead III, the atrial pacing spikes are not evident despite the fact that they clearly have occurred, as seen in leads I and II (recorded simultaneously with III). Furthermore, as seen in lead II the first three atrial spikes capture the atrium, as evidenced by the driven or paced P waves. The fourth atrial spike does not capture the atrium either because of insufficient output on the atrial lead or because a spontaneous atrial depolarization occurred immediately before or coincident with the atrial pacing spike. If the latter occurred, the atrial spike would be falling in the P-R segment which is not uncommon with DVI pacemakers, which are incapable of sensing atrial events. This unresponsiveness to spontaneous atrial event prevents DVI generators from responding to physiologic demands that require an accelerated heart rate.

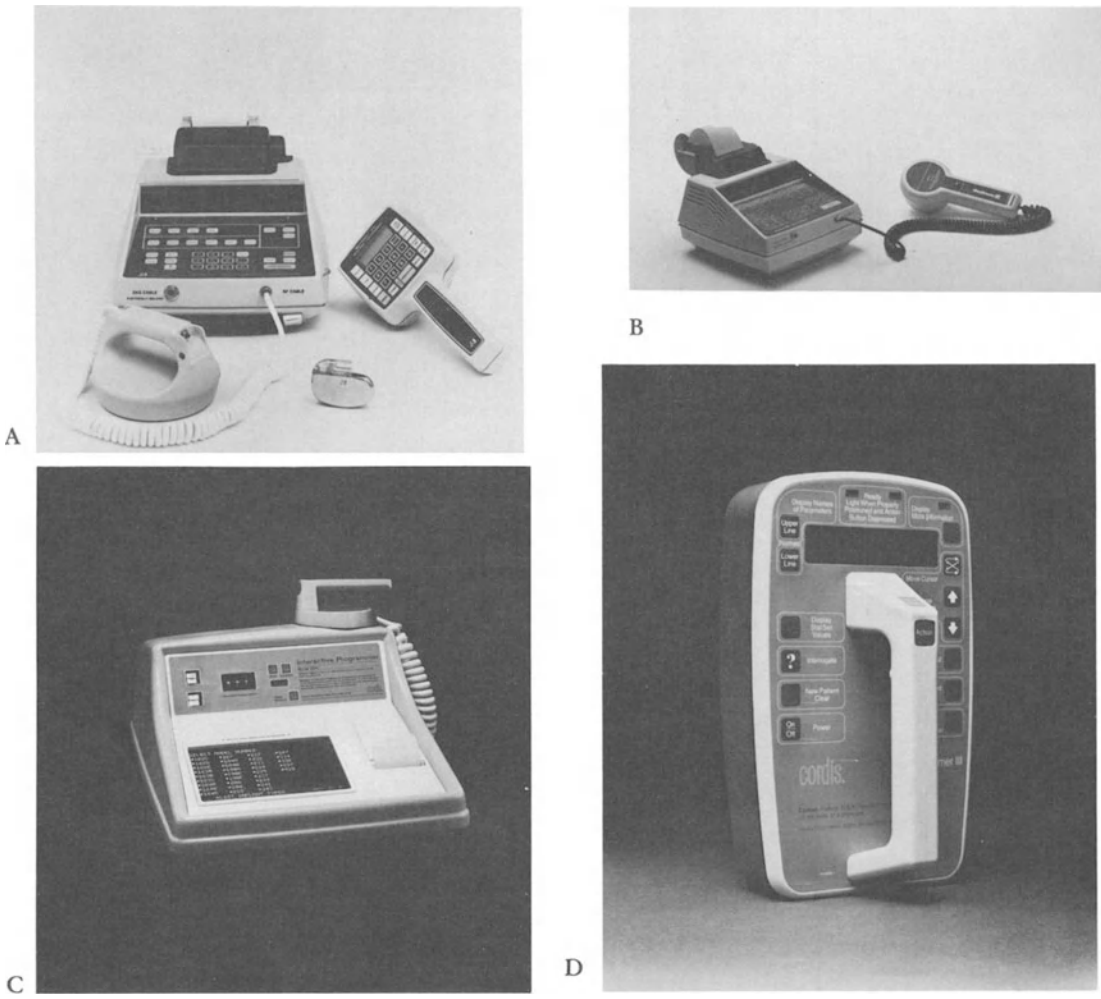


FIGURE 9–25. Examples of external noninvasive programmers for implanted permant generators. *A*, Medtronic 9701 (desk-top) and 9700 (hand-held) Spectrax programmer. *B*, Medtronic 9701A (desk-top) programmer for DDD, DVI, and VVI generators. *C*, Cordis 256A (desk-top) interactive programmer for all available Cordis generators. *D*, Cordis 255A (hand-held) programmer, which incorporates many of the features of the 256A device. (Courtesy of Medtronic and Cordis Corporation.)

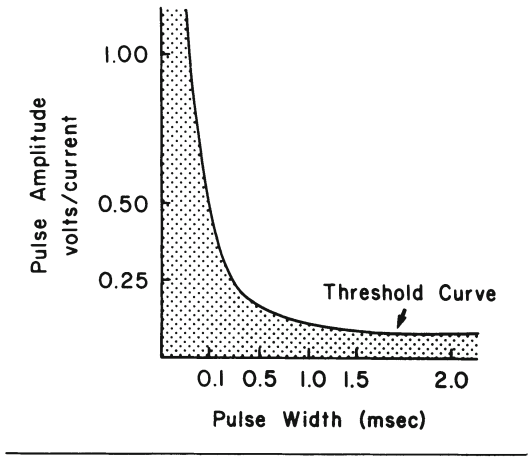


FIGURE 9–26. Strength duration curve showing the relationship between pulse amplitude (volts or current) and pulse width. Each point on the curve is the stimulation threshold for the respective pulse amplitude and width; the area above the curve represents those amplitude and width combinations that will stimulate an endocardial depolarization, while the area below the curve represents combinations insufficient to stimulate a depolarization. (From Byrd C: Permanent pacemaker implantation technique. In: *Cardiac pacing*, 2nd ed, Samet P, E1-Sherif N (eds), New York, Grune Stratton, 1980, p 248, by permission of the publisher.)

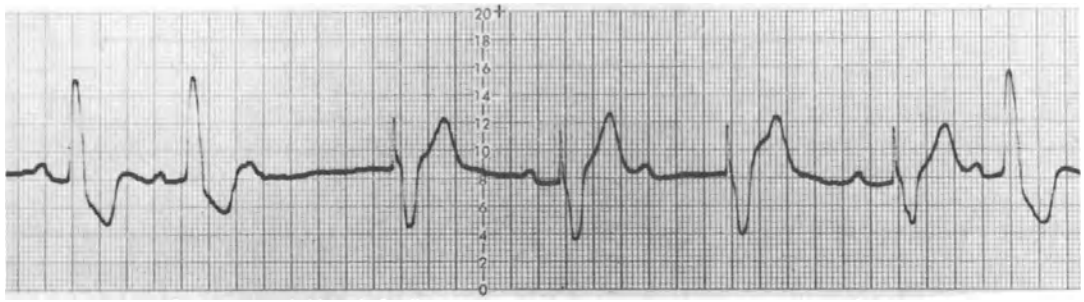


FIGURE 9–27. Rate hysteresis. This patient's generator is designed to allow the spontaneous ventricular rate to fall to 40 bpm (1,500-msec cycle length) before ventricular pacing occurs (third beat from left). When ventricular pacing begins, it is at a rate faster than the escape rate. In this instance the pacing rate is 50 bpm (1,200-msec cycle length; see three paced beats in center). A sensed ventricular event must occur at an interval less than the pacing rate (i.e., <1,200 msec) in order to inhibit the generator (final beat at right).

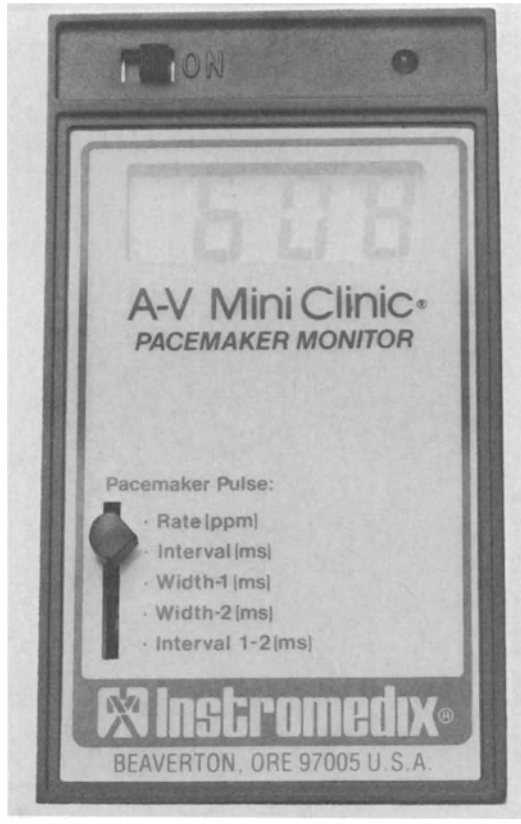


FIGURE 9–28. Hand-held device for measuring pacing intervals and pulse width. The back of the device has four metal footplates that will analyze the pacing spikes on the body's surface when they are held against the skin of the anterior thorax.

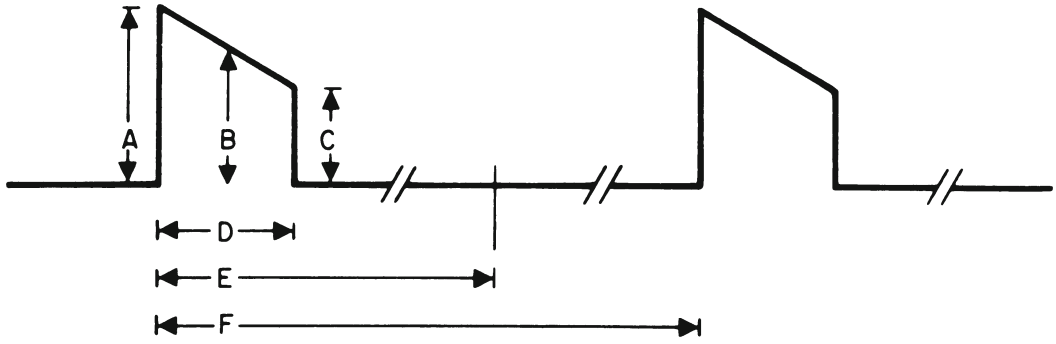


FIGURE 9–29. Typical electrical output of a pulse generator. Features of this amplified impulse are measured to evaluate pacemaker function. *A*, *B*, and *C* = Pulse amplitudes at leading edge, midpoint, and trailing edge, respectively; D = impulse duration; E = refractory period; F = impulse interval. (From Parsonnet V: Pacemaker implantation. In Efler DB (ed): *Blades' Surgical diseases of the chest*, 4th ed, St Louis, The CV Mosby Co, 1978, p 751.)

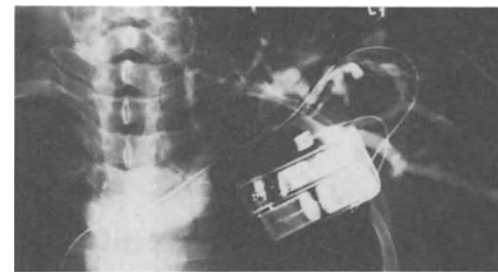


FIGURE 9–30. Thrombosis of subclavian vein with tortuous venous collaterals that developed after implantation of a permanent endocardial pacing lead.

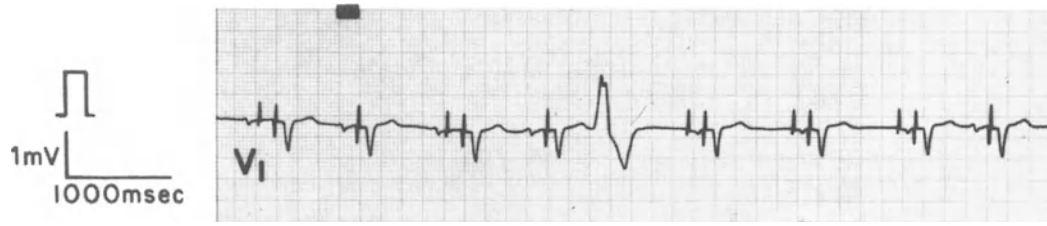


FIGURE 9–31. Intermittent malsensing on the atrial lead of a DDD system. The second, third, fourth, and ninth beats show normally functioning atrial triggered ventricular pacing. The sixth, seventh, and eighth beats show 100% AV sequential pacing. The first and third beats demonstrate improper sensing on the atrial lead; the spontaneous P wave should have been sensed and should have inhibited the atrial spike output. The VPB in the center of the strip is appropriately sensed on the ventricular lead, inhibits both atrial and ventricular output, and resets the timing cycle of the generator.

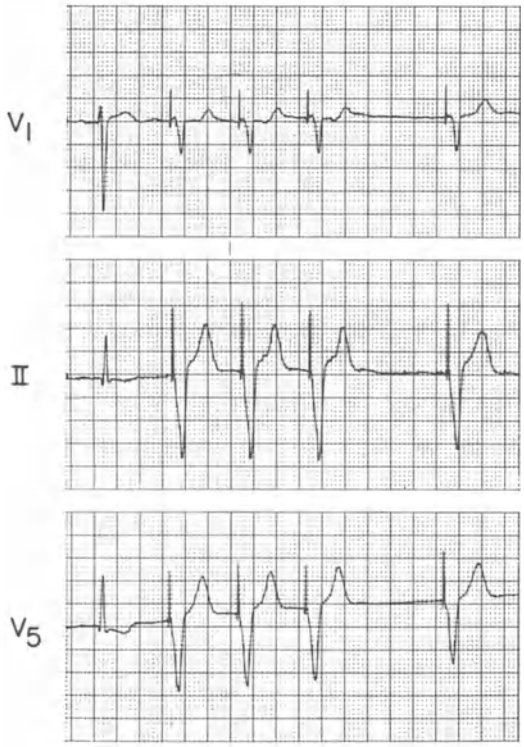


FIGURE 9–32. Threshold margin test of a Medtronic Spectrax-T generator (Model 8423). Application of a magnet causes the generator to emit three pulses at a rate of 100 bpm, irrespective of the programmed pacing rate. The pulse width of the third impulse is 75% of the pulse width of the first two, thereby providing a rough test of the margin of safety for capture of the myocardium. As seen in this figure, once the 3 test pulses are emitted, the pacemaker reverts to a VOO device at its programmed rate. Other manufacturers have similar types of magnet tests for assessment of the capture threshold (e.g., "Vario" function of Telectronics Optima-MP series).

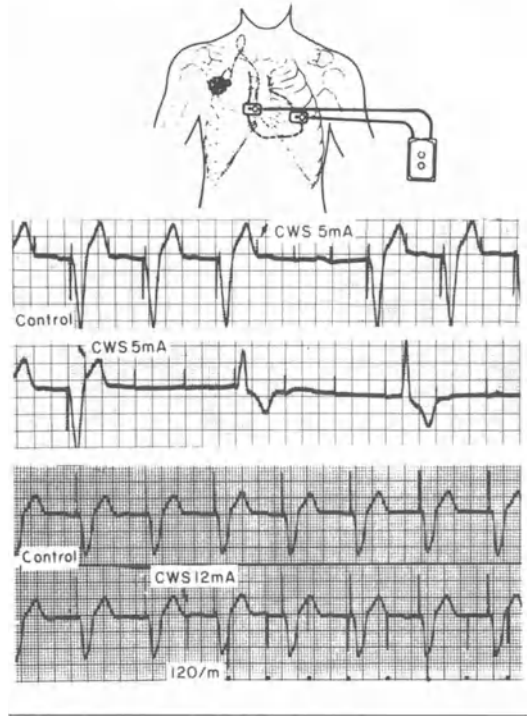


FIGURE 9–33. To check for pacemaker malfunction, chest wall stimulation (CWS) may be necessary. With electrodes applied as shown (*A*), this will determine whether appropriate sensing is taking place. In CWS with a QRS-inhibited pacemaker present, suppression of the permanent pacemaker is first intermittent (*B*, top) and then continuous when CWS is performed in the optimal location (*B*, bottom). In CWS with an asynchronous pacemaker present, external impulses (dots at lower left) do not influence permanent pacemaker activity (*C*). (From Pupillo JA: *The ECG of artificial pacemakers*. Parma, Ohio, Vismar Publ Co, 1979, p 69.)

interventions (e.g., edrophonium) can be employed. Next, application of skin electrodes connected to a temporary generator may be used for *chest wall stimulation* (CWS). The CWS test inhibits demand generators provided that the electrodes are oriented appropriately and that sufficient current is applied to the chest wall to produce a large enough electrical signal (figure 9–33). Direct recordings from the permanent endocardial leads may be evaluated using a pacing system analyzer (figure 9–34) in order to diagnose problems with the lead and myocardial-lead interface. Certain new devices allow noninvasive recordings of telemetry signals from the generator. The measured potential should then be compared with the sensitivity specifications for the particular device. Programmable generators may be adjusted to respond appropriately to the available endocardial signal; nonprogrammable devices require repositioning of the lead or insertion of a new lead to obtain a more satisfactory signal.

One problem of demand function unique to those physiologic pacing systems with atrial sensing capabilities (i.e., VDD, DDD) is induction of an "endless loop" or circus movement

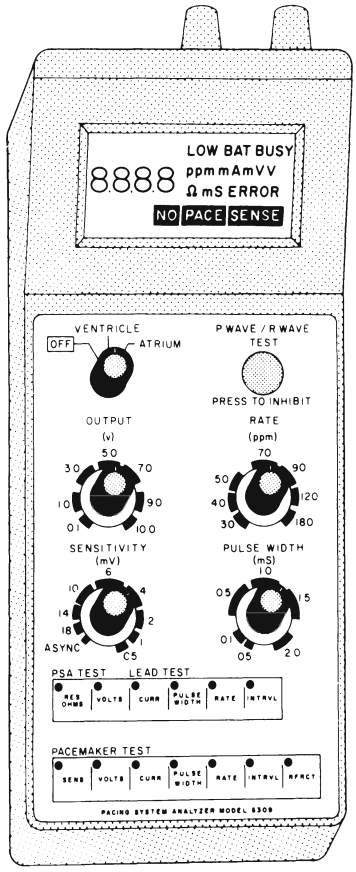


FIGURE 9–34. Pacing System Analyzer. Sophisticated instruments such as this Medtronic Model 5309 pacing System analyzer are used to access the electrical characteristics of the lead-myocardial system. In addition, testing of the output of the implantable pulse generator can be performed.

tachycardia that utilizes the generator as an accessory pathway of AV conduction (figure 9–35). In this situation, a retrogradely conducted ventricular depolarization produces an atrial depolarization that is sensed on the atrial lead and initiates a subsequent ventricular paced event after the programmed AV delay. This arrhythmia occurs at the upper rate limit for atrial "tracking." It can be interrupted by (1) placing a magnet over the generator to disable the sensing amplifiers, (2) programming the refractory period for sensing on the atrial lead beyond the period of VA conduction, (3) programming to the DVI mode, (4) increasing the programmed upper rate and/or narrowing the programmed AV interval to minimize the likelihood of VA conduction, or (5) administering a drug such as verapamil to block VA conduction. In order to circumvent the problem of pacemaker-related circus movement tachycardia, pacemaker manufacturers have designed the atrial refractory period for sensing to be programmable (at the expense of the maximum upper rate for atrial "tracking") or to be prolonged automatically after a ventricular premature depolarization.

Abnormalities of pacing function may be analyzed in a fashion similar to that for temporary pulse generators. Some variation in spike intervals may occur with alterations of body temperature. A reduction in rate below the specified or programmed rate usually indicates battery depletion. Modern generators do not lose battery power in an abrupt, all-or-none fashion; the "end-of-life" indicator, is understood to mean that the battery has become depleted to the point where the generator must be replaced.

Finally, in considering the vagaries of permanent cardiac pacing, once should remember that no matter how sophisticated a generator is, after implantation in a patient the entire pacing system is only as strong as its weakest link. Thus, a DDD generator or an expensive ultralong-lived nuclear powered generator cannot compensate for simple mechanical problems such as lead dislodgment or lead fracture (figure 9–36).

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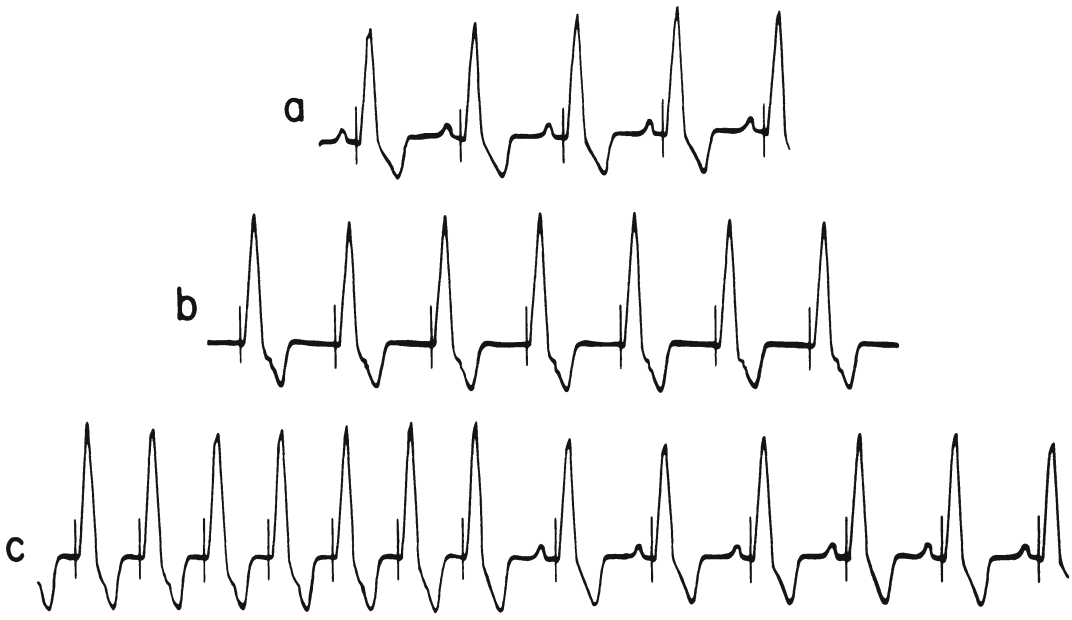
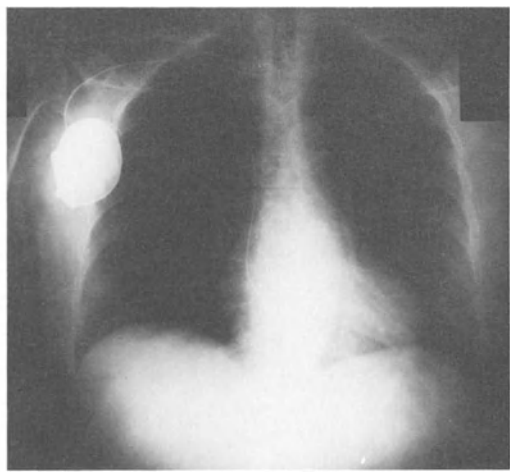


FIGURE 9–35. *a*, Normal operation of Medtronic Enertrax (Model 7100) pacemaker in the VDD mode. *b*, A magnet is applied, producing VOO pacing at a rate of 85 bpm. Retrograde (VA) conduction is present, as evidenced by the inverted P waves on the downslope of the T wave. *c*, Recording made when the magnet was removed after the recording in *B* was obtained. A circus movement tachycardia was initiated using the pacemaker as the antegrade limb and the AV mode as the retrograde limb. The rate of the tachycardia is the programmed upper rate limit of this device. After the seventh paced beat, VA conduction is absent and VDD pacing resumes thereafter. This individual was treated successfully with verapamil to block VA conduction. An alternative would have been to program the generator to a VVI mode. Had this been a DDD pacemaker, it might have been necessary to program the device to the DVI mode, unless the generator was designed to lengthen the atrial refractory period for sensing either automatically or through programming.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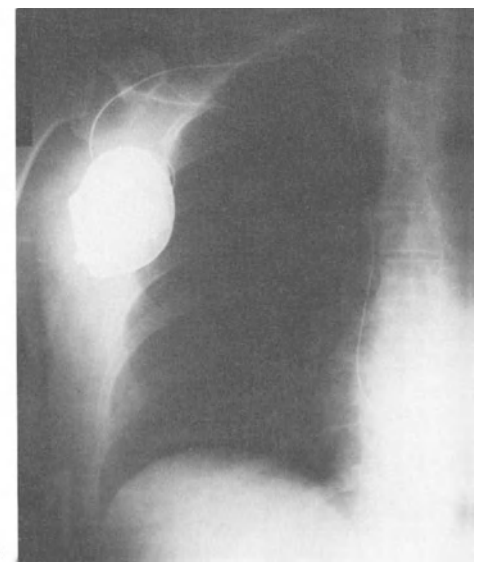
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FIGURE 9–36. Posteroanterior chest x-ray (*A*) and close-up view (*B*) showing fracture of a chronically implanted permanent endocardial lead.

10. CARDIAC ARREST AND RESUSCITATION

In the cardiac intensive care unit (ICU) staff should be mentally and physically equipped to deal with sudden cardiac arrest and initiate prompt resuscitative efforts. Such efforts fundamentally involve a coordinated system to provide artificial ventilation and artificial circulation (i.e., basic cardiopulmonary resuscitation [CPR]) that may be supplemented by advanced cardiac life support systems (e.g., oxygen, defibrillation, specialized medications). Many of the elements of advanced cardiac life support are reviewed in detail in other chapters of this book, as follows:

1. Recognition and treatment of arrhythmias (chapters 4, 5, and 6).

2. Cardioversion and defibrillation (chapter 7).

3. Recognition and treatment of conduction disorders (chapters 8 and 9).

4. Recognition and treatment of hemodynamic disorders, including heart failure and cardiogenic shock (chapters 11 and 12).

In this chapter we will emphasize important concepts of basic CPR; review essential drugs commonly used in resuscitative efforts; and propose an organized, integrated approach to the management of the various forms of sudden cardiovascular collapse.

1. Basic CPR [1,2]

1.1. ARTIFICIAL VENTILATION

Delivery of oxygen to the tissues is a critical element of basic CPR. It is important to establish whether spontaneous breathing of adequate depth and rate is present or absent. A variety of devices are available for clearing the airway, obstructing the esophagus and augmenting airflow to the trachea, directly intubating the trachea, and providing concentrated oxygen mixtures at a rapid rate by mechanical means. Figure 10–1 is an algorithm showing the approach to airway control and ventilation, and techniques for esophageal obstruction and tracheal intubation are depicted in figures 10–2 and 10–3.

Intubation equipment is commonly connected to a resuscitation bag-valve (Ambu) unit, which is used to inflate the lungs intermittently. The timing and coordination of lung inflation in relation to efforts to provide artificial circulation is a controversial subject and will be discussed later. We advise use of the bag-valve apparatus with 100 per cent oxygen during resuscitation until the patient is stabilized to a point where conversion to a mechanical ventilator may be carried out safely (table 10–1). The patient should remain connected to the ventilator until it is clear that weaning will be successful according to the guidelines shown in table 10–2.

1.2. ARTIFICIAL CIRCULATION

Manual external closed chest compression with the patient positioned supine on a firm, flat surface (e.g., floor, "arrest board") is the preferred emergency technique for providing artificial circulation. (Mechanical chest-compression devices not commonly available in most ICUs will not be discussed.) The proper position of the rescuer's hand on the victim's lower sternum is shown in figure 10–4. The rescuer's shoulders should be directly above the victim's sternum so that the elbows may be "locked" during chest

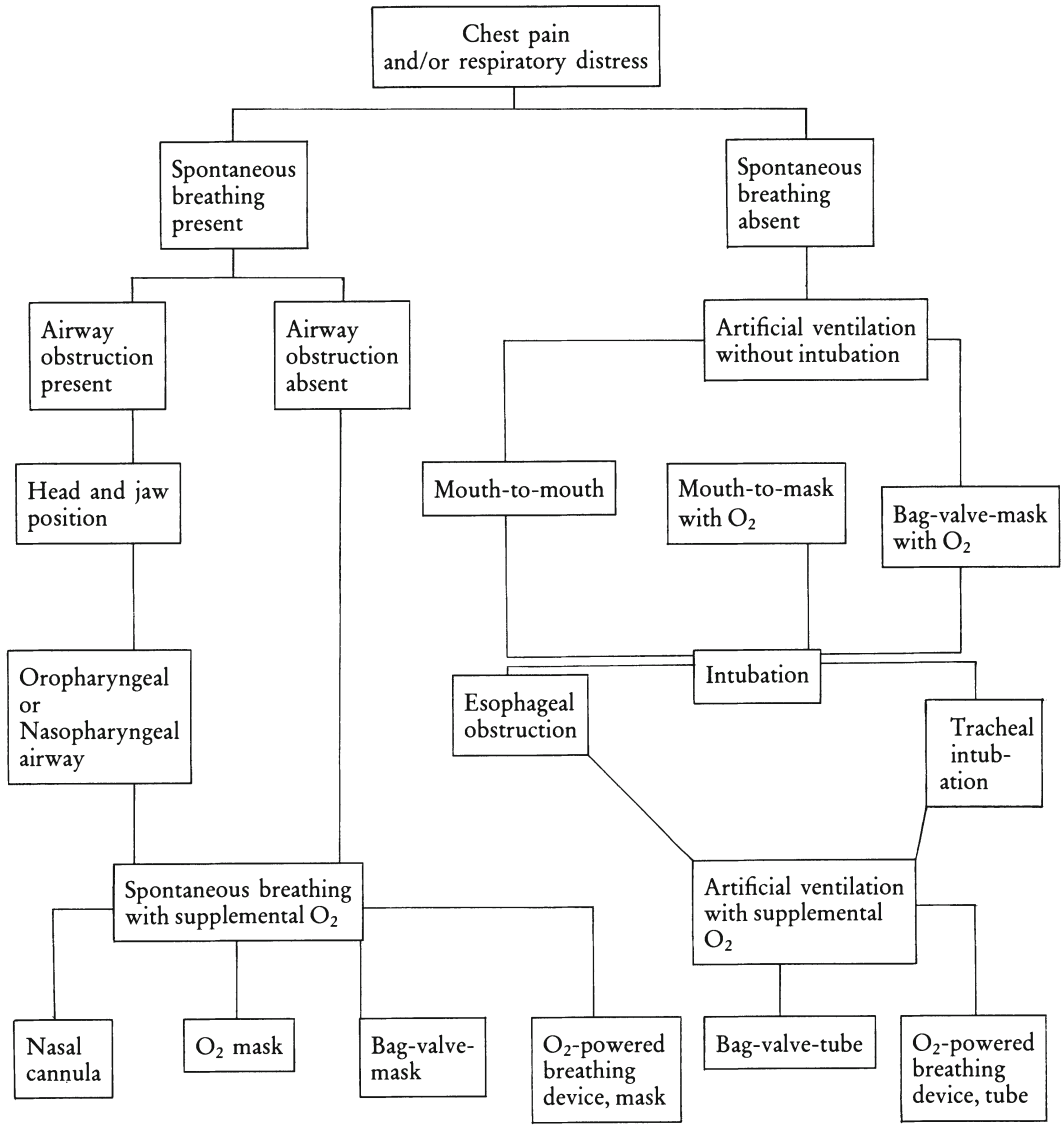

FIGURE 10–1. Approach to airway control and ventilation. (Adapted from McIntyre KM, Lewis AJ [eds]: *Textbook of advanced cardiac life support*, 1983, p IV–1, with permission from The American Heart Association, Inc.)

compression and sufficient force can be generated to depress the sternum 3 to 5 cm. Abnormally superior, inferior, or lateral compression may be ineffective and/or may result in fractures of the rib or sternum.

According to the classic view, the heart is a *volume pump*, and replaces the normal pumping mechanism by squeezing the heart between the sternum and vertebral spines [3]. Lateral displacement of the heart is restrained by the pericardium, and ventriculoatrial regurgitation of blood is prevented by the atrioventricular valves. Theoretically, important determinants of the minute output of such a volume pump would include the force of compression and the rate of compressions per minute rather than the

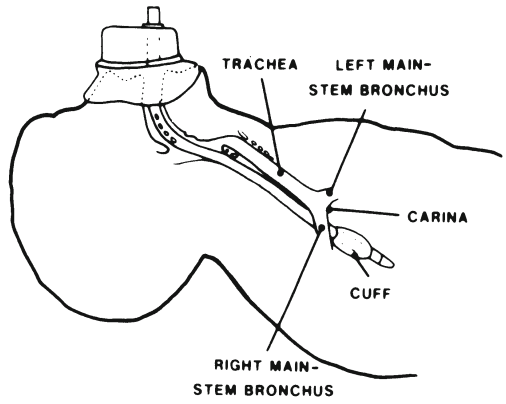

FIGURE 10–2. Proper position of obturator airway in esophagus. Rim of face mask must be sealed tightly against face to effect airtight seal. The esophageal obturator shown here is more appropriate for resuscitation "in the field." In the hospital, skillful resuscitation usually involves tracheal intubation. (From McIntyre KM, Lewis AJ [eds]: *Textbook of advanced cardiac life support*, 1983, p IV–3, with permission from The American Heart Association, Inc.)

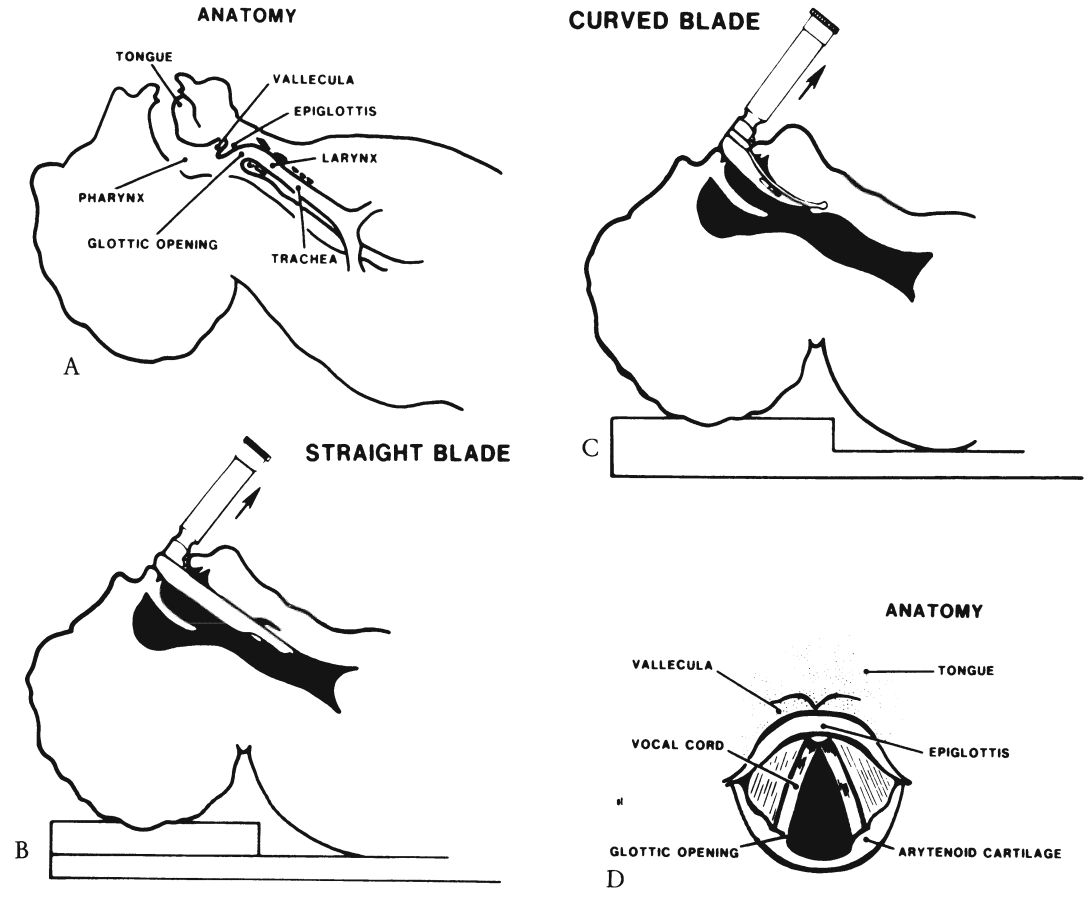

FIGURE 10–3. *A*, Essential landmarks in direct laryngoscopy. *B*, Technique using straight blade, with epiglottis elevated anteriorly to expose glottic aperture. *C*, When curved blade is used, epiglottis is displaced anteriorly by upward traction, with tip of blade in vallecula. *D*, Anatomical structure to be seen during direct laryngoscopy. (From McIntyre KM, Lewis AJ [eds]: *Textbook of advanced cardiac life support*, 1983, p IV–4 and IV–5, with permission from The American Heart Association, Inc.)

duration of individual compressions. However, this classic volume-pump theory may have to be revised based on recent experimental evidence (largely in dogs) as well as preliminary clinical evidence indicates that with external closed-chest compression the heart is in fact shifted off the vertebral spines and invades the pleural space [4–7]. Moreover, during cardiac arrest the AV valves are incompetent and thus allow ventriculoatrial regurgitation of blood [7]. One newly emerging theory of CPR holds that the heart-thoracic cage acts as a *pressure pump* during chest compression. Forward outflow per minute to vital vascular beds (such as the

TABLE 10–1. Commonly employed ventilators

	Bird Mark 7 (can be used as ventilator but needs adaptation for alarms)	Emerson 3-PV	Monaghan 225 SIMV
1. Modes			
Control	Yes	Yes	Yes
Assist/control	Yes	—	Yes
SIMV	No	—	Yes
CPAP	No	—	No
2. Drive mechanism	Pneumatic	Electrical	Pneumatic
3. Positive pressure ventilation	Yes, but is pressure-limited rather than volume-limited;	Yes	Yes
4. Tidal volume preset (ml)	Pressure-limited, V_T is determined by patient compliance	200 to 2,000	0 to 2,000
5. Respiratory rate (breaths/min)	Approximately 5 to 40	6 to 45	Approximately 5 to 40
6. Maximal pressure relief (cm H_2O)	Pressure-limited ventilation	Approximately 100	100
7. FiO_2 (%)	Approximately 40 to 100	21 to 100%	Approximately 21 to 100%
8. Maximal PEEP (cm H_2O)	N/A	With modification up to 15	15
9. Alarms	N/A-alarms only via individual adaptation		
Pressure loss		No	Yes
Volume loss		Yes	Yes
High excess pressure		Yes	Yes
Low O_2 line pressure		No	No
Loss of PEEP/CPAP		No	No
Apnea		No	No
Electrical loss		No	No
Low minute volume		No	No

CPAP = continuous positive airway pressure; PEEP = positive end expiratory pressure; SIMV = synchronized intermittent mandatory ventilation. N/A = not applicable.

cerebral, coronary, and renal beds) would thus depend more on the force of compression and the duration of individual compressions than on the rate of compressions per minute [6]. Furthermore, the rise in intrathoracic pressure from zero (during relaxation) to approximately 85 mm Hg (during compression) would be transmitted to the heart as a unit, and the degree of regurgitation of blood (and dissipation of pressure) to the large capacitance of the venous circulation, which is operating at a pressure of only 40 mm Hg would be limited [6].

It has been proposed that the limitation of retrograde flow from intrathoracic veins into

MA-1 Ventilator	Bennett MA-2 and MA-2+2	Bear I	Bennett 7200
Yes	Yes	Yes	Yes
Yes	Yes	Yes	Yes
Yes with modification	Yes	Yes	Yes
No	Yes	Yes	Yes
Electrical	Electrical	Electrical	Electrical
Yes	Yes	Yes	Yes
0 to 2,200	0 to 2,200	100 to 2,000	100 to 2500
6 to 60 (with IMV modification, 1 to 60)	6 to 60	1 to 60	0.5 to 70
20 to 80	120	100	120
21 to 100%	21 to 100%	21 to 100%	21 to 100%
With modification, up to 15	15	30	45
Yes	Yes	Yes	Yes
Yes	Yes	Yes	Yes
Yes	Yes	Yes	Yes
Yes	Yes	Yes	Yes
No	No	Yes	Yes
No	No	Yes	Yes
No	No	Yes	Yes
No	No	Yes	Yes

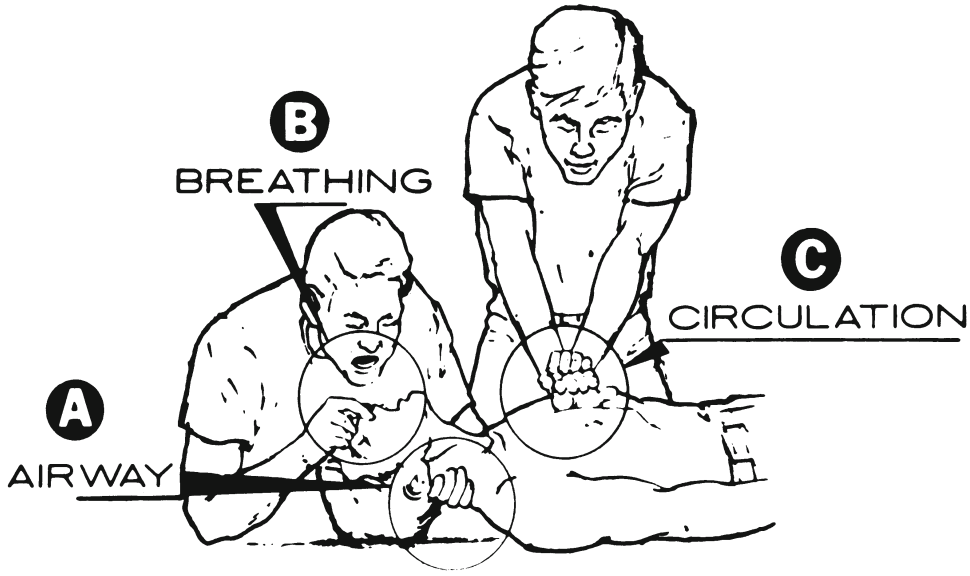

FIGURE 10–4. Cardiopulmonary resuscitation by two rescuers. If the victim's trachea has been intubated, lung inflation is easier and compression rates up to 80 per minute can be used, since breaths can be either interposed or superimposed. (From American Heart Association: *Standards for cardiopulmonary resuscitation [CPR] and emergency cardiac care [ECC]*, 1973, p 15.)

TABLE 10–2. Criteria for weaning ability

Tests of mechanical capability:
1. Vital capacity (VC) > 10 to 15 ml/kg body weight
2. Forced expiratory volume in 1 sec > 10 ml/kg body weight
3. Peak inspiratory pressure > −20 to −30 cm H_2O
4. Resting minute ventilation < 10 L/min (can be doubled with maximal voluntary ventilation)
Tests of oxygenation capability:
1. A-aDo_2 on 100% O_2 < 300 to 350 torr
2. Shunt fraction ($\dot{Q}_S/\dot{Q}_T$) < 10 to 20%
3. Dead space/tidal volume (V_D/V_T) < 0.55 to 0.6

From Snow JC: Respiration and respiratory care. In *Manual of Anesthesia*, Boston, Little, Brown and Co, 1977, pp 317–331.

the jugular vein is the result of extravascular compression due to elevated intrathoracic pressures and the presence of a bicuspid valve in the internal jugular vein that has recently been identified in the dog [5,6]. Blood continues to move forward out of the intrathoracic vasculature because of the extrathoracic arteriovenous pressure gradient. Augmented sympathetic tone prevents/reverses collapse of the critical arteries, such as the carotids, and the slightly higher arterial pressure head of the intrathoracic arteries also serves to propel blood into the systemic circulation [6].

Proponents of the new pressure-pump theory of CPR have shown experimentally that maneuvers which increase intrathoracic pressure — for example, coughing, ventilation at high pressures, simultaneous inflation of the lungs and chest compression, compression for longer than half of the cycle, and even binding of the chest and abdomen when combined with the use of epinephrine (to stiffen arterial walls and constrict nonessential arterial beds) will maximize cerebral and coronary blood flow [4,6].

It should be emphasized that these exciting new observations about the mechanisms of CPR are preliminary and need to be confirmed in larger studies before widespread general recommendations can be made. For the present, it seems clear that the classic volume-pump theory has flaws; prolonging individual compressions is beneficial as is an increasing tendency to administer epinephrine during resuscitation. Consideration should also be given to lung inflation during chest compression (particularly during difficult resuscitation attempts). The

TABLE 10–3. Drugs commonly used during resuscitative efforts*

Drug	Mechanism(s) of action	Dosage	How supplied	Comments
Sodium bicarbonate	Corrects metabolic and respiratory acidosis	1 mEq/kg initially followed by ½ initial dose every 10 to 15 minutes during arrest (see comments)	50 ml of 8.4% soln (50.0 mEq) 50 ml of 7.5% soln (44.6 mEq) 500 ml of 5% soln (297.5 mEq)	Excessive $NaHCO_3$ has been used in the past. Dose should preferably be determined by pH, pCO_2, and base deficit measurements rather than by empirical dose (at left): Total Body Bicarbonate Deficit = Base Deficit (mEq/L) $\times \frac{\text{Weight (in kg)}}{4}$
Epinephrine	Increases heart rate, myocardial contractility, systemic vascular resistance, arterial blood pressure, and automaticity	0.5 to 1.0 mg IV (5 to 10 ml of 1:10,000 soln) every 5 minutes during arrest. (May administer 1.0 mg directly into tracheobronchial tree if IV access is not available.)	*Ampules*: 1 ml (1 mg in 1:1000 dilution) *Prefilled syringes*: 10 ml (1 mg in 1:10,000 dilution)	Infusion of 1 mg/250 ml D_5W to run at 1 to 4 μg/min may be used as maintenance.
Calcium chloride	Increases myocardial contractility and automaticity	10 ml of 10% soln. $CaCl_2$ contains 13.6 mEq of Ca^{++} (100 mg = 1 ml). Usual dose is 5 to 7 mg/kg of 10% soln (2.5 to 5.0 ml of 10% soln) IV every 10 minutes.	*Ampules:* 10 ml calcium chloride (10%) *Prefilled syringes:* 10 ml calcium chloride (10%)	Calcium gluceptate and calcium gluconate salts do not provide as high or as predictable levels as calcium chloride and are therefore not recommended.
Atropine sulfate	Decreases vagal tone and increases sinus rate; accelerates AV nodal conduction	0.5 mg IV every 5 minutes to a maximum dose of 2.0 mg	*Prefilled syringes*: 10 ml: 1.0 mg/10 ml (0.1 mg/ml) 5 ml: 0.5 mg/5 ml (0.1 mg/ml) *Vials*: 20 ml: 0.4 mg/ml or 0.5 mg/ml	May markedly accelerate heart rate.
Isoproterenol	Positive inotropic and chronotropic effects	Infusion of 2 to 20 μg/min (about 0.1 μg/kg/min) titrated to heart rate and rhythm.	1-mg vial. A 2-μg/ml solution can be made by adding 1 mg to 500 ml D_5W.	May produce arrhythmias or extreme increase in heart rate. Drop in peripheral vascular resistance may cause fall in diastolic and mean arterial pressures.

*See chapter 6 for discussion of other cardiovascular agents.
Adapted from McIntyre KM, Lewis AJ (eds): *Textbook of advanced cardiac life support*, American Heart Association, Inc., 1983, pp VIII–1 to VIII–16 and IX–1 to IX–16.

TABLE 10–4. How to perform cardio-pulmonary resuscitation ("Run a code")

- Arrive at code
- Establish basic life support: check for pulse, open airway; determine whether paient is breathing
- *Simultaneously*, assess "code" status *and* initiate general "code" measures

Assess "code" status

Unmonitored arrest (e.g., pulseless and/or apneic patient with no ECG)

- Attempt thumpversion
- Check for pulse. If none, "blind shock" 200 to 400 ws
- Recheck for pulse. If none, resume CPR and check ECG.
- Prepare for second "blind shock" (200 to 400 ws) if delay in obtaining ECG
- When ECG available — see Monitored arrest.

Monitored arrest (see page 257)

Initiate general "code" measures

- Determine who will run code
- Attach ECG machine
- Effect IV access (at least 18 gauge): arm or leg vein, femoral vein, subclavian vein, internal jugular vein, cutdown on saphenous or basilic
- Obtain arterial specimen for blood gases
- Obtain venous specimen for electrolytes, glucose
- Obtain schedule of medications patient has received (from nurse)
- Assign someone to review chart if patient unknown
- Intubate as soon as skilled personnel arrive and confirm tube placement
- When IV in place:
  Begin D_5W to keep open
  Give $NaHCO_3$, 1 mEq/kg initially with subsequent doses based on arterial blood gases
  For totally unknown patient, consider giving Narcan (1 amp), Thiamine (100 mg), $D_{50}W$ (50 ml)

benefits of chest/abdominal binding of automatic devices which can be programmed to coordinate ventilations and compressions must be shown to outweigh such risks as internal organ laceration and contusion before approaches can be adopted.

2. *Drugs Commonly Used During Resuscitation Efforts [1,2]*

Information about five drugs that are often used during cardiac resuscitation is provided in table 10–3. The reader is also referred to Chapter 6 for specific information on antiarrhythmic agents.

3. *Algorithms for "Running a Code"*

CPR attempts involve a carefully coordinated and rehearsed sequence of events, with one member of the team designated as leader. Table 10–4 outlines techniques common to all "codes" as well as specialized therapies for cardiopulmonary arrest of various causes.

References

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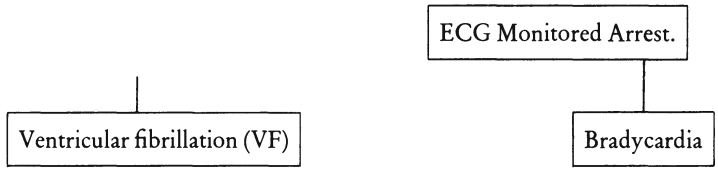

- Defibrillate *ASAP* (200 to 400 ws)
- If no response, deliver "double shock" (see Chapter 4)
- If VF is not terminated or recurs:
  Be certain $NaHCO_3$ was administered (see General Measures on page 256)
  Administer bretylium, 350 to 500 mg IV
  Start chest compression, 30 to 60 sec
  Repeat defibrillation attempt at 400 ws
- For refractory VF:
  Check oxygenation
  Repeat dose of bretylium
  Administer epinephrine, 0.5 to 1.0 mg IV
  Start chest compression, 30 to 60 sec
  Repeat defibrillation attempt, including "double shock" technique

Ventricular Tachycardia

- Perform cardioversion or defibrillation based on heart rate and ECG morphology (Chapter 4)
- Begin antiarrhythmic therapy to prevent recurrence (lidocaine, procainamide) (see Chapter 6)

Asystole

- Administer epinephrine, 1 mg IV (repeat every 5 min); $NaHCO_3$ if clinically indicated; and atropine, 1 to 2 mg IV
- Start chest compression, 30 to 60 sec
- If ineffective, administer $CaCl_2$ (10 ml of 10% soln) and repeat every 10 minutes
- Start chest compression, 30 to 60 sec
- If ineffective:
  Administer intracardiac epinephrine
  Initiate isoproterenol infusion, 2 to 20 μg/min
- For refractory asystole:
  Defibrillate at 400 ws
  Prepare for temporary pacing (external, transvenous, or transthoracic)

- Consider treatment if ventricular rate <40–50/min especially if associated with hypotension
- Administer atropine, 0.5 mg IV, to be repeated every 5 minutes as needed to a maximum dose of 2.0 mg
- Administer isoproterenol, 2 to 20 μg/min IV if atropine is insufficient to restore heart rate and blood pressure
- Consider pacemaker (external, transvenous if bradycardia persists)

Electromechanical Dissociation

- Maintain CPR while administering epinephrine, 0.5 to 1.0 mg IV, and $NaHCO_3$, 1 mEq/kg (see Table 10–3)
- In general, several potential causes require quick assessment in CCU:

CAUSES AND TREATMENT

Cardiac tamponade: Clues are inadequate pulse and oxygenation during CPR, elevated neck veins. Rx: Pericardiocentesis. Call surgeon.

Tension pneumothorax: Clues are deviation of mediastinum, unilateral absence of air entry during ventilation. Rx: Chest tube.

Hypovolemia: Clues are flat neck veins, evidence or suspicion of massive blood loss. Rx: Replace volume with saline, plasma or other blood products.

Global ischemia: Clues are history of preceding chest pain or MI, absence of causes 1 to 3 above. Rx: CPR while assessing candidacy for urgent restoration of coronary flow.

Massive pulmonary embolus: Clues are elevated neck veins, ECG evidence of right heart strain, inadequate oxygenation during CPR. Rx: Maintain CPR. Consider thrombolysis or pulmonary artery embolectomy.

Other less common causes: Aortic stenosis, aortic dissection, ball valve thrombosis of heart, occluded prosthetic heart valve, atrial myxoma.

11. HEMODYNAMIC MONITORING

1. General Principles

Changes in hemodynamics after an acute myocardial infarction depend on the amount of myocardial necrosis (i.e., the size of the infarct) and the site of the infarct. Although in the majority of patients myocardial necrosis involves the left ventricle, attention has recently been directed to the hemodynamic features and treatment of significant infarction of the right ventricle.

In general, the extent to which cardiac function is preserved after acute infarction is inversely proportional to infarct size. Autopsy studies reveal that necrosis of at least 40 per cent of left ventricular myocardium is a common feature in patients who suffer *cardiogenic shock* after infarction [1]. In this situation, such massive necrosis leads to loss of left ventricular pump function, low cardiac output and stroke volume, and hypotension and is usually fatal. Furthermore, most patients with cardiogenic shock have significant disease of the left anterior descending coronary artery associated with three-vessel disease. Although infarction alters the systolic contractile properties of the ventricle, ischemia and infarction also affect the diastolic pressure-volume relations of the ventricle. Ischemia results in abnormal ventricular relaxation, which in turn increases the resistance to ventricular filling. With the resultant combination of reduced contractility and delayed or incomplete relaxation of ventricular myocardium, ventricular filling pressures become elevated.

Initially after infarction, necrotic or noncontracting areas of myocardium can bulge passively during systole, leading to paradoxical systolic expansions of areas of myocardium. Although this reduces the stiffness of the ventricle, it also reduces stroke output. As the inflammatory process evolves, paradoxical systolic pulsation can diminish and ventricular function improves, at least temporarily. In this manner, significant amounts of myocardial necrosis will alter the properties of the ventricles during both systole and diastole and thus result in a wide spectrum of clinical and hemodynamic presentations. Clearly, the size of the myocardial infarction will determine the mode of presentation and ultimately the mortality (table 11–1).

2. Cardiac Performance and Filling Pressures

Hemodynamic monitoring is an important adjunct in the optimal management of patients with an acute myocardial infarction. Cardiac performance can be assessed more accurately when both the cardiac index (or stroke index) and the ventricular filling pressures are known.

TABLE 11–1. Classification of patients with acute infarction

NYHA class	Approximate % of LV infarcted	CCU % admissions	Clinical findings	Approximate mortality (%)
I	0 to 10	30 to 40	No LVF	0 to 5
II	10 to 20	30 to 50	Mild LVF	5 to 25
III	20 to 30	5 to 10	Significant LVF	20 to 50
IV	Over 40	10	Shock	80 to 100

LVF = left ventricular failure; LV = left ventricle.

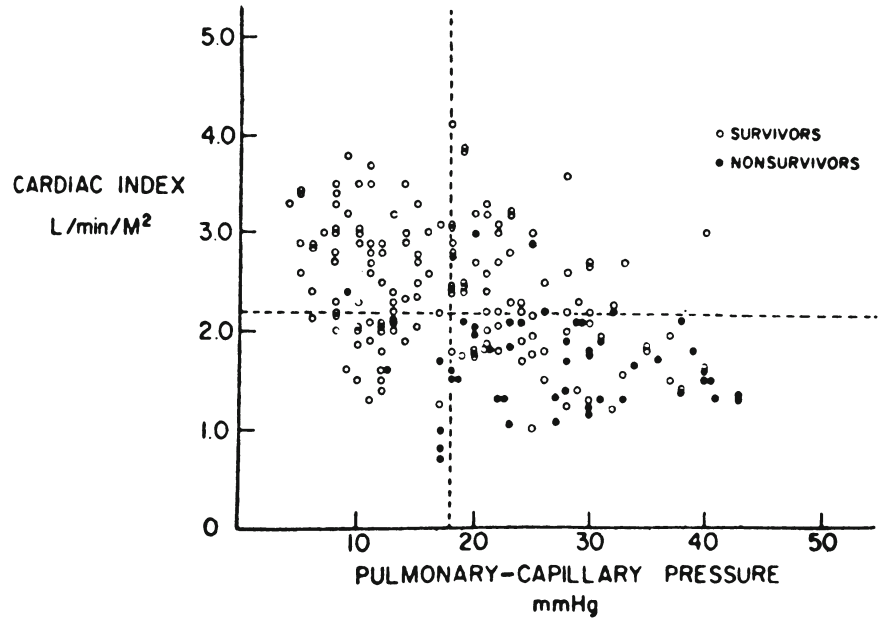

FIGURE 11–1. Relationship between cardiac index and pulmonary capillary pressure in 200 patients at the time of hospital admission. There is a wide degree of variability in left ventricular performance in patients with acute infarction, and mortality rate increases as cardiac performance deteriorates. The majority of nonsurvivors are those with cardiac indices below 2.2 L/min/m^2 and pulmonary capillary wedge pressures above 18 mm Hg at admission (dotted lines). [2]

Measurements of cardiac index alone will allow a relatively insensitive assessment of cardiac performance after infarction, since the range of normal values is wide.

In patients with an evolving myocardial infarction, clear therapeutic and prognostic implications can be deduced if one knows the relationships between cardiac work and filling pressures [2,3]. Forrester et al measured pulmonary artery wedge pressure and calculated cardiac index in 200 patients with acute myocardial infarction at the time of hospital admission [2] (figure 11–1). In assessing the relationship between these two variables it became apparent that cardiac performance varies widely after acute infarction. When cardiac index was less than 2.2 L/min/m^2 and pulmonary artery wedge pressure was greater than 18 mm Hg on admission, a higher inhospital mortality was likely. (This relationship is expressed in the lower right quadrant of figure 11–1.)

Monitoring of mean pulmonary artery wedge pressures within 12 hours of the onset of Q-wave infarction can identify a group of high-risk patients with pressures exceeding 18 mm Hg who have a higher mortality than those with lower initial left ventricular filling pressures [4] (table 11–2). Furthermore, if left ventricular filling pressures can be reduced to less than 18 mm Hg, survival will be better than in patients whose filling pressures remain persistently elevated above this level [4]. It should be noted that pulmonary artery wedge pressure often falls spontaneously during the first day after myocardial infarction [5].

TABLE 11–2. Relationship of early left ventricular filling pressure to mortality in evolving Q-wave infarction

Left ventricular filling pressure (mm Hg)	72-hour mortality	30-day mortality
<18	4%	10%
>18	21%	33%

Adapted from Shell W, et al: Prognostic implications of reduction of left ventricular filling pressure in early transmural acute myocardial infarction. *Am Heart J* 102:335, 1981.

Equally important is the identification of large numbers of patients with acute myocardial

infarction with normal ventricular performance. Representative normal waveforms are shown in figure 11–2.

Clearly, it is inappropriate to insert pulmonary artery balloon-tipped catheters (and/or arterial pressure monitoring lines) in all patients who have had an acute infarction. Indeed, about one-third of these patients will have no evidence of either increased pulmonary artery wedge pressure or decreased cardiac index according to subjective or objective criteria nor will they exhibit dyspnea, rales, radiographic evidence of pulmonary congestion, fatigue, obtundation, clinical evidence of hypotension, sinus tachycardia, cold extremities, or diminished urine output. However, other patients will exhibit either pulmonary congestion or peripheral hypoperfusion as determined by clinical criteria (or hemodynamic measurements), and four subsets with differing prognoses can be identified (table 11–3).

Most clinicians would agree that bedside examination will easily distinguish those patients with normal hemodynamics (and a low mortality) from those with evidence of both peripheral hypoperfusion and pulmonary congestion (cardiogenic shock with a high mortality). Nevertheless, in order to plan therapy for the latter group, one must be aware of changes in cardiac index and ventricular filling pressure after therapeutic maneuvers. Patients with isolated pulmonary congestion after acute infarction are usually detected because they show symptoms of dyspnea, signs of chest rales, or radiographic evidence of congestion, and treatment is usually straightforward.

Hemodynamic monitoring has identified the important group of patients with peripheral hypoperfusion but without pulmonary congestion due to inadequate ventricular filling pressures after acute infarction. Without treatment, mortality in this group of patients can be significant (table 11–3).

After acute myocardial infarction, higher than "normal" ventricular filling pressures may be required to maintain cardiac output because increased ventricular diastolic stiffness will impede ventricular filling. Central venous pressure monitoring alone is of no value in assessing the presence of left heart failure, and the relationship between right and left heart filling pressures in patients with acute infarction is not constant. Furthermore, monitoring of central venous pressure, which reflects only right ventricular filling pressure, does not accurately indicate a directional change in left heart filling pressure during fluid therapy [6]. Cardiac performance is affected by the level of ventricular filling pressure and diastolic ventricular stretch (preload). In the absence of mitral valve disease, mean left ventricular diastolic, pulmonary venous, and pulmonary artery wedge pressures are closely related. After infarction, if left ventricular filling pressure is inappropriately low, cardiac output may be inadequate (e.g., peripheral hypoperfusion in the absence of pulmonary congestion) or, alternatively, if left ventricular filling pressure is elevated, pulmonary congestion and edema may occur, increasing respiratory and cardiac work (e.g., pulmonary congestion with or without peripheral hypoperfusion).

2.1. LEFT VENTRICULAR FILLING PRESSURE

For practical purposes, mean pulmonary artery wedge pressure is identical to pulmonary venous pressure and thus to the principal hemodynamic determinant of the passage of fluids from the vascular space into the pulmonary interstitial and intraalveolar spaces. The optimal level of left ventricular filling pressure in patients with acute myocardial infarction averages 15 ± 2 mm Hg [7]. If saline solutions (or dextran) are administered to patients with reduced filling pressures (i.e., less than 13 mm Hg), there is a direct relationship between increasing filling pressure and cardiac stroke work index until a left heart filling pressure of about 18 mm Hg is reached. Manipulations that increase filling pressure above this level tend to impair rather than improve cardiac performance.

2.2. RIGHT VENTRICULAR FILLING PRESSURE

When right heart filling pressures (right atrial pressure) are increased up to 6 to 8 mm Hg, cardiac performance generally improves; however, above that value, there is no further improvement in right ventricular function [7]. Therefore, if a patient has a pulmonary artery occlusive wedge pressure below 13 mm Hg associated with hypotension and tachycardia, a state of relative hypovolemia might exist. Improvement in cardiac performance can be expected with elevation of the left ventricular (or right ventricular) filling pressure to the optimal range. In patients whose left ventricular filling pressures exceed 18 mm Hg or whose

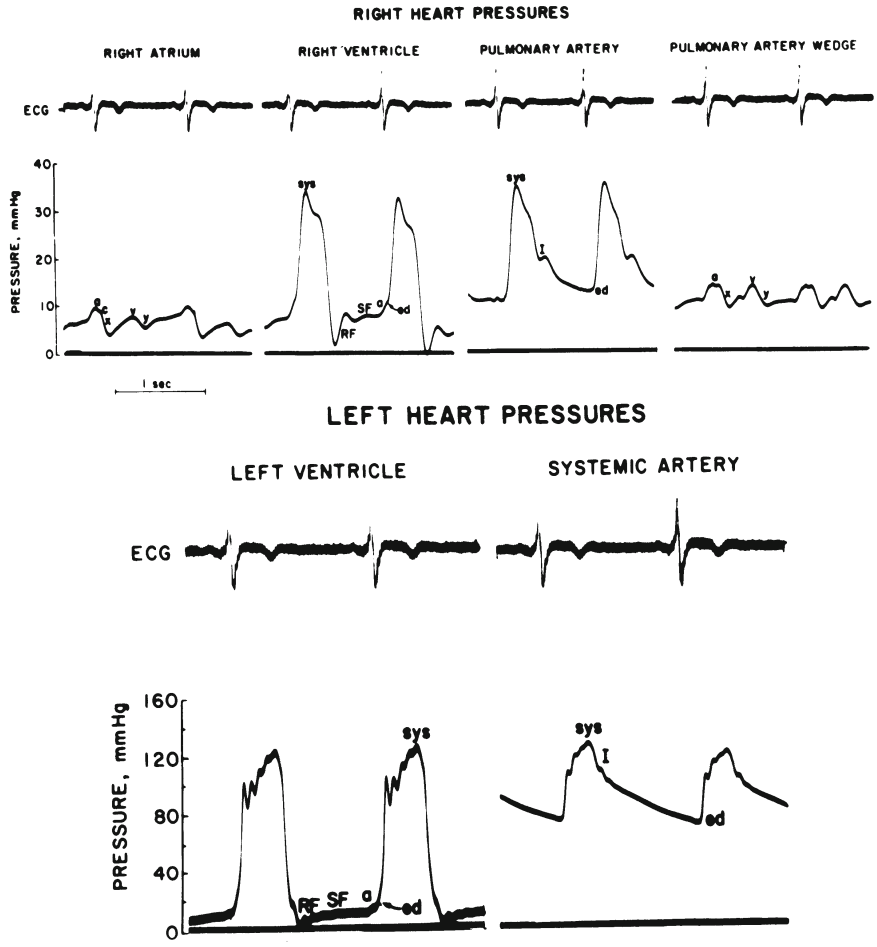

FIGURE 11–2. Intracardiac right heart and left heart pressures recorded with a fluid-filled catheter. The right atrial pressure waveform consists of a and v waves. The a wave immediately after the P wave in the ECG is due to atrial systole. The following decline in pressure (the x descent) shows a small positive deflection owing to tricuspid valve closure (the c wave). With atrial relaxation, right atrial pressure continues to fall even though the atrium is filling with blood. Eventually pressure in the atrium begins to rise, reflected by the v wave, which reaches its maximum just prior to opening of the tricuspid valve. With opening of this valve and emptying of the right atrium into the right ventricle, pressure in the atrium falls (the y descent). After the descent, right atrial pressure is equal to right ventricular diastolic pressure and slowly increases as the ventricle fills. The right ventricular waveform in diastole exhibits an early rapid filling wave (RF) followed by a slower filling wave (SF) and finally an atrial systolic wave (a). End-diastolic pressure of the right ventricle is measured immediately after the a wave (ed). The pulmonary artery exhibits a peak systolic pressure and an early diastolic pressure (ed), with an incisura (I) appearing when right ventricular pressure drops below pulmonary artery pressure and the pulmonic valve closes. Pulmonary artery wedge pressure should normally show a and v waves, reflecting left atrial systole and left atrial filling during left ventricular systole, respectively, and distinct x and y descents. One will also normally note respiratory variation in the pressure tracing. If vascular resistance in the pulmonary circulation is normal, end-diastolic pulmonary artery and mean wedge pressures will usually be nearly equal. Mean pulmonary artery pressure should always be higher than mean wedge pressure. The phases of left ventricular filling are the same as for the right ventricle, and the aortic pressure incisura (I) occurs at the time of aortic valve closure when left ventricular pressure falls below aortic pressure. (From Barry WH, Grossman W: Cardiac catheterization. In: *Heart disease*, 2nd ed, Braunwald E [ed], Philadelphia, WB Saunders Co, 1984, p 286.)

TABLE 11-3. Clinical and hemodynamic subsets and mortality rates

Clinical situation	Cardiac index ($L/min/m^2$)	Pulmonary capillary pressure (mm Hg)	Mortality (%)	
			Clinical subsets	Hemodynamic subsets
Normal hemodynamics	>2.2	<18	1	3
Pulmonary congestion without peripheral hypoperfusion	>2.2	>18	11	9
Peripheral hypoperfusion without pulmonary congestion	<2.2	<18	18	23
Combined peripheral hypoperfusion and pulmonary congestion	<2.2	>18	60	51

From Forrester JS, et al: Medical therapy by acute myocardial infarction by application of hemodynamic subsets. *N Engl J Med* 295:1356, 1976.

right ventricular filling pressures are high, after-load reduction of the ventricles may be appropriate.

For technical reasons it can be difficult to achieve accurate serial pulmonary artery wedge pressures and it is important to realize that an important relationship exists between pulmonary artery end-diastolic pressure and left ventricular end-diastolic pressure in patients with acute myocardial infarction. Usually, a direct linear relationship exists despite alterations in heart rate, changes in arterial oxygen tension, and the administration of various therapeutic agents. Conversely, this relationship does not exist if pulmonary vascular resistance is elevated or if the patient has mitral valve disease.

3. Balloon-Tipped Flow-Directed Catheters

The balloon-tipped flow-directed catheter usually passes easily through the right heart, even without fluoroscopic guidance. The inflated balloon at the tip of the catheter prevents the catheter tip from catching on cardiac structures during flotation or manipulation. The simple Swan-Ganz flow-directed catheter is made of polyvinyl chloride and has a soft, pliable shaft that becomes more flexible at body temperature. These catheters have a double lumen (a small one for balloon inflation and a larger one opening at the catheter tip for taking blood samples and measuring pressures). The adult external diameter sizes are No. 5 or 7 French and the catheter is radiopaque.

The catheter is inserted percutaneously or after venous cutdown. When inflated with 0.8 ml of gas (room air or carbon dioxide), the balloon protrudes above and around the tip of the catheter. Although room air may be used for inflation, it can be hazardous if the balloon ruptures when a right-to-left shunt exists or when the catheter is in the left heart (e.g., via a patent foramen ovale). Carbon dioxide diffuses through latex balloons, resulting in some deflation after 2 to 3 minutes. Balloon inflation must be gradual and pressures should be monitored continuously during passage of the catheter through the right heart. Characteristic pulmonary capillary wedge tracings can be confirmed when samples taken from the wedged catheter are fully saturated (e.g., 96%). (See chapter 9 regarding insertion of Swan-Ganz pacing catheters.)

Indications for inserting arterial lines and/or pulmonary artery catheters include hypotension or cardiogenic shock, severe left ventricular failure, persistent sinus tachycardia, refractory chest pain, and suspicion of significant mitral regurgitation or ventricular septal defect or pericardial effusion.

3.1. COMPLICATIONS OF FLOW-DIRECTED CATHETERIZATION

These include arrhythmias, pulmonary infarction (due to inadvertent prolonged wedging or emboli), infection, pulmonary arterial rupture,

balloon rupture, catheter knotting, pulmonic or tricuspid valve damage, or venous thrombosis (e.g., subclavian).

3.1.1. Arrhythmias. Arrhythmias are usually confined to ventricular premature beats as the catheter passes through the right ventricle but can be more serious if ventricular irritability complicates the early phase of acute infarction. Sometimes this is due to a tight loop of the balloon catheter as it passes from right atrium to pulmonary artery. Such arrhythmias can be minimized by injecting lidocaine intravenously (into the right atrium) before the balloon is inflated for passage to the pulmonary artery.

3.1.2. Prolonged Wedging of Catheters. Deflation of the balloon may not always allow withdrawal of the catheter from the pulmonary artery wedge position. Careful attention must be paid to the contour of the waveforms to ensure that the catheter is not persistently lodged in the wedge position, thus presenting the risk of pulmonary infarction. Once the pulmonary artery wedge and pulmonary artery end-diastolic pressures are calibrated and their relationship is determined, the catheter can reside in the proximal part of the main pulmonary artery (or in the right or left pulmonary artery) and hemodynamics may be monitored based on pulmonary artery diastolic pressure.

3.1.3. Infection. Infection is a potential hazard every time balloon-directed catheters are used. Provided that catheters are inserted under strict sterile conditions, with daily dressing changes, local application of an antibiotic to the cutdown site, and prompt removal of the catheter when intensive hemodynamic monitoring is not required, the likelihood of infection will be minimal.

3.1.4. Other Complications. Pulmonary artery rupture is a rare complication and has been reported only with larger angiographic balloon catheters. Balloon rupture of the Swan-Ganz catheter is not common provided that care is taken; knotting of the catheter can be avoided if fluoroscopy is used for optimal positioning of the catheter. Venous thrombosis of the subclavian vein has been reported after the use of right heart catheters.

Flow-directed catheters can provide important information after an acute myocardial infarction in patients with low output/hypoperfusion syndromes (to distinguish hypovolemia, cardiac tamponade, and inotropic failure) or syndromes with evidence of structural damage of the heart (to differentiate between mitral regurgitation and interventricular septal rupture) and can be used to diagnose and manage significant right ventricular infarction and noncardiogenic pulmonary edema ("shock lung").

4. *Measuring Cardiac Output by Thermodilution*

The thermodilution technique for measuring cardiac output involves use of a triple-lumen, flow-directed Swan-Ganz catheter. This catheter has one lumen for balloon inflation, a larger lumen that opens 30 cm from the catheter tip for injection of a cold indicator solution and a lumen at the tip for measuring pulmonary artery and wedge pressure. A thermistor to measure blood temperature is located 4 cm from the distal catheter tip. If performed carefully, the thermodilution method is accurate [8] and offers a number of advantages, such as avoidance of arterial puncture, simple and accurate calibration, and the fact that saline or 5% dextrose in water (whether at room temperature or ice cold) are good indicators.

As Forrester et al have described, marked discrepancies may be noted between clinical and hemodynamic assessments [2,3]. After the parenteral administration of diuretics such as furosemide, both pulmonary artery and wedge pressures can normalize despite the presence of rales in the chest and radiological signs of heart failure. Radiologic evidence of pulmonary edema or congestion may persist for up to 48 hours after the patient appears well clinically. Dyspnea and rales due to pulmonary disease may be associated with normal cardiovascular dynamics, and conversely, chronic compensated cardiac failure may be associated with a paucity of clinical signs in the presence of diminished cardiac output and abnormal ventricular filling pressures.

In a practical clinical sense, patients may be viewed as having one or more of the following:

5. *Hemodynamic Syndromes*

1. Normal hemodynamics.
2. A hyperdynamic circulatory state.
3. Hypovolemic hypotension.

4. Left ventricular failure.
5. Cardiogenic shock.
6. Right ventricular infarction.
7. Mitral valve insufficiency.
8. Ventricular septal rupture.

5.1. NORMAL HEMODYNAMICS

Patients with normal hemodynamics do not require any specific therapy. At present, the routine administration of beta-adrenoceptor blocking agents, calcium-channel blocking agents, or intravenous nitroglycerin to such patients cannot be recommended, although multicenter studies are now being carried out to assess this approach.

5.2. A HYPERDYNAMIC CIRCULATORY STATE

The hyperdynamic state may consist of sinus tachycardia, elevated arterial pressure, and an increased cardiac index. These appear to be manifestations of increased activity of the sympathetic nervous system in response to acute myocardial infarction. Logically, treatment with sedation and beta-adrenoceptor blockade has been adapted to reduce myocardial oxygen demands. Intravenous propranolol (if not contraindicated) may be administered in a total dose of 0.1 mg/kg divided into three equal doses given at 5-minute intervals. Clinical monitoring of heart rate, blood pressure, and lung fields is usually adequate for measurement.

5.3. HYPOVOLEMIC HYPOTENSION

Hypovolemia is a common cause of hypotension early after acute myocardial infarction. It is essential to recognize this disorder, since it can be readily corrected and is frequently overlooked. Invasive hemodynamic monitoring is necessary to document the presence of hypovolemia. Left ventricular filling pressures may be low, relatively normal, or even modestly increased compared with those in patients not suffering from acute myocardial infarction. However, because of reduced left ventricular compliance (or increased diastolic stiffness) due to infarction, filling pressures of at least 18 mm Hg may be necessary to optimize left ventricular performance. In other words, "normal" filling pressures may be inappropriately low after infarction. Clinically, such patients can exhibit sinus tachycardia, hypotension, clear lung fields (without evidence of left ventricular failure), low central venous pressure, and possibly diminished urine output.

If hypovolemia is documented, the fluid replaced should resemble the fluid lost — i.e., a low hematocrit should be corrected with an infusion of whole blood, while hypovolemia in the presence of a normal hematocrit should be corrected with crystalloid or colloid solutions. We measure cardiac output by the thermodilution technique and construct left ventricular function curves comparing cardiac outputs at various filling pressures to optimize hemodynamics on an individual basis.

5.4. LEFT VENTRICULAR FAILURE

The clinical signs and symptoms of left heart failure are related to the altered hemodynamics (reduced cardiac output and elevated pulmonary artery wedge pressure) and are proportional to, and a result of, cumulative damage to the left ventricle caused by the infarction. In patients with a history of previous infarction, it is not uncommon for a subsequent, relatively minor infarction to be associated with significant cardiac dysfunction. This relates to the cumulative ischemic damage incurred, which is the ultimate determinant of prognosis.

Although drugs with positive inotropic effects can be helpful, they are *not* the initial therapy of choice when left ventricular failure occurs in patients with acute myocardial infarction. Instead, meticulous attention should be paid to ventilation and to reducing blood volume and inappropriately elevated ventricular preload and afterload. Oxygenation may be impaired due to pulmonary vascular congestion, diminished pulmonary compliance, and respiratory depression accompanying analgesic therapy. Delivery of oxygen by face mask at high flow rates may be necessary. When the arterial oxygen saturation falls below 65 to 70 per cent despite inhalation of 100% oxygen delivered at 8 L/min by face mask, endotracheal intubation may be necessary. *Failure to ventilate* such patients early and adequately is all too common. Wheezing complicating pulmonary congestion should be treated with bronchodilating agents that cause the least cardiac stimulation. Thus, initial therapy should consist of isoetharine or metoproterenol aerosols followed by oral terbutaline and, finally, and intravenous infusion of aminophylline.

Patients with mild heart failure may be treated initially with intravenous diuretics such as furosemide in doses of 10 to 40 mg every 3 or 4 hours as needed. In addition to its diuretic action, furosemide decreases preload by directly

dilating peripheral veins and diminishing venous return. Lowering of pulmonary capillary wedge pressure and left ventricular wall tension will lead to clinical and hemodynamic improvements. Excessive diuresis (below left ventricular filling pressures of 18 mm Hg) may cause hypotension and tachycardia and should be avoided. In addition, hypokalemia should be prevented.

Although cardiac glycosides have been used for several decades in the treatment of patients with myocardial infarction, their continued use remains controversial [9]. In the absence of cardiac enlargement and congestive heart failure, administration of these drugs during acute infarction may actually increase infarct size and is therefore contraindicated. Some authors feel that digitalis is also not indicated in moderate to severe congestive heart failure, especially early in the treatment of acute infarction because of the potential development of cardiac arrhythmias or undesirable vasoconstriction (when the drug is administered rapidly intravenously) and the possible inability of ischemic tissue to respond to digitalis. However, digitalis glycosides continue to be indicated for the management of both arrhythmias (such as atrial flutter and fibrillation in order to slow the ventricular response) and heart failure that persists despite treatment with diuretic therapy after acute infarction [9].

Severe left ventricular failure is treated with a combination of beta-adrenoceptor agonists and vasodilators. The three most commonly employed positive inotropic agents are dopamine, the synthetic catecholamine dobutamine, and norepinephrine. As a group, these compounds have potent inotropic and pressor effects that increase vasoconstriction and the force of myocardial contraction. (Isoproterenol, which also has a marked inotropic effect, is not usually employed because of its potential vasodilatory effects and chronotropic properties, which may have adverse hemodynamic consequences that increase infarct size.) The various catecholamines differ in their relative cardiovascular effects and actions on vascular beds (e.g., renal vascular bed); the latter are summarized in table 11–4. The potentially deleterious alpha-adrenoceptor vasoconstrictor effects of dopamine and dobutamine fortunately occur only at relatively high doses. All catecholamines should be given carefully, with constant monitoring of the electrocardiogram, systemic arterial pressure, urine output, and (if possible) cardiac output and filling pressure of the left ventricle. Undue acceleration of the heart rate and initiation of ventricular arrhythmias should be avoided.

Heart failure complicating acute infarction is often associated with systemic vasoconstriction, which inappropriately elevates impedance and further depresses left ventricular performance. In this setting, drugs such as nitroprusside, nitroglycerin, and phentolamine can reduce high left ventricular filling pressures and maintain or increase cardiac output, particularly if arterial pressure is elevated. However, the use of agents with vasodilating properties during acute infarction may inappropriately lower systemic

TABLE 11–4. Sympathomimetic drugs

Receptor effects	Norepinephrine	Dopamine	Dobutamine	Isoproterenol
Alpha				
Arteriolar vasoconstriction	++++	++ Low dose +++ High dose	+	0
Dopaminergic				
Vasodilation in gut and kidney	0	++	0	0
$Beta_1$				
Increased myocardial contractility	++++	++++	++++	++++
Increased heart rate	+++	+++	++	++++
Increased AV conduction	++	++	++	++
$Beta_2$				
Arteriolar vasodilation	0	++	++	++++

Alpha stimulation: Vasoconstriction of peripheral arterioles. $Beta_1$ *Stimulation*: Increased heart rate, cardiac contractility, and atrioventricular conduction. $Beta_2$ *stimulation*: Vasodilation of arterioles and bronchodilation. *Dopaminergic stimulation*: Vasodilation of intestinal and renal beds.

arterial pressure (and hence coronary artery perfusion) and possibly reduce flow to ischemic areas of myocardium.

In the recently reported double-blind Veterans Administration Cooperative Study, the administration of intravenous sodium nitroprusside to patients with sustained, moderately severe elevation of pulmonary capillary wedge pressure may have had a beneficial effect on mortality rate [10]. It has been suggested that it would be prudent to confine infusion of sodium nitroprusside to patients with markedly elevated pulmonary artery wedge pressure (greater than 22 mm Hg) or who continue to have moderately elevated pulmonary wedge pressure (18 mm Hg more than 8 hours after the onset of the acute clinical event) [11].

5.5. CARDIOGENIC SHOCK

This serious hemodynamic complication of myocardial infarction may occur from extensive infarction and necrosis of ventricular myocardium. (Infarction of greater than 40 per cent of the left ventricular mass invariably results in shock and is usually fatal.) It may also be a consequence of a mechanical defect such as papillary muscle dysfunction, with mitral regurgitation, or ventricular septal rupture of the myocardium.

Cardiogenic shock is characterized by marked hypotension with systolic pressures less than 80 mm Hg and a striking reduction of the cardiac index (less than 1.8 L/min/m^2) in the face of elevated left ventricular filling pressures (pulmonary artery wedge pressures exceeding 18 mm Hg). Clinically, the patient appears cool and diaphoretic and may show mental obtundation, with a decreased urine output.

The diagnosis should be confirmed by means of careful hemodynamic monitoring. This is done to exclude spurious hypotension due to hypovolemia and to detect possible right ventricular infarction, mitral regurgitation, or a ventricular septal defect. In addition to insertion of a balloon flotation catheter for measuring right heart pressures and pulmonary artery wedge pressures, an intraarterial cannula should be inserted to monitor systemic arterial pressure and a urinary catheter should be placed to allow accurate quantitation of urine output. Arterial blood gases and electrolytes should also be measured in order to correct any serious derangements.

Because of uncertain or fluctuating metabolic and electrolyte status and renal perfusion, digitalis administration may be hazardous and is best avoided until the patient has been stabilized. An intravenous infusion of dopamine or dobutamine should be initiated at 2 to 5 μg/kg/min and titrated according to blood pressure and urine output. If systemic vascular resistance is not elevated, norepinephrine, which has both alpha- and beta-adrenoceptor agonistic properties, may be infused to correct hypotension in doses ranging from 2 to 10 μg/min.

For patients who fail to respond to the above measures and who are considered candidates for aggressive management, we utilize intraaortic balloon counterpulsation to increase diastolic coronary blood flow and to reduce afterload of the failing heart (see chapter 12).

5.6. RIGHT VENTRICULAR INFARCTION

The clinical significance of this syndrome was first described by Cohn et al [12]. Myocardial infarction most commonly involves the left ventricle and interventricular septum; however, the right ventricle is involved in about one-third of patients with inferior infarction. Among these patients, predominant right ventricular infarction occurs almost exclusively in those with transmural infarction of the inferoposterior wall and posterior portion of the septum [13]. While autopsy studies reveal that the right ventricular free wall is involved in 14 per cent of patients with left ventricular infarcts, the clinical incidence of predominant right ventricular dysfunction in all patients with acute myocardial infarction lies somewhere between 3 and 8 per cent [12,14].

Clinically, the syndrome of right ventricular infarction should be suspected in the presence of inferior or inferoposterior infarction along with elevated systemic venous pressure, clear lung fields, and frequently arterial hypotension. ST-segment elevation in lead V_4R may lead the clinician to consider this diagnosis. Lorell et al have provided hemodynamic information on patients with right ventricular infarction [14]. On average, right ventricular filling pressures are equal to or greater than left ventricular filling pressures. Others have confirmed and expanded on these hemodynamic features (table 11–5 and figure 11–3).

In the group of patients with dominant right ventricular infarction and hypotension, higher right ventricular end-diastolic pressures were noted (reflecting more extensive right ventric-

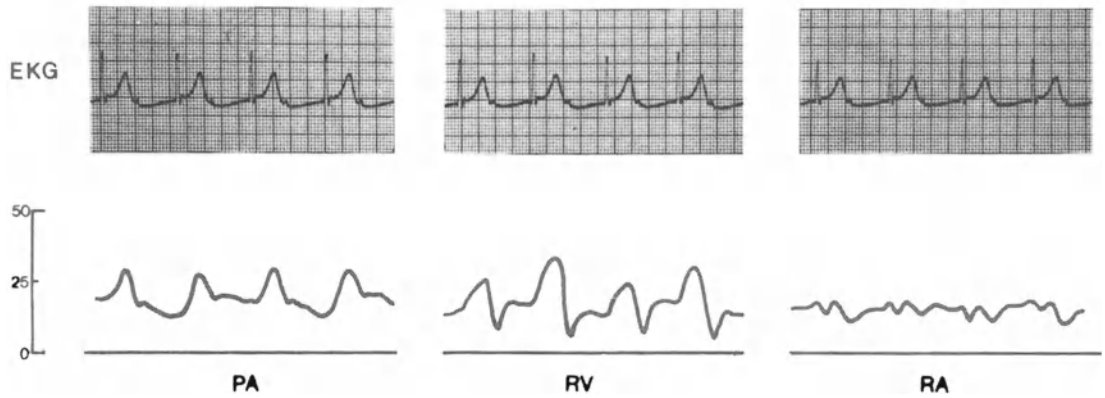

FIGURE 11–3. Swan-Ganz catheter tracings in a patient with right ventricular infarction. All pressures are displayed on a vertical scale of 0 to 50 mm Hg. Mean right atrial pressure (14 to 15 mm Hg) is elevated, and there is a prominent y descent in the waveform. The right ventricular pressure curve shows alternans owing to poor contractile performance of the infarcted chamber. In addition, early diastolic RV pressure is elevated (i.e., it does not approach 0 mm Hg as would be the case in constrictive pericardial disease, which can sometimes cause waveforms similar to those seen in RV infarction). Also, there is a "dip-and-plateau" pattern in the diastolic phase of the waveform. RV systolic pressure is low, and there is a narrow pulse pressure. The PA tracing also shows alternans, and PA diastolic and RV end-diastolic pressures are equal at about 15 mm Hg. Mean pulmonary capillary wedge pressure (not shown) was 12 mm Hg, completing the picture of predominant RV infarction.

TABLE 11–5. Hemodynamics of right ventricular infarction

Right atrial pressure	14 mm Hg
Right ventricular pressure	28/14 mm Hg
Pulmonary artery pressure	28/14 mm Hg
Pulmonary capillary wedge pressure	12 mm Hg
Systemic arterial pressure	95/60 mm Hg

Adapted from Lorell B, et al: Right ventricular infarction: Clinical diagnosis and differentiation from cardiac tamponade and pericardial effusion. *Am J Cardiol* 43:465, 1979.

ular damage) as well as higher pulmonary capillary wedge pressures (suggesting that additional inferior left ventricular dysfunction is a significant factor causing hypotension) [15]. If left ventricular dysfunction predominates, the only hemodynamic sign leading one to suspect right ventricular infarction may be a pressure waveform suggesting noncompliance of the right heart (i.e., the y descent is deeper than the x descent in the right atrial pressure tracing) [16].

On cardiac imaging, an enlarged, poorly contracting right ventricle is seen compared with a smaller, normally or near normally contracting left ventricle, and septal motion is often abnormal. This appearance is virtually pathognomonic of right ventricular infarction. The dilated and poorly contracting right-sided chamber observed with this technique differs strikingly from the small, vigorously contracting chambers seen in both cardiac tamponade and constrictive pericarditis, which at times can display hemodynamic features similar to right ventricular infarction. Echocardiography will almost always demonstrate increased right ventricular end-diastolic dimensions in the presence of right ventricular infarction.

The key to managing these patients includes correction of bradyarrhythmias, a trial of intravascular volume expansion in an attempt to increase the filling pressure of the left ventricle, since the right ventricle may be functioning almost as a passive conduit in this condition. Diuretic therapy is probably contraindicated if the wedge pressure is only mildly elevated and left heart filling is dependent on passive flow from the infarcted right heart. Pulmonary vascular resistance must be minimized by adequate oxygenation and, if necessary, after-

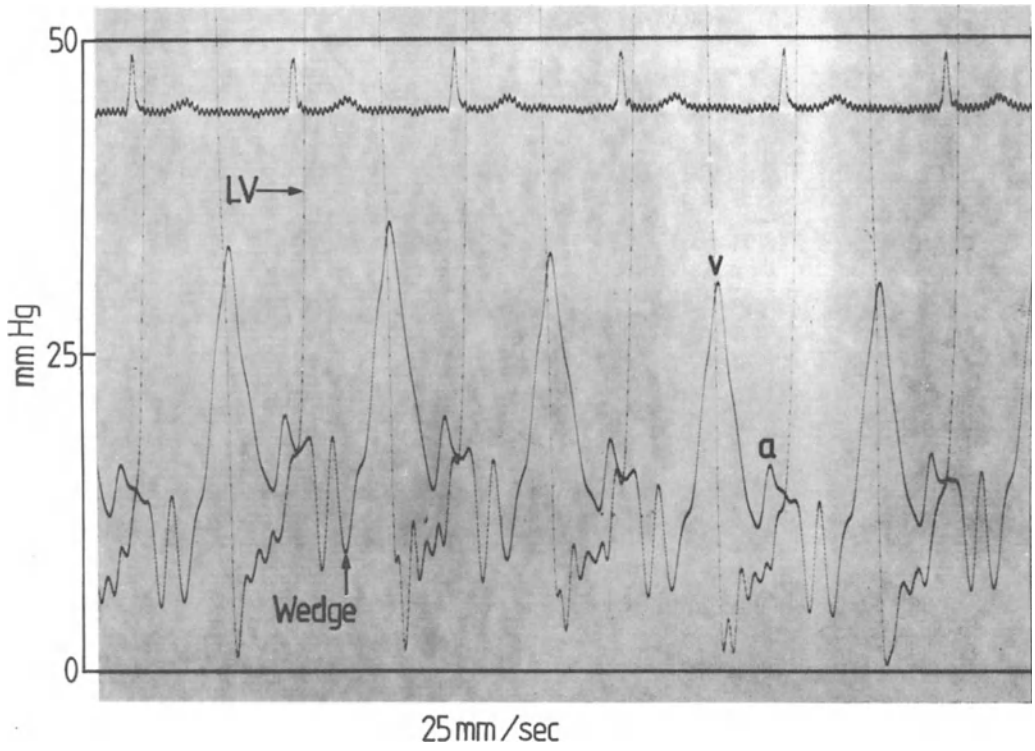

FIGURE 11–4. Simultaneous wedge and left ventricular pressures. The pressure gain is from 0 to 50 mm Hg and the paper speed is 22 mm/sec. Recordings are from a patient with acute mitral valve insufficiency. The v wave in the wedge tracing is on the order of 28 to 34 mm Hg, consistent with significant mitral regurgitation into a relatively noncompliant, small left atrium. A blood sample taken with the catheter in this wedge position was fully saturated with oxygen.

load reduction of the left ventricle. Agents that augment left ventricular emptying such as dopamine or sodium nitroprusside may encourage passive left ventricular filling and are particularly helpful if left ventricular dysfunction is significant [17]. If cardiac pacing is required, clinicians should consider AV sequential pacing, which may augment cardiac output, particularly in the presence of right ventricular infarction. A recent study revealed that the functional response of the right ventricle to infarction depends upon the site of the left ventricular infarction. Inferior infarction is generally associated with persistent impairment of right ventricular function as well as localized inferior left ventricular impairment, while anterior infarction is associated with persistent left ventricular regional impairment and transient global right ventricular impairment [18].

5.7. MITRAL VALVE INSUFFICIENCY

The diagnosis of acute mitral valve insufficiency complicating myocardial infarction is facilitated by use of the Swan-Ganz catheter. Giant regurgitant ("V") waves will be seen on the left atrial or pulmonary capillary wedge pressure tracing (figure 11–4). The normal v wave is due to the flow of blood from the pulmonary veins into the left atrium during left ventricular systole. While it is easy to envisage how giant V waves can be generated in acute mitral insufficiency, it is important to remember that normal pulmonary venous flow into a noncompliant left atrium (e.g., in left ventricular failure) or increased pulmonary flow (e.g., in ventricular septal defect [VSD]) can result in prominent V waves. Grossman notes that enormous V waves (greater than 50 mm Hg) can be seen in the absence of any mitral insufficiency when

TABLE 11–6. Minimal stepups in oxygen measurements required for oximetric detection of intracardiac left-to-right shunts

Reference	Age range (yr)	Technique of O_2 measurements	Method of comparison of samples*	*Level of shunt in right heart*					
				Atrium		Ventricle		Great vessels	
				Sat (%)	Content (vol %)	Sat (%)	Content (vol %)	Sat (%)	Content (vol %)
Present study	30 to 72	Whole blood oxygen fuel cell analyzer	Diff-Means	7	1.3	5	1.0	5	1.0
			Max-Diff	11	2.0	10	1.7	5	1.0
Dexter et al	7 to 57	Van Slyke	Max-Diff	—	2.0	—	1.0	—	0.5
Barratt-Boyes et al	13 to 44	Cuvette oximeter	Diff-Means of 2 paired samples	8	—	3	—	2	—
Rudolph et al	1 day to 50 years	Cuvette oximeter	1 pr samples	10	—	7	—	5	—
			2 pr samples	7	—	5	—	3	—
			3 pr samples	5	—	3	—	3	—
Freed et al	Pediatric age group	Reflectance oximeter or transmission spectrophotometer	Diff-Means	8	—	6	—	5	—

*Diff-Means = comparison of means of all values obtained in respective chambers; Max-Diff = comparison of maximal values obtained in two chambers.
From Antman EM, et al: Blood oxygen measurements in the assessment of intracardiac left to right shunts: A critical appraisal of methodology. *Am J Cardiol* 46:270, 1980.

infarction is complicated by VSD [19]. He suggests that when V waves are three times higher than the mean pulmonary capillary wedge pressure, severe mitral insufficiency is almost certain to be present; V waves twice as high as the wedge are suggestive of mitral insufficiency. Significant acute mitral insufficiency is unlikely to occur in the absence of a prominent V wave, although this has been known to be the case in the chronic form of this condition. Right-heart oximetry will fail to show a significant step-up in saturation at the ventricular or pulmonary artery level in the presence of mitral insufficiency. Indeed, pulmonary artery saturation may be very low if cardiac output in decreased. Thus, VSD with enormous V waves can be differentiated from acute mitral regurgitation; a significant step-up in saturation at the right ventricular or pulmonary artery level is the rule with VSD. Because of the expected amount of mixing of blood in the various right heart chambers, it is important to be aware of the criteria for a significant (e.g., greater than normal) step-up in oxygen saturation (table 11–6).

The severity of mitral insufficiency is determined by the clinical hemodynamic assessment and by left ventricular angiography. Although the angiographic assessment is subjective, the regurgitant fraction of blood passing through the mitral valve can be quantitated by calculating the forward stroke volume (using the Fick or indicator dilution technique) and the total left ventricular stroke volume (from the left ventriculogram). Thus, the regurgitant fraction can be calculated, and although its accuracy depends on a number of other variables, a fraction greater than 50% indicates significant mitral insufficiency. Assessments of left ventricular contractility, right heart pressures, and coronary anatomy will all be helpful if surgical intervention is contemplated. (See chapter 12, Complications of Acute Myocardial Infarction.)

5.8. VENTRICULAR SEPTAL RUPTURE

Rupture of the interventricular septum can occur as a complication of transmural anterior or inferior infarction. This usually occurs within a week of the event and is estimated to complicate 1 to 3 per cent of acute myocardial infarctions. With medical treatment alone, 80 per cent of patients die within 2 months and

over 90% within one year [20–22]. With the use of intraaortic balloon counterpulsation for support, cardiac investigations can be performed, surgical anatomy defined, and early surgical intervention contemplated [23–25]. The diagnosis is suspected after acute myocardial infarction when a new pansystolic murmur develops at the lower left sternal edge, often associated with a thrill. Sudden deterioration with left ventricular failure or hypotension should also alert one to this diagnosis.

When ventricular septal rupture is suspected, insertion of a Swan-Ganz flow-directed balloon-tipped catheter will confirm a significant step-up of oxygen saturation between right atrium and pulmonary artery; typical findings might include saturation of 48 per cent in the right atrium, 82 per cent in the pulmonary artery, and 94 per cent in the femoral artery. In the presence of a ventricular septal defect, pulmonary arterial blood will be at least moderately well saturated despite a low cardiac output, in contrast to the low saturation usually seen with significant mitral valve insufficiency. Cardiac catheterization is needed to show the contractile pattern of the left ventricle, the coronary artery anatomy and the presence or absence of associated mitral insufficiency. Early intraaortic balloon counterpulsation allows appropriate investigations to be performed at lower risk and permits cardiac surgery to proceed under optimal conditions. (See chapter 12, Complications of Acute Myocardial Infarction.)

6. *Arterial and Venous Access*

6.1. INSERTION OF ARTERIAL LINES

For pressure monitoring, arterial access is usually gained via the radial, brachial, or femoral artery. In most cases, percutaneous radial artery cannulation with a short 12- to 20-gauge plastic cannula will prove satisfactory. Brachial artery systolic, diastolic, and pulse pressures are all greater than central aortic pressure by a few millimeters of mercury. Occasionally, percutaneous femoral artery cannulation with monitoring of lower descending aortic pressure is required for accurate pressure monitoring, particularly in the setting of cardiogenic shock with marked circulatory collapse and peripheral vasoconstriction. Arterial lines can also be used to obtain samples for frequent blood gas measurements in extremely ill patients.

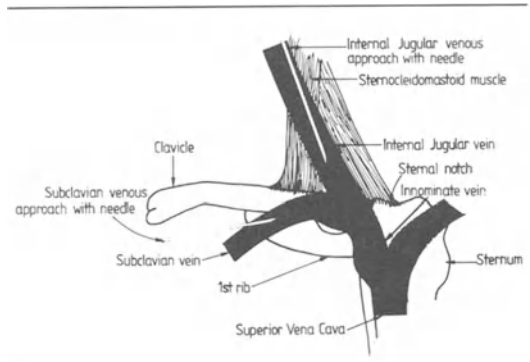

FIGURE 11–5. Venous access to the subclavian and internal jugular veins.

6.2. VENOUS ACCESS

Many veins can be used for access to the central venous system. In order of increasing risk, these include the median basilic vein, the external jugular vein, the internal jugular vein, and the subclavian veins. The femoral vein can also be used, but maintenance of a sterile entry site is difficult, movement of the patient's body is limited, and there is a risk of thrombosis. We do not recommend use of the cephalic vein, since manipulation of the catheter beyond the shoulder is often extremely difficult.

6.2.1. Percutaneous Puncture of the Subclavian Vein. With sterile technique, local anesthetic is injected inferior to the clavicle at the junction of the middle and inner third (figure 11–5). The patient is placed supine in a 15- to 20-degree head-down position. (If necessary, a small pad placed between the shoulder blades will allow the shoulders to drop posteriorly.) A skin incision is made, and a 14-gauge needle (about 2 inches long) attached to a small syringe is inserted through the skin, with the point of the needle aimed just behind the manubrium (the superior "crest" of sternum). (The operator's finger may be pressed into the suprasternal notch and the tip of the needle aimed toward the fingertip.) In this manner, the needle can be advanced, while hugging the inferior surface of the clavicle, over the first rib into the subclavian vein. Negative pressure is applied to the syringe, and successful entry into the vein will be noted upon the appearance of venous blood. The needle is advanced a little farther to ensure that it

is entirely within the lumen of the vein, and the syringe must then be removed from the needle hub. To avoid entry of air into the venous system, the hub of the needle is covered by the thumb or finger or, alternatively, the patient can be asked to perform the Valsalva maneuver, which will create a flow of blood out of the needle.

A radiopaque cannula is then introduced through the needle and threaded into the superior vena cava. The needle can be withdrawn and a plastic splint fitted over the junction of the needle and catheter to prevent the tip of the needle from piercing the catheter. At this point, the catheter can be used for infusions. Antibiotic ointment is applied at the site of the entry of the catheter into the skin and an occlusive dressing is placed. After the procedure, a chest x-ray is obtained to check the position of the cannula and to insure that pneumothorax has not occurred. Pneumothorax is the most common complication. As with other venous lines, the longer the cannula is in place the greater the risk of infection. When the venous cannula is removed, the tip should be routinely swabbed for microbiological examination. Other complications include hemothorax, air embolization, subcutaneous emphysema, and injuries to the subclavian artery and brachial plexus. The subclavian route is comfortable over the long term for patients who require large doses of drugs to treat infective endocarditis.

6.2.2. Internal Jugular Vein Cannulation. Percutaneous cannulation of the internal jugular vein is technically easier than subclavian vein cannulation, since the former is superficially located and the landmarks for access are definite. The patient should be supine, usually in a 15- to 20-degree Trendelenburg position, so that the neck veins are distended and visible during respiration. The internal jugular vein is located in the groove between the sternal and clavicular portions of the sternocleidomastoid muscle. The center of a triangle drawn from lines placed over these structures will be directly over the center of the internal jugular vein [26] (figure 11–5). The skin is infiltrated with local anesthetic at the apex of this triangle.

The needle is advanced at a 30-degree angle to the coronal plane and directed inferiorly. The carotid artery should be palpated to be sure that the point of the needle is not directed medially, since the common carotid artery lies medial and posterior to the internal jugular vein and might be punctured accidentally. If the internal jugular vein is not entered initially, the needle point is directed laterally by about 10 degrees. The catheter is then inserted through the needle and the needle is withdrawn. If an 8-inch catheter is used, the open end will be in or near the right atrium. Use of a sheath of appropriate size will facilitate flushing of the cannula and will ease insertion of either Swan-Ganz catheters or transvenous pacing catheters. The catheter should be secured to the skin near the puncture site.

Jernigan et al described a lateral approach for placing a venous catheter in the internal jugular vein [27]. The patient should be placed in a head-down position, with the head turned to the side opposite the cannulation, so that the veins will become distended. Infiltration of the skin with a local anesthetic is performed two fingerbreadths above the clavicle at the lateral border of the sternocleidomastoid. Since the vein lies slightly lateral to the midportion of this muscle, insertion of a needle passing from a point two fingerbreadths above the clavicle at the lateral border of the sternomastoid, just deep to the sternomastoid muscle and directed toward the suprasternal notch, should achieve access to the internal jugular vein.

If the right internal jugular vein is used, direct passage to the right atrium is more easily achieved than via cannulation of arm veins or leg veins. Placing the patient in a head-down position is essential to distend the neck veins and to avoid air embolization. The right internal jugular vein is preferred because both injury to the thoracic duct and a pneumothorax are less likely (since the dome of the pleura is higher on the left). Complications of internal jugular venous cannulation include hemopneumothorax, air embolization, carotid artery puncture, and neck hematomas.

6.2.3. The Brachial Approach. The usual method of exposing the brachial artery and basilic vein is by a cutdown in the antecubital fossa. After the brachial artery has been identified by palpation, a skin incision is made transversely proximal to the flexor sheath. The basilic vein and its branches lie superficial to the deep fascia and in a medial position. However, the brachial artery may lie under the biceps tendon and aponeurosis, so that slight rotation of the arm will make access easier. The tissues

are separated by blunt dissection, and the vein and artery are exposed and encircled by proximal and distal tapes or bands. It is important to expose and free up a reasonable length of artery and vein to allow easy access and repair. "Keyhole" incisions lead to trouble! Local anesthetic is infiltrated nearby, with additional doses administered around the exposed vessels and wound during the procedure. Using a needle or scalpel blade, one can gain access to either vessel and advance the cannulas. Vessels may be repaired with pursestring, interrupted, or continuous sutures. However, prior to repair, ascertaining proximal and distal free flow of arterial blood is mandatory. If this has not been achieved, a short metal probe can be passed proximally and distally or a Fogarty catheter can be used.

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12. COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION*

1. *Heart Failure*

Acute myocardial infarction is often accompanied by some degree of heart failure. In general, anterior infarction is associated with more severe pulmonary congestion than is inferior infarction. Inferoposterior infarction is occasionally associated with the syndrome of right ventricular infarction, i.e., hypotension with or without bradycardia, clear lung fields, and elevated right heart filling pressures. It is common for patients to have no symptoms of heart failure when an S_4 gallop rhythm is present (usually reflecting elevated left ventricular end-diastolic pressure) , and about half the patients with significant pulmonary congestion evident on chest x-ray have no abnormal physical findings.

The severity of hemodynamic abnormalities seen with either left or right heart failure is directly related to the cumulative extent of the infarction. The *Killip classification* of heart failure in patients with acute infarction is based mainly on the degree of left ventricular dysfunction and associated pulmonary congestion [1]:

Class I: No signs of heart failure.
Class II: Mild or moderate heart failure; rales over as much as 50 per cent of both lung fields.
Class III: Pulmonary edema; rales over more than 50 per cent of both lung fields.
Class IV: Cardiogenic shock; blood pressure by cuff less than 90 mm Hg; signs of inadequate peripheral perfusion (reduced urine flow, cold and clammy skin, cyanosis, and mental obtundation).

*This chapter provides a more detailed discussion of several of the topics covered in chapter 11.

Based on cardiac output and pulmonary capillary pressures, Swan et al have also identified four major hemodynamic subsets of acute infarction that reflect the clinical status of patients and degree of heart failure and indicate probable mortality (see chapter 11).

1.1. VENTILATION

Ventilatory management is crucial in the treatment of any degree of heart failure in patients with acute myocardial infarction. Hypoxemia is common and is usually secondary to ventilation-perfusion abnormalities, which are proportional to the severity of left ventricular failure. In such patients arterial oxygen tension correlates inversely with pulmonary artery diastolic pressure. Intrapulmonary shunting of blood has also been noted in patients with left ventricular failure complicating infarction.

If arterial oxygen tension is normal when the patient is admitted to the coronary care unit, oxygen therapy may be omitted. Obviously, augmenting the fraction of oxygen in inspired air will not significantly elevate oxygen delivery to tissues in patients who are not hypoxemic. In general, delivery of 2 to 4 liters/min of 100 per cent oxygen by mask or nasal prongs for 2 to 3 days is a satisfactory mode of therapy. If arterial oxygenation is still depressed on this regimen, the flow rate may have to be increased. If inhalation of 100 per cent oxygen, delivered at 8 liters/min by a face mask, fails to maintain arterial oxygen saturation above 65 to 70%, endotracheal intubation and assisted positive-pressure ventilation should be considered.

If wheezing complicates pulmonary congestion, bronchodilating agents that cause the least cardiac stimulation should be used initially, i.e., drugs with dominant actions on $beta_2$-

adrenergic receptors. Therefore, isoetharine or metaproterenol aerosols, followed by terbutaline administered orally and finally an intravenous infusion of aminophylline are recommended. These agents have fewer $beta_1$ agonist effects than agents such as isoproterenol and epinephrine and are less likely to provoke sinus tachycardia or ectopic tachycardias or to augment myocardial oxygen needs and intensify myocardial ischemia.

1.2. DIURETIC THERAPY

The next step in managing heart failure is to reduce blood volume and ventricular preload and afterload to appropriate levels. This is most effectively accomplished by diuretics. Intravenous administration of furosemide will reduce pulmonary vascular congestion and pulmonary venous pressure within 15 minutes, probably by its direct dilating effect on systemic venous beds. Initial doses of 10 to 40 mg of furosemide every 3 or 4 hours are usually appropriate. The lowered pulmonary capillary pressure and left ventricular wall tension result in clinical and hemodynamic improvement. Excessive diuresis (below a left ventricular filling pressure of 18 mm Hg) may cause hypotension and possibly hypokalemia, which is particularly hazardous in patients receiving digitalis (table 12–1).

1.3. DIGITALIS GLYCOSIDES

Cardiac glycosides have been used for several decades in the treatment of patients with acute myocardial infarction, and specific indications for their use have recently been refined [2]. In the absence of cardiac enlargement and congestive heart failure, digitalis glycosides may actually increase infarct size experimentally by increasing ventricular contractility and oxygen consumption. When heart failure is present, however, the diminution of heart size and wall tension frequently results in a net reduction in the myocardial oxygen requirement. Even so, some authors still feel that digitalis is contraindicated in moderate to severe heart failure, especially early in the treatment of acute infarction, because of the risk of cardiac arrhythmias or undesirable vasoconstriction (if the drug is administered rapidly intravenously) and the probable inability of ischemic tissue to respond to digitalis.

Most would agree that digitalis should be used to treat left ventricular failure unresponsive to diuretic therapy as well as in patients with atrial arrhythmias such as fibrillation or flutter (see chapter 4), which are usually associated with major infarctions and can be particularly harmful, since the rapid ventricular response increases myocardial ischemia and decreases cardiac output.

TABLE 12–1. Complications of furosemide.

Hypokalemia
Hyperuricemia
Hyperglycemia
Alkalosis
Deafness
Hepatic coma

1.4. OTHER DRUG THERAPY

More severe left ventricular failure is treated by a combination of beta-adrenoceptor agonists and vasodilators.

1.4.1. Beta-adrenoceptor agonists. The three most commonly employed agents are dopamine, the synthetic catecholamine dobutamine, and norepinephrine. As a group these compounds have potent inotropic and pressor effects that increase the force of contraction and vasoconstriction (table 12–2). Fortunately, the potentially harmful alpha-adrenoceptor vasoconstrictor effects of dopamine and dobutamine occur only at relatively high doses. The modes of action of norepinephrine and dopamine are illustrated in figure 12–1. All sympathomimetic amines should be given carefully, with constant monitoring of the electrocardiogram, systemic arterial pressure, pulmonary artery or capillary wedge pressure, and (if possible) cardiac output. Simple examples of calculations required for intravenous drug administration are showed in table 12–3. Undue acceleration of the heart rate and initiation of ventricular arrhythmias must be avoided.

Therapy with positive inotropic agents is usually necessary when the pulmonary capillary wedge pressure is at optimal or elevated levels and cardiac index is reduced below 2 liters/min/m^2 and/or systemic arterial pressure is lower than 90 mm Hg.

Dopamine can stimulate dopaminergic, alpha-adrenergic and beta-adrenergic receptors. In low doses (2 to 5 μg/kg body weight/min) the drug will increase coronary blood flow and myocardial contractility and induce peripheral

TABLE 12–2. Role of adrenergic and dopamine receptors

Actions of adrenergic and dopamine receptors			Relative actions on receptors		
Receptor	Location	Function	Norepinephrine (NE)	Dopamine	Dobutamine
Adrenergic Receptors					
β_1	Postsynaptic	Enhancement of cardiac contractility, heart rate, atrioventricular conduction	+++++	+++++ (50% due to NE release)	+++++
β_2	Postsynaptic	Vasodilation	-----	+	++
α_1	Postsynaptic	Vasoconstriction	+++++	++ to ++++ (with ↑ dose)	++
α_2	Presynaptic	Inhibition of norepinephrine release from sympathetic nerve endings	+++++	++ to ++++ (with ↑ dose)	-----
	Postsynaptic	Vasoconstriction			
Dopamine Receptors					
DA_1	Postsynaptic	Vasodilation (primarily in renal, mesenteric, coronary, and cerebral arterial beds)		++ to ++++ (with ↑ dose)	-----
DA_2	Presynaptic	Inhibition of norepinephrine release from sympathetic nerve endings; induction of emesis; inhibition of prolactin release	-----	+++	-----

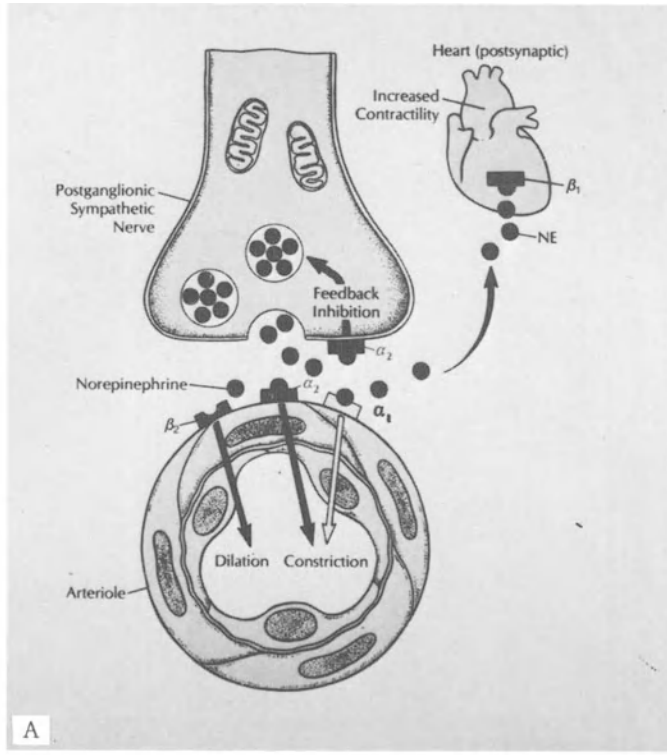
Absent action −, action present ++, slight action +++, moderate action ++++, major agonist +++++.
Adapted from Goldberg LI, and Rajfer SI: The role of adrenergic and dopamine receptors. *Hosp Prac* June 15, 1985, pp 67–80.

vasodilation (with an increase in renal blood flow) without much change in heart rate. In higher doses, activation of alpha-adrenergic receptors and $beta_1$ receptors causes systemic vasoconstriction (a reduction in renal blood flow) and tachycardia. The initial dose is usually 1 to 2 μg/kg/min with step increases to about 30 μg/kg/min. The aim is to reduce pulmonary capillary pressure to approximately 20 mm Hg and to elevate cardiac index to above 2 liters/min/m^2. With lower doses, the prominent nonadrenergic vasodilatory effect on peripheral vascular beds (particularly the kidney) and the positive inotropic effects on the heart generally improve hemodynamics and renal function (table 12–2). At higher doses, the potentially deleterious alpha-adrenergic vasoconstrictor effects exerted by dopamine may predominate.

Although *dobutamine* has comparable positive inotropic effect, it has little or no vasoconstrictor activity and a less prominent effect on heart rate and does not directly affect renal blood flow. Dobutamine may be administered at a starting dose of 2 to 5 g/kg/min and increased stepwise to a maximum of 30 g/kg/min.

1.4.2. Vasodilatory therapy. Myocardial oxygen requirements depend on left ventricular wall stress. Wall stress is proportional to the product of peak developed left ventricular pressure, volume, and wall thickness. Vasodilator therapy to reduce impedance to ventricular ejection and to increase stroke volume while reducing myocardial oxygen consumption is useful in patients with myocardial infarction complicated by hypertension, heart failure, mitral regurgitation, or a ventricular septal defect.

Careful hemodynamic monitoring is essential for the successful use of vasodilators to ensure that effective coronary perfusion pressure and ventricular filling pressures are maintained. Pulmonary capillary wedge pressure should be maintained at approximately 18 mm Hg and diastolic arterial blood pressure above 60 mm Hg in initially normotensive patients. In pa-


Heart (postsynaptic)
Increased Contractility
β_1
NE
Postganglionic Sympathetic Nerve
Feedback Inhibition
α_2
Norepinephrine
α_2
α_1
β_2
Dilation
Constriction
Arteriole
A

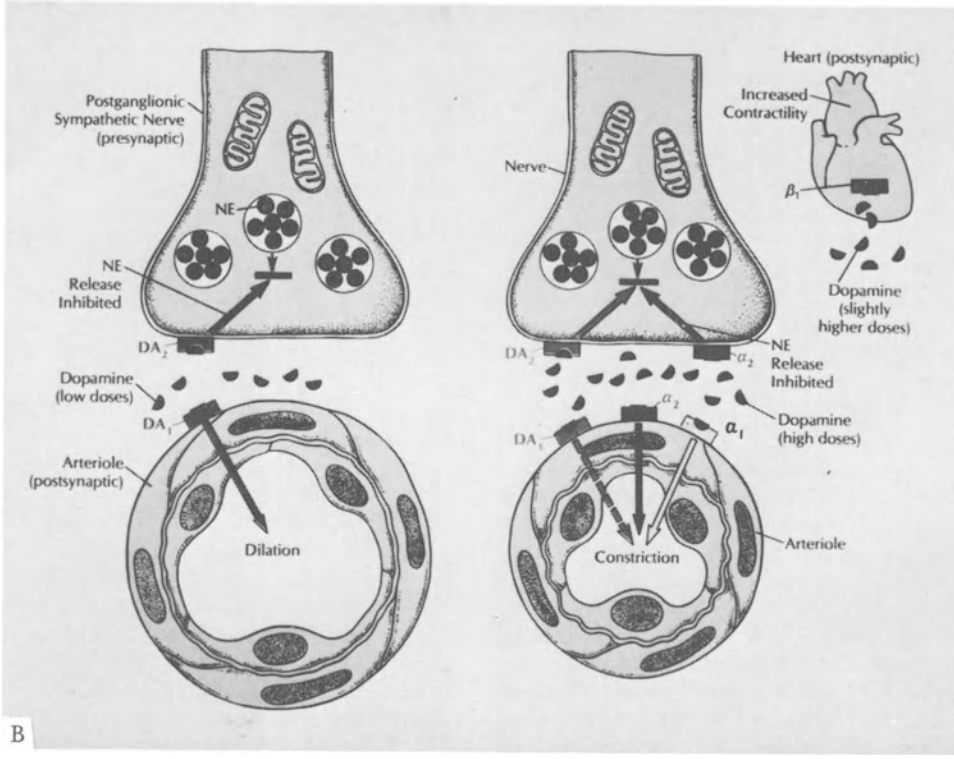

Postganglionic Sympathetic Nerve (presynaptic)
NE
NE Release Inhibited
DA_2
Dopamine (low doses)
DA_1
Arteriole (postsynaptic)
Dilation
Nerve
Heart (postsynaptic)
Increased Contractility
β_1
Dopamine (slightly higher doses)
DA_2
NE Release Inhibited
α_2
α_2
Dopamine (high doses)
DA_1
α_1
Arteriole
Constriction
B

TABLE 12–3. Calculations for intravenous drug administration

1. To calculate the *dose of drug* (μg/min) when the rate of infusion is known:

$$\text{Dose} = \frac{MR}{0.06\,V}$$

M = Mass of drug (mg) dissolved in volume (V) of fluid
R = Rate of infusion (ml/hr)
V = Volume of fluid in which drug is dissolved (ml)
(Formula is based on the assumption that the infusion pump delivers 60 microdrops per ml [60 mcgtt/ml].)
Example: Dopamine Hydrochloride (400 mg/5 ml) is made up to a solution of 400 mg in 250 ml. The rate of infusion (R) = 45 ml/hr. What is the dose of drug administered?

$$\text{Dose} = \frac{MR}{0.06\,V} = \frac{400 \times 45}{0.06 \times 250} = 1{,}200\ \mu g/min$$

If the patient weighs 65 kg (W):

$$\text{Dose} = \frac{MR}{0.06\,VW} = \frac{400 \times 45}{0.06 \times 250 \times 65}$$
$$= 18.5\ \mu g/kg/min$$

2. To calculate the *rate of drug infusion* to deliver a desired drug dose:

$$\text{Rate of drug infusion} = R = \frac{0.06\,DWV}{M}$$

R = Rate of drug infusion (ml/hr)
D = Drug dose (μg/min)
W = Weight of patient (kg)
V = Volume of fluid in which drug is dissolved (ml)
M = Mass of drug (mg) dissolved in volume (V) of fluid
Example: What is the rate of drug infusion required to deliver 5 μg/kg/min of dobutamine hydrochloride if 250 mg of the powder is made up to 500 ml with 5% dextrose in water?
If the patient weighs 72 kg:

$$R = \frac{0.06\,DMV}{M}$$
$$= \frac{0.06 \times 5 \times 72 \times 500}{250}$$

Rate of drug infusion = 43.2 ml/hr

FIGURE 12–1. *A*, In normal regulation of cardiac performance, the neurotransmitter norepinephrine (NE) is released from storage granules in cardiac sympathetic fibers to interact with β_1-adrenergic receptors so as to stimulate myocardial contractility. Generalized norepinephrine release from sympathetic nerve endings activates α_1 and α_2-adrenergic receptors on vascular smooth muscle cells to cause vasoconstriction, while NE binding to α_2-receptors on postganglionic sympathetic nerves inhibits further norepinephrine release from nerve endings to limit the vasoconstriction and the increase in cardiac contractility. Norepinephrine has insignificant actions on the β_2-adrenergic receptor that mediates vasodilation. *B*, Use of another endogenous catecholamine, dopamine, as a drug for heart failure is based on its actions on β_1-adrenergic receptors plus activation of specific dopamine receptors (DA_1 and DA_2). Dopamine (left), administered intravenously at low doses, acts on DA_1 receptors on the vascular smooth muscle cell and on postganglionic DA_2 receptors to inhibit norepinephrine release, thereby producing vasodilation. Slightly higher doses of dopamine (right) activate β_1-receptors and stimulate the heart, chronotropically as well as inotropically. In addition to these receptors, α_1- and α_2-receptors on the vascular smooth muscle cell are activated with large doses of dopamine to cause vasoconstriction, which thus masks the DA_1- and DA_2-mediated vasodilation; α_2-receptors on postganglionic sympathetic nerves are also activated to inhibit norepinephrine release. The synthetic catecholamine dobutamine acts on cardiac β_1-receptors and also on both α_1- and β_2-receptors on the vascular smooth muscle cell. Thus, it increases contractility of the heart without directly altering vascular resistance. (From Goldberg LI, Rajfer SI: The role of adrenergic and dopamine receptors. *Hosp Pract* June 15, 1985, pp 67–80.)

tients receiving large doses of diuretics, one must prevent excessive contraction of the effective circulating plasma volume when vasodilator therapy is initiated. Commonly, diuretic dosage needs to be decreased to avoid prerenal failure, hypotension, and tachycardia. Certainly the patient's weight, hematocrit, and renal function should be closely monitored.

While reducing peripheral vascular resistance and left ventricular afterload appears to be a major mechanism of action of arterial vasodilators, these agents may also dilate coronary arteries directly, thereby improving blood flow to ischemic areas of myocardium. This has been documented arteriographically in patients with coronary artery spasm in the setting of acute myocardial infarction. Vasodilator drugs vary in their effect on normal and abnormal vessels, in that certain conditions may potentially cause a "coronary steal." This occurs with dilation of coronary resistance vessels in nonischemic regions of the heart, producing a fall in the perfusion pressure proximal to areas of atherosclerotic narrowing. The most widely used vasodilators are sodium nitroprusside and nitroglycerin.

Nitroprusside increases cardiac output in patients with acute infarction complicated by left ventricular failure and reduces arteriolar resistance, impedance to left ventricular ejection, pulmonary capillary wedge pressure, and thus myocardial oxygen requirements. This drug may augment cardiac output even in patients with cardiogenic shock if arterial diastolic and coronary perfusion pressures are maintained by concomitant aortic balloon counterpulsation. Experimentally, coronary artery steal has been demonstrated after administration of nitroprusside. Initial doses are usually 0.5 μg/kg/min with a gradual increase to about 1.5 μg/kg/min.

Commercially available intravenous nitroglycerin administration kits are now marketed, although intravenous *nitroglycerin* preparation can also be derived from nitroglycerin tablets. Nitroglycerin tends to cause a greater reduction in left ventricular filling pressure than does nitroprusside because of its relatively greater effect on venous capacitance vessels. In contrast to nitroprusside, intravenous solutions of nitroglycerin do not need to be protected from exposure to light. Of great importance is the fact that nitroglycerin avidly adheres to polyvinylchloride intravenous tubing, a property that can affect dosage. Therefore, the minimum amount of tubing necessary for infusion should be used unless the nonpolyvinylchloride tubing supplied in the commercially available kits is employed.

Continuous infusions of nitroglycerin are generally begun at 10 to 15 μg/min and increased by 5 to 10 μg/min every 3 to 5 minutes in conjunction with careful hemodynamic monitoring. The dose is titrated based on the severity of angina, blood pressure, heart rate, and the development of headache. In the setting of acute infarction, it is wise not to allow heart rate to increase by more than 5 to 10 bpm or for arterial pressure to fall substantially. Potential complications of intravenous nitroglycerin include reversible hypotension and bradycardia, hypoxemia due to increased pulmonary ventilation-perfusion mismatch, methemoglobinemia, and headache. Recently, Yusuf and Collins pooled the results of randomized, controlled trials of intravenous nitroglycerin and nitroprusside therapy in acute myocardial infarction. Their rationale was that the individual trials have been too small to detect moderate reductions in mortality and thus, by pooling the results and using retrospective stratification, mortality information could be derived (table 12–4). Such analyses should be interpreted cautiously, however, for seven randomized studies of intravenous nitroglycerin administered following acute myocardial infarction, the mortality appeared to be reduced by approximately 30%. Using similar methodology, the effects of nitroprusside on mortality following acute myocardial infarction were studied in three randomized studies. However, the results were less compelling that this had a beneficial effect.

After initial stabilization of the patient, oral vasodilator therapy can be prescribed. Useful agents for this later phase of therapy include Isordil Tembids, 40 mg every 6 hours, or hydralazine, 10 to 50 mg orally 4 times daily. Newer agents such as prazosin and captopril are being used extensively in patients with chronic heart failure, but their role is yet to be defined in patients with acute myocardial infarction. The newer antianginal agent nifedipine can also be effective as an afterload-reducing agent in doses of 10 to 30 mg every 6 hours.

2. *Cardiogenic Shock*

Cardiogenic shock is an often fatal result of extensive myocardial infarction. Autopsy studies reveal that necrosis of at least 40 per cent of the left ventricular myocardium is a common feature. A shock state in patients with myocardial infarction appears to be a part of the vicious cycle of coronary obstruction leading to myocardial ischemia, which impairs myocardial contractility and ventricular performance and in turn reduces arterial pressure and therefore coronary perfusion pressure. This results in further ischemia and extension of necrosis until the left ventricle has insufficient contracting myocardium to sustain life. In most patients with cardiogenic shock there is significant stenosis in the major coronary vessels, usually including the left anterior descending coronary artery, and thrombosis of arteries supplying a major region of recent infarction. At autopsy, however, marginal extension of recent infarcts is a consistent finding. Focal necrosis is often noted in regions of the heart that are not adjacent to the major area of recent infarction and is probably due to the shock state itself.

Cardiogenic shock is characterized by systolic arterial pressure below 80 mm Hg, and a reduction in cardiac index to less than 1.8 liters/min/m^2 in the face of an elevated left ventricular filling pressure that exceeds 18 mm Hg.

Current modes of therapy include inotropic agents and vasodilators used in conjunction with intraaortic balloon counterpulsation (see below). Usually systemic arterial resistance will be elevated; if not, phenylephrine (which has both alpha- and beta-adrenoceptor agonistic properties) can be employed to increase arterial diastolic pressure, maintain coronary perfusion, and improve contractility (0.5 to 1.0 μg/kg/min).

Although modern invasive monitoring has allowed us to identify and treat various syndromes that can cause cardiogenic shock (e.g., hypovolemia, right ventricular infarction, ventricular septal rupture, papillary muscle rupture), survival is unlikely regardless of interventions when this condition is due to extensive, cumulative myocardial damage. Thus, the overall mortality rate is still 80 to 90 per cent. The use of intraaortic balloon counterpulsation has not substantially improved this extremely high mortality rate.

2.1. INTRAAORTIC BALLOON COUNTERPULSATION

This technique is utilized to treat acute myocardial infarction in three circumstances.

1. Cardiogenic shock unresponsive to medical treatment.

2. The presence of persistent ischemic pain during the postinfarction state.

3. Acute infarction in which the patient is hemodynamically unstable and requires support of the circulation during diagnostic studies to assess lesions that might be surgically corrected (e.g., mitral valve insufficiency, ventricular septal defect).

By either percutaneous entry or direct surgical cutdown, the intraaortic balloon is advanced from the femoral artery to the descending thoracic aorta and is timed to inflate with helium, a low-viscosity inert gas that moves rapidly, and to deflate in a cyclical manner. The balloon displaces a volume of blood from the thoracic aorta equal to the balloon volume. By timing the balloon to inflate at the moment of aortic valve closure (as noted from the ECG and arterial pressure pulse tracings), aortic diastolic pressure can be increased by 10 to 15 mm Hg (figure 12–2). Deflation occurs just prior to aortic valve opening, so that during systole left ventricular work diminishes. Therefore, the balloon acts to reduce oxygen demand and increase oxygen supply. An example of physicians orders for this form of treatment is provided (figure 12–3).

If the flow in the coronary arteries is pressure-dependent (e.g., in the presence of stenosis), intraaortic balloon counterpulsation will augment diastolic coronary flow. If cardiac output is diminished, owing to either left ventricular failure or severe myocardial ischemia, this maneuver will increase output by reducing afterload. In the presence of ischemia, the increased diastolic perfusion pressure of the coronary arteries will improve myocardial oxygenation.

Experimentally, balloon counterpulsation decreases afterload, preload, and myocardial

TABLE 12–4. Effect of IV Nitroglycerin on mortality

Study	Treatment	Placebo	Observed-expected mortality	Variance
Bussman	0/31	5/29	−2.6 ($p < 0.05$)	1.2
Chiche	3/50	8/45	−2.8	2.5
Jaffe	4/57	2/57	+1.0	1.4
Lis	5/64	10/76	−1.9	3.3
Flaherty	11/56	11/48	−0.8	4.3
Jugdutt	15/156	38/154	−11.7 ($p < 0.05$)	11.0
Korewicki	36/108	33/98	−0.2	11.5
	74/522 (14%)	107/507 (21%)	−19.0	35.2

POR = Pooled Odds Ratio = 0.66 (95% confidence 0.52 − 0.83, $p < 0.001$)
IV nitroglycerin appears to reduce mortality by about 30%

Calculation of observed-expected mortality

Study	Treatment	Placebo	O − E Mortality
Jugdutt	15/156	38/154	−11.7

O = Observed deaths in treated patients = 15
E = Expected number of deaths

$$= \frac{\mathcal{N} \cdot D}{N} = \frac{156.53}{310} = 26.7$$

$\mathcal{N}$ = treated patients = 156
D = total deaths = 53
N = total patients = 310

O − E = 15 − 26.7 = −11.7
Note: • If treatment does not affect mortality then O − E = zero
• If treatment is beneficial then O − E = negative
Adapted from Yusuf and Collins: *Circulation* 72 (Suppl III) 1985 (Abstract), Page 224.

oxygen consumption and increases coronary flow with an improvement in cardiac performance. The balloon appears to protect ischemic myocardium in experimental animals, based on analysis of myocardial creatine kinase depletion, ST-segment elevations, and histochemical and histological criteria of necrosis. There are no data suggesting that balloon counterpulsation alters the prognosis in patients with uncomplicated myocardial infarction; indeed, it is likely that the risks in such cases would outweigh the potential benefits.

This mode of therapy has a definite role (1) in stabilizing patients with severe unstable angina in whom maximal medical therapy has failed to control recurrent ischemia, (2) in patients with acute infarction in one area of myocardium who exhibit symptoms and ECG and hemodynamic evidence of a threat to large areas of myocardium in another location, and (3) in patients with intermittent global ischemia who must be stabilized prior to coronary angiography and possible revascularization.

Intraaortic balloon counterpulsation should be considered in cardiogenic shock (figure 12–4) and in myocardial infarction complicated by ventricular septal defect or severe mitral insufficiency. Since medical treatment of ventricular septal defect in this setting is associated with a high mortality, this maneuver will allow one to assess both ventricular function and coronary anatomy under relatively stable circumstances and to evaluate the feasibility of surgery.

For obvious reasons, intraaortic balloon counterpulsation is contraindicated in the presence of aortic valve insufficiency or aneurysms of the ascending aorta. Tachycardia is a relative contraindication, since augmentation of flow using the balloon may be impossible at rapid ventricular rates.

Insertion of the balloon by either direct exposure of the femoral artery or percutaneously carries the risk of arterial injury, aortic dissection, loss of distal pulses in the leg, infection, and perforation of the aorta. Even in experi-

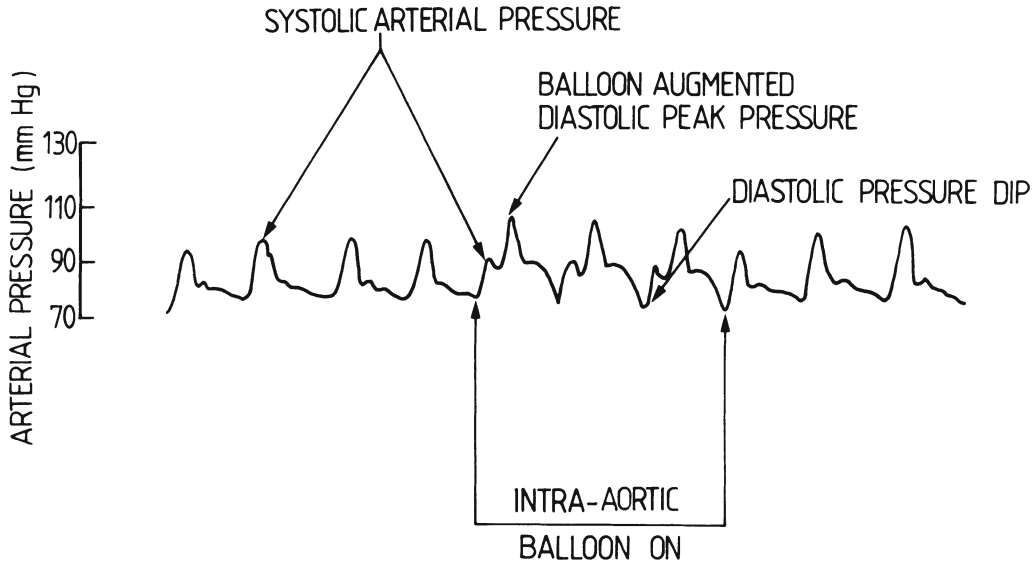


FIGURE 12–2. Arterial pressure tracing before, during, and after intraaortic balloon counterpulsation (IABP). The augmented peak diastolic arterial pressure will have a salutary effect on coronary blood flow; the fall in peak arterial pressure during counter-pulsation reflects afterload reduction.

Brigham and Women's Hospital
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PHYSICIAN'S ORDERS

Drug Allergies: _____

DATE	TIME	IABP STANDING PHYSICIAN'S ORDERS	POSTED
		DRAW A LINE THROUGH ORDERS WHICH DO NOT PERTAIN TO YOUR PATIENT	
		I. NURSING CARE ORDERS	
		1. BP, HR, RR ql hr; PAP q 1 hr; PCWP q 2 hr; Temp q 4 hr	
		Pedal pulses q 2 hr; OTHER _____	
		2. Bedrest; HOB elevated no greater than 30°; prevent hip Flexion	
		3. Balloon ratio is at (1:1, 1:2, 1:4) (please circle)	
		4. Evaluate IABP timing initially and q shift and adjust as needed	
		5. Maintain clear ECG and Arterial tracings for accurate signal for timing and tracing	
		6. Check Helium Tank q day and replace if pressure < 20PSI	
		7. Change Occlusive dressing q 48 hrs	
		8. Observe skin integrity by: tilting patient from side to side ql hr and massage back;	
		use air mattress or sheepskin; use heat pads prn	
		9. Keep comfortable with sedation as PRN orders	
		Explain routine & allow for pt. decisions if possible	
		10. Restrain leg	
		II. MEDICATIONS	
		1. Antibiotic:	
		2. Anticoagulant:	
		III. STUDIES	
		1. Daily CBC c diff, Platelets, BUN, Creat, PT, PPT	
		2. Daily Electrolytes and Cardiac enzymes	
		3. Type & X match for 1 unit of red blood cells	
		4. ABG's (how often?):	
		5. EKG QD and port. chest film stat β insertion and daily	
		(con't) _____, M.D.	

IMPORTANT — BE SURE TO IMPRINT PATIENT IDENTIFICATION

Brigham and Women's Hospital
A Teaching Affiliate of Harvard Medical School

PHYSICIAN'S ORDERS

Drug Allergies: _____

DATE	TIME	IABP STANDING PHYSICIAN'S ORDERS (PAGE 2)	POSTED
77		**IV. NOTIFY H.O. FOR:**	
		1. MAP > or < mg. Hg.	
		PCWP > or < mg. Hg.	
		Temp > 37.5° C PO	
		HR > or beats/min.	
		Serum K + > or < Meq.	
		Urine Output < 30cc/hr for two consecutive hrs.	
		New onset of back pain	
		_____, M.D.	

IMPORTANT — BE SURE TO IMPRINT PATIENT IDENTIFICATION

FIGURE 12–3. Example of physician's orders.

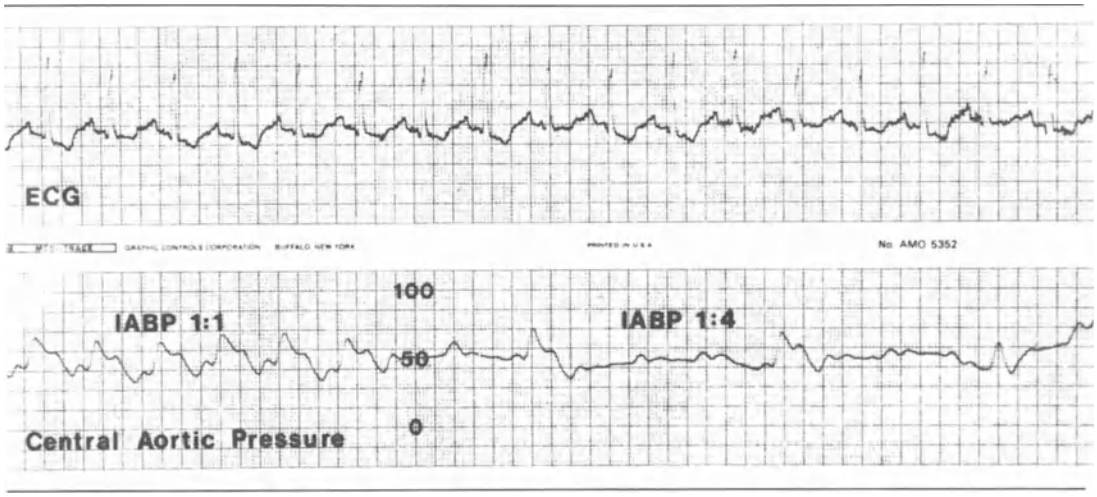

FIGURE 12–4. This 52-year-old man suffered an extensive anterior myocardial infarction and developed cardiogenic shock. An intraaortic balloon pump (IABP) was inserted (via the right femoral artery) and provided marginal hemodynamic support even with pumping in the 1:1 mode. The marked left ventricular power failure is especially evident from inspection of the central aortic pressure tracing with the IABP in the 1:4 mode. Unfortunately, no mechanical defects such as papillary muscle dysfunction or a ventricular septal defect were found and the patient died shortly after these recordings were made. As evidenced by this case, IABP support is usually not successful in treating cardiogenic shock due to global infarction.

enced hands, percutaneous insertion presents the same risk as conventional insertion, so that the ease of the percutaneous procedure does not constitute grounds for liberalizing indications in patients who can be managed without balloon counterpulsation.

3. *Arrhythmias (See chapter 4)*

4. *Ventricular Septal Rupture*

The condition probably complicates about 3 per cent of acute myocardial infarctions, with perforation usually occurring within the first week [3,4]. The prognosis is poor — about 80 to 90 per cent of patients managed medically die within 2 months [3,5]. Ventricular septal rupture is less common than rupture of the ventricular free wall, with which it is sometimes associated.

4.1. DIAGNOSIS

Acute myocardial infarction associated with ventricular septal rupture is usually a Q-wave infarction and is often the patient's first [4,6]. Septal rupture usually occurs in one of two locations and corresponds with the site of the infarct as detected on the electrocardiogram. With inferior and inferoposterior infarctions, rupture involves the inferobasilar septum. These infarcts more commonly involve the posterior papillary muscle and result in mitral insufficiency, making surgical repair technically more difficult. Anterior infarctions are associated with rupture in the anterior or apical septum.

Ventricular septal rupture is often preceded by chest pain, and invariably a new systolic murmur is heard. Sometimes the murmur is first heard after cardiopulmonary resuscitation. In about half the patients, a thrill accompanies the murmur, and it is often said that a loud murmur, maximal at the edge of the sternum and accompanied by a thrill, is virtually diagnostic of this condition [7]. Some have noted that neither the location of the murmur nor the existence of a thrill helps to distinguish patients with ventricular septal rupture from those with acute mitral insufficiency [4,8].

A *pansystolic precordial murmur* may be associated with a variety of conditions:

1. Mitral valve dysfunction complicating acute infarction due to papillary muscle dysfunction, chordal rupture, or rupture of the belly of the papillary muscle. The associated murmur is usually heard at the cardiac apex and transmitted to the axilla but may be transmitted to the sternal edge. Mitral dysfunction is usually associated with inferior or inferoposterior infarction. (Ventricular septal rupture occurs in inferior and anterior infarctions with equal incidence.) Presence of a thrill is unusual with papillary muscle rupture.

2. Tricuspid valve dysfunction associated with right ventricular infarction, in which the pansystolic murmur is heard at the left sternal edge.

3. A pericardial friction rub complicating acute infarction. This may simulate a systolic murmur and is best heard at the left sternal edge. A friction rub will usually change somewhat with postural changes and is usually a more superficial sound. The atrial systolic and ventricular diastolic components can often be identified upon careful auscultation during inspiration.

4. Rupture of the free wall, which can be accompanied by a murmur and a thrill.

Right-sided heart failure may overshadow left-sided heart failure in many patients with ventricular septal rupture. In such cases, jugular venous and right atrial pressures are almost always elevated despite an only modest elevation in left atrial pressure. For this reason the signs and radiological findings of pulmonary venous hypertension are not usually striking [4,8,9]. Increased vascularity and pulmonary markings consistent with plethora are obvious in about half these patients. Cardiogenic shock, which may be seen in about 50 per cent of cases, is a major determinant of prognosis. Impaired right ventricular function is probably as important as (if not more important than) impaired left ventricular function in the pathogenesis of shock complicating ventricular septal rupture [4].

When ventricular septal rupture is suspected, insertion of a Swan-Ganz flow-directed balloon-tipped catheter at the bedside will promptly confirm the diagnosis by revealing a step-up in oxygen saturation from the right atrium to the pulmonary artery [10]. (The formulas for calculating the shunt are noted in table 12–5.) An example of such a situation is provided in the accompanying case history. Any new systolic murmur, with or without a thrill, or any evidence of hemodynamic deterioration with the onset of hypotension or LV failure should cause the clinician to consider the diagnosis of ventricular septal rupture complicating acute infarction.

Case History:
A 69-year-old man experienced a one-hour episode of chest pain 3 months prior to hospital admission with a history of increasing shortness of breath, orthopnea, and nocturnal dyspnea. A new systolic heart murmur was heard and a thrill felt at the left sternal edge. The ECG showed Q-wave inferior infarction, and cardiomegaly, pulmonary edema, and pleural effusions were evident on chest x-ray.
Results of Cardiac Catheterization:
LV ejection fraction = 52%
Diastolic volume = 278 ml
Systolic volume = 134 ml

Pressures (mmHg)		O_2 *Saturation:*
Left ventricle	95/17	97%
Mean pulmonary artery	52/15	87%
Right ventricle	52/12	88%
Right atrium	8	58%
Superior vena cava		57%
Inferior vena cava		59%

Hb = 14.3 g/dl. BSA = 1.8 m^2
O_2 consumption = 178 ml/min

$$\text{Systemic blood flow } (Q_s) = \frac{178 \text{ ml/min}}{(0.97 - 0.58) \times 14.3 \times 10 \times 1.36} = 2.3 \text{ L/min} = 1.3 \text{ L/min/m}^2$$

$$\text{Pulmonary blood flow} = \frac{178 \text{ ml/min}}{(0.97 - 0.87) \times 14.3 \times 10 \times 1.36} = 9.1 \text{ L/min} = 5.7 \text{ L/min/m}^2$$

$$\frac{Q_p}{Q_s} = \frac{3.8}{1.0}$$

Left ventricular angiography revealed a large inferior infarct and an inferior ventricular septal defect. The right coronary artery was occluded proximally, and

TABLE 12–5. Calculation of a left-to-right shunt due to ventricular septal rupture

Standard flow equations:

$$\text{Systemic Blood Flow } (Q_s) = \frac{\text{Oxygen consumption (ml/min)}}{\text{Systemic arterial } O_2 \text{ content} - \text{Mixed venous } O_2 \text{ content}}$$

$$\text{Pulmonary blood flow } (Q_p) = \frac{\text{Oxygen consumption (ml/min)}}{\text{Pulmonary venous } O_2 \text{ content} - \text{Pulmonary artery } O_2 \text{ content}}$$

These equations are derived from the principle that the total uptake or release of any substance (in this case oxygen) by an organ is the product of the blood flow to the organ and the arteriovenous concentration difference of the substance.

In practice, the rate of oxygen consumption by blood from the lungs is not measured but rather the uptake of oxygen from room air by the lungs is measured. In a steady state, these measurements are equal. Generally pulmonary venous blood is not sampled for oxygen content; instead, systemic arterial blood is sampled and assumed to have an oxygen content representative of mixed pulmonary venous blood. (Because of brachial venous and thebesian drainage, the oxygen content of systemic arterial blood is lower than pulmonary venous blood as it leaves alveoli; if a right-to-left shunt is present, the assumption is clearly not valid. If the systemic arterial oxygen saturation is 95% or more, it is assumed that a right-to-left shunt is not present.)

Oxygen consumption is estimated by measuring the oxygen extracted by the lungs over a given "steady state" time period.

$$O_2 \text{ content of room air} = \frac{pO_2 \text{ room air}}{\text{Corrected barometric pressure}} \times 1{,}000$$

$$O_2 \text{ content of expired air} = \frac{pO_2 \text{ expired air}}{\text{Corrected barometric pressure}} \times 1{,}000$$

Thus, the difference between these values is the consumed O_2, the minute ventilation is calculated, and the consumed O_2/min is calculated.

O_2 content of blood (ml) = O_2 carrying capacity (ml O_2/L blood) = hemoglobin (gm/gl) × 1.36 (ml of O_2/gm of Hb) × 10. Calculation of Qp/Qs ratio will then determine the amount of pulmonary blood flow relative to the systemic blood flow, i.e., the degree of left-to-right shunting of blood.

there were significant lesions of the left anterior descending and proximal circumflex coronary arteries. The patient underwent surgical closure of the postinfarct defect and grafting to the anterior descending and midobtuse marginal branch of the circumflex. He is alive and well 48 months later.

If right heart catheterization cannot be performed easily, the echo-free zone associated with ventricular septal rupture can sometimes be visualized on echocardiography. Other less specific findings such as right ventricular dilatation, diminished or paradoxical septal motion, and unusual mitral valve motion may all assist in the diagnosis. Two-dimensional echocardiography may help indicate the site of the septal rupture.

The vast majority of patients with ventricular septal rupture complicating acute myocardial infarction will deteriorate within a few weeks and die if treated medically.

4.2. TREATMENT

We regard ventricular septal rupture as a surgical complication of acute infarction [11]. The presence (or absence) of cardiogenic shock appears to be a more important determinant of perioperative survival than does timing the operation soon after the onset of infarction. The Massachusetts General Hospital Surgical Group found that mortality was much higher after early operations in patients with cardiogenic shock than in those with severe heart failure but no cardiogenic shock [4]. If cardiogenic shock is present, intraaortic balloon counterpulsation should be instituted promptly to reduce the amount of left-to-right shunting and stabilize the situation during diagnostic studies (see 3. above).

Preoperatively, digitalization and diuretics to treat pulmonary congestion are in order. Care should be taken not to lower filling pressures of the right and left heart inappropriately. Intravenous sodium nitroprusside may have salutary effects by reducing afterload and left-to-right shunting. Dopamine` or dobutamine is given for hypotension. Intraaortic balloon

counterpulsation augments diastolic coronary blood flow and reduces afterload. Within the next 6 to 10 hours, cardiac catheterization, left ventriculography, and coronary arteriography should be performed. Two-dimensional echocardiography, if clinically feasible, will provide additional information about right ventricular function.

If cardiogenic shock is not present or heart failure is not rapidly advancing, vasodilator drugs may stabilize the patient sufficiently to allow angiography and operative repair to be carried out at a more leisurely pace. It is important to realize, however, that patients without a large left-to-right shunt or without evidence of heart failure can deteriorate rapidly. Ultimately, advanced age, severely impaired right and left ventricular function, and other coexistent medical conditions may all preclude surgery.

Ventricular septal repair should be carried out within 24 hours of the preliminary investigations, even if intraaortic balloon counterpulsation has produced apparent temporary hemodynamic stability. The operation usually involves ventriculotomy through the left ventricular infarction, infarctectomy, and repair of the defect. With apical defects, the cardiac apex is often amputated; posterior defects may require prosthetic replacement of part of the posterior wall with or without concurrent mitral valve surgery. Mitral valve replacement may be required when there is severe regurgitation in conjunction with ventricular septal rupture in patients with inferoposterior infarction. If feasible, aortocoronary bypass grafts should be placed on those vessels showing significant proximal stenoses.

Only about 15 per cent of patients can be managed by conventional medical measures for a period of 3 to 6 weeks [12]. In patients without cardiogenic shock, early surgery is associated with a relatively low mortality rate; if surgery is delayed, the outcome will be uncertain and the mortality high.

5. Mitral Valve Insufficiency

5.1. DIAGNOSIS

The most common cause of murmurs that develop within a few days of acute myocardial infarction is mild mitral valve insufficiency due to dysfunction of a papillary muscle [13]. The murmur is not loud, there is no thrill, and the finding has little prognostic importance.

A loud murmur usually means either rupture of a papillary muscle or perforation of the interventricular septum. Rupture of one of the muscular heads of a papillary muscle rather than the main papillary muscle occurs relatively infrequently but is a potentially treatable cause of death after acute infarction [14,15]. The infarct associated with papillary muscle damage may affect only a small percentage of myocardium. Cardiogenic shock associated with acute severe mitral insufficiency is potentially treatable by early replacement of the valve [14]; however, the outlook is grave, with an operative mortality of 58 per cent in one series of 43 patients [15].

Acute mitral insufficiency may arise within the first few hours after acute infarction or may become a dominant feature of the illness later, when the free wall of the ventricle becomes less edematous and begins to expand during ventricular systole. The anterolateral papillary muscle receives its blood supply from the left anterior descending artery and its branches as well as some branches of the circumflex artery, while the posterior papillary muscle is supplied by the circumflex artery. Rupture is six times more common in the posteromedial papillary muscle in association with posterior or inferior infarction.

Total rupture of the papillary muscle is a rare, but usually fatal, complication which most often occurs following transmural inferior infarction. Complete transsection of the left ventricular papillary muscle is incompatible with life because of the resulting sudden, severe mitral insufficiency. Rupture of a portion of a papillary muscle that results in severe, although not necessarily overwhelming, mitral insufficiency is much more frequent.

Clinically, the syndrome is suspected upon sudden development of acute pulmonary edema and a new apical pansystolic murmur. Although the murmur may be identical to that of chronic, significant mitral insufficiency, it may be deceptively soft and may decrease in intensity as the degree of regurgitation progresses. With the development of significant pulmonary congestion, associated hypotension commonly ensues.

The diagnosis is facilitated by use of the Swan-Ganz catheter. In acute mitral insufficiency, in addition to the large V wave in the pulmonary wedge pressure tracing (up to 60 to 70 mm Hg), blood samples from the pulmonary artery will have a very low oxygen content,

reflecting a low cardiac output. There will be no stepup in oxygen saturation within the right side of the heart. As the severity of the condition increases, left ventricular and left atrial pressures equilibrate during systole, producing an early systolic rather than a holosystolic murmur.

5.2. TREATMENT

The key to therapy is afterload reduction with agents such as sodium nitroprusside, which lowers systemic vascular resistance and decreases the amount of mitral regurgitation. If maximal medical management is unsuccessful, intraaortic balloon counterpulsation may improve cardiovascular hemodynamics dramatically and allow cardiac catheterization to be performed (see 3. above). Operability depends in large part upon residual left ventricular function.

If severe pulmonary congestion is present and persistent surgery is indicated and involves valve repair or replacement plus revascularization. The timing of surgical correction of a mechanical lesion is often a difficult issue. With each passing day the hemodynamic stress and volume overload continue; on the other hand, the infarct is healing, which will enable the myocardium to hold sutures better and will decrease the surgical risk. Early consultation with cardiac surgeons is helpful in planning management. Rarely, the mechanical defect can be repaired on a semielective basis; however, the vast majority of patients should be operated on within 48 hours of cardiac catheterization.

Prognosis depends to a great extent on the degree of left ventricular damage at the time of surgery. Patients with well-preserved left ventricular function have a good outlook, whereas those with severe dysfunction due to the recent infarct or to multiple old infarcts have a poor outlook. If appropriate and feasible, coronary artery bypass grafting can be performed. Operative mortality is reported to be as high as 50 per cent; however, without surgery, mortality after rupture of a papillary muscle approaches 100 per cent. In 41 patients treated surgically between 1965 and 1977 the mortality rate was 48 per cent; the rate was 87 per cent in 13 patients within one month of myocardial infarction, 50 per cent within the second month, and 33 per cent within the third month. Seventeen of 22 surviving patients had some degree of heart failure, and there were five late deaths [15].

6. Acute and Subacute Cardiac Rupture and Cardiac Tamponade

6.1. ACUTE CARDIAC RUPTURE

Rupture of the free wall of the ventricle occurs in up to 10 per cent of patients who die of acute infarction in the hospital. In one series of 2,244 infarctions, rupture occurred in 72 cases and led to death in 12 per cent [16]. Rupture causes hemopericardium and usually immediate death from cardiac tamponade. This complication of infarction usually occurs in patients 60 years of age or older. The incidence is greater in women but the overall occurrence rate is greater in men. Cardiac rupture appears to occur mainly in patients with left ventricular Q-wave first infarctions and at times is associated with hypertension during the acute phase. Rupture is most common 3 to 5 days after the onset of infarction but can occur from 24 hours to 3 weeks.

Steroid therapy at the time of acute infarction may constitute a risk factor. It is said that rupture of the wall of the heart is 8 to 10 times more common than rupture of a papillary muscle or of the ventricular septum. When pericardium, organizing thrombus, and hematoma seal the ventricle, incomplete rupture of the heart can occur. Thinning of the ventricular wall with disproportionate dilatation has been suggested as a pathogenetic factor by Schuster and Bulkley, who in a series of 110 patients found that 54 had ventricular expansion with a 43 per cent incidence of rupture compared with 56 cases without expansion and one case of rupture (2 per cent) [17]. Such thinning and expansion may be demonstrated on two-dimensional echocardiography.

Rupture may be heralded by persistent or recurrent pericardial pain, and a pericardial friction rub may or may not be present. Clinically, patients with ventricular free wall rupture usually experience sudden cardiovascular collapse that is often associated with electromechanical dissociation. Sinus or junctional bradycardia may be the first clue. In patients who do not die immediately, the echocardiogram may confirm the presence of a pericardial effusion. Thus, patients may have pericardial pain, a friction rub, signs of pericardial tamponade, or evidence of an effusion on echocardiography. The ECG usually shows Q-wave infarction in an anterior location. In addition, the presence of high peaked T waves with associated ST-

segment elevation or depression in the precordial leads has been emphasized [18].

External cardiac massage is ineffective; in fact, the inability to produce a peripheral pulse during massage may be a clue that cardiac rupture has occurred. If cardiac rupture is suspected, prompt pericardiocentesis is in order to establish the diagnosis. The pericardial aspirate, obtained using the subxiphoid approach* and a 5- to 6-inch 14-gauge needle, may include bloody fluid with a hematocrit identical to that of peripheral blood, and it may be impossible to tell whether the blood is intrapericardial or from a myocardial chamber. Electrocardiographic monitoring of the exploring electrode as described by Bishop et al may be helpful in elective pericardiocentesis but is seldom useful in the emergency situation [19]. Continuous drainage of the pericardium through a soft catheter with sideholes may allow time to transport the patient to the operating room. If cardiopulmonary bypass is not feasible, a thoracotomy may be carried out and, with luck, the free wall rupture may be closed. Only prompt intervention will occasionally be life-saving [20]. The long-term prognosis for patients who survive surgical repair of a ruptured ventricle may be excellent. Next to ventricular fibrillation and pump failure, rupture of the left ventricular free wall is the most common cause of death after acute myocardial inarction.

6.2. SUBACUTE CARDIAC RUPTURE

Rupture of the heart may be subacute rather than the usual acute form associated with cardiovascular collapse. With leakage of blood through the myocardial wall, a false aneurysm may form, and the patient may present clinically with hemopericardium or features of a ventricular aneurysm [21–23]. This diagnosis should be considered in patients with recurrent chest pain or persistent neck vein engorgement and minimal left heart dysfunction. Anticoagulant therapy should be considered a predisposing risk factor for subacute or acute cardiac rupture, especially in patients with a recent Q-wave infarction or pericardial friction rub. Echocardiography will allow rapid noninvasive evaluation, with fluid in the pericardial sac and the presence of good ventricular function despite compromised hemodynamics suggesting the diagnosis. Angiography may be required to define the anatomy of a false aneurysm (see section 12. below) and to assess the coronary vasculature, although invasive investigation should be justified on an individual basis. The need for revascularization has not yet been determined [24]. Good long-term results (10 years) have been reported [25].

*See figure 9–1 in chapter 9 for a depiction of this approach.

6.3. CARDIAC TAMPONADE

This disturbance is characterized by compression of the heart due to increased intrapericardial contents, which impairs diastolic filling. In order to occur, the rate of intrapericardial accumulation must exceed both the ability of venous return to maintain adequate right heart filling and the ability of the parietal pericardium to stretch. If intrapericardial bleeding occurs rapidly, 200 ml of accumulated blood can cause circulatory collapse. If accumulation of fluid is slow, compensatory mechanisms can cope with a much larger volume of intrapericardial fluid [26]. Initially, right atrial filling becomes compromised and cardiac output is maintained by tachycardia. With increasing obstruction to venous return, arterial pressure is maintained by increased peripheral resistance, but eventually cardiac output falls, as does arterial pressure [27]. When this critical stage is reached, small increases in intrapericardial fluid will cause major hemodynamic changes.

6.3.1. Diagnosis. Elevated central venous pressure with neck vein engorgement and a "paradoxical" arterial pulse are the hallmarks of cardiac tamponade. It is important to appreciate that the "paradoxical pulse" of cardiac tamponade represents exaggeration of a normal phenomenon. Normally systemic arterial pressure falls slightly during inspiration (up to 10 mm Hg); with cardiac tamponade, this fall is much greater than normal. Inspiratory augmentation of venous return to the right heart occurs as usual in the presence of cardiac tamponade but causes a greater than normal drop in arterial pressure. This is because systemic venous return and cardiac output are reduced slightly and inspiration augments right heart filling relatively more than normal.

A paradoxical pulse may be detected by palpating the radial or femoral pulse and noting that it becomes faint or even disappears during inspiration. The most accurate means of detection is by measuring the blood pressure. A cuff is placed around the arm and inflated to above

systemic pressure. As the air is slowly released, note the systolic blood pressure at which the first Korotkoff sounds appear. This will occur during expiration, with the sounds disappearing as the patient inspires. As the pressure falls, a level is reached at which the Korotkoff sounds last throughout the entire respiratory cycle.

The normal fall in systolic arterial pressure is 5 to 10 mm Hg; a clinically significant inspiratory drop should exceed this value. (This occurs commonly during acute asthmatic attacks.) Heart sounds may be soft because of the intrapericardial collection, and pericardial rubs may be heard. A third heart sound will not be present in uncomplicated cardiac tamponade. Inspiratory distention of the neck veins is *not* a feature of cardiac tamponade and, if present, should alert the clinician to the possibility of cardiac constriction. The ECG may show reduced QRS voltages. Electrical alternation of P waves and QRS complexes is virtually pathognomonic, and alteration of the QRS or QRST complexes is suspicious. The chest x-ray usually shows cardiomegaly, although the pulmonary vessels are often normal. Pleural effusions may be present. Echocardiography is the best method for determining at the bedside whether or not cardiac tamponade exists and will allow the amount of effusion to be estimated [28,29]. Normally, the clinical setting and the presence of elevated central venous pressure, paradoxical arterial pulsation, and a pericardial effusion establish the diagnosis. If cardiac catheterization is undertaken, the presence of a prominent *x* descent in the atrial pressure waveform and elevated ventricular diastolic pressures equal to mean atrial pressures indicate tamponade.

After acute myocardial infarction, ventricular rupture usually leads to cardiac tamponade and death within a few minutes. Occasionally, enough time elapses to allow a definitive diagnosis and surgical treatment. More commonly, tamponade develops later in the course of the infarction. Usually, these patients have had pericarditis associated with a Q-wave infarction and are receiving anticoagulant therapy.

6.3.2. Treatment. There are two approaches to the immediate but often temporary relief of tamponade:

1. *Pericardiocentesis*, in which a large-bore needle is introduced percutaneously into the pericardial space. The most popular approach is the subxiphoid, in which a 16-gauge short beveled needle is introduced below and slightly to one side of the xiphoid process and directed toward one shoulder. (Although aiming toward the right shoulder reduces the risk of lacerating a coronary artery, inexperienced operators may find it more difficult to enter the pericardial space, thus risking laceration of other mediastinal structures. Therefore, orienting the subxiphoid needle toward a point slightly lateral to the left earlobe with the patient's head placed frontally is probably the safest approach.) A unipolar lead from an electrocardiograph can be attached to the aspirating needle, and the ECG will show a pattern of injury when the needle contacts the epicardium; however, the logistics of obtaining properly grounded equipment and sterile cables and connectors, syringes, alligator clips, and so on make this technique impractical. Contact of the needle with the right ventricle usually triggers ectopic beats. An improved pulse pressure and a decrease in venous pressure will confirm that the blood is from the pericardial cavity. The hematocrit of pericardial fluid can be compared with that of venous blood drawn at the time of pericardiocentesis, and blood gas measurements will show marked oxygen desaturation. Even in extreme cardiovascular collapse, the venous saturation is rarely below 30.

2. *Direct surgical drainage*, in which a limited incision is made in the subxiphoid area and the pericardium is drained under direct but limited vision.

7. *Pericarditis and Dressler Syndrome*

For *pericarditis* to occur, myocardial necrosis must extend to the epicardium. Pathological studies reveal that virtually all patients with a transmural acute infarction develop at least a localized fibrinous pericarditis. Pericarditis causes anterior chest pain, often severe, and is easily confused with the continuing or recurrent pain of myocardial ischemia. It can be made worse by inspiration and in some instances lying flat. A pericardial rub may be heard with infarcts at any location, usually within the first 4 days. ECG changes with acute pericarditis tend to be manifested as abnormalities of the ST

segment or rhythm disorders. In 90 per cent of patients ST-segment elevation occurs within a few hours after the onset of chest pain or fever and is most frequently seen in ECG leads I, II, V_5, and V_6. Contrary to popular belief, ST-segment depression occurs in about two-thirds of patients, especially in leads aV_r and V_1. A friction rub can occur as late as 2 weeks after infarction, but pericarditis at this stage may represent extension of the infarct, a second infarct, or Dressler syndrome of early onset. In general the incidence of arrhythmias, heart failure, and cardiogenic shock is higher in patients with pericarditis. Symptoms can be so mild that therapy is not required. When pain is severe, agents such as aspirin, indomethacin, and corticosteroids may provide relief. Most dramatic and predictable relief of symptom occurs with administration of methylprednisolone. Because indomethacin may increase coronary vascular resistance and steroids may lead to scar thinning and myocardial rupture, we favor use of aspirin in such circumstances. If acute pericarditis is strongly suspected on clinical grounds, the physician should contemplate discontinuing anticoagulant therapy because of the risk of hemorrhagic pericardial effusion. This risk is probably low.

Dressler syndrome, or postmyocardial infarction syndrome, usually occurs 1 to 6 weeks after infarction and is probably due to an immune autoantibody response against certain pericardial-myocardial antigens exposed to the immune system at the time of infarction. Manifestations include fever, pericardial pain, pleuritis, and sometimes pneumonitis. Effusions and infiltrates in the lungs may be present, and antibodies may be detected in the blood. Therapy is similar to that for pericarditis; if aspirin and indomethacin fail, steroids may be used [30].

8. *Shoulder-Hand Syndrome*

The shoulder-hand syndrome can occur as a complication of myocardial infarction, for which there may be no apparent precipitating factor. (External trauma and operative procedures in the region of the shoulder may also provoke this syndrome.) It is characterized by pain, swelling, and limitation of movement of the upper extremity. The elbow is often spared, and the changes are usually unilateral. Onset may be slow or rapid and is characterized by initial acute pain, swelling, and vasomotor changes such as Raynaud's phenomenon. The skin may become shiny, and muscle atrophy with eventual stiffness and limited movements of the wrist and shoulder may develop. To avoid chronic disability it is important to recognize the condition and initiate treatment early. Physiotherapy with heat and exercise involving the hand, wrist, and shoulder should be combined with analgesia and antiinflammatory agents. Occasionally systemic steroid therapy is used. Early rehabilitation and arm motion after acute myocardial infarction will usually prevent this condition.

9. *Thromboembolic Complications*

Deep venous thrombosis and pulmonary embolism may also complicate myocardial infarction and are more likely to occur in obese patients who require prolonged bed rest and are suffering from severe heart failure. Early ambulation and minidose heparin (5,000 units subcutaneously every 8 to 12 hours) are probably useful measures for reducing the incidence of these complications of myocardial infarction (see chapter 3).

If pulmonary emboli do occur, intravenous heparinization is indicated. A loading dose of 5,000 to 10,000 units is followed by a constant infusion of 800 to 1200 units/hr until the partial thromboplastin time is approximately twice normal. Full heparinization is continued for up to 10 days, and oral anticoagulation with warfarin is started toward the end of this period. Warfarin therapy is generally continued up to 6 months after pulmonary embolism.

Arterial embolism can be a catastrophic complication of acute infarction (see chapter 3). It usually results from embolization of a thrombus that develops over the endocardial surface of a hypokinetic, infarcted area of the left ventricle. Peripheral thrombi are often treated surgically; if cerebral emboli occur, anticoagulants are withheld if one suspects intracranial hemorrhage. Otherwise, therapy consists of full-dose heparinization followed by oral anticoagulants.

10. *Hypertension*

In many patients admitted to a coronary care unit with acute infarction systemic arterial pressure will be mildly elevated owing to anxiety and/or persistent chest pain. This is usually

treated by adequate sedation (oral diazepam, 5 to 15 mg every 6 to 8 hours) and analgesia (morphine sulfate, 2 to 5 mg intravenously every 5 minutes, and/or nitrous oxide inhalation). Patients who remain hypertensive despite the initial measures (blood pressure >160/100 mm Hg by cuff) should be given intravenous furosemide, 20 to 40 mg, in conjunction with isosorbide dinitrate (5 mg sublingually or as chewable tablets). If the blood pressure responds, long-acting isosorbide dinitrate is prescribed (10 to 40 mg orally every 4 to 8 hours). If severe hypertension persists and more aggressive therapy is required, we administer intravenous nitroglycerin. (The initial dose is 10 to 15 μg/min, which can be increased 5 to 10 μg/min every 3 to 5 minutes to reduce systolic pressure effectively.) Patients undergoing intravenous antihypertensive therapy should usually undergo intraarterial blood pressure monitoring unless reliable blood pressure cuff measurements can be obtained frequently by the nursing staff. Oral antihypertensive therapy should be planned in conjunction with intravenous agents. A diuretic combined with alpha-methyldopa or hydralazine is often useful. In the absence of congestive heart failure, AV block, sinus bradycardia, or wheezing, a beta-adrenoceptor blocking agent can be added to the above regimen.

11. Left Ventricular Aneurysm

Aneurysms of the ventricle may develop at the site of acute myocardial infarction, at times within a matter of weeks, although more usually over several months. Anterior left ventricular aneurysms are often associated with intractable heart failure, a dyskinetic cardiac impulse, persistent ST-segment elevation on the electrocardiogram associated with a Q-wave infarction, and cardiomegaly. Ventricular aneurysms may develop in up to 10 per cent of patients who survive the infarction. The wall of the true ventricular aneurysm is composed of scar tissue and infarcted myocardium. This probably occurs when intraventricular tension stretches the noncontracting infarcted heart muscle to produce a thin, relatively weak layer of fibrous tissue and necrotic muscle, which bulges during ventricular systole.

False ventricular aneurysms are composed of organized thrombus capped by pericardium and probably result from transient hemorrhage through a ruptured infarct. These aneurysms are much more likely to rupture than are true ventricular aneurysms. When false aneurysms are recognized, surgical repair should be carried out promptly.

Complications of ventricular aneurysms include left ventricular failure, systemic emboli, and ventricular arrhythmias. During the acute phase of infarction, these difficulties can usually be controlled medically and only rarely require urgent surgical intervention. If refractory ventricular arrhythmias are associated with left ventricular aneurysm, new surgical techniques have been developed that may sometimes be helpful. To improve the likelihood of resecting that segment of ventricular myocardium which is responsible for the arrhythmias, aneurysmectomy is guided by electrophysiological mapping and may be combined with endocardial excision (see chapter 5). In patients with chronic left ventricular aneurysms, surgical therapy may improve heart failure. Generally, a combination of coronary vein graft surgery and aneurysm resection is most successful in patients who have a combination of chest pain and heart failure, whereas results tend to be disappointing in patients with heart failure alone.

12. Persistent Chest Pain

Persistent or recurrent chest pain after the initial acute treatment of myocardial infarction is always of concern to the physician. It may be due to continuing myocardial ischemia or merely a symptom of pericarditis complicating transmural infarction. If continuing ischemia is suspected, the patient should remain in the coronary care unit. Electrocardiograms should be obtained during pain, serial measurements of cardiac enzymes should be made, and aggressive antiischemic therapy should be instituted. Of particular concern are patients with an infarct in one area of myocardium but in whom there is a threat of infarction in other, distant areas of myocardium (e.g., intermittent anterior ischemia in a patient with completed Q-wave inferior infarction). In stepwise fashion, more aggressive therapy using the following measures may be indicated.

1. Short- and long-acting oral or cutaneous nitrates (e.g., isosorbide dinitrate, 10 to 60 mg orally every 6 hours, or nitroglycerin ointment, up to 2 inches every 6 hours percutaneously, or

transdermal nitroglycerin).

2. Intravenous nitroglycerin. This is administered initially in a dose of 10 to 15 μg/min and may be increased by 5 to 10 μg/min every 3 to 5 minutes, provided that systolic arterial pressure does not fail below 90 to 100 mm Hg and that heart rate does not increase more than 5 to 10 bpm. Intraarterial pressure monitoring is required in this circumstance.

3. Beta-adrenoceptor blocking agents. These may be used either orally or parenterally, provided that sinus bradycardia, AV block, asthma, or heart failure is not present. An intravenous loading dose to a total dose of 0.1 mg/kg of propranolol may be given initially or an oral dose of 10 to 60 mg may be given every 6 hours.

4. Calcium-channel blocking agents. Nifedipine can be administered orally in doses of 10 to 30 mg every 6 hours, and will not adversely affect atrioventricular conduction.

5. Intraaortic balloon counterpulsation (see section 3). This is used to treat angina that persists despite more conservative measures. It is particularly helpful when one is contemplating angiography with a view toward urgent revascularization.

If possible, surgical therapy should be avoided in patients with large infarcts and considerable increases in creatine kinase (CK). However, aggressive surgical intervention is often contemplated in patients with non-Q-wave infarctions and relatively minor increases in CK. Emergency revascularization in patients with acute myocardial infarction may be carried out safely, although this approach is still experimental and is associated with potentially high mortality and morbidity rates (31).

13. Myocardial Infarct Extension and Expansion

These two complications of myocardial infarction must be differentiated both clinically and pathophysiologically. *Myocardial infarct extension* refers to a recurrent infarction of myocardial tissue adjacent to the original zone of infarction. This may occur via lateral extension of a transmural infarction or extension of a nontransmural infarction to involve the full thickness of the ventricular wall. *Myocardial infarction expansion* is a condition characterized by disproportionate thinning and dilatation of the necrotic zone prior to development of a well healed scar. Clinical symptoms and signs of expansion include increased congestive heart failure and chest pain without evidence of recurrent infarction. Principles of management of myocardial infarct extension are similar to those for the original infarction and may require anticongestive measures, including digitalis glycosides, diuresis, and long-acting nitrates.

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13. MYOCARDIAL INFARCT SIZE REDUCTION

In 1912, Herrick concluded his classic article by presenting a logical approach to the treatment of myocardial infarction: "the hope for the damaged myocardium lies in the direction of securing a supply of blood through friendly neighbouring vessels so as to restore as far as possible its functional integrity" [1]. Thus, this distinguished physician anticipated by more than half a century the concept of limiting infarct size.

Management approaches to myocardial infarction may be viewed in terms of four broad areas:

1. For 40 years after the initial clinical description of myocardial infarction, the major objectives of treatment were to ensure physical rest and allow damaged cardiac muscle to heal. Complications such as heart failure and arrhythmias were treated and efforts were made to prevent thromboembolic complications.

2. In the 1960s, coronary care units evolved, and routine use of external electrical cardioversion/defibrillation, prophylactic antiarrhythmic therapy, and pacemakers spread. With the implementation of immediate medical treatment by trained personnel the mortality of acute infarction fell from around 30 to 15 per cent.

3. In the 1970s, hemodynamic monitoring developed and objective serial assessments of cardiac output and filling pressures allowed a rational approach to treating patients with hypotension and heart failure. Therapeutic decisions regarding volume replacement, diuresis, and/or inotropic support are now based on serial hemodynamic measurements in compromised patients.

4. The main factor altering the therapeutic approach to acute myocardial infarction over the last decade has been the knowledge that the extent of the mass of myocardium undergoing necrosis is the most important determinant of ultimate prognosis.

Both in-hospital complications of myocardial infarction and those immediate following discharge are related to infarct size. If, as a consequence of acute infarction, 40 per cent of the left ventricular myocardium undergoes necrosis, one can anticipate the onset of cardiogenic shock, congestive heart failure, and/or refractory ventricular arrhythmias [2,3]. For such patients, mortality exceeds 80 per cent despite therapy. At the other end of the spectrum are patients with small infarctions, no evolving hemodynamic deficit and a very low rate of mortality (see chapters 3 and 11).

If tissue damage after coronary occlusion can be effectively limited, severe pump failure and its consequences may be avoided. This direct relationship between infarct size and mortality is most obvious during hospitalization. Long-term mortality after recovery from myocardial infarction appears to be related to the cumulative amount of myocardial damage, the presence of ventricular arrhythmias, and the age of the patient.

The concept of attempting to limit infarct size in patients is based on extensive experimental studies in animals, which have indicated that factors other than the coronary anatomy could determine the quantity of myocardium that becomes necrotic after coronary occlusion [4]. Quantitative studies revealed that in a substantial portion of ischemic myocardium (i.e., myocardium deprived of oxygen secondary to

reduced perfusion) infarction could be prevented [5–8]. Myocardium distal to a major coronary occlusion usually consists of a central region of necrosis surrounded by a patchy region of abnormal but potentially viable myocardial tissue. Endocardial regions tend to be more necrotic, while epicardial myocardium may comprise a mixture of necrotic, ischemic, and normal tissue. Myocardium adjacent to the central necrotic region differs from the necrotic zone in terms of blood flow, metabolic changes of ischemia and necrosis, electrical behavior, and contractility. The viability of this border zone may depend on development of a collateral circulation or reperfusion. It is likely that a significant mass of myocardium distal to a major coronary occlusion is capable of recovery for 3 to 6 hours after the occlusion.

There are several potential mechanisms by which infarct size might be reduced (table 13–1). Since resting myocardium extracts virtually all its oxygen from coronary arterial blood (cardiac venous blood contains only five volumes per cent of oxygen), any increases in myocardial oxygen demand must be met primarily by increases in coronary blood flow. Therefore, attempts to improve the supply/demand ratio are designed to decrease myocardial oxygen requirements (e.g., beta-adrenoceptor blockade) or increase myocardial oxygen supply (e.g., coronary reperfusion or improvement in collateral flow) (figure 13–1). Other interventions are aimed at augmenting anerobic metabolism (e.g., glucose-insulin-potassium), stabilizing cell membranes (e.g., corticosteroids), reducing cell swelling (e.g., mannitol and hyaluronidase), and reducing the inflammatory response. Interventions that *increase* infarct size in experimental animal models include tachycardia, hypotension, hypoxia, hypoglycemia, and the administration of isoproterenol.

In general, interventions shown to have a salutary effect on direct measurements of infarct size in animals can be administered safely to patients under appropriate circumstances but in many cases are still investigational or of unproven benefit clinically.

TABLE 13–1. Interventions that may reduce myocardial injury after coronary artery occlusion in humans

1. *Decrease myocardial oxygen requirements*
   Beta-adrenoceptor blockade
   Afterload reduction in hypertensives
   Cardiac glycosides in heart failure
   Sedation
   Intraaortic balloon counterpulsation
2. *Increase myocardial oxygen supply*
   Coronary artery reperfusion (e.g., thrombolytic agents, coronary artery bypass grafts, percutaneous angioplasty) Arterial oxygen tension elevation in hypoxemia Augmentation of blood flow through coronary arteries or collateral vessels (e.g., intraaortic balloon counterpulsation, nitroglycerin)
3. *Augment anerobic metabolism*
   Glucose–insulin–potassium
4. *Protect against autolytic and heterolytic processes*
   Corticosteroids (may cause cardiac rupture)

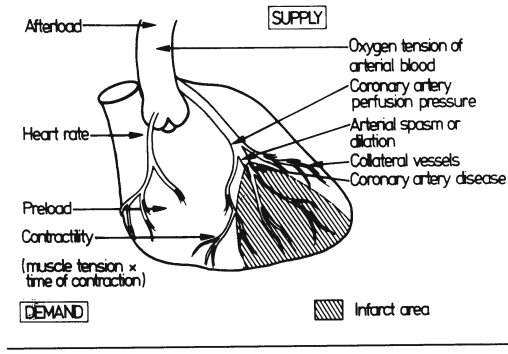

FIGURE 13–1. Factors influencing myocardial oxygen supply and demand.

1. *Indices of Infarct Size*

Most of the current "infarct-sizing" methods employed in patients provide only *indices of infarct size* rather than *quantitative* measurements. In humans, the only direct method of sizing infarcts is through analysis of autopsy specimens:

1. Release of cardiac enzymes (e.g., creatine kinase).
2. Precordial electrocardiographic mapping.
3. Scintigraphic measurements of infarct size.

1.1. RELEASE OF CARDIAC ENZYMES

Myocardial ischemia impairs the functional integrity of the sarcolemma. Initially, small constituents of the cytoplasm, such as potassium

and lactate, are released into the circulation. As cell membrane injury increases the release of macromolecular enzymes occurs, and this correlates anatomically with cell death.

Using independent morphometric techniques of analysis, experiments have shown that depletion of myocardial creatine kinase (CK) activity from animal hearts is proportional to the extent of infarction. In patients, enzymatic estimations of infarct size have been derived from analyses of plasma CK time-activity curves [9] and from curves obtained by quantitative assay of plasma samples to determine activity of its subfraction, CK-MB [10,11].

Serum CK curves can be used to *measure* and *predict* infarct size based on the rate of CK release from necrotic myocardium, the CK distribution state and the rate at which CK is removed from the serum. By performing frequent measurements of plasma concentrations of CK (or CK-MB) one can construct a time-concentration curve and thus quantify infarct size (in gram-equivalents). Reasonably accurate predictions of entire plasma CK disappearance curves can be made from analysis of several plasma samples taken soon after the enzyme is first released (7 hours in patients). From these initial plasma samples infarct size can be *predicted* and later, after an intervention, the *observed* infarct size can be determined.

The disadvantages of this predictive enzymatic method of infarct sizing are the need for multiple, early serum samples and the delay before a potentially beneficial intervention can be undertaken. Certain additional confounding variables are associated with enzyme release methods. For example, the rate of entry of CK from the myocardial cytoplasm into the circulation may vary, depending on whether the lesion is a "stuttering" infarct, on the rate of washout from underperfused infarcted myocardium, and on destruction of the enzyme in venous blood and cardiac lymph. Also, the disappearance of CK from the circulation depends on reticuloendothelial system function, which differs among patients. Finally, since patients usually arrive in the hospital some hours after the onset of infarction, early measurements of CK are often impossible.

1.2. PRECORDIAL ELECTROCARDIOGRAPHIC MAPPING

ST-segment elevation can be considered an index of the extent of myocardial ischemia provided that other potential causes are excluded [12], and analyses of changes in electrocardiographic QRS patterns allow assessment of irreversible myocardial damage [13]. By analyzing the alterations in *both* the ST segments and the QRS complexes, one can evaluate the effect of interventions administered to limit infarct size versus results with placebo.

In the absence of pericarditis and other causes of ST-segment change, ST-segment elevation in the precordial leads reflects areas of "threatened or vulnerable" myocardium in the early hours after infarction. Patients in both placebo and treatment groups can be compared by determining how many precordial sites with initial evidence of ischemia (ST-segment elevation) develop evidence of necrosis (QRS changes, including loss of R-wave height and development of Q waves). This method of evaluation is suitable only in patients with acute anterior or lateral transmural myocardial infarctions of recent onset. Acute inferior myocardial infarction is electrically "silent" on a precordial map. Multiple-lead precordial maps are required prior to randomization (to placebo or treatment groups) and additional precordial maps using the same sites are needed at various intervals after randomization. Major evolving changes in electrical axis, development of conduction defects and significant alterations in electrolytes all preclude serial comparison of precordial maps [14].

1.3. SCINTIGRAPHIC MEASUREMENTS OF INFARCT SIZE

1.3.1. "Hot-spot" scintigraphic techniques (e.g., technetium-99m stannous pyrophosphate [^{99m}Tc–PYP]). This radionuclide appears to be selectively concentrated in ischemic or infarcted myocardium (or both) as a "hot spot"; normal myocardium fails to accumulate this radiotracer. It has been postulated that the phosphate radical forms complexes with intracellular calcium deposits located in the mitochondria of necrotic myocardial cells. However, substantial radioactivity also accumulates in the cytoplasm of the cells. Both myocardial necrosis and a residual blood supply to infarcted myocardium are essential for uptake of the tracer. Maximum radionuclide accumulation occurs in areas of infarction where residual flow is maintained at 30 to 40 per cent of normal [15]. Because of this dependency on

blood flow, a simple, direct relationship does not exist between the extent of necrosis and the amount of myocardial uptake.

The maximal abnormality is detected 48 to 72 hours after the onset of infarction and many scans revert to normal within 7 to 14 days. This method of infarct detection has a sensitivity of over 90 per cent in detecting acute Q-wave infarctions; non-Q-wave infarcts are not detected as reliably [16].

False-positive scans may occur with rib fractures, left ventricular aneurysms, and calcified cardiac structures. Furthermore, one-third of patients with unstable angina will demonstrate a diffuse pattern of ^{99m}Tc-PYP uptake [16]. Autopsies in patients with unstable angina reveal small islands of infarcted myocardial cells that had gone undetected by electrocardiographic or enzyme evaluations. This may be due to accumulation of ^{99m}Tc-PYP in ischemic as well as in necrotic tissue. Persistently positive scans (for weeks or months) suggest either ongoing necrosis or aneurysm formation and are associated with impaired LV function.

Quantitative correlations have been noted between the size of experimental myocardial infarctions and scintigraphic evidence of infarction [17,18]. With routine two-dimensional imaging anterior transmural infarcts can be sized. Tomographic images may also allow one to calculate the sizes of inferior and posterior infarctions. Interestingly, the size of pyrophosphate uptake during acute infarctions has some predictive prognostic value. As the extent of pyrophosphate uptake increases there is an increase in the frequency of cardiogenic shock, ventricular arrhythmias, ensuing unstable angina, infarct extension, and death. At present the use of scintigraphic images to determine infarct size is investigational. When normal myocardium is superimposed on areas of necrosis, detected radioactivity will be attenuated, leading to possible underestimation of infarct size.

1.3.2. "Cold-spot" techniques (e.g., thallium-201). The properties of thallium resemble those of potassium. Thallium is actively transported into cells by the sodium-potassium ATPase system. After intravenous injection, thallium is found mainly in normal heart and kidney. Decreased myocardial thallium uptake may be related to diminished regional blood flow or to depressed membrane transport (e.g., after drugs, ischemia, or hypoxia). Areas of infarction, ischemia, or scar tissue are characterized by a defect or "cold spot" surrounded by normal thallium uptake [19].

Because myocardial flow can be completely homogeneous in the presence of severe coronary artery stenoses, thallium studies often reveal more information if performed under conditions of increased oxygen demand. Exercise studies with thallium will test coronary vascular reserve. Regions of myocardial ischemia will develop defects of thallium uptake and a heterogeneous pattern. Defects noted only during exercise testing are consistent with the presence of myocardial ischemia; defects noted at rest, which do not change with exercise, are consistent with previous infarction and/or scar formation.

The thallium scan is 70 to 80 per cent sensitive in identifying patients with coronary artery disease. However, if this test is combined with electrocardiographic exercise testing, its sensitivity is increased to 80 or 90 per cent. An exercise thallium study can safely be called "negative" only if an adequate heart rate-blood pressure response is achieved. When patients with acute myocardial infarction are studied within 6 hours of the onset of chest pain, thallium-201 imaging will detect virtually all patients with an abnormality. The sensitivity of imaging decreases 24 hours after the onset of infarction and is lowest with "small" infarcts.

Thallium-201 imaging has been used to quantify the size of myocardial infarction. One group of investigators noted a good correlation between the area of the defect on imaging ante mortem and the postmortem assessment of infarct size in humans [20]. A single thallium study during acute infarction will not discriminate among old infarction, new infarction, or a region of myocardial ischemia.

1.3.3. Dynamic myocardial scintigraphy (i.e., determination of ventricular function by first-pass or equilibrium [ECG gated] techniques.) In the *first-pass method* of dynamic myocardial scintigraphy, an intravenous bolus injection of radiotracer (e.g., technetium-labeled human serum albumin or red cells) is followed during its initial transit through the right heart, lungs, and left heart. On reaching the systemic circulation, the bolus disperses, and its usefulness for cardiac imaging is lost. The alternative method, the *equilibrium*

method, involves labeling the entire blood pool and "gating" the images to the ECG. Once achieved, the labeling is usually fairly stable, and repeat imaging can be performed serially after the initial injection.

The major advantage of the first-pass method is the short time required for data acquisition. The equilibrium method allows multiple serial studies after a single injection of radioactive material to be performed and improved imaging can be obtained by collecting more counts. Global ventricular function can be assessed by both methods subjectively and quantitatively. Ejection fraction is estimated utilizing methods that depend on a linear relationship between detected counts and ventricular volume; this is a reproducible technique that largely agrees with the angiographic estimations.

The clinician can utilize these radionuclide techniques as noninvasive means of measuring ventricular performance in patients recovering from a myocardial infarction and can thus monitor therapeutic interventions. In acute infarction, both global and regional dysfunction are found in virtually all anterior infarcts and in over half of inferior infarcts. Serial systolic ventricular performance after infarction can now be evaluated routinely at the bedside, and the findings are likely to have important therapeutic implications.

2. *Specific Interventions*

Careful attention to physiological variables during the evolution phase of infarction can improve the balance between myocardial oxygen supply and demand (table 13–2). By treating pain effectively and promptly and caring for the patient in a calm, quiet atmosphere, one can lower heart rate, a major determinant of myocardial oxygen consumption. All forms of tachyarrhythmias should be treated promptly. Since both clinical and experimental evidence suggests that increased oxygen in the inspired air protects ischemic myocardium in hypoxemia, oxygen should be administered to patients with myocardial infarction and arterial hypoxemia. Several treatments that may have a salutary effect during acute infarction are currently being investigated and will now be considered.

TABLE 13–2. Clinical measures to improve the balance between myocardial oxygen supply and demand

1. Bed rest
2. Sedation
3. Pain relief
4. Oxygenation if hypoxemic
5. Transfusion if hematocrit < 30%
6. Avoid deviation of systolic blood pressure by more than 30 mm Hg from usual levels
7. Prompt treatment of
   a. Fever
   b. Infection
   c. Tachycardia (rule out decreased volume, congestive heart failure)
   d. Heart failure
   e. Arrhythmias
8. Continue beta blockade if patient previously receiving treatment for high blood pressure or angina (i.e., avoid beta-blocker withdrawal syndrome)

2.1. HYALURONIDASE

Bovine testicular hyaluronidase (BTH) has reduced the amount of ischemic myocardial necrosis in several animal models of infarction [21–24], and clinical studies have suggested that this may be true in myocardial infarction in humans as well [25]. BTH is associated with a variety of changes in transport mechanisms and metabolism in ischemic myocardium. Early reports suggested that BTH increased the permeability of connective tissue by degrading a mucopolysaccharide ground substance and enhanced the bulk flow of water through biological tissues. In addition, the transport of proteins between the lymphatic and intravascular space was demonstrated to be enhanced by hyaluronidase [26]. After it was observed that water content increased in regions of myocardial ischemic injury in dogs, it was found that BTH reduced this accumulation of water.

BTH also causes certain biochemical changes in ischemic myocardium. After coronary artery occlusion, BTH attenuates myocardial CK depletion [21], increases tissue concentrations of high-energy phosphate stores [23], lowers concentrations of lactate [23], lowers intramural carbon dioxide tension, reduces NADH accumulation, and preserves myocardial glycogen deposits.

The molecular mechanism of the myocardial protective effect of BTH is not totally clear. One attractive hypothesis has been that depolymerization of hyaluronic acid (by BTH)

might create conditions that would enhance transport processes and be responsible for myocardial salvage.

Both serum [27,28] and myocardial tissue [29] show endogenous hyaluronidase activity. However, intravenously administered serum BTH has a very short half-life (approximately 2 minutes) and additional incremental doses fail to maintain sustained serum levels of the enzyme. This is probably because mammalian serum contains a potent inhibitor of BTH. When Wolf et al performed studies to test the ability of intravenous BTH to depolymerize myocardial hyaluronic acid, they found that, in the presence of coronary artery occlusion, this substance reduced the total hyaluronic acid content of myocardial extracts [30]. They also demonstrated that in the presence of myocardial ischemia, when intravenous BTH is less likely to reach myocytes at risk, the conditions of local acidosis may enhance BTH activity. These studies are the first to confirm that exogenous BTH can, in fact, depolymerize myocardial hyaluronic acid.

Administration of hyaluronidase to humans might offer several potential advantages compared with other interventions that might reduce infarct size: (a) its toxicity level is low, (b) allergic reactions are rare and are completely preventable if a skin test is performed and positive reactors are eliminated, and (c) BTH does not depress cardiac contractility or cause hypotension.

Maroko et al randomized 91 patients with anterior infarctions to placebo or BTH treatment [25]. Precordial electrocardiographic maps taken before treatment and 7 days later showed that Q waves developed more frequently in ischemic regions of the placebo-treated patients than in similar locations of the BTH-treated patients. This indicated a reduction in the extent of myocardial infarction but did not provide quantitative information.

One study designed to detect a 50 per cent reduction in "infarct size" (as assessed by the serial CK technique) showed no beneficial effect of hyaluronidase [31]. In the MILIS Study (Multicenter Investigation of the Limitation of Infarct Size) in which five clinical centers randomized 851 patients with suspected or acute myocardial infarction to either placebo or hyaluronidase in double-blind fashion, treatment was administered an average of 9.4 hours after the onset of pain. The primary end point, namely the infarct size index based on CK-MB estimates, was not reduced by hyaluronidase treatment even if the drug was administered within 8 hours of onset of pain, nor did hyaluronidase reduce the incidence of infarction or positive pyrophosphate images, enhance improvement in left ventricular ejection fraction in the first 10 days, or prevent R-wave loss on the electrocardiogram. Short- and long-term survival was similar in the placebo- and hyaluronidase-treated patients [32]. However, treatment with hyaluronidase was associated with a significant improvement in left ventricular ejection fraction within 10 days of infarction in a subgroup of the study population who demonstrated early peaking of plasma CK–MB (less than 15 hours after the onset of pain). In addition, patients treated with hyaluronidase with initial non-Q-wave changes on the ECG had a reduced mortality. These latter findings suggest that hyaluronidase may in some way influence early reperfusion and consequent myocardial salvage [33].

2.2. BETA-ADRENOCEPTOR BLOCKADE

The place of beta blockers in the treatment of acute myocardial infarction has been debated for over 15 years. There are theoretical reasons why beta blocking agents might be effective in the management of acute infarction as well as in angina pectoris, in which their efficacy has been well established. Beta-blocking agents have been shown to limit the response of myocardium to stress and exercise by decreasing heart rate, blood pressure and contractility at any level of exercise. One of these agents, propranolol, also reduces myocardial oxygen requirements for any given physiological load [34], mainly by reducing heart rate, with lesser reductions in arterial pressure and myocardial contractility [35]. Conversely, this drug increases myocardial oxygen requirements by increasing end-diastolic volume [35,36]. However, the net effect of these actions appears to be a reduction in the oxygen requirement.

Other effects of potential benefit in patients with ischemic heart disease include reversal of abnormal platelet aggregability, a reduction in the affinity of hemoglobin for oxygen, and a reduction in the uptake of free fatty acids by ischemic myocardium while glucose uptake is increased [37]. High-density lipoproteins (which appear to confer a protective effect when elevated) can fall with a concomitant rise in

triglycerides after the administration of beta blockers [38].

Propranolol has been shown to reduce infarct size after experimental coronary occlusion in anesthetized animal preparations [4,6,39]. In conscious dogs, propranolol induced a significant redistribution of myocardial blood flow in ischemic hearts, with flow falling in normal zones and rising in moderately and severely ischemic zones [40]. This improvement in flow occurred concomitantly with a depression of cardiac function (and work) and a decrease in the extent of paradoxical bulging or passive stretching in severely ischemic regions of myocardium. This study suggests two possible salutary actions of propranolol in the treatment of myocardial ischemia in which cardiac decompensation is not a factor — i.e., an oxygen-sparing effect on ischemic myocardium, because of slight reductions in cardiac rate and contractility, coupled with an increase in blood flow to ischemic tissue.

Recent reports provide evidence that postinfarction beta blocker therapy can reduce mortality [41–47]. Among the recent large studies there are only three in which intervention was early enough to have a potential effect on infarct size [41,45,48] (table 13–3). When beta blockers have been given within 12 hours of the onset of suspected or evolving myocardial infarction, some studies have shown beneficial effects as evidenced by electrocardiographic and enzymatic indices of infarct size.

Intravenous propranolol administered within 8 hours of the onset of anterior infarction has been shown to reduce ST-segment elevation [49], and intravenous atenolol administered within 12 hours of the onset of suspected infarction enhanced R-wave preservation [50]. Both intravenous atenolol and propranolol administered within 12 and 4 hours, respectively, of the onset of suspected acute infarction resulted in fewer completed infarctions as determined by electrocardiographic criteria in treated patients compared with those given placebo [50,51].

In several studies of suspected or evolving acute infarction, beta blockers have been shown to inhibit somewhat the release of cardiac enzymes. Intravenous propranolol has been shown to reduce CK release when given within 4 hours of acute infarction [52]. In addition, peak plasma levels of lactic dehydrogenase, types 1 and 2 (LDH-1 and LDH-2), were significantly lower in patients treated with intravenous metoprolol given within 5 to 7 hours of the onset of infarction than in placebo-treated patients [53], and in another controlled study total CK-MB release was reduced by administration of intravenous atenolol within 12 hours of suspected infarction [50].

Although these preliminary studies in humans showed encouraging trends with regard to the influence of beta blockers on indices of infarct size, the MILIS study failed to show beneficial effects [48]. Propranolol (0.1 mg/kg) was given intravenously to patients with suspected or evolving infarction and then continued orally for 9 days to keep the heart rate between 45 and 60 bpm. Half the patients received therapy within 8 hours of the onset of chest pain, less than 2 per cent were treated within 4 hours, and the remainder were treated between 8 and 18 hours. The primary end point evaluated was infarct size index, as estimated from plasma MB-CK activity, which was found to be virtually identical in placebo- and propranolol-treated groups (averaging 13.6 and 13.3 gram-equivalents of MB-CK/m^2 respectively.) Other end points that were similar in treated and untreated patients included peak plasma levels of CK, changes in left ventricular ejection fraction, extent of area involved in pyrophosphate uptake, R-wave loss on 12-lead electrocardiograms, and 3-year mortality.

Although earlier reports suggested that treatment was more effective in anterior infarctions [44] and in younger patients who had not had a previous myocardial infarction [45], more recent trials do not confirm these findings [46, 47].

It appears that beta blockers can be administered safely in acute myocardial infarction provided that heart rate and arterial pressures are monitored and that the agent is not administered in the presence of bradycardia, hypotension, left ventricular failure, or atrioventricular block [48].

In summary, propranolol does not appear to decrease infarct size when given 4 to 18 hours after the onset of suspected or evolving myocardial infarction. Based on these findings as well as data from recent experimental animal work and observations following reperfusion of occluded coronary arteries, it seems that agents such as beta blockers would have to be administered within about four hours of the onset of infarction in order to reduce the size of an infarct.

TABLE 13–3. Large, randomized beta blocker trials*

Trial	Agent	Time given after infarction	Duration of treatment	Number of randomized patients	Mortality (%)	Infarct size indices
Andersen *et al* 1979 (45)	Alprenolol, 5 to 10 mg IV then 400 mg/day	< 6 hr in 50%	1 year	≤65 yr Placebo = 142 Alprenolol = 140 >65 yr Placebo = 100 Alprenolol = 98	29 13 $p < 0.01$ At 1 year 35 48 NS	
Hjalmarson *et al* 1981 (41)	Metoprolol, 15 mg IV, then 200 mg/day	11.3 + 0.3 hr (69% within 12 hr)	3 months	Placebo = 697 Metoprolol = 698	At 3 months 62 40 $p < 0.03$	15% reduction in enzyme estimated infarct size if treated within 12 hr
Roberts *et al* (MILIS Study), 1984 (48)	Propranolol, 0.1 mg/kg IV, then orally for 10 days	8.5 hr (0 to 18 hr)	10 days	Placebo = 135 Propranolol = 134	At 36 months 15% 18% NS	CK-MB gm-equivalent/m2 Placebo = 13.6 Propranolol = 13.3 NS No difference in change in LV ejection fraction, area of pyrophosphate uptake or R-wave loss

*Treatment was begun within hours of a definite or suspected infarction.

A number of recent studies have shown that beta blockade during the early convalescent phase in survivors of acute infarction is associated with a reduction of mortality [41,44–47] (table 13–4). In addition, these drugs have been shown to lower the incidence of sudden death in these patients [42–44,46–47]. Although a reduction in reinfarction rate has been demonstrated in some studies [43,46], other researchers report no difference in this rate [42,44,54]. A recent international study showed that intravenous metoprolol administered within 24 hours of the onset of definite or suspected acute myocardial infarction and continued orally for 15 days did not reduce mortality at 15 days [55].

2.3. NITRATES

The use of nitrates during evolving acute myocardial infarction also continues to be a controversial issue. Since nitroglycerin reduces systemic arterial pressure with a concomitant reflex increase in heart rate, it can be potentially harmful to patients with acute infarction if it is not given in appropriate dosage associated with hemodynamic monitoring.

In experimental animals, intravenous nitroglycerin has been shown to reduce the magnitude and extent of ischemic injury after coronary artery occlusion, to elicit small reductions in total coronary vascular resistance, and to improve the ratio of endocardial to epicardial flow in ischemic zones of myocardium. In humans, intravenous nitroglycerin is useful in acute infarction as a vasodilator in patients with left ventricular failure and for the relief of persistent ischemic pain. Safe use of this agent depends on avoiding inappropriate tachycardia, hypotension, and a decrease in ventricular filling pressures to suboptimal levels. Several clinical studies have indicated that nitroglycerin may have beneficial effects on ischemic injury and possibly on infarct size.

Sublingual nitroglycerin administered to 11 patients with acute anterior infarction within 6 hours of the onset of chest pain decreased the sum and average of ST-segment elevations on precordial maps as well as the number of leads in which this occurred [56]. In another study, however, sublingual nitroglycerin given early after acute myocardial infarction had a beneficial effect on precordial ST-segment elevations only in patients with heart failure [57]. It should be noted that the latter study included patients with inferior infarctions, making interpretation of ST-segment shifts on precordial maps difficult.

Intravenous nitroglycerin administered to patients early after the onset of acute myocardial infarction has been shown to decrease ST-segment elevations on precordial maps [58–60] and to preserve R-wave amplitude [59]. More impressive, however, are two studies showing that intravenous nitroglycerin had a beneficial effect on enzymatically calculated indices of infarct size. In a randomized prospective study of 85 patients, intravenous nitroglycerin was given within 10 hours of the onset of symptoms. Estimated infarct size using serial CK values was significantly smaller in nitroglycerin treated patients who had suffered inferior and subendocardial infarctions; no difference was noted in anterior infarctions [61]. In another study when intravenous nitroglycerin was administered early or late (within 8 or 24 hours) after the onset of symptoms, treated patients had lower peak CK and CK-MB levels and a lower calculated infarct size than did control patients, and these findings were more impressive in patients treated early [62].

These studies in humans suggest that intravenous nitroglycerin after acute infarction may have a beneficial effect on myocardial ischemia and possibly on infarct size reduction provided that therapy is carefully monitored to avoid undue tachycardia, hypotension, and reductions in preload.

As noted in chapter 12, when the results of seven randomized trials using intravenous nitroglycerin in acute myocardial infarction are pooled, then intravenous nitroglycerin appears to reduce mortality by about 30%. Further prospective, randomized, large-scale trials are needed before such therapy can be routinely recommended when congestive heart failure or persistent angina is absent.

2.4. THROMBOLYSIS

Events that initiate acute myocardial infarction are complex and suggest a multifactorial origin. The relative roles of coronary artery thrombosis, atherosclerotic plaques, and coronary vasospasm still remain to be defined. However, recent reports suggest that intracoronary thrombosis, superimposed on severe atherosclerotic coronary stenosis, occurs frequently in patients with acute Q-wave infarction. Disruption of the intima of a plaque can almost certainly lead to platelet aggregation and pre-

cipitate an intracoronary clot. Furthermore, coronary spasm may be evoked by the release of vasoactive substances during platelet aggregation [63]. It seems that in the first 12 to 24 hours of infarction a dynamic process occurs and interventions may be possible. Platelet aggregation, vasospasm, and thrombus formation, with the possibility of clot lysis, may be important determinants of the eventual outcome of an acute episode. Therefore, it is logical to conclude that thrombolysis, initiated early after thrombosis, may restore coronary blood flow, reverse myocardial ischemia, limit necrosis, and thus reduce mortality [64].

Streptokinase itself is not a fibrinolytic agent but is a plasminogen activator and can dissolve blood clots. It combines with plasminogen to form an activator complex that transforms plasminogen into plasmin. Plasminogen, with a high affinity for fibrinogen and fibrin, is absorbed by the thrombus, and lysis proceeds (figure 13–2).

2.4.1. Intracoronary Streptokinase. Recently, there has been a tremendous wave of enthusiasm for the use of intracoronary thrombolysis in patients with evolving acute infarction. Initial reports (table 13–5) suggested that intracoronary infusion of thrombolysin (streptokinase and plasmin) [65] or streptokinase [66–68] to vessels supplying the area of infarction might result in rapid recanalization of the vessel, restoration of antegrade coronary flow, and significant relief of ischemic chest pain [65–67], with potential salvage of myocardium (table 13–6). The success rate of antegrade reperfusion of coronary arteries (using a combination of intracoronary nitroglycerin, guidewire manipulation, and thrombolytic therapy) averaged 80 per cent in four series of patients with evolving acute myocardial infarction [65–68]. Despite reportedly successful reperfusions, Q-wave infarcts still evolved in many cases [65,67]. It is no surprise that severe stenoses were often noted at the site of coronary occlusions [68] and that about one-third of the patients in these studies subsequently underwent surgical revascularization. This form of therapy did not seem as effective at the site of subtotal lesions [66,67], or in patients with unstable angina [66]. Remarkably, in these studies the majority of patients received the interventions within 6 hours of the onset of symptoms.

Improvement in ventricular function after reperfusion is difficult to assess. A number of reports suggest that after routine management of patients with acute evolving myocardial in-

TABLE 13–4. Large, randomized trials of beta blockers given to survivors of acute myocardial infarction

Trial	Agent	Time given after infarction	Duration of treatment
Wilhelmsson et al, 1974 (42)	Alprenolol, 400 mg/day	1 to 3 weeks	2 years
Ahlmark et al, 1974 (43)	Alprenolol, 400 mg/day	2 weeks	2 years
Multicentre International Study (44)	Practolol	1 to 4 weeks (mean = 13 days)	2 years
Baber et al, 1980 (54)*	Propranolol, 120 mg/day	2 days to 2 weeks (mean = 8.5 days)	3 to 9 months
Norwegian Multicentre Study Group, 1981 (46)	Timolol, 20 mg/day	1 to 4 weeks (mean = 11 days)	12 to 33 months (mean = 17 mo)
BHAT-Multicenter, 1981 (47)	Propranolol 120 to 240 mg/day	5 to 21 days (mean = 13.8 days)	30 months

*Anterior infarcts. Study designed to show 50 per cent reduction in mortality.

farction, overall left ventricular function does not change from the time of hospitalization to discharge. Some studies have reported improvement in postintervention ejection fractions estimated 2 to 3 weeks after thrombolytic therapy [67,68] as well as in thallium-201 perfusion studies [69,70], and wall motion abnormalities [64]. Other authors report no improvement in either overall or regional ventricular function following streptokinase reperfusion [71,72] while others report an early improvement in radionuclide left ventricular ejection fraction [73,74], and regional function [74] that is sustained at 6 months. Intracoronary streptokinase administered during evolving acute infarction has been reported to reduce mortality at one month [76] and at one year in patients in whom thrombolysis results in complete reperfusion [77]. A reduction in mortality over the longer term has also been demonstrated in patients who did not initially have cardiogenic shock or pulmonary edema [74].

In a randomized European thrombolysis trial, patients received either conventional medical therapy (264 patients) or thrombolytic therapy (269 patients) which consisted of intracoronary streptokinase (152 patients) and a combination of intravenous and intracoronary streptokinase (117 patients). When compared with conventional therapy, thrombolytic therapy reduced one-month mortality (5.9 versus 12%), 12-month mortality (9 versus 16%), the incidence of cardiogenic shock (4.8 versus 9.1%), and ventricular fibrillation (14.1 versus 23%). In the patients randomized to thrombolytic therapy, there was a higher incidence of recurrent myocardial infarction (13 versus 6.1%) and bleeding (20 versus 2.7%) [75].

Complications attributed to intracoronary administration of streptokinase are mainly due to heparinization, bleeding from the arterial puncture site and reperfusion arrhythmias; otherwise, patients appear to tolerate the procedure surprisingly well. Hemorrhagic infarcts have not been noted at the time of surgery [67].

Early administration of intracoronary streptokinase has proved over the last 3 years to be an enormous exercise in logistics. The drug is expensive, is available only to patients arriving at hospitals equipped with catheterization facilities, and is subject to delays in the delivery of the active agent to infarcting myocardium. The key issue remains that most pharmacological agents cannot be delivered in sufficient concentration very early after the onset of acute myocardial infarction. Because of the practical difficulties posed by early administration by the intracoronary route, interest in the use of in-

Number of patients	Sudden death		Total		Re-infarction	
Placebo = 116	11	$p < 0.05$	14	NS	18	NS
Alprenolol = 114	3		7		16	
Placebo = 93	9	$p < 0.05$	11	NS	15	NS
Alprenolol = 69	1		5		4	
Placebo = 1,533	78	$p < 0.01$	175	$p < 0.01$	97	NS
Practolol = 1,520	48		123		75	
Placebo = 365			27	NS	14	NS
Propranolol = 355			28		15	
Placebo = 939	95	$p < 0.001$	152	$p < 0.001$	20%	$p < 0.001$
Timolol = 945	47		98		14%	
Placebo = 1921	89	$p < 0.05$	183	$p < 0.01$		
Propranolol = 1916	64		135			

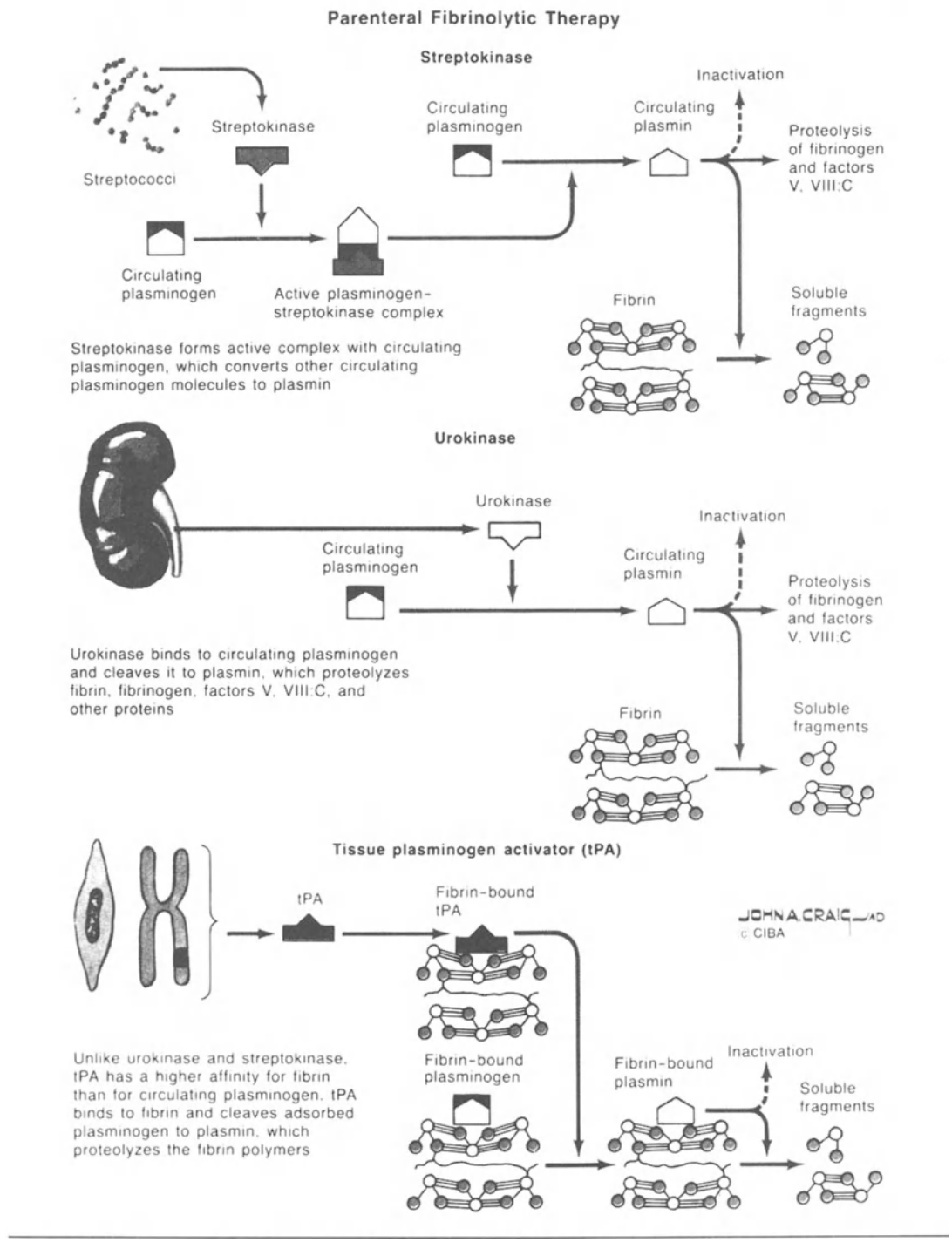

FIGURE 13–2. Mode of action of different forms of lytic therapy. (From Moake JL, Levine JD: Thrombotic disorders. *Clinical Symposia*, 37:18, 1985, New Jersey, CIBA-Geigy Corporation, with permission.)

travenous streptokinase has been rekindled.

2.4.2. Intravenous Streptokinase. Intravenous streptokinase was first used in the treatment of acute myocardial infarction in 1959 [78]. Subsequently, a number of clinical trials on thrombolytic agents in acute infarction revealed a trend toward reduced mortality rates in patients treated with intravenous streptokinase [79]. In many, the institution of thrombolytic therapy was relatively late, i.e., 12 to 24 hours after the onset of symptoms. Prospective, randomized trials have shown that intravenous streptokinase is less effective than intracoronary streptokinase with an intravenous dose of 0.5 million units [80]. However, in a small group of patients who received a higher dose of intravenous therapy (1.5 million units) the success rate of thrombolysis appeared better than that achieved with the lower intravenous dose. High-dose, short-term intravenous streptokinase infusion in patients with acute infarction has a dose-dependent thrombolytic effect. Thrombolysis occurred in 10 per cent of patients receiving 0.5 million units of streptokinase intravenously and 44 per cent receiving 1.0 million units intravenously over a 45-minute period [81]. Other studies support the fact that brief, high-dose (1.5 million units), administration of intravenous streptokinase can be a safe and effective means of restoring coronary blood flow early after acute infarction [82,84]. It will be interesting to see whether future prospective, randomized trials show high-dose intravenous therapy given soon after the onset of infarction will have a beneficial effect. If so, this drug could be administered to most patients with evolving acute infarctions.

In a recent clinical trial conducted in Israel, intravenous streptokinase (750,000 units) was adminstered to patients with a history of chest pain of 0.5 to 4 hours duration (unresponsive to 5 mg of isosorbide dinitrate and 10 mg of nifedipine sublingually) who demonstrated ST elevation of 0.2 mV in two ECG leads. The treatment was administered a mean of 1.7 ± 0.8 hours after the onset of chest pain. In those patients who received intravenous streptokinase within 90 minutes of the onset of chest pain (compared with those who received the treatment between 90 minutes and four hours after the onset of chest pain) at the time of cardiac catheterization four to nine days later, there appeared to be a lower QRS score on the electrocardiogram (a measure of electrocardiographic damage) and higher global and regional ejection fraction of the left ventricle. Most patients developed Q-wave infarctions but of the eight who evolved non-Q wave infarctions, six were in the very early treatment group [83]. This study illustrates that very early intervention with intravenous streptokinase is possible and may be effective if given within 90 minutes of the onset of symptoms of acute infarction.

2.4.3. Tissue plasminogen activator (t-PA). Since streptokinase activates both circulating and fibrin-bound plasminogen in a relatively indiscriminate manner, there has been a search for thrombolytic agents that will activate plasminogen locally on the fibrin clot surface. A human tissue-type plasminogen activator (t-PA) has been developed and purified in relatively large quantities [85]. This agent, administered intravenously to dogs with experimental infarction, has produced rapid thrombolysis and restored myocardial perfusion [86]. In addition, a human tissue-type plasminogen activator gene has recently been synthesized and cloned, and its products have been found to have thrombolytic properties similar to those of the natural activator (r-TPA) [88]. These exciting new developments may provide a safe intravenous thrombolytic agent with a high affinity for recently formed clots.

A preliminary report of a study designed to assess the relative thrombolytic activity and side effects of intravenous t-PA and of intravenous streptokinase in patients with acute myocardial infarction has recently been published [89]. With the primary end point of the study being recanalization of a totally occluded infarct-related artery 90 minutes after IV drug infusion, t-PA was found to be almost twice as effective as intravenous streptokinase in opening occluded arteries (table 13–7). No major unexpected side effects or toxicity was noted with t-PA, and no clear-cut instances of fatal or central nervous system hemorrhages were noted in either treatment group. Hematoma at the catheterization site occurred in almost half the patients and gastrointestinal bleeding in 6 to 10 per cent.

A single-blind randomized European cooperative study examined the patency of the infarct-related coronary in patients with acute myocardial infarction of less than six hours

TABLE 13–5. Initial studies of intra-coronary thrombolytic therapy in acute myocardial infarction

Study	Patients	Angiography	"Reperfusion"	"Failure"	Comments
Ganz et al, 1981 (65)	20 with severe pain, ST elevation (8 anterior, 12 inferior), no Q waves.	8 anterior (6 LAD occlusion, 2 LAD narrowing)	4/20 with SK (2000 IU/min), 15/20 with SK (4,000 IU/min) Time of symptoms = 2.8 to 5.8 hr (mean 4 hr).	1/20 showed RCA occlusion, catheter no closer than 5 cm. Subsequent VSD and postoperative death.	Reperfusion accompanied by arrhythmias, pain relief, evolution of Q waves, and improvement in regional wall motion at 10 to 12 days.
Thrombolysin	Seen about 2.7 hr after onset of pain.	12 inferior (3 Cx occlusion, 9 RCA occlusion)	Reperfusion with low-dose SK in 43 min and high-dose SK in 21 min		Surgical revascularization in 7/20.
Rentrop et al, 1981 (66) Streptokinase (1,000 to 1,200 u/min)	Acute infarction (29) Unstable angina (5) with ECG ischemia initially. Angiography within 5.6 + 0.4 hr of onset of pain.	29 infarct patients (total occlusion in 20 and subtotal in 9)	22/29 showed re-opening or increase in diameter (4 with NTG or nifedipine, 1 with guidewire and SK). Severe stenoses evident after reperfusion.	7/29 (3 had complete occlusion and 4 had subtotal lesions).	Continuing pain relieved in 13/14, Q waves evolved in 29/34, ↓ LVEDP and ↑ EF with reperfusion. Patent "infarct" vessel in 18/19 at 25 ± 11 days. Surgical revascularization in 10/29.
		Subtotal occlusion in 5 unstable angina patients.	0/5 showed no diameter change.	5/5	Surgical revascularization in 3/5

Mathey et al, 1981 (67)	41 with severe pain, ST elevation (15 anterior, 26 inferior), no Q waves seen within 3 hr of onset of pain. 6 with cardiogenic shock.	Total coronary occlusions: LAD = 15, RCA = 16, Cx = 10	30/41. Seen within 29 ± 15 min. Patent vessel in 12/15 at 3 weeks. Severe stenoses evident after reperfusion in all patients.	11/41 after 99 ± 17 min SK infusion. Causes unclear.	Reperfusion accompanied by arrhythmias, pain relief, new Q waves or R fall in 24/30 of reperfused group, 3 reperfused patients reinfarcted. Ejection fraction improved at 1 to 3 wk, patent infarct vessel in 12/15 at 1 to 3 weeks Surgical revascularization in 10/30.
Reduto et al, 1981 (68)	32 with severe pain, ST elevation (17 anterior, 15 inferior). 18 had Q waves. Seen within 18 hr of onset of pain.	26 total occlusion of infarct vessel.	18/26 with SK in 23 ± 12 min. 1/26 with NTG. 17/18 had severe stenoses after reperfusion.	7/26 after NTG and SK. 1/26 improved with NTG, no SK.	Reperfusion accompanied by no *immediate* change in LVEDP or EF. No increase in EF seen at time of discharge.
Streptokinase (2,000 u/min)		6 severe proximal stenoses of infarct vessel.	0/6 showed no improvement with NTG and SK.	6/6	Surgical revascularization in 10/32.

NTG = nitroglycerin; NTS = nitrates; SK = streptokinase.

TABLE 13–6. Noninvasive markers of coronary reperfusion

1. Rapid ECG evolution toward normal
2. Ventricular arrhythmias
3. Relief of chest pain
4. Early peaking of creatine kinase
5. Improved hemodynamics

duration, 75 to 90 minutes after intravenous administration of human tissue-type plasminogen activator, or intravenous streptokinase. The dose of streptokinase was 1½ million IU administered over 60 minutes. While the patency of the infarct-related vessel prior to administration of these agents was unknown in this study, there was a higher patency rate after treatment in the tissue-type plasminogen activator-treated group of patients (70 versus 55%). Activation of the systemic fibrinolytic system was far less pronounced with recombinant human tissue-type plasminogen activator than with streptokinase. Hospital mortality was identical in the two treatment groups [87]. These results indicate that t-PA may offer a chance to favorably influence the evolution of acute myocardial infarction. (The properties of t-PA and other thrombolytic agents are compared in table 13–8.)

Even if routine coronary thrombolysis does become possible, it is only the first step. After clot lysis, maintenance of coronary flow becomes the next priority, and it remains to be seen whether this can be achieved over the long term with agents such as anticoagulants, aspirin, or dipyridamole. In the future, initial thrombolysis combined with later surgical revascularization or coronary angioplasty may constitute optimal management for many patients presenting with early evolving acute myocardial infarction [90]. However, future clinical trials will have to demonstrate that this approach is feasible, beneficial, and cost-effective.

2.5. CORONARY ARTERY BYPASS GRAFTING

If irreversible myocardial injury has already occurred after acute infarction, coronary bypass surgery will neither improve left ventricular performance nor salvage myocardium, and the patient will be subjected to the risks of a major operation. The mortality rate associated with coronary bypass surgery in patients with chronic ischemic heart disease is around 1 per cent, but can be 10 or 20 times greater if the operation is performed within the first 24 hours after the onset of infarction.

Under most circumstances, emergency revascularization as a treatment for acute myocardial infarction is not justified. The treatment is clearly contraindicated in low-risk patients or those with uncomplicated transmural infarcts if revascularization cannot be accomplished within 4 to 6 hours after the onset of the event. Nevertheless, if during cardiac catheterization an infarction appears to be acutely evolving, or if the patient exhibits global ischemia, emergency operation should be considered and may prove effective. Similarly, if a patient whose coronary anatomy has been reviewed in preparation for subsequent surgery presents in an early acute phase of infarction, the bypass operation may be feasible. This is particularly true if facilities are available to provide circulatory support by intraaortic balloon counterpulsation while arrangements for emergency surgery proceed.

Interestingly, two recent reports reveal that emergency revascularization of patients with acute myocardial infarction may not be as hazardous as was previously believed [91] and

TABLE 13–7. Preliminary results of TIMI trial*

Drug	Number of patients	Reperfusion at 90 min		Death
Streptokinase	115	40 (35%)	$p < 0.001$	12/147 (8%)
r-TPA	99	59 (60%)		7/143 (5%)

END POINT: Recanalization of totally occluded infarct-related artery 90 min after IV drug infusion
Onset of pain to drug infusion = 4 hours and 47 minutes.
Drug infusion to best reperfusion = 60 minutes.
The Thrombolysis in Myocardial Infarction (*TIMI*) Trial: Phase I findings. *N Engl J Med* 312:932, 1985.

TABLE 13–8. Properties of thrombolytic agents

	Streptokinase	Urokinase	Pro-urokinase	Tissue type plasminogen activator
Molecular weight and forms	~47,000	~55,000 (HMW) double-chain (i.e., Breokinase) ~33,000 (LMW) single-chain (i.e., Abbokinase)	~55,000 Single-chain forms	~72,000 Single- and double-chain forms
Enzymatic activity (IU/mg)	0 Not a protease. Forms equimolar complex with plasminogen (enzymatic activator complex)	~100,000 (HMW) ~200,000 (LMW)	0 (a proenzyme)	~90,000 for both forms
Integrity in plasma	Complexation with antibodies (before activator complex)	Complexation with inhibitors	Stable	Complexation with inhibitors
Interaction with fibrin clot	Little	Little	Dependent on for activation in plasma	Strong binding and potentiation of lytic activity
Fibrin clot specificity	Little	Little	High	High
Systemic effect	Significant	Significant	Little to none	Little to none
Half-life in circulation	18 to 23 min (biphasic)	16 min	Unknown for man	2 min
Antigenicity	+	0	0	0
Physiologic concentration in blood	0	0	5 to 10 μg/L	5 to 10 μg/L

may result in a lower in-hospital and long term mortality when compared with medical treatment [92]. In one study, 75 patients underwent emergency saphenous vein bypass grafting within 6.5 hours (range = 3.5 to 25 hours) of the onset of severe, unrelenting chest pain [91]. Sixteen patients were unstable, 14 being hypotensive and requiring vasoactive medications and two being in cardiogenic shock that required intraaortic balloon counterpulsation and catecholamines. In this group there were one operative and two late deaths. In the 59 hemodynamically stable patients (five of whom required direct-current shock preoperatively for ventricular fibrillation) there were no early or late deaths over an average followup of 18 months. The average preoperative creatine phosphokinase (CPK) in the unstable group of 16 patients was 892 compared with 504 IU/L in the hemodynamically stable patients ($p < 0.05$). In 40 patients subsequently restudied, ejection fraction and stroke volume increased while ventricular end-diastolic pressures and end-systolic and end-diastolic volumes were reduced. Overall operative mortality was 1.3 per cent and late mortality 1.8 per cent [91].

In another dramatic study, two types of therapy for patients with acute myocardial infarction were compared [92]. One group underwent usual medical therapy and a second group underwent early coronary artery bypass grafting, i.e., within 6 hours of the onset of pain. In the surgically treated group, the in-hospital and long-term mortality rates were lower than those in the medically treated group.

These studies suggest that emergency revascularization is feasible during evolving infarction and may be beneficial if the patient is experiencing intractable chest pain and the CPK has not risen too high (<1000 IU/L, or 5 times normal) [91]. Such a situation can occur in patients with recent non-Q-wave infarction in

whom other large areas of myocardium are threatened or in those with intractable pain or ECG evidence of ischemia (with or without hemodynamic compromise) and who are unresponsive to aggressive medical therapy.

Whether emergency revascularization surgery has more than a limited role in acute myocardial infarction remains to be evaluated by careful, prospective, randomized trials.

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14. CORONARY ARTERY SPASM

Coronary artery spasm has provoked considerable interest as an etiological factor in chest pain syndromes, as a diagnostic challenge, and as a treatable form of cardiac pain that may not respond to traditional therapy. In order to place the concept of coronary spasm in perspective, it is important to consider the normal features of coronary flow and resistance.

1. Coronary Flow and Resistance

Coronary blood flow (Q) is related directly to the perfusion pressure gradient (ΔP) and inversely to resistance (R) of the coronary vascular bed. This is mathematically summarized in the following equation:

$$Q = \frac{\Delta P}{R}$$

Klocke has proposed that total coronary resistance may be considered the sum of three separate resistances that are identified on a functional rather than an anatomical basis:

$R1$ = *basal viscous resistance*, defined as the impedance to flow offered by the entire coronary vascular bed during diastole, when it is fully dilated.

$R2$ = *autoregulatory resistance*, the major component of resistance and thought to result from tonic contraction of vascular smooth muscle at the arteriolar level.

$R3$ = *compressive resistance*, representing increases in resistance during the cardiac cycle due to compression of vascular structures by intramyocardial pressure.

Unlike other vascular beds, myocardial blood flow varies strikingly during different phases of the cardiac cycle. At the onset of isovolumic ventricular contraction, myocardial compressive forces ($R3$) reduce coronary flow in arteries supplying the left ventricle; as ventricular systole progresses, this extravascular compression persists. With isovolumic relaxation, myocardial compression of the coronary arteries diminishes and coronary blood flow rises markedly. Throughout the remainder of diastole, coronary blood flow declines gradually as perfusion pressure slowly falls. This marked, cyclical variation in flow is less prominent in arteries supplying the right ventricle, since here extravascular compression by the myocardium is considerably less.

Different levels of the coronary arterial bed also react differently to physiological stimuli and pharmacological agents. Large epicardial or "conductance" vessels contribute little to overall coronary vascular resistance ($R1$), whereas intramyocardial or "resistance" vessels ($R2$) have a well-developed media and a smaller diameter, allowing profound changes in coronary artery resistances. The resistance vessels respond to the demands of the myocardium for oxygen by altering their intrinsic tone. When myocardial oxygen demands increase, these vessels dilate and allow flow to increase proportionately. Therefore, under normal conditions, the large vessels contribute little to overall coronary vascular resistance, and fluctuations in resistance primarily reflect changes in the lumina of small vessels. Indeed, accumulation of myocardial metabolites (such as H^+, K^+ and lactic acid), increased partial pressure of CO_2, and reduced partial pressure of O_2 are all thought to reduce coronary vascular resistance by causing dilatation of the small, precapillary resistance vessels. (These vessels are *not* visualized on routine clinical coronary arteriograms.)

The concept that coronary blood flow is regulated primarily by the metabolic requirements of the myocardium has been placed in

perspective by more recent studies demonstrating profound neural influences on coronary vascular tone. Early experimental studies using either in vitro techniques or anesthetized, often open-chest preparations showed that coronary blood flow was in large part regulated by myocardial metabolic requirements and that under these conditions neural influences were relatively unimportant in controlling flow. In marked contrast, more recent investigations in conscious animals have shown that coronary blood flow *is* markedly affected by neural influences, with the *large* epicardial or conductance coronary arteries richly supplied by alpha-adrenergic receptors. (These vessels *are* visualized on coronary arteriography.) These profound differences between anesthetized and conscious animals resulted from the differences in the experimental conditions: Anesthetic agents are known to diminish reflex control of the circulation, to depress myocardial contractility, and to have a direct dilating effect on coronary resistance vessels. However, in the normal conscious animal (and in humans) neurogenic influences on the coronary circulation are potentially of great importance. Therefore, it becomes easier to accept the concept that *coronary tone in large vessels can vary in both a minor and a major way — i.e., dynamic changes in tone may occur* [1].

2. *Clinical Evidence of Coronary Spasm*

In the last decade, coronary artery spasm has been documented as the major cause of variant or Prinzmetal's angina [2–4]. This observation has led to the concept that myocardial ischemia resulting in angina pectoris may be due to two basic mechanisms: (a) *fixed* coronary artery stenosis can cause angina when myocardial demand exceeds the flow capacity of the diseased vessel, or (b) *variable* stenosis due to "spasm" of coronary arteries (or sudden changes in tone) can cause angina by abruptly decreasing flow to the myocardium. Probably both these mechanisms are at work in individual patients (figure 14–1).

3. *Historical Perspective*

Since the initial descriptions of angina pectoris the role of coronary artery spasm in the genesis of cardiac pain has been postulated. Heberden,

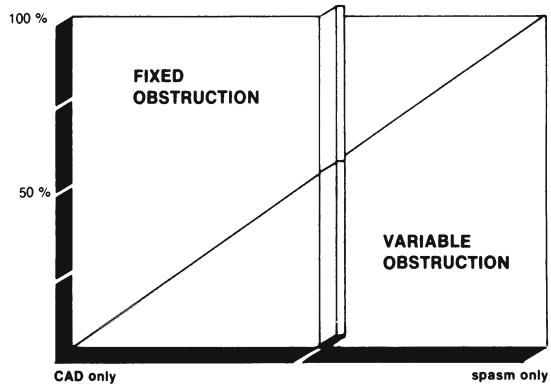


FIGURE 14–1. Different mixtures of fixed and variable obstruction may produce myocardial ischemia. The vertical bar represents a patient in whom both spasm (variable obstruction) and fixed obstruction play significant roles in occluding a coronary artery. This variable mixture of spasm and fixed obstruction may be present not only in Prinzmetal's angina but in classic angina and acute myocardial infarction as well. (From Muller JE: Prinzmetal's angina: A model for the role of spasm in ischemic heart disease. *J Cardiovasc Med* 5:1–7, 1980, Figure 3).

Latham, and Osler suggested spasm of the heart and coronary arteries as a pathophysiological mechanism [5]; however, pathological studies in 1940 correlated postmortem evidence of coronary artery disease with the clinical syndrome of angina pectoris [7] and provided a basis for the concept that angina and myocardial ischemia occur when myocardial oxygen demands outweigh the capacity of diseased coronary arteries to deliver oxygen. Initially, under these circumstances, angina pectoris would be expected to occur at times of increased myocardial demand (e.g., during exercise, with anxiety, or after heavy meals). With the passage of time and increasing severity of the coronary artery obstruction, symptoms would occur at lower levels of oxygen demand, and finally one could imagine angina occurring during minimal activity and perhaps at rest.

With the focus on the relationship between coronary artery disease and angina, the notion of coronary artery spasm as a pathogenic mechanism faded. Nevertheless, Prinzmetal and coworkers described "a variant form of angina pectoris" based on a study of 12 cases

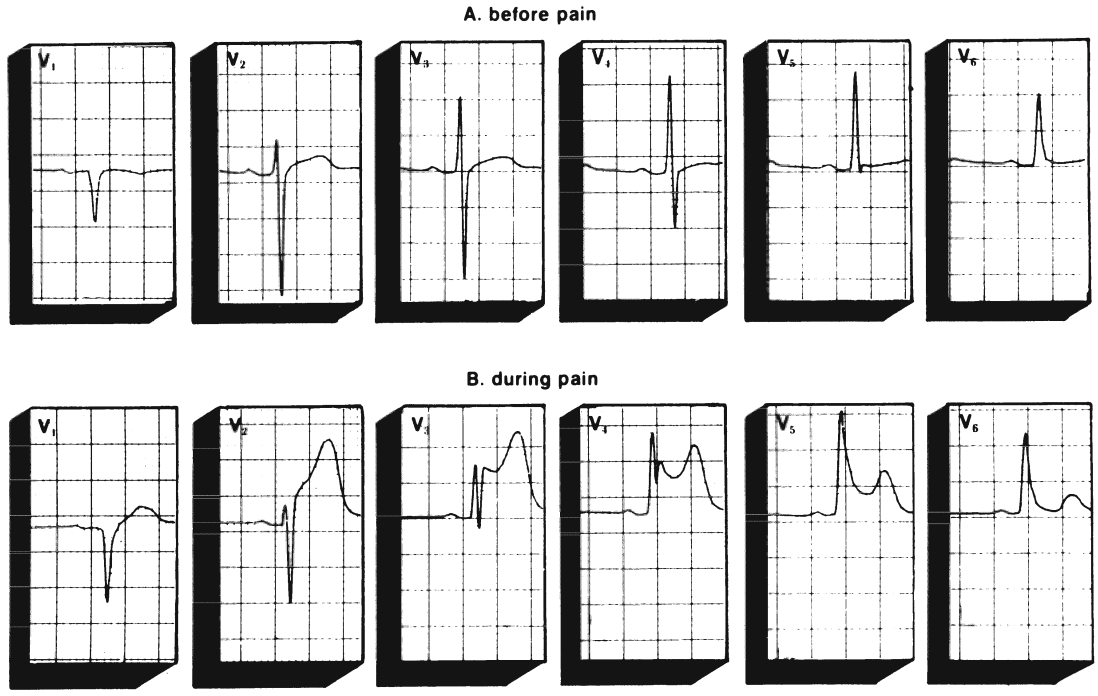


FIGURE 14–2. Classic ECG changes in Prinzmetal's angina. Minor ST-T changes were present before pain (*A*) and during pain (*B*). ST-segment elevation was indicative of transmural anterior ischemia. ST-segment depression and T-wave changes are also known to occur during episodes of coronary spasm. (From Muller JE: Prinzmetal's angina: A model for the role of spasm in ischemic heart disease. *J Cardiovasc Med* 5:1–7, 1980, Figure 1.)

previously described in the literature and of 20 cases observed in their own experience. Among some 250 articles on atypical angina pectoris, they found reports of 12 patients whose clinical picture and electrocardiographic pattern suggested the diagnosis of variant angina [8]. The pain, which was identical to angina pectoris with respect to location, occurred when the subject was at rest or during ordinary activities and did not appear to be precipitated by increased cardiac work. In addition, this type of angina was more severe and of longer duration than classic angina pectoris and tended to occur at the same time each day. The pain was not typically relieved by rest, although nitroglycerin led to prompt relief, as with classic angina. Arrhythmias, often ventricular, occurred in about half the patients during the peak of the attack, but the ECG had remained unchanged during mild attacks or during the early phase of severe attacks. At the peak of severe attacks, ST-segment elevations (with reciprocal depressions) were noted in the areas of distribution of a large coronary artery (figure 14–2). The R waves became taller and broader in some cases or even disappeared temporarily during an attack. ST-segment elevation was noted to disappear completely relatively soon after the painful episode ended. Atherosclerosis of at least one large coronary vessel was felt to be the major cause of both the angina and subsequent infarction, if this occurred.

Variant angina, they suggested, originated from temporary occlusion of a large diseased artery (with a narrow lumen) due to an increase in vascular tone that occurred characteristically when the subject was at rest. This accounted for the transient nature of the attacks, the rapid reversion of abnormal ECG changes to normal, and the similarities between the areas of ST elevation during the anginal attacks and the areas supplied by major coronary arteries. The

TABLE 14–1. Clinical and ECG differences between Prinzmetal's variant angina and classic effort angina

	Prinzmetal's Variant Angina	Classic Effort Angina
1. Type of activity during anginal attack	Rest	Exertion
2. Type of pain	More severe and often of longer duration	Less severe and of shorter duration
3. Cyclical pattern	Often present; patient may be awakened from sleep at nearly same time	Not present
4. Response to nitroglycerin	Relief	Relief
5. ECG during pain	ST-segment elevation with reciprocal depression	ST-segment depression
6. Arrhythmias	Frequently seen; may include ventricular tachycardia/fibrillation or complete heart block	Not particularly common
7. ECG during exercise	May be normal	ST-segment depression associated with chest pain
8. Correlation of ECG pattern of ischemia with coronary arteriograms	Ischemia reflected in anticipated ECG leads based on coronary obstruction (i.e., spasm occurs at site of coronary stenoses)	Ischemia may be reflected in leads other than those expected on basis of coronary obstructions

syndrome did not appear to be rare, and death might occur during an attack due either to arrhythmias (ventricular fibrillation) or to myocardial infarction. It was noted that it was not uncommon for both the variant and classic forms of angina to occur together, in the same patient, either concurrently or in sequence.

The key to diagnosis was thought to depend on a careful history, specifically noting the cyclical nature of the pain, whether it occurred at rest, the waxing and waning periods of equal length, the arrhythmia at the peak of the attack, whether it recurred at about the same time every 24 hours, the failure of excitement to induce the attack, and the occasional relief obtained upon exertion. It was postulated that variant angina was due to coronary artery spasm producing acute transmural, reversible myocardial ischemia. Important clinical and ECG differences between Prinzmetal's variant angina and classic exertional angina are summarized in table 14–1. (As will be discussed later, a clear distinction between these two clinical profiles may not be possible in many patients. Current clinical concepts suggest considerable interpatient and intrapatient variability, so that a more *dynamic* view of coronary artery disease is needed.)

In 1973, Oliva et al conclusively demonstrated coronary artery spasm occurring simultaneously with Prinzmetal's variant angina [2]. A 46-year-old woman was admitted to the hospital because of a 15-minute episode of severe, substernal chest pain that awakened her and was associated with shortness of breath, sweating, dizziness, and nausea. Each attack was accompanied by subsequent sweating and hypotension, ST-segment elevation, and the development of complete heart block. Coronary arteriograms obtained during several fully developed, spontaneous attacks showed spasm of a right coronary artery that appeared to be anatomically normal. The site extent, and degree of obstruction varied during individual attacks. Immediately after the attack subsided the coronary artery appeared normal. A example of angiographic appearances of coronary artery spasm is seen in figure 14–3.

Prinzmetal's variant angina is associated with a *primary decrease* in myocardial oxygen supply. There is no change in the left ventricular pressure-time index (i.e., the product of left ventricular mean systolic pressure, heart rate, and systolic ejection period) either prior to or during episodes of pain [9]. These observations have been supported by hemodynamically monitored and recorded variant anginal episodes showing unequivocal ECG alterations followed, rather than preceded, by reductions

in cardiac output and arterial pressure, lengthening of isovolumic contraction time) decrease in the mean rate of isovolumic pressure development, and a reduction in mean systolic ejection rate. Finally, with the ECG reverting to the pre-attack configuration, cardiac performance has at times been noted to improve to a "supernormal phase" for about 2 minutes [10].

Thus, hemodynamic measurements have shown that episodes of Prinzmetal's variant angina are not precipitated by increased myocardial oxygen demands but by a sudden reduction in myocardial oxygen supply due to severe coronary spasm, with resultant transmural ischemia evidenced by ST-segment elevation in the appropriate ECG leads. In addition, by the thermodilution technique coronary blood flow has been shown to fall during an episode of spontaneous variant angina and then manifest a hyperemic response after disappearance of the chest discomfort. Sophisticated nuclear imaging techniques have shown transmural deficits of tracer uptake during episodes of chest pain with ST-segment elevation. In the same patients, however, scintigrams and ECGs obtained in the absence of chest pain may be completely normal.

4. *Clinical Settings Where Spasm May Be Encountered*

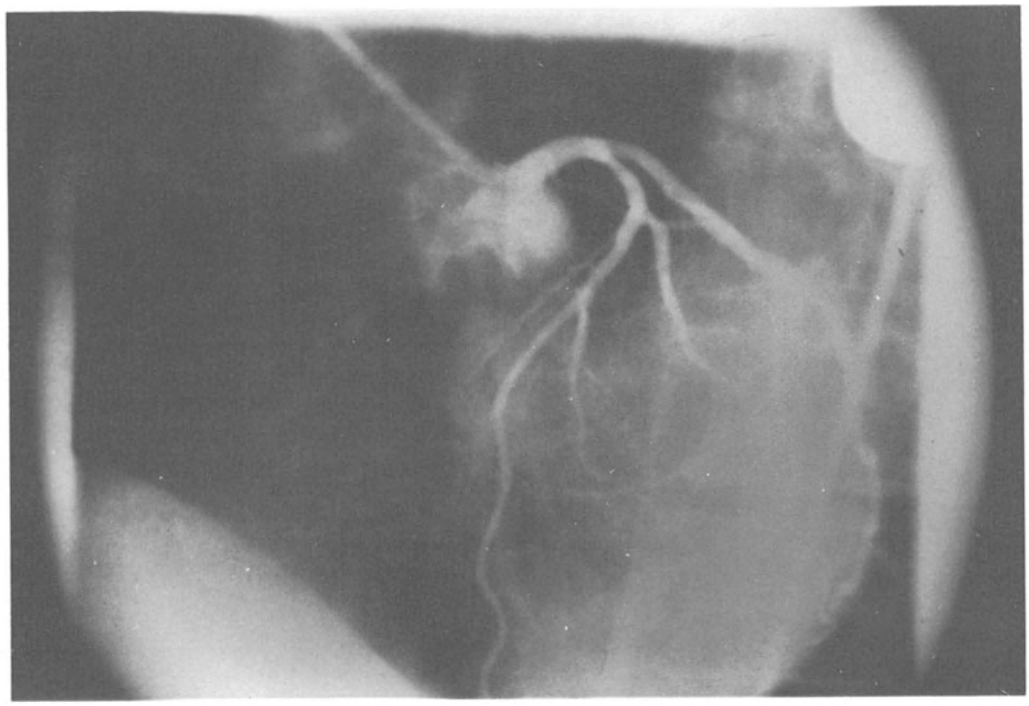
Coronary artery spasm plays a role in a number of coronary disease states, including *variant angina, stable angina, unstable angina, myocardial infarction*, and *perhaps sudden death* [11–14]. It is clear that spasm can occur with or without fixed coronary artery stenoses. Recent elegant studies of episodes of angina pectoris at rest indicate that a reduction in myocardial perfusion, probably initiated by coronary constriction or spasm, can precede the onset of hemodynamic and ECG changes typical of transient, acute myocardial ischemia [15]. In 137 episodes of rest angina studied in six patients, ST elevation occurred in 28 episodes, ST-segment depression in three, and pseudonormalization of previously inverted or flat T waves in 106. Oxygen saturation of the great cardiac vein in 135 anginal episodes prior to the onset of hemodynamic changes and anterior ST and T-wave changes was consistently *followed* by signs of impairment of left ventricular function and was never preceded by any detectable increase in the hemodynamic determinants of myocardial oxygen consumption.

Therefore, these episodes of rest angina were probably initiated by primary reductions in regional myocardial perfusion. The fact that typical anginal pain was associated with only 10 of 137 ischemic episodes and if present, always occurred 50 to 120 seconds after the onset of the ST and T-wave changes was of interest. Pain does not appear to be a reliable and sensitive marker of transient, acute myocardial ischemia. Qualitatively similar hemodynamic patterns were observed in episodes accompanied by ST-segment elevation and pseudonormalization of negative or flat T waves. *Thus, even electrocardiographic findings previously considered nonspecific must be regarded as indicative of possible transient, acute myocardial ischemia in some patients with rest angina.*

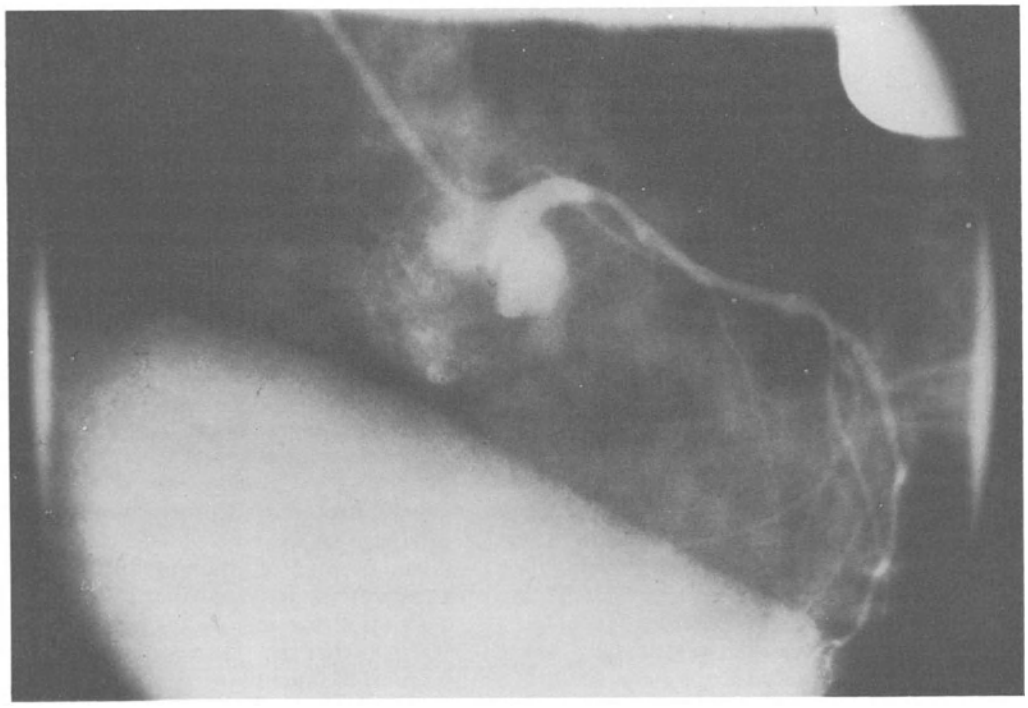
5. *Mechanisms of Coronary Artery Spasm*

Coronary artery spasm may be idiopathic, may be associated with cardiac catheterization, and may occur during exercise or after myocardial revascularization. Its underlying mechanism is unknown. There has been considerable speculation that a potent arterial constrictor, thromboxane A_2, might provoke coronary artery spasm in humans. Most evidence today suggests that while thromboxane A_2 does not initiate spasm, it may be released during an episode. Thromboxane A_2 may in some way be involved in a series of humoral or neural events that initiate coronary spasm or changes in arterial tone in susceptible patients [16,17].

Current clinical research suggests that spasm results from hyperreactivity of the vascular wall secondary to a loss of endothelial integrity. The ultimate pathophysiologic mechanism appears to involve an increase in the flux of calcium ions (Ca^{++}) across the vascular smooth muscle cell membrane. (In the experimental laboratory this is induced by the factors listed in table 14–2.) When intracellular Ca^{++} concentration rises to 10^{-6} M, Ca^{++} binds to the regulatory protein calmodulin, which activates the enzyme myosin kinase. This enzyme phosphorylates the light chain of myosin, thus permitting myosin to interact with actin and thereby leading to contraction of the smooth muscle cell and in turn vasoconstriction. Hence, drugs such as the calcium-channel blocking agents, which inhibit the increase in Ca^{++} influx, have emerged as potent coronary spasmolytic agents [18].



A



B

Coronary artery spasm can be induced mechanically by manipulation of cardiac catheters and is seen most often during selective arteriography of the right coronary artery. Absence of reflux of contrast from the coronary orifice or the presence of an obstruction at the catheter tip might indicate spasm. Usually catheter-induced spasm does not obstruct coronary blood flow and consequent overt myocardial ischemia is rare. Sublingual nitroglycerin administered prior to arteriography will reduce the likelihood of this problem and will usually effectively relieve a catheter-induced episode. The catheter should be withdrawn promptly from the coronary artery if spasm at the tip is observed. Subsequent provocative ergonovine tests are usually negative.

Although several case reports have suggested a link between exercise-induced vasospasm and typical angina pectoris there is only one report linking coronary artery spasm in atheroma-free arteries to classic effort angina with ST-segment depression [19]. Boden *et al* described a case of reversible acute coronary spasm associated with typical effort angina, large perfusion defects of the anterior walls of the left ventricle, and anterior wall ST-segment depression in the absence of demonstrable coronary atherosclerotic narrowing. Two studies have described exercise-induced coronary spasm with ST-segment elevations [20,21]. Several reports have shown that spasm in the presence of a fixed atherosclerotic coronary lesion can produce ST-segment depression. This has been interpreted as representing nontransmural rather than transmural ischemia. Accordingly, it is conceivable that spasm occurring during exercise might cause subtotal occlusion, with nontransmural ischemia and ST-segment depression. Such unusual possibilities provide clues to the full clinical spectrum of coronary artery spasm.

TABLE 14–2. Factors that cause an increase in transmembrane Ca^{++} influx in the laboratory

1. High extracellular $[K^+]$
2. Quick stretch
3. Exposure to vasoactive substances:
   a. Acetylcholine
   b. Serotonin
   c. Histamine
   d. Ergonovine
   e. Cardiac glycosides
   f. Alpha-adrenergic agents following beta-adrenoceptor blockade

Coronary artery spasm has been implicated as a cause of myocardial infarction and death after coronary artery bypass [22–24]. Although sudden circulatory collapse after successful revascularization is relatively rare, the possibility that spasm is the etiological factor should be considered since it may be reversed with direct intracoronary injection of nitroglycerin or sublingual nifedipine. Interestingly, the ECG pattern of acute transmural ischemia (i.e., ST-segment elevation) has been noted in such patients in regions of myocardium perfused by coronary arteries that are not critically diseased. Some affected patients have a history of preoperative variant angina. The cause of postoperative spasm is unknown; however, several potential factors in the perioperative period include elevated blood pH, excess alpha-adrenoceptor activity, physical manipulation of a coronary artery during dissection for placement of a graft, and release of vasoconstrictor substances by platelets. Patterns of nonsignificant abnormalities of dominant right coronary arteries and significant occlusions in the left coronary circulation have been

FIGURE 14–3. A 55-year-old male had a history of episodic severe retrosternal chest pressure provoked only by eating oriental-style food. There was no history of exertional angina and he had a normal electrocardiogram at rest and during exercise. He had a normal exercise capacity. A diagnostic cardiac catheterization was performed. *A* shows an angiogram of the left coronary artery in a left anterior oblique projection. The proximal left anterior descending showed a nonhemodynamically significant lesion prior to the first septal branch. During this part of the procedure he was free of pain and had a normal electrocardiogram. *B* shows an angiogram of the left coronary system in the same left anterior oblique projection following administration of ergonovine. After four doses of 0.05 mg given five minutes apart he developed severe retrosternal chest pressure and anterior ST-segment elevation along with occasional ventricular premature depolarizations. The angiogram shows complete obliteration of the left anterior descending coronary artery. The symptoms, electrocardiographic changes, and angiogram were promptly restored to baseline following administration of sublingual nitroglycerin.

noted on arteriograms of patients with profound hypotension and recurrent ST-segment elevations [23].

Efforts to revive these patients should be directed toward reversing spasm by means of intracoronary nitroglycerin or sublingual calcium antagonists rather than with circulatory support with catecholamines, which may in fact stimulate coronary artery constriction.

6. *Diagnosis of Coronary Artery Spasm*

An accurate diagnosis of coronary artery spasm often requires a combination of careful history taking, frequent ECG monitoring, and sophisticated angiographic techniques. Because coronary spasm may be an episodic event, it may be difficult to diagnose, and the clinician may be uncertain about the existence of spasm in a given individual. (Table 14–3 presents evidence of spasm in descending order with respect to certainty of the diagnosis.) It is important to pursue the diagnosis of spasm clinically in order to define appropriate medical therapy and because the incidence of cardiac arrhythmias and possibly sudden cardiac death in these patients is high.

Although the early description of variant angina by Prinzmetal et al [8] emphasized ST-segment elevation as the prominent ECG finding (figure 14–2), more recent clinical studies show that a variety of ECG patterns may accompany coronary artery spasm. Presumably, these are due to the differing degrees of myocardial ischemia that may exist during the attacks (e.g., transmural vs nontransmural vs widespread) (figure 14–4).

Provocative testing for coronary artery spasm can be performed using *ergonovine maleate*, an ergot alkaloid and alpha-adrenoceptor agonist that has a direct constrictive effect on vascular smooth muscle. This agent is thought to be relatively sensitive and specific for provoking spasm in patients with variant angina [25]. In cumulative doses exceeding 0.40 mg or in increments of greater than 0.15 mg, ergonovine may cause severe coronary vasospasm that is unresponsive to oral or intravenous nitrates but that may be reversed by intracoronary nitroglycerin. To minimize this risk some recommend a protocol of serial doses of no more than 0.05 mg of ergonovine given 5 or 6 minutes apart. No further ergonovine should be given if spasm is observed or if chest pain with ST-segment changes occurs [26]. Direct intracoronary nitroglycerin should be available in bolus doses of 100 to 300 μg and should be given until the spasm is relieved angiographically, chest pain ceases, and the ECG becomes normal.

TABLE 14–3. Approach to diagnosis of coronary artery spasm*

1. Spontaneous focal spasm documented arteriographically associated with chest pain and ST-segment elevation on ECG
2. Ergonovine-induced focal spasm documented arteriographically associated with chest pain and ST-segment elevation
3. Spontaneous or ergonovine-induced focal spasm documented angiographically with neither chest pain nor ST-segment elevation
4. Clinical history of rest pain with associated reversible ST-segment elevation on ECG Holter monitoring
5. Response to empirical clinical trial with potent spasmolytic therapy, including calcium-channel blocking agents and nitrates

*Evidence is presented in descending order with respect to certainty of the diagnosis.

Because of the hazard of serious complications, ergonovine should be given in gradually increasing doses and under carefully controlled circumstances, with appropriate resuscitative equipment, personnel, and drugs readily available. Because of the occasional need for intracoronary nitroglycerin, many investigators suggest that ergonovine testing *not* be performed outside the catheterization laboratory In normal patients, ergonovine reduces coronary artery caliber, so that it would be hazardous to administer this drug to patients with hemodynamically significant coronary artery stenoses.

In general ergonovine testing should be performed when there is a need to know whether coronary artery spasm is contributing to a patient's clinical symptoms and when there are no contraindications to the test (table 14–4). Most investigators will not proceed with such provocative testing unless the coronary angiograms are normal or show absolutely minimal disease.

7. *Therapy for Coronary Artery Spasm*

7.1. NITRATES

Like classic angina pectoris, variant angina responds promptly to sublingual or intravenous

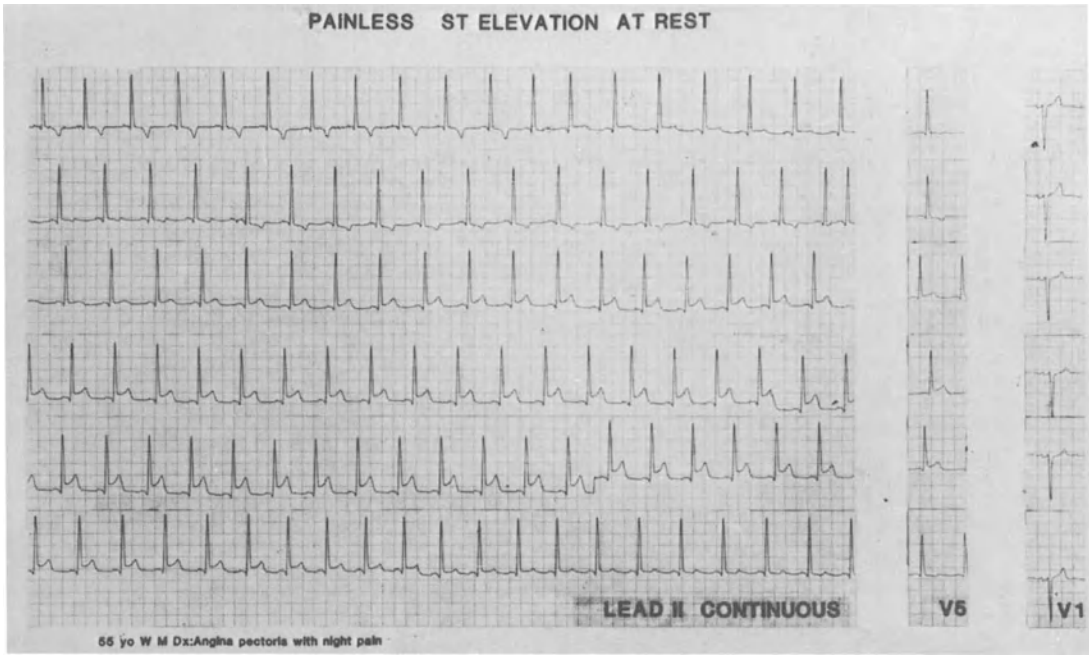


FIGURE 14–4. During prolonged ECG monitoring, this patient demonstrated transient striking ST-segment elevation that was not accompanied by angina pectoris. (From Cohn PF, Wynne J: *Diagnostic Methods in Clinical Cardiology*. Boston, Little, Brown, and Company, 1982. Chapter 3, Figure 13, page 46.)

TABLE 14–4. Factors to consider when selecting a patient for provocative testing with ergonovine

Appropriate candidates:
1. Individuals with normal or near normal coronary arteries and
   a. Transient nonspecific abnormalities on ECG during chest pain
   b. Ventricular arrhythmias or syncope during chest pain
   c. Ischemic type chest pain with normal ECG during pain
   d. Left bundle branch block with rest angina
   e. Pacemaker rhythm with rest angina
   f. Rest angina but no ECG recorded during pain
2. Patients with persistent chest pain after coronary artery surgery

Contraindications:
1. Acute myocardial infarction
2. Uncontrolled chest pain
3. Uncontrolled ventricular arrhythmias
4. Amenorrhea in premenopausal female
5. Severe hypertension
6. Severe left ventricular dysfunction
7. Severe aortic stenosis
8. Significant left main coronary artery disease (>50% diameter reduction)

Relative Contraindication:
≥90% stenosis of a major epicardial coronary artery

Adapted from Conti CR, Pepine CJ, Feldman RL: *Coronary Artery Spasm*. Baylor College of Medicine Cardiology Series, Vol 4, No 2, 1981.

nitroglycerin. Experience has shown that all forms of nitrates, including agents such as isosorbide dinitrate and nitroglycerin paste, can be effective in controlling episodes of coronary artery spasm in a variety of clinical settings. (Table 14–5 lists data on the clinical pharmacology of the available nitrate preparations.) In travenous nitroglycerin is a rapidly acting coronary spasmolytic agent (figure 14–5).

The technique for administering intravenous nitroglycerin is important and relates to dose. Since nitroglycerin may adhere to the polyvinyl chloride (PVC) tubing used in standard setups

for intravenous drug administration, several companies offer a non-PVC "infusion set" along with preparations of intravenous nitroglycerin (table 14–6). Initially, an infusion rate of 5 to 10 μg/min should be used followed by an increase of 5 μg/min every 5 minutes, as dictated by the clinical situation. When PVC tubing is used it is not uncommon to encounter patients who require more than 100 μg/min for control of angina. The dose is usually lower when non-PVC administration sets are used. Unfortunately such special infusion sets are expensive, are not readily available, and in certain circumstances are not compatible with automated drug infusion equipment. Because of a variety of factors (length of tubing, nitroglycerin concentration, flow rate), no simple calculation or correction factor can be relied upon to determine how much intravenous nitroglycerin is actually adsorbed to PVC tubing, so that one should use the *minimum* amount of tubing needed to deliver the drug.

Complications of IV nitroglycerin are listed in table 14–7.

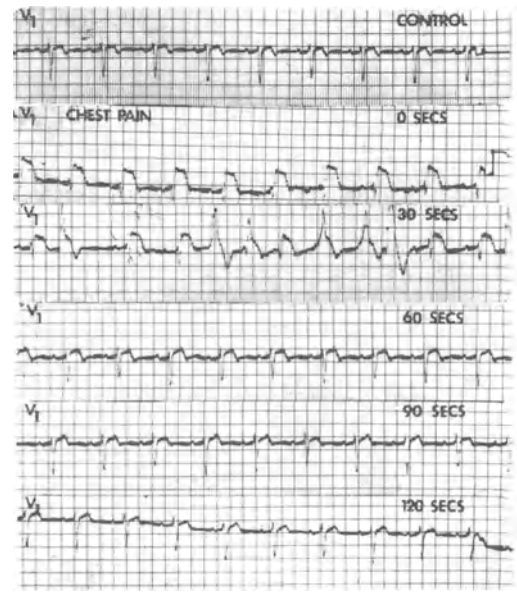


FIGURE 14–5. Noncontinuous rhythm strips showing the time course of disappearance of ischemic ST changes after administration of 100 g intravenous bolus of glyceryl trinitrate at time 0 seconds. (From Antman EM, Gunther S, Barry W: Beneficial effects of intravenous glyceryl trinitrate in a case of Prinzmetal's angina. *Br Heart J* 43:88–91, 1980.)

7.2. CALCIUM-CHANNEL BLOCKING AGENTS

These agents inhibit contraction of smooth muscle cells by diminishing the cellular uptake of calcium thus interfering with a process fundamental to cellular contraction (see section 5.). Two commonly used agents (e.g., nifedipine and verapamil) are coronary vasodilators that are effective in preventing coronary artery spasm.

In a large study of nifedipine therapy in 127 patients with symptoms of myocardial ischemia associated with ECG and/or angiographic evidence of coronary spasm, this drug significantly reduced the mean weekly rate of anginal attacks from 12 to 2 [27]. Most patients in the study were refractory to conventional antianginal therapy, including nitrates and beta blockers, and one-third had a history of at least one episode of ventricular tachycardia during an attack of angina. The effectiveness of nifedipine was suggested by marked reductions in the nitroglycerin requirements, complete control of anginal attacks in two-thirds of patients, and a reduction in anginal frequency in virtually all patients (figure 14–6). Although this study was neither randomized nor blinded, the decreases in attack rate and nitroglycerin requirements appeared marked and sustained considering the fact that these patients had not previously responded to conventional therapy. The drug was generally well tolerated. Only 5 per cent of patients had to discontinue the drug because of intolerable side effects (e.g., dizziness, flushing, pedal edema, hypotension).

Similar beneficial effects in cases of coronary spasm have been reported with verapamil and diltiazem. Important data on the clinical pharmacology of calcium-channel blocking agents are summarized in table 14–8.

7.3. BETA-ADRENOCEPTOR BLOCKADE

Propranolol is very effective in patients with classic angina, since it diminishes the increases in myocardial oxygen demand that initiate cardiac pain. In coronary artery spasm, a decrease in myocardial oxygen supply may be the principal determinant of the onset of angina, so that the theoretical benefits of beta blockade are not as compelling. In theory, beta-adrenoceptor

TABLE 14–5*A*. Commonly used generic preparation of nitroglycerin-related compounds for which there are adequate preliminary scientific data regarding duration of action and dosage (effective dose, onset, and duration of action may very greatly)

Drug	How supplied	Dose	Onset of action	Duration	Limitations
Amyl nitrite	Ampule inhalant, 0.18 ml or 0.30 ml	1 ampule 0.18 ml or 0.30 ml, as required	2 to 5 sec	Peak action 12 to 50 sec	Brief duration of action; reflex tachycardia or hypotension occasionally severe; mainly used for diagnostic purposes; methemoglobinemia reported in animals and humans after nitrites
Isosorbide dinitrate (includes isordil, sorbitrate)	Isosorbide dinitrate: Sublingual tablets, 2.5 or 5 mg; oral tablets, 10 or 20 mg; chewable, 5 mg	*Sublingual*: 1 to 2 every 2 to 3 hr	5 min (10 mg) 10 min (5 mg) 15 min (5–15 mg) Under 45 min 15–30 min (5–10 mg)	At least 1 hr At least 65 min 90 min (CHF pts) At least 100 min 3 to 4 hr (CHF, AMI pts) 2 to 4 hr	Delayed onset in most cases
			1 hr 1 hr	4 hr	
		Oral: 5 to 30 mg four times daily	15 min (5-30 mg) 20 min (20 mg)	Greater than 2 hr 4.5 hr (CHF pts) Effective at 60 min (10 mg) Up to 4 hr (AMI pts) On average, to 4.2 hr (range 1 to 24 hr)	Delayed onset in most cases
			Under 1 hr (20 mg) 4 hr (20 mg) 5 min (10 mg)	4 hr 6 hr 3 hr	
		Chewable: 1 every 2 to 4 hr			
Nitroglycerin ointment	2% nitroglycerin ointment	½ to 2 inches every 4 hr (typically)	<15 min (1.2 in) 20 min (1½ to 4 in) <1 hr 30 to 60 min (½ to 1½ in)	1 hr 6 hr (CHF pts) 3 hr or more 5 hr (AMI pts)	Delayed onset in most cases; cosmeticaly displeasing
			<2 hr	Up to 5 hr or more Up to 8 hr	
Sublingual nitroglycerin	Sublingual nitroglycerin tablets, 0.3, 0.4, or 0.6 mg	1 sublingually till relief	About 2 min (0.4 mg) 3 min (0.6 mg) <5 min (0.6 mg) 15 min	Effect absent at 55 min 8 min 15 min (CHF pts) 30 min	Brief duration of action

Note: CHF pts = patients with congestive heart failure; AMI pts = patients studied during acute myocardial infarction.
[a]Effective dose may often be greater than that recommended by manufacturer.

TABLE 14–5*B*. Commonly used commercial preparations of nitroglycerin-related compounds for which there are inadequate data regarding onset of action, duration, and dose

Preparation	Drug and how supplied	Conventional dose	Onset	Duration	Limitations
Antora TD	Pentaerythritol tetranitrate, 30 mg capsule; "B" includes secobarbital, 50 mg	1 orally every 12 hours on empty stomach	Unknown but likely very delayed	Long	Probably equivalent to oral isosorbide dinitrate
Cardilate-Cardilate P	Erythrityl tetranitrate, 5, 10, or 15 mg tablets oral or sublingual; 10 mg chewable; "P" has 10 mg oral with 15 mg phenobarbital	5 to 30 mg three times daily	Probably comparable to isosorbide dinitrate	Probably comparable to isosorbide dinitrate	Delayed onset sublinqual, oral
Cartrax	Pentaerythritol tetranitrate tablets, 10 mg or 20 mg, with hydroxyzine hydrochloride, 10 mg	1 to 2 three times daily or four times daily orally	Unknown but likely very delayed	Long	Probably equivalent to oral isosorbide dinitrate
Corovas	Pentaerythritol tetranitrate, 30 mg capsule with 50 mg secobarbital	1 orally every 12 hours on empty stomach	Unknown but likely very delayed	Long	Probably equivalent to oral isosorbide dinitrate
Duotrate-Duotrate 45	Pentaerythritol tetranitrate, 30 mg or 45 mg alone or with 45 to 48.8 mg phenobarbital	1 orally every 12 hours on empty stomach	Unknown but likely very delayed	Long	Probably equivalent to oral isosorbide dinitrate
Isobid	Isosorbide dinitrate, 40 mg capsules	1 orally every 12 hours on empty stomach	Unknown but likely very delayed	Long	Delayed onset
Isordil Tembids	Isosorbide dinitrate sustained-action 40 mg Tembids	1 orally every 12 hours on empty stomach	Unknown but likely delayed	Long	Delayed onset

Neocorovas 30	Like Corovas without secobarbital				
Neocorovas 80	Pentaerythritol tetranitrate, 80 mg timed disintegrating capsule	1 orally every 12 hours on empty stomach	Unknown but very delayed	Long	Delayed onset
Nitrobid	Oral 2.5 and 6.5 mg nitroglycerin prolonged-action capulse	1 orally two or three times daily or more	Unknown but very delayed	Long	Delayed onset
Nitroglyn	Nitroglycerin, 1.3, 2.6, or 6.5 mg sustained-action tablets for oral use	1 orally two or three daily or more	Very delayed	Long	Delayed onset
Nitrong	Nitroglycerin, 2.6 mg oral sustained-released tablet	As for Nitroglyn 2.6 mg			
Nitrospan	Nitroglycerin, 2.5 mg oral	1 orally every 12 hours	Unknown but very delayed	Long	Delayed onset
Pentritol 60 mg	Pentaerythritol tetranitrate, 60 mg timed disintegrating tempule	As for Neocorovas 80			
Peritrate SA	Pentaerythritol tetranitrate, 80 mg sustained-action tablet	As for Neocorovas 80			
Peritrate	Pentaerythritol tetranitrate, 10 mg and 20 mg	10 to 40 mg four times daily orally	Unknown but very delayed	Long	Delayed onset

From Warren SE, Francis GS: Nitroglycerin and nitrate esters. *Am J Med* 65:53–62, 1978.

TABLE 14–6. Clinical pharmacology of intravenous nitroglycerin

	American Critical Care	Parke-Davis	Marion Labs
Trade name	Tridil	Nitrostat IV	Nitro-Bid IV
Concentration	5 mg/ml	0.8 mg/ml	5 mg/ml
Size	50 mg/10 ml	8 mg/10 ml	50 mg/10 ml
Propylene glycol content	30%	0%	45 mg/ml = 4.5
Alcohol content	30%	5%	70%
Stability	If glass container, diluted solution is stable up to 48 hours at room temperature and up to 7 days under refrigeration.	If glass container, solution is stable for at least 96 hours at controlled room temperature (15 to 30°C) or under refrigeration. Stable in solution with pH 3.5 to 6.5.	Stable at ambient temperature below 40°C. If glass container, solution is stable for at least 24 hours at room temperature. Stable in solution with pH of 3.0 to 6.5.
Storage	Protect from freezing	59 to 86°F (15 to 30°C)	Protect from freezing; do not store above 40°C.
Expiration	36 months	36 months	24 months
Percentage of polyvinyl chloride that binds	40 to 80%	40 to 80%	40 to 80%
	Rates of absorption are higher when flow rates are low, nitroglycerin concentration is high, and tubing is long. The rate of loss is highest during the early phase of infusion (when flow rates are lowest). Because the loss is neither constant nor self-limiting, no simple calculation or correction can be performed to convert the theoretical infusion rate (based on the concentration of the infusion solution) to the actual delivery rate.		
Infusion set available	Tridilest (loss less than 1%)	Nitrostat IV infusion set (loss less than 5%)	Not available.

TABLE 14–7. Complications of intravenous nitroglycerin

Reversible hypotension and tachycardia.
Hypoxemia (pulmonary V/Q mismatch)
Methemoglobinemia
Headache

blockade allows unopposed alpha-receptor-mediated coronary artery vasoconstriction to occur, which could aggravate coronary spasm and might increase the overall alpha-vasomotor tone of the coronary arteries, thus promoting primary decreases in the supply of oxygen. It is not yet clear whether $beta_1$ selective drugs such as metoprolol or atenolol offer any advantage.

7.4. CORONARY ARTERY BYPASS SURGERY

In patients with normal coronary arteries and demonstrable spasm, medical therapy with nitrates or calcium-channel blocking agents is effective, and vascular surgery is unlikely to be

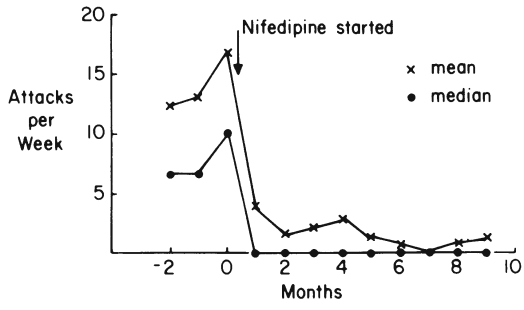


FIGURE 14–6. Mean and median weekly angina attack rates, before and after initiation of nifedipine therapy, in 127 patients with documented coronary artery spasm who were for the most part refractory to conventional antianginal therapy. During nifedipine treatment a prompt, dramatic, and sustained decrease in angina attack frequency was observed. (From Antman EM, *et al*: Nifedipine therapy for coronary artery spasm: Experience in 127 patients. *N Engl J Med* 302:1269, 1980.)

TABLE 14–8. Clinical pharmacology of calcium-channel blocking agents

Drug	Dose	Absorption	Onset of action	Peak effect	Plasma half-life	Protein binding (%)	Metabolism and elimination	Side effects
Nifedipine	10 to 20 mg every 4 to 8 hr SL or orally	>90% SL and orally	<1 min IV <3 min SL <20 min orally	1 hr orally	4 hr	90	Extensively metabolized to inert products; 80% excreted via kidney	Headache, hypotension, flushing, digital dysesthesias, leg edema
Verapamil	75 to 150 μg/kg IV; 80 to 160 mg every 8 hr orally	>90% orally	<2 min IV 2 hr orally	10 to 15 min IV 5 hr orally	3 to 7 hr	90	Extensively metabolized in liver; 85% first-past hepatic elimination after oral administration; 75% excreted via kidney	Constipation, headache, vertigo, hypotension, atrioventricular conduction disturbances
Diltiazem	75 to 150 μg/kg IV	>90% orally	15 min orally	30 min orally	4 hr	80	Extensively metabolized; 60% excreted via liver, 35% via kidney	Headache, dizziness, flushing, atrioventricular conduction disturbances

IV = intravenously; SL = sublingually.
From Stone PH, Antman EA (eds): Calcium channel blocking agents in the treatment of cardiovascular disorders. Mt. Kisco, NY, Futura Publishing Co, 1983, p. 194.

of help. However, many patients have fixed coronary artery disease with superimposed spasm. In some cases, full medical therapy fails to relieve symptoms. If coronary bypass surgery is contemplated, it is useful to know the characteristics of the preoperative spasm, i.e., which vessel is involved and when spasm occurs.

At the time of operation, grafts should be inserted distal to any areas known to have been spastic in the past, and perioperative treatment with nitrates and calcium-channel blockers should be continued in an attempt to prevent perioperative spasm. Such patients should remain on long-term calcium-channel blocker therapy. If such combined medical and surgical treatment is not coordinated during the perioperative period, results are likely to be disappointing. Antiarrhythmic and alpha-adrenoceptor blocking agents have a limited role in treating spasm.

8. *Natural History of Coronary Artery Spasm*

The natural history of patients with coronary artery spasm is poorly defined because of the intermittent nature of the disease process, difficulties with diagnosis, variations in the degree of underlying fixed coronary lesions, and the variety of therapeutics that have been used in the past. It is clear, however, that risk of myocardial infarction, a relatively frequent complication, appears to be greatest soon after spasm is diagnosed. Sudden death resulting from malignant ventricular arrhythmias or complete heart block and asystole is also a possibility during an attack of coronary spasm.

Studies by Severi et al [28] and Waters et al [29] suggest that the risk for major cardiac complications and death decreases almost exponentially with time. During the initial phase of the disease myocardial infarction can occur in relatively frequent and unpredictable fashion but subsequently the prognosis appeared good [29]. One recent study revealed that the incidence of major cardiac complications was lower in patients with known coronary artery spasm (i.e., focal or diffuse dynamic narrowing of the lumen by 80 per cent or more) but who either had less than 50 per cent fixed narrowing or had previously undergone coronary bypass graft operations [30].

Thus, although long-term followup of patients treated more recently with calcium-channel blocking agents is not yet available, it appears that patients without significant coronary artery disease do well on medical therapy. Finally, variant angina and the propensity for coronary artery spasm are episodic phenomena with a tendency to remit and recur, and decisions regarding long-term therapy should take this into account.

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15. POST-HOSPITAL MANAGEMENT OF MYOCARDIAL INFARCTION

1. Non-Q-wave and Q-wave Infarction

Over the last decade there has been considerable interest in analyzing differences in outcome among patients with "nontransmural" versus "transmural" infarction [1–10]. Although these terms have been used for many years to classify patients after serial electrocardiographic evaluation, the correlation between "transmural" and Q-wave infarction or between "nontransmural" and non-Q-wave infarction with regard to pathological findings is imperfect [11]. Infarctions found to be transmural on pathological examination can occur in the absence of Q waves on the ECG, while those found to be nontransmural may be associated with the appearance of new Q waves [12]. We prefer to describe infarcts as being either Q-wave or non-Q-wave on the basis of serial ECG evaluation. In most instances of Q-wave infarction, the infarct will most likely, but not necessarily, be transmural.

1.1. CLINICAL COURSE

Comparisons of the clinical course of patients with Q-wave and non-Q-wave infarctions reveal some interesting trends (table 15–1). A major flaw in most studies to data has been the inclusion of a high percentage (20 to 46 per cent) of patients who have had previous infarctions, which has affected data on early and late prognosis after either Q-wave or non-Q-wave infarctions [1–8]. Since mortality after infarction(s) ultimately relates directly to the *cumulative* amount of myocardial necrosis, it is obvious that a patient with an initial non-Q-wave infarction with a relatively small rise in serum creatine kinase (CK) is likely to have a vastly different outcome from that of a patient with the same infarction who has had a previous substantial Q-wave infarction in another location. In the latter instance, total cumulative myocardial necrosis could be extensive, with a correspondingly worse prognosis. In recent studies the short-term [9] and long-term [10] prognoses after an *initial* Q-wave or non-Q-wave infarction have been analyzed in a substantial number of patients.

1.2. MORTALITY

In spite of these difficulties in assessing prognosis, mortality in the early postinfarction period (less than one month) seems to be higher among patients with Q-wave infarctions [4–9]. Overall mortality seemed lower and the difference smaller in two studies comparing first Q-wave and non-Q-wave infarctions [6,9]. Some studies have shown a greater incidence of congestive heart failure in patients with Q-wave infarctions [1,6] while others have not [2,3]. It has been suggested that early mortality relates not only to the appearance of Q waves but also to the peak serum glutamic oxaloacetic transaminase (SGOT) level. In patients with Q-wave infarctions and SGOT levels exceeding 240 IU/L 6-month mortality rates are 12% with a rate of 3.8 per cent per year thereafter, whereas in those with Q-wave infarctions and an SGOT level less than 240 IU/L the cardiac mortality rate is 3.1 per cent per year with a more favorable in-hospital clinical course [9,10]. Interestingly, in several studies, mortality rates after 6 months appear to be similar for Q-wave and non-Q-wave infarctions, i.e., at 20 months [2], 31 months [6], 36 months [4,10], 48 months [7], and 5 years [5]. In one study death from cardiac causes at 36 months seemed twice as

TABLE 15–1. Non-Q wave versus Q-wave infarction

	Number of patients		Prior infarct (%)		< 1 month		Mortality (%) 6 months		1 to 5 years		Sudden death	
	Non-Q	Q	Non-Q	Q	Non-Q	Q	Non-Q	Q	Non-Q	Q	Non-Q	Q
Madias et al, 1974 (1)	43	61	37	36	9.3	9.8						
Rigo et al, 1975 (2)	49	111	20	16	13	22			19 (20 months)	18		
Cannom et al, 1976 (3)	36	119	33	25	8	17			42 ($p < 0.05$) 36 month	24	33 ($p < 0.02$) 36 months	15
Szklo et al, 1978 (4)	283	953	34	28	18 ($p < 0.01$)	30			28 (36 months)	27		
Fabricius-Bjerre et al, 1979 (5)	98 51*	127	24 24*	9					49 59*	41	24 28*	17
Boxall and Saltups, 1980 (6)	70	259	29	25	1.4 ($p < 0.05$)	11 4+			16 (31 months)	22		
Hutter et al, 1981 (7)	67	66A 63I	46	45	9 ($p < 0.04$)	20A 19I	14 ($p < 0.02$) 3 months	29A 27I	40 All groups 48 months			
Marmor et al, 1982 (8)	125	225	29%		10 ($p < 0.01$)	23						
Thanavaro et al, 1980 (9)	124	621	None		3 ($p < 0.01$)	11						
Krone et al, 1983 (10)	94 SGOT ≤240 IU/L >240	499	None				2.1	3.9 12.2	17 2.3 (36 months)	20 5.8 9.1		

* Nondiagnostic ECGs but positive enzymes and symptoms.
+ First coronary event.
A = anterior; I = inferior.

frequent in patients with non-Q-wave infarctions, apparently owing to twice the incidence of sudden death [3].

It appears that early mortality relates directly to infarct size, with higher rates seen in patients with Q-wave compared with non-Q-wave infarctions (usually with a greater cardiac enzyme release). After one year, however, mortality in the two groups seems to be similar. These trends are exemplified by the study by Krone *et al* in which early Q-wave infarctions with SGOT levels below 240 IU/L are associated with early mortality rates similar to those in non-Q-wave infarctions (3.9 versus 2.1 per cent); this differs from Q-wave infarctions with SGOT levels above 240 IU/L which are associated with a higher early mortality rate (12.2 per cent) [10]. Mortality after non-Q-wave infarctions was still low at 24 months, but by 36 months the rate for non-Q-wave infarctions had risen to 12.3 per cent while that for Q-wave infarctions was 5.8 to 9.1 per cent.

1.3. RECURRENT INFARCTION

It has often been said that non-Q-wave infarctions represent "unfinished business." There are probably some patients with non-Q-wave infarctions who are, for various reasons, at high risk for recurrent infarction or instability of symptoms. In fact, several studies have indicated a greater incidence of recurrence after initial non-Q-wave compared with Q-wave infarctions. Hutter et al noted a higher recurrence rate for non-Q-wave infarctions compared with Q-wave infarctions at 9 months (21 versus 3 per cent) and at 54 months (57 versus 12 to 22 per cent) [7] as did Marmor et al (43 versus 8 per cent) [8] and Krone et al (7.4 versus 1.8 per cent) [10]. It would appear that a subgroup of patients with non-Q-wave infarctions is likely to experience recurrent infarction and perhaps is at greater risk for sudden death [3,5]. Not unexpectedly, older patients with infarcts complicated by heart failure and arrhythmias, those who require medical treatment on discharge, and those with a history of previous cardiac disease have a worse outlook [5].

1.4. LONG-TERM PROGNOSIS

The similarity in long-term prognosis for patients with non-Q-wave and Q-wave infarctions is not surprising, since there is no difference between the two groups with respect to the prevalence of single-, double-, or triple-vessel coronary disease; left ventricular ejection fraction; or the percentage of akinetic-dyskinetic myocardial segments 10 to 24 days after acute infarction [13]. Unfortunately, these data were influenced by the fact that 41 per cent of patients with non-Q-wave infarction had a history of previous myocardial infarction while this was true for only 29 per cent of patients with Q-wave infarction. It is possible — perhaps probable — that there would be differences in left ventricular function (reflecting cumulative myocardial necrosis) between Q-wave and non-Q-wave infarction in patients presenting with a *first* ischemic incident. In an early study that examined coronary anatomy and early prognosis of patients presenting with chest pain, serum enzyme elevations, and persistent new T-wave inversions and/or ST-segment depression in the absence of new Q waves, 60 per cent of patients had either double- or triple-vessel disease; during a followup period of 10 months, 30 per cent had stable angina, 46 per cent had unstable angina [14].

Prognosis after either non-Q-wave or Q-wave infarction may also be related to baseline QRS appearances (table 15–2). After the onset of symptoms, the outcome appears different for patients with an abnormal QRS complex on the initial electrocardiogram (secondary to Q waves, bundle branch block, or ventricular hypertrophy) compared with patients with a normal QRS complex [15]. After acute infarction, the outcome for patients who did not develop new Q waves was worse in those whose baseline ECG showed Q waves, bundle branch block, or left ventricular hypertrophy than in those who had an initially normal QRS (i.e., 30-month survival was 12 versus 45 per cent, respectively). A normal QRS at baseline seems to be a favorable feature in patients who develop new Q waves, since the 30-month mortality for those with an initially normal QRS was 12 per cent versus 34 per cent in those with new Q-wave infarctions superimposed on baseline ECGs showing Q waves, bundle branch block, or left ventricular hypertrophy. Mahoney et al therefore suggest that whether or not patients develop new Q waves during an evolving infarction their outlook depends on the normality or abnormality of QRS complexes on ECGs recorded after the onset of symptoms. Patients with abnormal baseline QRS complexes have an unfavorable outlook, irrespective of the development of new Q waves.

TABLE 15–2. Early and late mortality after infarction related to initial and evolving QRS

Initial ECG	Normal QRS	Normal QRS	Abnormal QRS	Abnormal QRS
Serial ECGs	No evolving Q waves	New Q waves	No evolving Q waves	New Q waves
Hospital mortality	0%	8%	13%	20%
30-month mortality	12%	12%	45%	34%
	n = 24	n = 17	n = 152	n = 342
			$p < 0.001$	
		$p < 0.001$		

Adapted from Mahoney C, et al: Prognostic differences in subgroups of patients with electrocardiographic evidence of subendocardial or transmural myocardial infarction. The favorable outlook for patients with initially normal QRS complex. *Am J Med* 69:183–186, 1980.

For the individual patient, it is important to consider certain characteristics of the current ischemic event — i.e., whether the event was a Q-wave or a non-Q-wave infarction and the degree of enzyme release — as well as the details of previous coronary events — i.e., previous infarction, non-Q-wave or Q-wave, degree of enzyme release, and complications. The extent of cumulative myocardial necrosis will provide the best prognostic information and will guide short- and long-term management. In patients with completed large infarctions with major enzyme release or with extensive total cumulative myocardial necrosis, early operative revascularization will seem unattractive. For patients with first infarctions and limited necrosis, periinfarction ischemia and early positive exercise tests may lead to a more aggressive management approach, with early angiography and consideration of surgery.

2. *Secondary Prevention*

2.1. DIET AND SERUM LIPIDS

The diet of a population is in some way related to the etiology of atheroma and the development of cardiovascular disease. Apparently, hypercholesterolemia encountered in affluent societies results from an imbalance between the intake and excretion of dietary cholesterol, which is catalyzed by excessive intake of saturated fat and calorie storage. Epidemiological studies clearly show that high serum total cholesterol levels are precursors of coronary heart disease. Total serum cholesterol is made up of three components: low-density lipoproteins (LDL cholesterol, which promotes atherogenesis), high-density lipoproteins (HDL cholesterol, which in some way appears to exert a protective effect) and very low density lipoproteins (VLDL cholesterol which is possibly inert) [16]. In the Framingham Study the risk of developing coronary heart disease was directly related to the serum cholesterol concentration in men 30 to 49 years of age at the time of entry to the study. The presence of other coronary risk factors and the occurrence of an elevated cholesterol level at a young age accentuate the risk of a given total serum cholesterol level. In addition, a large amount of the HDL fraction appears to exert some protective effect, whereas a large amount of the LDL fraction appears atherogenic. Therefore, the ratio of HDL to LDL cholesterol is an important determinant of risk [17].

Serum triglyceride levels do not appear to contribute independently to atherosclerotic cardiovascular disease. If the serum cholesterol value is known, the level of triglycerides does not seem to add useful predictive information. (Triglyceride values can be of help in estimating LDL values without direct measurement — i.e., total cholesterol — HDL — triglycerides divided by 5 = LDL.) If serum triglycerides are found to be elevated, the level of alcohol intake, glucose intolerance, and obesity may be contributors. Epidemiological and clinical studies indicate that a diet high in cholesterol, often with saturated fat, is usually required for the development of atherosclerosis and subsequent coronary artery disease.

The Coronary Drug Project provides information about prognostic factors after recovery from myocardial infarction [18]. In 2,789 men ages 30 to 64 years who had recovered

from one or more documented infarctions and were treated with placebo, the baseline fasting serum cholesterol level was significantly related to death from all causes, death from coronary heart disease, sudden death due to coronary heart disease, and incidence of nonfatal myocardial infarction plus coronary death during a 5-year followup period. (More powerful factors relating to long-term prognosis were those reflecting the status of the myocardium, e.g., ECG evidence of Q waves, ST-segment depression at rest, conduction defects, ventricular premature contractions or ventricular tachycardia, and evidence of cardiomegaly.) Baseline fasting serum triglyceride levels were not positively related to any of these end points. [19]

Not only is serum cholesterol a significant independent risk factor for a first major coronary event but it also has significance for long-term prognosis after one or more myocardial infarctions. The Coronary Drug Project data support the inference that dietary changes may be a safe and useful means of reducing serum cholesterol after infarction as part of the total therapeutic regimen to improve long-term prognosis.

In a multifactorial intervention program in Finland, 375 consecutive patients below the age of 65 years who had had an acute infarction were randomized to either an intervention or a control group. The intervention team included a doctor, a social worker, a psychologist, a dietician, and a physiotherapist. Health education consisted of anti-smoking and dietary advice and discussions about psychosocial problems, and the physical exercise program was tailored to the individual's working capacity. The rehabilitation program was most intensive during the first 3 months after infarction. The intervention group underwent medical examinations at least monthly for 6 months and, when necessary, every 3 months thereafter. At the end of 3 years, body weight, serum cholesterol and triglyceride levels, and arterial blood pressure were all significantly lower in the intervention group than the control group — a difference observed as early as the first annual visit. The numbers of cigarette smokers and cigarettes smoked were reduced by about 50 per cent in both groups. Significantly more patients in the intervention group were taking beta blockers at 3 years (45 versus 27 per cent). The 3-year cumulative mortality rate was significantly lower in the intervention group than in the control group (18.6 versus 29.4 per cent), owing mainly to a reduction in sudden deaths in the former (5.8 versus 14.4 per cent) [20].

The reinfarction rate was not reduced in the intervention group, who in fact had a higher incidence of reinfarction during the first year after acute myocardial infarction than the control group. At 2 years the mortality due to coronary heart disease was 14 per cent in the intervention group and 15 per cent in the control group.

In the Swedish Control Trial of Post-infarction Patients there was a significant reduction in nonfatal reinfarctions but only a trend to reduced mortality [21]. The 2-year coronary heart disease mortality in this group was 9 per cent in the intervention group and 15 per cent in the reference group, i.e., there was a higher incidence of nonfatal reinfarction in the Swedish patients but a smaller 2-year coronary heart disease mortality.

The results of the Finnish study suggest that a comprehensive rehabilitation and intervention program after acute myocardial infarction may have some beneficial effects. A number of trials have been performed to test the hypothesis that reducing serum lipid levels through pharmacological or dietary intervention will lower cardiovascular morbidity and/or mortality in survivors of one or more myocardial infarctions [22]. Diet and the use of various drug regimens, including conjugated equine estrogens, ethinylestradiol, dextrothyroxine, clofibrate, and nicotinic acid, either alone or in combination, resulted in mean reductions in serum cholesterol levels of 6.5 per cent [22]. In no trial did these reductions have a statistically significant impact on mortality. Overall, the results do not suggest that lowering lipids will prolong life in the post infarction population. It has been pointed out that the patients selected for these trials were not chosen because of initially high levels of serum cholesterol, and in many cases only modest reductions were achieved. In fact, the drugs themselves led to a variety of adverse effects.

2.2. SMOKING

It is well known that cigarette smoking is a major risk factor for coronary heart disease. Although the mechanism by which smoking enhances atherogenesis or increases the risk of heart attacks is not known, the amount of smoking has been found to be proportional to the degree of the atherosclerosis. The Pooling

TABLE 15–3. Relationship of smoking habits to morbidity and mortality during 2-years after first infarction in males

	Nonsmokers n = 45	Exsmokers n = 78	Stopped smoking	Continued smoking
Reinfarctions (%)	7	14	9	18
Cardiovascular deaths (%)	7	5	5	10

Adapted from Wilhelmsson C, et al: Smoking and myocardial infarction. *Lancet* 1:415–419, 1975.

Project showed that over a 10-year followup period, the risk of a major coronary event (angina, infarction, or sudden death) was 3.2 times greater among men 30 to 59 years of age who smoked more than 20 cigarettes a day compared with nonsmokers. This was based on data from several large prospective studies [23]. Stopping smoking seems to lower coronary disease mortality rates, an effect that was noted immediately in the Framingham Study [24]. Some critics say that various studies showing that ex-smokers have a lower coronary risk are invalid because they fail to allow for the fact that ex-smokers are self-selected and have a lower coronary risk than those who continue to smoke [25]. Most people believe that those who stop smoking will reduce their coronary risk, particularly if they do so before they reach 65 years of age.

No controlled trials have been carried out to determine whether stopping smoking after myocardial infarction improves prognosis. A study relating smoking habits to morbidity and mortality during the 2 years after a first infarction in men showed that patients who stopped smoking had a more favorable clinical course than did those who continued to smoke (table 15–3). The patients who stopped had only half the rate of nonfatal recurrences and half the cardiovascular mortality rate of those who continued to smoke [26]. In the 5-year followup of 2,789 men who had sustained one or more infarctions at least 3 months previously, the smokers had higher mortality (mortality ratio = 1.29) and nonfatal reinfarction rates than nonsmokers [19]. In prospective followup study (North Karelia Project) of male patients under the age of 65 years who had had a myocardial infarction and survived 6 months, a 3-year followup showed that the cumulative all-causes mortality among patients who were still smoking 6 months after the event was 1.7 times that of patients who had stopped smoking within the first 6 months. The impact of smoking was greatest in the subgroup of patients with an otherwise good prognosis [27].

Observational data suggest that stopping smoking substantially reduces coronary and total mortality. This conclusion, however, cannot be explained based on the baseline characteristics of the population before they ceased smoking. It seems more likely that long-term mortality after successful recovery from infarction is adversely affected by smoking and that the reinfarction rate might also be influenced [26], although this latter finding has not been confirmed by others [28].

2.3. PHYSICAL ACTIVITY

A number of studies indicate that an active rather than sedentary lifestyle reduces the annual mortality rate without affecting the prevalence of nonfatal forms of coronary heart disease [29–35]. Deaths per thousand are more frequent in patients with a sedentary as compared with an active lifestyle in a ratio of 1.8 to 2.8:1. Vigorous exercise during leisure time (likely to reach peaks of energy expenditure of 7.5 kcal/min) will lead to fewer fatal and nonfatal clinical manifestations of coronary heart disease over a period of 8.5 years [36]. Physical training can be associated with increased levels of high-density lipoproteins (HDL), which may confer some protection from ischemic events [37,38]. Others have shown that long-term moderate physical exercise [39] and a long-term physical training program in otherwise sedentary men [40] do not substantially influence HDL cholesterol or other lipid levels [39], weight, blood pressure, serum lipids, smoking habits, and physical working capacity [40]. In a study of moderate exercise for 10 weeks (three aerobic 15- to 20-minute sessions per week at 70 per cent maximal heart rate) favorable changes

were noted in HDL and HDL/LDL ratios in men but not in women [41].

The benefit of exercise or training programs on survivors of acute infarction is not clear. Symptomatology and the functional capacity of those who have recovered from infarctions can be improved by exercise conditioning programs, but the prognosis or risk of sudden death does not appear to be affected favorably [22]. Probably none of the trials have included a large enough population to demonstrate a difference in total mortality between the exercise and control groups when factors such as medications, crossover to surgery, and withdrawal are accounted for. The psychological benefits of exercise are difficult to quantitate and there have been few controlled trials assessing the effects of exercise on mood elevation in normal subjects and as an antidepressant in depressed subjects. Nevertheless, many physical fitness, jogging, and gymnastic programs have shown that regular participants are less likely to be depressed than infrequent participants. The psychological benefits of such programs in postinfarction patients are obvious. Several studies suggest that as individuals improve in physical fitness, they tend to report less depression. Furthermore, those in the poorest physical and/or psychological condition tend to derive the greatest benefit from exercise, both physically and psychologically, the risk of participating in a supervised exercise program of rehabilitation seems relatively small. In one program there was one cardiac arrest per 6,324 supervised man-hours of exercise training or one arrest per 717 months of exercise training. All patients were successfully resuscitated by physicians present [42].

2.4. OBESITY

Moderate obesity with no other associated major risk factors carries very little risk of cardiovascular disease. The Framingham Study demonstrates, however, that as weight increases, an unfavorable LDL/HDL cholesterol ratio develops and that obese people are more likely to have higher blood pressures, diabetes, and a higher prevalence of gout. Weight loss is accompanied by a corresponding reduction in the level of major risk factors for atherogenesis [43]. After infarction, it seems entirely reasonable to try to achieve normal weight, which obviously offers several physical and risk factor benefits. In women, the presence of obesity, diabetes, and low- or high-density lipoprotein cholesterol seems to carry a particularly high risk of coronary disease [44].

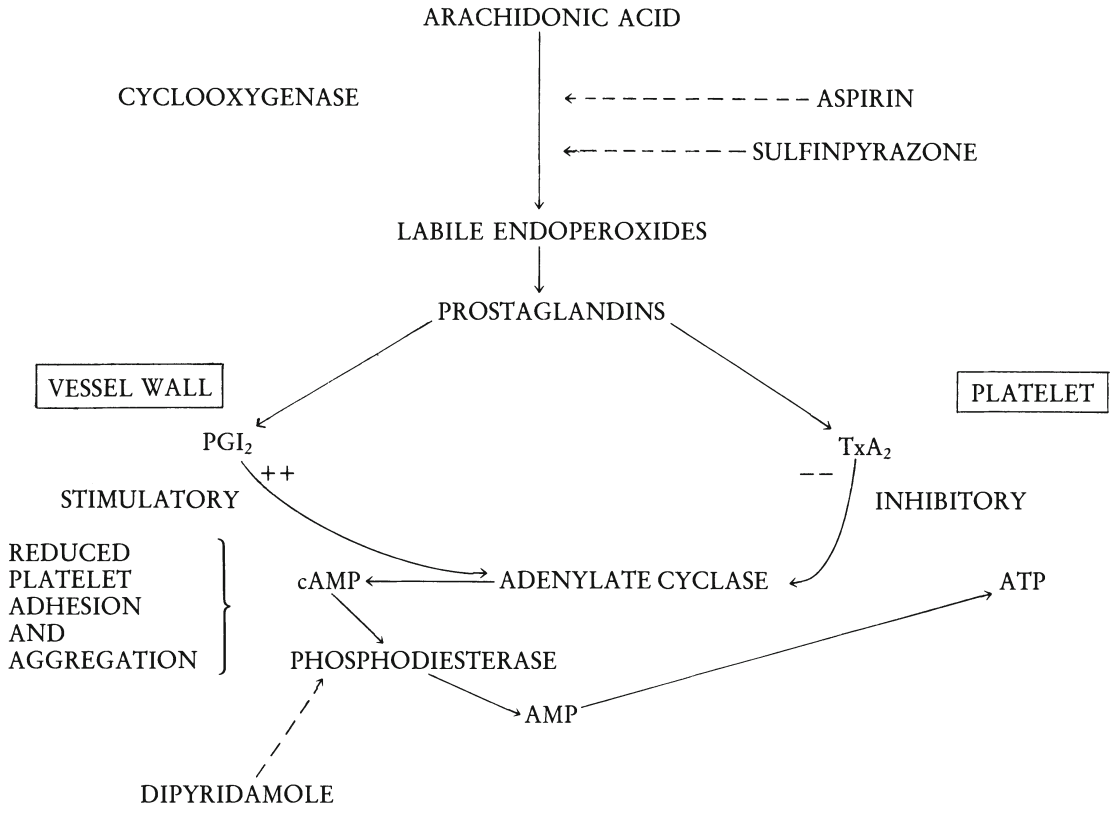
2.5. MYOCARDIAL INFARCTION IN YOUNG PATIENTS

Myocardial infarction is rare in premenopausal women but not so rare in men under the age of 40 years. A number of studies have documented various aspects of this phenomenon [45–50]. Most physicians and nurses will at some time have a young patient with myocardial infarction. Because of the small numbers of patients involved it is difficult to make generalizations; however, most studies agree that young people with myocardial infarction tend to be smokers and are predominantly males. About 80 per cent are found to have significant atherosclerotic coronary artery disease on angiography, and the remainder have either normal coronary arteries; congenital abnormalities of the coronary arteries; or evidence of vasculitis, coronary artery embolism, or dissection. Usually, one or more risk factors are present in such patients, although occasionally a patient may have a myocardial infarction with no apparent predisposing cause. After the acute period, a careful review of factors such as smoking history, serum lipids, family history (with review of lipids in family members when appropriate), hypertension, and body weight is in order. Rare anatomical variations of the coronary arteries and unusual causes can often be identified only by means of coronary arteriography.

3. Use of Drugs After Myocardial Infarction

3.1. ASPIRIN

Injury to the endothelium of blood vessel walls, particularly if it exposes subendothelial collagen, initiates a complex series of events that ultimately lead to formation of a plug of aggregated platelets. Normally the blood vessel wall is a surface that resists thrombosis. This is due in part to the synthesis of prostacyclin (PGI_2), a potent inhibitor of platelet aggregation. Platelets adhere to the exposed collagen and release material such as adenosine diphosphate (ADP) and fibrinogen, which encourage platelet aggregation at the injury site. During this process, arachidonic acid is oxygenated, forming labile endoperoxides that are rapidly metabolized to produce prostaglandins. Thromboxane



PGI_2 = prostacyclin; TxA_2 = thromboxane A_2.

FIGURE 15–1. Site of action of aspirin, sulfinpyrazone, and dipyridamole in pathways leading to platelet aggregation.

A_2 (TxA_2) is released from platelets and is a potent vasoconstrictor promoting aggregation and release of ADP. Adenosine monophosphate (AMP) acts to inhibit platelet adhesion, aggregation, and ADP release.

At low doses, aspirin acetylates cyclooxygenase in platelets, leading to irreversible inhibition of TxA_2 formation and platelet aggregation. Platelets then have to be produced for subsequent TxA_2 formation, since only about 10 per cent of platelets recover from acetylation to synthesize new enzyme molecules. At higher concentrations aspirin inhibits not only platelet production of TxA_2 but also endothelial cell cyclooxygenase. Cyclooxygenase inhibition in vessel walls is reversible, since endothelial cells can resynthesize the enzyme in less than 24 hours in arteries.

Most of the large trials using aspirin after infarction have used doses of approximately 10 mg/kg/day. Furthermore, it is known that a single low dose of aspirin (about 2 mg/kg) can completely inhibit platelet cyclooxygenase in humans without inhibiting the synthesis of PGI_2 in the blood vessel walls (figure 15–1). The optimal daily dose of aspirin needed to block TxA_2 formation without inhibiting prostacyclin formation is unknown. It is likely, however, that the optimal dose will be nearer 150 mg of aspirin per day than the high doses used in the major reported studies.

Since 1970 there have been six studies investigating the effects of aspirin on long-term mortality after acute myocardial infarction (table 15–4) [51–56]. All were prospective, randomized, double-blind trials. Aspirin was used in daily doses of 300 to 1,500 mg, and in the Persantin Aspirin Reinfarction Study (PARIS)

trial some patients received aspirin and dipyridamole [56]. None of the six studies demonstrated a statistically significant difference in total mortality between the intervention and control groups. In the largest trial of platelet-active drugs, the Acute Myocardial Infarction Study (AMIS) the findings were negative [55], although the other studies showed a trend in favor of the platelet-active agent. Despite the fact that in five of the studies the dose of aspirin was 900 mg per day or more, there was still a positive trend [22].

3.2. DIPYRIDAMOLE

Dipyridamole is a coronary vasodilator that also blocks the enzyme phosphodiesterase and its analogues, potentiating the increase in cyclic AMP and platelet inhibition produced by vessel wall PGI_2. This drug partially inhibits the deposition of platelets on damaged endothelium but probably has only a weak effect on circulating platelets. In the PARIS trial, in which patients were randomized to treatment with dipyridamole plus aspirin, aspirin alone, or placebo, there was no suggestion that the combination of aspirin and dipyridamole was better than aspirin alone. There was no significant difference in the total mortality between the treatment and placebo groups over the 41-month followup period. Experimental studies suggest that dipyridamole has a greater effect than aspirin on reducing platelet adhesiveness, while having a weaker effect in preventing platelet aggregation. Interest will therefore continue in the use of these drugs in combination.

3.3. SULFINPYRAZONE (ANTURANE)

In the Anturane Reinfarction Trial 1,629 patients were randomized in a prospective, double-blind manner to placebo or sulfinpyrazone, 800 mg daily 25 to 35 days after infarction [57]. The mean length of followup was 16 months. Mortality was 10.9 per cent in the control group and 9.1 per cent in the intervention group (difference not significant, $p = 0.26$). The initial report of the study indicated that sulfinpyrazone reduced the incidence of sudden cardiac death after infarction by 74 per cent at 2 to 7 months and by 43 per cent at 24 months. When the case records were subsequently reviewed by the FDA, assignments as to the cause of death were questioned. Initially the reviewers stated that the results showing an effect on total cardiac mortality were not convincing because they depended heavily on retrospective exclusion from analysis of certain patients who had died while receiving the drug. When an independent third group reviewed the results in blinded fashion [58], they concluded that the reduction in mortality after 2 years was 24 per cent ($p = 0.16$) and the reduction in sudden death was 36 per cent ($p = 0.10$); these revised figures did not reach statistical significance, although reanalysis did show a statistically significant reduction in sudden death after 6 months. A study from Italy of sulfinpyrazone seemed promising, but when it was analyzed according to "intention to treat," the number of deaths in the treated and control groups was virtually identical [59].

In the studies involving aspirin, dipyridamole, and sulfinpyrazone administered after infarction, delays in the treatment may have affected the results. Furthermore, regarding the aspirin studies, it is possible that the dose was too high, so that not only was TxA_2 formation inhibited but the salutary effects of PGI_2 may also have been inhibited. At present, routine postinfarction treatment with aspirin, dipyridamole, or sulfinpyrazone — either alone or in combination — does not seem justified.

3.4. COMBINATIONS

Recently a multicenter, randomized clinical trial compared the effects of aspirin (1,500 mg daily) and oral anticoagulants given to 1,303 men and women an average of 11.4 days after the onset of myocardial infarction. Patients were followed from 6 to 59 months (mean = 29 months) [60]. There were 65 deaths among the 652 patients in the anticoagulant group and 72 deaths among the 651 patients in the aspirin group, and the number of reinfarctions was higher in the aspirin group (33 versus 20). None of these differences was statistically different. Gastrointestinal events occurred in 54 per cent more patients in the aspirin group, and episodes of severe bleeding were four times more common in the anticoagulant group. It was concluded that in this dose aspirin is probably not more effective than oral anticoagulants in reducing mortality and morbidity over an average of 29 months after infarction.

3.5. ANTIARRHYTHMIC DRUGS

Controlled studies of antiarrhythmic drugs (with the exception of beta blockers) given over the long term after infarction have recently been

TABLE 15–4. Results of postinfarction aspirin trials

Trial	Number randomized	Entry window	Aspirin dose (mg/day)	Mean followup (mo)	Mortality (%) control	Mortality (%) intervention	p value
Elwood et al, 1974 (51)	1,239	<6 months	300	12	9.8	7.6	0.22
Coronary Drug Project Aspirin Study (CDPA), 1976 (52)	1,529	Weeks to years	972	22	8.3	5.8	0.071
German-Austrian Multicenter Prospective Clinical Trial, 1977, 1979 (53)	626	28 to 42 days	1500	24	7.1	4.1	0.14
Elwood and Sweetman, 1979 (54)	1,725	Days to weeks	900	12	14.5	12.2	0.18
Aspirin Myocardial Infarction Study (AMIS), 1980 (55)	4,524	2 to 60 months	1000	40	9.7	10.8	0.22
Persantine Aspirin Reinfarction Study (PARIS), 1980 (56)	2,026	2 to 60 months	972	41	12.8	10.5	0.27

Adapted from May GS, et al: Secondary prevention after myocardial infarction: A review of long-term results. *Progr. Cardiovasc. Dis.* 24:331–352, 1982.

TABLE 15–5. Antiarrhythmic drugs after infarction

Trial	Type of control	Number randomized	Entry window	Intervention	Mean followup (mo)	Mortality (%) control	Mortality (%) intervention	p value
Collaborative Group — Australia/Britain, 1971 (61)	Low-dose phenytoin	568	At hospital discharge	Phenytoin, 300 to 400 mg/day	12	8.1	9.2	0.75
Ryden et al, 1980 (62)	Placebo	162	<2 days	Tocainide, 750 mg IV stat + 1,200 mg/day	6	8.9	8.9	1.00
Bastian et al, 1980 (63)	Placebo	146	7 to 10 days	Tocainide, 1,200 mg/day	6	4.1	5.6	0.97
Chamberlain et al, 1980 (64)	Placebo	344	6 to 14 days	Mexiletine, 600 to 750 mg/day	4 (3 months no intervention)	11.7	13.3	0.78
Ghent-Rotterdam Study (65)	Placebo	305	<14 days	Aprindine, 100 to 200 mg/day	12	12.5	7.8	0.25

Adapted from May GS, et al: Secondary prevention after myocardial infarction: A review of long-term results. *Prog Cardiovasc Dis* 24:331–352, 1982.

analyzed [22] (table 15–5). Five of six controlled studies were double-blind. Three studies had unselected patient populations [61–63]. Chamberlain *et al* enrolled patients with a high risk of dying because of the presence of sinus tachycardia, left bundle branch block, ST-segment elevation, or pulmonary edema [64]. The Aprindine Study selected patients who at 10 days showed evidence of ventricular tachycardia or ventricular premature beats [65]. Analysis of the available morbidity data does not suggest that antiarrhythmic therapy prolonged life in these heterogeneous patient groups. Studies of certain subgroups of patients, particularly those with impaired ventricular function, may reveal some benefits of therapy.

3.6. ANTICOAGULANTS

The use of anticoagulants after myocardial infarction was discussed earlier (see chapter 4).

3.7. BETA BLOCKERS

Secondary prevention trials in survivors of acute infarction have provided data indicating that prophylactic beta-adrenoceptor blockade has a favorable effect on sudden death and possibly on reinfarction [66] (see chapter 4). Pooling the results of the major randomized, prospective, placebo-controlled trials shows a 20 per cent reduction in mortality (95 per cent confidence limits = 12 to 28 per cent). In trials in which beta blockers were started within 24 hours of the onset of infarction there was an 8 per cent reduction in mortality overall, while in trials in which beta blockers were given later this value was 26 per cent (95 per cent confidence limits = 17 to 35 per cent) [67,68]. Despite these persuasive data, it must be remembered that large percentage alterations in mortality may result from relatively small absolute numbers of patients being saved from sudden death. By some estimates these trials show that in order to prevent sudden death in three to six patients over 100 patients must receive continuous treatment for 1 to 2 years.

The published studies do not indicate any advantage in initiating therapy with beta blockade earlier than one week after infarction in order to reduce mortality. It should be remembered that in many of the "early intervention" trials, adequate blood levels of these drugs could not have been achieved within 48 hours of the event.

The three most widely quoted studies involved treatment with timolol, metoprolol, and propranolol [69–71]. These trials involved large numbers of patients; were prospective, randomized, and double-blind; and were analyzed according to the principle of intention to treat.

Appropriately, the benefits of giving beta blockers for more than 12 months after an acute myocardial infarction has been questioned [68], but evidence from the Beta-Blocker Heart Attack Trial (BHAT) suggested that the beneficial effect of propranolol seemed most pronounced in the first 12 to 18 months after infarction, although the effect was sustained for the duration of the trial (an average of 25 months and a maximum of 39 months) [71]. These investigators recommend administering propranolol for at least 3 years in patients who have had a recent infarction when there are no contraindications to beta-adrenoceptor blockade.

Physicians often wonder whether one beta blocker may have an advantage over another in terms of reducing postinfarction mortality. Cardioselective beta blockers block cardiac receptors (beta-$_1$) more readily than they block receptors in the bronchi and peripheral vasculature (beta-$_2$). It has been thought that agents such as metoprolol are less likely to cause bronchospasm. Most physicians would agree that in patients with a tendency toward wheezing or bronchospasm beta blockers are absolutely contraindicated, regardless of their cardioselectivity. Membrane-stabilizing activity, seen with both propranolol and metoprolol, means that these agents could potentially be more effective in preventing arrhythmias; this property is probably important only when high doses are used. Agents with intrinsic sympathomimetic activity, such as alprenolol, are said to stimulate beta receptors when sympathetic tone is low and to block beta receptors when sympathetic tone is high (beta-$_1$ receptors). In man, such agents are said to cause less bradycardia at rest. Cardiac beta blockade appears to be the essential property of the agents; their membrane-stabilizing activity, intrinsic sympathomimetic activity, and cardioselectivity have not been clearly demonstrated to be helpful in reducing mortality after infarction (table 15–6) [72].

Many favor identifying high-risk subgroups of infarct survivors for treatment. It must be remembered that patients at greatest risk for sudden death are those with low ejection frac-

TABLE 15–6. Pharmacological comparison of beta blockers

	Intrinsic sympathetic activity	Cardio-selectivity	Membrane-stabilizing Activity	Lipid solubility	Maintenance dose (mg/day)	Elimination
Propranolol	0	0	++	+++	160 to 480	Hepatic
Timolol	0	0	0	+	20 to 60	Hepatic and renal
Metoprolol	0	+	0	++	200	Hepatic
Atenolol	0	+	0	+	50 to 100	Renal
Pindolol	+	0	+	++	15 to 60	Hepatic and renal
Nadolol	0	0	0	+	80 to 320	Renal
Acebutolol	+	+	+	+	400 to 800	Hepatic and renal

tions — a group who often cannot tolerate beta blockers. It is easy to justify beta blocker therapy after myocardial infarction in patients with hypertension and persistent angina.

Survivors of infarction whose exercise test is strongly positive at a low level of activity may benefit from beta blockers, as may those with complex arrhythmias. One recent study compared the effects of propranolol and placebo on sudden cardiac death in a high-risk group of survivors of acute infarction [73]. In this prospective, randomized, double-blind trial 560 patients, 35 to 37 years of age, were stratified into two high-risk groups. Most patients had exhibited one or more of the following signs: sinus tachycardia, heart failure, new atrial fibrillation or flutter, and/or ventricular tachycardia. Some had been treated for ventricular fibrillation, asystole, or prolonged ventricular tachycardia. During the first week after infarction treatment was begun with propranolol, 40 mg four times a day, or placebo. During the first year, the rate of sudden deaths was 50 per cent lower in the propranolol-treated group, with benefit noted during the first 6 months and fewer overall deaths. By one year, the reinfarction rate was lower. This significant reduction in the number of cardiac deaths was maintained during the observation period, indicating a true reduction in mortality and not merely a postponement of the time of death.

We suggest that patients who might receive a beta blocker after acute infarction would be those with persistent angina, a strongly positive exercise test, high-grade complex arrhythmias during the convalescent period, and hypertension. Patients at greatest risk for sudden death, i.e., those with major cumulative myocardial damage and a low ejection fraction, are likely to tolerate beta blockers least well.

4. Testing After Myocardial Infarction

4.1. EXERCISE TESTING

Exercise testing carried out soon after acute myocardial infarction has been discussed (chapter 4). In the early weeks after infarction, low-level exercise testing on a treadmill is recommended in all patients who have no contraindications. Those with unstable angina or pain at rest during the previous few days, evidence of significant cardiac dysfunction (heart failure or a gallop rhythm), complex ventricular ectopy, or significant arterial hypertension should be excluded from such testing. The occurrence of ischemic ST-segment depression during low-level exercise testing identifies a group of patients with a worse prognosis and who are at higher risk for subsequent coronary events. This is true whether or not the ST-segment depression is associated with angina. Angina alone, without ischemic ST-segment depression, does not adversely affect prognosis. Other factors such as angina accompanied by ST-segment depression occurring at a low heart rate, early in the protocol (equivalent to Stage II of the Bruce protocol or less), and accompanied by a drop in blood pressure should alert the physician to the presence of significant ischemia and possibly either left main or severe three-vessel coronary artery disease. Conversely, the absence of ischemic ST-segment depression or ventricular ectopic activity identifies a group of patients with an excellent prognosis over the next few years. Abnormal ST-segment responses have been associated with a 22 to 25 per cent mortality at one year, whereas patients without abnormal responses have a mortality of about 1 per cent at one year [74–77].

4.2. RADIONUCLIDE STUDIES

If certain patterns on the ECG preclude interpretation of a low-level exercise test (e.g., left bundle branch block, drug effects, and the like), myocardial perfusion scintigraphy with thallium-201 can be useful in predicting the severity of coronary artery disease. Patients with multivessel disease can be identified by means of low-level exercise testing with concurrent scanning [78].

Radionuclide ventriculography will provide reliable information about right and left ventricular performance. Patients with normal or near-normal ejection fractions early after infarction have a good early and later prognosis, whereas those with low ejection fractions have a less favorable early and late prognosis [79,80]. If radionuclide ventriculography is performed during exercise, a fall in ejection fraction from previously normal levels can indicate multivessel disease [81] and may also be helpful in determining prognosis during the first year after infarction.

Radionuclide studies are relatively expensive, and it remains to be seen whether or not they are more informative than low-level exercise in patients able to undergo such testing. Obviously, they offer advantages when detection of ischemia on the ECG during exercise is not possible. They also allow accurate serial evaluation of ventricular function in patients with complicated infarction who are undergoing various modes of therapy that require monitoring (e.g., use of vasodilators in the presence of heart failure).

4.3. AMBULATORY ECG MONITORING

It is well accepted that 24-hour ambulatory ECG monitoring after infarction is a sensitive method of detecting the occurrence of complex arrhythmias that would be missed on routine exercise test assessments and bedside monitoring of patients at rest. In general, the presence of simple or high-grade ventricular postinfarction ectopy is associated with a worse long-term prognosis. This is of greatest significance when left ventricular function is impaired. Patients with ventricular ectopy and ejection fractions below 40 per cent seem at particular risk for sudden death in the year after infarction [82]. Patients with high-grade ectopy and impaired ventricular function are most likely to benefit from antiarrhythmic therapy; unfortunately, however, these are the very patients who tolerate such therapy relatively poorly. It may be that patients who exhibit overdrive suppression of ectopy during exercise constitute a relatively low-risk group, whereas patients with high-grade ectopy and impaired left ventricular function at rest or those with increased ectopy during exercise constitute groups who are more likely to derive benefit from future antiarrhythmic therapy. We recommend ambulatory monitoring, particularly in patients with clinical evidence of impaired ventricular function and those who exhibited high-grade ectopy early in the course of infarction prior to discharge from the hospital.

In a recent review of the role of noninvasive cardiac testing after uncomplicated infarction, Cohn stated, "Probably the single most important of these procedures is the low-level exercise test performed 10 to 21 days after infarction. This readily available procedure will greatly help the primary physician to determine which postinfarction patients without complications have an increased risk of dying in the subsequent year. The risk may be as high as 5 to 10 times that of patients with normal responses. The risks are especially great when ST-segment depression is combined with hypotension or when it is marked (greater than or equal to 2 mm). Patients with these responses often require a particularly aggressive approach, including coronary arteriography and coronary bypass surgery. By contrast, patients with completely negative tests seldom require an aggressive approach" [83]. We would support this view based on the available evidence.

4.4. INDICATIONS FOR CARDIAC CATHETERIZATION AND SURGICAL INTERVENTION AFTER ACUTE MYOCARDIAL INFARCTION

This subject has also been recently reviewed [84]. After acute myocardial infarction patients with persistent recurrent angina and those with surgical complications of infarction (e.g., ventricular septal perforation, severe mitral insufficiency due to papillary muscle dysfunction or rupture) warrant cardiac catheterization with a view to surgery. Other patients considered to be at risk for either recurrent infarction or death during the first year include those with significant ST-segment depression on exercise ECG testing performed within the first month after infarction and those with impaired ventricular function, especially when it is coupled with

ventricular ectopy. When left ventricular function is severely impaired owing to myocardial necrosis, coronary artery bypass grafting is not likely to be helpful, although prompt and appropriate antiarrhythmic therapy may be beneficial.

In the Coronary Artery Surgery Study (CASS) patients 65 years of age or younger who had mild angina or an infarction more than 3 weeks previously were randomized to medical or surgical therapy if they had significant, operable, coronary artery disease [85]. (Patients with severe stenoses of the left main coronary artery or with an ejection fraction of less than 35 per cent were excluded from the study.) Both the randomized patients and those "randomizable but not randomized" had similar outcomes. Annual mortality rates in single-, double-, and triple-vessel disease were not significantly different between patients in the surgical and the medical groups. In patients with left main coronary artery disease both the Veterans Administration Study and the CASS demonstrated prolonged survival with surgery compared with medical treatment. Results of the European Coronary Surgery Study (ECSS) were also compatible with this.

Thus, in patients with mild to moderate angina and in angina-free survivors of myocardial infarction, prompt elective coronary artery bypass surgery does not improve longevity when compared with medical management unless worsening symptoms make surgery necessary. In patients with unimpaired ventricular function the survival curves with medical and surgical therapy for single-, double-, and triple-vessel disease are indistinguishable. In patients with impaired ventricular performance, a statistically nonsignificant survival trend in favor of surgery is evident from the CASS. This may represent a true survival advantage for patients assigned to surgical therapy; however, owing to insufficient numbers of patients in this subgroup, rigorous testing of this hypothesis has not been completed.

Neither the ECSS nor the CASS demonstrated a beneficial effect of surgery over medical therapy in preventing recurrent infarction. These trials suggest that coronary artery surgery does not appear to confer any advantages over medical therapy in mildly symptomatic or asymptomatic survivors of acute infarction in the presence of normal ventricular function and single-, double-, or triple-vessel disease. Exceptions to this are patients with significant left main coronary artery disease, and probably patients with double- or triple-vessel disease who have two or more additional risk factors, such as an abnormal resting ECG, ST-segment depression greater than 1.5 mm on exercise, peripheral arterial disease, or proximal left anterior descending stenoses.

In order to determine appropriate future therapy, some physicians argue that it is necessary to assess both left ventricular function and coronary artery anatomy. In the CASS population of patients with mild angina or asymptomatic patients who survived infarction, 4.3 per cent of patients showed narrowing of the left main coronary artery luminal diameter exceeding 70 per cent. Identification of left main coronary stenosis argues in favor of exercise testing for patients presenting with coronary artery disease but does not necessarily argue in favor of coronary arteriography. In a New Zealand study of patients who had suffered a single myocardial infarction, a left main coronary artery lesion was present in 4 per cent of patients and was associated with a strongly positive exercise test in 14 of 15 patients [86].

Coronary arteriography should be performed in patients whose symptoms persist despite medical therapy. Patients who have mild stable symptoms and can complete Stage III of the Bruce exercise testing protocol (or its equivalent) can be reasonably reassured [87]. However, patients who exhibit early positivity on an exercise test, particularly at a low heart rate or associated with a fall in blood pressure or a global pattern of ECG ischemia should undoubtedly be considered for coronary arteriography. In other patients who survive infarction and who have a reassuring exercise testing result, it does not seem justified at present to recommend routine coronary arteriography. For most patients who are asymptomatic or who have mild symptoms and who have completed a degree of exercise equivalent to Bruce protocol Stage III (in the absence of ischemia or untoward physiological responses), arteriography will not lead to surgery.

Prospective, randomized trials have examined the place of coronary artery surgery in patients with unstable angina (i.e., those with a progressive, changing pattern of angina or rest angina with evidence of ischemia on ECG but without infarction) [88]. Surgically treated patients achieve a better symptomatic status than

medically treated patients, but the incidence of early or late myocardial infarction or risk of death is not diminished in the former group.

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16. PROGNOSIS AFTER HOSPITALIZATION WITH CHEST PAIN OR MYOCARDIAL INFARCTION

1. International Trends in Coronary Heart Disease Mortality

In the late 1960s and early 1970s, a decline in coronary heart disease mortality was noted in different parts of the world. This downward trend has since continued in North America, Belgium, Finland, Israel, Japan, Australia, and New Zealand [1–3], and data from Australia suggest that it is evident in all age groups [4]. In contrast, in most eastern European countries, Russia, and Sweden, death rates from coronary heart disease are increasing.

Community-based studies carried out in Rochester, Minnesota, showed that the incidence of coronary heart disease had been increasing up until 1959 but over the next 5 years fell to the level recorded in 1954 and thereafter slowly declined until 1969; between 1969 and 1975 there was virtually no change [5,6]. These observations applied to angina pectoris, myocardial infarction, and sudden unexpected death, the greatest fall being noted in the incidence of sudden death. This drop in coronary heart disease incidence was followed a decade later by a drop in the annual mortality rate and probably was a contributing factor. In 1960 the annual mortality rate was 140 per 100,000; by 1969 it had increased to 184 per 100,000 but over the next 9 years fell to 113 per 100,000. These changes in mortality rate were observed in all age groups. A reduction in case mortality rate was also observed for patients with myocardial infarction and angina. In the late 1960s, early mortality after infarction was 18 per cent, but this declined to 9 per cent in the early 1970s. The 5-year survival of patients with angina improved from 75 per cent in the years 1950 to 1970 to 87 per cent during the years 1970 to 1975.

It remains to be seen whether the decline in coronary heart disease mortality is due to a reduction in incidence, a change in case fatality rates, or both these factors. Changing incidence might suggest that preventative programs are having an impact, whereas changes in case fatality rates suggest improvements in medical and surgical management of patients known to have coronary heart disease. The decline in mortality noted in different countries, with different health systems, and in all age groups appears to be genuine rather than a result of changes in methods for classifying patients with coronary heart disease. The studies in Rochester, cited above, suggest that both the incidence and case fatality rates may be falling. Because the trend was first noted in the late 1960s, it was probably not due to the increased use of beta-adrenoceptor blocking agents or to coronary artery surgery or even treatment of hypertension or changes in smoking habits. As educational health programs are becoming more widespread, informed patients may be presenting earlier with less severe manifestations of coronary artery disease.

2. Outcome of Patients Hospitalized with Chest Pain

Studies of outcome of patients with chest pain thought to be definitely (or possibly) due to an acute myocardial infarction and leading to hos-

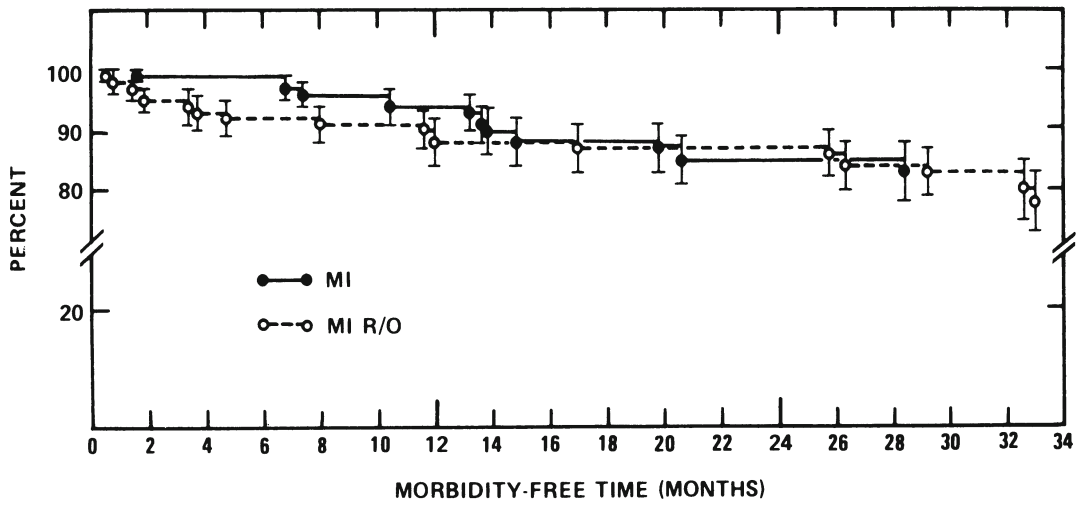

FIGURE 16–1. "Myocardial infarction-free" curves after hospitalization for 88 patients in whom infarction was ruled out (MI R/O) and for 78 patients who survived infarction (MI). After a mean followup of 27.8 months, 17 per cent of MI patients and 22 per cent of MI R/O patients had a subsequent infarction. During the first 6 months, MI R/O patients were more likely to suffer a myocardial infarct. After 6 months, the morbidity-free curves were similar for the two groups. Compared with the MI group, the MI R/O group included more patients with a history of previous infarction (41 vs 19 per cent) and with stable angina (52 vs 32 per cent). (From Schroeder JS, et al: Do patients in whom myocardial infarction has been ruled out have a better prognosis after hospitalization than those surviving infarction? *N Engl J Med* 303:1, 1980.)

pital admission have shown that subsequent morbidity and mortality can be the same whether or not an infarction evolves. In a prospective study of patients admitted to a coronary care unit with chest pain, outcome at 2 years was compared for 89 patients without infarction and 84 patients with an evolving infarction [8]. The rate of infarction or death in patients discharged from the hospital was similar in the two groups at 6 months and at 27.8 months (figures 16–1 and 16–2). The occurrence of congestive heart failure, cardiomegaly, and angina after hospital discharge tended to increase the risk of morbidity and mortality in individuals in both groups. The group in whom myocardial infarction was ruled out included more patients with a history of previous infarction (40.9 vs 19.2 per cent) and with stable angina before hospitalization (52.3 vs 32.1 per cent) than the group in whom infarction evolved [8]. It would be interesting to know whether patients analyzed in a similar manner who have no previous history of infarction would have similar morbidity-free and survival periods during followup.

Nevertheless, this study comprises the types of patients admitted by many medical care units and the inferences apply. The most important finding is that the rate of combined coronary events (infarction, death, or both) during the first 6 months after hospital discharge is similar for the patient with infarction "ruled out" and for the patient who initially had an infarction. The high incidence of previous infarction in the patients found not to have an infarction during the index admission and the subsequent adverse influences of cardiomegaly, congestive heart failure, and angina after hospital discharge reflect the fact that those patients with ventricular damage or ongoing ischemia are most likely to have subsequent coronary events.

This notion was confirmed in a later retrospective study in which the incidences of acute myocardial infarction and death after discharge from a coronary care unit were recorded for patients with and without a confirmed diagnosis of acute myocardial infarction [9]. During the first 2 years, no significant differ-

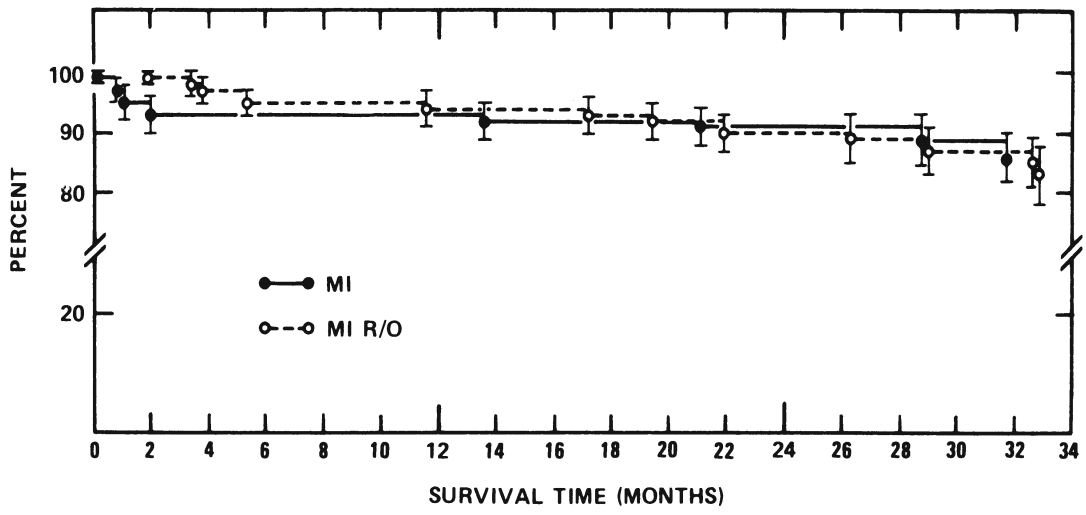

FIGURE 16–2. Survival curves during a mean 27.8-month followup of 78 patients with myocardial infarction (MI) and 88 patients in whom infarction was ruled out (MI R/O). At the end of the followup period, 86 per cent of MI patients and 83 per cent of MI R/O patients were alive. (From Schroeder JS, et al: Do patients in whom myocardial infarction has been ruled out have a better prognosis after hospitalization than those surviving infarction? *N Engl J Med* 303:1, 1980.)

ences were found with regard to cardiac events, sudden death, and acute infarction. At 3 years mortality rates were similar — 18.3 per cent in patients without infarction and 22.4 per cent in those with an evolving infarction. Interestingly, patients in whom infarction was not diagnosed during this particular episode but who had either previous acute myocardial infarction, angina, or ST-segment and T-wave abnormalities on ECG accounted for most of the observed cardiac events. Mortality appeared highest during the first 6 to 12 months after discharge.

Once again, these studies indicate that mortality after acute myocardial infarction or chest pain syndromes resembling angina pectoris depends on the cumulative amount of myocardial necrosis. It is irrelevant whether or not the index episode of chest pain requiring hospital admission evolves into an acute infarction. Patients with no infarction during this index episode but a history of previous infarction and angina, transient ST-T-wave changes, cardiomegaly, or congestive heart failure, all of which reflect either ongoing ischemia or previous myocardial damage, seem to be at particular risk for future morbid events.

3. *Coronary Prognostic Indices*

In the 1960s a number of investigators sought to determine the factors which might influence the short- and long-term outcome following myocardial infarction. In general, they examined early measurable clinical parameters evident upon admission to hospital and derived prognostic markers.

3.1. INDICES OF NORRIS ET AL [10–14]

After prospectively recording the clinical factors present in 757 patients admitted over a 12-month period (1966 to 1967) to three general hospitals, Norris et al used the method of discriminant analysis and found six easily measurable factors associated with hospital mortality from acute myocardial infarction [10,11]. In approximate order of importance, these prognostic factors were:

1. Systolic blood pressure on admission to hospital.
2. Patient's age.
3. Presence or absence of cardiac enlargement on the first chest x-ray after admission.

TABLE 16–1. The Norris coronary prognostic indices (X and Y values)

	Short-term index		*Long-term index*	
	X	Y	X	Y
Age (yr):				
<50	0.2		0.2	
50–59	0.4		0.4	
60–69	0.6	3.9	0.6	4.9
70–79	0.8		0.8	
80–89	1.0		1.0	
Heart size:				
Normal	0		0	
Doubtfully enlarged	0.5	1.5	1.0	1.7
Definitely enlarged	1.0		1.0	
Lung fields:				
Normal	0		0	
Venous congestion	0.3		0.3	
Interstitial edema	0.6	3.3	1.0	5.1
Pulmonary edema	1.0		1.0	
Previous ischemia:				
No ischemia	0		0	
Previous angina	1.0	0.4	0	3.5
Previous infarction	1.0		1.0	
Systolic blood pressure on admission (mm Hg):				
<55	1.0			
55 to 64	0.7			
65 to 74	0.6			
75 to 84	0.5		Nil	Nil
85 to 94	0.4	10.0		
95 to 104	0.3			
105 to 114	0.2			
115 to 124	0.1			
>125	0			
Position of infarction:				
Anterior transmural	1.0			
Left bundle branch block	1.0	2.8	Nil	Nil
Inferior transmural	0.7			
Subendocardial	0.3			

*See text for explanation of X and Y values.

4. Presence or absence of pulmonary congestion or edema on the first chest x-ray.
5. Position and extent of infarction based on ECG criteria.
6. Occurrence of previous angina or infarction.

According to discriminant analysis, the effects of these factors were summated to a number constituting the *short-term coronary prognostic index* (table 16–1). Each clinical factor was assigned a severity weighting of 0 to 1 (X values). Each X value was then multiplied by a number found by means of discriminant analysis to express the importance of this particular factor relative to the other five factors (Y values). The coronary prognostic index was then expressed as the sum of $X_1Y_1 + X_2Y_2$ up to X_nY_n, the value of n in this case being 6. The six factors with their X and Y values are shown in the left-hand column of table 16–1 under the heading "Short-term Index." By computing the total weighting (prognostic index) for each patient and dividing the patients into six groups according to these index values, this method can be used to classify patients based on grades of severity (figure 16–3). Thus, hospital mortality

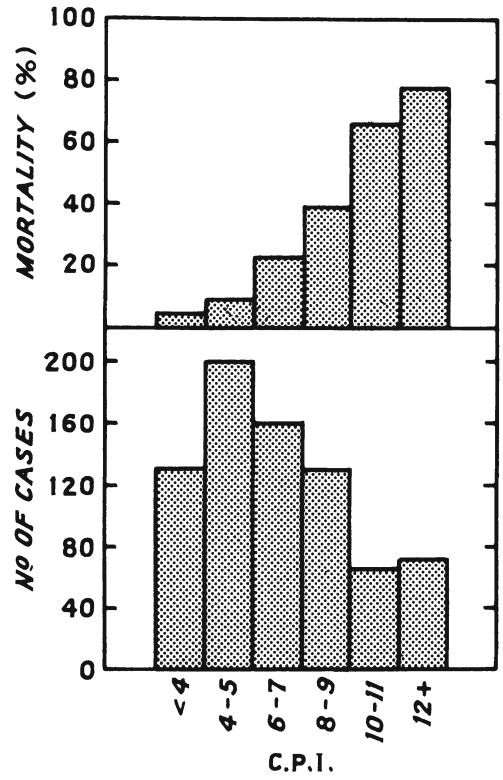

FIGURE 16–3. Coronary prognostic index (CPI) of Norris et al constructed from numerical weightings given to six factors (age, ECG assessment of position and extent of infarction, systolic blood pressure on admission, heart size, degree of congestion of lung fields on chest x-ray, and history of previous ischemia). This index provides prognostic information on hospital mortality for different groups of patients. The 757 patients studied were divided into six groups according to CPI, and the lower histogram shows the number of patients in each group. With increasing CPI there was a gradual increase in hospital mortality ranging from 3 per cent when the index was less than 4 to 78 per cent when it was 12 or more. (From Norris RM, et al: A new coronary prognostic index. *Lancet* 1:274, 1969.)

for a group of patients with a prognostic index of less than 4 would be 3 per cent, whereas this rate would be 78 per cent if the index were 12 or more.

This coronary prognostic index can be applied prospectively using factors that can easily be measured at the time of hospital admission. It can be used to compare groups of patients selected at random for trials of different forms of therapy but is of less value in predicting outcome in individual cases. Norris et al found that the hospital mortality rate was significantly reduced among patients with moderately severe infarction treated in the CCU compared with patients treated without monitoring in a general medical ward (figure 16–4). Interestingly, survival was unaltered by the different methods of management in patients with either a low or a high short-term prognostic index, indicating either a very good or a very bad prognosis, respectively. It is evident that, apart from the age of the patient at the time of admission to hospital, several of the factors reflect the cumulative amount of myocardial damage and thus infarct size (namely cardiac enlargement and heart failure) while a low systolic blood pressure on admission to hospital usually reflects "power failure" of the heart associated with extensive myocardial necrosis. Factors not significantly associated with hospital mortality were sex of the patient, time of admission after the onset of infarction, and a history of hypertension or diabetes.

These same investigators followed hospital survivors from the original cohort prospectively recruited in 1966–1967 and examined the effect of prognostic factors at 3 years [12], 6 years [13], and 15.5 years [14]. Four factors contributed to a coronary prognostic index that predicted long-term survival after recovery from myocardial infarction (table 16–1):

1. Patient age.
2. Presence or absence of cardiac enlargement on the first chest x-ray after admission.
3. Presence or absence of pulmonary congestion or edema on the first chest x-ray.
4. Presence or absence of previous infarction at the time of the index infarction.

The site of the infarct and systolic blood pressure at the time of initial admission had fully expressed themselves in terms of prognosis prior to three-year followup and were not significant factors long term.

As in many other studies, age at the time of index infarction was the most powerful predictor of long-term survival. Out of a total of 757 patients 595 had died by the 15.5-year followup (including those who died in the hospital), giving a mortality of 79 per cent (figure 16–5).

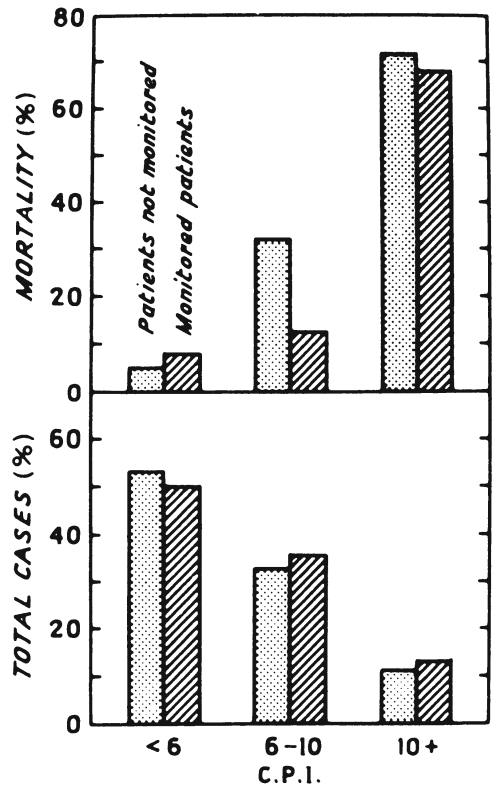

FIGURE 16–4. Using the coronary prognostic index (CPI) of Norris et al, groups of patients selected at random can be compared when different forms of therapy are used. Hospital mortality is contrasted between 545 patients under 70 years of age who were treated in a hospital without a CCU (patients not monitored) and 300 patients of similar age distribution treated one to two years later in a CCU (monitored patients). The mortality rate is significantly lower among patients with a CPI of 6 to 10 who had coronary care. Interestingly, survival rates were not altered by the different methods of management in patients with either a low or a high short-term prognostic index, which indicates either a very good or a very bad prognosis, respectively. The lower part of the figure shows the distribution of patients among the CPI grous in each series. (From Norris RM: Prognosis in myocardial infarction. *Heart and Lung* 4:75, 1975.)

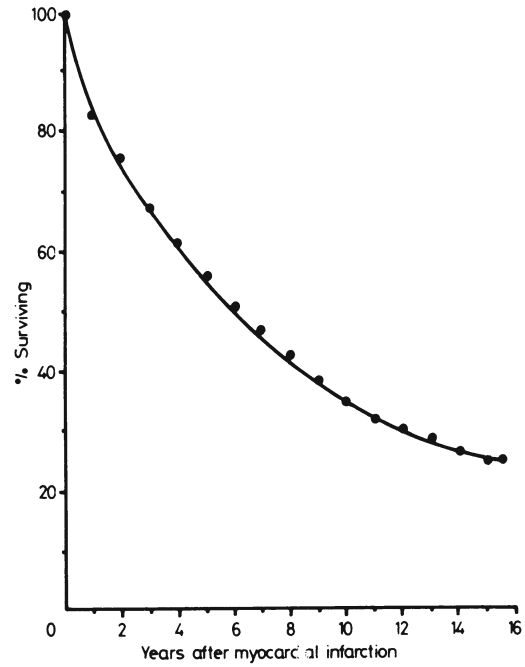

FIGURE 16–5. Survival curve during a mean follow-up period of 15.5 years for patients discharged with acute myocardial infarction. The total number of patients traced for followup after discharge from hospital was 519 out of 549 (95 per cent). Of 519 patients traced, 387 (75 per cent) had died. Out of a total of 757 patients admitted with myocardial infarction, 595 died, including those who died in the hospital, giving a mortality of 79 per cent after 15.5 years. (From Merrilees MA, et al: Prognosis after myocardial infarction. Results of 15 year follow up. *Br Med J* 288:356, 1984.)

These four prognostic factors, the effects of which are shown in figure 16–6, form the basis of the long-term Norris coronary prognostic index.

Both early and late prognosis after infarction are related to the age of the patient at the time of index infarction and the severity of cardiac dysfunction (i.e., presence or absence of cardiac enlargement, of pulmonary congestion, and of previous infarction). These long-term observations in a large group of patients with a very complete followup at 15.5 years — i.e., 99 per cent of the patients alive at 6 years and 95 per cent of those originally discharged from the hospital were traced — emphasized that cumulative myocardial necrosis is the ultimate determinant of prognosis after acute infarction(s). If infarct size can be reduced by various therapeutic measures instituted early after the onset of infarction, long-term prognosis might be improved.

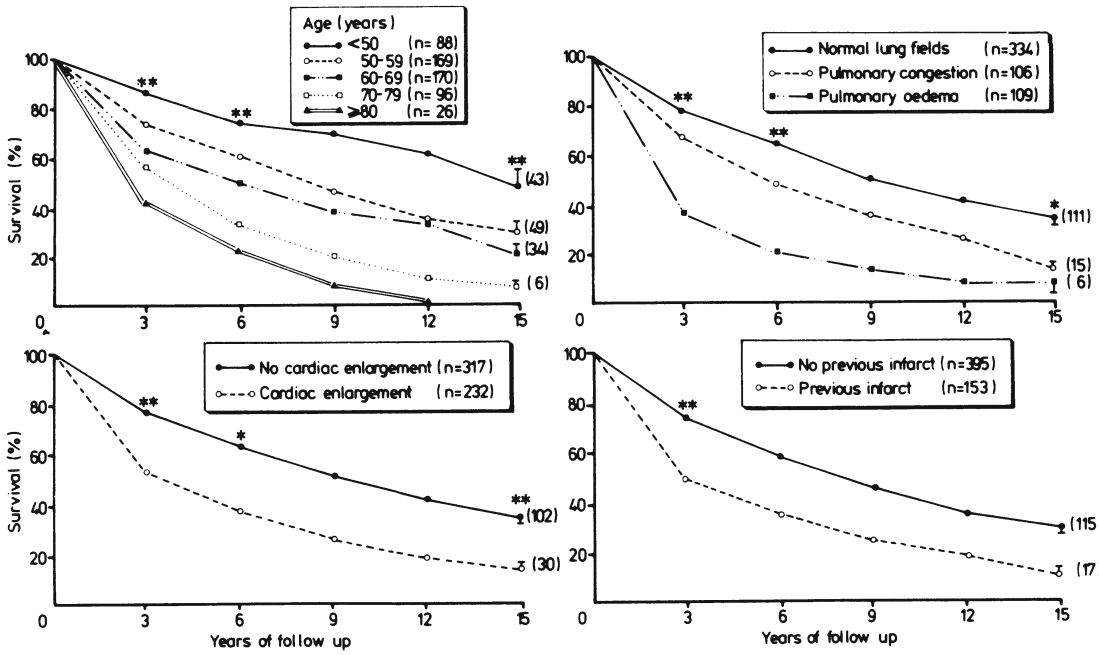

FIGURE 16–6. The effect of four factors on long-term survival after acute myocardial infarction as determined by Norris et al (i.e., age, presence or absence of cardiac enlargement on the first chest x-ray after hospital admission, presence or absence of pulmonary congestion or edema on the first chest x-ray, and presence or absence of previous infarction at the time of index infarction). Vertical bars indicate standard errors of estimates; values at 15 years indicate numbers of survivors. (* = $p < 0.05$, ** = $p < 0.01$.) (From Merrilees MA, et al: Prognosis after myocardial infarction. Results of 15 year follow up. *Br Med J* 288:356, 1984.)

Interestingly, the condition of the heart at the time of initial infarction continued to affect prognosis among these patients who had already lived for 6 years after their index infarct (table 16–2). If the index infarction was a recurrence, survival was adversely affected mainly for the first 3 years, although a small effect on mortality was still evident 6 to 15 years after the event. Mortality during long-term followup is shown according to the score obtained using the coronary prognostic index at the time of the index infarction. The significant increase in mortality with increasing coronary prognostic index at 3- and 6-year followup was still apparent during the 6- to 15-year followup (figure 16–7).

TABLE 16–2. Late prognosis after infarction

Coronary prognostic index: at index infarction	Mortality 6 to 15 years after infarction	
<3	36%	$p < 0.01$
3 to 5.9	61%	
6 to 8.9	68%	
>9	74%	

Adapted from Merrilees MA, et al: Prognosis after myocardial infarction: Results of 15 year followup. *Br Med J* 288:356, 1984.

3.2. INDEX OF PEEL ET AL [15]

Peel et al devised an index to assess prognosis for the first 4 weeks after acute myocardial infarction. Factors that they had previously thought important included age, sex, previous history, degree and severity of cardiogenic shock, presence and severity of heart failure, cardiac rhythm, and the nature and extent of ECG signs. They tested their prognostic index (table 16–3) among two series of patients.

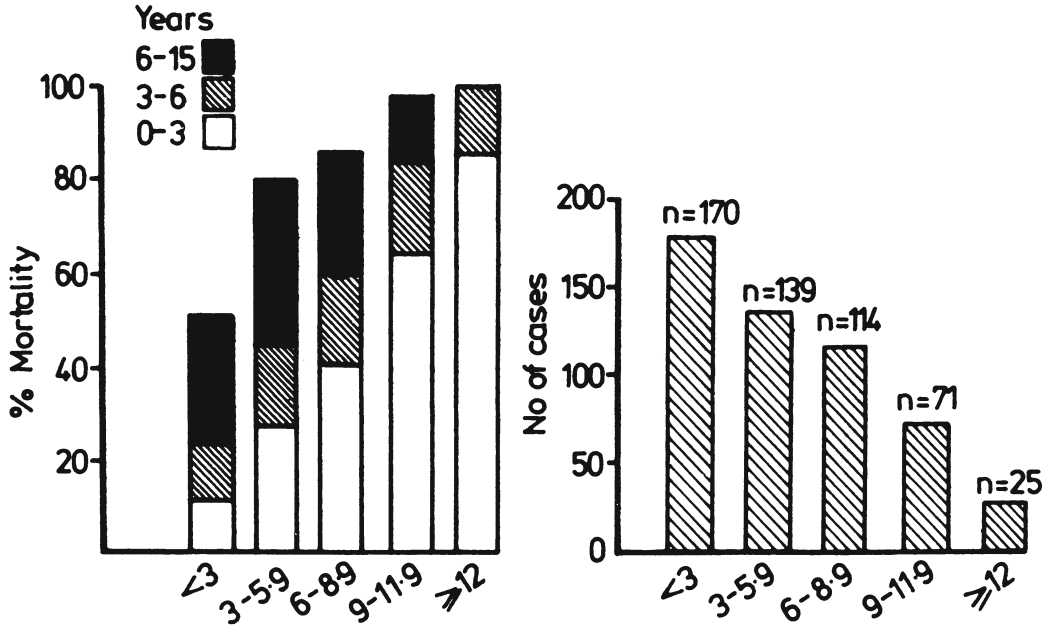

FIGURE 16–7. Mortality for the three periods of followup (0 to 3 years, 3 to 6 years, and 6 to 15 years) according to the coronary prognostic index (CPI) score at the time of index infarction. The significant increase in mortality with increasing index noted at 3 and 6 years was still apparent over the 6- to 15.5-year period. Mortality 6 to 15 years after infarction was 36 per cent among patients with a CPI less than 3, 61 per cent among those with a CPI of 3 to 5.9, 68 per cent among those with a CPI of 6 to 8.9, and 74 per cent among those with a CPI greater than 9. The difference in mortality from 6 to 15 years after infarction between patients with a CPI less than 3 and those with a CPI greater than or equal to 3 was highly significant. (From Merrilees MA, et al: Prognosis after myocardial infarction. Results of 15 year follow up. *Br Med J* 288:356, 1984.)

Although the index was designed for use during the first 2 days after infarction, the authors felt the mortality figures would be valid for any series composed of patients entering within 4 days of onset. Combining three series of cases, they derived a "standard mortality" for various coronary prognostic index ranges (table 16–4). Using this index, one can compare different forms of therapy and the composition of treatment groups. In practice, use of this index to predict early mortality presents some difficulties, since the categorization of varying degrees of shock is relatively subjective, as is the clinical assessment of heart failure.

3.3. KILLIP AND KIMBALL CLASSIFICATION [16]

To provide a clinical estimate of severity of myocardial infarction, Killip and Kimball classified patients into one of four groups:

I = *No heart failure:* No clinical signs of cardiac decompensation.
II = *Heart failure:* Diagnostic criteria include rales, S_4 gallop, and venous hypertension.
III = *Severe heart failure:* Frank pulmonary edema.
IV = *Cardiogenic shock:* Signs include hypotension (systolic pressure of 90 mm Hg or less) and evidence of peripheral vasconstriction such as oliguria, cyanosis, and diaphoresis. Heart failure, often with pulmonary edema, is also present in the majority of these patients.

The study group consisted of 250 consecutive patients with acute myocardial infarction. The incidence of life-threatening arrhythmias, cardiac arrest, and hospital mortality rose with increasing degrees of clinical severity (table

TABLE 16–3. Prognostic index of Peel et al

Patient characteristics	Score
Sex and age:	
Men: 54 or under	0
55 to 59	1
60 to 64	2
65 or over	3
Women: 64 or under	2
65 or over	3
Previous history:	
Previous cardiac infarct.	6
Other cardiovascular diseases or history of exertional dyspnea	3
Angina only	1
No cardiovascular disease	0
Shock:	
Absent	0
Mild — transient at onset	1
Moderate — present on admission but subsiding with rest and sedation	5
Severe — persisting despite rest and sedation	7
Failure:	
Absent	0
Few basal rales only	1
One or more of the following: breathlessness, acute pulmonary edema, orthopnea, gallop rhythm, liver enlargement, edema, or jugular vein distension	4
Electrocardiogram:	
Normal QRS; changes confined to R-T segment or T wave	1
QR complexes	3
QS complexes or bundle branch block	4
(If no ECG obtained, mark 4)	
Rhythm:	
Sinus	0
One or more of the following: atrial fibrillation, flutter, paroxysmal tachycardia, persistent simple tachycardia (110 bpm or more), frequent E.S., nodal rhythm, or heart block	4
TOTAL PATIENT SCORE = PROGNOSTIC INDEX	

Adapted from Peel AAF, et al: A coronary prognostic index for grading the severity of infarction. *Br Heart J* 24:745, 1962.

TABLE 16–4. Peel index score relative to early mortality

Peel score	Early mortality
1 to 8	3%
9 to 12	12%
13 to 15	24%
17 to 20	54%
21 to 28	88%

Adapted from Peel AAF, et al: A coronary prognostic index for grading the severity of infarction. *Br Heart J* 24:745, 1982.

16–5). In patients with cardiogenic shock the incidence of life-threatening arrhythmias was 94 per cent and that of hospital mortality was 81 per cent.

When the authors compared data from 100 consecutive patients admitted to the coronary care unit (CCU) with those from 100 patients admitted to regular care during the same period, results were at first discouraging. Hospital mortality was similar in the regular-care and CCU-treated groups (30 and 32 per cent, respectively). After this comparison, three major policy changes in care of patients were instituted:

1. Immediate defibrillation by the available trained professional, nurse, or physician.
2. Initiation of prompt treatment for life-

TABLE 16–5. Killip and Kimball Clinical Class*

	I No CHF	II CHF	III Pulmonary edema	IV Cardiogenic shock
Distribution (%)	33	38	10	19
Life-threatening arrhythmias (%)	36	46	73	94
Incidence of cardiac arrest (%)	5	15	46	77
Hospital mortality (%)	6	17	38	81

*Outcome of 250 consecutive patients with definite myocardial infarction 1965–1966.
From Killip T, Kimball JT: Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol* 20:457, 1967.

TABLE 16–6.

Variable*	Explanation	Unit
X_1	Admission systolic blood pressure	mm Hg
X_2	Highest blood urea nitrogen (in CCU)	mg/dl
X_3	Atrial arrhythmias+ (in CCU)	Absent = 0 Present = 1
X_4	Angina >3 months or previous myocardial infarction	Absent = 0 Present = 1
X_5	Ventricular ectopic beats >1/hr on dynamic ECG	Absent = 0 Present = 1

*Variables in the discriminant function.
+Atrial arrhythmias = more than one atrial ectopic bpm, atrial tachycardia, flutter, or fibrillation.
From Luria MH, et al: Survival after recovery from acute myocardial infarction. Two and five year prognostic indices. *Am J Med* 67:7, 1979.

threatening arrhythmias, heart failure, and hypertension.

3. A range of standard treatment programs was initiated.

In response to these measures the incidence of life-threatening arrhythmias in patients without cardiogenic shock fell from 51 to 41 per cent, the incidence of cardiac arrest fell from 22 to 9 per cent, and mortality fell from 26 to 7 per cent. In the absence of cardiogenic shock, aggressive medical management in the CCU reduced mortality from 26 to 7 per cent, although mortality for patients with myocardial infarction complicated by cardiogenic shock remained high.

It is clear from the work of Norris, Peel, and Killip and coworkers that indices of the mechanical dysfunction of the heart which reflect cumulative myocardial necrosis or infarct size are potent determinants of prognosis. It next became important to try and evaluate the relative effect of arrhythmias on long-term prognosis.

3.4. INDICES OF LURIA ET AL [17]

Data of 143 consecutive survivors of acute myocardial infarction over a 2.5-year period beginning late in 1970 were analyzed at 2 and 5 years. Discriminant function analysis was carried out and the corresponding probability of survival was calculated in a stepwise fashion. This type of analysis identifies the significant variables, weights them, and then expresses the weighted sum as a discriminant function. The score obtained for an individual patient can be related to the probability of his or her survival or may be used to classify a patient into a high- or low-risk group.

Five variables were found to be important for 5-year survival classification (table 16–6). The recommended 5-year discriminant function was $0.016X_1 + 0.038X_2 + 2.04X_3 + 2.03X_4 +$

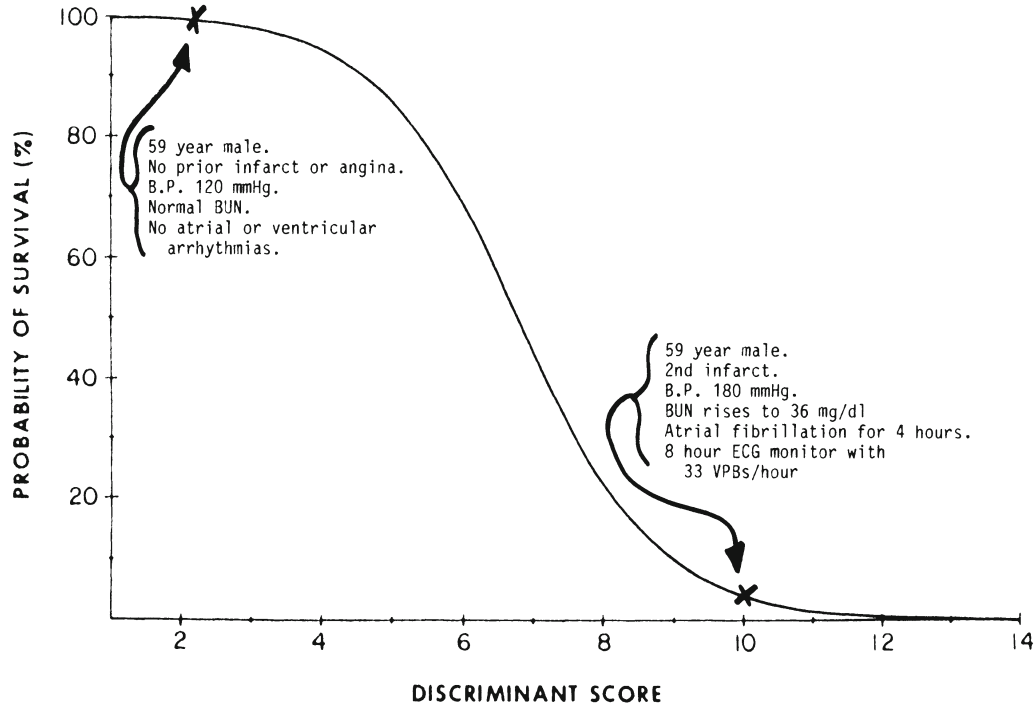

FIGURE 16–8. The discriminant score of a particular patient can be obtained from the discriminant function analysis, and can in turn be converted to a probability of 5-year survival. A 59-year-old man without previous angina has a systolic blood pressure of 120 mm Hg, highest blood urea nitrogen of 8 mg/dl, no atrial arrhythmias, and no ECG evidence of a previous infarction at the time of hospital admission. Before discharge a dynamic ECG reveals an average of less than one ventricular ectopic beat per hour. By reference to table 16–6 and substitution into the 5-year discriminant function, the discriminant score is 2.2. The 5-year probability of survival is therefore 99 per cent. The probability of survival of a subject at high risk may also be determined: A 59-year-old man is hospitalized with a second infarction. Systolic blood pressure on admission is 180 mm Hg, blood urea nitrogen rises in the CCU to 36 mg/dl, and he experiences a 4-hour transient bout of atrial fibrillation. Prior to discharge, a dynamic ECG demonstrates 33 ventricular ectopic beats per hour. Substitution into the 5-year discriminant function indicates a discriminant score of 10.05 and the 5-year probability of survival is 4 per cent. (From Luria MH et al: Survival after recovery from acute myocardial infarction. Two and five year prognostic indices. *Am J Med* 67:7, 1979.)

$1.76X_5$ (X_1 to X_5 are defined in table 16–6). The discriminant score of a particular patient can be obtained from the discriminant function and converted to a probability of 5-year survival by reference to a curve plotting discriminant score versus probability of 5-year survival (%) (figure 16–8). The cumulative 5-year survival rate of 68 per cent in this study agrees with rates of 65 to 70 per cent noted in other studies. These authors also demonstrated a high post-hospital first- and second-year mortality, followed by an average yearly mortality of 4.5 to 5.0 per cent up to 5 years after infarction.

Congestive heart failure and cardiomegaly were not significant discriminators for long-term mortality; however, low systolic blood pressure and high blood urea nitrogen reflect low cardiac output and diminished peripheral perfusion, and atrial arrhythmias are usually associated with elevated left ventricular end-diastolic pressure in the setting of acute infarction.

The prognostic indices derived by this group included the number of ventricular ectopic beats

per hour recorded on an 8-hour ambulatory ECG just prior to hospital discharge (about days 11 to 14). Thus, ambient arrhythmias occurring later in the hospital admission are included in the analyses as well as factors analyzed upon admission to the CCU. When the five factors from their discriminant analyses are considered together, it is evident that they may reflect the extent of myocardial impairment. Patients at lower risk can also be identified. These would be patients with normal systolic pressure on admission, normal blood urea nitrogen while in the CCU, no evidence of atrial arrhythmias, no previous history of angina pectoris or ECG evidence of a previous infarction, and an ambulatory ECG just prior to discharge revealing less than one ventricular ectopic beat per hour. In such a situation, the probability of 5-year survival could be 99 per cent.

3.5. INDICES OF BIGGER ET AL [18]

In this study, 100 patients who survived for 10 days after being admitted to the hospital with acute myocardial infarction were assessed. Again, ventricular arrhythmias occurring late after admission affected prognosis. Unvariates showing the strongest association with mortality during the 6 months after enrollment included blood urea nitrogen level, serum creatinine level, serum uric acid level, enlarged heart 2 weeks after infarction, ventricular tachycardia 2 weeks after infarction, peak creatine kinase level, and left ventricular failure in the CCU. The incidence of cardiac death in the first 6 months after discharge was almost four times greater than in the subsequent 6 months. Variables reflecting the extent of acute myocardial infarction, cardiac arrhythmia, and left ventricular dysfunction seemed to be most strongly associated with cardiac death in the 6 months after recovery from acute infarction.

3.6. EARLY POST-HOSPITAL PROGNOSTIC STRATIFICATION BY MOSS ET AL OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION [19]

Prognostic stratification was carried out for 518 patients discharged from the hospital after a definite or probable acute infarction and followed for 4 months. Prognostic stratification schemes were developed on 272 patients hospitalized in 1973 and tested on 246 patients hospitalized in 1974. The 4-month post-hospital cardiac mortality rate was 3 per cent in the low-risk group and 14 per cent in those at high risk ($p < 0.003$). The high-risk group was characterized by two or more of the following characteristics, while the low-risk group had none or only one of these characteristics:

1. History of angina at ordinary levels of activity or rest.
2. Hypotension and/or congestive heart failure while in the CCU.
3. Ventricular premature beat frequency >20/hr on a 6-hour ECG recording.

The prognostic power of this stratification scheme was such that 16 per cent of the post-hospital population could be identified as high-risk, and this subgroup contained 46 per cent of patients who died of a cardiac cause in the 4-month post-hospital interval.

3.7. LONG-TERM PROGNOSTIC INDICES OF KITCHIN AND POCOCK [20]

These indices were defined in a group of 420 patients who were admitted to a coronary care unit between 1966 and 1969 and subsequently discharged. Followup lasted for 5 to 7 years after acute infarction. Using multivariate analysis, the authors assessed the following factors that adversely affected long-term prognosis:

1. History of previous infarct.
2. History of hypertension.
3. Sinus tachycardia (highest pulse rate $\geq$ 100 bpm during two or more consecutive 4-hourly recordings).
4. Cardiac arrest.
5. Ventricular arrhythmias.
6. Atrial fibrillation.

A prognostic equation was devised to indicate the probability of survival for 5 years (P):

$$\ln \frac{P}{(1 - P)} = + 1.842$$
$$-0.846 \text{ (if previous myocardial infarct)}$$
$$-0.998 \text{ (if previous hypertension)}$$
$$-0.903 \text{ (if highest pulse rate} \geq 100)$$
$$-1.215 \text{ (if cardiac arrest)}$$
$$-0.630 \text{ (if ventricular arrhythmia)}$$
$$-1.353 \text{ (if atrial fibrillation)}$$

where the prognostic equation is the natural logarithm of the odds of surviving 5 years.

For example, if the patient has none of these six characteristics, the probability of surviving

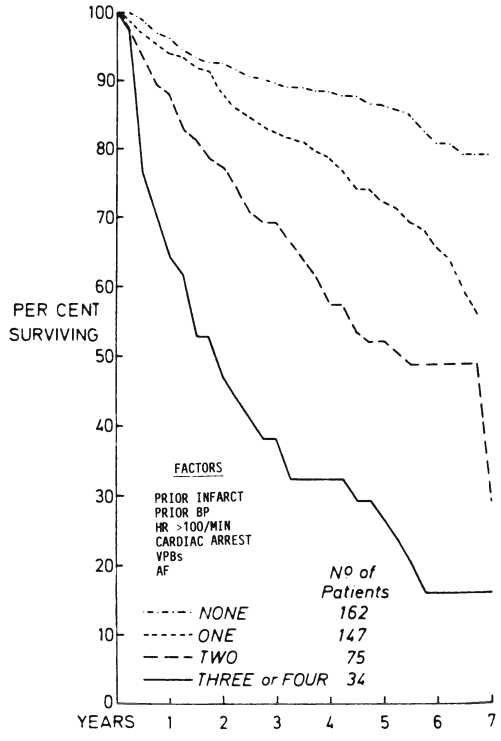

FIGURE 16–9. By multivariate analysis Kitchin and Pocock identified six factors that adversely affected long-term prognosis: a history of previous infarct, history of hypertension, sinus tachycardia (pulse rate greater than 100 bpm), cardiac arrest, ventricular arrhythmias, and atrial fibrillation. Long-term survival relative to the presence or absence of these six unfavorable characteristics is clearly shown in the survival curves for patients categorized according to the number of unfavorable characteristics during a 7-year period of followup. Five year survival is 86 per cent for patients with none of the characteristics, 52 per cent for those with two characteristics, and 27 per cent for those with three or more characteristics. (From Kitchin AH, Pocock SJ: Prognosis of patients with acute myocardial infarction admitted to a coronary care unit. II. Survival after hospital discharge. *Br Heart J* 39:1167–1171, 1977.)

5 years (P) is 0.86. If the patient has had a previous infarct and the highest pulse rate exceeds 100 bpm, this value (P) would be 0.52. The 5-year survival in this series for male patients discharged after an acute infarction was 70 per cent and 75 per cent for patients with first infarctions. Increasing age and a previous history of angina were found to be of borderline significance. Long-term survival was related to the presence or absence of the six unfavorable characteristics (figure 16–9).

The studies of Luria, Bigger, Moss, Kitchin and co-workers all illustrated the prognostic importance of mechanical dysfunction and cardiac arrhythmias and an attempt was next made to assess their independent contribution to outcome from infarction.

3.8. THE MULTICENTER POSTINFARCTION RESEARCH GROUP [21]

During 1979–1980, 866 postinfarction patients from four geographic locations and a heterogeneous group of university and community hospitals were enrolled in a risk-stratification program. Prior to hospital discharge, patients underwent 24-hour computer-analyzed Holter recordings and radionuclide determination of ejection fraction. During the average followup period of 22 months (range = 1 to 3 years) 101 patients died. The majority of deaths occurred during the first year after discharge (a 9 per cent mortality rate); 82 per cent of the deaths were classified as being due to atherosclerotic coronary heart disease (cardiac death) and 37 per cent were categorized as sudden (i.e., death within one hour of symptoms or during sleep).

Radionuclide ejection fractions and ventricular ectopic activity were related to cardiac mortality. One-year mortality increased progressively as the ejection fraction fell below 0.40 (figure 16–10) and as the frequency of ventricular ectopic beats per hour rose (figure 16–11). Ejection fractions had a considerably stronger effect on mortality than did ectopic depolarization.

Univariate analysis of the associations between baseline characteristics and survival or death during followup revealed that the variables most closely associated with subsequent mortality were those related to mechanical cardiac dysfunction either before or during acute hospitalization (New York Heart Association [NYHA] functional class, rales, and ejection fraction). Arrhythmias were less strongly associated with mortality than were the mechanical variables. Ischemia (angina pectoris before discharge) did not significantly discriminate between those who survived and those who died.

Analyses indicated that abnormal preadmission NYHA classification, extensive pulmonary

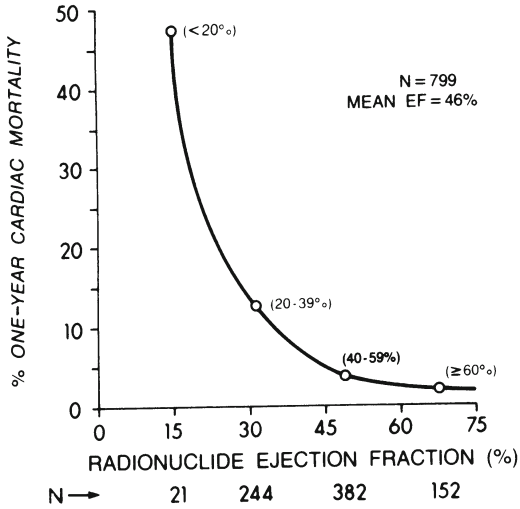

FIGURE 16–10. Univariate analysis showed a progressive increase in cardiac mortality at one year as the ejection fraction fell below 0.40. The graph shows one-year cardiac mortality in four categories based on radionuclide ejection fraction (EF) determined before discharge. N = number of patients in the total population and in each category. Of 811 patients in whom EF was recorded, 12 were lost to followup during the first year after hospitalization. (From The Multicenter Postinfarction Research Group: Risk stratification and survival after myocardial infarction. *N Engl J Med* 309:331, 1983.)

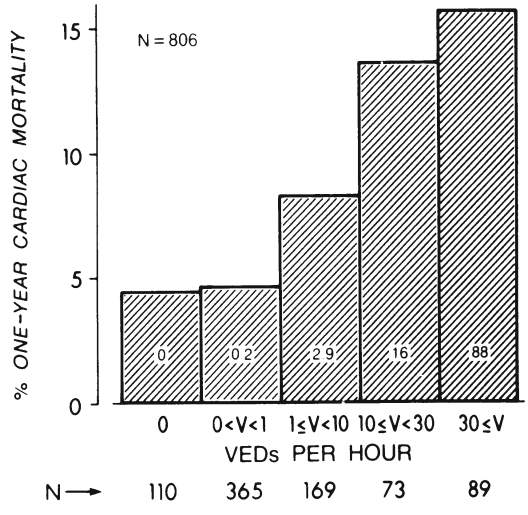

FIGURE 16–11. Twenty-four hour Holter monitoring was recorded before discharge in 819 patients enrolled in the Multicenter Postinfarction Research Group Study. Five categories for frequency of ventricular ectopic depolarizations (VEDs) were determined, and percent one-year cardiac mortality was analyzed. N = number of patients in the total population and in each category. The numbers within each of the boxes denote the median frequency of ventricular ectopy. As the frequency of VEDs rose above one/hour, there was a progressive increase in one-year cardiac mortality. While ejection fraction and ectopic depolarization both made significant contributions to the survival model, a low ejection fraction had a 1.5-fold stronger effect on mortality than did frequent ectopic depolarization. (From The Multicenter Postinfarction Research Group: Risk stratification and survival after myocardial infarction. *N Engl J Med* 309:331, 1983.)

rales while in the CCU, and a heart rate exceeding 90 bpm on the qualifying electrocardiogram made significant contributions to the survival model ($p < 0.01$). These three variables were added to the survival model, and the final model included ejection fraction, ventricular ectopy (>10 beats/hour), rales, and NYHA functional class.

The contributions of these risk factors to the final survival model are shown in terms of the relative risk, i.e., the ratio of the risk of dying, per unit of time, when a factor is present to the risk when the factor is absent. The relative risks were of similar magnitude (range = 1.6 to 3.3) (table 16–7). Pulmonary rales had the most significant effect and ventricular ectopy the least. The concept of relative risk permits quantification of the joint risk when two or more factors coexist. The combined risk is simply the product of the relative risks of the coexisting factors. For example, a patient with a low ejection fraction and frequent ventricular ectopy has a 3.8 ($2.4 \times 1.6 = 3.8$) increased risk of cardiac death when compared with a patient without these risk factors.

The important finding here is that this study substantiates the independent contributions that radionuclide ejection fraction and ventricular ectopy make to risk stratification. A low ejection fraction appears to have a 1.5-fold stronger effect on mortality than does frequent ventricular ectopy. The finding that pulmonary rales made an independent contribution to the survival model over the above radionuclide ejection fraction was of interest and suggests that these factors measure different aspects of cardiac

TABLE 16–7. The Multicenter Postinfarction Research Group: contribution of preselected factors to final survival model

Factor	Relative risk*	Chi square value	P value
Ejection fraction <0.40	2.4 (1.5,3.7)	12.3	<0.001
VED >10/hr†	1.6 (1.0,2.6)	3.8	<0.05
Rales > bibasilar	3.3 (2.1,5.2)	20.5	<0.001
NYHA Class II to IV ‡	1.9 (1.2,3.0)	8.1	<0.01
Time after hospitalization			
0 to 3 mo	4.0 (2.2,7.2)		
3 to 6 mo	2.8 (1.6,5.1)	33.5	<0.001
6 to 12 mo	1.3 (0.8,2.4)		

*Ratio of the risk of dying per unit of time (hazard rate) for patients with factor present to risk for patients with factor absent. For the time factors, the risks are relative to the probability of dying 12 to 36 months after discharge. Relative risk ratios were derived from survival analyses; 95 per cent confidence intervals are shown in parentheses.
†VED = ventricular ectopic depolarization.
New York Heart Association functional class one month before entry.
‡ From The Multicenter Postinfarction Research Group: Risk stratification and survival after myocardial infarction. *N Engl J Med* 309:331, 1983.

function. Pulmonary rales were recorded early after hospital admission and ejection fraction was measured about a week later. Therefore, the presence of extensive pulmonary rales is likely to have provided information about the extent of early dysfunction, whereas ejection fraction provided information about residual function at one week. When these two indicators of myocardial dysfunction coexist, they increase the relative mortality risk almost eight times. (Relative risk for ejection fraction × risk for rales = 7.9.)

The clinical significance of ventricular ectopic beats in the early post-hospital phase of myocardial infarction was also studied by some of the Multicenter Postinfarction Research Group participants [22]. Analyses of 6-hour Holter recordings taken before discharge and 5 months later showed that ventricular ectopy tended to increase in frequency and complexity during this interval. Interestingly, frequent ventricular ectopy was associated with increased cardiac mortality early after hospital discharge but not after 6 months, leading the authors to postulate that over time there might be a progressive loss of prognostic specificity of this sign. If this is true, post-hospital Holter monitoring may have limited prognostic usefulness. However, an alternative explanation may be related to the experimental design of this particular study, the sample size, and the small number of cardiac deaths (six during the 5- to 12-month followup interval).

It is now accepted that low ejection fraction and significant ventricular ectopy post infarction are important independent determinants of prognosis and that the combination of these factors may be particularly ominous.

In the past five years it has become common for patients to have coronary angiography post infarction. It is therefore important to evaluate whether the angiographic extent of coronary artery disease post infarction is an important independent prognostic factor.

4. Angiographic Factors and Prognosis after Acute Myocardial Infarction

4.1. AFTER FIRST INFARCTION

An Australian group prospectively catheterized 197 survivors of first myocardial infarction, age 60 years or less, within 2 weeks of hospitaliza-

tion [23]. Half the population had anterior infarctions and two-thirds had Q-wave infarctions. Surprisingly, single-vessel coronary disease was present in 62 per cent, two-vessel disease in 23 per cent, and three-vessel disease in 7 per cent. In 16 patients (8 per cent) no vessel showed greater than 70 per cent stenosis of the luminal diameter. Ejection fraction was greater than 50 per cent in 61 per cent of patients and less than 30 per cent in 5 per cent. Patients with Q-wave infarctions had significantly lower ejection fractions that did those with non-Q-wave infarctions (49 vs 59 per cent). The life table survival of patients with single-vessel disease was 99 per cent at one year and 97 per cent at two and three years. Since there were no significant differences between life table survival of patients with two- and three-vessel disease, these groups were pooled as having "multivessel disease." Their survival rate remained 90 per cent at one, two, and three years. Nineteen patients underwent coronary bypass surgery. Left ventricular ejection fraction was unrelated to the presence of angina before admission, age of the patient, site of infarction, or occurrence of ventricular tachycardia or fibrillation in the CCU. According to the authors, the two major findings of this study were (1) a high prevalence of insignificant and single-vessel coronary artery disease (70 per cent) and (2) a good overall prognosis. The high prevalence of single-vessel disease or insignificant disease in part resulted from the selection of patients under 60 years without previous infarction.

In a study by Norris et al, 325 male survivors of a first infarction under 60 years of age were prospectively studied with cineangiography and exercise testing within 4 weeks of the acute event [24]. Multivariate analysis using the proportional hazards model confirmed that the risk of cardiac death was increased by a low ejection fraction and a high coronary prognostic index. Surprisingly, neither the myocardial score (based on the severity of individual obstructive lesions of the coronary arteries and the amount of left ventricular myocardium supplied by each involved vessel) nor any other variables, including the exercise test, provided any significant additional information.

Sudden death occurred in 23 per cent of 52 patients whose ejection fractions were less than 40 per cent and in only 4 per cent of 272 patients with higher ejection fractions at the time of left ventricular angiography. Half the patients who died suddenly with a normal ejection fraction had suffered reinfarction between the time of angiography and death. Compared with the survivors, those who died suddenly did not appear to have a higher incidence of anterior infarction, cardiac enlargement or radiography, or a positive exercise test, although their left ventricular end-diastolic and end-systolic volumes were higher.

4.2. ANGIOGRAPHIC FEATURES OF SURVIVORS OF INITIAL OR RECURRENT MYOCARDIAL INFARCTION

Angiographic predictors of late mortality were identified in 259 consecutive male survivors of acute infarction who were catheterized one month after hospital admission and then followed for a mean of 34 months [25]. Based on Cox regression analysis, the only independent predictors of survival were left ventricular ejection fraction, number of diseased vessels, and occurrence of congestive heart failure in the CCU. Risk stratification showed that the probability of survival at 4 years was highest in patients with normal ejection fractions (greater than 96 per cent) and lowest in those with ejection fractions below 20 per cent (30 to 75 per cent).

Kaplan-Meier survival curves in patients with one-vessel, two-vessel, and three-vessel disease according to the degree of left ventricular dysfunction are shown in figure 16–12. Patients with normal ejection fractions had the longest life expectancy regardless of the number of arteries involved. In patients with ejection fractions between 21 per cent and 49 per cent the probability of survival was 78 per cent in those with three-vessel disease, and 95 per cent in those with single-vessel disease. The prevalence of left main coronary artery stenosis was low (1.2 per cent).

Nine per cent of the participants had a history of myocardial infarction. Although univariate analysis showed that previous infarction was common among patients who died during the followup period, multivariate regression methods failed to identify this factor as an independent variable influencing survival. It is likely that ejection fraction and previous infarction are closely linked and that the amount of additional information provided by the latter is not statistically significant once ejection fraction

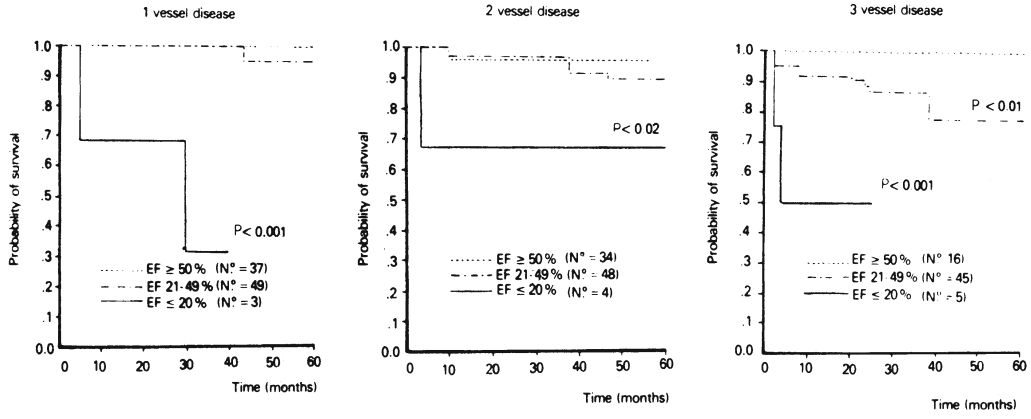

FIGURE 16–12. Predictors of late mortality were identified in 259 consecutive male survivors of acute infarction who were catheterized one month after hospital admission and the followed for a mean of 34 months. The only independent predictors of survival were left ventricular ejection fraction (EF), number of diseased vessels, and occurrence of congestive heart failure in the CCU. Kaplan-Meier survival curves of patients with one-, two-, and three-vessel disease, stratified according to EF are shown. P values represent differences (log-rank test) between the group with an EF of 50 per cent and the other two groups. The longest life expectancy was observed among patients with normal EFs regardless of the number of vessels involved. In patients with EFs between 21 and 49 per cent, the probability of survival was 78 per cent in patients with three-vessel disease and 95 per cent in patients with one-vessel disease. (From Sanz G, et al: Determinants of prognosis in survivors of myocardial infarction. A prospective clinical angiographic study. *N Engl J Med* 306:1065, 1982.)

— the variable most strongly related to survival — is selected.

Another study prospectively examined survivors of acute myocardial infarction admitted to a CCU [26]. Thirty-nine per cent of eligible patients agreed to have coronary and left ventricular angiography prior to hospital discharge, and all patients were followed for 30 months. A history of previous infarction was noted in 26 per cent. Univariate analysis showed that a low ejection fraction, proximal left anterior descending coronary artery disease (>50 per cent luminal diameter narrowing), and significant disease in all three coronary arteries were associated with a high risk of sudden cardiac death. Multivariate analysis of 30 clinical and laboratory variables identified previous myocardial infarction and ejection fraction less than 40 per cent as the best predictors of mortality during the followup period. All 13 patients who died were identified by these two variables. Interestingly, three-vessel coronary artery disease, proximal left coronary disease and complicated late hospital-phase ventricular arrhythmias assessed by 24-hour electrocardiographic recordings before hospital discharge did not provide additional information about mortality once the information provided by a history of previous myocardial infarction and low ejection fraction was considered. Multivariate analyses identified hypertension, three-vessel coronary disease, postinfarction angina and previous acute infarction as significant predictors of recurrent infarction during the followup period [26].

5. *Other Prognostic Indicators*

5.1. MYOCARDIAL INFARCT SCINTIGRAPHY

Technetium-99m stannous pyrophosphate myocardial scintigrams after acute myocardial infarction have some prognostic value. Patients with a pattern of massive uptake have a higher complication rate during hospital admission and during the first 6 months after discharge [27]. Similarly, a doughnut pattern of myocardial

radionuclide uptake may indicate a poor long-term prognosis. This pattern was associated with mortality rate of 83 per cent 2 years after infarction compared with 6 per cent associated with focal uptake and 0 per cent associated with diffuse uptake [28]. Patients with a persistently positive scan seem more likely to die and to have recurrent infarction or unstable angina or heart failure compared with those with negative scans obtained a mean of 8 months after infarction [29]. Measurement of infarct size using single-photon emission computed tomography and technetium-99m pyrophosphate has also shown a direct relationship between infarct size and patient prognosis in preliminary studies [30]. During a followup period of 18 months, complications were common in patients with infarcts greater than 40 grams.

5.2. BUNDLE BRANCH BLOCK AFTER ACUTE INFARCTION

Long-term followup of patients with myocardial infarction complicated by bundle branch block shows a significantly higher mortality for left than for right bundle branch block (68 vs 33 per cent). Left anterior hemiblock in the presence of right bundle branch block neither worsened the prognosis nor increased the risk of complete heart block [31].

In patients with bundle branch block complicating acute anteroseptal infarction the incidence of sudden death and late ventricular fibrillation is high in the first 6 weeks after infarction. However, if such patients survive the first 1 to 2 months, they have a relatively good prognosis during the first year [32]. Permanent prophylactic pacing may not affect prognosis in such patients. Measurement of H-V intervals in the acute phase of infarction with bundle branch block does not appear to help select patients who might benefit from prophylactic long-term pacing [33].

5.3. RELATION OF PSYCHOSOCIAL FACTORS TO MORTALITY

Male survivors of acute infarction were interviewed, and then single-lead ECG monitoring was recorded for an hour. These patients were followed prospectively for 3 years and those with more than 9 complex ventricular premature beats per hour had a different risk of sudden coronary death, depending on their amount of education. Men with little education had more than three times the risk of sudden coronary death than better educated men with the same arrhythmia (cumulative mortality rates = 33 and 9 per cent, respectively). There was no relation between educational level and risk of recurrent infarction. No such difference appeared in the absence of complex ventricular premature beats [34]. The same investigators found that patients classified as being socially isolated and having a high degree of life stress had more than four times the risk of death of men with low levels of stress and isolation. In addition, high levels of stress and social isolation were most prevalent among the least educated men [35]. The increase in risk associated with these factors applied to both total deaths and sudden cardiac deaths and was noted among men with both high and low levels of ventricular ectopy during hospitalization for acute infarction.

5.4. FACTORS SUGGESTING A GOOD PROGNOSIS AFTER MYOCARDIAL INFARCTION

Various studies examining both short- and long-term prognosis indicate that several clinical and investigative features may be associated with a better prognosis after acute infarction and are often evident at the time of hospital admission or over the next few days. Absence of a previous history of angina or myocardial infarction is a favorable feature. During the acute phase absence of evidence of extensive ventricular damage such as sinus tachycardia, hypotension, left ventricular failure, or cardiomegaly indicates a better prognosis. Atrial arrhythmias in the acute phase usually reflect impaired ventricular function.

It is apparent that most studies suggest that a low ejection fraction and a history of previous myocardial infarction are among the strongest predictors of longevity. Frequent premature beats or complex arrhythmias during Holter monitoring, particularly if associated with a low ejection fraction, appear to act independently as adverse prognostic factors.

While three-vessel coronary disease, left anterior descending disease, and a low ejection fraction with or without angina may be determinants of either sudden death or recurrent infarction, ventricular function appears to be more important than the extent of coronary artery disease as a determinant of future prognosis.

Recent randomized trials of coronary artery

surgery also provide some information about postinfarction prognosis in medically treated patients. In the Coronary Artery Surgery Study (CASS), 63 per cent of patients age 65 or less with mild angina or a myocardial infarction more than 3 weeks earlier had a history of prior infarction [36]. Patients with severe stenoses of the left main coronary artery or with a recognized ejection fraction below 35 per cent were excluded; however, in the medically treated group, 21 per cent had ejection fractions between 35 and 50 per cent, while 73 per cent had ejection fractions exceeding 50 per cent. Q-wave infarction was present in 29 per cent of patients, and the distribution of one-, two-, and three-vessel disease was 27 per cent, 38 per cent, and 35 per cent, respectively. After 5-year followup, annual mortality in those receiving medical therapy was only 1.6 per cent. Annual mortality rates in patients with one-, two-, and three-vessel disease in the medically treated group were 1.4 per cent, 1.2 per cent, and 2.1 per cent, respectively. In patients with ejection fractions greater than 50 per cent, annual mortality in the medically treated group with one-, two-, and three-vessel disease was 1.1 per cent, 0.6 per cent, and 1.2 per cent, respectively. The annual rate of bypass surgery in patients initially assigned to receive medical treatment was 4.7 per cent.

In a prospective, randomized trial of patients who had survived two or three myocardial infarctions the actuarial survival curves showed an annual mortality rate of 3 to 4 per cent for all patients studied during a mean followup of 4.5 years. There was no advantage for patients randomized to surgery over those who received medical therapy. The low mortality rate of the medically treated patients in this study was also striking [37].

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