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EARLY INTERVENTIONS IN ACUTE MYOCARDIAL INFARCTION

edited by

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PREFACE

Our understanding of the pathophysiology of acute myocardial infarction has grown enormously in recent years. This has led to an increasingly aggressive approach to management, designed to blunt the extent of infarction by salvaging acutely ischemic myocardium. Alternatives now include thrombolysis, PTCA with and without prior thrombolysis, and emergency bypass surgery, as well as the more aggressive use of a variety of drugs. This book consists of a series of chapters by experienced cardiologists and cardiovascular surgeons that present today's state of the art in managing acute myocardial infarction. It is written with the purpose of presenting practical approaches of value to the clinician related to the more complex problems faced in dealing with patients undergoing myocardial infarction.

EARLY INTERVENTIONS IN ACUTE MYOCARDIAL INFARCTION

1. MANAGEMENT OF ARRHYTHMIAS IN THE CORONARY CARE UNIT

NORA GOLDSCHLAGER, RODERICK WOODS, AND NEAL BENOWITZ

With the advent of coronary care units, mortality from cardiac arrhythmias occurring during acute myocardial infarction has been unquestionably and dramatically reduced. In addition, continuous electrocardiographic monitoring has resulted in the recognition of specific arrhythmias related to acute ischemic heart disease and thus to the development of appropriate strategies for their management.

This chapter will review certain specific aspects of those bradyarrhythmias and atrial and ventricular tachyarrhythmias that are seen most commonly in acute myocardial infarction. Pharmacologic therapy, including the use of some of the newer antiarrhythmic agents, will be discussed, as will pacemaker therapy of both bradyarrhythmias and tachyarrhythmias.

PHARMACOKINETIC CONSIDERATIONS IN ANTIARRHYTHMIC DRUG THERAPY

Concepts of pharmacokinetics have been developed with the assumption that the effect of a drug is proportional to its concentration at the target organ. At steady state, when the concentration of a drug in the blood is in equilibrium with the concentration in tissue, the blood concentration is proportional to the tissue concentrations. For most antiarrhythmic drugs, blood concentrations at steady state correlate with the magnitude of the effect and can be used as predictors of the therapeutic effect or toxicity. Pharmacokinetic principles deal with the quantitative relationship between the dose of a drug and the con-

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centration of a drug in the blood, and hence drug action. Pathologic processes such as cardiac failure or renal failure require adjustments by altering specific pharmacokinetic variables (absorption, distribution, metabolism, and excretion). The three basic pharmacokinetic parameters are volume of distribution, clearance, and half–life.

Absorption and bioavailability

Absorption refers to the movement of a drug from the site of dosing into the bloodstream. *Bioavailability* refers to the percentage of a drug that reaches the systemic circulation. Even if a drug is 100% absorbed, bioavailability may be incomplete due to metabolism in the gut lumen or wall, the portal venous blood, or the liver prior to reaching the systemic circulation.

Most antiarrhythmic drugs are given by the oral route. Absorption is primarily from the small intestine. The rate of absorption is dependent in large part upon the rate of gastric emptying and may be delayed or reduced in various disease states. For example, cardiac failure may reduce the extent of absorption by producing intestinal mucosal edema and/or by reducing intestinal blood flow. Drug therapy for specific cardiac conditions, such as the use of narcotics in acute myocardial infarction, will slow gastric emptying and may slow the rate (but not the extent) of absorption of antiarrhythmic drugs. Specific drugs such as antacids combine with antiarrhythmic drugs, thereby reducing their absorption. The presence of disease states or concomitant drug therapy may influence bioavailability independently of absorption. For example, the presence of chronic liver disease or the administration of drugs, such as cimetidine, that impair hepatic drug metabolism will increase the bioavailability of certain drugs such as propranolol.

Intramuscular administration of drugs generally results in rapid absorption. In cardiac emergencies, where vascular access is not readily available, intratracheal routes have been used for administration of antiarrhythmic drugs such as lidocaine. During cardiac arrest, the rate of absorption and time of onset of action may actually be faster by intratracheal compared to peripheral intravenous dosing. This is probably due to slow venous flow during cardiac arrest.

Distribution

Once a drug is absorbed into the blood stream, it is distributed to various body tissues. The phrase *volume of distribution* (V_d) relates the amount of drug in the body to the concentration of drug in the blood or plasma (C) as follows:

V_d = amount of drug in the body/C.

Drugs with large volumes of distribution, such as digoxin, are extensively distributed to body tissues. Drugs with small distribution volumes, such as warfarin, are found primarily in the vascular space (due to extensive plasma protein binding). The factors influencing tissue distribution from the blood are plasma protein binding, tissue solubility, and tissue blood flow.

The unbound drug is the form that is active at tissue sites. Drugs are bound by plasma proteins to variable degrees. Diseases or other drugs may affect binding and may thereby alter the response to a given dose of a drug and/or the relationship between total drug concentration and effect. For example, during acute myocardial infarction, there is an increase in alpha-1 acid glycoprotein, the major binding protein for lidocaine. In the days after acute myocardial infarction, the concentration of this glycoprotein, and therefore the percent binding of lidocaine, increases, explaining in part rising lidocaine concentrations despite constant dosing; it may also explain why there can be an antiarrhythmic effect that is less than expected for a given lidocaine concentration after myocardial infarction.

Drugs take time to distribute from the blood to tissues, and the blood concentration of a drug may not correlate with the tissue levels immediately after administration. The time course of distribution depends in part on blood flow to body organs. Blood flow may be profoundly altered in cardiac disease states. Consideration of the time course of distribution and the influence of the disease state are important for optimal drug dosing and monitoring, particularly after intravenous administration.

For example, in response to impaired cardiac output, sympathetically mediated vasoconstriction occurs, which results in redistribution of blood flow. A relatively large fraction of the available cardiac output is delivered to heart and brain, and less to muscle, skin, splanchnic organs, and kidney. Thus, blood flow and distribution of drugs to locations other than the heart and brain is delayed. Drug concentrations are higher than normal minutes after drug administration during cardiac failure, owing to reduced tissue perfusion. Drug concentrations may also be initially higher in well-perfused tissues such as brain than in other tissues. This explains why cardiac or central nervous system toxicity may result when standard doses of some drugs, notably lidocaine, are administered to patients with circulatory failure. Thus, individuals with myocardial infarction and circulatory failure can convulse after a single rapid injection of 75 mg or 100 mg of lidocaine despite subtherapeutic blood concentrations measured shortly thereafter.

Drug clearance

Drug clearance is the principal term used to describe drug metabolism or excretion processes. *Clearance* (CL) is defined as the rate of elimination of a drug (by all routes) relative to its concentration in the blood or plasma (C) and is calculated as follows:

$$CL = \text{rate of administration} / C.$$

Drug metabolism

The rate of hepatic drug metabolism is determined by both the intrinsic metabolic capacity and the rate of drug delivery to the liver (hepatic blood flow) (table 1–1). Drugs for which the intrinsic hepatic metabolizing capacity

Table 1–1. Properties of antiarrhythmic agents used in acute myocardial infarction

Drug	Intravenous dose	Oral dose	Metabolism	Time to peak effect	Half-life	Therapeutic serum level	Acute adverse effects	Cautions & comments
Lidocaine	*Loading* 1) 1–2 mg/kg at 50–100 mg/min; may repeat 1 mg/kg bolus after 5 min if no response; a third 1 mg/kg bolus may be tried after 10 min; or, 2) 50–75 mg IV every 5 min to maximum of 2 mg/kg *Maintenance* 30–35 μg/kg/min continuous infusion (1–4 μg/min)	(IM loading dose 400 mg)	Exclusively hepatic	20 min	1.5 hr	1.5 μg/ml	CNS — dose-related confusion, paresthesia, delirium, seizures, stupor, coma cardiac — occasional sinus node and His-Purkinje exit block.	– Low serum levels 20–40 mins after single bolus followed by continuous infusion: may require second bolus of 1 mg/kg to restore therapeutic levels – Reduce maintenance dose in elederly, and patients with reduced hepatic flow, hepatic disease, or CHF – Use with caution in patients with high-degree AV block
Procainamide	*Loading* 20–50 mg/min up to total of 1 gram, or arrhythmia is controlled, or hypotension, or QT interval prolongation is greater than 50% *Maintenance* 2–6 mg/min continuous infusion	*Loading* 500–1000 mg (IM loading is same) *Maintenance* 350–1000 mg q 3–6 hr depending on preparation	Predominantly renal	IV — 20 min Oral — 60 min	3–5 hr (NAPA-8 hrs or longer)	4–10 μg/ml (PA + NAPA 15–25 μg/ml)	GI — nausea, vomiting, diarrhea Cardiac — sinus node depression, orthostatic hypotension, polymorphic ventricular tachycardia	– Active metabolite NAPA may have prolonged half-life at larger procainamide doses (>10 hrs); dosage should be decreased in patients with decreased renal function
Quinidine	6–10 mg/kg at 0.3–0.5 mg/kg/min	*Loading* 600–1000 mg *Maintenance* 200–600 mg QID	Predominantly hepatic	IV — sulfate 90 min, gluconate 3.5 hr	6 hr	3–6 μg/ml	GI — diarrhea, nausea, vomiting, abdominal pain Cardiac — significant hypotension common with IV infusion; this route is not advised. Prolongation of QRS duration, QT interval, polymorphic ventricular tachycardia CNS — tinnitus, hearing loss, confusion, delerium Hematologic — thrombocytopenia	– Anticoagulant drugs may shorten half-life and reduce serum concentration – Lower doses may be required in patients with decreased hepatic function and CHF – May increase serum digoxin level, thus requiring digoxin dosage reduction

Tocainide	500–750 mg over 15 min, immediately followed by 800 mg orally	*Loading* 400–600 mg *Maintenance* 400–800 mg q 8–12 hr	Predominantly hepatic but renal significant	Oral — 1 hr	12–16 hr	6–10 μg/ml	CNS — same as for lidocaine	– Narrow therapeutic to toxic ratio – Elimination impaired in patients with renal insufficiency, and 50% dose reduction is recommended; no evidence of impaired hepatic elimination in mild CHF
Flecainide	1.5–2 mg/kg	100–300 mg q 12 hr	Predominantly hepatic	Oral — 1–6 hr	20 hr	0.2–1.0 μg/ml	Cardiac — negative inotropic effect common; AV and His-Purkinje conduction block CNS — metallic taste, blurred vision, dizziness, headache, nausea	– Initial dose should not exceed 100 mg q 12 hr – Avoid doses >400 mg/day in CHF, renal failure, elderly, <50 kg weight – Contraindicated in cardiogenic shock – Cimetidine reduces both renal and nonrenal clearance, and dosage reduction is required
Encainide	0.6–0.9 mg/kg over 5 min	25–75 mg q 6–8 hr	Predominantly hepatic	Oral — 1–2 hr	3–4 hr	0.5–1.0 μg/ml	Cardiac — prolongs PR, HV & QRS intervals, polymorphic ventricular tachycardia in absence of prolonged QT interval CNS — dizziness, diplopia, ataxia	– Two highly active metabolities (ODE, mode) – Plasma concentrations vary as much as 50-fold; therefore, adjust dosage based on response of arrhythmia, QRS widening, or tolerance
Propranolol	0.1–0.5 mg every 5 min to total of 0.20 mg/kg	10–200 mg q 6–8 hr	Hepatic	IV — 1–5 min Oral — 1–3 hr	3–6 hr	0.04–0.90 μg/ml	Cardiac — negative inotaropy, bradycardia (sinus bradycardia, AV block), hypotension after IV administration CNS — depression GI – nausea, vomiting Other — bronchospasm, impaired glucose tolerance, masking of response hypoglycemia	– If used to treat intractable VT of VF, must be used with extreme caution

Table 1–1. Continued

Drug	Intravenous dose	Oral dose	Metabolism	Time to peak effect	Half-life	Therapeutic serum level	Acute adverse effects	Cautions & comments
Esmolol	*Loading* 500 μg/kg bolus *Maintenance* 50–250 μg/kg continuous infusion	—	Blood, liver	5 min	10 min	—	Hypotension	– Cardioselective – Ultrashort-acting beta-adrenergic blocking agent; no effect seen 30 min after discontinuation of infusion
Bretylium	*Loading* 500 μg/kg bolus over 1 min followed by 50– 250 μg/kg continuous infusion	—	Renal	IV — 5–30 min	8–14 hr	0.5–1.5 μg/ml	Nausea with rapid IV administration; hypertension followed by hypotension; anxiety, flushing, substernal pressure, nasal stuffiness	– Initial hypertension can be blocked by pretreatment with beta-adergenic blocking agent – May prove useful in refractory VT or VF – Hypotension may require dopamine – Contraindicated in digitalis toxicity – May be less effective at low serum potassium levels
Bethanidine	5–20 mg/kg	*Loading* 20–30 mg *Maintenance* 5–10 mg/kg q 8 hr	Renal	Oral — 30–60 min	14 hr	0.18–1.5 μg/ml	Orthostatic hypotension common unless pretreatment with tricyclic antidepressant	– Chemical structure and pharmacologic properties simlar to bretylium tosylate but oral absorption is better – May be less effective at low serum potassium levels
Amiodarone	2.5–10 mg/kg over 30 min*	*Loading* 800–1200 mg QID for 1–4 weeks	Hepatic	IV — 10 min Oral 4 hr	30–50 days	0.15–5 μg/ml	Hypotension; worsened conduction system disease, depressed cardiac	– Oral absorption slow and and erratic – Hypotension common

		Maintenance 200–800 mg QID					index, polymorphic ventricular tachycardia: constipation, tremor, ataxia, thyroid dysfunction, pulmonary fibrosis	at 5 mg/kg IV administration rate – If concomitant digoxin therapy, decrease digoxin dose
Verapamil	*Loading* 0.075–0.15 mg/kg, or 10 mg IV over 1–2 min *Maintenance* 0.005 mg/kg/min continuous infusion	80–160 mg every 6–8 hr	Hepatic	IV — 3–5 min Oral — 60–120 min	3–7 hr	0.1–0.15 μg/ml	Negative intropic effect, hypotension, bradycardia, AV block	– Use caution when giving to patients with depressed myocardial function – Avoid if patient is receiving beta-blocking agents – Contraindicated in advanced heart failure, and in 2° or 3° AV block without pacemaker in place – Can increase serum digoxin level
Digoxin	*Loading* 0.75–1.0 mg in 24 hrs (or less in atrial fibrillation)	*Loading* 1–2 mg in 24 hr *Maintenance* 0.25–0.75 mg depending upon ventricular response to atrial fibrillation	Hepatic	IV — 1–5 hr Oral — 2–6 hr	40 hr	0.5–2.5 ng/ml	Peripheral vaso-constriction with hypertension (uncommon)	– Serum levels increased by quinidine, verapamil, amiodarone, some antibiotics – May increase myocardial oxygen demand – Cardioversion not contraindicated if serum level is in therapeutic range, or low energy used – In atrial fibrillation dose should be titrated against ventricular rate

Abbreviations: AV = atrioventricular; SA = sinoatrial; CHF = congestive heart failure.
* Investigational only as of this writing.

is high are rapidly and extensively cleared from the hepatic blood, and their rate of metabolism is dependent primarily on hepatic blood flow. Lidocaine is such a drug, and hepatic lidocaine clearance has been correlated with hepatic blood flow. In circulatory failure, decreased cardiac output is associated with a proportional decrease in hepatic blood flow, and metabolic clearance of lidocaine is therefore diminished. This may have substantial therapeutic implications. The elimination half-life of lidocaine has been shown to be prolonged up to threefold in patients with myocardial infarction without overt cardiac failure, and up to sixfold in those with overt cardiac failure. Just as circulatory failure may decrease hepatic blood flow and may impair the clearance of highly extracted drugs by the liver, drugs that impair hepatic blood flow, such as propranolol, by lowering cardiac output, may have the same effect.

Drugs such as digoxin and quinidine, for which the intrinsic hepatic metabolizing capacity is low, are, by contrast, slowly and incompletely cleared from the hepatic blood. Their rates of metabolism are relatively independent of hepatic blood flow and are determined instead primarily by the intrinsic metabolic capacity of the liver. Injury to hepatocytes due to reduced perfusion, arterial hypoxemia, or passive congestion can impair intrinsic metabolic capacity and slow the metabolic clearance of these drugs.

Active metabolites

Metabolites of antiarrhythmic medications may contribute to therapeutic or toxic effects. Procainamide, lidocaine, and encainide are examples of drugs with active metabolites. Procainamide is acetylated to N-acetyl-procainamide (NAPA), which has antiarrhythmic activity. The rate of acetylation to NAPA is bimodal, genetically determined. In "rapid acetylators," NAPA concentrations are higher and may contribute substantially to the pharmacologic actions of procainamide. Lidocaine is metabolized to monoethylglycine xylidide (MEGX), a metabolite with minimal antiarrhythmic activity but with potent central nervous actions, including seizures. These patients have apparent lidocaine toxicity and have low lidocaine, but high MEGX, concentrations. Encainide is metabolized to at least two active metabolites, which are more potent and accumulate to a much higher concentrations than does the parent drug. The metabolites account for most of the antiarrhythmic activity, and patients who do not metabolize encainide by this route may not gain therapeutic benefit from the drug.

Drug excretion

Renal excretion of drugs or metabolites must be considered in designing dosing regimens for several antiarrhythmic drugs, particularly digoxin, procainamide, and disopyramide (table 1–1).

Circulatory failure, with the resulting decrease in renal blood flow, may have several important effects on the renal excretion of drugs. The kidney does

have a modest capacity for autoregulation, and when renal blood flow is moderately reduced (10% to 20%), the glomerular filtration rate (GFR) does not fall. However, further reductions in renal blood flow lower the GFR and consequently slow the excretion of drugs cleared by filtration, such as procainamide and digoxin. The tubular reabsorption of drugs may be increased as a consequence of decreased urine flow accompanying a decrease in GFR, as well as by sympathetically mediated shunting of blood from cortical to juxtamedullary nephrons, but documentation of clinically important decreases in drug excretion due to these mechanisms is lacking. Reduced renal blood flow might also be expected to slow the elimination of drugs that are actively secreted by reducing their rate of delivery to secretion sites. Digoxin is excreted by both filtration and secretion, and impaired digoxin secretion due to hypovolemia has been postulated in patients in whom renal digoxin clearance is impaired to a greater extent than creatinine clearance. Thus, renal hemodynamic changes induced by circulatory failure may necessitate reductions in the maintenance dose of drugs that depend on renal elimination.

Principles of oral dosing

Two decisions need to be made when planning oral therapy: the amount of drug to be given per dose and the dosing interval. The amount of drug per dose (maintenance dose) needed to achieve a particular steady-state blood level (CSS) depends upon its clearance (dosing rate = CL × CSS) and its bioavailability [dosing rate = (dose × bioavailability)/(dosing interval)]. Clearance and bioavailability are estimated on the basis of the characteristics of the drug, the weight and age of the patient, and the presence of modifying disease states.

The dosing interval is important in determining the swing in levels between the peak and trough concentrations. The concept of half-life is essential to selecting dosing intervals. Half-life is the time it takes for a drug concentration to fall by one half. It is a function of both the volume of distribution of the drug and the clearance ($T_{1/2} = 0.63 \times V_d/CL$). Dosing at intervals equal to one half-life results in approximately a twofold swing of levels from peak to trough. For most drugs such a swing is tolerable with respect both to not exceeding toxic levels and to not falling below "therapeutic" levels. For drugs with very short half-lives, intravenous infusion is required. For drugs with intermediate half-lives, it is necessary to dose at intervals of 3–4 hours to maintain therapeutic levels. For this reason sustained-release preparations are preferred. Drugs with half-lives longer than 24 hours, such as digoxin, are generally given once daily (table 1–1).

The half-life also predicts the time course of accumulation of a drug in the body at steady state. With constant dosing, steady state is approximated in 3.5 half-lives; thus, therapeutic levels will require this amount of time if dosing is constant. For drugs with short half-lives, accumulation is rapid. For drugs with long half-lives, such as amiodarone (half-life 30 or more days), it may take weeks or months to reach therapeutic levels if a patient is started on a

maintenance dose. Where immediate therapeutic levels are required, or where accumulation is very slow, loading doses must be given prior to beginning a maintenance dose.

Principles of intravenous dosing

A variety of dosing regimens have been proposed for the rapid achievement and maintenance of therapeutic blood concentrations of drug. Intravenous infusion at a constant rate is sufficient for some drugs. The rate at which a drug achieves a steady-state plasma concentration is determined by the drug's elimination half-life. For a rapidly eliminated drug such as epinephrine (half-life 2 minutes), this would take only 7 minutes. For lidocaine (half-life 1.5 hours) the corresponding time would be 5.2 hours, so that a more rapid method of initially achieving a therapeutic blood concentration of drug is required. A single intravenous bolus injection (loading dose) can produce a therapeutic concentration almost immediately but may be maintained only briefly because of rapid and extensive tissue distribution.

A larger bolus would prolong the therapeutic effect somewhat, but concentration would initially be in the toxic range. Combination of a bolus dose and a constant-rate infusion is often sufficient to achieve and maintain an effective drug concentration. Even with this method, however, some patients have a dip in blood concentration of the drug to subtherapeutic levels 20 to 30 minutes after the initial bolus injection. Other loading regimens have been used to overcome this problem: two or three boluses plus infusion, rapid infusion followed by slow infusion, and bolus plus rapid and slow infusions. All these methods offer advantages over the single bolus plus infusion, but they also require increasing amounts of attention and patient monitoring.

After a desired steady-state drug concentration has been achieved, it may become necessary to increase or decrease the blood concentration of drug because of an inadequate or excessive drug effect. If this is accomplished by increasing or decreasing the drug infusion rate, the time required to reach the new steady-state concentration will again be about 3.5 half-lives. For drugs with long half-lives, a small bolus dose can be used to approach a new higher steady-state concentration more rapidly. Similarly, achievement of a lower steady-state concentration can be hastened by discontinuing the drug infusion entirely until an appropriate plasma concentration is obtained and then resuming the infusion at a slower rate.

Blood-level monitoring

Because of individual variability in pharmacokinetic characteristics, it is impossible to predict with certainty what blood level will be produced by a particular dosing regimen. Blood-level monitoring for antiarrhythmic drugs is useful for documenting that levels are in a therapeutic range and for minimizing the probability of toxicity. Therapeutic ranges have been established for most antiarrhythmic drugs (table 1–1). Important considerations in inter-

preting blood levels include the specificity of the assay, the influence of altered protein binding, the time of sampling, and the presence of active metabolites. For example, some laboratories use a nonspecific assay for quinidine. This assay detects the presence of inactive metabolites as well as quinidine. In the presence of renal insufficiency, the metabolites accumulate. Thus, the quinidine levels measured by a nonspecific assay will be higher than the actual quinidine levels.

Most drug assays measure total drug concentration (bound and unbound drug). Altered protein binding can influence the therapeutic range, which is based on average values of protein binding. Time of sampling is important because most drugs have absorption or distribution phases that last from 2 to 6 hours after an oral dose. Therapeutic ranges are based on steady-state or trough levels. Therefore, it is best to monitor blood concentrations prior to the next scheduled dose or at least 6 hours after the dosing period. In any case, the time of the last medication dose and the time of blood sampling should be clearly documented for proper interpretation of drug levels.

Finally, the presence of active metabolites may alter the apparent therapeutic range. For example, in patients with high NAPA concentrations, a low concentration of procainamide may be adequate for antiarrhythmic efficacy; conversely, for encainide, the appropriate assay may actually be for the metabolite, which has most of the antiarrhythmic activity.

BRADYCARDIAS IN ACUTE MYOCARDIAL INFARCTION

Bradycardias (heart rate less than 60 beats/minute) occur in up to 35% of patients seen within the early hours of myocardial infarction [1–3]; both atrial bradycardia and ventricular bradycardia due to atrioventricular conduction disturbances are more common in patients with inferior wall myocardial infarction than in those with anterior wall infarction. Since up to half of patients seen within the first 60 minutes of acute infarction have evidence of enhanced parasympathetic tone [3] manifested by bradycardia and/or hypotension, and since enhanced parasympathetic tone is significantly more common with inferior compared to anterior wall infarction, much of the observed bradycardia can be ascribed to autonomic nervous system imbalance. The incidence of autonomic dysfunction declines rapidly after the first postinfarction hour, such that after the second hour less than 10% of patients have significant bradyarrhythmias.

The more precise mechanisms of bradycardia in acute inferior wall myocardial infarction are multiple and may include ischemia of the sinus and/or AV nodes due to thrombotic or spastic occlusion of the right coronary artery; stimulation of vagal receptors in and around the AV node, coronary sinus, posterior interatrial septum, left coronary artery, and left ventricle [4]; and ischemia-related inhibition of cholinesterase with consequent accumulation of acetylcholine. The hypotension that often accompanies the bradycardia may reflect a failure of peripheral vasoconstrictive response, possibly due, in part,

to activation of stretch receptors in ischemic myocardium [5], or to a primary peripheral vascular response to an increase in parasympathetic tone [6].

With the exception of bradycardia-dependent ventricular arrhythmias [7–9], bradycardias occurring in the setting of acute myocardial infarction are treated not because of slow rate *per se* but because of the hemodynamic embarrassment (table 1–2, figure 1–1). High-dose isoproterenol, intravenous atropine, and/or temporary ventricular or atrioventricular sequential pacing may be used; isoproterenol is generally not advised due to its propensity to cause tachyarrhythmias as well as to increase myocardial oxygen demand and thus exacerbate the ischemic state.

Intravenous atropine is extremely useful in the management of sinus bradycardia and type I (Wenckebach) second-degree AV block, with or without hypotension; occasionally the hypotension may respond to the drug in the

Table 1–2. Principles of management of arrhythmias occurring in acute myocardial infarction

Type	Treatment
TACHYARRHYTHMIAS	
Sinus tachycardia	No specific treatment indicated. Correct CHF and hypovolemia, and treat pain if present. If evidence of significant increase in myocardial O_2 consumption, beta blockade.
Ectopic atrial tachycardia	If hemodynamic compromise, beta blockade or calcium-channel blockade. If digitalis toxic, withdraw digitalis.
Atrial flutter	Direct current cardioversion (low energy levels usually suffice); pace termination; intravenous verapamil or propranolol will slow ventricular rate; digitalis and quinidine.
Atrial fibrillation	Intravenous digitalis, verapamil and/or propranolol to slow ventricular response (if necessary). Direct current cardioversion if hemodynamic compromise and ventricular response is rapid.
Accelerated junctional rhythm and accelerated ventricular rhythm	None required; increase in sinus rate will eliminate the rhythm.
Ventricular ectopy (couplets, triplets, multiform complexes, sustained tachycardia, fibrillation)	Intravenous licocaine, procainamide, bretylium, tocainide; cardiac pacing if due to bradycardia or associated with long QT interval. Direct current cardioversion or defibrillation.
BRADYARRHYTHMIAS	
Sinus bradycardia, including sinus arrest and sinoatrial block	No specific therapy. If hemodynamic decompensation or bradycardia-dependent tachyarrhythmias, intravenous atropine, cardiac pacing.
Vagotonic atrioventricular block	No specific therapy. Atropine if sustained.
Atrioventricular block type I (Wenckebach)	If hemodynamic compromise, atropine, intravenous isoproterenol, cardiac pacing.
Type II (Mobitz II) high degree or complete	Cardiac pacing.

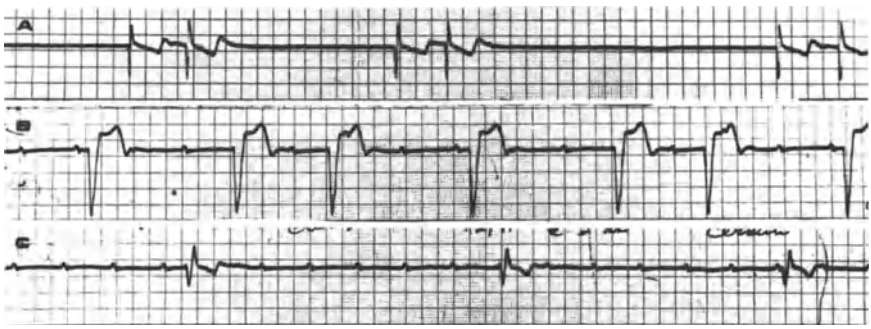

Figure 1–1. Bradyarrhythmias that require temporary cardiac pacing.

A: Extreme sinus bradycardia is present, with prolonged pauses is sinus rhythm that are terminated by junctional escape beats. Note the irregularity in the length of the pauses and the absence of the expected junctional escape rate of 40–70 beats/min. This rhythm was unresponsive to intravenous atropine.

B: High-grade AV block occurring during inferior wall myocardial infarction in a patient with prior left bundle branch block. The third and sixth QRS complexes are early and represent capture beats in which the sinus impulse is conducted (with delay) to the ventricles. A junctional escape rhythm is present at other times, due to failure of conduction of most of the atrial impulses. No improvement in AV conduction was noted with intravenous atropine. The bradyarrhythmia resolved within 12 hours.

C: Complete AV block occurring in a patient with anterior wall myocardial infarction and new-onset, right bundle branch block with leftward deviation of the electrical axis (bifascicular block). The complete AV block with Purkinje or ventricular escape rhythm failed to respond to intravenous atropine.

All rhythm strips are MCL_1.

absence of an appreciable change in heart rate; conversely, heart rate may increase without a concomitant increase in blood pressure. In patients with sinus bradycardia, atropine might accelerate the rate of an AV junctional focus to a greater extent than that of the sinus node (figure 1–2). Chadda and colleagues [10, 11] have described a dose-related response to intravenously administered atropine, with ventricular rates of less than 100 beats/min being achieved with 0.4 mg – 0.6 mg and rates exceeding 100 beats/min being achieved with doses exceeding 0.8 mg, the higher heart rates were noted to be accompanied by an increased frequency of ventricular ectopic activity (figures 1–3 and 1–4) as well as chest pain in some patients. In the studies of Chadda and coworkers [10, 11], about two thirds of patients responded favorably to a single dose of atropine; 21% developed an inappropriately high ventricular rate, and the remainder required a second dose of the drug. Pantridge et al. [3] and Webb and colleagues [12] have noted that correction of parasympathetic overactivity may unmask sympathetic overactivity in some patients, helping to explain the inappropriately rapid heart rates and perhaps also the more malignant ventricular tachyarrhythmias [13–15] occasionally observed.

Temporary transvenous pacing is indicated in all patients with hemodynamic

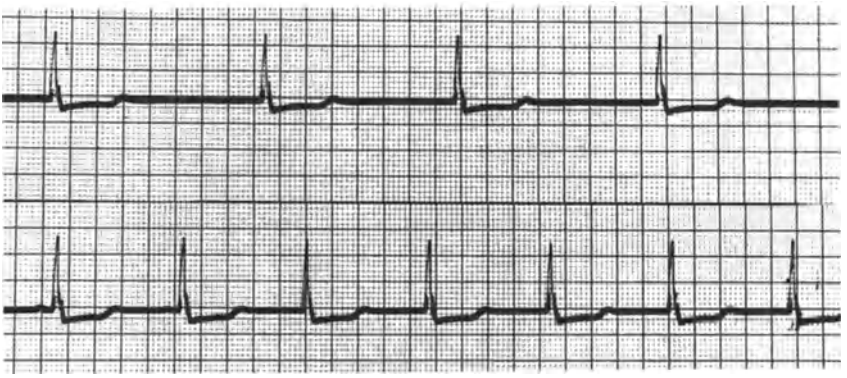

Figure 1–2. Response to intravenous atropine (0.6 mg) in a patient with acute inferior-wall myocardial infarction. The rhythm in the **top** strip is junctional in origin and no atrial activity is discerned. Intravenous atropine results in an acceleration of the junctional rate, but sinus node function has not been affected (**bottom** strip). It is not possible to predict whether the response of a QRS rhythm to intravenous atropine will be an increase in the automatic rate of the junctional tissues or the emergence and enhancement of sinus rhythm. Mere acceleration of the rate of a ventricular rhythm by atropine may be insufficient to restore compensation in a hemodynamically compromised patient; atrial or atrioventricular sequential pacing with provision of atrial "kick" may be necessary to restore hemodynamic equilibrium.

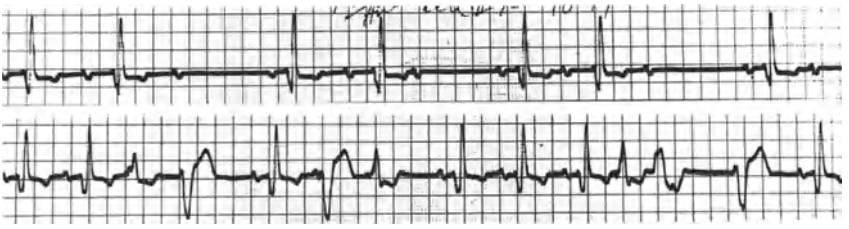

Figure 1–3. Response to intravenous atropine in a patient with acute inferior-wall myocardial infarction. The rhythm on admission to the coronary care unit (**top** strip) is sinus with type I (Wenckebach) second-degree AV block and right bundle branch block. The PR interval of the first beat of the Wenckebach period is prolonged. After 0.8 mg of intravenous atropine (**bottom** strip), the sinus rate has increased and AV conduction has normalized. However, multiform ventricular doublets are now present, suggesting the possibility of myocardial ischemia due to the increase in ventricular rate. The ventricular ectopy was short lived, and the patient made an uneventful recovery.

compromise caused by bradycardias as well as in those patients with anterior wall myocardial infarction who are recognized to be at high risk for the development of transient paroxysmal high-grade complete AV block — specifically those with a new onset of bifascicular block with or without PR interval prolongation, and alternating bundle branch block with or without

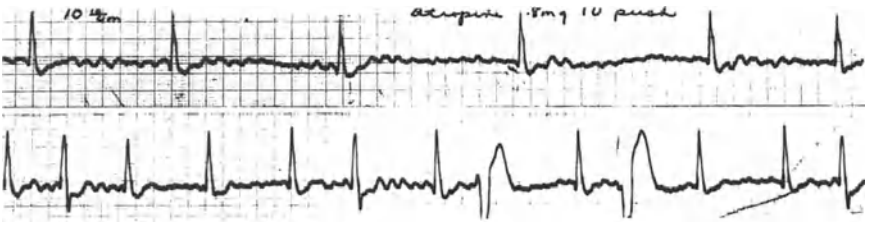

Figure 1–4. The effect of intravenous stropine (0.8 mg) in a patient with acute inferior-wall myocardial infarction and atrial fibrillation with a slow ventricular response. In this clinical setting the slow ventricular rate may reflect enhanced vagal tone, resulting in depressed conduction through the AV node. Atropine results in enhancement of conduction of atrial fibrillatory impulses through the AV node, with the expected increase in the ventricular rate. The occurrence of the premature ventricular complexes may indicate that the resulting ventricular rate was detrimental to the patient's myocardial oxygen supply-demand relationship. This case illustrates that the ventricular rate after intravenous atropine may not be inordinately high in order to potentially cause an unwanted increase in myocardial oxygen demand.

PR interval prolongation [16–18]. AV sequential pacing, or atrial pacing if AV conduction is intact, is extremely beneficial in patients with right ventricular myocardial infarction accompanying inferior wall infarction [19] since in this condition the right ventricle is often markedly dilated and hypokinetic, and does not generate sufficient pressure to fill the left atrium; atrial systole, properly timed in relation to ventricular systole, is then required for enhanced right-heart stroke volume.

All patients receiving a temporary pacing system in the setting of acute myocardial infarction should have a paced 12-lead electrocardiogram recorded during pacing, as well as an anteroposterior and trans-table lateral chest X-ray. Ventricular (and atrial where applicable) electrograms and myocardial stimulation thresholds should be performed daily in both unipolar and bipolar configurations. These procedures will help in the recognition and management of pacing lead dislodgement, sensing and capture problems, and myocardial penetration [20].

TEMPORARY CARDIAC PACING IN ACUTE MYOCARDIAL INFARCTION: SPECIFIC ASSOCIATED PROBLEMS

Sensing problems

Acute myocardial infarction provides a milieu for potential problems related to both myocardial stimulation (pacing) and to sensing of intracardiac electrical activity. Sensing problems may be due to malposition of the temporary electrode catheter(s), pulse generator malfunction, or to poor intracardiac signal quality. Suboptimal signals for sensing are characterized by inadequate voltage, a slow rate of change of voltage (slew), and/or prolonged duration [21–23].

Electrode catheter position

The location of a temporary transvenous ventricular electrode catheter may be evaluated by noting its position on anteroposterior and trans-bed lateral chest X-rays, which should first be obtained immediately after lead placement and then should be obtained daily thereafter, since late lead dislodgement is not uncommon. A right ventricular apical position of the transvenous pacing lead is suggested by an anteriorly and inferiorly directd lead tip, which lies well to the the left of the spine near the left cardiac border. A right ventricular outflow tract position of the pacing lead is suggested by an anteriorly and superiorly directed lead tip, which overlies the spine. Abutment of the pacing catheter on the interventricular septum results in a lead-tip position that may be anteriorly, or slightly posteriorly, and either superiorly or inferiorly directed. A much more sensitive evaluation technique is a 12-lead electrocardiogram recorded during pacing. Right ventricular apical pacing is characterized by a superiorly directed frontal plane axis of the paced QRS complexes, right ventricular outflow tract pacing by an inferiorly directed frontal plane QRS axis, and right ventricular inflow tract or septal pacing by a normal or near-normal frontal plane QRS axis. As pacing from anywhere in the right ventricle produces paced QRS complexes having a left bundle branch block pattern, the mean frontal plane axis of the paced complexes (rather than the pattern of intraventricular activation) becomes a much more specific indicator of pacing catheter position.

Pulse generator malfunction

Rarely, the pacemaker generator itself is the cause of sensing problems. Temporary pulse generator sensing function is easily evaluated using a pacing system analyzer. With the temporary generator connected to the analyzer, stimuli of varying magnitude are delivered from the analyzer to the generator, with note being made of the response of the "sense" deflection or light; in this manner, the minimum amplitude of the signal that is sensed can be ascertained. Oversensing, with resulting pauses in paced rhythm, can result from sensing of atrial electrical activity by a pacing lead positioned in the vicinity of the tricuspid valve, from sensing of T waves of paced or spontaneous QRS complexes, and from sensing of voltage transients caused by lead wire fracture, environmental interference, or signals generated within the pacemaker itself (autointerference) [24]. Not uncommonly, the movement of extension cables connecting the pulse generator to the pacing lead produces electrical signals; these signals, if detected by the generator, inhibit it and produce a pause in paced rhythm.

Signal quality

The most common cause of sensing problems in patients with acute myocardial infarction is the suboptimal nature of the intracardiac signal, which, falling below the sensing threshold of a pacemaker generator, is sensed

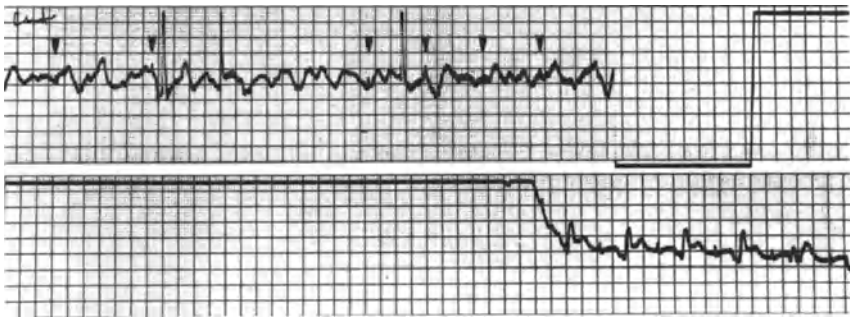

Figure 1–5. Defibrillation in a patient with a permanent ventricular pacing system in place. Ventricular fibrillation is present in the **top** strip. The fibrillatory complexes are sensed only intermittently by the implanted pacemaker generator (**arrows** indicate pacing stimuli delivered at the programmed rate due to failure to sense the fibrillation). Defibrillation results in the restoration of a QRS rhythm in which each QRS complex is preceded by a pacing stimulus at an interval of about 0.20 seconds. Whereas failure to capture due to dislodgement of the pacing electrode from the apex of the right ventricle is possible in the setting of cardiopulmonary resuscitation, it is rare. The likely explanation for the prolonged interval between the pacing pulse and the QRS complex is the phenomenon of *latency*. Latency represents a form of exit block from the delivery of the pacing stimulus to the surrounding myocardial tissue due to acidosis, hypoxemia, and/or hyperkalemia. Normal relationships between the pacing artifact and the QRS complex can be restored if electrolyte and metabolic abnormalities can be rectified. The strips are continuous.

intermittently or not at all [21–23]. Sensing problems resulting from poor signal quality should not be considered sensing "failure" since pulse generator malfunction is not the cause. Borderline intracardiac signals, as well as the changing nature of intracardiac signals in acute myocardial infarction, may be due to ischemia, acidosis and alkalosis, ventricular dilation, myocardial cellular edema, local conduction delay with failure of propagation of the depolarization wavefront to the area of the electrodes, and alterations in local drug and/or electrolyte concentrations. The effect of metabolic acidosis and alkalosis on intracardiac signal quality has not been systematically investigated, but it is conceivable that pH derangements, such as are seen during and after cardiac arrest or in association with cardiogenic shock, might distort intracardiac electrical signals, making them suboptimal for sensing (figure 1–5). Myocardial cellular edema and ventricular dilation have been shown to produce such signal distortion [25. 26]. Ectopic impulses arising in ventricular tissue are often not sensed because of their poor quality, a circumstance that can lead to repetitive ventricular beating [27]. Because of the dynamic nature of the infarction process, sensing problems are often transient, and unless life-threatening pacemaker-related arrhythmias occur as a result of unsensed spontaneous complexes, they may be managed by close observation alone. It must be emphasized that intracardiac signals "seen" by the catheter electrodes have no relationship to surface electrocardiographic complexes. Thus, com-

plexes or signals that are either not sensed or are sensed inappropriately (oversensed) cannot be predicted from the surface electrocardiogram.

Undersensing occurring during temporary cardiac pacing may be managed by turning the sensitivity setting of the pulse generator to the full demand (clockwise) position; this maneuver will optimize its ability to sense signals of low amplitude but at the same time may contribute to oversensing problems. Unipolarization of a bipolar temporary pulse generator in order to augment the intracardiac signal may also be tried; unipolarization is accomplished by connecting the negative terminal of the pulse generator to one of the lead electrodes and the positive terminal to a surface (skin) electrode. The free end of the unused lead electrode should be encased in rubber to prevent accidental conduction of current directly into the heart. That intracardiac signals sensed by unipolar and bipolar electrode catheters are not necessarily identical has been documented [28]. The signal sensed by a bipolar pacing lead reflects the potential difference between the distal (tip) and proximal (ring) electrodes; the interelectrode distance, and thus the time taken by the impulse to travel from one electrode to the other; and the orientation of the electrodes relative to the depolarization wavefront [28]. In contrast, the electrical signal sensed by a unipolar lead reflects electrical activity present only at the intracardiac (cathodal) electrode, the anode being extracardiac in location, thus serving as an indifferent electrode. The unipolar signal may be quite large compared to the bipolar signal in individual patients, but this is by no means always the case. It is advisable to record the intracardiac signal in both bipolar and unipolar (from both distal and proximal electrodes) configurations on a daily basis in order to observe any changes in signal magnitude that might occur and to select optimal sensitivity settings on the pulse generator.

Pacing problems

Failure to capture during acute myocardial infarction may be due to malposition of the lead or to an increase in the myocardial stimulation threshold. Changing stimulation thresholds resulting in failure to capture are common during infarction and often, but not always, occur concomitantly with sensing problems. Underlying causes for failure to capture due to an increased stimulation threshold include local hyperkalemia associated with tissue necrosis, severe acidosis, shock, and high concentrations of type I antiarrhythmic agents (quinidine, procainamide, and disopyramide) (table 1–3). Failure to capture may be intermittent or complete, and may take the form of type I (Wenckebach) or type II exit block. Although frequently a harbinger of electromechanical dissociation, with appropriate pharmacologic therapy and correction of hemodynamic abnormalities, normal pacing function can often be restored unless the patient is moribund.

Failure to capture may be managed by repositioning the lead, increasing the current output of the external pulse generator, or by unipolarizing the system if the (tip of ring) unipolar stimulation threshold has been demonstrated to be lower than the bipolar stimulation threshold.

Table 1–3. Classification of antiarrhythmic agents*

CLASS I: DRUGS THAT DEPRESS PHASE 0 AND THE FAST RESPONSE (SODIUM-DEPENDENT)
Qunidine
Disopyramide
Procainamide
Lidocaine
Tocainide
Encainide
Flecanide
Aprindine
Mexiletine
Lorcainide
Propafenone
CLASS II: BETA-RECEPTOR BLOCKING DRUGS
Propranolol
Timolol
Metropolol
Nadolol
Labetolol
Esmolol
Pindolol
CLASS III: DRUGS THAT INCREASE THE ACTION POTENTIAL DURATION
Amiodarone
Bethanidine
Bretylium
Sotalol
CLASS IV: DRUGS THAT DEPRESS THE SLOW RESPONSE (CALCIUM-DEPENDENT)
Verapamil
Diltiazem

* Agents are classified according to their predominant electrophysiologic effect, although many drugs have more than a single action.

ATRIAL TACHYARRHYTHMIAS

Sustained, significant atrial arrhythmias occur in about 10%–15% of patients with acute myocardial infarction [29, 30]. In some reported series [31], atrial fibrillation is most commonly observed; ectopic atrial tachycardia is also frequent, and atrial flutter is considerably rarer. Reentrant supraventricular (AV nodal and atrioventricular) arrhythmias and multifocal atrial tachycardia are not considered to be ischemic in origin. The development of atrial arrhythmias during acute infarction does not appear to be related to its location [29, 30]. The impact of abnormal atrial rhythms on in-hospital mortality has been related not to the tachyarrhythmias per se but to the location of the infarction. Thus, the occurrence of supraventricular arrhythmias in patients with anterior and anterior-inferior wall myocardial infarction is associated with a significantly higher mortality (33%) than is their occurrence in patients with inferior wall myocardial infarction (9%) [29], where the arrhythmia does not seem to influence prognosis to any significant degree. In addition, in one report, a poor clinical status on admission, as assessed by the prognostic index of

Norris et al. [32], was associated with a higher prevalence of supraventricular arrhythmias [29]. These observations suggest that different mechanisms might be involved in the production and maintenance of atrial arrhythmias in anterior compared to inferior infarctions. Prompt treatment is indicated to avoid the potential hemodynamic consequences of a sustained supraventricular arrhythmia as well as to facilitate early transfer out of the coronary care unit (tables 1–1 and 1–2).

Atrial tachyarrhythmias occurring de novo during acute myocardial infarction may be related to concomitant pericarditis, bradycardia-tachycardia syndrome, significant left ventricular dysfunction, enhanced sympathetic tone, and sinus node and/or atrial infarction. Of these, sinus node and/or atrial infarction are the most difficult to diagnose clinically and also appear to be the least common causes of rhythm disorders, as suggested by electrocardiographic [31–36] and autopsy studies [37, 38]. The electrocardiographic signs of atrial infarction have included depression of the PR segment; elevation of the Ta wave of atrial repolarization [36]; and abnormalities in P-wave contour such as notching, amplitude changes [39], and occurrence of atrial arrhythmias. While evolutionary changes in P-wave configuration suggest atrial injury, the specificity of all of these abnormalities for the autopsy-proven documentation of atrial myocardial infarction is unclear. On the other hand, in cases of proven atrial infarction, supraventricular arrhythmias have been reported to occur in 66% of patients, compared with only 12% in cases of pure ventricular infarction; atrial fibrillation has been reported to be the most common rhythm disorder [34].

Atrial fibrillation

Atrial fibrillation is the most commonly observed atrial arrhythmia that occurs in acute myocardial infarction, aside from atrial premature depolarizations [31]. Several studies of large numbers of patients have documented the association of atrial fibrillation with increased age [34]; left ventricular functional impairment, as attested to by an S3 gallop and congestive heart failure; and hypotension [40, 41]. In these circumstances the atrial fibrillation may be related to pump dysfunction with consequent atrial muscle stretch, which is itself arrhythmogenic [41] and possibly also to poor perfusion. Patients who develop atrial fibrillation during the course of acute infarction are at higher risk for in-hospital mortality due not to the rhythm per se, but to underlying large anterior and anterior-inferior infarctions, as well as to the complications of cardiogenic shock and pulmonary edema. In one large study of over 900 patients with acute infarction [30], patients developing atrial fibrillation also had a higher incidence of ventricular tachycardia and fibrillation, and of bundle branch block.

The management of atrial fibrillation in the setting of acute myocardial infarction depends in great part on the associated clinical condition of the patient. If the ventricular rate is rapid enough to result in hemodynamic

deterioration and/or ischemic chest pain, DC cardioversion may be carried out as an urgent measure. However, more often than not, slowing of the ventricular rate rather than conversion of the rhythm to sinus is all that is required to restore compensation. Reduction in ventricular rate is best achieved using intravenous digoxin, which may be administered every 2–3 hours, as needed, to achieve a reasonable ventricular rate of about 80–90 beats/min, at which time an oral maintenance dose may be begun. Often, the increased sympathetic tone that accompanies the acute infarction acts to facilitate AV nodal conduction, resulting in inability to achieve an optimum ventricular rate using digitalis alone. In these cases, we have had success with the addition of intravenous or oral verapamil, which acts directly on the slow-channel cells of the AV node to depress conduction and thus synergizes with the vagal effects of the digoxin. Verapamil can be administered as a bolus of 5 mg–10 mg administered intraveneously followed by either an oral regimen beginning with 80 mg three times daily or an intravenous infusion of 0.005 mg/kg/minute; the oral regimen is generally preferred (table 1–1). Use of verapamil in the setting of acute infarction must be undertaken with caution since hypotension, often profound, can result from its peripheral arteriolar dilating effects. Even though the hypotension is generally responsive to volume expansion, we prefer to avoid the use of verapamil unless necessary in these patients. Orally administered beta-blocking agents may be used in addition to digitalis; small doses should not produce undesirable negative inotropic effects.

It must be emphasized that control of ventricular rate in atrial fibrillation will not be achieved unless concomitant conditions that act to maintain high sympathetic tone are treated simultaneously. Thus, ischemic pain and congestive failure, if present, should be treated aggressively, recalling that vasodilators and diuretics can themselves cause increased sympathetic tone and enhanced AV conduction if their use results in intravascular volume depletion.

Conversion of atrial fibrillation to sinus rhythm may be undertaken with quinidine or procainamide when the clinical condition is improved. DC cardioversion can be electively performed if pharmacologic therapy fails. It is important to recognize that the serum level of digoxin that will be required to maintain adequate control of ventricular rate in atrial fibrillation will often lie in the "toxic" range; this does not indicate that the patient himself is "digitalis toxic." We have not observed dangerous postcardioversion rhythms in patients with atrial fibrillation undergoing DC cardioversion who have the usual serum levels in this clinical circumstance. Indeed, we feel that digoxin levels in patients who have atrial fibrillation without clinical or electrocardiographic manifestations of digitalis toxicity are not clinically useful. Because postconversion arrhythmias are uncommon in the digitalized patient, digitalis preparations do not need to be discontinued prior to DC cardioversion of atrial fibrillation [42, 43].

Although both myocardial infarction and the use of digitalis might be

expected to lower the threshold for ventricular fibrillation, patients with atrial fibrillation who undergo DC cardioversion usually do not respond to low shock strengths; we usually employ energies of 200 joules followed by 300 joules, and finally 400 joules, in an attempt to reestablish sinus rhythm. Anticoagulation is not used. After cardioversion, oral quinidine or procainamide preparations are administered for 6–8 weeks, after which they are discontinued if atrial ectopic activity is not present. Sinus rhythm may not be maintained if recurrent myocardial infarction, postinfarction ischemia, and/or congestive heart failure occur, and measures should be taken to prevent their appearance. If atrial fibrillation is part of an infarction-related bradycardia-tachycardia syndrome, prevention of atrial bradycardia is also important, since bradycardia dependence may have a contributing role in the genesis of atrial (as well as ventricular) tachyarrhythmias.

Ectopic atrial tachycardia

Ectopic atrial tachycardia is a rhythm disturbance that is due to enhanced automaticity; abnormal triggering may play a role, but definitive studies are lacking. This dysrhythmia may constitute up to 30% of all atrial arrhythmias seen in the infarction setting [31]; it is often presaged by frequent atrial premature depolarizations. In our experience, ectopic atrial tachycardia is usually shortlived and does not lead to either atrial flutter or fibrillation, although all these arrhythmias may be seen in the same patient. Atrial tachycardia is unrelated to infarction site, the presence of associated conditions such as obstructive pulmonary disease, and to digitalis therapy. Unlike atrial fibrillation, there is no clear-cut relationship to left ventricular dysfunction.

If frequent and/or sustained, the rhythm is best managed by type I antiarrhythmic agents in this clinical setting (tables 1–1 and 1–3), although beta-blocking or calcium-channel-blocking drugs are useful, provided no contraindication to their use is present. Atrial pacing has been employed in the management of ectopic atrial tachycardia [44], but not specifically in patients with acute myocardial infarction. In general, atrial pacing is performed at rates exceeding the tachycardia rate with the intention of interrupting it by overdrive suppression, in order to produce AV block with consequent slowing of the ventricular rate, or to induce atrial fibrillation, which allows better and smoother control of ventricular rate. The experience with pacing for ectopic atrial tachycardia does not appear to be as good as that for atrial flutter. Due to its brevity, atrial tachycardia is usually not a hemodynamically compromising rhythm in the setting of acute infarction; thus, pacing therapy is probably not indicated in this setting.

Atrial flutter

Atrial flutter is the least commonly observed atrial arrhythmia occurring de novo in acute myocardial infarction, although in one series it was reported to occur in over 25% of patients developing atrial arrhythmias [31]. In some

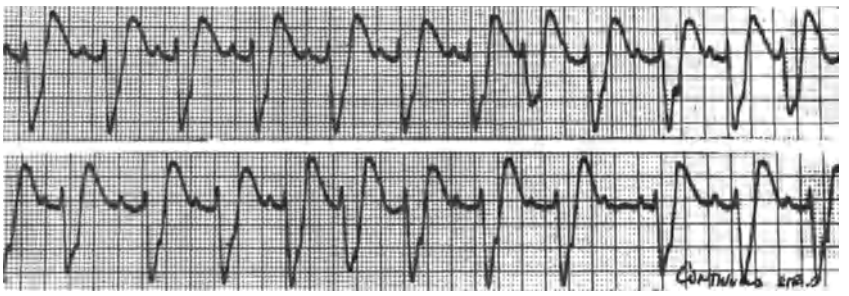

Figure 1–6. Continuous lead MCL_1 rhythm strips in a patient with preexisting left bundle branch block. The rhythm appears at first glance to be sinus with junctional extrasystoles (8th and 12th QRS complexes in the top strip and sixth QRS complex in the bottom strip). However, the PR intervals vary, and the pause in ventricular rate in the bottom strip reveals the presence of an atrial rhythm at a rate of about 180 beats/min. Although the atrial rate suggests the diagnosis of either ectopic atrial tachycardia or atrial flutter, the P-wave morphology in the inferior leads indicate flutter. Thus, the rhythm is atrial flutter with 2:1 and Wenckebach conduction. Slow atrial rate in atrial flutter can be seen in patients with atrial hypertrophy and/or intraatrial conduction delay, and in those receiving type I antiarrhythmic agents.

patients, atrial flutter is associated with the development of atrial fibrillation [29]. While an association between atrial flutter and severe left ventricular dysfunction has been recognized, in our experience flutter does not necessarily connote marked hemodynamic impairment. The atrial rate in flutter may be unexpectedly slow in the presence of atrial infarction [45], but the differential diagnosis of slow atrial rate in atrial flutter also includes type I antiarrhythmic therapy, atrial hypertrophy, and interatrial conduction delay (figure 1–6).

The AV conduction ratio of flutter in the clinical setting of myocardial infarction is most often 2:1; AV nodal Wenckebach and higher AV conduction ratios may often be seen in patients with inferior wall myocardial infarction with its attendant AV nodal ischemia. The Valsalva meneuver, such as accompanies vomiting and retching, can result in long pauses in ventricular rhythm in the presence of atrial flutter due to repetitive concealed conduction of the flutter impulses into the AV node. Management of vagally induced pauses in ventricular rhythm consists of avoiding hypervagotonic states and not of cardiac pacing.

In contrast to atrial fibrillation, the use of intravenous digitalis to slow the ventricular rate in atrial flutter is of limited value, and ventricular arrhythmias and/or clinical signs of digitalis toxicity frequently occur well in advance of achieving satisfactory control of ventricular rate. Similarly, intravenous verapamil is not especially helpful due to the transient nature of the slowing of the ventricular rate; oral verapamil may be used to better advantage in this setting. Beta-blocking agents may also be given together with digoxin if there is no contraindication to their use.

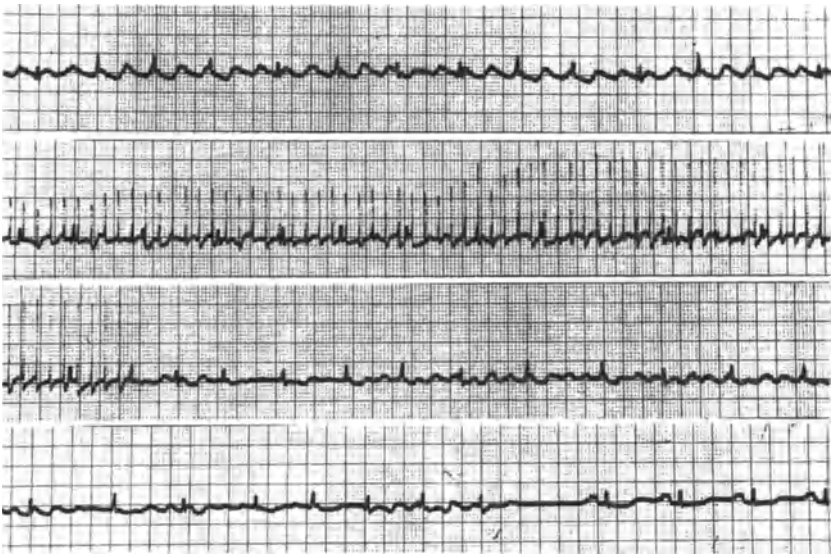

Figure 1–7. Use of overdrive atrial pacing to terminate atrial flutter. The first and second strips are noncontinuous; the third and fourth are continuous. Atrial flutter with a ventricular rate of about 100 beats/min is present in the **top** strip. With the atrial pacing catheter placed at the junction of the superior vena cava and the right atrium, atrial pacing is begun and increased to a rate of about 450 beats/min (**second** strip); note the increase in magnitude of the stimulus artifact as the current strength is increased to 20 mA. Atrial capture is indicated by the change in ventricular rate, even though discrete, paced P waves cannot be discerned from the surface ECG at this atrial paced rate. Pacing is abruptly terminated (**third** strip), resulting in transient atrial fibrillation. The fibrillation converts spontaneously to sinus rhythm after several seconds (**fourth** strip).

Since atrial flutter is an unstable rhythm, and since control of ventricular rate is difficult and is not always achieved within a reasonable period of time, we prefer to perform DC cardioversion as soon as is feasible, provided that concomitant conditions such as pericarditis and congestive failure have been treated. Low energy levels, beginning with 10–25 joules, often suffice to convert the rhythm. Occasionally, transient atrial fibrillation precedes the restoration of sinus rhythm, so several minutes should elapse before the decision is made to perform a second cardioversion.

Rapid atrial pacing is a relatively recently described therapeutic modality for atrial flutter that has been applied in the postoperative patient as well as in patients undergoing elective cardioversion [46, 47]. While its use in the coronary care unit setting is not widespread, it is a promising technique, especially in patients with recurrent flutter. Briefly, a pacing catheter is placed near the area of the sinus node, at the junction of the superior vena cava and the right atrium. While correct positioning of the catheter placed at the bedside can

be guided by evaluation of the atrial electrogram, optimal positioning is best achieved with fluoroscopic guidance. While recording a surface electrocardiogram that displays the flutter waves clearly (usually lead II), atrial pacing is begun at rates exceeding the flutter rates (often as high as 600–800 beats/min) at a current output at which atrial capture occurs (often as high as 15–20 mA) (figure 1–7). The requirement for rapid rates has been emphasized [47]. As atrial capture cannot always be verified due to the large magnitude of the pacing artifact in relation to the small magnitude of the P wave, capture may be assumed if there is a change in ventricular rate. Pacing is terminated abruptly after 30–60 seconds; conversion of the flutter to sinus rhythm is expected to occur, although a brief period of atrial fibrillation may be seen (figure 1–7). The pacing catheter may be left in place for future use if desired. After conversion of flutter to sinus rhythm, we recommend the administration of oral quinidine and digoxin for the first 4–8 postinfarction weeks.

VENTRICULAR TACHYARRHYTHMIAS

Ventricular arrhythmias are seen in almost all patients admitted to the coronary care unit with acute myocardial infarction [3]. Whereas many are of no consequence, the most lethal rhythm disturbances is acute infarction are ventricular in origin. The decline of in-hospital mortality with the advent of coronary care units has been due in greatest part to the immediate detection and aggressive management of lethal ventricular arrhythmias.

Prophylactic antiarrhythmic therapy in acute myocardial infarction

The R-on-T phenomenon

The *R-on-T phenomenon* is characterized by the superposition of a ventricular extrasystolic depolarization on the T wave of the QRS complex preceding it. Until relatively recently, it has been considered to represent an ominous arrhythmia in the setting of acute myocardial infarction in its potential to cause sustained ventricular tachycardia or ventricular fibrillation [48] (figure 1–8). More recent studies, however, have demonstrated clearly that the predictive capability of the R-on-T phenomenon for the occurrence of sustained life-threatening arrhythmias is far from good (figure 1–9).

The potential malignancy of an early-cycle premature ventricular depolarization, of which the R-on-T complex is an example, lies in its occurrence during the "vulnerable" phase of ventricular repolarization, during which time ventricular tissue is inhomogenously excitable or refractory [49]. This, together with the demonstration that the threshold for ventricular fibrillation is lowered in acute myocardial infarction, led to the concept that the R-on-T ventricular depolarization is a harbinger of ventricular fibrillation [50]; in fact, the R-on-T premature ventricular compex receives the highest grade of severity in the Lown classification of ventricular arrhythmias [51], regardless of its frequency. However, both animal experiments and studies performed in

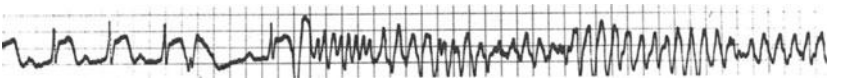

Figure 1–8. Ventricular fibrillation occurring in a patient without warning arrhythmias, except for the single (R-on-T) premature ventricular complex following the fourth sinus-generated QRS complex. The ventricular fibrillation is bradycardia dependent in that it follows a premature ventricular complex, which is closely coupled to a QRS complex that terminates a relative pause in ventricular rhythm. Bradycardia-dependent tachyarrhymias are often successfully managed with pacing therapy.

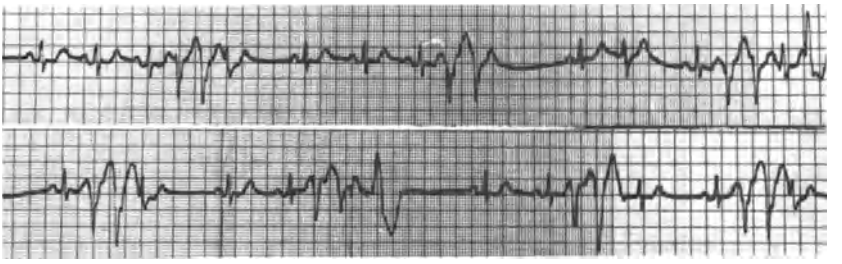

Figure 1–9. Continuous lead II rhythm strips illustrating early cycle premature ventricular depolarizations that fail to initiate sustained ventricular tachycardia or ventricular fibrillation. There is a repetitive nature to the groups of beats, with two or three normal sinus beats being followed by a doublet or salvo of multiform ventricular complexes. The initiating complex of the salvo shows the R-on-T phenomenon, with subsequent premature ventricular complexes occurring on the T waves of the ectopic depolarizations preceding them. Despite this potentially malignant situation, deterioration in cardiac rhythm did not occur.

patients hospitalized in coronary care units indicate that many instances of sustained ventricular tachycardia or ventricular fibrillation are preceded by premature ventricular depolarizations occurring late in diastole [40, 52] and that many episodes of early-cycle premature ventricular complexes are not followed by sustained tachyarrhythmias [53, 54] (figure 1–9). These observations, as pointed out by Engel and colleagues [55], can be reconciled by considering that the QRS complex that is inscribed on the surface electrocardiogram and that represents ventricular depolarization reflects the pathway taken by the ectopic impulse from its site of origin in ischemic myocardium through myocardium that is variably ischemic to its exit at the epicardial surface, and the conduction time through that pathway. The coupling interval of a premature ventricular depolarization, therefore, is determined as much by underlying myocardial structural pathology and intramyocardial activation time as by its site of origin, explaining its lack of adequate predictive accuracy for lethal arrhythmias.

Warning arrhythmias

Warning arrhythmias have been considered to represent complex ventricular arrhythmias (multiform complexes, doublets, triplets, and R-on-T phenomena) that are closely associated with, if not predictive of, ventricular fibrillation [48]. However, early in the 1970s it became clear that such arrhythmias were not necessarily "warning" at all [56], since they occurred without further progression to sustained ventricular tachycardia or fibrillation, and since sustained ventricular arrhythmias could occur in their absence [53]. Lie and colleagues [57] showed, in a large series of patients, that 40% of patients developing ventricular fibrillation did not have warning arrhythmias and that 59% of patients with such arrhythmias did not develop ventricular fibrillation; similar observations have been made by others [58]. Moreover, in one study [59], warning arrhythmias persisted after administration of lidocaine whereas ventricular fibrillation was not observed. These observations suggest either a different mechanism or a different threshold for the two types of rhythm disorders; they also confirm the lack of predictive accuracy of warning arrhythmias as premonitory signs of ventricular fibrillation.

Because of the lack of a clear-cut and predictable relationship of ventricular extrasystolic activity to sustained ventricular tachycardia and/or fibrillation in the setting of acute myocardial infarction, many authorities recommend the routine use of prophylactic antiarrhythmic agents (usually intravenous lidocaine) in all patients suspected of having myocardial infarction, so as to preclude the development of sustained arrhythmias and to reduce in frequency or eliminate any other already existing ventricular arrhythmia. Since up to 10% of episodes of ventricular fibrillation are not successfully terminated in the coronary care unit [48], and since the in-hospital recurrence rate of primary ventricular fibrillation is also about 10% [60], but as high as 50% in patients with secondary ventricular fibrillation occurring in the presence of congestive heart failure and/or shock [60], antiarrhythmic prophylaxis may be a reasonable approach in these patients, after appropriate correction of dosage for the underlying hemodynamic state is made. In addition to these points, sustained tachyarrhythmias are detrimental to hemodynamic function, and repeated cardioversions and defibrillations may cause additional myocardial depression or damage; their prevention may thus be warranted from the standpoint of pump function.

It must be emphasized, however, that whereas abolition of sustained ventricular tachycardia or ventricular fibrillation is a reasonable goal, elimination of all venticular ectopy might not be, in that this goal might not be capable of being achieved. In addition, elimination of complex ventricular ectopy does not predict the absence of occurrence of sustained ventricular tachycardia or fibrillation that is initiated by a single premature ventricular depolarization [61].

There are several problems associated with the use of prophylactic antiarrhythmic agents to prevent ventricular fibrillation. First, they must be

administered immediately upon admission to the hospital, since the incidence of ventricular fibrillation is highest in the early stages of infarction [60] and declines rapidly thereafter. If more than 6 hours have elapsed since the onset of chest pain, there is little evidence to suggest benefit from antiarrhythmia prophylaxis [62]. Thus, all patients admitted with suspected myocardial infarction will receive these drugs despite the fact that many will not evolve an infarction — a costly measure. Second, even in patients subsequently documented to have suffered a myocardial infarction, the overall in-hospital incidence of ventricular fibrillation is below 5% [63]; thus, most patients will have been administered a drug unnecessarily. Third, the incidence of drug toxicity is far from trivial. The toxic reactions to intravenously administered lidocaine, the most commonly used agent, range from confusion to paranoia with delusions and hallucinations to generalized seizures; cardiac toxicity manifested as sinoatrial and atrioventricular block with asystole have also been observed [64], as have acceleration of ventricular rate in atrial fibrillation [65] and the rate of ventricular tachycardia [66]. Management of these iatrogenically induced problems is also costly. Fourth, and most important, evidence demonstrating conclusively that arrhythmia prophylaxis prevents in-hospital death in myocardial infarction in patients with either primary or secondary ventricular fibrillation is not available despite newer, more carefully designed, investigative attempts in this direction [61, 67, 68]. Studies using intravenous and oral beta-blocking agents as antiarrhythmia prophylaxis in the early stages of infarction are currently in progress to answer this question.

Ventricular tachycardia

Ventricular tachycardia is generally defined as three or more consecutive ventricular complexes occurring at a rate faster than the intrinsic firing rate of Purkinje or ventricular tissue. Ventricular tachycardia occurring during acute myocardial infarction may be characterized as *sustained* (figure 1–10) or *nonsustained* (figure 1–11). Although there is no agreement as to the exact definition of sustained and nonsustained ventricular tachycardia, it is useful to consider an arrhythmia as sustained if it has a duration exceeding 30 seconds or if it is accompanied by rapid hemodynamic deterioration requiring immediate treatment. Sustained monomorphic ventricular tachycardia is not frequent, occurring in about 1%–2% of patients [61], whereas polymorphic ventricular tachycardia is commonly observed (figures 1–10 and 1–12).Polymorphic ventricular tachycardia can resemble *torsades de pointes* in its undulation about an isoelectric baseline, but the QT interval is usually normal (figure 1–10). Distinguishing the more general polymorphic ventricular tachycardia from the more specific long QT interval-related *torsades de points* (figure 1–12) is useful. Some instances of ventricular tachycardia are bradycardia dependent, that is, they occur following a relative pause in the QRS rhythm (figures 1–10 and 1–12). Such tachycardias respond well to atrial or ventricular pacing (figure 1–13) or to measures that increase the underlying heart rate, such as high-dose

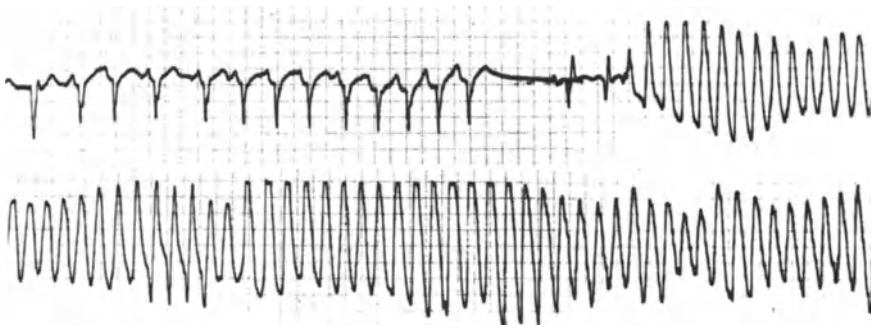

Figure 1–10. Polymorphic ventricular tachycardia occurring in a patient with acute myocardial infarction and chronic obstructive pulmonary disease. The basic rhythm is sinus with paroxysms of atrial tachycardia. Ventricular tachycardia follows closely after termination of a postextrasystolic pause, and thus may in part be bradycardia dependent. Note that the QT interval is normal.

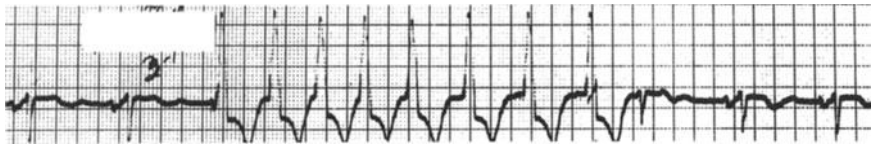

Figure 1–11. "Warmup" and "warmdown" phenomena are illustrated in this MCL_1 rhythm strip. A nonsustained nine-beat run of ventricular tachycardia is initiated by a late-diastolic premature ventricular depolarization and is terminated by a fusion complex. Although variation in tachycardia rate such as is seen here can result from exit block from the tachycardia focus, warmup and warmdown have classically been described for automatic foci.

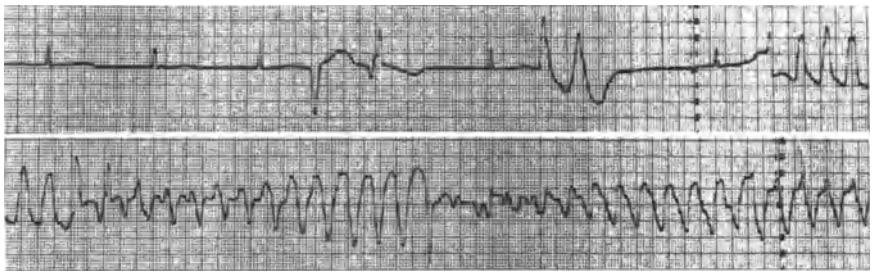

Figure 1–12. Bradycardia-dependent polymorphic ventricular tachycardia occurring in a patient with anterior wall myocardial infarction who had been receiving oral beta-blocking medication for hypertension and angina. The continuous lead II rhythm strips illustrate junctional bradycardia with a long QT interval (0.60 seconds). Ventricular doublets are followed by post extrasystolic pauses. The second post extrasystolic pause is terminated by a junctional beat whose QT interval is markedly prolonged. An R-on-T ventricular extrasystole initiates the tachycardia. Bradycardia-dependent ventricular tachycardia is best managed by atrial or ventricular pacing.

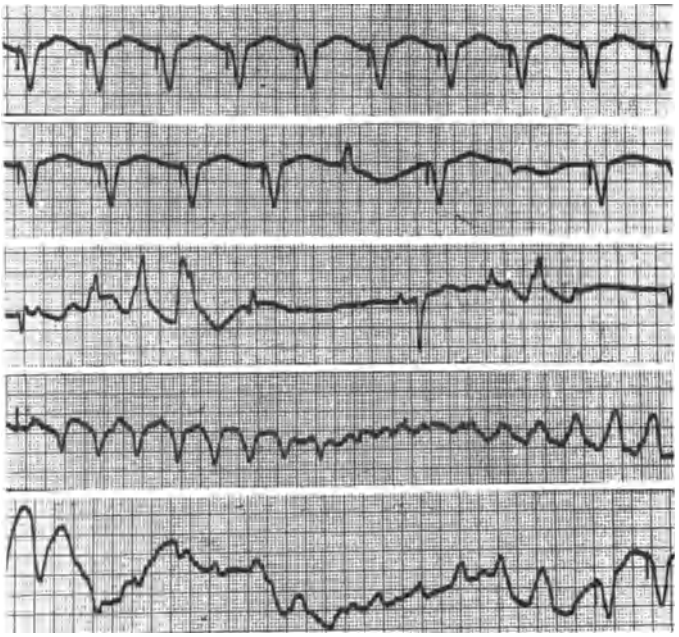

Figure 1–13. Use of ventricular pacing to prevent bradycardia-dependent ventricular tachycardia and fibrillation in a patient with acute anterior wall myocardial infarction. As the pacing rate is decreased (**top two strips**), an irregular ventricular rhythm occurs (**third strip**), which degenerates rapidly to a polymorphous ventricular tachycardia. Restoration of pacing (last two QRS complexes in **bottom strip**) eliminates the arrhythmia. The patient subsequently underwent implantation of a permanent ventricular pacemaker.

isoproterenol. Isoproteronol must be used with extreme caution in the setting of acute myocardial infarction, however, since the drug is itself arrhythmogenic, and, because it increases myocardial oxygen consumption, it can be detrimental to myocardial function.

Nonsustained ventricular tachycardia may take the form of an accelerated ventricular rhythm or a paroxysmal tachycardia whose rate exceeds the intrinsic ventricular rate (figure 1–11).

Accelerated ventricular rhythm

Accelerated ventricular rhythm is a wide QRS rhythm that appears when the sinus rate slows, however slightly; as such, it is an escape rhythm having rates that "hone in" to the prevailing sinus rates and is usually between 60 and 100 beats/min. Its onset and offset are characterized by fusion complexes between the sinus-generated and ectopic ventricular QRS complexes (figure 1–14). Once the accelerated ventricular rhythm is established, it becomes dissociated

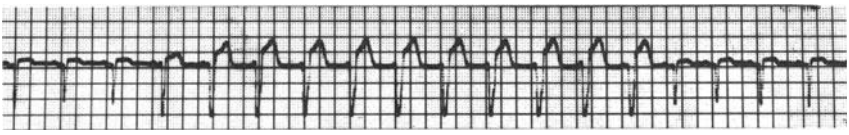

Figure 1–14. MCL_1 rhythm strip recorded in a patient with acute inferoposterior myocardial infarction. The initial rhythm is sinus. The sinus rate slows slightly, leading to an accelerated wide QRS complex rhythm. The onset of the wide QRS complex rhythm (fourth and fifth QRS complexes) occurs via fusion between the sinus and extrasystolic impulses (note the shorter than normal PR intervals of these P-QRS complexes). The wide complex QRS rhythm occurs at a slow rate, and AV dissociation is present. Sinus P waves are again apparent beginning with the 13th complex; sinus rhythm is restored in the 15th P-QRS complex after acceleration of the sinus rate to exceed that of the acclerated ventricular rhythm. The rhythm was transient and unassociated with symptoms. No treatment was given.

from the sinus impulses. When the sinus rate increases, the accelerated ventricular rhythm will be overridden and normal sinus rhythm with normal sinus-generated QRS complexes will resume.

Accelerated ventricular rhythm has no special prognostic significance in the setting of acute myocardial infarction, although a relationship to ventricular tachycardia in some patients has been occasionally observed in one study [69]. It is observed in from 8% to 36% of patients [70, 71]; this prevalence may be an underestimation depending upon rhythm monitoring techniques. The rhythm has been considered to be common in digitalis toxicity, but it is neither specific for nor predictive of this diagnosis. It is important to recognize the rhythm, however, since no treatment is required. Atropine may be used to accelerate the sinus rate and to overdrive the accelerated rhythm. Accelerated ventricular rhythm must be distinguished from "slow ventricular tachycardia" (initiated not by a fusion complex but by a premature ventricular complex, the ensuing tachycardia occurring at a relatively slow rate), which does require suppression.

Paroxysmal ventricular tachycardia

Paroxysmal ventricular tachycardia is a wide QRS complex rhythm that may be regular or irregular. We have been impressed with the very frequent marked irregularity in the rate of the tachycardia in the coronary care unit setting; the briefer the paroxysm, the more irregular the rhythm. *Warmup* (increase in the rate of the rhythm) suggesting an automatic focus of origin has been observed, as well as *warmdown* (decrease in the rate of the rhythm) prior to termination (figure 1–11). Occasionally an increase in rate occurs prior to tachycardia termination, which might suggest progressive exit block out of the tachycardia focus.

Ventricular tachycardia that causes hemodynamic embarrassment must be terminated urgently. This is best done by DC cardioversion. The synchronized cardioverter senses the QRS complex through a bedside monitor or directly

through the defibrillator paddles. The synchronized shock should be delivered 20–50 milliseconds after the point of sensing so that it falls on the R wave. Depolarization of the myocardium allows for resumption of normal rhythm after excitability is restored.

It is most important to observe closely on the cardiac monitor the deflection that represents the point at which the cardioverting shock will be delivered. The deflection must fall consistently upon the R wave and not on latter portions of the QRS complex; delivery of electrical energy during an inappropriately late portion of the QRS complex can cause ventricular fibrillation (figure 1–15).

Unlike defibrillation in which shocks of relatively high energy levels are required, DC cardioversion of ventricular tachycardia may often by accomplished at very low energies (10–50 joules). Because of the lowered ventricular fibrillation threshold in acute myocardial infarction, low energy levels to cardiovert ventricular tachycardia should always be tried initially.

Along with DC cardioversion, antiarrhythmic drug therapy should be begun or continued after giving an additional bolus in those patients already receiving these agents. Lidocaine is often used initially or is rebolused at half the loading dose, followed by an increase in the infusion rate of the drug (table 1–1). Procainamide is also a useful agent in ths setting and may be used when the patient is already receiving maximal doses of lidocaine. Loading (table 1–1) is followed by a continuous infusion. It has been stated that response to intravenous procainamide will be seen after the first 100 mg has been administered; in our experience, however, the usual dose resulting in conversion of the rhythm approaches 500 mg.

Ventricular tachycardia that is refractory to these agents may sometimes respond to intravenously administered propranolol (table 1–1) or to bretyllium administered as intravenous boluses followed by a constant infusion. Caution is warranted when using bretyllium, since the initial hypertensive response due to the release of catecholamines is almost always followed by hypotension, requiring intravenous fluids and dopamine. Monitoring lines are useful adjuncts when bretyllium is used. The recent development of bethanidine, an agent with properties similar to bretyllium but which is available for oral as well as intravenous use (table 1–1), will hopefully expand the therapeutic armamentarium for refractory ventricular tachycardia [72].

On occasion the presence of a regular wide QRS complex tachycardia leads to uncertainty as to its origin — ventricular or supraventricular with intraventricular aberration, due either to preexistent bundle branch block or to rate-dependent bundle branch block. As reentrant supraventricular tachycardia is not expected to occur in the setting of acute myocardial infarction, the differential diagnosis includes sinus tachycardia with P waves being hidden in the T waves of preceding QRS complexes, and atrial flutter either with alternate P waves not capable of being discerned or with slow flutter rate and indiscernible flutter waves. Since ventricular tachycardia occurring during acute infarction is

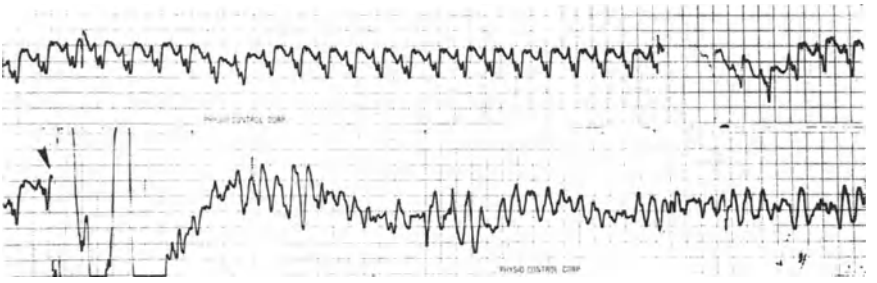

Figure 1–15. Attempt at DC cardioversion of ventricular tachycardia results in ventricular fibrillation due to the shock being delivered at an inappropriate time. The rhythm strips are direct recordings from the cardiovertor-defibrillator machine. The **top** strip depicts the tachycardia. In the **bottom** strip the cardioverting shock can be seen to be delivered at the terminal portion of the QRS complex (**arrow**) during the vulnerable period, as evidenced by the ensuing ventricular fibrillation. The patient was successfully defibrillated. The figure illustrates that care must be taken in assessing precisely where the synchronized shock will be delivered relative to the QRS waves; if necessary, repositioning the skin electrodes or selecting another monitor lead (through which the signal is delivered to the cardiovertor), in order to optimize proper timing of the synchronized shock, must be performed.

often irregular, it may be mimicked by ectopic atrial tachycardia in which the P waves are ill defined. When the surface electrocardiogram does not provide the clues to correctly diagnose the rhythm (such as clear atrial activity, AV dissociation, and capture beats), an atrial electrogram may be obtained and the atrial electrical activity may be related to ventricular activity. The atrial electrogram may be obtained by transesophageal passage of an electrode catheter to an area that lies posterior to the atrium, or by percutaneous passage of an electrode to the right atrium, and recording simultaneously from the intraatrial electrode and the body surface (lead II is usually best). By inspection of the simultaneous recording, atrial and ventricular activity can be identified and related to surface electrocardiographic events. A 1:1 relationship between atrial and ventricular activity is not helpful in establishing the origin of the tachycardia, since the direction of impulse propagation (ventricular with 1:1 retrograde activation of the atria, or supraventricular with 1:1 antegrade activation of the ventricle) is not known; carotid sinus massage or any other maneuver that changes the AV conduction ratio must be performed in order to evaluate the direction of impulse conduction. However, if a dissociation between atrial and ventricular activity can be demonstrated, the diagnosis is that of ventricular tachycardia.

Ventricular pacing for ventricular tachycardia

Ventricular tachycardia has been terminated by ventricular pacing techniques for over a decade. The paced rate may be slower (underdrive pacing), or slightly or substantially higher, than the rate of the tachycardia (overdrive

pacing). In the first circumstance, pacing stimuli are delivered asynchronously, with the expectation that a single stimulus delivered at a critical coupling interval to a tachycardia complex will depolarize a portion of the tachycardia pathway, rendering it refractory and thus eliminating the reentry circus movement. In the second circumstance, the expectation is that pacing at a rate slightly faster than that of the tachycardia will capture the ventricular myocardium; subsequent slowing or abrupt termination of pacing may allow normal supraventricular impulses to be conducted to the ventricles, depolarizing them over the normal AV-node–His-Purkinje pathways (figure 1–16). In the last circumstance, bursts of very rapid pacing stimuli are expected to terminate the ventricular tachycardia within the briefest period of time; the mechanism is currently uncertain. Whereas the first two techniques have been widely used in patients with ventricular tachycardia accompanying acute myocardial infarction, burst ventricular pacing is relatively new and has been applied primarily in patients with chronic recurrent ventricular tachycardia unrelated to acute infarction [73]. (Similarly, the developing methodology of transvenous low-energy endocardial cardioversion of ventricular tachycardia [74, 75] has not as yet been systematically applied in patients with acute infarction.)

Burst pacing consists of delivering a selected number of ventricular pacing stimuli at short cycle lengths, the shortest of which depends upon the ventricular refractory period, for 1–3 seconds. At the present time, the number of stimuli, cycle length, and duration of burst pacing must all be determined for each patient on an individual basis, and no uniform protocols exist. Burst pacing has been reported to terminate over 90% of episodes of ventricular tachycardia but has also been associated with acceleration of the tachycardia rate in 3%–5% of patients (mitigated by concomitant use of antiarrhythmic agents) and with the occurrence of ventricular fibrillation in 1%–2% of patients [73]. Unsuccessful attempts at ventricular tachycardia terminiation by burst pacing have been related to tachycardia rates exceeding 250 beats/min and to the presence of shock.

Burst pacing constitutes a superior method of ventricular tachycardia termination than does asynchronous underdrive pacing, since the time taken to terminate the dysrhythmia is shortened considerably using the burst method, and the potential occurrence of ventricular fibrillation due to delivery of an asynchronous pacing stimulus in the vulnerable period of ventricular myocardium is avoided. Burst pacing may also be superior to overdrive pacing, with reported success rates of over 90% for burst methods, compared to less than 15% for overdrive methods [73].

Pacing therapy for ventricular tachycardia occurring in the setting of acute myocardial infarction should be employed only in those patients who are unresponsive to maximally tolerated doses of the usual antiarrhythmic medications and who have had any attendant infarction-related problems such as ischemia and congestive failure already optimally managed. Antiarrhythmic drug therapy should be continued during pacing therapy since the tachycardia

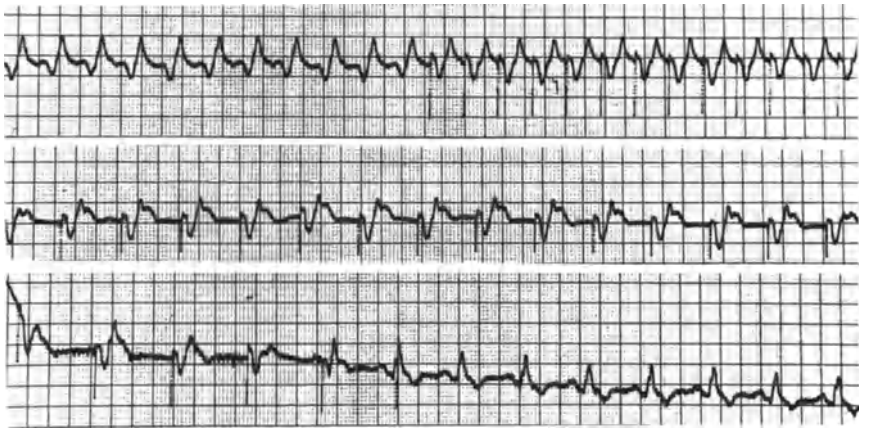

Figure 1–16. Use of overdrive pacing to convert ventricular tachycardia. The strips are non-continuous but are recorded only seconds apart. In the **top** strip, ventricular tachycardia at a rate of about 160 beats/min is present. In the middle of the top strip, ventricular overdrive pacing at a rate of about 180 beats/min is begun; the pacing stimuli capture the ventricle. The pacing rate is slowed in the **middle** strip (note that 1:1 ventriculoatrial conduction is now present). In the **bottom** strip, as the pacing rate is further slowed, sinus P waves emerge and are conducted to the ventricles (fifth and following QRS complexes) in a normal manner.

rate is often slowed by these agents, allowing for easier termination of the dysrhythmia by electrical techniques [76]. For some patients who require multiple cardioversions, burst ventricular pacing may be a reasonable therapeutic option, but more clinical experience is necessary before this technique becomes widely used.

Ventricular fibrillation

Ventricular fibrillation occurring in the setting of acute myocardial infarction is classified as *primary* and *secondary*. Primary ventricular fibrillation occurs in the absence of congestive heart failure or shock, and is present in 1%–10% of patients admitted with acute infarction. Secondary ventricular fibrillation occurs in the presence of severe infarction-related complications, such as congestive heart failure and/or shock, and is seen in 20%–50% of these patients. The location of the infarction or its transmural or nontransmural extent are not relevant per se to the designation of the ventricular fibrillation (although it is certainly true that large anterior transmural infarctions are more likely to be associated with important left ventricular functional impairment).

Primary and secondary ventricular fibrillation have different time courses of appearance and disappearance in acute infarction, as well as different prognostic outcomes. About 70% of all cases of primary fibrillation occur within the first 4 hours of infarction, 80%–85% within the first 8 hours, 90% within

the first 12 hours, 96% within the first 24 hours, and 100% within the first 48 hours [60, 63]. the recurrence rate after the first 48 hours is less than 10% [60]. In contrast, secondary ventricular fibrillation may occur at any time after the acute infarction [63], in relation to the decompensated hemodynamic state and its attendant metabolic, electrolyte, and pH abnormalities. The recurrence rate in secondary ventricular fibrillation is much higher than that in primary fibrillation, reported to be up to 50% [60], and defibrillation is less likely to be successful in secondary ventricular fibrillation [77].

Both early and late prognosis of patients with primary ventricular fibrillation is generally good, whereas that in patients with secondary fibrillation is extremely poor. The in-hospital mortality of patients with ventricular fibrillation in the presence of congestive heart failure has been reported to be 60%–100% [78], exceeding the mortality of equally decompensated patients who do not have ventricular fibrillation. Moreover, because of the underlying severe ventricular dysfunction, studies of postinfarction prognosis suggest a 30%–50% mortality in the first postinfarction year. The differences between the two patient groups suggest that appropriate management strategies should include ongoing measures to optimize left ventricular function, as well as to prevent ventricular arrhythmias in patients in whom secondary ventricular fibrillation has occurred.

Management of ventricular arrhythmias with intravenous lidocaine requires a loading dose (table 1–1) followed by a continuous infusion for at least 24 hours. The dose should be reduced in patients with congestive heart failure or intrinsic liver disease, and in elderly or frail individuals. Caution must also be used in patients with hypotension and in those with bradycardia, especially bradycardia due to AV block.

The expected beneficial effects of lidocaine on ventricular arrhythmias may not be observed, especially within the first hour after infarction [3], in the presence of sympathetic overactivity associated with significant sinus tachycardia [50], and when the blood levels are subtherapeutic. Even at therapeutic blood levels, however, ventricular arrhythmias may not be suppressed, or a dichotomous response may be observed in which complex ventricular ectopic beats are reduced in frequency or are even eliminated, but ventricular tachycardia or fibrillation are not. The limited effectiveness of intravenous lidocaine in the very early stages of infarction has been explained by the early arrhythmias being due to local conduction block and microreentry within the infarcted or ischemic border zone, thus being responsive to this drug. Ventricular arrhythmias that occur later are considered to be due to abnormal automaticity in Purkinje fibers and are more responsive to the therapeutic effects of lidocaine.

In contrast, intravenously administered procainamide is extremely useful in the management of early ventricular arrhythmias. The procainamide is given as a loading dose (table 1–1), with close monitoring of blood pressure. Thereafter, a continuous infusion is administered. The optimal duration of procai-

namide administration is not clear from the available data, but it seems reasonable, in view of its electrophysiologic actions, to discontinue it within the first 12–24 hours, substituting intravenous lidocaine if further antiarrhythmic treatment is necessary.

Refractory ventricular tachycardia and fibrillation have been managed with intravenous propranolol, 1 mg–10 mg. Data on the efficacy of this measure are sparse, and no controlled studies are available. Needless to say, the administration of a drug with negative inotopic actions is fraught with potential dangers in the setting of acute infarction and should therefore be reserved for only the most refractory cases.

Ventricular defibrillation in acute myocardial infarction

Fibrillation is characterized by highly disorganized, random, continuous waves of excitation travelling through excitable myocardial tissue. The refractory period of the excitable muscle cells, the velocity of propagation of the excitation wavefronts, and the mass of myocardial tissue involved determine whether or not the fibrillation will be maintained. The necessity of a critical mass of myocardium in the perpetuation of fibrillation is known from animal studies [79, 80].

The principle of electrical termination of ventricular fibrillation is to deliver a current of sufficient intensity so as to depolarize and render refractory a critical mass of myocardium. When the myocardium has recovered excitability, it can accept a normal stimulus to depolarize and contract. In the clinical setting, the magnitude of the defibrillating current that will be required to terminate the abnormal rhythm will depend upon the resistance of the subject (usually between 25 and 125 ohms [81]) and the mass of involved myocardium. Thus, higher energies may be required for thick-chested and emphysematous or markedly obese individuals, and possibly also for patients with myocardial hypertrophy. Although earlier studies suggested that the energy requirement for successful ventricular defibrillation was related to body weight, subsequent studies hae refuted the conclusion [3, 77, 82–84], both with regard to body weight and also to heart weight determined at autopsy. It should be remembered that the actual energy delivered to the patient at a particular energy output setting is in fact a fraction of that setting, averaging 80%–85%.

The defibrillating electrodes may both be placed on the precordium (one at the upper-right sternal border and the other at the apex of the left ventricle) or anteroposteriorly. Although little difference between the two methods has been demonstrated in human beings with regard to success of defibrillation at any energy level, clinical observations, albeit anecdotal, suggest that anteroposterior electrode placement may be superior. Delivery of defibrillating shocks to the patient may be begun at relatively low levels (100 joules), with or without [3] increases in shock strength with successive attempts, or may commence at higher energy levels with the intent to convert the rhythm with

the first shock. Although the total energy delivered to the patient by these means may be higher using one method versus the other, measurable detriment to myocardial pump function depending upon the method used has not been demonstrated.

Myocardial necrosis as a result of defibrillation is difficult to evaluate in view of the clinical settings in which ventricular fibrillation occurs. While some studies suggest that defibrillating currents can cause elevation in the myocardial fraction of creatine kinase as well as post defibrillation arrhythmias and scintigraphic evidence of myocardial necrosis, others fail to corroborate these observations. Actual deterioration in myocardial hemodynamic function has not been conclusively shown in any patient group receiving any strength of defibrillating shocks.

In managing ventricular fibrillation, the chances of successful defibrillation of the abnormal rhythm using successive shocks decreases in the presence of cardiovascular collapse [1], doubtless due, at least in part, to acidosis; hypoxia [83]; local ionic imbalance, especially involving potassium; and continued ischemia and necrosis. Such conditions, if persistent over many minutes, often fail to respond to pharmacologic attempts at reversal. For this reason, we prefer to employ relatively high defibrillating shocks at the outset (200 joules or greater), unless the arrhythmia is detected precisely at its onset and defibrillation is effected within seconds. In this regard, Adgey et al. [1] found a 67% incidence of successful ventricular defibrillation in patients who had experienced ventricular fibrillation for 2 minutes or less; the success rate fell to 50% if the fibrillation had been present for more than 2 minutes. If vigorous resuscitative efforts can be carried out continuously prior to defibrillation, however, late successful defibrillation (after 30 minutes and more) has been reported to occur [77].

There is evidence that transthoracic resistance decreases with delivery of successive shocks [85]; however, we have not observed successful defibrillation unless the shock strength has been increased, suggesting that the potential positive effects of reduction in transthoracic resistance with consequent actual delivery of higher current to the fibrillation myocardium is offset by the negative hemodynamic and metabolic effects of the continuing rhythm. This observation has been corroborated in patients undergoing cardioversion [86].

The effect of drugs and electrolytes on the threshold for ventricular defibrillation has been investigated [87, 88], and its importance in successful defibrillation, at least in the experimental animal, has been emphasized. Digitalis lowers the amount of energy required for defibrillation (as well as the threshold for induction of ventricular fibrillation) by about 27% in dogs [87]. Thus, in a digitalized patient lower initial shock strengths (sometimes on the order of 5–10 joules) are recommended. (Cardioversion of tachyarrhythmias in digitalized patients is not expected to result in postconversion digitalis-toxic arrhythmias [42] unless the original rhythm is a digitalis-toxic one; in these cases, cardioversion should be avoided, if at all possible, or should be per-

formed at the lowest allowable energy settings.) Both lidocaine and quinidine have been shown in acute animal studies to transiently increase the defibrillation energy requirement [88]; the relevance of such studies to the clinical setting is not clear.

Defibrillation in patients with cardiac pacemakers

The requirement for defibrillation in patients with acute myocardial infarction who have permanent pacemakers in place arises not infrequently. Pacemaker generators are designed so that the sensing and pacing circuitry is protected from excessive electrical energy, but on occasion the protective mechanisms may fail, resulting in pulse generator malfunction.

General guidelines for electroversion in patients with pacemakers include adequate separation between defibrillator paddles, avoidance of paddle placement within three to five inches of the pulse generator, and ensuring that the dipole created by the defibrillator paddles is perpendicular to that between the electrode catheter tip and the generator in unipolar pacing systems, or to that between the electrodes of the lead in bipolar pacing systems.

Despite these precautions, abnormalities of pulse generator function following defibrillation have been reported and include failure to capture due to current drain [89], myocardial burns due to high current flow along the pacing lead [89], and unwanted programming of automatic rate function in some programmable units [89, 90]. The reasons for defibrillator-produced reprogramming of permanent pacemaker generators are not entirely explained, but have been considered to be due to the interaction between the generator's circuitry and electrical noise artifacts and static discharges occurring during placement of the defibrillator paddles on the body surface. The pacemaker malfunction may be transient, with restoration of normal function within a short period of time [91], or more permanent, warranting early pulse generator replacement.

Sensing problems developing after defibrillation may be due to pulse generator malfunction but are more likely to be related to the electromechanical effects of the dysrhythmia itself and/or defibrillation-related myocardial injury resulting in distortion of intracardiac signals, making them suboptimal for sensing.

It is advised to test all parameters of pacemaker generator function, including automatic (free-running) and magnet rates, and the integrity of programmable parameters, as soon as the patient is stabilized. In pulse generators having the capability of transmitting stored information by telemetry, interrogation may reveal a change from previously programmed parameters, signifying misprogramming by the defibrillation procedure. It must be underscored, however, that the interrogation command itself may be faulty in defibrillated patients. Failure of pulse-generator function to return to normal within a reasonable period of time mandates generator replacement.

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2. THROMBOLYSIS IN THE MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION

H.J.C. SWAN

PATHOPHYSIOLOGIC BASIS

Myocardial infarction is due to the cessation of coronary blood flow to a region of myocardium for a time interval sufficient to cause its necrosis. The exact mechanism of this relationship is not precisely defined and may be due to deprivation of metabolic substrate, incomplete removal of metabolic products, both processes, or other mechanisms. Whatever the cause, necrosis commences approximately 20–30 minutes following complete deprivation of blood flow at normal body temperature and progresses outward from the subendocardial zone myocardium to the subepicardial zones [1]. The rate of progression varies between and within animal species including humans. In the canine experimental model, at least two thirds of the myocardial territory at risk is necrotic at 3–4 hours and 100% is necrotic at 6 hours [2]. Other species vary somewhat: In the pig, transmural necrosis is seen within 1 hour. In patients with preexisting coronary artery disease and complete occlusion of the coronary circulation, with blood flow approaching zero in the most severely affected areas — those physiologically remote from any source of blood flow, the time over which necrosis in the myocardial "territory at risk" is proceeding seems to vary between ½ and 3½ hours — similar to the canine model in most instances. This variation may relate to the nature of the coronary artery disease, the presence of collaterals and the degree of, or lack of, compensatory circulatory responses in an individual human subject at the time of complete coronary occlusion. The relevant *time window* then is limited to the interval

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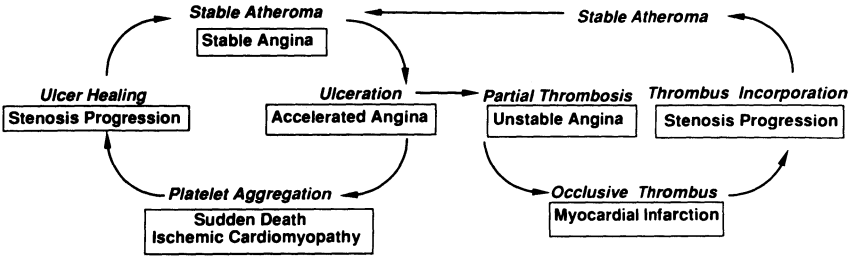

Figure 2–1. The ulceration-thrombosis cycle. Relation of the changing surface pathology to clinical presentations in acute coronary syndromes. From Forrester and associates [5] with permission.

within which a significant proportion of myocardium in the territory at risk remains ischemic but viable. The maximal rate of decline in the *viable fraction* probably occurs between ½ hour and 3 hours following complete coronary occlusion in most instances. More recent clinical trials have confirmed that benefit is maximized in those patients treated early, that is, within 2–3 hours.

The pathologic substrate of acute myocardial infarction is underlying coronary artery disease in 99% of subjects. The process can involve disease in any artery or in any location in an artery. For practical purposes, however, proximal location and a sizable territory at risk (10%–40% myocardial mass) are involved in patients who present with clinical myocardial infarction. The degree of obstruction caused by coronary atherosclerosis varies from subtotal (90%–99%) to mild (less than 60% of luminal cross sectional area). The specific pathology involving coronary arteries themselves is complex. Extremely high degrees of stenosis (99%) may so limit flow that minimal change at the point of atherosclerosis is sufficient to cause subendocardial necrosis in response to an increased demand. In patients with lesser degrees of coronary obstruction (50%–95+%) *instability* — change or breach of the endothelial lining of the atherosclerotic lesion — appears to trigger thrombus formation — the proximate cause of clinical acute myocardial infarction [3]. An apparent analogous situation in patients with unstable angina pectoris has been demonstrated since complex plaque and thrombus have been found in patients with unstable angina pectoris without infarction. Some patients with unstable angina have demonstrated increases in cardiac enzymes, suggestive of the presence of limited necrosis within the territory at risk. The relevant *ulceration-thrombus-healing* cycle in patients with coronary heart disease has been described by Forrester and colleagues [4]. (figure 2–1).

UNIFYING CONCEPT

The syndrome of unstable angina pectoris is due to the formation of a partial thrombus on an ulcerated plaque [4]. Such thrombi are consistently observed

in patients coming to surgery early in the course of their acute presentation. Thrombus actually invades the fissured surface of the plaque and may also liberate vasoactive substances. In unstable angina patients, the nonoccluding thrombus was generally firm and not easily displaced from its attachment. It is probable that a similar process — but progressing to complete coronary occlusion — underlies acute infarction. One can readily develop a temporal relation between the duration of total (or near total) occlusion to the syndromes of prolonged myocardial ischemia, ruled-out myocardial infarction, non-Q-wave myocardial infarction, postthrombolysis myocardial infarction, completed myocardial infarction, and completed myocardial infarction with late spontaneous recannulization (table 2–1). In the syndromes of prolonged myocardial ischemia and ruled-out myocardial infarction, necrosis has been negligible due to the short duration of complete ischemia. In the other syndromes of more prolonged occlusion, enzymatic evidence of necrosis is present.

Myocardial necrosis is proportional to the magnitude of the territory at risk and is reflected functionally in the concept of hemodynamic subsets [5] in which cardiac performance and, subsequently, short- and long-term outcomes are related [6].

Thus, for each location and degree of obstruction of a coronary artery, the possibility exists that it may become the site of a complete occlusion with a resulting infarct. In the majority of instances (90+%) of clinical myocardial infarction, the proximal cause is the development of an acute thrombus on a preexisting but ulcerated coronary atherosclerotic plaque; other dynamic factors include vasomotion, spasm, or platelet-plugging. In many examples of myocardial infarction, late restoration of blood flow through vessels that supply areas of scar (as in ventricular aneurysm) are demonstrable by angiography. This spontaneous reperfusion in 20%–30% of clinical cases may occur beyond the limits of this ischemic time window and thus is too late to allow for salvage of substantive quantities of at-risk myocardium. Some patients with early spontaneous reperfusion may present clinically as prolonged myocardial ischemia without infarction or as ruled-out myocardial infarction. Spontaneous reperfusion may be increased to 50% in patients receiving heparin and aspirin.

Table 2–1. Temporal subsets of total coronary occlusion

Duration*	Clinical syndrome
< 5 minutes	'Prolonged' angina
5 < 15 minutes	Severe myocardial ischemia
15 < 45 minutes	'Ruled-out' M.I.
45 < 90 minutes	'Non-Q' M.I.
1½ < 4 hours	Post-lysis M.I.
4 < 10 hours	Transmural M.I.

* Approximate — modified by collaterals, etc.

The exact distribution and the severity of the atherosclerotic disease in the artery of infarction is highly variable. As a generalization, it appears likely that moderate degrees of atherosclerotic occlusion (70±%) that frequently do not produce angina pectoris and greater, but noncritical narrowing (80%) may be a common site of thrombotic coronary occlusion. Minimally diseased vessels (less than 50% cross-sectional reduction), not ordinarily associated with symptomatic cardiac ischemia, may be the site of thrombotic occlusions in 10%–20% of cases and may precipitate acute myocardial infarction.

TEMPORAL SUBSETS

The clinical consequences of acute coronary thrombosis cannot be considered under a single pathophysiologic heading. It is essential to define at least four pathophysiologic phases [8] to roughly encompass those elements of the illness that are fundamentally different from one another in their nature and require separate consideration and therapy (table 2–2): 1) the phase of ischemia — the myocardium in the territory at risk that is noncontractile and probably noncompliant, yet has not proceeded to necrosis and will ultimately regain function if blood flow is restored; 2) the phase of necrosis during which all of the myocardium in the territory at risk destined to undergo necrosis has become necrotic; 3) the phase of compensation — associated with thinning and absorption of the necrotic myocardium and increased activity of the neurohumoral compensatory mechanisms; and 4) the phase of healing — dominated by the formation and maturation of scar tissue and limitation of the adverse mechanical consequences of the infarction per se. Clearly, these pathologic subsets overlap considerably.

Of critical importance to the topic of this chapter, coronary reperfusion, is the phase of ischemia (phase 1). It is convenient to develop a subset within this phase, during which an increasing proportion of myocardium in the territory at risk is passing from the state of ischemia into the state of necrosis (phase 1A — phase of mixed pathology). From the definitions above, it is obvious that the primary role of thrombolytic therapy can only be in the phase of ischemia or mixed pathology. As the proportion of myocardium within the territory at risk (which becomes necrotic) increases, the potential efficacy and long-term benefit of thrombolysis declines (figure 2–2). Reestablishment of perfusion in

Table 2–2. Temporal subsets of myocardial morphology following complete coronary occlusion

Phase	Morphology	Time
I	Ischemic	½ hour
Ia	Mixed	½–6 hours
II	Necrotic	hours–days
III	Absorbtive	days
IV	Healing	weeks–months

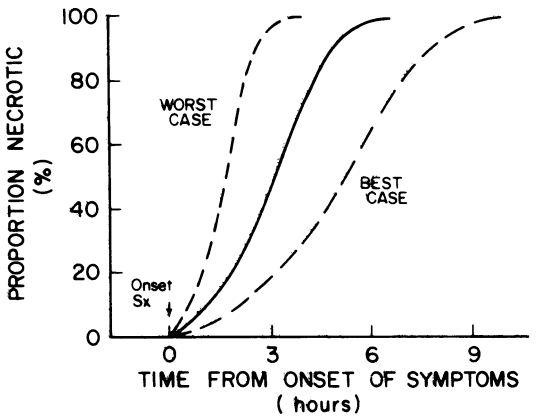

Figure 2–2. Time course of necrosis. The vertical axis identifies the proportion of the territory at risk that has become necrotic after different intervals of profound ischemia. The solid center line represents a best estimate of necrosis from experimental data and also indicates completion of necrosis between 4 and 6 hours; at 2–3 hours 30%–40% of myocardium has already become necrotic. Other possibilities include a more rapid necrosis (no collaterals, acute severe hypotension) or a slowed or incomplete necrosis (generous collaterals, hypertensive response).

the territory at risk is most useful when significant jeopardized, yet still viable myocardium is present. Interventions designed to result in revascularization, after the phases of ischemia and mixed pathology are completed, can have no influence in the preservation of ischemic and jeopardized myocardium. No evidence of salvage could be demonstrated from the multitude of clinical studies based on pharmacologic (nonthrombolytic) interventions [9]. However, beneficial effects can be demonstrated from late interventions and are likely to be associated with mechanisms other than preservation of ischemic myocardium in the inital territory at risk, such as endothelial healing and prevention of reocclusion.

It must be evident from the above considerations that thrombolysis is not a comprehensive single treatment for an evolving acute myocardial infarction. It addresses only one part of the issue, albeit an important one, namely, the proximate cause of the acute obstruction. That further obstruction may occur due to rethrombosis or coronary spasm, or that other changes may cause further myocardial damage, is unquestioned. The philosophic goal of coronary reperfusion is fundamentally to restore the patient to the situation prior to the onset of thrombosis to the greatest degree possible, and to allow for a more considered evaluation of the unstable coronary pathology present, without paying the penalty of extensive myocardial damage. The primary physiologic objective is to preserve myocardial viability and function, which remains the single most important determinant of prognosis [6].

Thus, at least four specific elements are relevant to the patient with an acute syndrome leading to myocardial infarction: atherosclerosis, thrombosis, myocardial response, and arrhythmias. It is appropriate to define the objectives of management of acute myocardial infarction as: preservation of life, salvage of the maximum amount of jeopardized myocardium, stabilization of disorders of cardiac function or cardiac rhythm, and evaluation and management of underlying coronary disease. Prompt revascularization probably has an effect in all of these elements.

EXPERIMENTAL INVESTIGATIONS

In the complex setting of acute myocardial infarction, investigative work in many disciplines becomes relevant. These include thrombosis and thrombolysis, coagulation and anticoagulation, atherosclerosis, endothelial function, vascular ulceration and repair, platelet activity, ischemic myocardinal injury and necrosis, myocardial metabolism, recovery of ventricular function, and hypertrophy. A few highlights are relevant to the appreciation of the current clinical situation. In 1954, Agress and colleagues [10] directed specific experiments towards the genesis of thrombus in the coronary arteries and its dispersion by fibrinolysis. After initiating development of acute fibrin thrombus in appropriate canine coronary vessels, fibrinolysis (Armour) caused dispersion of the thrombus, restoration of blood flow, normalization of the electrocardiogram, improvement in survival, and absence of or smaller infarcts in comparison to a control group of animals.

Concerning the frequency of recanalization, Ganz and colleagues [11] demonstrated that in freshly induced experimental intracoronary thrombi, 30-minutes-to 3-hours-old, near uniform recanalization utilizing streptokinase or thrombolysin (streptokinase with plasmin) could be achieved. Net systolic wall thickening was examined in animals who underwent 2- or 4-hour occlusions of the left anterior coronary artery, followed by reperfusion [12]. For 2-hour reocclusions, segments that demonstrated both initial moderate or severe dysfunction showed significant improvement at 1 month. However, dogs occluded for 4 hours did not demonstrate significant improvement, although dyskinetic segments became akinetic. In 1-hour interval occlusions, all segments improved over a 4-week period [13]. From these experimental data, it must be concluded that *early reperfusion is essential* if the objective is the restoration of ventricular function.

CLINICAL APPLICATION OF NONSURGICAL REPERFUSION

In spite of prior experiences with pharmacologic thrombolysis (intravenous) in the 1960s and early 1970s, reinterest in nonsurgical reperfusion dates from the single catheterization experience of Rentrop [14] in dispersing a thrombus in a right coronary artery by use of a guidewire, with striking clinical benefits and the subsequent demonstration by De Wood [3] of the incidence of occlusive thrombosis in early clinical infarction. Direct mechanical dispersion of an intra-

coronary thrombus with immediate dilatation (angioplasty) of the underlying coronary disease has again been recommended as a primary mode of treatment for acute evolving myocardial infarction [15]. Direct infusion of thrombolytic substances into the acutely obstructed coronary artery was demonstrated to result in restoration of blood flow shortly thereafter. In the majority of cases, the time from symptom onset to initiation of treatment varied between 2 and 8 hours. However, intracoronary administration of thrombolytic agents requires the establishment of a complex logistic system at institutions to provide this service. These include effective transportation and emergency-room services with a stand-by catheterization laboratory and a workable on-call system. Under favorable circumstances, these factors increase the minimal interval from identification to initiation of effective thrombolytic therapy by 1 to 1½ hours. In addition, this application of thrombolysis was restricted to hospitals with effective catheterization laboratories — less than 10% of community hospital facilities.

In spite of the impression of little benefit in prior studies on the intravenous use of thrombolytic agents, early intravenous administration of relatively large doses of thrombolytic agents (streptokinase) have now been employed extensively. This approach had significant advantages over intracoronary administration, including a reduction in the delay from the onset of coronary occlusion to application of therapy, wider application of early reperfusion to institutions without catheterization facilities, the potential of reducing the interval to treatment even further by application of thrombolytics in transportation or home, and a possible reduction in overall cost. Also, the occluding thrombus appears to become progressively more resistant with time to thrombolytic agents, possibly because of maturation and also by extension distally or proximally. A lower blood concentration of thrombolytic agent is achieved by intravenous, in comparison to local concentration during intracoronary administration; however, a systemic lytic state accompanies the latter. Thus, a larger dose must be given when venous application is used, and bleeding complications may be more frequent in intravenous, in comparison to intracoronary, administration. With experience and careful patient selection, bleeding complications may be minimized.

MECHANISMS OF ACTION OF THROMBOLYTIC AGENTS [16]

Plasminogen, an inactive proteolytic enzyme, is incorporated during the formation of thrombus to bind with fibrin. Thus, the plasminogen-plasmin enzyme system is already present in the thrombus and requires activation. Plasminogen activator divides the plasminogen molecule, activating plasminogen to plasmin and thereby causing the dissolution of fibrin strands within the thrombus. All of the currently used thrombolytic agents effect their action as plasminogen activators. However, intermediate steps in the actions of the various thrombolytic agents differ considerably, although their common characteristic is to achieve a sufficient concentration in the systemic circulation

to cause maximal activation of the fibrin-bound plas-minogen. Thrombolytic agents also react with circulating plasminogen to a greater or lesser degree. However, the development of a lytic state pertaining to the systemic circulation may result in lysis of a hemostatic plug, since thrombolytic agents do not distinguish between "good" plugs and "bad" clots. Reduction in serum fibrinogen does not necessarily indicate a greater or lesser degree of susceptibility to bleeding. The possibility of bleeding is also favored by impaired platelet adhesion to the denuded plaque site and to other platelets.

PHARMACOLOGICAL THROMBOLYSIS

The agents currently in use (1988) for intravenous thrombolysis in acute myocardial infarction are streptokinase (SK) and recombitant tissue plasminogen activator (rt-PA). Anisoylated plasminogen streptokinase activator complex (APSAC) has been approved for clinical use in West Germany, Belgium, and the United Kingdom and is apparently soon to be marketed in the United States. Urokinase and recombitant single-change urokinase plasminogen activator (scu-PA) and additional lytic substances are being tested. Ingenious systems to deliver the lytic agent to fibrin more effectively are under development, but will not be considered in detail in this chapter.

CHARACTERISTICS OF DESIRABLE THROMBOLYTIC AGENTS (TABLES 2–3 [16] AND 2–4 [17])

The broad criteria for optimal action of any drug includes rapid effectiveness in a high proportion of recipients, with negligible complications. To these criteria may be added ease of administration and overall costs. Efficacy may be judged in several ways. From the patient's viewpoint, effective reduction in mortality and morbidity, restoration of functional state, and absence of symptoms are paramount. From the standpoint of the investigative cardiologist, tests of ventricular function and vascular patency may suffice, together with resolution of the underlying atherosclerotic lesion and absence of reocclusion. While ease of administration might be best facilitated by oral ingestion, intravenous injection is necessary to rapidly attain high blood concentrations of the agent. Recognizing that time is of the essence in the administration of lytic agents, the ideal agent should be available for simple administration in the home or during transportation of the stricken patient. Regarding costs, it must suffice to indicate that current pricing in regard to rt-PA represents a serious limit to its broadest application.

For streptokinase and streptokinase-complex (APSAC), there is a small incident (5%) of mild allergic responses — chills, erythemia, and edema — and severe reactions are rare, possibly one in one thousand or two thousand patients. Both streptokinase and APSAC also exhibit antigenicity, and antibodies peak at titers 100–1000 times greater than the basal level. These values return to pretreatment levels 6 months later.

Significant hypotension occurs in approximately 10% of patients treated

Table 2–3. Pharmacologic and clinical features of thrombolytic preparations.

	SK	APSAC	UK	SCU PA	rt-PA	
					2-chain	1-chain
Half-life (min)	23	90	16	7	8	5
Fibrin enhancement	1+	1+	2+	4+	4+	3+
Plasma proteolytic state	4+	4+	3+	2+	2+	1+
Duration of infusion	60 min	2–5 min	5–15 min	several hours	several hours	several hours
Thrombus specificity (vs. hemostatic plug)	0	0	0	0	0	0
Incidence of reperfusion (% within 3 hr)	60–70	60–70	60–70	60–70	60–70	60–70
Speed of reperfusion (min)	45	45	45	45	45	45
Frequency of reocclusion (estimated %)	15	10	10	na	20	20
Simultaneous administration of heparin	no	no	no	yes	yes	yes
Bleeding complications	4+	4+	4+	4+	4+	4+
Allergic side effects	yes	yes	no	no	no	no
Antigenicity	yes	yes	no	nk	nk	nk
Expense	1+	2+	3+	4+	4+	4+

Abbreviations: NA = not applicable; NK = not known. From Marder and Sherry [16] with permission.

Table 2–4. Characteristics of current thrombolytic agents.

Type of plasminogen	Site	Result	Effect
Soluble plasminogen	Plasma	Fibrinogenolysis	Impaired coagulation Impaired aggregation
Fibrin bound	Clot	Fibrinolysis	Clot dissolution
	Hemostatic plug	Fibrinolysis	Hemostatic plug lysis
Platelet bound	Platelet surface	Response to agonists ↓	Impaired aggregation
		Platelet GPIb ↓	Impaired adhesion
		Platelet GPIIb/IIIa ↓	Impaired aggregation
Thrombospondin bound	Platelet aggregate	Thrombospondin ↓ Fibronectin ↓ Fibrinolysis Fibrinogenolysis	Platelet disaggregation Impaired adhesion
Endothelial-cell bound	Endothelium	Platelet glycoproteins ↓ Fibrinolysis	Impaired aggregation Fibrin dissolution

From Sherry [17] with permission.

with rapid-dose streptokinase. This is apparently due to acute vasodilatation and is usually transient. Approximately 2% of patients have severe sustained hypotension, which requires the discontinuance of streptokinase and the use of dopamine. APSAC has a lesser hypotensive effect. Such reactions are not seen with rt-PA and urokinase.

Bleeding is by far the most important complication (table 2–5) [17] and has

been reported with each of the thrombolytic agents. Although rt-PA was introduced with the expectation that bleeding complications would be minimal, this has not proven to be the case. For currently recommended dosages, the incidence of bleeding with rt-PA, streptokinase, and APSAC appear to be approximately equivalent. Bleeding is most common at puncture sites. Therefore, subclavian and internal jugular vein insertion sites should be avoided. Other bleeding complications include hemotoma, epistaxis, hematuria, hematemesis, cerebral hemorrhage (0%–4%), and anemia. Indeed, there is a suggestion that the incidence of cerebral bleeding may be greater in patients receiving rt-PA.

Concern over bleeding complications and, in particular, stroke, require specific exclusions of certain patients from consideration for thrombolytic therapy. Recommendations as to exclusions differ between groups, but specific conditions include: a prior history of bleeding, particularly hemorrhagic stroke or gastrointestinal hemorrage; severe hypertension (diastolic pressure greater than 100 mmHg); any other form of intercerebral disease or head trauma; cardiopulmonary resusitation; recent abdominal or thoracic surgery; a significant malignancy; and primary bleeding disorders and concomitant important medical illnesses.

Table 2–5. Practical considerations in the selection of a thrombolytic agent.

Agent	Advantages	Disadvantages
Streptokinase	Least expensive Reduces infarct size and mortality	Hemostatic defect Increased bleeding risk Antigenic Occasional allergic reaction Least clot selective
Urokinase	Modest clot selectivity Nonantigenic Bolus injection	Hemostatic defect Increased bleeding risk Expensive
APSAC	Bolus injection Prolonged action	Hemostatic defect Increased bleeding risk Antigenic Occasional allergic reaction More expensive than streptokinase
rt-PA	Activator nonantigenic Highly clot selective	Hemostatic defect Simultaneous heparin reaction required Increased bleeding risk Short half-life prolongs reaction Other antigens? Very expensive
r pro-urokinase	Activator nonantigenic Highly clot selective	Hemostatic defect Simultaneous heparin reaction required Increased bleeding risk Short half-life Other antigens? Very expensive

From Sherry [17] with permission.

STREPTOKINASE

By far the greatest experience worldwide is available for streptokinase [18–22]. Streptokinase is given intravenously, usually 1.0–1.5 million units are given over intervals as short as 10 minutes and as long as 60 minutes. More rapid infusion rates are associated with an increased incidence of hypotension; slow infusions may delay reperfusion. Under optimal conditions, average opening rates of approximately 60% should be achieved with the use of streptokinase. However, streptokinase is less effective with "old" thrombi, particularly those of over 6 hours. Thus, streptokinase given within the first 90 minutes may be expected to have a high opening rate, possibly exceeding 75%, but less than 45% in later clots.

It is generally considered that once effective thrombolysis has been achieved and reperfusion has commenced, the patient remains at risk for reocclusion by reformation of the thrombus. Effective anticoagulation in the hours immediately following reperfusion appears necessary. A variety of regimens for anticoagulation have been used. Ganz [23] recommends a bolus intravenous injection of 40 μ/kg of heparin prior to or immediately following streptokinase, with a continuous intravenous infusion of 15 μ/kg/hr. To maintain the prothombin time (PT) at approximately 100 seconds, the infusion of heparin is continued without interruption until coronary arteriography has been performed and into the initiation of cardiac surgery, if so indicated. After 3–5 days of heparin anticoagulation, gradual replacement with coumadin is commenced, maintaining the prothrombin time at approximately 25 seconds. Anticoagulation with coumadin is recommended for 3 months.

RECOMBINANT TISSUE-DERIVED PLASMINOGEN ACTIVATOR [24]

rt-PA was thought to offer an exciting new possibility with high efficacy due to its apparent clotting specificity and a low incidence of primary bleeding complications because of a lesser effect on circulating fibrinogen. Recommended dosing levels have varied as experience with the agent has grown. rt-PA must be given by continuous intravenous infusion. An initial protocol called for 150 mg given over a period of 6–8 hours. Modification of dosing has included 1) a first hour dose of 60 mg, the remainder being administered over 5 hours, and 2) a total dose of 1 mg/kg body weight, with 10% given as an initial bolus and 0.75 mg/kg given over 90 minutes. Because of the short half-life of rt-PA, heparin is recommended as an anticoagulant, commencing with the initiation of thrombolytic therapy.

A number of comparisons against placebo or streptokinase in terms of angiographic patency or the frequency of opening a completely occluded vessel have been performed. In an early comparison versus placebo, 75% of treated patients demonstrated recanalization within 90 minutes of the initiation of therapy [25]. A subsequent study demonstrated 61% patency, versus 21% for placebo. In a direct comparison with streptokinase, rt-PA was effective in 70% of cases, while streptokinase was effective in 61% of cases [26]. A

direct comparison in the TIMI-1 study showed a 64% patency rate for rt-PA, but only a 32% patency rate for streptokinase [27]. This magnitude of difference was not observed by other investigators. The average interval to treatment in the TIMI-1 trial was 4.7 hours, implying that many patients were entered with a thrombus in situ for 5 hours or more. In addition, hyperosmotic radiologic contrast solutions may have affected the surface of the thrombus. Marder and Sherry [16] observed that the difference between the two agents was not significant in studies in which patients were treated within 3–4 hours — the most critical interval to preserve myocardium and to favorably influence survival. Further differences in reperfusion rates are mitigated by the higher rate of coronary artery reocculsion associated with tissue plasminogen activator [16].

rt-PA has certain specific advantages over both streptokinase and APSAC. It does not cause allergic reactions. Hypotension, a clinically important problem in 10% of patients receiving high-dose streptokinase, is not seen. Reduction in circulating fibrinogen is greatly reduced in comparison to streptokinase and APSAC, although the clinical significance of this finding is uncertain. The true incidence of hemorrhagic complications due to rt-PA is further complicated by the number of confounding procedures such as pretreatment angiography, posttreatment immediate angiography, emergent angioplasty, late angioplasty, as well as the changing dosage schedule [28]. A consensus indicates that the incidence of bleeding complications is approximately the same for rt-PA in effective doseranges as it is for streptokinase or for APSAC.

ANISOYLATED PLASMINOGEN STREPTOKINASE ACTIVATOR COMPLEX (APSAC) [29]

APSAC powder (20 units) is reconstituted with 5 ml water and administered over 2–5 minutes within 30 minutes of reconstitution. This dosing technique appears to provide important thrombolytic effects over a wide range of patients. APSAC has a distinct advantage over streptokinase in not causing more severe degrees of hypotension in susceptible patients, although its use is associated with a mean reduction in blood pressure of approximately 5–10 mmHg in systolic pressure. APSAC has similar allergenic properties to streptokinase.

APSAC resulted in a reperfusion pattern similar to that of streptokinase [30]. In patients treated within 4 hours, a reperfusion rate of 60% was obtained, compared with 33% for those treated after 4 hours. There was a significant effect on plasminogen and fibrinogen concentrations and of antiplasmin. Reperfusion rates are dose dependent.

EFFICACY OF THROMBOLYTIC THERAPY

A first-order marker of therapeutic efficacy must be a significant reduction in all-cause mortality. Reduction in morbidity and improved symptom status are necessary to identify a favorable change in the quality of life, as well as in its

Table 2–6. Randomized trials of streptokinase and APSAC: Short-term effect

Trial	No. patients	Time to Rx (hrs.)	Mortality % Placebo	Rx	% Δ
W. Washington [31a]	194	< 3	11.3	5.2	54
	368	1–6	9.7	6.3	35
Gissi [18]	6,094	< 3	12.0	9.2	23[a]
	11,806	1–12	13.0	10.7	18[a]
ISAM [22]	940	< 3	6.5	5.2	20
Auckland [20]	219	< 4	12.9	2.5	80[a]
ISIS-2 [21]	4,000	< 4	12.0	8.0	33[a]
AIMS[b] [30]	660	< 4	9.2	5.4	42[a]
	1,004	1–6	12.2	6.4	48[a]

[a] Statistically significant. [b] APSAC.

duration. An improved short-term mortality (7–30 days) allows for considered treatment of the underlying athero-sclerotic-ulcerative thrombotic disorder by a variety of pharmacologic and mechanical interventions. One-year mortality discounts the importance of these interventions as routines. The outcome of published randomized trials is given in table 2–6. The great majority of these involves streptokinase as well as single randomized trials of APSAC [29] and of rt-PA [32].

A few comments on these randomized trials appears appropriate. Consistent reductions in mortality appear to be achievable on the order of approximately 40%. However, there is considerable variation between studies. The confidence interval for the Auckland (New Zealand) trial [20] possibly does not sustain the estimated 80% reduction in mortality. Nevertheless, this trial from a single internationally respected coronary care center included over 98% of all patients deemed eligible.

RESULTS ON MORTALITY OF THE LARGE RANDOMIZED TRIALS

In 1986 the short-term results of the GISSI trial were published [13]. In this trial, 11,712 patients were randomized to receive either standard care according to the practices of the unit to which they were admitted plus a placebo infusion or the same care with 1.5 million units of streptokinase given intraveneously. Compared to placebo, the patients receiving streptokinase had a high significant reduction of 18% in overall mortality at 3 weeks. However, there was a maximal reduction in mortality of 47% for the treated patients in comparison with controls for those entered within 1 hour of the onset of symptoms. Bleeding complications in the patients receiving streptokinase were greater than in the control group, but the majority of these events were minor, with few requirements for active treatment such as transfusion. In the second study, the mortality at 1 year was determined in 98.3% of the patients who had been randomized [19]. The beneficial effects (gain) were maintained. Additional late mortality of the patients who had received streptokinase was identical for the

control patients and amounted to 8.7% of those treated with streptokinase and 8.6% for controls. In this large scale study, very few patients underwent angiography or myocardial revascularization, and this cohort is not reported upon in detail. Thus the benefit of thrombolysis is confined to the acute phase. The distribution of the use of antiplatlet agents, calcium-channel antagonists, and nitrates was identical in the followup treated and control groups.

The second International study of Infarct Survival (ISIS-2) collaborative group reported on the randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected mycardial infarction [21]. These patients entered a total of 417 hospitals worldwide within 24 hours (median 5 hours) after the onset of suspected acute myocardial infarction. The absolute accuracy of prerandomization diagnosis has been questioned (unstable angina) in some patients. The groups entered one of four treatment regimens in addition to the practices of the various hospitals. These included 1) a 1-hour intravenous infusion of 1.5 million units of streptokinase 2) 1 month of 160 mg per day of enteric-coated aspirin, 3) both active treatments, or 4) neither. Each of the active treatment (streptokinase, aspirin) produced a highly significant reduction in 5-week vascular mortality. The mortality of the patients receiving placebo lay between 12% and 11.8%, for those receiving streptokinase mortality was 9.2%, and for those receiving aspirin it was 9.4%. This outcome represented an odd reduction in mortality of 25% and 23%, respectively. However, the combination of streptokinase and aspirin was significantly better, yielding a 5-week vascular mortality of 8.0% compared to 13.2% for those receiving placebo. Additionally, there was evidence of benefit for each agent, even for patients treated late after the onset of pain. For example, the odds reduction for mortality for combination therapy was 53% at 0 to 4 hours, but remained high, at 38% of the patients treated, between 13 to 24 hours. Streptokinase alone or in combination was associated with excessive bleeding complications requiring transfusion (0.590 vs. 0.2%), but there was no increase in total strokes (0.7% streptokinase vs. 0.8% for placebo). The late benefit of streptokinase, aspirin alone, or the combination was not anticipated. The antiplatlet effect of aspirin may have caused a significant reduction in the incidence of reocclusion.

The Anglo-Scandinavian Study of Early Thrombolysis (ASSET) studied the effectiveness of tissue plasminogen activator in mortality reduction in acute myocardial infarction [31]. In this study, 13,318 patients were admitted to 52 coronary care units. Sixty-two percent were excluded, mainly because their symptoms had begun more han 5 hours prior to entry. The remainder were randomized to rt-PA 100 mg plus heparin or placebo plus heparin. At 1 month, the overall case fatality rates were 7.2% and 9.8%, respectively, or a risk reduction of 26% in comparison to placebo. Overall mortality in the excluded patients was 13.1% (17.1% in those confirmed to have acute myocardial infarction). It is of some interest that a slightly greater (35%) mortality reduction was achieved in patients aged 66–75. Of the patients re-

ceiving rt-PA, 6.3% had bleeding complications, compared to 0.8% receiving placebo. The incidence of strokes was similar in both groups.

These three major mortality trials, together with the somewhat smaller AIMS trial of APSAC versus placebo [30] allow one to conclude that significant mortality reduction was achieved. These trials included very few patients in which angiography or invasive procedures were used, even in those in whom instability persisted. As the ASSET authors concluded [31], "the superiority of rt-PA over streptokinase in reperfusion reported no striking differences in fatality rate. Furthermore, rt-PA treatment does not appear to be associated with fewer bleeding complications than does treatment with streptokinase despite its theoretical clot specificity."

In addition to these conclusions, the striking effect of aspirin alone or in combination in ISIS-2 underscores the obvious need for attention to vascular healing and prevention of reocclusion. This problem was apparent in studies on patients who received continuous infusion of heparin (but not aspirin) along with an 80 mg infusion of rt-PA [32]. In a small group of patients, sustained perfusion of the infarct-related artery was observed in 14 of 21 or 67% of initially reperfused patients, representing a greater than 30% late reocclusion rate.

Consideration of angiographic studies in placebo and prethrombolysis patients suggests that 20%–30% of patients with completed occlusions undergo spontaneous lysis [33]; this may be greater if the patients are receiving heparin and aspirin [20]. Additionally, in day-to-day clinical practice, plaque instability may blur the borders between unstable angina, complete occlusion that is brief, and high-grade obstruction (TIMI grade 1). Such obstructive lesions are dynamic and may be favorably affected by both natural lytic effects and by pharmacologic intervention.

CLINICAL SIGNS OF REPERFUSION

In practice, clinical markers are frequently used to identify the occurrence and timing f reperfusion [23]. Not all of the markers are present in every patient and their intensity varies considerably. However, as a general constellation, they serve to indicate the probable occurrence of reperfusion. Early-release serum creatine kinase (CK) and its MB isomer appear to give a more specific indication of the occurrence of reperfusion than other "softer" criteria. Recognition of reperfusion is usually based upon 1) abrupt and rapid relief of chest discomfort and other symptoms, if present, and the development of a sense of well-being within the patient; 2) rapid resolution of abnormal deviations of the ST segment; 3) specific reperfusion arrhythmias (ectopic ventricular beats, vidio ventricular rhythm, or both) — these arrhythmias are usually self-terminating are require no treatment; 4) reversal of atrioventricular or intraventricular block, if present; and 5) a prompt rise in the CK and its MB isomer after effective reperfusion. Substantive evidence now exists that

reperfusion causes a "washout" of CK and its MB isomer from the myocardium [34]. Reperfusion allows for 75–90% of the CK lost from myocardial cells to be recovered in the serum. In contrast, when reperfusion is not achieved, removal of CK from the injured tissue is slow, peaking at 24–30 hours and then slowly declining. Transport may be via the lymphatic system, or, alternatively, if may be due to a washout through the coronary sinus due to minimal collateral flow into the area of necrosis. Whether due to metabolic alteration or to other causes, approximately 20% of the released CK is recovered in the absence of reperfusion.

Although clinical criteria for reperfusion or reocclusion are considered imprecise and at times nonspecific, the obverse, namely, persistence or increase in pain, continued or increasing abnormalities of the electrocardiogram and the development of further arrhythmias, and clinical deterioration, strongly suggest continued significant ischemia.

In the great majority of instances, the clinical course of patients following successful early reperfusion is benign, not significant different from patients recovering from uncomplicated myocardial infarction. Electrocardiographic changes consistent with a subendocardial infarct are the rule. As alluded to above, diagnostic levels of cardiac enzymes are detected in the bloodstream. It had been estimated that as much as 80% of enzymes within necrotic myocardium are released into the coronary sinus after thrombolytic reperfusion. Both spontaneous and pharmacologic reperfusion may result in early liberation of enzymes. In the absence of reperfusion, there is a slow, inconstant washout of the enzyme content from the necrotic tissue, amounting to 20%–35% of the released enzymes. Differing magnitudes of collateral coronary blood flow may influence the quantity liberated into the bloodstream. Two important conclusions may be reached. First, necrosis — essentially subendocarial — is present in all patients who require thrombolytic therapy. Second, estimation of infarct size from creatine kinase release values is a complex function governed by factors that vary markedly from individual to individual. While such estimates have value in a group study, they should be applied to the individual patient with extreme caution.

CONCLUSION AS TO ACUTE LYSIS

It is apparent that acute thrombosis or a failure of prompt natural lysis is the proximate cause of acute myocardial infarction. It is also clear that large patient groups receiving a variety of thrombolytic agents have benefited in terms of long- and short-term mortality, ventricular function, and vessel patency. However, the selection of thrombolytic therapy for the individual patient remains a matter for physician judgment. Those patients deriving the greatest benefit are those suffering a first myocardial infarction involving the septum, and anterior and antrolateral aspects of the left ventricle (the left anterior

descending coronary artery distribution) and who are treated within 3 hours from the onset of symptoms.

For patients with different presentations, the net benefit may be smaller; hence the indication for thrombolytic therapy may be less strong. Some physicians will not treat inferior infarctions, although they are associated with severe hemodynamic impairment in 10%–15% of instances. Others will not treat patients seen 4 or more hours after the onset of continued pain. Overall mortality is clearly related to the magnitude of necrosis. Reduction in mortality is acheived by limiting necrosis in those at risk for loss of a large proportion of myocardium. A reasonable strategy may be to withhold lytic therapy from patients presenting late, with early relief from pain and without evidence of continuing ischemia, arrythmias, or hemodynamic instability.

Cardiogenic shock is a special situation that suggests a large territory (30%–40% of myocardium) has been rendered acutely ischemic with profound reduction in cardiac output. If the patient can be taken rapidly to a catheterization laboratory, this may offer the more favorable option [35]. Reperfusion of a near completely occluded left main coronary artery, of a dominant anterior descending, or of a circumflex with posterior to anterior collaterals could potentially result in tissue survival if reperfusion is achieved.

Selections of patients *not* to receive thrombolytic therapy must take into account relative contraindications, including patients with hypertension responsive to treatment, those who have a history of a bleeding disorder in the remote past, older patients, those with multiple infarctions, and perhaps patients with uncomplicated inferior myocardial infarctions with rapid stabilization, prompt disappearance of chest pain, and normal heart rate and blood pressure. Enthusiasm for selection of thrombolytic therapy is highest in the patient treated within 1 hour, is significant for patients treated within 3 hours, and is low for a patient in whom treatment has been deferred to 5 hours and later.

LOGISTICAL ARRANGEMENTS

Patients presenting with acute myocardial infarction are conventionally transported to the closest emergency facility. Clearly, emergency facilities and their staffs must be prepared to initiate thrombolytic therapy, although the feasibility of in-home therapy [36] has been demonstrated and the rapid application of lytic agents in emergency transport vehicles is clearly possible. The introduction of APSAC, which can be administered as a slow (1–3 minute) bolus injection has a practical advantage over, for example, rt-PA, which must be given over a period of several hours, or streptokinase, which causes significant hypotension in 10%–15% of patients and must be given over a period of 15 minutes or more. Nevertheless, it is obvious that emergency-room personel are pivotal to the application of thrombolytic therapy on a community-wide basis.

The procedures to be followed after stabilization and initiation of thrombolytic therapy in the emergency room, varies with the size and technical sophistication of the hospital. For small hospitals and stand-alone emergency rooms, a preestablished logistical arrangement with a specialty institution providing cardiac catheterization, cardiac surgery, and angioplasty services appears essential. For small hospitals with a coronary care unit, the patients should be admitted to such a unit and observed. Although 10%–15% of patients will develop reperfusion arrhythmias including, but not limited to, atrial fibrillation, ventricular premature contractions, complex ventricular ectopy, and ventricular tachycardia, these events are usually limited in duration and are relatively easy to treat. Of much greater concern are later complications such as return of symptoms of pain, sweating and dyspnea, development of new ischemic changes in the electrocardiogram and hemodynamic instability. Such patients must be transferred rapidly to a medical institution with full cardiologic capabilities. However, over 70% of patients under-going thrombolysis will have a smooth course and may be mobilized on the third postadmission day. Recent studies have demonstrated the potential for early discharge from the hospital. If the ulcer-thrombus concept presented earlier [4] is the pathophysiologic basis of the obstructive process, then the use of antiplatelet agents and anticoagulants must be a cornerstone for treatment. In those patients in whom complications do not develop and in whom residual stenosis is mild or moderate, then the conventional approach to the non-Q-wave infarct patient would appear to pertain. Reocclusion is directly associated with the severity of the residual stenosis and the presence of residual thrombus at the site of the primary thrombosis. Of these two, the latter appears to be of greater importance. In fact, remodeling of the atherosclerotic lesion appears to occur in at least 20% of patients over the first 7 to 10 days, possibly by further lysis of thrombus at or within the atherosclerotic ulcerated lesion.

It is necessary to give heparin concomittantly with rt-PA. For thrombolytic treatment using streptokinase or APSAC, heparin is started 2–4 hours after the primary intervention. Concerns exist that under certain circumstances, heparin may be procoagulant. Nevertheless, at least in the case of streptokinase (and presumably APSAC), late management with heparin appears to minimize rethrombosis.

New trials are underway on the use of other pharmacologic agents in association with thrombolytic agents and antiplatelet and anticoagulant management. It is known that endothelial-derived constrictor and dilator factors, thromboxin A_2, serotonin, histamine, and other vasoactive agents may be released by platelets, thrombus, collagen, and plaque debris. For this reason, the use of nitrates and calcium-channel blocking agents has been advocated. Intravenous nitroglycerin (possibly in an interrupted dosage schedule to avoid tolerance), oral, bucal, or nitroglycerine; dinitrates; or 5-mononitrates may inhibit local coronary vasoconstriction. Calcium-channel blocking agents may have similar effects. Important antiplatelet properties of nitrates and other

vasodilators may have significance, but their importance in treatment has yet to be proven.

ANGIOGRAPHY

Indications for prompt angiography include patients presenting with severe hemodynamic derangement early in the course of the illness and those with contraindications to the use of intravenous thrombolytic agents. In addition, patients who have been successfully reperfused by intravenous thrombolysis who demonstrate recurrence of hemodynamic instability, electrocardiographic alteration, or the development of recurrent chest pain require emergency angiography to define the status of the coronary arteries. This should comprise no more than 20% of all patients presenting in the early phases of acute myocardial infarction. While there are no specific contraindications to angiography per se, the procedure carries increased risk and hazard with particular reference to extensive intracoronary thrombosis in the acute (first 24 hours) pathology. Hence, angiography should be deferred for at least a week in patients who do not demonstrate an urgent or emergent need.

For the nonemergent patient, this author favors a conservative approach in regard to angioplasty. Angioplasty, when necessary, should be delayed to 7–14 days following the acute presentation in order to maximize vascular healing. According to the practice of a given coronary care unit, a low level predischarge exercise test should be carried out when the patient is considered stable. If the patient has had an uncomplicated course and no abnormality is demonstrated, then he or she should be discharged on aspirin oral anticoagulants and a beta-blocking drug. The patient should be tested at 3–4 weeks by a submaximal stress test including objective studies to define reversible coronary reperfusion defects and/or wall motion. If these are present, then the patient should be admitted for routine cardiac catheterization to demonstrate the underlying coronary anatomy. In the case of the patient who demonstrates unstable hemodynamics or symptom status, or who develops evidence of myocardial ischemia on a rate-limited stress test, the patient should be taken to angiography prior to primary discharge.

CORONARY ANGIOPLASTY, MYOCARDIAL REVASCULARIZATION

Percutaneous balloon angioplasty provides permanent relief (1–5 years) in a significant proportion of patients with obstructive coronary artery disease. Clearly it has an application in selected patients following acute myocardial infarction [37]. Contraindications to balloon angioplasty following thrombolysis include nonobstructive (less than 60%) coronary lesions and technically difficult lesions (length greater than 20 mm, involving bifurcation, distal, or beyond a tortuous proximal vessel). If the infarct-related lesion is part of a compromised coronary circulation, then careful judgment must be exercised. At the present time there are no grounds for cosmetic angioplasty following

thrombolytic therapy. Because of the substantive regression seen in many patients due to remodeling of the obstructive lesion with time, appropriate judgment as to the need for angioplasty should be made on a late rather than a very early (24-hour) angiogram [38]. The reocclusion rate of patients with chronic stable angina following angioplasty remains at 25%–35%. Whether or not this also applies to patients undergoing angioplasty postthrombolysis is at the present time unknown. Emergent angioplasty (within 24 hours) is associated with increased mortality [38].

In the opinion of this author, bypass surgery offers a logical therapeutic alternative to angioplasty [39]. It is particularily indicated in multivessel coronary artery disease, in patients with left main coronary artery disease, and in patients with failed angioplasty. The outcome of coronary bypass utilizing both saphenous-vein and internal-thoracic-artery implants is now well known. Symptom status is markedly improved, duration of life is obviously prolonged, and recurrence rate due to obstruction of the conduit appears to be small. Thoracic artery graft failures are extremely low.

Selection of patients for permanent revascularization should be on the basis of demonstrated myocardial ischemia, as in coronary patients without acute myocardial infarction. Selection of the method for revascularization must depend upon the coronary anatomy and, to a significant degree, on the skill of the cardiac surgeon or the invasive cardiologist. If high-quality angioplasty is available, then the results, at least in the intermediate term, should be satisfactory. Long-term benefit should be anticipated from a skilled cardiovascular surgical group.

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3. THE ROLE OF FREE RADICALS IN THE PATHOGENESIS OF POSTISCHEMIC REPERFUSION INJURY

JAY L. ZWEIER AND JOHN T. FLAHERTY

Spontaneous thrombosis of a coronary artery produces regional myocardial ischemia and ultimately an acute myocardial infarction. Recently, thrombolytic agents including streptokinase, urokinase, and tissue plasminogen activator (t-PA) have been used to dissolve the intracoronary thrombus within the early hours of an acute myocardial infarction. More recently percutaneous transluminal coronary angioplasty (PTCA) has also been utilized to reverse an acute coronary occlusion. Both of these procedures result in reperfusion of myocardium at risk for infarction. However, there is controversy as to whether reperfusion, while terminating ischemia, may actually cause a new form of damage to the region of myocardium at risk.

This new form of injury is termed *reflow injury* or *reperfusion injury* and is characterized histologically by contraction-band necrosis and the formation of calcific granules within mitochondria as well as by cellular swelling and disruption of sarcoplasmic and mitochondrial membranes. Several mechanisms have been proposed to account for this reperfusion injury. These include rapid entry of sodium ions and water into myocardial cells producing intracellular edema; rapid entry of calcium ions, which produce the contraction bands and mitochondrial granules; loss of vascular integrity, which results in hemorrhage into the infarct; and finally the production of reactive oxygen free radicals, which could be responsible for peroxidation of membrane lipids, resulting in disruption of membrane integrity. The generation of reactive free radicals on

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reperfusion of the postischemic myocardium could be the primary insult that triggers all of other observed mechanisms of cell injury.

Superoxide anions ($^{\cdot}O_2^-$), the one-electron reduced form of molecular oxygen, are generated in mitochondria during electron transport, by xanthine-oxidase-catalyzed reactions, by prostaglandin synthesis in the cytoplasm, and by activated phagocytes in the extracellular space. Superoxide anions react with each other to form hydrogen peroxide (H_2O_2), the two-electron reduced form of molecular oxygen, and oxygen in a dismutation reaction. Spontaneous dismutation occurs rapidly at acidic pH (near pH 4.8) but slowly at physiological pH. Therefore mammalian cells employ predominantly enzymatically catalyzed dismutation by superoxide dismutase. The highly reactive hydroxyl radicals ($^{\cdot}OH$), the three-electron reduced form of molecular oxygen, are generated by the Fenton reaction, in which hydrogen peroxide reacts with the reduced form of a trace metal (such as ferrous iron) to yield a hydroxyl radical ($^{\cdot}OH$):

$$H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + {}^{\cdot}OH + OH^-.$$

The ferrous ion is in turn regenerated by the Haber-Weiss reaction, in which ferric iron is reduced to ferrous iron by electron transfer from a superoxide anion:

$$^{\cdot}O_2^- + Fe^{3+} \rightarrow Fe^{2+} + O_2.$$

Thus, in the presence of iron and superoxide anion there will be a redox cycle of iron, resulting in the generation of a hydroxyl radical. Iron is present in all cells bound to the iron storage and transport proteins ferritin and transferrin, and also in the form of low molecular weight chelates. Therefore these iron-catalyzed reactions could be observed in cellular systems.

Reduced oxygen free radicals are known to damage cellular lipid membranes, proteins, and DNA. However, the exact mechanisms by which oxygen-derived free radicals and their metabolites cause cell membrane injury remain speculative. Lipid peroxidation of cell membranes occur by a three-step process: 1) free radicals (e.g., $^{\cdot}OH$) interact with polyunsaturated fatty acids, extracting a proton and forming fatty-acid radicals (initiation phase); 2) fatty-acid radicals then react with oxygen to generate lipid-peroxide radicals (propagation phase); 3) lipid-peroxide radicals ($ROO^{\cdot}$) are then free to react with lipids, proteins, or free radicals, perpetuating the generation of more free radicals. The mechanisms by which these peroxidation reactions can be terminated include: 1) glutathione peroxidase, which can enzymatically reduce lipid hydroperoxides to nonreactive hydroxy fatty acids; 2) bond rearrangement, which may cause formation of diene conjugates or degradation products such as malondialdehyde; and 3) reduced oxygen free radicals can react with specific sites on proteins and enzymes, resulting in structural alteration and

functional inactivation. It is also well known that these radicals cleave DNA.

There are a number of cellular mechanisms of protection against oxygen-free-radical-induced injury. In 1969, McCord and Fridovich isolated an enzyme, superoxide dismutase (SOD), that catalyzes the dismutation of superoxide ions to hydrogen peroxide and oxygen by the equation:

$$\cdot O_2^- + \cdot O_2^- + 2H^+ \rightarrow H_2O_2 + O_2.$$

The enzyme exists in at least two forms, a manganese-containing form in mitochondria and a copper-zinc-containing form in the cytosol. SOD synthesis can be shown to be stimulated by exposure to increased oxygen tension. Exogenously administered SOD has been shown to prevent cell and tissue injury induced by activated phagocytes or superoxide-generating enzyme systems.

Cellular detoxification of H_2O_2 can be accomplished by catalase, a cytoplasmic heme-enzyme that catalyzes the divalent reduction of H_2O_2 to water, the synthesis of which can be shown to be stimulated by hyperoxic conditions. Alternatively, glutahione peroxidase, a selenium-dependent enzyme that is present in significant concentrations in the cytoplasm of mammalian species, also detoxifies H_2O_2 to H_2O through the oxidation of reduced glutathione (GSH) to oxidized glutathione (GSSG). Reduction of the oxidized form is performed by glutathione reductase, which utilizes NADPH, generated principally by the hexose monophosphate shunt. Release of the oxidized form of glutathione into the circulation can be used as an in-vivo index of the cellular detoxification of H_2O_2 ("oxidative stress") [1]. Since glutathione peroxidase is effective at low concentrations of H_2O_2, while catalase is effective in vivo only under conditions of high H_2O_2 production, glutathione peroxidase, which is also present in greater quantity, is felt to play a more significant protective role against oxygen induced injury.

α-tocopherol (vitamin E) functions as a free-radical scavenger and may play an important role in protecting and maintaining the integrity of cell membranes against lipid peroxidation by free radicals. Vitamin E has been shown to be in high concentration in mitochondrial membranes, sarcoplasmic reticulum, and red-cell membranes. α-tocopherol terminates free radical reactions by competing for peroxy free radicals forming tocopherol dimers or quinones. Deficiency of vitamin E in animals is manifest by increased susceptibility to free-radical oxidative injury, which can be inhibited by administration of antioxidants.

Over the last decade a large number of experimental studies have been performed that support the free-radical hypothesis of reperfusion injury. Unsaturated fatty acids esterified into lipids are the major components of cell membranes susceptible to oxidation by oxygen free radicals. Peroxidation of these membrane lipids has been shown to result in increased membrane permeability [2], decreased calcium transport into sarcoplasmic reticulum [3],

altered mitochondrial function [4], and formation of toxic metabolites, which may further impair cardiac function [5]. Del Maestro has suggested that disease states such as ischemia/reperfusion could well be modified by increasing intracellular scavenging potential [6]. The use of liposomes to deliver a hydrophilic scavenger (SOD) into the intracellular space has recently been reported by Freeman et al. [7].

Indirect support for the hypothesis that oxygen free radicals are at least in part responsible for vascular permeability changes has been obtained in the studies of small-bowel ischemia by Parks and Granger [8]. Pretreatment with superoxide dismutase significantly attenuated the increased capillary permeability induced by ischemia. Slafer et al. reported improved preservation of contractile function when the combination of SOD and catalase were added to a crystalloid cardioplegic solution in a non-blood-perfused preparation [9]. These authors also reported, in a blood-perfused model, improved protection when SOD and catalase were included in both the cardioplegic solution and the reperfusate [10].

Roy and McCord recently demonstrated that the rate of interconversion of xanthine dehydrogenase to xanthine oxidase induced by ischemia was most rapid in the small intestine, with a half-time for conversion of 4 seconds. Importantly, heart demonstrated the next most rapid interconversion, with a half-time of 300 seconds, while liver, spleen, lung, and kidney all demonstrated half-times six times greater than the heart [11]. Hess and coworkers reported reduced calcium uptake rates by sarcoplasmic reticulum (SR) with no effect on ATPase activity when SR was exposed to free radicals and the pH was lowered to 6.4 [3]. At pH 7.0 depression of both calcium uptake and ATPase activity was shown to result when SR was exposed to oxygen free radicals, and this depression was totally reversible by SOD. In contrast, at pH 6.4 the hydroxyl radical scavenger, mannitol, was required, in addition to SOD, for reversal. These authors concluded that excitation contraction uncoupling observed in postischemic myocardium might be explained by an interaction between hydrogen ions and oxygen free radicals. Following hypothermic ischemia, these authors were able to demonstrate similar depression of calcium uptake without depression of ATPase activity [12]. Administration of arachidonic acid and prostaglandin G_2 have also been shown to reduce SR calcium uptake and ATPase activity at pH 7.0. These effects were also reversible by SOD pretreatment [13]. At pH 6.4 the combination of SOD and mannitol were again required.

Guarnieri and coworkers recently demonstrated that α-tocopherol attenuated the deleterious effects of hypoxic perfusion followed by reoxygenation in isolated Langendroff-perfused rabbit hearts [14]. Infusion of α-tocopherol acetate reduced depletion of ATP and phosphocreatine, deterioration of mitochondrial function, and leakage of myocardial enzymes, presumably by exerting membrane stabilization and antioxidant effects during hypoxia and reoxygenation, respectively.

Xanthine, hypoxanthine, and inosine have been found to accumulate during periods of myocardial ischemia as ATP is stepwise degraded. Oxidation of both hypoxanthine and xanthine by xanthine oxidase results in the generation of superoxide anions, providing an additional source of oxygen free radicals. Allopurinol, a specific inhibitor of xanthine oxidase, has been shown to reduce myocardial injury following postischemic reperfusion and reoxygenation [15], although these authors attributed the beneficial effects to another mechanism, that is, to prevention of irreversible loss of nucleotide bases.

Exogenously administered superoxide dismutase would not be expected to enter cells. However, it is possible that damage to myocardial cells could occur by free-radical attack on their exterior cell surfaces. Phago-cytically active granulocytes could release superoxides into the extra-cellular space [16]. Furthermore, the extracellular space is nearly devoid of superoxide dismutase [17]. Thus, administration of exogenous enzyme might be expected to exert beneficial effects extracellularly, in vivo, or in vitro with whole-blood perfusion where granulocytes are prevalent. Release of oxygen free radicals by cellular lysis into the extracellular space would allow attack on the external surfaces of adjacent cells, providing a possible meahanism of benefit for SOD in non-blood-perfused preparations [8, 9, 18]. Furthermore, since xanthine oxidase has been shown to be in highest concentration in vascular endothelial cells [19], exogenously administered SOD could react at the vascular interface to prevent free-radical-induced damage.

Activities of intracellular free-radical scavenging enzymes could also decrease during hypoxia or ischemia, making cells even more vulnerable to damage by oxygen free radicals generated by mitochondrial respiration and/or xanthine-oxidase-catalyzed reactions following reoxygenation. Guarnieri et al. demonstrated a decrease in both superoxide dismutase and glutathione peroxidase activity in Langendorff-perfused rat hearts subjected to 80 minutes of hypoxic perfusion [20].

Electron paramagnetic resonance (EPR) spectroscopy has been used for many years to measure free radicals in basic chemical systems. We have recently begun to employ EPR spectroscopy to measure, quantitate, and characterize free radical generation in normal, ischemic, and postischemic hearts. Experiments were performed using the isolated isovolumic Langendorff-perfused, rabbit-heart model. We examined hearts that were freeze clamped at 77°K after either 10 minutes of stable function; 10 minutes of normothermic, global 37°C ischemia; or 10 minutes of normothermic ischemia followed by 10 seconds of reflow with oxygenated perfusate [21]. All of these hearts initially exhibited a developed pressure of 130 ± 10 mmHg. The EPR spectra of these hearts exhibit three different signals with different power saturations and temperature stability: Signal 1 was isotropic with a g value of 2.004, consistent with a carbon centered free radical; signal 2 was anisotropic with axial symmetry and $g_{11} = 2.033$ and $g_1 = 2.005$, consistent with an oxygen centered radical; signal 3 was an isotropic triplet with $g = 2.000$ and hyperfine splitting of 24 G,

consistent with a nitrogen-centered free radical. In control hearts, only signal 1 was observed. In ischemic hearts, signal 1 decreased in intensity but signals 2 and 3 appeared. In reflowed hearts, all three signals markedly increased in intensity. Following reflow with N_2-equilibrated perfusate, all three radical signals were unchanged from the intensities observed at the end of ischemia. A subsequent time-course study demonstrated maximum free-radical concentrations 10–30 seconds following oxygenated reflow. These experiments directly demonstrate the generation of the reactive oxygen-derived free radicals following reperfusion of ischemic hearts.

We have also begun to study specific interventions designed to scavenge free radicals generated by reoxygenation in an attempt to reduce peroxidative damage to cellular membranes. To test the hypothesis that membrane damage related to superoxide anions generated at reflow could be reduced by exogenous administration of the specific enzyme catalyzing the dismutation reaction, recombinant human superoxide dismutase (h-SOD), produced by genetic engineering, was administered to eight Langendorff-perfused rabbit hearts as a bolus of 60,000 IU just prior to reflow, followed by 40,000 IU infused during the first 15 minutes of reflow, followed by 30 minutes of normothermic global ischemia [22]. Nine control hearts received a bolus of perfusate prior to reflow, followed by 45 minutes of standard normothermic reperfusion. ^{31}Phosphorus nuclear magnetic resonance was employed to monitor ATP and phosphocreatine (PCr) contents during ischemia and following reflow, with data expressed as percent of the preischemic control value. Recovery of systolic ventricular function was assessed by isovolumic developed pressure, and diastolic function was by measured isovolumic end-diastolic pressure. At the end of 30 minutes of normothermic ischemia, ATP content had fallen to 33 ± 6% and 34 ± 4%, and PCr content to 10 ± 5% and 8 ± 3% of control in SOD and untreated hearts, respectively. Following 45 minutes of reflow, although the ATP content was not significantly different, the PCr content was very different, with 93 ± 9% of control in SOD-treated hearts but only 69 ± 7% of control in untreated hearts, ($p < .05$). Furthermore, developed pressure recovered to 71 ± 6% of control for SOD-treated hearts versus 47 < 5% for untreated hearts ($p < .01$); likewise, end-diastolic pressure returned to 27 ± 4% mmHg and 48 ± 7 mmHg for SOD-treated and control hearts, respectively ($p < .01$). These data clearly demonstrate that the severity of the ischemic insult, as quantitated by the degree of fall in ATP and PCr during the ischemic period, was equal, yet hearts receiving SOD just prior to and during early reflow recovered substantially better systolic and diastolic functions as well as higher myocardial PCr contents. Thus, SOD would appear to provide a means of reducing an oxygen-radical-mediated component of reflow injury.

Superoxide-dismutase-catalyzed dismutation of superoxide radicals will lead to increased formation of hydrogen peroxide, which could potentially cause myocardial damage. To determine whether catalase, an enzyme capable of scavenging hydrogen peroxide, is beneficial when added to treatment with

SOD, 36 Langendorff-perfused rabbit hearts were subjected to 30 minutes of normothermic (37°C) total global ischemia [23]. At the time of reperfusion, 12 hearts received 60,000 IU of recombinant human SOD (h-SOD) as a bolus followed by 100 IU/ml for 15 minutes; 12 hearts received h-SOD + 60,000 IU of catalase as a bolus followed by 100 IU/ml of both enzymes for 15 minutes; and 12 hearts received a bolus and 15 minutes of normal perfusate. All hearts then received standard perfusate for 30 additional minutes. The three groups of hearts demonstrated equal falls in ATP and PCr content by the end of 30 minutes of ischemia (Ns among groups). In contrast, at the end of reflow, h-SOD-treated hearts recovered 68 ± 6% of control developed pressure, h- SOD plus catalase treated hearts recovered 66 ± 6%, and untreated hearts developed 48 ± 4% of control ($p < .05$ versus both groups of treated hearts). Likewise, PCr content recovered 88 ± 8% in h-SOD treated, 83 ± 6% in h-SOD plus catalase treated, and only 65 ± 5% in control (untreated) hearts ($p < .05$ versus both groups of treated hearts). These data indicate that despite compariable depletion of ATP and PCr content by the end of the ischemic period, recovery of ventricular function and PCr content was equally improved in h-SOD and h-SOD + catalase-treated hearts compared to untreated control hearts. Thus, while h-SOD administration alone resulted in a significant reduction in reflow injury, catalase provided no additional benefit. These results would suggest either that the hydrogen peroxide generated by SOD is not harmful or that endogenous mechanisms are capable of scavenging the quantities of hydrogen peroxide generated by the dismutation reaction.

Ambrosio and Becker recently demonstrated, in an intact dog model, a 36% reduction in infarct size expressed as a fraction of the area of myocardium at risk [24]. These investigators began the administration of h-SOD with a bolus just prior to reflow and then followed it with a 1-hour infusion. These results would appear to confirm, in a blood-perfused regional ischemic model, our studies described above, which utilized a non-blood-perfused globally ischemic rabbit-heart model.

In summary, we feel that evidence is accumulating that strongly supports a free-radical-mediated component of reperfusion injury, which is largely prevented by the timely administration of a free-radical scavenger such as SOD. Whether such an intervention will prove clinically useful in the setting of thrombolysis in acute myocardial infarction or in the cardiac surgical setting remains to be determined in carefully controlled randomized clinical trials.

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4. PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY IN ACUTE MYOCARDIAL INFARCTION

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During the last five years, there has been a striking change in the early management of acute myocardial infarction. This results from several hemodynamic investigations that clearly established that thrombosis [1–2] plays a major role in this disease. Both early and late mortality of patients after myocardial infarction is mainly related to the degree of dysfunction of the left ventricle, which in turn depends on the size of the initial infarct. Therefore, it has been attempted to obtain immediate reperfusion of the infarction myocardium. Immediate thrombolytic therapy is a rational mean of achieving early reperfusion. Several thrombolytic agents are now available and can be administered by either the intracoronary or intravenous routes. However, after successful thrombolysis residual high-grade obstruction often persists at the site of the previous occlusion and could be responsible for continued myocardial ischemia and/or reocclusion. Therefore, percutaneous transluminal coronary angioplasty (PTCA) was proposed after successful thrombolysis. Later on, the ability to perform this technique in patients with acute myocardial infarction led several investigators to try percutaneous transluminal coronary angioplasty as the primary approach to reperfusion of the myocardium. Thus, we will address the problem of PTCA preceded by thrombolysis and primary PTCA in patients with acute myocardial infarction.

SECONDARY PTCA AFTER THROMBOLYSIS

Thrombolysis can be performed by intracoronary or intravenous infusion; the strategy for secondary coronary angioplasty is slightly different in these two situations.

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Intracoronary thrombolysis

Intracoronary infusion of streptokinase results in recanalization of approximatively 75% of completely occluded infarct-related vessels (table 4–1). However after reperfusion, the coronary angiogram shows a residual atherosclerotic narrowing.

This residual stenosis is certainly the cause of reocclusion, which is observed in 17% to 45% of the recanalized vessels restudied by angiography within the first 3–4 weeks. Reocclusion of coronary arteries after recanalization by an intracoronary thrombolytic agent has been associated with reinfarction and death [4]. Therefore, it seemed logical to maintain and augment flow to the reperfused myocardium. Thus, bypass surgery or angioplasty has been proposed [10–11]. Meyer [12–14] was the first person to perform PTCA in 21 patients who had been successfully treated with intracoronary streptokinase. This group was compared with a second group of 18 patients who were angiographic candidates for PTCA but were not treated. The clinical course of this latter group was similar to the usual course of patients with a relatively severe myocardial infarction: 3 died, only 44% were in class II, and 4 underwent surgery. However, PTCA was successful in 17 patients, and all patients were in class II. Four patients with an unsuccessful PTCA procedure were operated on and two developed reinfarction.

Table 4–2 shows the results obtained in patients treated with intracoronary streptokinase followed by coronary angioplasty.

These studies emphasize the role of coronary angioplasty after intracoronary thrombolysis. After reperfusion by streptokinase, a residual stenosis persists. In a few cases, the narrowing is nonsignificant and should not be dilated. Most often, a severe residual stenosis persists. Harrison et al. [18] demonstrated in 1984 that rethrombosis of the vessel is in fact related to the size of the residual lesion immediately after reperfusion. Vessels with residual stenotic cross-sectional areas less than 0.4 mm^2 are at high risk for reocclusion, whereas vessles with normal cross-sectional areas greater than 0.4 mm^2 are unlikely to develop rethrombosis. However, Cribier et al. [19] showed that the severity of

Table 4–1. Recanalization and reocclusion rates after intracoronary thrombolysis

Author		n	Total occlusion	Recanalization	Short-term reocclusion
Serruys [3]	1982	83	64 (77%)	41/64 (64%)	5/34 (14%)
Serruys [20]	1983	105	89 (84.7%)	64/89 (72%)	11/64 (17%)
Gold [4]	1983	40	40 (100%)	28/40 (70%)	5/22 (22.7%)
Cribier [5]	1983	80	74 (92%)	39/61 (64%)	10/38 (26%)
Kennedy [6]	1983	134	108 (80%)	73/108 (68%)	– –
Ferguson [7]	1984	77	65 (84%)	34/65 (52%)	7/34 (20.5%)
Leiboff [8]	1984	55	43 (78%)	15/22 (68%)	5/11 (45%)
Rentrop [9]	1984	62	43 (67%)	32/43 (74%)	4/24 (17%)
French Coop. Study	1985	564	510 (90.4%)	375/510 (73%)	(19.1%)

Table 4–2. PTCA after intracoronary thrombolysis in patients with total occlusion or residual stenosis

	Total occlusion		Residual stenosis	
	n	Primary success	n	Primary success
Serruys [20]			18	18 (100%)
Hartzler [30]	52	46 (88%)	26	24 (92%)
Valeix [16]			9	9 (100%)
Gold [15]	16	11 (69%)	12	9 (75%)
Papapietro [31]	7	4 (57%)	11	9 (82%)
Erbel [17]			63	46 (73%)
Total	75	61 (82%)	129	95 (80%)

residual stenosis is time dependent. Thus, the reduction of luminal diameter (75 ± 19% after successful thrombolysis) decreased to 63 ± 17% 10 days later and even reached 43 ± 21% when a third coronary angiogram was performed 3 months later. With quantitative coronary angiography, Serruys et al. [20] demonstrated that coronary angioplasty was recommended when the degree of residual stenosis reached 58%. Although percutaneous transluminal coronary angioplasty has most often be used after recanalization with streptokinase, it has also be suggested to attempt mechanical recanalization with a balloon catheter when streptokinase fails to open the occluded vessel [21–23].

Intravenous thrombolysis

The reality that most hospitals do not have catheterization laboratories on duty 24 hours and the recognition of the economic and logistic impediments to emergency catheterization have stimulated a reevaluation of IV thrombolysis that was first proposed 25 years ago. Moreover, several studies showed that in many instances reperfusion could be achieved more quickly with IV administration than with the intracoronary route.

Today, a certain number of large studies (GISSI, ISAM, ISIS-2 studies) [21–24] have clearly established the benefits of IV thrombolysis: 1) The reperfusion rate is 31%–62% with streptokinase, 45%–62% for r-tPa, and 51%–64% with APSAC. 2) The mortality rate decreases by 12% to 42% and can even reach 52% with APSAC in the AIMS study.

Whatever the drug intravenously infused, the fear of early reocclusion/reinfarction is still present, and the possibility that PTCA might be a useful adjunct to IV thrombolysis has been investigated. In this matter, four large trials have clearly addressed the problem. In the TAMI study [25], 197 patients who had patent infarct–related vessel 90 minutes after r-tPa were randomized to immediate PTCA or to deferred angioplasty if still indicated 7–10 days later. The reocclusion rate (11% vs. 13%), mortality (4% vs. 1%), LV ejection fraction and segmental wall motion were similar in both groups.

In the European Cooperative Study [26], 367 patients who had received 100 mg r-tPa within the first 5 hours were randomized to immediate coronary angiography and PTCA, if possible, or to conventional medical treatment and PTCA, only if indicated by clinical events. Mortality at 14 days was 1% in the PTCA group vs. 3% in the non-invasive group while recurrent ischemia within 24 hours occurred, respectively, in 17% and 3%. Hypotension, ventricular fibrillation and bleeding were more frequent with immediate PTCA. The TIMI IIA trial [27] indicated no benefit from 2 hours vs. 18–48 hours PTCA and a trend toward more frequent serious complications with the acute (2 hours) intervention.

More recently a large trial (TIMI IIB) [28], including 3,262 patients, compared "conservative" strategy vs. "invasive" strategy. Conservative strategy means that coronary angiography and PTCA, if possible, were only performed if spontaneous or provoked ischemia (exercise test, thallium scintigraphy) was demonstrated. In the other arm of the study, the patients had coronary angiography and PTCA, if suitable lesions, within 24–48 hours. In both groups, mortality or reinfarction rate was similar, but objective evidence of myocardial ischemia was significantly higher in the conservative group at discharge than in the other group. However, the comparative survival figures employed an "intention to treat" analysis of the data: Thus, 30% of patients assigned to "conservative strategy" crossed over to urgent PTCA or bypass. On the other hand, 30 of the 38 patients who died within the first 24 hours in the "invasive group" never had PTCA or coronary angiography. These studies provide evidence that immediate (24–48 hours) PTCA has no advantage over the policy of medical management and invasive therapy only if indicated by clinical events. Further studies comparing conservative strategy vs. delayed coronary angiography (7–8 days) and PTCA, if possible, are needed. Moreover, the results of the TIMI IIB trial do not mean that coronary angiography should not be performed within the hospitalization period: This investigation offers the opportunity to detect left main narrowing or severe triple vessel disease. In this latter case, is it better to dilate only the infarct-related vessel or to recommend bypass surgery if possible? Obviously, many new problems are now emerging and require further trials.

PRIMARY ANGIOPLASTY

Emergency penetration of a thrombus by a guidewire followed by PTCA may also be used as a primary approach (without previous thrombolysis) to reperfusion of the myocardium in patients with acute myocardial infarction. In a group of 78 patients treated with PTCA (70 successful PTCA), Hartzler et al. [29–30] performed successful coronary angioplasty without previous thrombolysis in 29 patients.

More recently, Rutherford and Hartzler [46] published a study of a large series of patients with acute myocardial infarction treated by primary PTCA. One hundred and seven patients had anterior myocardial infarction, and 115

patients had inferior myocardial infarction. PTCA was performed 1–24 hours following the onset of symptoms. Sixty percent of the patients had total occlusion of the infarct-related vessel and 40% had severe stenosis. Initial successful PTCA was achieved in 203 patients (91%), and the total in-hospital mortality was 7%. Twenty-three patients (10%) reoccluded the infarct artery and six developed early restenosis in the post-PTCA period. At a mean period of 10 days, 81% of dilated arteries remained patent, and in these patients the mean ejection fraction improved from 47% prior to PTCA to 59% after PTCA.

In table 4–3, are listed other results published in the literature. It is clear that primary angioplasty offers a number of potential advantages over thrombolysis:

1. PTCA is certainly the most effective initial treatment for rapidly restoring coronary flow. Pepine et al. [39] stated that PTCA recanalized the artery within 20 minutes of introduction of catheters. In the French Cooperative study [40], patients were treated 2 hours after the onset of symptoms (range, 30 minutes to 5 hours) and the mean duration of the procedure was 30 minutes. Caster et al. [40] recanalized infarct-related vessels within 14 to 50 minutes.
2. When an infarct-related artery is totally occluded, PTCA achieves the most complete treatment of both the thrombus and the atherosclerotic plaque. A high success rate is observed and averages 92.8% [29, 31, 47–52].
3. Residual stenosis is less significant after immediate PTCA than after streptokinase: 49% versus 85% in the series of O'Neill [53].
4. Primary PTCA avoids the hemorrhagic complications of thrombolytic therapy.
5. The procedure is relatively safe and does not require surgical backup. In-hospital mortality is 6.3% (range, 0% to 9.7%)
6. The rate of reocclusion is roughly 13.5% (range, 0% to 22.2%) of the patients who have been angiographically restudied. In the randomized

Table 4–3. Primary coronary angioplasty in acute myocardial infarction

	n	Primary success	Mortality	Reocclusion
Hartzler [29]	29	29/29 (100%)	7.7%	9.7%
Rutherford [46]	222	203/222 (91%)	7%	10%
Holmes [52]	11	10/11 (91%)	?	?
Kalbfleish [51]	15	14/15 (93.3%)	1 (6.6%)	0%
Pepine [47]	7	7/7 (100%)	0	?
Valeix [48]	22	18/22 (82%)	2 (9.1%)	17.6%
O'Neill [53]	23	18/23 (78%)	?	?
Caster [50]	41	38/41 (93%)	4 (9.7%)	22.2%
Rothbaum [54]	75	67/75 (89%)	5 (6.3%)	7/46 (15%)

studies of Holmes [52], the patency rate was significantly highly in the group treated with PTCA alone than in the group treated with streptokinase. However, in the randomized series of O'Neill [53], the rate of reocclusion was similar. The late followup showed that at 6.6 months in the series of Hartzler [29], 91% of the patients were symptomatic. However, in the series of Caster [50] and in the French cooperative study [48], only 63% of patients were free of symptoms.

Kander [55] showed that successful PTCA during acute myocardial infarction improves 6-month survival, while Arie [56] concluded that PTCA was effective in improving both early and late ventricular function.

In true cardiogenic shock, emergency PTCA associated with thrombolysis and intraaortic balloon pumping was able to decrease the mortality rate up to 30%, a rate never obtained with any other treatment (IABP, CABG, etc.) [57–60]. However, there are no randomized trials comparing emergency primary PTCA vs. intravenous thrombolysis in acute myocardial infarction.

CONCLUSIONS

Over the past three years, several studies have clarified the exact role of coronary angioplasty in the management of acute myocardial infarction. PTCA in patients with acute MI could be considered in the following conditions:

1. Primary emergency PTCA combined with intravenous thrombolysis is the first choice treatment of true cardiogenic shock.
2. Primary PTCA could be considered in patients admitted within the first four hours of MI and who had absolute contraindications to lytic therapy.
3. After IV thrombolysis:
   3.1. Coronary angiography should be done on emergency or semi-emergency basis if recurrent episodes of myocardial ischemia occurred. In this particular group of patients, PTCA will be performed if there are suitable lesions of the infarct-related vessel.
   3.2. In the absence of new events within the hospitalization period, the detection of myocardial ischemia with exercise test or tomographic thallium scintigraphy and coronary angiography will select those patients who require myocardial revascularization with PTCA or bypass surgery.

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5. THE ROLE OF EMERGENCY BYPASS SURGERY IN ACUTE MYOCARDIAL INFARCTION

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A number of interventions have been proposed to reduce myocardial damage following acute myocardial infarction, primarily by improving the balance between myocardial oxygen supply and demand. Experimental studies have demonstrated that increasing the oxygen supply by reperfusion can result in the salvage of substantial myocardium and that this is more effective than pharmacologic techniques aimed at reducing oxygen demands. Despite a large experience in animals that has defined the time limits for successful reperfusion, the precise limits in humans have not been determined. While reperfusion in animals following acute occlusion of a coronary artery must be carried out within 1–2 hours to salvage substantial myocardium, the presence of collateral circulation to areas of myocardium at risk in humans, as well as the occurrence of subtotal occlusions, may permit successful reperfusion for up to 6–8 hours, or even longer, after the onset of symptoms of acute myocardial infarction. For this reason, emergency coronary artery bypass grafting has been evaluated as a method to establish immediate reperfusion to the ischemic zone. It provides the additional theoretical advantage of permitting simultaneous revascularization of areas of jeopardized myocardium remote from the area of infarction. In this chapter, the role of emergency surgical revascularization in several clinical settings of acute myocardial infarction is reviewed.

CURRENT INDICATIONS AS PRIMARY THERAPY FOR ACUTE MYOCARDIAL INFARCTION

The relative safety and effectiveness of emergency myocardial revascularization was demonstrated by several groups in the early era of coronary artery

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bypass grafting [1–4]. More recently, extensive experience with emergency bypass surgery for acute myocardial infarction has been accumulated at two centers. DeWood et al. [5] performed emergency revascularization within 24 hours of the onset of symptoms in 701 patients during a 10-year interval. Among 440 patients with transmural infarction, hospital mortality was 5.2% (23 patients), and among 261 patients with nontransmural infarction hospital mortality was 3.1% (8 patients). For patients with transmural infarction, the hospital mortality was highest, 9% for those with three-vessel disease, and was also influenced by the timing of the operation, being 3.8% for 291 patients operated upon within 6 hours and 8% for 149 patients operated upon more than 6 hours after the onset of symptoms ($p = 0.05$). The presence of preoperative cardiogenic shock was an important determinant of hospital death among the patients with transmural infarction and was associated with a hospital mortality of 28%. Hospital mortality in the absence of preoperative cardiogenic shock was 2.8%. Phillips et al. [6] observed a hospital mortality of 2.6% (4 patients) among 160 patients undergoing primary surgical revascularization within 36 hours after the onset of symptoms. All four patients were in cardiogenic shock preoperatively. The time from the onset of symptoms to the operation was not a determinant of operative risk.

Although the safety of emergency coronary artery bypass grafting following acute infarction, particularly in the absence of cardiogenic shock, has been conclusively demonstrated, uncertainties regarding the role of surgery as the primary intervention for acute myocardial infarction remain. It has not been conclusively shown that surgical reperfusion within the time frames of these two studies (up to 24–36 hours) results in salvage of significant myocardium at risk and preservation of ventricular function. Comparison of the results of bypass grafting in this series with conventional medical therapy is difficult because of the absence of preoperative data that provide important prognostic information (i.e., severity of left ventricular dysfunction). Patients were selected for surgical therapy in a nonconsecutive, nonrandom manner, and certain subgroups were "not recruited aggressively" [5]. Thus, it is likely that patients with a more favorable prognosis may have been selected for operative therapy. Furthermore, the cost effectiveness of surgical intervention in comparison with other forms of therapy is unknown. The efficacy of emergency myocardial revascularization in comparison with other forms of therapy can only be determined by randomized clinical trials.

Following thrombolytic therapy and angioplasty

With the emergence of thrombolytic therapy with or without associated coronary artery angioplasty (PTCA) as an effective form of treatment for acute myocardial infarction, the role of surgical revascularization has been evaluated at varying time intervals following infarction and thrombolysis. Skinner et al. [7] performed emergency coronary artery bypass grafting in 24 of 184 patients who received streptokinase therapy with or without PTCA within 6 hours of

the onset of chest pain. The patients were operated upon within 10 hours of the onset of symptoms because of failure of thrombolysis of a major vessel, failure of PTCA to relieve a critical stenosis following successful thrombolysis, occlusion of a coronary artery after PTCA, or continuing profound cardiac decompensation refractory to medical management. Hospital mortality was 25% (table 5–1). The majority of deaths occurred in patients with profound cardiac decompensation preoperatively. Severe preoperative left ventricular dysfunction was also an important determinant of operative risk. Postoperative bleeding was substantial, and an average of 8.2 units of blood per patient were transfused perioperatively. These authors no longer attempt emergency revascularization in this setting unless a stable hemodynamic state can be obtained preoperatively.

A more selective approach with delayed coronary artery bypass grafting (CABG) has been evaluated in several centers [8–12] (table 5–1). The majority of the patients in these series underwent thrombolytic therapy within 4–6 hours after the onset of symptoms. CABG was performed from 1 to 90 days following infarction. Indications for operation included persisting symptoms, the presence of high-grade residual stenosis in arteries supplying both the involved and noninvolved areas, and hemodynamic or electrical instability. Hospital mortality with this selected approach did not exceed 3%.

Although CABG is technically feasible following thrombolytic therapy, its effectiveness in reducing infarct size and in preventing subsequent myocardial injury is not clearly established. In an attempt to identify those patients who will most likely benefit from early CABG following thrombolytic therapy, Krebber et al. [13] employed intracoronary thallium-201 scintigraphy before and after intracoronary thrombolysis to determine the extent of reperfusion, and correlated these findings with changes in left ventricular wall motion

Table 5–1. Coronary artery bypass grafting after thrombolytic therapy

	SK No. of Patients	CABG No. of patients	Onset symptoms to SK (hours)	Onset symptoms to CABG (days) mean (range)	Hospital mortality
EMERGENT					
Skinner et al. [7]	184	24	< 6	< 10 hours	25%
URGENT OR ELECTIVE					
Krebber et al. [8]	72	20	< 4	3.9 (1–12)	0
Messmer et al. [9]	84	17	< 4	* (1–11)	0
Wilson et al. [10]	136	51	< 7	16 (1–90)	0
Sterling et al. [11]	*	41	< 18	* (3–10)	2%
Wellons et al. [12]	184	106	< 6	3.3 (0–11)	3%

Abbreviations: SK = streptokinase; CABG = coronary artery bypass grafting; * = not stated.

Table 5–2. Comparison of sequential thallium scintigraphy and regional wall motion following intracoronary thrombolysis

	Regional Wall Motion (%)		
	Acute (mean ± SD)	Chronic (mean ± SD)	
Group 1: Unsuccessful thrombolysis no thallium uptake (n = 5)	19.9 ± 11.8	16.5 ± 12.6	NS
Group 2: Successful thrombolysis, no or poor thallium uptake (n = 6)	19.1 ± 11.1	17.3 ± 10.0	NS
Group 3: Successful thrombolysis, good thallium uptake (n = 12)	20.1 ± 8.7	51.4 ± 18.3	< 0.05

NS = not statistically significant, $p > 0.05$. From Krebber et al. [13] with permission.

obtained from ventriculograms early and 2–4 weeks following therapy. Among 11 patients with unsuccessful (5) or successful (6) thrombolysis but with no or poor thallium uptake, no improvement in regional wall motion was observed (table 5–2). Among 12 patients with successful thrombolysis and good thallium uptake (>50% reduction of the initial defect), a significant improvement in wall motion was observed. They concluded that patients with evidence for substantial reperfusion following thrombolysis in areas where residual high-grade coronary artery obstructions exist would be optimal candidates for early CABG to prevent loss of additional myocardium from subsequent reocclusion.

Using gated blood-pool imaging techniques to determine the global ejection fraction, Sterling et al. [11] observed a significant improvement in the mean ejection fraction following thrombolytic therapy in patients in whom reperfusion occurred. Subsequent CABG did not increase ejection fraction beyond the level achieved after thrombolysis (table 5–3). Among patients in whom reperfusion did not occur, no increase in ejection fraction was observed

Table 5–3. Global ejection fraction following thrombolytic therapy and coronary artery bypass grafting

		Ejection fraction (%) (mean + SD)		
	No. of patients	Admission	After thrombolytic therapy	After coronary bypass grafting
Reperfusion	28	38 ± 14	47 ± 13[a]	44 ± 16[b]
No reperfusion	4	50 ± 17	50 ± 21[b]	46 ± 15

[a] $p < 0.001$ as compared to previous column. [b] Not statistically significant as compared to previous column. Modified from Sterling et al. [11] with permission.

following lytic therapy or CABG. These results and those of Krebber et al. [13] suggest that CABG after thrombolysis will not result in a further reduction of infarct size and an improvement in left ventricular function.

Harrison et al. [14] have shown that the severity of the residual stenosis following thrombolytic therapy is an important determinant of rethrombosis. Using quantitative coronary angiography, they found that patients with a minimal residual cross-sectional area of less than 0.4 mm^2 in the involved vessel had a high incidence of rethrombosis (7 of 12 arteries) 8–14 days after streptokinase. In contrast, none of 12 patients with cross-sectional areas greater than 0.4 mm^2 had rethrombosis ($p < 0.005$). Seven of 14 patients with a percent area stenosis greater than 90% had rethrombosis, while none of the 10 with lesions of less than 90% area stenosis had rethrombosis ($p < 0.001$). These data suggest that patients with high-grade residual obstructions following thrombolytic therapy should be considered candidates for revascularization, either by PTCA or CABG, to prevent reocclusion and subsequent infarction.

The definitive role of CABG following thrombolytic therapy for acute myocardial infarction remains to be determined. However, the available data permit some reasonable conclusions regarding the indications and contraindications for operation in this setting (table 5–4). Emergent operation should be considered when there has been failure of thrombolysis, failure of PTCA, occlusion of the artery after PTCA, or continued pain and electric or hemodynamic instability *if* reperfusion has been attempted within 4–6 hours and *if* there is a high probability that viable myocardium remains in the area of the occluded artery. The risk of operation in this setting will be substantial if cardiogenic shock or preexisting left ventricular dysfunction are present. Urgent or elective CABG should be considered for patients who have residual high-grade stenoses not amenable to angioplasty, continued instability, left-main or multiple-vessel disease, or preexisting left ventricular dysfunction. Hospital mortality will be low in this setting, except for patients with severe ventricular dysfunction. However, this group has a poor long-term prognosis with nonoperative therapy, and operation is advisable for most patients.

Table 5–4. Indications for coronary artery bypass grafting after thrombolytic therapy

EMERGENT		
Failure of thrombolysis		Reperfusion within 4–6 hours
Failure of PTCA	IF	Viable myocardium in area of occluded artery
Occlusion after PTCA		
Continuing instability		
URGENT OR ELECTIVE		
Residual high-grade stenoses		
Continuing instability		
Left-main or three-vessel disease		
Preexisting left ventricular dysfunction		

PTCA = percutaneous transluminal coronary angioplasty.

Persisting ischemia and recurrent infarction

Patients with evidence for myocardial ischemia following infarction are at increased risk for recurrent infarction and death in the months following the initial infarction [15–19]. Mortality in patients after recurrent infarction is substantially higher than for those without extension [17, 19]. Recurrent infarction occurs much more frequently following subendocardial (43%) than transmural infarction (8%) [19]. If cardiogenic shock occurs after infarction, the mortality with medical therapy approaches 80%–90% [20–24]. Patients with postinfarction angina are thus at high risk for both immediate and late complications, which include infarct extension, arrhythmia, cardiogenic shock, and death. Early revascularization by coronary artery bypass grafting or angioplasty offers the potential for prevention of infarct extension as well as salvage of myocardium at risk in areas remote from the infarction that are supplied by critically stenotic arteries.

The safety of urgent catheterization and coronary artery bypass grafting early after myocardial infarction have been demonstrated [25, 26]. The optimal timing for surgical intervention, however, is not clearly established. The initial reports of coronary artery bypass grafting early after myocardial infarction noted a substantial operative mortality [1–4]. More recently, Jones et al. [27] reported a series of 116 patients operated upon between 1 and 30 days following myocardial infarction with no hospital mortality. The majority of the patients had transmural myocardial infarction. The mean ejection fraction for the entire series was 0.55, suggesting that the majority of these patients had minimal impairment of ventricular function. Perioperative use of the intraaortic balloon was required in seven patients (6.1%). Perioperative infarction occurred in 4 of 80 patients (5%), with data suitable for analysis. Actuarial survival at 18 months was 97%. These results demonstrate that myocardial revascularization can be safely performed in patients following myocardial infarction in whom there is no severe left ventricular dysfunction. More recently, Hochberg et al. [28] evaluated the results of early myocardial revascularization after acute myocardial infarction in 174 patients. Overall hospital mortality was 16% and was directly related to the preoperative ejection fraction. All patients with an ejection fraction equal to or greater than 50% operated upon at any time after infarction survived the hospital course, with only one late death among 50 patients. Conversely, among the 124 patients with an ejection fraction less than 50% operated upon during a 7-week interval, there were 27 hospital deaths (22%). In the latter group, survival rates steadily improved if revascularization was performed at a time more remote from the infarction. The difference in mortality between these two groups was highly significant ($p < 0.001$). Hochberg concluded that in patients with a depressed ejection fraction early after myocardial infarction, the operation should be performed electively whenever feasible, preferably after a minimum of 4 weeks to allow healing of the infarction. Urgent revascularization will be required for patients with continued pain and hemodynamic or electric instability. Mortality in this group will be substantial. In a study by Roberts et al. [29], where medical therapy

was applied for 1–2 weeks following myocardial infarction and prior to bypass grafting, the ejection fraction following operation was depressed in the early postoperative period among those patients who had a transmural myocardial infarction as compared to those with a nontransmural infarction. Although no mortality was encountered with this delayed surgical approach in either group, the data suggest that left ventricular function will be further depressed postoperatively in patients who have sustained transmural myocardial infarctions. This provides further supportive evidence for attempts at stabilization of such patients prior to bypass grafting.

The effectiveness of coronary bypass grafting in patients with postinfarction angina, in comparison with continued medical therapy or with other interventions such as angioplasty, can be best evaluated by controlled randomized trials. Such information is currently lacking. Until such data become available, urgent revascularization in symptomatic patients with multivessel coronary disease and preserved ventricular function seems appropriate. It is our practice to defer operation whenever possible in patients with depressed ventricular function in order to reduce immediate mortality and morbidity.

In conjunction with repair of mechanical complications of myocardial infarction

Urgent surgery is frequently required for the mechanical complications of acute myocardial infarction, such as rupture of the ventricular septum, rupture of a papillary muscle, rupture of the ventricle, and resection of areas of acute infarction or ventricular aneurysms. The efficacy of adjunctive coronary bypass grafting in this setting is uncertain. The numbers of patients requiring surgical procedures for treatment of these complications is relatively small, and coronary bypass grafting has been inconsistently applied. We believe that, whenever possible, coronary arteriography should be carried out in all patients who sustain these complications of acute infarction. If major obstructions in the proximal segments of the three major coronary systems are identified, we perform CABG of the involved arteries at the time of repair or correction of the mechanical defect. Although our experience is small, we have not observed an increase in mortality or morbidity by addition of bypass grafting in this setting. Because of this and because CABG may prevent subsequent myocardial infarction, we continue to perform bypass grafting in this setting.

Following elective angioplasty

Emergency revascularization for complications of percutaneous transluminal angioplasty are required in 7%–18% of patients. [30–33] (table 5–5). Hospital mortality for these procedures has ranged from 0% to 6% following angioplasty for single-vessel disease and up to 11% for multivessel disease. Acute myocardial infarction has occurred in from 21% to 44% of patients. These mortality and morbidity rates are substantially higher than those observed for elective surgery in patients with similar degrees of coronary artery disease and left ventricular dysfunction [31, 32]. Thus, emergent operation is not totally

Table 5–5. Mortality and perioperative myocardial infarction following emergency operation for failed angioplasty

	No. of PTCA	No. with SVD	Emergent operation	Hospital mortality	Perioperative myocardial infarction
PTCA Registry [30] (1977–1982)	3079	75%	7%	6%	41%
Emory University [31] (1981)	338	92%	8%	0	21%
Texas Heart Institute [32] (1977–1983)	518	> 50%	14%	6%	33%
Mid-America Heart Institute [33] (1980–1984)	3000	25%	4%	11%	44%

Abbreviations: PTCA = percutaneous transluminal angioplasty; SVD = single-vessel disease.

effective in preventing the loss of substantial myocardium following an emergent operation after failed angioplasty. The incidence of postoperative complications, such as hemorrhage and sternal problems, is substantially higher than in patients undergoing elective surgery.

SUMMARY

Although studies carried out in the last 5 years have generated important information on the effectiveness of invasive interventions, including emergency bypass grafting, in limiting myocardial infarct size, additional data must be acquired before definitive conclusions regarding the role of these interventions in the treatment of acute myocardial infarction can be made. The results of emergency surgical revascularization to date indicate that the procedure can be safely applied to selected subsets of patients following myocardial infarction. Perioperative mortality and morbidity rates for the procedures are higher than those encountered in patients without acute infarction, but may be less than those observed with other forms of therapy for acute infarction, and the long-term benefits may be significant. If salvage of substantial myocardium can be conclusively demonstrated when CABG is the primary intervention for acute myocardial infarction or following thrombolytic therapy, then emergency surgical revascularization will assume an even larger role in the management of patients with acute infarction. As with other techniques for early reperfusion, such as thrombolytic therapy and angioplasty, which are currently undergoing intensive evaluation, the ultimate role of coronary artery bypass grafting in the management of acute myocardial infarction will best be determined by controlled randomized trials.

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6. THE ROLE OF NITROGLYCERIN IN ACUTE MYOCARDIAL INFARCTION

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Since Murrell's initial description in 1879, sublingual nitroglycerin has been the cornerstone of therapy for angina pectoris [1]. Long-acting oral forms of nitroglycerin and cutaneous nitroglycerin ointment have been used prophylactically to prevent anginal attacks for more than 25 years. As recently as 1966, Friedberg's *Textbook of Cardiology* warned that nitroglycerin was contraindicated in patients with acute myocardial infarction [2]. Using careful electrocardiographic and blood-pressure monitoring, cardiologists at The Johns Hopkins Hospital began studying the short-term hemodynamic and antiischemic effects of intravenous nitroglycerin in patients with acute myocardial infarction more than 15 years ago [3–6]. We have also completed a randomized placebo-controlled trial of 48-hour infusion of intravenous nitroglycerin in patients with acute infarction. The endpoints of this longer term study were "infarct size" and clinical outcome [7].

Based on our extensive clinical experience with the intravenous administration of nitroglycerin, this chapter will concentrate on the clinical use of intravenous nitroglycerin in acute myocardial infarction as well as in post-infarction unstable angina. Since 1981 intravenous nitroglycerin has been available for general clinical use. The initial indications approved by the FDA included 1) unstable angina, 2) left ventricular failure complicating acute myocardial infarction, 3) perioperative hypertension complicating cardiac surgery, and 4) controlled hypotension during noncardiac surgery (table 6–1).

The following pages will review 1) the pharmacology of intravenous

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Table 6–1. Clinical uses of intravenous nitroglycerin

Current uses approved by the Food and Drug Administration:
1. Ustable angina
2. Congestive heart failure complicating acute myocardial infarction
3. Perioperative control of blood pressure in patients undergoing coronary artery bypass surgery
4. Controlled hypotension on during noncardiac surgery

nitroglycerin, 2) hemodynamic responses in patients with acute myocardial infarction to short-term infusion, 3) results of our published clinical trial reporting on longer term infusion in patients with acute myocardial infarction, 4) clinical studies from other institutions utilizing intravenous nitroglycerin to reduce "infarct size," 5) contrasting hemodynamic and intercoronary collateral flow effects of nitroglycerin and nitroprusside, 6) results of two recently published clinical trials of nitroprusside in acute myocardial infarction, 7) the pathophysiology of unstable angina and the role of intravenous nitroglycerin in the management of postinfarction unstable angina, and 8) the limitations, adverse reactions, and contraindications to intravenous nitroglycerin therapy.

INTRAVENOUS NITROGLYCERIN IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

We have been administering intravenous nitroglycerin to patients with acute myocardial infarction with the goal of reducing the severity of regional myocardial ischemia and, when possible, improving left ventricular function since 1972. Since by lowering coronary perfusion pressure, ischemia could potentially be made worse rather than better, ST-segment changes were monitored using precordial ST-segment mapping. In our initial study only a lowering (7 mmHg or 7%) of mean blood pressure was induced. In all patients a reduction in the sum of the ST-segment voltages during short-term (1–3 hour) infusion of nitroglycerin was documented [3].

Based on our initial favorable results, we began to administer higher infusion rates, which resulted in a 15–30 mmHg reduction of mean arterial pressure [4]. Again, reduction in the severity of regional ischemia was demonstrated in patients from all hemodynamic subgroups, irrespective of the presence or absence of left ventricular failure. At lower infusion rates, nitroglycerin appears to act principally as a venodilator, lowering left ventricular filling pressure while causing minimal lowering of mean arterial pressure. At higher infusion rates, nitroglycerin appears to provide more balanced venous and arterial dilating effects, resulting in little further lowering of left ventricular filling pressure but progressively greater lowering of mean arterial pressure or systemic vascular resistance. Beneficial effects on left ventricular hemodynamics were most marked in those patients with the most severe degree of left ventricular failure (figure 6–1). In the subgroup of patients without left ventricular failure, nitroglycerin resulted in a decrease in stroke

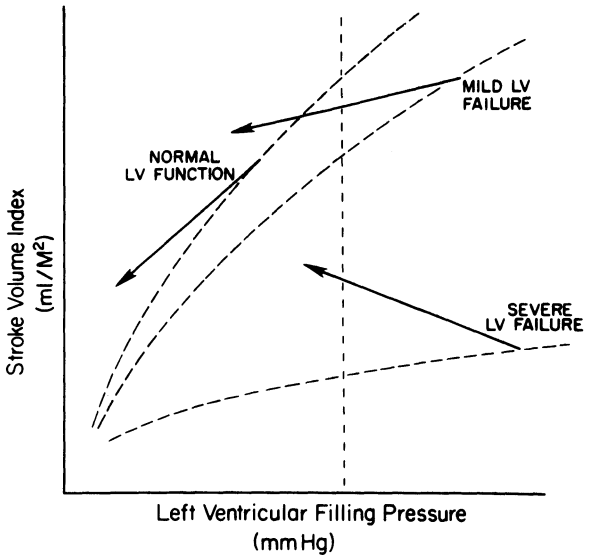

Figure 6–1. Hemodynamic effects of intravenous nitroglycerin in the presence and absence of left ventricular (LV) failure. Stroke volume index (ml/m^2) is plotted versus LV filling pressure (mmHg). The responses obtained with intravenous nitroglycerin for individual hemodynamic subgroups are indicated by arrows. A family of hypothetic Starling ventricular function curves are indicated by dashed curves with diminished contractility expressed by downward and rightward displacement of the curves. The vertical dashed line indicates an upper limit of normal for LV filling pressure.

volume and a decrease in the left ventricular filling pressure, most likely the result of predominant preload lowering or the "diuretic-like" effect induced by venodilation. In the subgroup of patients with mild left ventricular failure, as evidenced by an elevated left ventricular filling pressure and a normal stroke volume, a similar lowering of left ventricular filling pressure was observed. However, in these patients stroke volume was maintained, suggesting that nitroglycerin was inducing both venous and arterial dilation. Finally, in the subgroup of patients evidencing the most severe degree of left ventricular failure, maximally beneficial hemodynamic effects were observed. Left ventricular filling pressure was again lowered but, in contrast, stroke volume increased, compatible with a proportionately greater arterial dilating effect. Similar differential hemodynamic responses in patients with various degrees of left ventricular dysfunction have been reported for nitroprusside [8, 9]. The differential effects of vasodilators on stroke volume for a given lowering of peripheral vascular resistance are demonstrated in figure 6–2 for patients with normal left ventricular function and for patients with mild, moderate, or severe degrees of left ventricular failure. In our clinical studies of intravenous nitroglycerin in patients with acute myocardial infarction, while there were

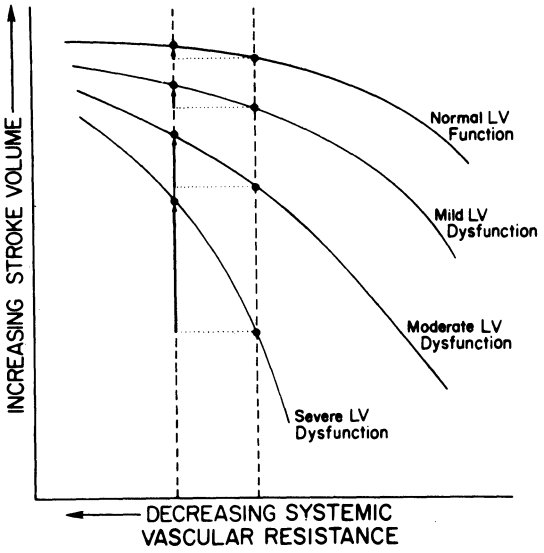

Figure 6–2. Differential effects of afterload reduction on stroke volume for a different hemodynamic subgroup. Curves shown are for patients with normal left ventricular (LV) function as well as for patients with mild, moderate, and severe degrees of LV failure. Vertical dashed lines indicate pretreatment (right) and posttreatment (left) levels of systemic vascular resistance (SVR). Vertical arrows indicate the magnitude of the increase in stroke volume index that would be expected from this given reduction in SVR for each hemodynamic subgroup.

differential hemodynamic responses in various hemodynamic subgroups, a beneficial antiischemic effect, as evidenced by a reduction in the sum of precordial ST-segment voltages, was observed in all hemodynamic subgroups.

In summary, short-term administration of intravenous nitroglycerin to patients with acute myocardial infarction resulted in an acute reduction in regional ischemica in all subgroups of patients. Patients with the most severe degree of left ventricular failure obtained the most positive hemodynamic response, demonstrating both a reduction in pulmonary venous congestion and an improvement in forward cardiac output. Careful upward titration of the infusion rate allowed these beneficial antiischemic and hemodynamic effects to be obtained without excessive lowering of coronary perfusion pressure and without inducing a reflex tachycardia. In fact, mean heart rates during intravenous nitroglycerin administration tended to be lower than controls, especially in the subgroup of patients with severe left ventricular failure.

Two subsequent clinical studies have been performed at Johns Hopkins to determine if the antiischemic effects of intravenous nitroglycerin could be augmented by the addition of 1) phenylephrine, which, by maintaining coronary perfusion pressure, might augment the antiischemic effects of nitrogly-

cerin or 2) propranolol, which, by adding negative inotropic and negative chronotropic effects, might further reduce myocardial oxygen demands. Adding phenylephrine resulted in not only a restoration of coronary perfusion pressure, but also a rise in left ventricular filling pressure and at the same time a reversal of the beneficial antiischemic effects obtained by nitroglycerin infusion alone [15]. Addition of propranolol also resulted in a reversal of the left ventricular filling pressure lowering obtained with nitroglycerin and, when the nitroglycerin infusion was discontinued, resulted in an increase in left ventricular filling pressure above control levels, especially in patients with underlying left ventricular dysfunction [6].

Based on the favorable results of our studies utilizing a short-term infusion of intravenous nitroglycerin, a randomized controlled prospective trial was undertaken to determine if longer term treatment would reduce infarct size [7]. Patients with acute myocardial infarction received a 48-hour infusion of either nitroglycerin or placebo followed by cutaneous application of nitroglycerin or placebo ointment for an additional 72 hours. Included in this study were patients with electrocardiographic changes suggestive of acute myocardial infarction, presenting within 12 hours of the onset of chest pain. Exclusion criteria included systolic blood pressure less than 95 mmHg, heart rate less than 55 beats/min, or age greater than 75 years. Also excluded were patients with severe hypertension from whom intravenous vasodilator therapy could not ethically be withheld, patients unable or unwilling to given informed consent, or patients with life-threatening diseases of other organ systems.

A control thallium-201 perfusion scan and a technetium-99m-labeled gated blood-pool scan were obtained prior to beginning the study drug infusion. A computer-assisted scoring technique yielded a thallium defect score that quantified the extent and severity of the pretreatment myocardial perfusion deficit [10]. The thallium defect score also provided an estimate of the total area at risk, including both infarcted and adjacent reversibly ischemic myocardium. The gated blood-pool scan provided a pretreatment left ventricular ejection fraction as well as pretreatment segmental wall motion. Two-dimensional echocardiography was also employed to assess the effects of nitroglycerin therapy on regional and global left ventricular function.

Infusion of nitroglycerin was begun at 5 μg/min to 10 μg/min, and the infusion rate increased in a stepwise manner until a 10% lowering of mean arterial pressure was obtained, as monitored with an ultrasonic blood-pressure cuff. Once this endpoint had been reached, the final infusion rate was continued for 48 hours, unless side effects or hemodynamic instability required reduction or discontinuation of the infusion. The mean infusion rate required to obtain the 10% lowering of mean arterial pressure was 90 μg/min. After 48 hours of intravenous therapy, the patients were begun on one inch of nitroglycerin ointment every 4 hours, and the dosage was increased until the arterial pressure previously obtained with intravenous therapy was reached. Control patients received placebo ointment every 4 hours. Seven to 14 days after study

entry a repeat thallium-201 myocardial perfusion scan and a gated blood-pool scan or a two-dimensional echocardiogram were obtained. Comparison of pretreatment and posttreatment myocardial perfusion and left ventricular function in nitroglycerin and placebo-treated patients allowed separation of the effects attributable to nitroglycerin from the effects attributable to time alone.

Fifty-six patients were randomized to receive nitroglycerin, and 48 patients received infusion of placebo. There were no significant differences in admission clinical, laboratory, or scintigraphic parameters between the nitroglycerin and placebo-treated groups. Treatment groups were then divided into early and late treatment subgroups, according to the time interval between the onset of chest pain and the initiation of treatment. Patients treated less than 10 hours from the onset of symptoms were defined as having been treated early, and those treated 10 hours or more after the onset of chest pain were defined as having been treated late. A cutoff at 10 hours was chosen because it divided the 56 nitroglycerin-treated patients into two equal subgroups. The mean time interval from the onset of chest pain to the initiation of therapy in the total population of 104 patients was also 10 hours.

Examination of clinical outcomes revealed a lower 3-month mortality in the early nitroglycerin treatment subgroup (14%), when compared with the other three treatment subgroups (21%–28%). The clinical outcomes of in-hospital death, infarct extension, and/or the development of new congestive heart failure were examined separately. While differences favored early nitroglycerin treatment, only the combined incidence of any one of these three unfavorable outcomes reached statistical significance ($p = .003$).

Patients with abnormal ejection fractions on admission receiving early treatment with nitroglycerin demonstrated a significant 11% improvement in left ventricular ejection fraction. Patients with initially abnormal ejection fractions receiving late treatment with nitroglycerin or early or late placebo treatment demonstrated no significant change. All patients with an initially normal ejection fraction (>50%) demonstrated a mean decrease in ejection fraction between day 1 and days 7–14 irrespective of treatment. It seems likely that admission ejection fractions were artificially increased by the high circulating catecholamine blood levels associated with acute myocardial infarction. Seven to 14 days later, in the absence of pain, and therefore with less catecholamine stimulation, a lower resting ejection fraction could be expected. Early nitroglycerin treatment also resulted in a greater number of patients showing a decrease in the number of akinetic or dyskinetic left ventricular segments.

We further analyzed the responses of left ventricular ejection fraction to treatment by dividing the patient responses into *responder*, *nonresponder*, and *neutral responder* categories. Responders were defined by an improvement in ejection fractions of 10% or more. In contrast, nonresponders were defined by an admission ejection fractions less than 50%, that failed to improve by 10% or more; or an ejection fractions that was initially normal (that is, greater than or equal to 50%) but fell more than 25%. Neutral responders had a normal

admission ejection fraction that increased less than 10% or decreased less than 25%. The majority of these neutral response consisted of small (2%–10%) reductions in ejection fraction, with the final ejection fraction remaining within the normal range. A significantly higher incidence of responders was noted among early nitroglycerin-treated patients compared with the other three treatment subgroups ($p = .004$).

Comparison of the pretreatment and posttreatment thallium perfusion defect scores revealed decreases in the mean defect scores of 10% to 60% in the four subgroups between day 1 and days 7–14. The greatest mean decreases were noted in early nitroglycerin- and early placebo-treated patients. Individual patient responses were again dividing into responder, nonresponder, and neutral response categories. A responder was defined by an admission thallium defect score of greater than 1.0 unit (i.e., above the normal limit) that decreased 75% or more. A nonresponder was defined by an initial defect score of greater than 1.0 unit that decreased less than 75% or actually increased or worsened. A neutral responder was defined by an initial thallium defect score of less than 1.0 unit (i.e., within the normal range) that remained less than 1.0 unit on followup scintigraphy. As with ejection fraction responses, there was a significantly higher incidence of thallium responders among early nitroglycerin-treated patients compared with the other three treatment subgroups ($p = .039$).

There were no significant differences in peak creatine-kinase blood levels or in creatine-kinase infarct size demonstrated among the treatment subgroups. However, creatine-kinase blood levels did tend to increase faster and peak earlier following early nitroglycerin administration, suggesting increased washout of these enzymes from infarcted myocardium. Precordial QRS mapping studies performed in patients with anterior infarctions did not reveal significant differences in the preservation of precordial R waves. However, nitroglycerin treatment did show an acute antiischemic effect, as evidenced by a greater reduction in the sum of precordial ST-segment voltages during the first 1–2 hours of nitroglycerin therapy compared to placebo treatment over the same time period. Adverse reactions, which included hypotension, headache, or nausea, were uncommon and for the most part were quickly reversed by reduction of the nitroglycerin infusion rate.

Retrospective examination of the characteristics of patients meeting thallium and/or ejection fraction responder criteria revealed that the most important factors were timing of treatment, admission thallium defect score, and admission ejection fraction. More than 80% of responders received treatment within 10 hours of the onset of chest pain. Responders also tended to have lower initial thallium defect scores and higher admission ejection fractions. Likewise, nonresponders tended to have higher initial thallium defect scores and lower initial ejection fractions. These patients with low admission thallium defect scores who were nonresponders had most often been treated more than 10 hours after symptom onset. Responders also tended to have a longer

duration of chronic stable angina and inferior, rather than anterior, transmural infarctions.

In summary, a higher incidence of significant scintigraphic improvement was observed when intravenous nitroglycerin therapy was initiated within 10 hours of the onset of symptoms of acute myocardial infarction. The longer mean duration of angina pectoris among responders might suggest that responders had better developed intercoronary collateral channels, which could allow beneficial effects of nitroglycerin on collateral flow to be manifested. The higher incidence of nonresponders among patients with large anterior transmural infarctions might be explained by a limited inability of collateral channels to significantly increase blood flow to the ischemic zone when the zone of myocardium at risk for infarction is very large.

That effects on collateral flow might be playing a major part in the reduction of "infarct size" with intravenous nitroglycerin was suggested by Jugdutt et al. [11]. Using an unanesthetized canine model of acute myocardial infarction, these authors demonstrated a 50% increase in intercoronary collateral flow and a 47%–50% reduction in infarct size with intravenous nitroglycerin therapy. In their experimental protocol, nitroglycerin was infused for 6 hours beginning 3 minutes after coronary artery ligation, using the titration end-point of a 10% lowering of mean arterial pressure, which was identical to that employed in our clinical trial.

OTHER CLINICAL TRIALS OF INTRAVENOUS NITROGLYCERIN IN ACUTE MYOCARDIAL INFARCTION

In addition to our study at Johns Hopkins, three other clinical trials have employed long-term infusion of nitroglycerin in an attempt to reduce infarct size (table 6–2). Bussman et al. studied 31 patients with acute myocardial infarction treated with intravenous nitroglycerin for 48 hours and 29 control patients not receiving nitroglycerin [12]. These authors included only patients with pulmonary artery diastolic or pulmonary capillary wedge pressures greater than or equal to 12 mmHg with transmural infarction, as evidenced by ST-segment elevation and the subsequent development of pathologic Q waves. Blood pressure was monitored noninvasively. Treatment was initiated 1.5–23.3 hours after the onset of symptoms of acute infarction (mean, 10.2 hours). Nitroglycerin was titrated to lower the pulmonary diastolic pressure while avoiding excessive lowering of arterial pressure. Nitroglycerin infusion rates of 12 μg/min to 100 μg/min were employed (mean 47 μg/min). Creatine-kinase (CK) infarct size was found to be 23% lower (44 $\pm$ 22 gEq vs. 57 $\pm$ 32 gEq) for nitroglycerin-treated versus control patients, respectively ($p < .05$). Similarly, CK-MB infarct size was also lower with nitroglycerin treatment compared with standard clinical management.

These authors also used a Swan-Ganz catheter, which allowed documentation of the hemodynamic effects of nitroglycerin as well as the spontaneous hemodynamic changes in control patients. Pulmonary artery diastolic pressure

Table 6–2. Clinical trials of intravenous nitroglycerin (TNG) in acute myocardial infarction

Authors	Patients (n)	Inclusion criteria	Mean time from symptom onset to Rx (hrs)	TV ING		Titration endpoint	Outcome
				Mean dose	Duration		
Flaherty et al. [7]	104	All infarcts	10	90 μg/min	48 hours	↓ MAP 10%	EF ↑ ≥ 10% in 35% of early TNG treated patients & T1-201 perfusion defection score ↓ ≥ 75% in 48% of early TNG treated patients
Bussman et al. [12]	60	Only transmural infarcts with LVEP > 12 mmHg	10	47 μg/min	48 hours	↓ LVFP	CK infarct size ↓ 23%
Jaffe et al. [13]	85	All infarcts	6	54 μg/min	24 hours	↓ SAP 10%	CK infarct size ↓ 37%, but only for inferior transmural infarcts
Derrida et al. [14]	24	All infarcts	10	51 μg/min	1–7 days	↓ SAP 20 mmHg	In-hospital mortality ↓ from 23% to 5% and precordial R waves better preserved for anterior infarcts

decreased from 19 ± 4 mmHg to 11 ± 3 mmHg ($p < .005$ vs. control), and cardiac output increased from 5.1 ± 1.2 L/min to 5.5 ± 1.4 L/min ($p < .025$ vs. control) after 48 hours of nitroglycerin infusion. Heart rate increased only slightly from 88 ± 19 beats/min to 93 ± 16 beats/min (NS vs. control). Mean arterial pressure decreased from 108 ± 19 mmHg to 93 ± 13 mmHg, but this decrease was not significantly different than the spontaneous decline in blood pressure observed in control patients.

In a randomized, prospective, placebo-controlled study reported by Jaffe et al., 85 patients received a 24-hour infusion of nitroglycerin or placebo beginning within 10 hours of symptoms of acute infarction (mean 6 hours) [13]. The nitroglycerin infusion rate was titrated to lower systolic blood pressure by 10%, unless heart rate increased by 20 beats/min or a maximum dose of 200 μg/min was reached (mean, 54 μg/min). Enzymatic infarct size was 36% lower (12 ± 2 gEq vs. 19 ± 4 gEq) with nitroglycerin treatment in the subgroup of patients with inferior transmural infarction ($p < .05$). In contrast, patients with anterior transmural infarction show no evidence of benefit (14 ± 3 gEq vs. 14 ± 3 gEq), and patients with subendocardial infarction demonstrated an intermediate response.

In another randomized prospective study of intravenous nitroglycerin, Derrida et al. reported a significant reduction in in-hospital mortality from 23% to 5% in 74 patients with acute myocardial infarction [14]. Nitroglycerin infusion was titrated to lower systolic arterial pressure 20 mmHg, with the infusion maintained for 1–7 days. The mean nitroglycerin infusion rate was 51 μg/min, and the mean interval between the onset of symptoms and the initiation of therapy was 10 hours. Precordial ST-segment and QRS mapping studies in 46 patients with anterior transmural infarction revealed significantly better preservation of R waves in those precordial leads initially demonstrating ST-segment elevation of greater than 1.5 mm and persistent R waves.

COMPARISON OF THE EFFECTS OF NITROGLYCERIN AND NITROPRUSSIDE

Several studies have directly compared the hemodynamic and antiischemic effects of nitroglycerin and nitroprusside (table 6–3). Chiarello et al., in 10 patients with acute anterior transmural myocardial infarction, administered sodium nitroprusside at an infusion rate sufficient to lower mean arterial pressure by 25 mmHg [15]. Following the initiation of the nitroprusside infusion, all 10 patients showed an increase or worsening of their precordial ST-segment elevations, suggesting worsening rather than improvement in the severity of regional myocardial ischemia. Following discontinuation of the nitroprusside infusion, 5 of the 10 patients were given sublingual nitroglycerin in a dose that lowered mean arterial pressure 14 mmHg. All five patients demonstrated a decrease in their precordial ST-segment elevations, suggesting an improvement in regional ischemia. In order to define the mechanism responsible for these apparent opposite effects of nitroglycerin and nitroprusside, these same investigators carried out an analogous study in an open-chest

Table 6–3. Comparison of intravenous nitroglycerin with nitroprusside

Study	Nitroglycerin	Nitroprusside
Chiarello et al. [22]		
Patients with anterior transmural myocardial infarction	↓ ST elevations	↑ ST elevations
Open-chest anesthetized dog model with acute coronary ligation	↓ ST elevations and ↑ MBF	↑ ST elevations and ↓ MBF
Mann et al. [23]		
Patients with angiologically visible intercoronary collateral channels	↑ CBF	↓ CBF
Hillis et al. [37]		
Open-chest anesthetized dog model with acute coronary ligation	↓ $PmCo_2$ and NC—CBF	NC—$PmCO_2$ and ↓ CBF

Abbrevations: CBF = collateral blood flow; $PmCO_2$ = intramural carbon dioxide tension; NC = no change.

canine model. Following ligation of the left anterior descending coronary artery, nitroprusside was infused at a rate sufficient to lower mean arterial pressure 20 mmHg. After the nitroprusside infusion was discontinued and hemodynamic parameters were allowed to return to baseline values, nitroglycerin was infused at a rate sufficient to lower mean arterial pressure by an equal amount. Using the radioactive microsphere technique, these investigators found that regional myocardial blood flow in the region of myocardium supplied by the ligated left anterior descending coronary artery decreased and epicardial ST-segment voltages increased or worsened during nitroprusside infusion. In contrast, when a comparable lowering of blood pressure was obtained with nitroglycerin, regional myocardial blood flow increased and epicardial ST-segments decreased, suggesting an improvement in the severity of ischemia. Since the left anterior descending coronary artery remained occluded, the improvement in regional myocardial blood flow observed with nitroglycerin must be related to an increase in flow through intercoronary collateral channels. In contrast, during nitroprusside infusion, collateral flow to the ischemic zone was found to decrease as flow to the nonischemic zone increased, suggesting the development of a coronary steal.

Marcho and Vatner demonstrated in a conscious, previously instrumented, dog model that nitroglycerin induces less dilatation of the small resistance vessels and greater dilatation of the large (conductance) coronary vessels, which include intercoronary collateral channels [16]. In contrast, nitroprusside induces a greater reduction in the small resistance vessels. Fifteen minutes after discontinuation of a constant infusion, residual large extramural coronary artery dilatation persisted with nitroglycerin but not with nitroprusside. Thus, in normal conscious dogs, nitroglycerin and nitroprusside have differential effects on large and small coronary arteries and on intercoronary collateral channels, with nitroglycerin having greater and longer lasting vasodilating effects on the conductance vessels than nitroprusside. Under normal conditions, the contribution of large conductance coronary vessels to total coronary

resistance is minimal, but in the presence of a critical coronary stenosis, changes in large coronary vessel diameter and/or changes in the diameter of the coronary stenosis [17] could be critical for improving flow to ischemic regions of myocardium. Since nitroglycerin has greater vasodilating effects on the large conductance coronary vessels and less on the smaller resistance vessels, nitroglycerin should less likely induce the coronary steal phenomenon described above for nitroprusside.

In a subgroup of patients with angiographically visible intercoronary collaterals, Mann et al. demonstrated that myocardial blood flow distal to a severe coronary artery stenosis increased with nitroglycerin and decreased with nitroprusside using the Xenon washout technique [18]. Capurro et al., using an open-chest anesthetized dog model with well-developed intercoronary collateral channels induced by previous implantation of an ameroid constrictor, demonstrated greater sensitivity of collateral vessels to the vasodilating effects of nitroglycerin than those of nitroprusside [19]. At lower infusion rates (10 μg/min to 30 μg/min), nitroglycerin was significantly more effective than nitroprusside in reducing collateral resistance. At higher infusion rates (>30 μg/min), the effects of nitroprusside on the systemic vascular circulation were significantly greater than those of nitroglycerin, resulting in greater lowering of coronary perfusion pressure at comparable infusion rates.

Hillis et al. studied the effects of nitroglycerin on metabolic parameters during regional ischemia induced by temporary coronary artery ligation in open-chest anesthetized dogs [20]. Myocardial carbon dioxide and oxygen tensions were measured by mass spectrometry and provided quantitative indices of the severity of regional ischemia [21]. Regional myocardial blood flow was measured by the radioactive microsphere technique. Infusion rates of nitroglycerin and nitroprusside were matched to provide comparable lowering of left ventricular filling pressure and mean arterial pressure. Nitroglycerin resulted in a significant decrease in the severity of regional ischemia, as evidenced by a lower myocardial carbon dioxide tension. In contrast, nitroprusside failed to reduce myocardial carbon dioxide tension. Myocardial blood flow to the ischemic region decreased significantly with nitroprusside but, in contrast, was either maintained or increased slightly with nitroglycerin. Thus, in an experimental model of acute infarction, nitroprusside resulted in no improvement in the severity of regional ischemia, while lowering collateral blood flow to the ischemic region. Nitroglycerin, in contrast, improved regional ischemia, presumably by reducing determinants of myocardial oxygen demand, while at the same time maintaining blood flow to the ischemic region despite a lower coronary perfusion pressure.

Although one must be cautious when extrapolating to patients data obtained in animal models, nitroglycerin and nitroprusside appear to exert similar effects on systemic hemodynamics, but substantially dissimilar effects on intercoronary collateral blood flow and thereby on the severity of regional myocardial ischemia (table 6–4). These differences, which were also evident in

Table 6–4. Potential advantages of intravenous nitroglycerin over nitroprusside

Nitroglycerin (TNG)	Nitroprusside (NP)
TNG dilates conductance coronary arteries and intercoronary collaterals channels, thereby increasing blood flow to ischemic regions.	NP predominantly dilates resistance coronary vessels, which may result in decreased blood flow to ischemic regions ('coronary steal').
TNG predominantly dilates veins at lower infusion rates and adds increasing degrees of arterial dilatation at higher doses, thereby facilitating its use in borderline hypotensive patients.	NP provides more balanced venous and arterial dilatation across a wide range of infusion rates, which can result in excessive lowering of arterial arterial pressure even at low doses.
TNG appears to cause greater lowering of pulmonary artery pressure and less intrapulmonary shunting than NP	NP has less pulmonary vascular effect at doses causing an equal lowering of arterial pressure and consistently worsens intrapulmonary shunting.

the clinical studies of Chiarello et al. and of Mann et al., would appear to make intravenous nitroglycerin preferable to nitroprusside for the management of patients with significant fixed coronary artery disease.

CLINICAL TRIALS OF NITROPRUSSIDE IN ACUTE MYOCARDIAL INFARCTION

In two randomized, prospective, placebo-controlled trials, nitroprusside or placebo was administered to patients with acute myocardial infarction in an attempt to reduce infarct size and/or improve short-term mortality (table 6–5). In the large, multicenter Veterans Administration Cooperative Trial, which enrolled 812 patients, nitroprusside was titrated to reach 1 of 4 endpoints: 1) a reduction of left ventricular filling pressure to less than 60% of control, 2) a lowering of systolic arterial pressure to 20% of the control pressure + 76 mmHg, 3) the development of significant side effects, or 4) a maximum infusion rate of 200 μg/min [22].

Included in this trial were patients with onset of chest pain less than 24 hours prior to admission, transmural infarction evidenced by ST-segment elevation, and pathologic Q waves or a new conduction defect on their admission electrocardiogram. Approximately two thirds of the patients studied had anterior wall infarctions. A left ventricular filling pressure of greater than or equal to 12 mmHg was also required for admission to the study. Excluded were patients with 1) normal left ventricular filling pressures (less than 12 mmHg), 2) cardiogenic shock, 3) hypertension requiring vasodilator therapy, 4) severe bronchopulmonary disease or other serious illness, or 5) a systolic blood pressure of less than 100 mmHg.

Patients received either 48-hour infusion of nitroprusside or placebo. The mean time interval between the onset of symptoms and initiation of therapy was 17 hours. Three-week mortality was 10.4% in placebo-treated and 11.5% in nitroprusside-treated patients (NS). Likewise, 13-week mortality was 19%

Table 6–5. Clinical trials of intravenous nitroprusside (NP) in acute myocardial infarction

Clinical trial	Early treatment group	Late treatment group
Cohn et al. [22] 812 patients, mean time of Rx 17 hrs after onset of symptoms. Only transmural infarcts with LVFP > 12 mmHg	↑ Mortality (13 wks) (24% for NP vs. 13% for placebo).	↓ Mortality (13 wks) (14% for NP vs. 22% for placebo)
Durrer et al. [23] 328 patients, mean time of Rx 5 hrs after onset of symptoms. All infarcts. (Patients with hypertension on admission not excluded).	↓ Mortality (4 wks) (6% for NP vs. 12% for placebo) ↓ Peak MB-CK blood levels (anterior infarcts only)	

Abbreviations: LVFP = left ventricular filling pressure; MB-CK = MB isoenzyme of creatine kinase.

in placebo-treated and 17% in nitroprusside-treated patients (ns). There were no significant differences noted in the peak blood levels of the MB isoenzyme of creatine kinase between the two treatments. However, when patients were subdivided into early and late treatment, with early treatment defined as treatment initiated less than 9 hours after the onset of chest pain, 13-week mortality was 24% in those receiving early treatment with nitroprusside compared to only 13% in those treated early with placebo ($p < 0.025$). In those patients treated more than 9 hours after symptom onset, 13-week mortality was found to be reduced with nitroprusside treatment (14%) compared to 22% with placebo treatment ($p < 0.04$).

Several possible explanations were offered for the apparent opposite effects of nitroprusside in early- versus late-treated patients. A spontaneous decline in left ventricular filling pressure has been shown to occur during the early hours of an acute myocardial infarction. It is possible, therefore, that many of the patients included in the early treatment subgroup would have been excluded from the study had their Swan-Ganz catheter been placed later. Thus, the early treatment subgroup could contain more patients with mild left ventricular dysfunction. In such patients, by lowering coronary perfusion pressure and dilating small-resistance vessels supplying nonischemic myocardium more than intercoronary collateral channels, nitroprusside might have made regional ischemia worse by causing a coronary steal. These potential deleterious effects on oxygen supply would be unopposed by beneficial effects obtained from greater reduction in oxygen demand in patients with markedly elevated left ventricular filling pressures. In contrast, patients who were seen late, having persistently elevated left ventricular filling pressure, might obtain on balance a beneficial effect due to a greater reduction in wall tension, and thereby oxygen demand, and at the same time greater improvement in subendocardial perfusion due to the removal of the flow-limiting effects of a high end-diastolic pressure in the left ventricular cavity.

In a second randomized clinical trial, Durrer et al. administered nitroprus-

side or placebo for 24 hours to 328 patients with acute myocardial infarction [23]. Nitroprusside infusion was titrated to lower systolic blood pressure to 100 mmHg or to a maximum infusion rate of 500 μg/min. For this study, inclusion criteria included 1) chest pain of 1 or more hours duration and 2) electrocardiographic changes, consisting of ST-segment elevation or depression or T-wave inversion, thereby including subendocardial as well as transmural infarctions. Approximately one half of the infarctions were anterior in location. Swan-Ganz catheters were not routinely placed, and therefore patients with both normal and abnormal left ventricular filling pressures were included. Exclusion criteria included 1) cardiogenic shock, 2) pulmonary edema, 3) hypotension (systolic blood pressure less than 95 mmHg), 4) heart rate greater than 120 beats/min, and 5) patients in whom infarction was unlikely, or in whom the time of onset of symptoms was uncertain.

The mean time interval between the onset of symptoms and the initiation of therapy was 5 hours, which was much shorter than the mean time interval in the VA study (17 hours). Durrer et al. found a significant reduction in 23-day mortality with nitroprusside compared to placebo-treated patients. Eighteen patients in the placebo-treated group died, compared with only five in the nitroprusside-treated group ($p < 0.05$). Seven of the 18 deaths in the placebo-treated group occurred within 24 hours and the remaining 11 occurred within the first week. In contrast, none of the five deaths in the nitroprusside treatment group occurred during the first 24 hours, with all five deaths occurring later in the first week. The cause of death in 9 of the 18 placebo-treated patients was rupture of the left ventricular free wall, a papillary muscle, or the interventricular septum. This relatively high (7%) incidence of myocardial rupture of one form or another in a population of patients that included both subendocardial and transmural infarctions and normal, as well as abnormal, left ventricular filling pressures, seems high. Patients with significant hypertension at the time of admission appeared not to have been excluded from this study. The incidence of myocardial rupture, which is reported to be higher in hypertensive patients, might have been lowered by nitroglycerin treatment. A reduction in peak blood levels of the MB isoenzyme of creatine kinase was noted only in patients with anterior infarctions. In any event, the results of these studies do not clearly support the use of nitroprusside in patients with acute myocardial infarction, and on balance we would continue to recommend the use of intravenous nitroglycerin when possible in this clinical setting.

PATHOPHYSIOLOGY OF UNSTABLE ANGINA

Before discussing the use of intravenous nitroglycerin in patients developing unstable angina following an acute myocardial infarction, it might be useful to review the factors that are thought to be important in the pathogenesis of unstable angina. In the cardiac catheterization laboratory, Chierchia et al. documented that the initial change that can be observed in patients experiencing a spontaneous episode of rest angina is a fall in the coronary venous

oxygen saturation [24]. This fall in coronary sinus oxygen saturation preceded impairment in relaxation of the left ventricle and subsequent depression of left ventricular contractility. ST-segment changes and chest pain, neither of which were consistently present during episodes of ischemia, occurred even later. Increases in heart rate and/or blood pressure always followed changes in the biochemical and mechanical indices of ischemia, suggesting that the primary event causing an episode of ischemia at rest was a decrease in myocardial oxygen supply rather than an increase in myocardial oxygen demand. In this population of patients studied by Chierchia et al., coronary angiography revealed normal coronary arteries in 8% of patients, with an equal mixture of single-, double-, and triple-vessel disease in the remaining 92%. Thus, episodes of rest angina were found to occur both in the presence and the absence of fixed coronary artery disease. Vasospasm, when documented angiographically, occurred most often in the vicinity of a fixed coronary-artery lesion.

Life-threatening arrhythmias in the form of ventricular tachycardia, ventricular fibrillation, or complete heart block were observed in 20% of the patients studied by Chierchia et al. during their ischemic episodes. More than 75 years ago Sir William Osler noted out that "in a few fatal cases no lesions whatever were found, and we must accept the fact than angina pectoris may kill without signs of obvious disease in the heart or blood vessels" [25]. Osler was most likely describing sudden death secondary to a ventricular arrhythmia in patients with vasospastic angina and normal coronary arteries, a syndrome that has subsequently been called *Prinzmetal's angina.*

Variation in coronary vasomotor tone has also been implicated in the pathogensis of effort angina as well. Yasue et al. demonstrated that patients with vasopastic angina can have variable exercise tolerance with a diurnal pattern [26]. When exercised early in the morning, their patients had positive stress tests. When these same patients were exercised later in the day, a significant increase in exercise duration was observed, suggesting that vasomotor tone was increased in the morning. The effect of a change in coronary vasomotor tone would be particularly important in the region of an eccentric atherosclerotic plaque. Even a small change in vasomotor tone in the remaining circumference of the vessel could result in the development of rest angina. Such an occurrence has been documented angiographically by Brown and has been termed *dynamic stenosis* [17].

The therapy of angina pectoris has traditionally focused on reduction of myocardial oxygen demand rather than on improvement of oxygen supply. Beta blockers, for example, primarily decrease heart rate and contractility, and only secondarily redistribute coronary blood flow to deeper subendocardial layers. In contrast, nitroglycerin not only reduces myocardial oxygen demand by decreasing systolic arterial pressure and left ventricular end-diastolic pressure, but also dilates epicardial coronary arteries and intercoronary collateral channels, thereby also increasing myocardial oxygen supply. Calcium-channel

blockers both relax peripheral vascular smooth muscle and depress myocardial contractility, which would act to reduce myocardial oxygen demand. Calcium blockers also improve oxygen supply by dilating or preventing vasospasm in coronary arteries. The effects of calcium blockers on intercoronary collateral channels are less clear.

In summary, the results of the study by Chierchia et al. appear to document that a decrease in oxygen supply, rather than an increase in demand, is the stimulus for the majority of episodes of rest angina. Ischemic episodes were followed and not preceded by increases in heart rate and/or blood pressure. It would seem rational, therefore, for management of unstable angina to focus on pharmacologic and/or mechanical therapies that act primarily, albeit not solely, on the supply side of the myocardial supply/demand equation. Increasing coronary perfusion pressure, without increasing myocardial oxygen demand, can only be accomplished with an intraaortic balloon pump. Inotropic agents, such as epinephrine or isoproterenol, increase myocardial contractility and arterial pressure and thereby coronary perfusion pressure, but at the cost of increased myocardial oxygen demand. Nitroglycerin, on the other hand, by means of its relatively specific vasodilating effect on intercoronary collateral channels, has the potential of increasing blood flow to ischemic regions of myocardium without excessively lowering coronary perfusion pressure, because of its relatively greater venous versus arterial dilating effects [19, 27].

Rational approach to management of unstable angina

Treatment of patients admitted to a coronary care unit with unstable angina having failed routine medical therapy varies from institution to institution and from cardiologist to cardiologist. The following is a stepwise approach to management of such patients that has been found to be both rational and effective. First, beta blockers and calcium-channel blockers, if present, are maintained at their preadmission doses, while long-acting oral and/or transcutaneous nitrates are discontinued and an intravenous infusion of nitroglycerin begun. A 10% lowering of mean arterial pressure, which is approximately equivalent to a 10%–15% lowering of systolic pressure, can be used as an initial titration endpoint. The need for further upward titration of the nitroglycerin infusion rate can then be dictated by the occurrence of subsequent episodes of chest pain. Alternatively, Kaplan et al. have suggested titrating initially to an infusion rate of 50 μg/min and then waiting for the development of additional episodes of chest pain before increasing the infusion rate by 50 μg/min increments [28].

Both Mikolich et al. [29] and Kaplan et al. documented the efficacy of adding intravenous nitroglycerin to prior oral or topical medical therapy of patients with unstable angina. Kaplan et al. studied 35 patients with episodes of rest angina unresponsive to standard medical therapy, which at the time of his

study consisted of only nitrates and beta blockers. Prior medications, including oral and topical nitrates, were continued at their pre-CCU admission doses and an infusion of intravenous nitroglycerin was begun at 10 μg/min and titrated upward to the initial predetermined endpoint of 50 μg/min. If an adverse reaction was encountered, the titration was stopped. If another episode of rest angina occurred, the nitroglycerin infusion was increased stepwise to 100 μg/min. This sequence was repeated following each subsequent episode of rest chest pain using 50 μg/min increments until the patient either stopped having episodes of pain or an adverse reaction prevented further upward titration.

Twenty-five of 35 (71%) patients treated by Kaplan et al. became pain-free following addition of intravenous nitroglycerin therapy, without adjustment of other antianginal medications. An additional eight (23%) of their patients showed a greater than 50% decrease in the frequency of episodes of rest pain. Only two patients (6%) demonstrated no improvement, requiring institution of intraaortic balloon pump therapy and urgent bypass surgery. The mean final nitroglycerin infusion rate utilized in Kaplan's study was 140 μg/min (range, 50–350 μg/min). This sevenfold difference in final infusion rates points out the wide patient-to-patient variability int he nitroglycerin infusion rate required for "effective" therapy. No significant adverse effects were encountered by these investigators. Only one patient developed headache of sufficient severity to require back titration of the nitroglycerin infusion rate. Ten patients had the infusion of intravenous nitroglycerin continued until bypass surgery could be performed. In all ten patients, attempts at discontinuing intravenous nitroglycerin therapy resulted in recurrence of rest anginal episodes.

We recently performed in our coronary care unit a study of the efficacy of intravenous nitroglycerin therapy in patients with unstable angina [30]. This study was designed with two purposes in mind: 1) to examine the safety and efficacy of titrating the nitroglycerin infusion to a predetermined hemodynamic endpoint as the initial therapeutic maneuver and 2) to test the hypothesis that those patients who had responded to the addition of intravenous nitroglycerin to their previous antianginal regimen could be crossed over to nitroglycerin administered by one of the new transdermal delivery systems (Nitro-Dur, Key Pharmaceuticals). In a prospective protocol, nine patients had their nitroglycerin infusion titrated upward at 3–10 minute intervals until a 10% lowering of mean arterial pressure was obtained. If a subsequent episode of rest angina occurred then further upward titration was allowed. This titration protocol and initial hemodynamic endpoint proved safe and effective for controlling episodes of rest chest pain in all nine patients. Subsequently we employed this treatment strategy in 17 consecutive patients with unstable angina treated in our coronary care unit during a 1-month period and examined their clinical outcomes retrospectively. Fifteen of 17 patients became pain-free following the addition of intravenous nitroglycerin to their previous medical therapy,

with the remaining two not responding to maximal medical therapy and therefore undergoing urgent bypass surgery. Ten of the 15 successfully treated patients had an ischemic etiology for their chest pain documented by cardiac catheterization and had no change in their antianginal and/or antihypertensive drug therapies during the period of intravenous nitroglycerin administration of during crossover to transdermal nitroglycerin therapy. In this well-defined subgroup of ten patients, nitroglycerin infusion lowered mean arterial pressure from 101 ± 18 mmHg to 87 ± 11 mmHg, requiring a mean infusion rate of 84 ± 74 μg/min (range, 10–200 μg/min). The mean duration of intravenous nitroglycerin therapy was 36 ± 12 hours. In 4.8 ± 0.9 hours all ten patients had their nitroglycerin infusion tapered and discontinued and were then crossed over in a stepwise fashion to a mean dose of 45 ± 20 cm^2 or 22.5 ± 10 mg per 24 hours of transdermal nitroglycerin patches (range, 10–80 cm^2 or 5–40 mg per 24 hours). The crossover protocol was designed to maintain the mean arterial pressure previously obtained following the initiation of intravenous therapy. Mean arterial pressure was 86 ± 11 mmHg during intravenous nitroglycerin therapy immediately prior to instituting crossover and was at 83 ± 9 mmHg and 85 ± 11 mmHg, 1 and 24 hours following crossover to transdermal nitroglycerin therapy, respectively. Two patients had an episode of chest pain occur during the first 24 hours of transdermal therapy. Both became pain-free following the addition of one 10 mg per 24 hours transdermal patch. Of these ten patients, seven experienced no further pain episodes during the remainder of their hospitalization. One patient developed a single episode of rest angina following transient interruption of transdermal nitroglycerin therapy, and one other patient had a single episode of pain develop following transient reduction in the transdermal dose. Both patients remained pain-free until hospital discharge after the transdermal therapy was reinstated at its original postcrossover dose. The remaining patient developed a recurrence of unstable angina that was unresponsive to the reinstitution of intravenous nitroglycerin therapy and underwent urgent coronary bypass surgery. The results of our study suggest that 1) intravenous nitroglycerin, titrated initially to lower mean arterial pressure by 10%, is a safe and effective treatment for patients with unstable angina treated in a coronary care unit and 2) transdermal nitroglycerin delivery systems, when titrated to an individual patient's hemodynamic response, can successfully maintain the beneficial antiischemic effects obtained with intravenous nitroglycerin therapy.

Mechanisms of action of nitroglycerin in unstable angina

The potential mechanisms by which nitroglycerin might prevent episodes of rest chest pain in patients with unstable angina are multiple. First, most authors agree that nitroglycerin acts primarily by dilating systemic and splanchnic veins, reducing preload, and thereby reducing left ventricular cavity size.

Since the radius of the left ventricular cavity is a major determinant of ventricular wall tension, myocardial oxygen demand or consumption will be reduced. At higher doses (>30 μg/min), nitroglycerin also dilates peripheral arteries, reducing systolic and diastolic blood pressure, and thereby reduces left ventricular afterload, another important determinant of myocardial oxygen demand. Nitroglycerin also exerts direct dilating effects on the coronary circulation. Marcho and Vatner have demonstrated that nitroglycerin dilates primarily the large epicardial conductance coronary arteries [16]. In contrast, nitroprusside or dipyridamole dilate primarily the smaller intramyocardial resistance arteries. The coronary steal previously reported with nitroprusside and dipyridamole is thought to be due to predominant dilation of resistance vessels supplying regions of nonischemic myocardium. Resistance vessels supplying ischemic regions of myocardium are presumably already vasodilated. Dilating resistance vessels in adjacent normally supplied myocardium would therefore shunt coronary blood flow away from ischemic and toward nonischemic regions. There is experimental evidence to support the contention that such a differential effect might be encountered clinically in patients with severe coronary artery disease. Both Chiarello et al. and Mann et al. demonstrated beneficial effects of nitroglycerin and harmful effects of nitroglycerin on intercoronary collateral blood flow [15, 18].

Nitroglycerin has also been shown by several investigators to possess a potent dilating effect on intercoronary collateral channels. Capurro et al. utilized an ameroid constrictor to induce the development of a rich intercoronary collateral network in a canine model [19]. These investigators found greater sensitivity of these intercoronary collateral channels to the vasodilating action of nitroglycerin that to nitroprusside. In the cardiac catheterization laboratory, intracoronary nitroglycerin is commonly employed to reverse spontaneous or catheter-induced coronary vasospasm. Controversy remains as to whether nitrates or calcium blockers should be first-line therapy for patients with documented vasospastic angina.

Advantages of intravenous administration of nitroglycerin in patients with unstable angina

Potential advantages of administering nitroglycerin by the intravenous route include steady nitroglycerin blood levels. In addition, the short half-life (2–3 minutes) of intravenous nitroglycerin allows more rapid titration to a clinically effective dose. The short half-life also allows for rapid reversal of nitroglycerin's hemodynamic effects in the event that an adverse reaction or a sudden change in the patient's clinical status occurs.

Stepwise approach to therapy of patients with unstable angina failing to respond to intravenous nitroglycerin

In our clinical experience, approximately 10%–20% of patients with unstable angina will fail to respond to the addition of intravenous nitroglycerin to prior

medical therapy, as described in detail above. In these patients a second step is required: beta blockers are in general maintained at their pre-CCU admission doses, intravenous nitroglycerin is maintained at its final infusion rate, and one of the calcium blockers is added and the dose is increased stepwise as tolerated. Owing to the potent blood-pressure lowering effects of the calcium blockers, the infusion rate of intravenous nitroglycerin frequently must be reduced in order to avoid excess lowering of coronary perfusion pressure.

In a randomized, placebo-controlled, clinical trial carried out in our coronary care unit, we were able to demonstrate significant beneficial effects of adding the calcium-channel blocker, nifedipine, to prior beta-blocker and nitrate therapy [31]. It is important to point out, however, that in this study prior nitrate therapy consisted of relatively low doses of orally or cutaneously administered nitrates. Since all calcium-channel blockers have potent negative inotropic effects, they must be added cautiously in patients with significant left ventricular dysfunction. Furthermore, since verapamil and diltiazem also have potent negative effects on atrioventricular conduction, they should not be administered to patients with significant conduction system disease unless artificial pacemaking is provided.

If a patient with unstable angina fails to respond to the addition of maximally tolerated doses of intravenous nitroglycerin and an oral calcium-channel blocker, then a third step, the addition of, or an increase in, the dose of a betablocker may be recommended. In patients with resting sinus tachycardia in the absence of congestive heart failure, adding or increasing the dose of a betablocker might, in fact, be recommended even earlier in this stepwise approach to the therapy for unstable angina. A beta blocker would slow the resting heart rate and decrease contractility, and thereby decrease myocardial oxygen demand. As with the calcium blockers, the addition of, or the increase in, the dose of a beta blocker must be done cautiously in patients with significant left ventricular dysfunction. The development of an ultra-short-acting beta blocker that can be titrated intravenously in a manner similar to intravenous nitroglycerin may provide the rapid reversibility of adverse reactions required for a safe therapeutic trial of beta blockers in patients with unstable angina and borderline depression of left ventricular function [32]. Persistently elevated arterial pressure in the presence of both calcium blockers and intravenous nitroglycerin would also provide a rationale for the addition of, or the increase in, the dose of a beta blocker. Whether beta blockers can cause significant coronary vasconstriction by unopposed alpha stimulation remains speculative, especially when other potent vasodilating agents such as intravenous nitroglycerin and/or calcium blockers are being used concomitantly.

For patients continuing to experience episodes of rest chest pain despite maximal medical therapy including intravenous nitroglycerin, calcium blockers, and beta blockers, most cardiologists would move to intraaortic balloon pump therapy, if it is available. Five years ago, intraaortic counterpulsation balloon therapy was probably employed in 5%–10% of patients treated in our

coronary care unit for unstable angina. Following the addition of intravenous nitroglycerin and calcium-channel blockers to our medical armamentarium, success with medical therapy is now more common, and use of balloon counterpulsation has declined to perhaps 1%–3% of patients admitted to the CCU with unstable angina. With the intraaortic balloon catheter pump in place, patients can safely undergo coronary angiography and, if the anatomy is suitable, have either percutaneous transluminal angioplasty or aortocoronary bypass surgery performed on an urgent basis.

LIMITATIONS

On the basis of the demonstrated efficacy of intravenous administration of nitroglycerin in unstable angina, patients may be quite sensitive to the failure of infusion pumps to deliver drug at the desired rate or to errors in management of the infusion. While recurrence of angina may result from inadequate drug delivery, undesirable hypotension can result from accidental infusion of excess drug.

When treating patients with severe left ventricular failure or hypertension complicating acute myocardial infarction, intravenous nitroglycerin, even at higher infusion rates, may not produce adequate afterload lowering in all patients. For such "nitroglycerin-resistant" patients, the addition of an intravenous infusion of sodium nitroprusside may be required to adequately lower systemic vascular resistance and/or to maximally increase forward cardiac output. Oral hydralazine, captopril, or prazosin may then be utilized to maintain the desired afterload lowering.

In a study involving patients with acute hypertension developing early after coronary artery bypass surgery, we found approximately 15% of patients to be nitroglycerin resistant [33]; that is to say, nitroglycerin infusion rates of more than 1100 μg/min failed to match the arterial blood-pressure lowering obtained with nitroprusside. For such resistant patients, nitroprusside would appear to remain the drug of choice, at least until the stimulus to arterial vasoconstriction (e.g., circulating catecholamines and/or sympathetic stimulation) subsides.

ADVERSE REACTIONS

Potential adverse reactions to intravenous nitroglycerin include hypotension, sinus tachycardia, sinus bradycardia, headache, and nausea or vomiting. Drug-induced hypotension is in most cases quickly reversed by discontinuing or reducing the rate of infusion. Only occasionally is a significant increase in sinus rate encountered with the intravenous route of administration. When sinus tachycardia is observed, it is most often in patients with low left ventricular filling pressures. In approximately 4% of patients, marked sinus bradycardia and hypotension is encountered. Discontinuing the nitroglycerin infusion with or without elevation of the legs is usually all that is required. However, if the

bradycardia persists, a small dose of atropine (0.5 mg) can be administered intravenously, which will usually reverse both the bradycardia and the hypotension [34]. Headache and nausea or vomiting appear to be dose-related. When not controllable with symptomatic treatment, these side effects can usually be reversed by reducing the rate of infusion [7]. Methemoglobinemia appears not to be a problem with the range of infusion rates that are usually employed clinically (5–500 μg/min) (35). Increased intrapulmonary shunting could result in hypoxemia, especially in patients with significant underlying lung disease, but would appear to be less of a problem with nitroglycerin than with nitroprusside [33].

Sinus tachycardia and sinus bradycardia are more likely to occur if blood pressure is lowered too rapidly. Such reflex effects can be minimized by slowly increasing the infusion rate. Blood pressure can be monitored non-invasively for the majority of clinical applications. Therefore, routine insertion of an intraarterial catheter is not required but may be recommended in patients receiving intravenous nitroglycerin with borderline blood pressure. In the presence of severe left ventricular failure, precise quantitation of preload and afterload may be helpful. Placement of a thermodilution balloon flotation catheter into the pulmonary artery, which allows measurement of both pulmonary capillary wedge pressure or pulmonary artery diastolic pressure and cardiac output, will allow more efficient administration of intravenous nitroglycerin.

CONTRAINDICATIONS

Intravenous nitroglycerin should not be administered to patients with 1) preexisting hypotension (<90/60 mmHg), uncorrected hypovolemia, or possibly right ventricular infarction; 2) increased intracranial or intraocular pressure; 3) constrictive pericarditis or pericardial tamponade; 4) inadequate cerebral perfusion; or 5) known hypersensitivity to nitroglycerin (table 6–6).

It is worth reemphasizing that nitroglycerin should not be administered to patients with a known or suspected elevation of intracranial pressure. When intracranial pressure is high, the rigid cranial vault will not allow for dilatation of blood vessels [36]. Vasodilation of intracranial arteries and veins could cause a further increase in intracranial pressure and could result in a neurologic catastrophe.

Table 6–6. Contraindications to the use of intravenous nitroglycerin

1. Hypotension, uncorrected hypovolemia and possibly right ventricular infarction.
2. Increased intracranial or intraocular pressure
3. Pericardial constriction or tamponade
4. Inadequate cerebral perfusion
5. Known hypersensitivity to nitrates

APPENDIX

Intravenous nitroglycerin preparations and guidelines for administration and dosage

Nitroglycerin for intravenous infusion is a sterile, nonpyrogenic, nonexplosive aqueous solution of 1,2,3-propanetriol trinitrate supplied in both 5 ml and 10 ml stock solutions at concentrations varying between 0.8 mg/ml and 5 mg/ml. The risk of inducing hypotension makes bolus injection inadvisable unless invasive monitoring techniques are being employed and the clinical situation is sufficiently urgent to warrant the risk. Continuous infusion using a volume infusion pump is recommended for accurate intravenous delivery of the drug. The concentration of nitroglycerin infused will generally be dictated by constraints of fluid management and the final infusion rate required to achieve the desired clinical effect.

Nitroglycerin is readily and continuously absorbed into polyvinyl plastic bottles and tubing at an unpredictable rate. Therefore, nitroglycerin for intravenous infusion should be prepared only in glass bottles. Special polyethylene tubing sets can be used to minimize loss of the drug. Since infusion rates are in general titrated in each patient to obtain a given hemodynamic effect, the higher cost of the special tubing may not warrant its routine use for short-term infusion, especially when infusion rates are greater than 60 ml/hour [37]. These special polyethylene infusion sets may, however, be useful when lower infusion rates are employed or when patients are particularly unstable from a hemodynamic or ischemic viewpoint.

Infusions are generally begun at 5–10 μg/minute. The infusion rate can then increased stepwise at 5–20 μg/min increments every 3–5 minutes until a predetermined lowering of arterial pressure is reached or until a further reduction of arterial blood pressure is deemed undesirable. Another possible endpoint for titration is reduction of pulmonary capillary wedge pressure or systemic vascular resistance to a clinically desired level, as assessed using a thermodilation balloon-tipped catheter placed in the pulmonary artery. The cessation of spontaneous episodes of chest pain in patients with unstable angina is also a third possible titration endpoint.

Clinical pharmacology

The hemodynamic actions of nitroglycerin are primarily mediated by relaxation of vascular smooth muscle. Nitroglycerin's vasodilating effects have been attributed to activation of guanylate cyclase to produce cGMP, a potent vasodilating substance, following nitroglycerin binding to reduced sulfhydryl groups on a poorly defined nitrate receptor in vascular smooth-muscle cells [38]. Alternatively production of prostaglandin I_2, another potent vasodilator, has also been demonstrated following nitroglycerin administration and may play a role in sustaining a vasodilating effect [39]. Although dilation of systemic and splanchnic vessels predominates at lower infusion rates (< 30 μg/min),

nitroglycerin at higher infusion rates is a mixed venous and arterial dilator. This differential venous and arterial dilating effect allows for a dose-dependent reduction in systolic or mean arterial pressure. Venodilation results in peripheral venous pooling and thereby reduction in right and left ventricular preload. Arterial dilation results in a reduction of peripheral and pulmonary vascular resistances and thereby reduction in afterload of the left and right ventricle, respectively. Dilation of large extramural coronary arteries and, more recently, dilation of some "fixed" coronary stenoses has also been demonstrated [40, 41]. Nitroglycerin dilates intercoronary collateral channels, thereby increasing blood flow to ischemic regions and also redistributes transmural myocardial blood flow from the epicardial to the more vulnerable subendocardial layers.

Nitroglycerin has a large volume of distribution such that the plasma contains less than 1% of the total body nitroglycerin content. Nitroglycerin is metabolized in the liver by glutathione organic nitrate reductase and in the blood by the same enzyme, which is contained within red blood cells. Intravenous nitroglycerin has an in-vivo half-life of 2–3 minutes. Hemodynamic alterations or adverse reactions can therefore be quickly reversed by discontinuing an intravenous infusion.

Nitroglycerin blood levels are measured by gas liquid chromatography capillary columns or electron capture. Therapeutic venous blood levels in the 0.1 ng/ml to 2.0 ng/ml range have been shown to correlate with hemodynamic changes following transcutaneous or sublingual administration [42]. Nitroglycerin is approximately 60% protein bound. Tolerance to nitroglycerin has been evidenced in vitro by decreased guanylate cyclase activity in aortic strips obtained from animals having prior exposure to nitroglycerin [38]. Clinical tolerance to nitrates appears to take the form of partial attenuation of hemodynamic effects following chronic therapy. Attenuation is more marked for the arterial compared to the venodilating effects. The clinical importance of tolerance, however, remains controversial. A nitrate-free interval has been proposed as one mechanism for avoiding the development of hemodynamic attenuation. Withdrawal symptoms from nitrates have been observed in munitions workers, but clinically significant withdrawal has not been seen when nitroglycerin therapy is discontinued abruptly, either in patients receiving short-term intravenous or long-term long-acting nitroglycerin preparations.

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7. THE ROLE OF CALCIUM ANTAGONISTS IN ACUTE MYOCARDIAL INFARCTION

BRAMAH N. SINGH AND WINIFRED NAYLER

Mortality and morbidity that result in the wake of acute myocardial infarction appear to stem fundamentally from the extent of tissue damage that occurs following coronary artery occlusion and the propensity of the ischemic and infarcting myocardium to develop electrical instability. In recent years, a number of modalities of therapy have been utilized in an effort to improve prognosis in the survivors of acute myocardial infarction by limiting infarct size, thereby improving ventricular ejection fraction and preventing the development of potentially malignant ventricular tachyarrhythmias.

This chapter is predominantly concerned with the possibility of using slow-channel blockers to protect the myocardium against the deleterious effects of ischemia in the early stages of infarction. Although attention will be directed towards the experimental data, which provide the basis for the conclusion that these substances can confer protection under these conditions — provided that their administration is not delayed [1, 2], potential therapeutic implications will be placed in perspective. Although the bulk of this chapter is devoted to a consideration of data obtained from the use of either verapamil, nifedipine, or diltiazem, it is not meant to imply that the more recently developed slow-channel blockers [5] will not be just as effective. Instead, it is a reflection of the fact that the general field of Ca^{2+} antagonism is developing so rapidly that relevant data have not yet been obtained for the more recently developed compounds.

As a background against which these beneficial effects of pretreatment with

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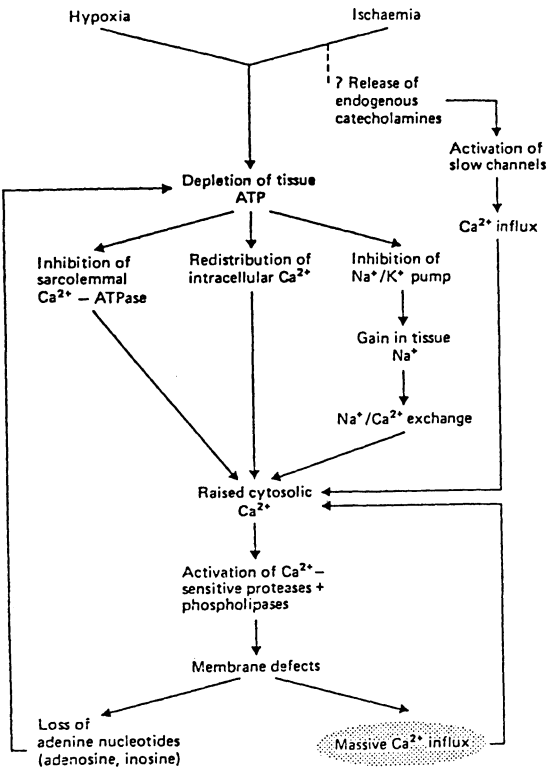

Figure 7–1. Schematic representation of events during an ischemic episode. Note the multifactorial changes caused by ATP depletion.

slow-channel blockers can be discussed, we should consider briefly the metabolic and morphological disturbances (figures 7–1 and 7–2) that are triggered by episodes of ischemia and reperfusion.

Essentially we are concerned with the fact that the survival and normal functioning of cardiac myocytes depends ultimately on their ability to maintain ionic homeostasis. This, in turn, requires an uninterrupted supply of energy in the form of adenosine triphosphate (ATP), which is required as substrate for the various pumps that facilitate the movement of ions, including Na^+, K^+, and Ca^{2+}, against their respective ionic gradients. Since the myocardium is essentially an aerobic organ [6], deriving almost all of its energy from oxidative metabolism, it is not altogether surprising to find that hearts that are either deprived of, or at best receive only an inadequate supply of, blood lose their capacity to maintain homeostasis. Under these latter condition, K^+ is lost from the cells to accumulate in the extracellular space [7]. At about the same time, or perhaps even earlier, tissue Na^+ and H^+ rises [7], and the cells become edematous [8] and accumulate Ca^{2+} from the extracellular

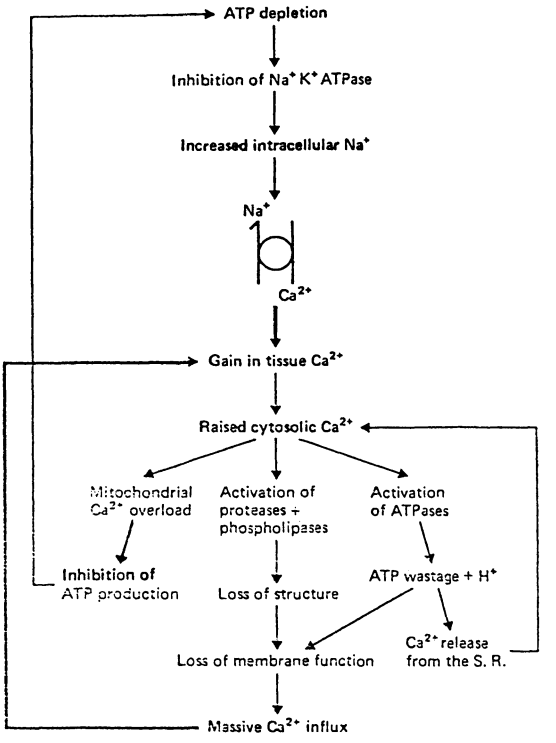

Figure 7–2. Possible involvement of the Na^+:Ca^{2+} exchange reaction in overloading cardiac tissue with Ca^{2+}.

fluid [1]. At the outset, therefore, and irrespective of whether a normal flow of blood is resumed, short periods of either global or low-flow ischemia, including those associated with vasospastic episodes [9], precipitate a spectrum of disturbances that culminate in the loss of excitability, electrical instability, and mechanical failure. Naturally many of these disturbances are exacerbated upon reperfusion [10], this being accompanied by a renewed supply of Ca^{2+} and Na^+. A reasonably detailed account of these processes that provide the background to the potential role of calcium-channel blockers in the setting of acute myocardial infarction has been presented elsewhere [11]. Only the issue of calcium overload resulting in the wake of myocardial ischemia will be discussed here, prior to the discussion of the cardioprotective effects of calcium-channel blockers.

POSSIBLE ROUTES OF CA^{2+} ENTRY DURING POSTISCHEMIC REPERFUSION

Although it is often assumed that the excessive entry of Ca^{2+} that occurs during postischemic reperfusion is due to the entry of Ca^{2+} through the

voltage-activated slow channels, there are several reasons for believing that this may be an oversimplification. Firstly, electrophysiologic studies indicate the slow-channel activity is reduced by ischemia at a time when the fast inward Na^+ current is unchanged. At the outset, therefore, this argues against an excessive entry of Ca^{2+} accumulated during postischemic reperfusion being reduced if some of the extracellular Na^+ is replaced [11] by Li^+, even though Li^+ has no effect on the voltage-activated inward displacement of Ca^{2+} through the slow channels. Instead it inhibits an uptake of Ca^{2+}, which occurs in exchange for Na^+.

Another observation that supports the hypothesis that the postischemia-induced acceleration in the rate of Ca^{2+} uptake does not depend simply upon the uptake of Ca^{2+} through the slow channels comes from the observation that although verapamil protects against this Ca^{2+} uptake when it is administered before coronary flow is interrupted [1], this drug provides no protection when added only at the time of reperfusion [2].

What, then, are the other possible routes of Ca^{2+} entry? These [12] include an entry of Ca^{2+} by passive diffusion across a damaged, and hence leady, cell membrane or an entry of Ca^{2+} in exchange [13] for Na^+. Recent studies have shown that there is a stoichiometric relationship for this latter process, with three Na ions exchanged for one Ca ion. It is also clear that Na^+ provides the dominant signal for the Na^+:Ca^{2+} exchange reaction. Hence, it is possible, but not yet proven, that some of the Ca^{2+} that is accumulated during the reperfusion process enters in exchange for Na^+, the levels of which are already high. The possibility that Ca^{2+} enters by way of passive diffusion during the early part of the reperfusion process can probably be discounted, because experiments in which relatively large macromolecules have been used as extracellular markers have shown that these markers do not have uncontrolled entry, as would be expected if the cells had been rendered freely permeable to substances in the perfusion medium.

Probably no single mechanism is responsible for the uncontrolled entry of Ca^{2+} that occurs upon reperfusion. Instead, it seems more than likely that a cascade or sequence of events is involved. Certainly there is an early loss of ionic homeostasis, which results in the cells losing K^+ and gaining Na^+. This may then establish an ionic milieu such that when reperfusion occurs, the cells will gain a small amount of Ca^{2+} in exchange for Na^+. It is unlikely, however, that this accounts for the total Ca^{2+} overloading that occurs, because the Na^+:Ca^{2+} exchange system is pH sensitive and is inhibited under acidotic conditions. Nevertheless, the Ca^{2+} that enters through this route, particularly if it accumulates in a pool close to the cell membrane, may be sufficient to establish intracellular levels that, in turn, will activate the Ca^{2+}-sensitive endogenous phospholipases and proteases. Under these circumstances, we can anticipate loss of membrane viability with an ensuing rapid and massive overloading of the tissue with Ca^{2+}.

CONSEQUENCES OF CA^{2+} OVERLOAD

The tendency of ischemic heart muscle to accumulate large amounts of Ca^{2+} upon reperfusion [14] probably signals the death of the cells that are involved. Either because of ATP-depletion-induced failure, because the functioning of the sarcoplasmic reticulum and the plasmalemmal Ca^{2+} ATPase has been impaired [15], or because the intracellular ionic milieu favors release of Ca^{2+} from the endogenous stores rather than uptake, the Ca^{2+} that is taken up by the tissue is retained and not expelled back into the environment. Consequently it accumulates in the mitochondria [1], where it disturbs the oxidative phosphorylating activity of the mitochondria [1]. In addition, some of the Ca^{2+} may interact with the myofibrils to enhance end-diastolic resting tension [16] or it may activate the endogenous Ca^{2+}-sensitive ATPases, phospholipases, and proteases. Under these conditions, ATP wastage will ensue (figure 7–2), accompanied by a further acidification. At the same time, membrane structure and function will be further impaired, and ATP production (figure 7–2) further reduced, even though the substrate and O_2 supply may have been restored.

In this chapter, however, we will concentrate on the possibility of using slow-channel blockers to minimize Ca^{2+} overloading and hence to protect the ischemic myocardium. At the outset, however, it should be emphasized that the proposed use of such compounds under these conditions is not based on the supposition that the excessive uptake of Ca^{2+} involves or is restricted to the entry of these ions through the slow channels.

Before dealing with the experimental data that show the slow-channel blockers confer protection against the deleterious effects of ischemia and reperfusion, provided they are used prophylactically, it may be useful to summarize the overall consequences of an enhanced rate of Ca^{2+} influx. This has been attempted in figure 7–3, which shows that the functioning of the nodal and conducting tissues as well as smooth-muscle and cardiac-muscle cells, would also be affected by loss of Ca^{2+} homeostasis. This same figure shows that whereas activation of the sympathetic system can be expected to cause an exacerbation of these deleterious effects of ischemia that are caused by raised tissue levels of Ca^{2+}, the slow-channel blockers may, in theory, work in the opposite direction.

CARDIOPROTECTIVE EFFECTS OF SLOW-CHANNEL BLOCKERS

The bulk of the data dealing with the carioprotective actions of this class of agents deal with the effects of verapamil, nifedipine, and diltiazem. The effect of the newer agents is under intensive investigation.

One of the first studies in which verapamil was used for this purpose was that of Reimer et al. [17], who found that this drug reduced the amount of cardiac necrosis that occurred in dogs following coronary artery occlusion. An

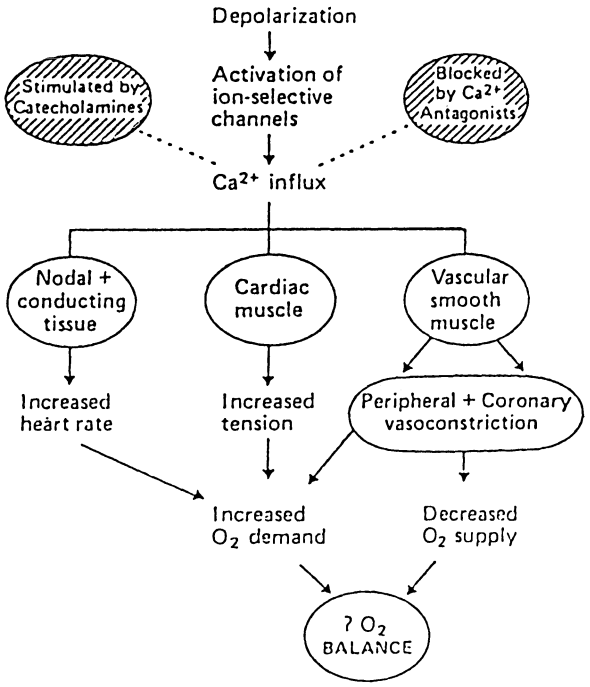

Figure 7–3. Schematic represention of the consequences of catecholamines and slow-channel blockers on Ca^{2+} influex.

undisputed protection effect has also been shown in other experiments in which animals have been pretreated [1, 4, 7] with verapamil. As emphasized earlier in this chapter, adding verapamil *after* making the hearts ischemic is less effective. Different parameters have been used to assess the efficacy of these agents, including decreased elevation of the ST-segment, reduction in infarct size [18], maintenance of a mitochondrial function and preservation of mechanical activity [1, 19], protection against vulnerability to ventricular fibrillation [20, 22, 41], and reduction in mitochondrial Ca^{2+} overload [23]. In some studies, the protective effect has been combined with that of hypothermia [24]. Some of these indices of salutary effects of slow-channel blockers in the ischemic myocardium will be discussed further.

PREVENTION OF MITOCHONDRIAL CA^{2+} OVERLOAD

The importance of preventing mitochondrial Ca^{2+} overload is shown in figure 7–9, where mitochondrial Ca^{2+} has been plotted against percentage recovery of developed function upon reperfusion [11]. The simplest explanation for these findings would be to assume that the presence of the slow-channel blocker directly reduced Ca^{2+} influx into the reperfused ischemic tissue. Since

this is known not to be true, another explanation must be sought. Possibly, it involves maintenance of the ATP-generating activity of the mitochondria [1]. Hence, one of the ways whereby these drugs can be protective is to maintain the endogenous stores of high-energy phosphates, so that sufficient ATP remains available to maintain ionic homeostasis [1].

Not all of the Ca^{2+} antagonists seem to act in precisely the same way. For example, whereas verapamil and nifedipine protect mitochondrial function [1, 24] (by indirectly preventing Ca^{2+} overloading from occurring), diltiazem [25] may not share this property. Nevertheless, diltiazem certainly improves the recovery of mechanical function upon reperfusion [26] and protects mitochondria from phosphate-induced damage [56]. Nifedipine is equiprotective [28], and in at least two studies [27, 28] has been used in combination with hypothermia with and without cardioplegia. As with verapamil [1], pretreatment with nifedipine [1, 23] prevents mitochondrial Ca^{2+} overload.

Whilst there is no paucity of experimental data that confirms the ability of the slow-channel blockers to protect against the deleterious effects of ischemia and reperfusion, nor is there any doubt as to the necessity of using these substances prophylactically [1, 2] so that they can act as energy-sparing agents prior to the onset of ischemia and reperfusion, the complexity of their pharmacology almost certainly ensures that their ability to protect the ischemic heart does not have a simple explanation. Their ability to reduce afterload, their ability to prevent norepinephrine being released from the endogenous stores under these conditions [29], as well as their ability to slow the rate of depletion of the energy-rich phosphate reserves during ischemia and upon reperfusion [1, 29], and their ability to dilate the coronary vasculature are probably all of significance. Of overriding importance, however, is the fact that by preserving the energy reserves of the myocardium, these drugs facilitate the maintenance of ionic homeostasis during prolonged periods of ischemia and reperfusion. Hence, the cascade of events normally triggered by an ischemic episode is either prevented or slowed. These cellular, biochemical, and ionic effects are, in all probability, related to the salutary effects on regional myocardial function and perfusion as well as to anatomic, enzymatic, and electrocardiographic infarct size.

EFFECTS ON MYOCARDIAL REGIONAL FUNCTION

The effects of various calcium antagonists on regional and global ventricular function in the ischemic myocardium have not been fully evaluated. However, in the intact canine model with coronary artery ligation, these compounds have been reported to increase regional myocardial contractility [23, 29–31], to improve diastolic function [32], and to increase left-ventricular segmental relaxation [33] in the ischemic myocardium. These data are in line with the beneficial effects on mechanical function in ischemic-reperfused isolated heart models [34–36] and with the contractility measurements in ischemic muscle fibers in vitro [25]. However, the data are not entirely concordant. There is a

possibility that different calcium antagonists may exert varying responses with respect to their effects on function of the ischemic myocardium. For example, whereas Sherman et al. [37] found that verapamil may improve the function of the mechanical performance of acutely ischemic and reperfused myocardium, a selective depression of regional contractility following coronary ligation has been reported by Smith et al. [38]. Differences among various agents have also been suggested from studies in healthy sedated dogs [39] as well as in perfused rat hearts [35]. All doses of diltiazem, verapamil, and nifedipine produced nearly identical effects on heart rate and blood pressure; diltiazem had no effect on indices of contractility, whereas both verapamil and nifedipine exerted a depressant action. This difference was maintained following beta blockade and during intracoronary injections of the drugs, indicating the differential selectivity of their myocardial actions. The data are consistent with the observations of Hamm and Opie [35], Himori et al. [40] and particularly with those of Ono and Hashimoto [41], who showed that diltiazem, unlike verapamil and nifedipine, had 1.5 times the potency for vasodilatation as for its negative inotropic propensity. However, whether these differences are translatable into corresponding clinical effects are at present uncertain but merit critical appraisal.

CALCIUM ANTAGONISM AND MYOCARDIAL PERFUSION IN ISCHEMIA

Numerous observations have confirmed the coronary vasodilatory properties of calcium-channel blocking drugs. Thus it must be recognized that observed beneficial effects of calcium antagonists in myocardial ischemia may be mediated through improved regional perfusion, in addition to their cellular effects and to those effects due to their actions on myocardial oxygen demand resulting from afterload reduction. However, the data are somewhat in conflict [43]. For example, no increase in collateral flow to the most severely ischemic part of the myocardium in conscious [44] or anesthetized [45] dogs with coronary artery occlusion resulted from continuous nifedipine or tiapamil administration, although increased perfusion was evident in the peripheral ischemic zones. Selwyn et al. [46] found that nifedipine had no significant effect on collateral perfusion in the ischemic myocardium. A similar lack of increase in regional myocardial blood flow was also reported by Karlsberg et al. [47] in the case of verapamil. However, preliminary data indicate that diltiazem may have a specific action in augmenting coronary blood flow to the ischemic myocardium, but there may be species differences. For instance, there appears to be a modest increase in coronary flow to the moderately ischemic zone in the pig model of ischemia [48], with little or no flow change in the dog given intravenous diltiazem 40 minutes after coronary ligation [49].

EFFECTS ON MYOCARDIAL INFARCT SIZE AND ISCHEMIC INJURY

Although the data are not uniformly concordant [46, 47], over the last 10 years there has been an increasing consensus that, as a class of drugs, calcium antagonists have the propensity to reduce infarct size and to minimize ischemic

myocardial injury following experimental coronary occlusion [42]. Their beneficial effects on cellular necrosis, mitochondrial function, regional perfusion, and function have been discussed above. Other salutary effects include amelioration in electrocardiographic and hemodynamic abnormalities [42, 45], magnitude of myocardial enzyme release [46, 50], disturbances in enzyme histochemistry [32, 51], and in the incidence of ventricular fibrillation (see below) following coronary occlusion [22, 52]. It is possible that the observed discrepancies in the reported data may relate to differences in experimental conditions such as species of animals used, model of ischemia developed (permanent or temporary occlusion), and the site of coronary occlusion. It may also be due to the endpoints for gauging the severity of ischemia [42, 53] and to the nature of the calcium antagonist, its dose, route, and, particularly, the timing of its administration relative to coronary occlusion [42]. However, some conclusions can be drawn. Much of the data are consistent with the belief that the maximal cardioprotection occurs when the test agents are given *prior* to coronary occlusion and benefit may not always ensue when they are administered *after* coronary ligation [17, 42, 47]. Moreover, at present the available data do not permit a resolution of the issue of whether the protection afforded by calcium antagonists to the ischemic myocardium is of a temporary or permanent nature. Thus, the possibility remains that these agents may merely delay the onset of irreversible tissue damage rather than prevent it, an issue of much potential clinical importance.

CALCIUM ANTAGONISM AND EXPERIMENTAL ISCHEMIC VENTRICULAR ARRHYTHMIAS

There is much experimental evidence indicating the beneficial effects of calcium antagonists on ischemic ventricular arrhythmias in a variety of animal models [21, 22, 54–57]. Particularly noteworthy is the observation of Kaumann and Aramendia [22], who showed that verapamil, when given intravenously *prior* to the occlusion of the left arterior descending coronary artery in the anesthetized dog, significantly reduced the incidence of ventricular fibrillation; animals that survived lived considerably longer than those that were pretreated with quinidine or with sotalol. The presumption was that the prolongation in survival was due to an improvement in hemodynamic performance consequent upon reduced ischemic injury due to verapamil.

Fondacaro et al. [54] showed that ventricular ectopic beats occurring in the wake of acute coronary artery occlusion were markedly reduced by intravenous verapamil. Thandroyen [53] showed that a variety of calcium antagonists elevated the ventricular fibrillation threshold of the isolated rat heart. However, for the present, the significance of these experimental observations to the control of clinically occurring ventricular arrhythmias remains uncertain.

CLINICAL STUDIES AND POTENTIAL THERAPEUTIC APPLICATIONS

The experimental data suggests perhaps three areas in which the myocardial protective actions of calcium antagonists might be of potential clinical utility in

the early stages of acute myocardial infarction: 1) salvage of ischemic myocardium during the early stages of acute myocardial infarction, 2) ischemic ventricular arrhythmias following acute infarction, and 3) prevention of sudden death and reinfarction in survivors of acute myocardial infarction. At present there is not sufficient data to allow definitive conclusions for any of these potential uses.

Effects of calcium antagonists on infarct size in humans

Despite the sound theoretical basis and the promising experimental data (summarized above), the data on the effects of calcium antagonists on infarct size in humans remains uncertain and in conflict [58, 59]. However, in the case of verapamil, Bussman et al. [60] recently reported a prospective controlled study in which 29 patients received IV verapamil (5–10 mg/hour) for 2 days at a mean duration of 8 hours after the presumed onset of chest pain, and another 25 patients served as controls. Verapamil significantly reduced maximal creatine-kinase activity and its MB fraction (figure 7–4); the enzymatically estimated infarct size (figure 7–5) was reduced by 30% [60]. It must be emphasized that the determination of infarct size in human by means of CK and CK-MB enzyme activity curves is controversial [58], although a reasonable validation of the approach has been reported [59]. These data are consistent with experimental finding [45, 50]. However, it must be emphasized that the effects of all the calcium antagonists in this setting are not identical. The differences may relate to variations in the net pharmacologic effects on heart rate and blood pressure relative to oxygen supply and demand balance. For example, in the study reported by Muller et al. [61], in which 105 eligible patients with threatened infarction chest pain exceeding 45 minutes in duration and 66 patients with acute myocardial infarction were randomly assigned to receive nifedipine (20 mg orally every 4 hours for 14 days) or placebo in addition to standard care. Treatment was initiated at 4.6 ± 0.1 hours after the onset of pain. Infarct size, calculated by the MB-CK method, was expressed as CK-gEq/m^2 plus or minus standard errors of the means.

The data revealed that the incidence of progression to infarction among patients with threatened infarction was not significantly altered by nifedipine (33 of 48 for placebo treatment and 43 of 57 in the nifedipine-treated group). Moreover, the infarct size index did not differ between the two groups (16.9 ± 1.5 MB-CK gEq/M^2 for placebo, n = 65; 17.0 ± 1.5 MB-CK gEq/M^2, n = 68 for the nifedipine-treated group) for the patients with threatened infarction progressing to infarction and for those who came to the hospital with unequivocal criteria for acute myocardial infarction. It was also noteworthy that at 2 weeks the mortality for the placebo group was 0%, whereas for the nifedipine group it was 7.9% ($p < 0.018$) but at 6 months there were no significant differences (8.5% vs. 10.1% for nifedipine). The conclusion that can be drawn from this study is that nifedipine had no beneficial effect on the outcome of threatened infarction; this is supported by other studies [62].

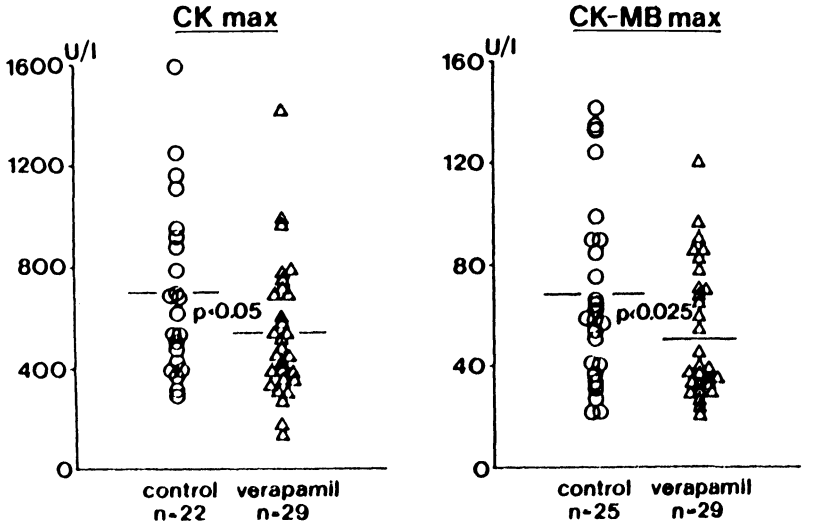

Figure 7–4. The effects of verapamil on the peak (max) creatine kinase (CK) and CK-MB enzyme levels; they were generally lower in the verapamil-treated group than in the control group. There was a significant difference in the means. With the permisison of the authors [60] and of the *American Journal of Cardiology*.

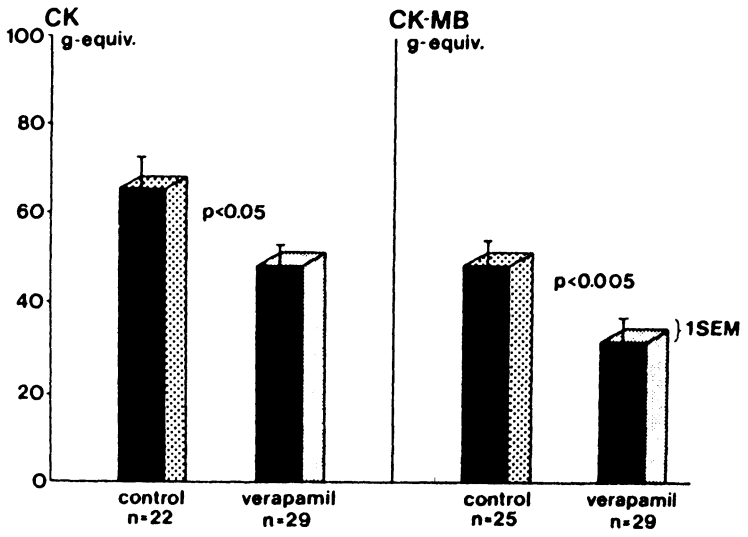

Figure 7–5. CK and CK-MB infarct size in 54 patients. Reduction in infarct size as determined by CK and CK-MB enzyme activity during verapamil therapy. The differences were clearer with the isoenzyme CK-MB. SEM = standard error of the mean. With the permission of the authors [60] and the *American Journal of Cardiology*.

Unlike verapamil, the drug did not reduce enzymatically estimated myocardial infarct size. The reasons for the difference are not clear, but it may be related to the tachycardia effect of the dihydropyridines in contrast to those of verapamil and diltiazem, which have either no effect on heart rate or may decrease it. The heart-rate lowering effect of certain calcium antagonists may therefore be of crucial importance in altering ischemic damage in the early phases of acute myocardial infarction, a consideration that is clearly of practical importance in the choice of an agent for cardioprotective actions in patients with infarction.

Whether infarct-size modification in the early stages of acute myocardial infarction by drug therapy is an established therapeutic modality is a controversial issue. No definitive conclusions can be reached on the basis of secure data. However, it is clear that in the case of calcium antagonists, the experimental basis for the clinical approach is reasonably compelling. On the other hand, the clinical data appear to be less decisive and vary with the individual agent and the time and possibly route of administration. The role of calcium antagonists in this setting needs to be evaluated relative to the effects of early intravenous administration of beta blockers and to those of thrombolytic therapy with or without the addition of aspirin.

Ischemic ventricular arrhythmias and calcium antagonists

The experimental basis for the possibility that certain ventricular arrhythmias complicating myocardial ischemia or acute infarction [22, 54] might be sensitive to calcium antagonists has briefly been alluded to above. The clinical data, essentially of an anecdotal type, is conflicting. Perhaps the earliest report was that of Heng et al. [63], who gave 10 mg IV verapamil to patients with sustained ventricular tachycardia in the context of recent myocardial infarction; conversion to sinus rhythm occurred in only one, but it was uncertain whether this was related to drug effect or whether the conversion was merely spontaneous and fortuitous. It is of interest, however, that Filias [64] reported a reduction in the number of premature ventricular contractions (PVCs) complicating acute infarction in patients given intermittent or continuous intravenous infusion. Similar results have been reported by Fazzini et al. [65], who noted that 0.10 mg/kg of intravenous verapamil given over 2 minutes resulted in complete abolition of PVCs in 7 of 8 patients who exhibited persistent frequent PVCs during the first 48 hours of acute myocardial infarction. Favorable responses have also been reported in sustained arrhythmias in this setting. For example, Sclarovsky et al. [66] administered 3–5 mg of intravenous verapamil to eight patients with multiform accelerated idioventricular rhythm occurring during the first 12 hours of acute myocardial infarction. The arrhythmia was abolished in six, slowed in one, and was without effect in the remaining patient. Successful control of polymorphous ventricular tachycardia by verapamil treatment was also recently reported by Grenadier et al. [67] in 3 of 4 patients during acute myocardial infarction. These three patients had failed

on lidocaine, class 1 agents, overdrive pacing, and repeated cardioversion. However, these and others [68] are uncontrolled studies that raise the possibility of but do not provide conclusive proof that calcium antagonism by verapamil might be effective in controlling ventricular tachyarrhythmias. It can be considered that the apparent salutary effect might result from improved ischemia and myocardial conduction [69, 70] rather than as a consequence of a direct antiarrhythmic effect of the drug in ventricular muscle or in the Purkinje fibers. Improvement in ischemia in this situation might be effective in reversing reentry triggered, as well enhanced, automaticity. Moreover, it must be emphasized that in the context of myocardial ischemia, verapamil and other calcium antagonists may exert a potent effect in reversing coronary artery spasm or vasoconstriction and thus may relieve ischemia and ischemia-induced ventricular tachyarrhythmias. Such an effect must be regarded as a secondary antiarrhythmic effect that is likely to be most readily apparent in the the setting of Prinzmetal variant angina [71].

Calcium antagonism and sudden death and reinfarction in survivors of acute myocardial infarction

On theoretical considerations and based on the available experimental data, calcium-channel blockers appeared to offer a large potential for the reduction in the incidence of sudden death and in the reinfarction rate in the survivors of acute myocardial infarction. They are potent coronary dilators and potent antiischemic agents. Like beta blockers, they raise the ventricular fibrillation threshold in the ischemic myocardium. However, to date, the promise of their expected cardioprotective actions in the survivors of acute myocardial infarction is essentially unfulfilled. The underlying reasons for the variable or negative effect in this setting are unclear, but they may at least in part relate to the lack of a depressant effect on the heart rate. The reduction in heart rate appears to be the common denominator in the case of beta blockers having a salutary effect on sudden death and reinfarction rate in patients surviving acute infarction [72]. For example, in the case of verapamil, the first calcium antagonist that has been investigated with the aim of reducing mortality and the reinfarction rate in survivors, the results inconclusive [72–76]. In this 1436 patient study, 717 were treated with verapamil and 719 with placebo. At the end of 6 months, the mortality in the treated group was 12.8% and 13.9% in the placebo series. At 12 months, the corresponding figures were 15.2% versus 16.4%. Although a trend in mortality reduction was evident in this study, it is clear that the drug, given early, did not significantly influence early mortality from acute myocardial infarction.

Yusuf and Furberg [77] have recently reviewed all the randomized trials of calcium antagonists following acute myocardial infarction. They combined all the mortality data by the Mantel-Hanszel method [77, 78] for each of the calcium antagonist for which data were available from short-term and long-term trials and for all the trials in total. They calculated a pooled odds ratio and

its 98% confidence limits, aiming at providing a typical estimate of the effects of the individual agents on mortality.

The data (summarized in table 7–1) indicated that 13, 139 patients were studied in nine randomized controlled trials [61, 75, 79–85]. It was noteworthy that 8 of the 9 trials showed *a small excess of mortality* in the treated group, although the difference from the effects of placebo did not reach statistical significance. There were 574 deaths among the 6567 patients randomized to the active treatment group (8.7%); in the control group, there were 545 deaths in a population of 6572 (8.3%). This gave an odds ratio of 1.06, with a 95% confidence interval of 0.94 to 1.20. The results were similar when the data were split according to whether the trials were evaluated early in the treatment or when treatment was delayed 1–2 weeks following myocardial infarction. It was of interest that an excess but nonsignificant mortality was consistently observed with all of the above agents. However, it should be emphasized that while the data on verapamil (one trial with 3464 patients), lidoflazine (one trial with 1792 patients), and nifedipine (five trials with 7309 patients) were derived from reasonably large population samples, the data on diltiazem are limited (only 576 in one trial). Thus the potential beneficial effect of diltiazem on mortality in patients with myocardial infarction cannot be excluded. As stressed by Yusuf and Furberg [77], the unexpectedly disappointing results on mortality following calcium antagonists are consistent with the failure of this class of drugs to exhibit an unequivocally beneficial effect on infarct size, on the development of myocardial infarction, or on the development reinfarction in trials of myocardial infarction or unstable angina [86]. However, the positive data from the recent trial of diltiazem in patients

Table 7–1. An overview of mortality in trials evaluating calcium-channel blockers following myocardial infarction

Agent (no. studies)	Deaths/patients: Calcium blockers	Deaths/patients: Controls	Observed-expected	Variance
A. ACUTE, SHORT-TERM STUDIES				
Verapamil (1)	0/8	2/9	−0.9	0.5
Nifedipine (4)	171/2509	157/2521	+7.5	76.5
Diltiazem (1)	11/287	9/289	+1.0	4.8
Subtotal (6)	182/2802	168/2819	+7.6	82.0
B. LONG-TERM STUDIES				
Nifedipine (1)	66/1140	64/1139	+1.0	30.7
Lidoflazine (1)	177/896	168/896	+4.5	69.7
Subtotal (2)	243/2036	232/2035	+5.5	100.4
C. ACUTE AND LONG-TERM STUDIES				
Verapamil (1)	149/1729	145/1718	+1.5	67.2
Total (9)	574/6567	545/6572	+14.6	249.6

Typical odds ratio of 1.06; 95% confidence interval (CI) of .94 to 1.2, NS. Reproduced from Yusuf and Furberg [77] with permission.

with non-Q-wave infarction merits consideration [87]. This multicenter, randomized, double-blind trial [87], involved 576 patients recovering from non-Q-wave infarction. Diltiazem (360 mg/day) was given to 278 patients and placebo was given to 289 patients for 14 days after acute myocardial infarction. The two groups were identical. The 14-day mortality was similar in both groups, but reinfarction occurred in 26 patients on placebo and in 11 patients in the diltiazem group. The difference of 42% was significant ($p < 0.04$). It is striking that there was a very low incidence of mortality (3%) in both the treated as well as the placebo groups, but one important feature of the patients entering the study was that 61% of them were treated concurrently with beta blockers. It may well be that the demonstrated salutary effect of diltiazem on reinfarction may be greatest in the presence of beta blockade, a finding also noted in trials involving patients with unstable angina [86].

CONCLUSIONS

There is a substantive body of experimental data indicating that calcium antagonists administered before or shortly (1–3 hours) after coronary artery occlusion exert a beneficial effect on ischemic ventricular arrhythmias, reduce myocardial infarct size, and raise the ventricular fibrillation threshold. They improve conduction velocity in the ischemic ventricular myocardium. This aggregate of pharmacologic effects suggests that, as a class, calcium antagonists may be expected to be effective in controlling ischemic ventricular arrhythmias, in decreasing sudden cardiac death, and in preventing reinfarction in patients surviving acute infarction. The available data from existing clinical trials are indecisive. The pooled data from all trials indicate about a 5%–6% excess in mortality following prophylactic treatment with calcium antagonists. One trial, however, suggested a reduction in the reinfarction rate of non-Q-wave infarction after 14 days of treatment without an effect on mortality. As far as the benefit on mortality is concerned, the analysis of confidence intervals of the pooled data from all trials indicated a small reduction in mortality, probably not exceeding 5%. Thus, the available data indicate that the prophylactic administration of calcium antagonists to survivors of acute infarction in the absence of defined indications (e.g., hypertension, angina, supraventricular arrhythmias) cannot as yet be recommended until evidence for a clear reduction in mortality is established by future trials.

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8. POSTINFARCTION ANGINA

ELLIOT RAPAPORT

Curves of serum creatine kinase activity against time following an acute myocardial infarct suggest that the usual Q-wave infarct evolves over a 24–36 hour period. Consequently, recurrent chest pain after its initial subsidence during this interval cannot be attributed a priori to reversible ischemia but may arise from the evolving infarct. However, after the first 1–2 days, recurrence of chest pain presumably reflects either reversible ischemia or an extension of the original infarct.

PROGNOSIS

Prognosis following recovery from a myocardial infarction primarily depends upon the state of left ventricular function, the presence or absence of ventricular ectopy, particularly complex ectopy, and the presence of continuing myocardial ischemia. Continuing ischemia may manifest itself either by episodes of recurrent ischemic chest pain, which in the immediate post-infarction period is designated *postinfarction angina*, or it may be latent and become evident only with noninvasive laboratory investigations such as stress electrocardiography, exercise-stress thallium scintigraphy, or ambulatory monitoring. Postinfarction angina occurs two to three times as frequently among patients who experienced angina before their infarct than in those without prior angina [1, 2] and occurs in approximately one third of patients following myocardial infarction.

Clinical postinfarction angina, particularly when it becomes evident during

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the first few days or weeks after a myocardial infarct, generally implies a serious prognosis. Mortality statistics among various cohorts of postinfarct patients demonstrating postinfarction angina vary significantly [1–6]. The most dramatic report of a poor outcome was the study by Schuster and Bulkley [3]. In a group of 70 patients, many of whom were referred specifically because of continuing postinfarction angina, an overall 56% mortality was observed within the first 6 months following myocardial infarction among patients treated medically. Mortality was significantly greater among those with remote ischemia compared to those where the ischemia was arising in the infarct zone. The best prognosis is the experience reported by the Multicenter Post-Infarction Research Group (MPIP), who have observed only a 17% 3-year mortality in patients with postinfarction angina [2]. This startling difference reflects both differences in cohort definitions as well as surgical intervention in some of the MPIP cases. Regardless of whether the true figure more closely approximates the MPIP or the Johns Hopkins experience, medical management of patients demonstrating postinfarction angina has clearly been disappointing.

Similarly, even patients with silent myocardial ischemia detected by a positive stress test, ST-segment changes on Holter monitoring, reversible segmental wall motion abnormalities observed during an exercise radionuclide ventriculogram, or a reversible defect on an exercise thallium scintigram prior to hospital discharge, have a higher 1-year mortality and/or cardiac event rate. In their study of a large number of patients who underwent low-level exercise stress tests prior to hospital discharge, DeBusk and his associates found a threefold increase in cardiac events over the following 2 years among those who demonstrated a positive low-level stress test compared to those who demonstrated a negative test [7]. Similar results have been observed by others [8, 9]. Recently, Gottlieb and his collaborators reported an increased 1-year mortality among high-risk postinfarction patients who demonstrated silent ischemia on a predischarge Holter monitor [10]. A similar increased mortality has been reported by this group for hospitalized patients with unstable angina who demonstrated silent ischemia during the first 48 hours of hospitalization [11].

Postinfarction angina predisposes a patient to infarct extension, particularly in non-Q-wave infarcts. In the MILIS trial, infarct extension was observed in 71 of 848 patients or 8.4%. Multivariate analyses revealed that extension was more likely to occur when the admission ECG revealed ST-segment depression, the usually accepted criterion for the designation of a non-Q-wave infarct [12]. Among studies of patients with postinfarction angina, infarct extension has been reported in 20% to 40% of cases [13]. Infarct extension carries an increased mortality risk during the initial hospitalization. Among 58 patients with Q-wave infarcts who extended, Maisel et al. [14] reported 14 deaths, or 24% mortality. Nine non-Q-wave infarct cases died out of 23 who extended their infarcts, a 39% in-hospital mortality. These high rates

are contrasted in the series reported by Maisel et al. to an 8% in-hospital mortality among patients without detectable extension.

Late mortality has also been reported to be increased in patients who experience an initial infarct extension. The most dramatic data are again those reported by Maisel et al. [14]. They observed a 1-year mortality of 66% among non-Q-wave infarct patients who had extended their infarct, compared to 16% among those without extension. Q-wave infarct cases had a 34% mortality rate after extension, compared to 18% without extension, but this was not a statistically significant difference. In contrast, the MILIS trial showed no subsequent difference in late mortality rates over the first year after the initial hospital mortality differences occurred.

MANAGEMENT

It is disappointing that no randomized clinical trials have been carried out evaluating medical compared to surgical management among patients demonstrating postinfarction angina. Comparisons of surgery with medical management have been carried out in asymptomatic myocardial infarct patients as part of the CASS trial. In this situation, no overall reduction in mortality was demonstrated among those randomized to surgery compared to those receiving medical management [15]. Similarly, patients who have suffered a recurrent myocardial infarction have been randomized subsequently to medical compared to surgical management [16]. Again, surgical intervention under these circumstances was not found to be beneficial from the standpoint of an improvement in overall mortality over time. However, the subset of patients with early postinfarction angina alone have not been specifically studied with survival as the endpoint in a randomized clinical trial evaluating medical compared to surgical management. It is therefore necessary for us to utilize the available observational data to determine appropriate management of this problem.

Coronary artery bypass graft surgery

Surgical management of the postinfarction patient is generally accomplished with a good immediate and long-term outcome. In an analysis of patients undergoing coronary artery bypass surgery at the University of Oregon, Rahimtoola found an 83% 10-year survival among patients with postinfarction angina, a value that was comparable to other patients undergoing surgery for unstable angina [17]. However, in many cases these patients were operated many months after recovering from their infarct. It seems appropriate to distinguish between postmyocardial infarct patients who develop either rest or exercise angina within days or weeks after their infarct and those who develop angina months to years later from progression of their coronary artery disease. It is the former group who appear to be at a particularly high risk for an extension of their infarct or sudden death. Therefore, the more relevant

analyses of surgical results are among patients operated upon during the first few days and weeks following a myocardial infarct because of continuing ischemia, particularly clinical postinfarction angina.

In general, the operative mortality during the first 6 weeks following coronary bypass graft surgery for postinfarction angina is comparable to that observed in other types of unstable angina [18–23]. If left ventricular ejection fraction is essentially normal, the timing of surgery appears less crucial; however, when there is significant impairment of left ventricular contractility, early intervention within a matter of days following the onset of the original infarction is likely to be associated with a poorer outlook than if surgery can be postponed. Hochberg et al. [24] reported a 16% hospital mortality among 174 patients undergoing myocardial revascularization within 7 weeks of their infarct. Hospital mortality was 46% for those patients operated upon within 1 week, but many of these cases reflected patients in cardiogenic shock; nevertheless, survival rates steadily improved when revascularization was delayed and became more remote from the onset of the infarction. It is of interest that 138 of the 174 patients studied by Hochberg had elective myocardial revascularization, in that the patients were either experiencing stable angina pectoris or underwent surgery because of ominous pathology on coronary arteriography despite the fact that they were asymptomatic. When the patients were looked at in terms of left ventricular contractility, all patients with a normal ejection fraction survived their hospital course regardless of the time of surgery. Although all patients with ejection fractions over 50% survived, surgery within the first 2 weeks following infarction in those patients with a reduced ejection fraction was associated with a survival under 80%. In contrast, when surgery was performed after week 4, survival in patients with impaired left ventricular contractility was over 90%. It would thus appear desirable to delay surgery at least until 2 weeks have passed, and, if possible, even 4 weeks after the original infarction.

Our approach is to ensure that all patients demonstrating continuing ischemia prior to hospital discharge, either clinically or through non-invasive testing, are studied by coronary arteriography. Arteriography in the postinfarct period is accomplished readily and does not appear to add to the risk that a patient normally faces from this procedure. When obstructive coronary artery lesions are demonstrated, supplying an area from which ischemia appears to arise, the patient is a candidate for surgical revascularization or PTCA.

PTCA

An alternative to early CABG surgery is coronary angioplasty. Angioplasty is particularly attractive when the patient is relatively refractory to medical management and revascularization must be performed within the first week or two after the infarct. Angioplasty avoids the stress of major anesthesia and the trauma of operative intervention. Additionally, it is likely to be associated

with a reduced hospital stay and cost. Results suggest that this expectation is being met. Several reports of angioplasty in postinfarction angina describe results comparable to that observed in chronic stable angina pectoris [25–28]. Furthermore, myocardial infarction is more commonly associated with single-vessel than multivessel disease. In the trials evaluating PTCA after thrombolytic therapy in acute myocardial infarction, approximately 50% of the cases were suitable for angioplasty. Percutaneous transluminal coronary angioplasty is preferred to bypass surgery if single-vessel disease is present, although if multivessel disease is seen, our practice more commonly is to undertake surgical intervention. Although single-vessel disease is common in patients experiencing acute myocardial infarction, postinfarction angina is usually seen in patients demonstrating triple-vessel disease [3].

Timing of intervention

The major problem that one faces under these circumstances is the issue of timing of the intervention. Among patients developing postinfarction angina in the hospital, the average onset is between 3 and 4 days after the acute infarction [3]. When postinfarction angina appears within days, the question arises as to whether one should try to temporize through vigorous medical management and postpone coronary arteriography and subsequent coronary bypass surgery or PTCA as long as possible within the initial hospital period, or whether one should immediately intervene with coronary arteriography and revascularization. One always faces the prospect of an actual extension of the original infarction if one temporizes. This is particularly true if one is dealing with a non-Q-wave infarction. Patients with non-Q-wave infarction do well during the initial hospital phase. Hospital mortality is well under 5% and significantly less than that which is usually experienced among patients presenting with so-called Q-wave infarction. However, non-Q-wave infarct patients are prone to develop reinfarction in the early days and weeks following their initial infarction, and by the end of 1 year the occurrence of reinfarction, as well as sudden death, approaches that observed among Q-wave infarct cases. It would appear that the non-Q-wave infarct represents an incomplete infarction, possibly reflecting early spontaneous reperfusion following plaque rupture and transient coronary occlusion. In any case, such patients have a greater likelihood of both clinical and laboratory evidences of continuing ischemia. Increasingly, therefore, patients with non-Q-wave infarct before leaving the hospital are being studied with coronary arteriography regardless of whether postinfarction angina occurs. However, when non-Q-wave infarction is also associated with postinfarction angina, immediate arteriography is justified. In other cases of postinfarction angina, it is reasonable to attempt to defer catheterization to the end of hospitalization since if one undertakes coronary arteriography immediately after the first episode of postinfarction angina, looking toward subsequent bypass surgery, the

operative intervention may occur at a time when the risk of surgery is higher than that which would exist if several weeks were allowed to go by. However, even in Q-wave infarct cases, immediate study is warranted if more than one episode of postinfarction angina occurs despite medical management.

Medical management

Our approach is to attempt to temporize initially. Patients experiencing a recurrence of ischemic chest pain after the first 24–36 hours following the onset of a myocardial infarction are usually treated initially with intravenous nitroglycerin. Several studies have shown that pain relief is accomplished in the majority of cases [29, 30]. Nitroglycerin should be infused up to a rate sufficient to either eliminate rest pain or cause significant side effects such as nausea, vomiting, or headache. One must be cautious not to lower systolic arterial pressure more than 10–15 mmHg. If intravenous nitroglycerin fails to eliminate chest pain initially, one should administer small amounts of morphine sulfate to ensure full pain relief. If nitroglycerin is ineffective, a beta blocker is also added. Early use of beta blockers in acute myocardial infarct patients may reduce the need for analgesics as well as reduce the likelihood of reinfarction. It is therefore an appropriate drug in the patient with early postinfarction angina, particularly in a patient exhibiting hypertension and/or sinus tachycardia. Intravenous atenolol or metoprolol are usually given initially, followed later by oral administration.

Calcium antagonists have not been shown to benefit mortality in randomized trials of patients with acute myocardial infarction [31]. This has raised the question of the desirability of using this class of drugs in early postinfarction angina. To the extent that increased coronary vasomotor tone reflecting plaque rupture with associated platelet aggregation and the release of vasoactive substances may play a role in the genesis of postinfarction angina, calcium antagonists should be helpful. Furthermore, a multicenter, randomized trial of diltiazem in non-Q-wave infarction demonstrated an approximate 50% reduction in the cumulative 14-day reinfarction rate among the diltiazem-treated group compared to the placebo group [32]. A similar reduction was observed in the incidence of refractory postinfarction angina. Although these observations suggest a use for the calcium antagonist, other data are contradictory. Crea et al. failed to observe any benefit from verapamil compared to placebo in preventing early postinfarction angina in Q-wave infarct patients [33]. In addition, no reduction was observed in a randomized trial of nifedipine on the incidence of recurrent chest pain in a group of non-Q-wave infarct patients. From the above, it seems prudent to approach the patient with postinfarction angina initially with intravenous nitroglycerin followed by the addition of beta blockers if pain continues. Only if this combination still proves ineffective is the calcium antagonist added. It would seem that diltiazem is probably the calcium antagonist of choice under these circumstances.

Intravenous heparin is frequently used, although not routinely so, in acute myocardial infarction. When thrombolytic treatment is given, it is always followed by heparinization. Similarly, many groups, including our own, routinely give heparin in patients hospitalized with unstable angina characterized by rest pain. It is my view that a patient in whom postinfarction angina develops within days of a myocardial infarction, even in the absence of prior thrombolytic therapy, should be on a heparin drip.

Aspirin should also be started to maximize protection against development of recurrent thrombosis in a vessel in which spontaneous reperfusion may have occurred or where a new thrombosis in a different vessel is threatening to occur. The specific value of antiplatelet agents in postinfarction angina has not been established; there is a good theoretical basis, however, for their use. First, aspirin has been shown to be highly advantageous in patients with unstable angina characterized by rest pain and associated ECG changes. In the Veterans Administration Cooperative Study, over a 50% reduction in both 12-week reinfarction rate and mortality was observed among those patients randomized to a single aspirin tablet a day compared to those receiving placebo. Similarly, studies in the postinfarct patient data from pooled trials on the use of long-term aspirin administration suggest an 8%–10% reduction in long-term mortality. These observations, together with evidence that platelet hyperactivity is present for several weeks following a myocardial infarction, make aspirin a desirable treatment for patients with postinfarction angina. That platelet aggregation may be playing a role in the propensity of patients with acute myocardial infarction to have coronary artery spasm induced is an interesting speculation. Bertrand has presented evidence to suggest that many coronary arteries can be induced to demonstrate spasm with ergonovine administration during the first 6 weeks after myocardial infarction. It is, therefore, tempting to speculate that episodes of intermittent chest pain in patients recovering from myocardial infarction may be triggered by intermittent coronary artery spasm from the release of vasoactive substances resulting from platelet aggregability and resultant activation. The above-described medical management may successfully result in disappearance of the anginal episodes. Under these circumstances, the patient should be allowed to recover without intervention until just prior to hospital discharge. At that point and before the patient leaves the hospital, coronary arteriography should be performed. There is no need for prior low-level stress tests or other noninvasive tests designed to uncover silent ischemia. The patient has already demonstrated the presence of continuing clinical ischemia. If recurrent chest pain develops despite medical management during this recovery period, immediate catheterization should be undertaken without delay. The risk of temporizing in terms of infarct extension outweighs the benefits of postponing intervention. If rest angina continues to occur despite medical management while preparing to carry out arteriography, consideration should be given to insertion of an intraaortic balloon pump.

The increasing use of thrombolytic therapy may increase the frequency of

postinfarction ischemia. Early experience in the management of myocardial infarction suggests that residual ischemia is more likely to occur in a patient who has received thrombolytic therapy compared to one in whom it is not used. It may be inferred that thrombolytic therapy results in areas of the myocardium that might have otherwise infarcted but that were salvaged yet remain susceptible to recurrent ischemia. This view is supported by the observation that patients with transmural myocardial infarction treated with thrombolytic therapy have a decreased incidence of pericarditis compared to those who do not receive this therapy. This suggests that portions of the epicardium may be salvaged with thrombolytic therapy that might not otherwise have occurred. In a sense, part of the infarct process has been converted from a potential Q-wave to a non-Q-wave infarction, and such myocardium may be at greater risk for subsequent ischemia. Observations of new non-Q-wave infarct cases suggest a high likelihood of continuing ischemia manifested by either extension of infarction at the time of the original infarct or increased mortality or reinfarction in the months that follow. It seems clearly desirable that infarct patients treated with thrombolytic therapy be studied by coronary arteriography if evidence of subsequent ischemia appears. We extend this view to all patients with non-Q-wave infarction as well, provided there are no other medical reasons that would preclude subsequent PTCA or surgical intervention. Our current practice is to study such patients with coronary arteriography prior to hospital discharge because of the high likelihood of continuing ischemia, particularly among patients in whom anterior myocardial infarction is present.

Complex ventricular ectopy is an independent risk factor for subsequent death in patients during the first year following recovery from myocardial infarction [34]. It is of some interest that this risk primarily results from that subgroup of patients who have experienced a non-Q-wave infarct [5]. This suggests that it may well be the underlying subclinical ischemia that may be promoting the observed ectopy and leading to the subsequent occurrence of sudden death or myocardial reinfarction.

Recently there has been an increasing interest in the role of silent ischemia in patients with coronary artery disease. Silent ischemia present in the postmyocardial infarction patient is usually discovered either by a positive low-level treadmill stress test or low-level thallium scintigraphy prior to hospital discharge in a patient without clinical symptoms. It may also be picked up by routine ambulatory monitoring in an asymptomatic patient prior to hospital discharge. We have carried out such examinations for many years, primarily to detect unrecognized complex ectopy; however, such examinations may also uncover long periods, during the 24 hours of observation, in which the patient may demonstrate significant ST-segment elevations (or depression) in the absence of any clinical symptoms. Figure 8–1 is an example of a 24-hour predischarge Holter monitor in one of our patients who was asymptomatic while recovering from an acute anterior infarction. She demonstrated either

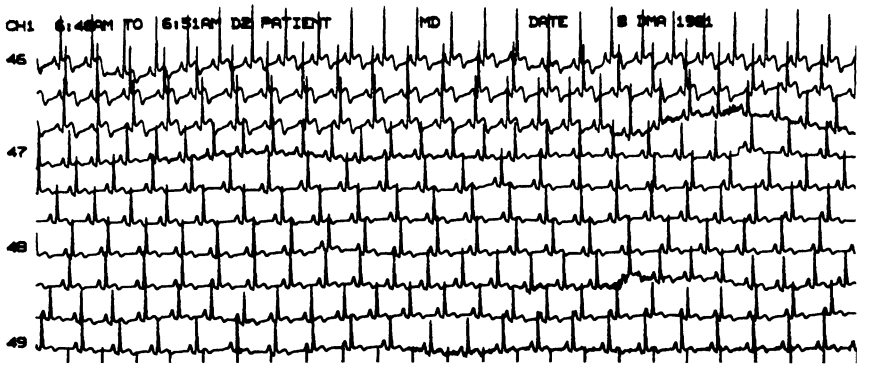

Figure 8–1. Section of continuous Holter monitoring of a patient 7 days following acute anterior myocardial infarction. During minute 46, ST-segment elevation is apparent. During minute 47, the ST segment becomes isoelectric and the T wave becomes diphasic. In other sections clear-cut ST-segment depression was also seen.

ST-segment elevation or ST depression for a total of almost 2 hours during the 24-hour period in which ambulatory monitoring was taking place. During these periods, this electrocardiographic evidence of ischemia was unassociated with chest pain. I believe it is desirable to study such patients with coronary arteriography prior to hospital discharge in light of the increased risk of mortality. In this patient, significant left main coronary artery disease was uncovered as well as 95% obstruction in the left anterior descending coronary artery and less significant lesions in the right and circumflex coronary arteries. The patient was scheduled for urgent coronary artery bypass graft surgery, which was carried out uneventfully.

A more difficult decision is the appropriate management when silent ischemia is discovered many months or years after recovery from a myocardial infarct. It is our feeling that such patients need to be treated with medical management when this finding is discovered, even if they are totally asymptomatic. Silent ischemia cannot be ignored. Furthermore, followup monitoring should be carried out, and if the patient continues to demonstrate silent ischemia despite adequate medical management, coronary arteriography should be performed with a view toward the subsequent performance of PTCA or even bypass surgery.

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9. THE MANAGEMENT OF PUMP FAILURE

KANU CHATTERJEE

Pump failure has emerged as the principal cause of death in patients with acute myocardial infarction, since mortality from primary dysrrhythmias has declined as a result of advances in their detection and management. The severity of pump failure is related, in general, to the total amount of non-functioning myocardium, which includes recently infarcted segments, scar tissue from remote infarction, and ischemic but viable myocardial segments. If one can decrease the extent of myocardial injury and improve function of ischemic myocardium, the severity of pump failure is expected to be less and immediate, and the late prognosis is expected to be better. Potential exists for decreasing the "infarct size" and improving global and regional myocardial function with reperfusion therapy. Thus, thrombolytic therapy, primary angioplasty, or both deserve consideration for the management of pump failure complicating myocardial infarction. However, recanalization of the infarct-related coronary artery is not always associated with preservation of ischemic myocardium; furthermore, even when salvage of ischemic myocardium is achieved, its function may not improve immediately because of the phenomenon of "stunned myocardium" [1]. Thus, in practice, aggressive supportive therapy is required to improve pump function in those patients who develop pump failure following acute myocardial infarction, even when recanalization of the infarct-related artery occurs and the extent of myocardial injury is reduced with reperfusion therapy. This chapter deals with the supportive therapy of pump failure complicating myocardial infarction. Some complications of

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Table 9–1. Complications of acture myocardial infarction associated with low cardiac output

1. Primary dysrhythmias
2. Predominant right ventricular infarction
3. Hypovolemic shock
4. Left ventricular failure
   a. Without mechanical defects
   b. With mechanical defects
      i) mitral regurgitation
      ii) ventricular septal rupture
      iii) ventricular aneurysm
5. Cardiac tamponade (free-wall rupture)
6. Pulmonary embolism

acute myocardial infarction can precipitate severe pump failure, even when the extent of myocardial damage is relatively small. This includes acute mitral regurgitation due to papillary muscle infarction and/or ventricular septal rupture. Predominant right ventricular infarction may also be associated with "low-output syndrome" resulting from right ventricular failure. Cardiac tamponade due to "free wall" rupture and pulmonary embolism may also precipitate a severe low-output state. It should be recognized that bradyarrhythmias and tachyarrhythmias, and hypoxia and acidosis, if unrecognized and untreated, may also precipitate severe pump failure in patients with recent myocardial infarction. Thus, in addition to the extent of nonfunctioning myocardium, several complications may be contributory. The potential complications that can be associated with low cardiac output following acute myocardial infarction are summarized in table 9–1.

RIGHT VENTRICULAR INFARCTION

Right ventricular infarction is a frequent accompaniment of inferior or inferoposterior myocardial infarction. The incidence of right ventricular infarction, estimated by clinical, electrocardiographic, echocardiographic, scintigraphic, and hemodynamic studies is approximately 30%–50% in patients with inferior myocardial infarction [2]. However, only about 10% of these patients develop overt right heart failure, hypotension, and a low-output state [2, 3].

Diagnosis of right ventricular infarction can be made with a high degree of sensitivity and specificity by recognizing abnormal clinical and electrocardiographic findings. Clinical findings of right ventricular failure, with or without tricuspid regurgitation, in the absence of overt left ventricular failure and pulmonary arterial hypertension, provide evidence for right ventricular infarction. Kussmaul's sign has been reported to have a high predictive value in the diagnosis of acute right ventricular infarction [2, 4]. Certain electrocardiographic findings also appear to have a high degree of sensitivity and specificity for the diagnosis of right ventricular infarction: ST elevation in lead V_1, and sometimes extending to even lead V_5; ST elevation in leads V_4, and loss of "r" waves in these leads are virtually diagnostic of right ventricular

infarction in the presence of inferior or inferoposterior myocardial infarction [5]. Marked elevation of the enzyme creatinine-kinase in uncomplicated inferior myocardial infarction should also raise the possibility of right ventricular infarction. Assessment of right and left ventricular function by echocardiography and gated blood-pool scintigraphy usually demonstrate increased right ventricular dimensions and compromised systolic function of the right ventricle, when left ventricular ejection fraction may be relatively preserved [6]. ^{99m}Tc pyrophosphate scintigraphy reveals uptake in the free walls of the right ventricle, as well as in the inferior part of the intraventricular septum and inferior walls of the left ventricle [7]. Abnormal hemodynamics reflect the pathophysiologic abnormality in right ventricular infarction. Depressed right ventricular systolic function is associated with elevation of right ventricular end-diastolic and right atrial (central venous) pressures. As left ventricular failure may not occur, pulmonary capillary wedge pressure may remain normal or only slightly elevated. Thus, the ratio of right atrial pressure to pulmonary capillary wedge pressure becomes abnormal and exceeds the normal value of 0.7 [8]. In the presence of right ventricular failure, right atrial, pulmonary-artery diastolic, and pulmonary capillary wedge pressures may be similar, suggesting equalization of the "diastolic pressures" [9].

The mechanism for equilization of diastolic pressures appears to be due to increased intrapericardial pressure, which results from acute right ventricular dilatation following infarction and the constraining effects of the pericardium. With an open pericardium, the equalization of the diastolic pressures is not observed [10]. Besides right ventricular infarction, other conditions such as pulmonary embolism, cardiac tamponade, severe tricuspid regurgitation, and restrictive cardiomyopathy may also be associated with a similar hemodynamic profile, i.e., disproportionate elevation of right atrial pressure and equalization of right atrial and pulmonary capillary wedge pressures. As cardiac tamponade may also be a complications of acute myocardial infarction, echocardiography should be performed for the differential diagnosis. In cardiac tamponade, in addition to pericardial effusion, right ventricular diastolic compression is present; right ventricular infarction, on the other hand, is associated with a dilated an poorly contracting right ventricle.

Decreased systemic output following right ventricular infarction results from inadequate left ventricular preload. In experimental animals, induction of isolated right ventricular infarction causes right ventricular dilatation and decreased left ventricular size [11]. Increased right ventricular volume and transmural pressure are accompanied by decreased left ventricular volume and transmural pressure. A number of interrelated functional and hemodynamic abnormalities contribute to reduced left ventricular preload (figure 9–1). Compromised contractile function of the right ventricle decreases right ventricular stroke volume. Right ventricular dilatation is associated with increased right ventricular afterload and increased resistance to right ventricular ejection, which also tend to decrease right ventricular stroke volume. Increased

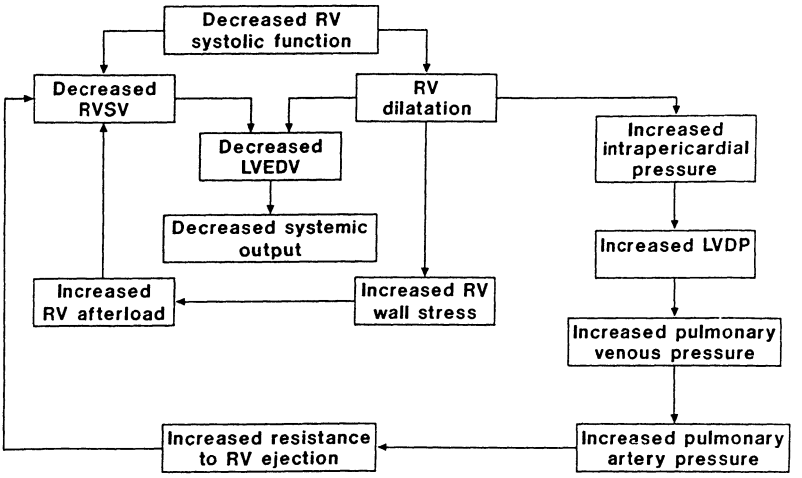

Figure 9–1. The various mechanisms that may contribute to low systemic out-put in right ventricular infarction.

intrapericardial pressure and the leftward shift of the interventricular septum may be associated with a substantial increase in left ventricular diastolic and pulmonary venous pressures. Consequently, pulmonary artery pressure may also rise, which increases right ventricular ejection impedance. Decreased right ventricular stroke volume produces inadequate left ventricular filling. The constraining effect of the pericardium and the encroaching of the left ventricular cavity by the interventricular steptum also contribute to decreased left ventricular preload.

It is apparent that to increase systemic output, maintenance of adequate left ventricular preload is necessary. Intravenous fluid therapy has been suggested to increase left ventricular preload and has been found effective in some patients with right ventricular infarction [12]. Also in animals with isolated right ventricular infarction, volume expansion is associated with increased cardiac output [13]. Although it was initially thought that the passive filling of the left ventricle is the mechanism for increased preload during volume expansion, experimental studies suggest that improved right ventricular pump function contributes to increased left ventricular preload [13]. With intravenous fluid administration, right ventricular diastolic volume and transmural pressure increase with concomitant increases in left ventricular diastolic volume and transmural pressure. Thus, the improvement in both right and left ventricular systolic function appears to result from improved Starling function. As during volume expansion, improvement in right ventricular function is related to its so-called Starling reserve; it is unlikely that intravenous fluid therapy will cause any substantial increase in stroke volume, if the right ventricle is already markedly dilated. Indeed, in patients with significantly elevated right atrial

pressure and pulmonary capillary wedge pressure (≥15 mmHg), volume expansion does not increase cardiac output significantly [14, 15]. Furthermore, an excessive dilatation of the right ventricle can cause a disproportionate increase in right ventricular wall stress (afterload), which potentially can decrease right ventricular stroke volume. A reduction of right ventricular ejection impedance is expected to increase right ventricular stroke volume and left ventricular preload. This is the rationale for the use of pharmacologic agents such as sodium nitroprusside and nitroglycerin, which can reduce pulmonary artery pressure and pulmonary vascular resistance. However, during vasodilator therapy, concomitant intravenous fluid therapy is usually required to prevent excessive reduction of ventricular preload.

Inotropic agents, dobutamine and dopamine, are also effective in increasing cardiac output [14]. The mechanism appears to be improved right ventricular systolic function, as its ejection fraction tends to increase significantly. Enhanced ejection fraction results from decreased end-systolic volume and increased stroke volume, without any significant change in right ventricular end-diastolic volume. Although dopamine has been shown to increase cardiac output in right ventricular infarction, it may be less effective than dobutamine. Dopamine can cause an increase in pulmonary capillary wedge pressure and pulmonary arterial resistance. Thus, an increased resistance to left ventricular ejection may curtail the expected increase in right ventricular stroke volume from its positive inotropic effect. The use of dopamine, therefore, should be restricted to those patients who remain hypotensive. Dobutamine also appears to be more effective than sodium nitroprusside in improving sytemic output in patients with right ventricular infarction. In the study reported by Dell'Italia, et al. [14], there was no significant increase in cardiac index, stroke volume index, and right ventricular ejection fraction with sodium nitroprusside; dobutamine, however, increased systemic output significantly.

When severe left ventricular dysfunction coexists, the use of an intraaortic balloon counterpulsation or left ventricular assist device may result in an improvement in both right and left ventricular function. In a few patients with severe right ventricular failure, pulmonary artery counterpulsation has been attempted with variable success. The majority of patients, however, recover from the low-output state with conservative therapy. Bradyarrhythmias are more frequent in right ventricular infarction and can precipitate severe hypotension and low output, even in the absence of extensive right ventricular damage [16]. Clinical experience suggests that the maintenance of timed atrial systole, with atrioventricular sequential pacing or atrial pacing, is more effective than ventricular pacing in increasing cardiac output in the presence of atrioventricular block, junctional rhythm, or sinus bradycardia. At an identical pacing rate, stroke volume is considerably greater with atrioventricular pacing than with ventricular pacing [17]. Thus, atrioventricular or atrial pacing is preferable to ventricular pacing in the management of bradyarrhythmias complicating right ventricular infarction. The suggested therapeutic approach for the management of right ventricular infarction is outlined in Table 9–2.

Table 9–2. Right ventricular infarction, diagnostic and therapeutic approach

1. Suspect the diagnosis in patients with inferior infarction when there is
   a. Evidence of right ventricular failure in the absence of overt left ventricular failure
   b. Kussmaul's sign
2. Noninvasive investigations usually confirm the diagnosis
   a. Electrocardiogram: ST-segment elevation in V_1hr, V_4R, V_3R in the presence of evolving inferior or inferoposterior myocardial infarction
   b. Echocardiography: dilated, poorly contracting right ventricle; no evidence of cardiac tamponade
   c. Radioisotope ventriculography: decreased right ventricular ejection fraction, left ventricular ejection fraction may be normal
   d. ^{99m}Tc pyrophosphate scintigraphy: uptake by the free wall of the right ventricle
3. Hemodynamic monitoring is recommended during mangement of low-output state
   a. Low cardiac output; right atrial pressure and pulmonary capillary wedge pressures are < 15 mmHg: ⟶ intravenous fluid ⟶ inadequate response ⟶ vasodilators if blood pressure is adequate ⟶ inadequate response ⟶ dobutamine
   b. Low cardiac output; right atrial pressure and pulmonary capillary wedge pressures are > 15 mmHg: ⟶ dobutamine or nitroprusside ⟶ inadequate response ⟶ combined dobutamine and nitroprusside
   c. Low cardiac output; right atrial pressure and pulmonary capillary wedge pressures are > 15 mmHg and hypotension: ⟶ dopamine ⟶ inadequate response ⟶ add dobutamine ⟶ inadequate response but blood pressure is higher ⟶ add nitroprusside
   d. In the presence of left ventricular failure: intraaortic balloon counterpulsation, in addition to vasodilator therapy and inotropic agents, may be required.

Although the outcome is generally favorable, some complications may be associated with an adverse prognosis in patients with right ventricular infarction. The degree of concomitant left ventricular dysfunction appears to be the most important determinant [18]. Significant pulmonary arterial hypertension may be associated with a worse prognosis, presumably due to a considerable increase in right ventricular ejection impedance. Severe tricuspid regurgitation, either due to infarction of the right ventricular papillary muscle or marked right ventricular dilatation, may cause severe hemodynamic compromise [19]. Marked arterial desaturation may occur in occasional patients from a right-to-left shunt through a patent foramen ovale [20]; until rapid decompression of the right atrium is achieved, hypoxemia persists, which is associated with an unfavorable prognosis. Rupture of the free wall of the right ventricle, with our without rupture of the interventricular septum, is also associated with a very poor prognosis [21]. In some patients, recurrent pulmonary emboli may occur from a right ventricular mural thrombus, which can be associated with significant pulmonary arterial hypertension and a relatively poor prognosis [22]. It needs to be emphasized that the majority of patients with right ventricular infarction recover, and the long-term prognosis also remains quite favorable. Haines et al. [23] reported that only 3 of 27 patients (11%) with right ventricular dysfunction accompanying acute inferior wall myocardial infarction died during the average followup period of 24

months. Right ventricular ejection fraction improves considerably in the recovery period, and the improvement has been observed as early at 10 days after acute right ventricular infarction. Klein et al. [24] reported that right ventricular ejection fraction at 2 months increased to 43 ± 9% from 21 ± 8% in 37 of 54 patients studied.

LEFT VENTRICULAR FAILURE

The clinical syndrome of left ventricular failure in acute myocardial infarction manifests with evidence for pulmonary congestion and/or hypoperfusion. The hemodynamic correlates are elevated pulmonary capillary wedge pressure and low cardiac output. Based on the clinical manifestations and the hemodynamic abnormalities,a number of subsets can be identified [25] (table 9–3). The hospital mortality is lowest in subset I (1%–3%) and highest in subset IV (50%–60%). In the patients with pulmonary congestion only, or with elevated pulmonary capillary wedge pressure but adequate cardiac output, the mortality is approximately 10% and is higher (18%–23%) in patients with hypoperfusion and without pulmonary congestion (subset III).

The hemodynamic abnormalities accompanying left ventricular failure may result from one or more of the following pathophysiologic mechanisms: 1) predominantly abnormal diastolic function with relatively preserved systolic function; 2) predominantly depressed systolic function, primarily due to decreased overall contractile function, but also due to a compensatory inappropriate increase in systemic vascular resistance; 3) relative hypovolemia and decreased intracardiac volumes; and/or 4) mechanical complications, such as severe mitral regurgitation and rupture of the interventricular septum or ventricular free walls.

Decreased left ventricular distensibility may be caused by a number of mechanisms. At the onset of myocardial infarction, a relatively large segment of myocardium may be ischemic rather than infarcted. Ischemic myocardium is less distensible because of an alteration in its relaxation properties. Relative hypertension, which is observed in some patients at the onset of infarction, may cause an upward shift of the left ventricular diastolic pressure-volume curve associated with an increased left ventricular diastolic pressure with little or no change in diastolic volume. Such a shift occurs from the constraining effects of the pericardium and ventricular interaction. Right ventricular dilatation and systolic dysfunction accompanying right ventricular ischemia or infarction may also cause a substantial increase in left ventricular diastolic pressure, without any increase or even a decrease in left ventricular diastolic volume. These hemodynamic abnormalities, indicating decreased left ventricular compliance, result from leftward bulging of the interventricular septum and increased intrapericardial pressure. Alterations is viscoelastic properties of the ischemic and necrotic tissue, due to cellular and interstitial edema in the acute phase and leukocyte infiltration and fibrosis in the subacute and chronic

Table 9–3. Subsets of acute myocardial infarction

Subset	Clinical manifestations		Hemodynamic correlates	
	Pulmonary congestion	Hypoperfusion	PCWP (mmHg)	CI (L/min/m^2)
I	Absent	Absent	≤ 18	> 2.2
II	Present	Absent	≥ 18	> 2.2
III	Absent	Present	≤ 18	< 2.2
IV	Present	Present	≥ 18	< 2.2

Abbreviations: PCWP = pulmonary capillary wedge pressure; CI = cardiac index.

phase, also contribute to decreased compliance [26]. The consequences of decreased compliance are downward shifts of left ventricular function curves; thus, with similar infarct size and a similar reduction in stroke volume, left ventricular diastolic pressures are higher. An increase in end-diastolic volume, to compensate for the declining stroke volume, is also associated with an excessive increase in end-diastolic pressure. The pathophysiologic mechanism for hemodynamic abnormalities in patients in subset II (table 9–3) is likely to be decreased left ventricular diastolic compliance.

The mechanism for decreased cardiac output with normal pulmonary capillary wedge pressure in patients in subset III is not entirely clear. A substantial reduction in left ventricular end-diastolic volume or transmural pressure is unlikely to occur following acute myocardial infarction. In the presence of predominant right ventricular infarction, left ventricular transmural pressure and diastolic size may decrease without a marked increase in pulmonary capillary wedge pressure and may explain hypoperfusion without pulmonary congestion. Decreased left ventricular preload, resulting from relative or absolute hypovolemia, is an uncommon complication of acute myocardial infarction. The mechanisms for a hypovolemic state are not clear, but prior or excessive use of diuretics or venodilators and marked diaphoresis or excessive vomiting at the onset of infarction causing dehydration may precipitate hypovolemia. In experimental animals, an increase in left ventricular compliance has been observed soon after induced myocardial infarction [27]. Increased diastolic compliance may explain a reduction in cardiac output without an excessive increase of left ventricular diastolic pressure. However, whether such a phenomenon also occurs in patients with acute myocardial infarction has not been adequately investigated. The hemodynamic correlates of hypoperfusion and pulmonary congestion are decreased cardiac output and increased pulmonary capillary wedge pressure, respectively, and usually result from a marked depression of left ventricular systolic function. Left ventricular stroke volume is reduced and end-systolic and end-diastolic volumes are increased, resulting in a decreased ejection fraction. The degree of depression of left ventricular function is related to the total amount of nonfunctioning myocardial segments, which may consist of recently infarcted areas and also of previously infarcted areas, as well ischemic but viable myocardial segments

[28, 29]. During therapy for pump failure, therefore, consideration should be given to the preservation of ischemic myocardium.

The principal mechanism for depressed left ventricular function following myocardial infarction is decreased contractile function of the infarcted and ischemic myocardial segments. Forward stroke volume will decline, depending on the size of the nonfunctioning myocardium. However, a number of central and peripheral compensatory mechanisms may be activated to maintain adequate cardiac output and organ perfusion [30]. Noninfarcted and nonischemic myocardial segments may be hypercontractile, presumably due to the activation of the sympathoadrenergic system. As residual volume and end-diastolic volume also increase, a further compensation of declining stroke volume may also occur via the Frank–Starling mechanisms. The mechanisms for increase in end-diastolic volume are not clear; in addition to increased residual volume, infarct expansion might be contributory. Infarct expansion results from stretching, lengthening, and thinning of the infarcted segment, probably reflecting disruption of the connective tissue framework [31, 32]. Considerable systolic bulging of the stretched infarcted segment (acute left ventricular aneurysm) is associated with a further reduction in stroke volume. An acute left ventricular aneurysm with dyskinetic wall motion can precipitate a severe low-output state. When a relatively large area is involved, a significant proportion of the ejection volume may be trapped in the aneurysm during systole and can be associated with a marked reduction in forward stroke volume and cardiac output [27].

Increased end-diastolic volume, although contributory to the maintenance of forward stroke volume, is accompanied by increased left ventricular diastolic and pulmonary venous pressure — the hemodynamic determinants of pulmonary congestion. A concomitant decrease in left ventricular diastolic compliance will cause a further increase in venous pressure.

As forward stroke volume declines, there is a compensatory increase in heart rate to maintain adequate cardiac output. Tachycardia is likely to be caused by enhanced sympathetic activity. Excessive tachycardia, however, may produce deleterious effects by increasing myocardial oxygen requirements. Myocardial perfusion may also be compromised because of reduction in diastolic perfusion time and impaired relaxation.

Peripheral circulating changes also occur in response to decreased cardiac output and arterial pressure, resulting from pump failure following acute myocardial infarction. Systemic vascular resistance is frequently higher than normal and peripheral venous tone is augmented. Increased venous tone contributes to maintenance of an adequate ventricular preload and to increased stroke volume via the Frank–Starling mechanism. Increased systemic vascular resistance helps to maintain arterial pressure, which is necessary for tissue perfusion. These compensatory adjustments in the peripheral vascular tone are mediated by activation of the sympathetic nervous system, by the release of endogenous vasoactive substances, and by local vasoregulatory

mechanisms [33]. Vagal tone decreases and sympathetic tone increases due to blunted baroreceptor activity resulting from decreased mean arterial pressure, pulse pressure, and rate of arterial pressure rise. Adrenal medullary synthesis and the release of catecholamines are augmented by heightened sympathetic activity. Profound tissue ischemia may also enhance sympathoadrenal activity due to activation of the chemoreceptor reflexes.

Changes in vascular tone in the presence of shock or severe pump failure, however, are not uniform in all peripheral vascular beds. Vasoconstriction is most pronounced in cutaneous, splanchnic, and skeletal-muscle vascular beds, whereas coronary and cerebral circulations are less affected. This allows a relatively better myocardial and cerebral perfusion, despite lower cardiac output. Precapillary resistance tends to increase to a greater extent than the postcapillary resistance in response to increased sympathoadrenal activity. This facilitates the movement of interstitial fluid to the intravascular compartment and an increase in intravascular volume.

In the shock state, the renin-angiotensin-aldosterone system may be activated [34, 35]. Decreased renal perfusion pressure and renal sympathetic stimulation enhance renin production, which is accompanied by increased production of angiotensin II and aldosterone. Increased activity of the renin-angiotensin-aldosterone system contributes to higher peripheral vascular tone and increased intravascular volume. Baroreceptor-mediated increased release of vasopressin from the posterior pituitary may also occur in response to hypotension and may play a role in volume regulation during shock. Although these abnormal neurohumoral responses have been well documented in experimental animals and in patients with severe chronic congestive heart failure, there is a paucity of information regarding the neurohumoral changes in patients with acute myocardial infarction, pump failure, and/or shock.

Local vasoregulatory mechanisms may be activated in the initial stages of circulatory shock to maintain regional perfusion. Accumulation of vasoactive metabolites, resulting from tissue ischemia, is associated with vasodilation of arterioles and precapillary sphincters, which increase regional blood flow. The capillary surface areas increase with decreased tone of the precapillary sphincters, which facilitate blood-tissue exchange. Tissue hypoxia also causes arteriolar vasodilation, which promotes regional blood flow. These autoregulatory mechanisms to maintain regional blood flow are most pronounced in the coronary, cerebral, and renal circulations; skeletal-muscle and skin vascular beds exhibit weak autoregulation.

It is apparent that during the initial stages of severe pump failure and shock, several interacting central and peripheral circulatory compensatory responses occur to maintain cardiac output and tissue perfusion (figure 9–2). When these compensatory mechanisms are insufficient to restore adequate cardiac output, arterial pressure, and tissue perfusion, or when hemodynamic and circulatory abnormalities cannot be corrected by therapeutic interventions, severe pump

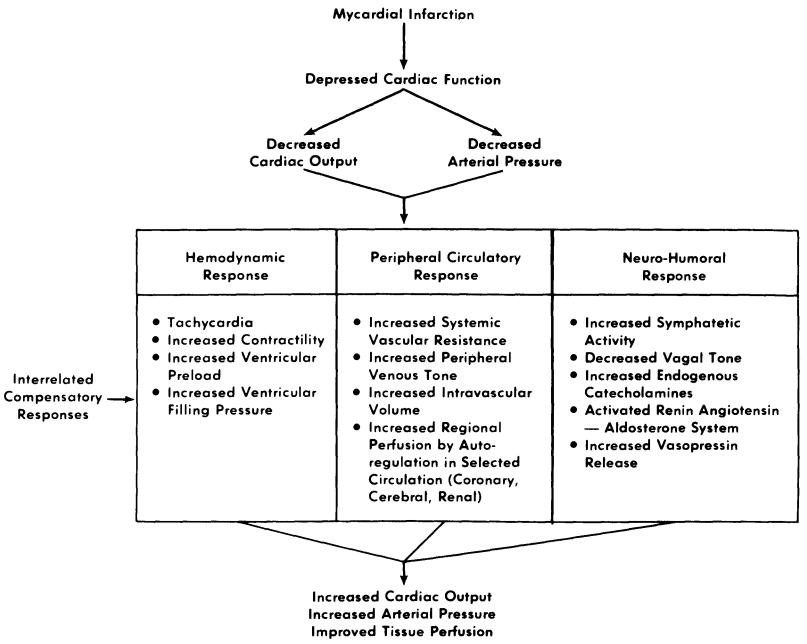

Figure 9–2. Central and peripheral compensatory mechanisms in pump failure following acute myocardial infarction. From Chatterjee [30], reproduced with permission.

failure and a shock state continue, and irreversible cellular damage occurs, resulting in death.

It needs to be recognized that some of the compensatory responses can produce adverse effects on cardiac dynamics and myocardial metabolic function. Tachycardia and increased contractility due to activation of the sympathetic system increase myocardial oxygen requirements. Tachycardia may also impair myocardial perfusion because of decreased perfusion time. Increased left ventricular diastolic volume is associated with increased wall tension, which increases myocardial oxygen consumption. Although total thrombolytic occlusion of the infarct-related coronary artery is commonly observed in the early stages of myocardial infarction [36], hemodynamically significant stenoses involving other coronary arteries frequently coexist. Thus, potentially, myocardial ischemia or infarction in a new vascular territory, or extension of the initial infarction may result from an excessive increase in myocardial oxygen requirements, causing further deterioration in cardiac function.

Elevation of left ventricular diastolic pressure, accompanying increased left ventricular diastolic volume, may compromise subendocardial perfusion. Intramyocardial tension and, therefore, myocardial oxygen consumption are

higher in subendocardial than in subepicardial layers. The transmyocardial pressure gradient decreases with elevated left ventricular diastolic pressure, making the subendocardium more vulnerable to ischemia. Furthermore, increased pulmonary venous pressure associated with increased left ventricular diastolic pressure also contributes to arterial hypoxemia.

An inappropriate increase in systemic vascular resistance produces deleterious effects on cardiac performance. Elevated systemic vascular resistance increases resistance to left ventricular ejection, which is associated with decreased stroke volume and cardiac output, as an inverse relation exists between left ventricular ejection impedance and its stroke volume [37]. Furthermore, increased afterload imposes increased myocardial oxygen requirements. Thus, although increased systemic vascular resistance helps to maintain arterial pressure, an excessive increase may cause deterioration of cardiac function.

MANAGEMENT

The management of left ventricular "pump failure" is better approached by determining the clinical, and if necessary, the hemodynamic subsets. Hemodynamic monitoring is not required in clinically uncomplicated patients who do not exhibit any clinical manifestations of hypoperfusion or pulmonary congestion. Normal blood pressure, heart rate less than 100 beats/min, adequate urine output, warm periphery, normal systemic venous pressure, an absent S_3 gallop and clear lungs, and the absence of pulmonary venous congestion on chest x-ray all indicate the absence of left ventricular failure, and these patients are categorized in subset I (table 9–3). Invasive hemodynamic monitoring is useful in complicated patients in order to clarify the mechanisms for hypoperfusion, hypotension, and pulmonary congestion [11], and to assist in the selection of appropriate therapeutic intervention and to follow the response to therapy. Hemodynamic monitoring should be considered in those patients who demonstrate clinical evidence of severe and persistent pulmonary congestion, low output state, persistent hypotension and shock, persistent tachycardia, or evidence of mechanical defects, such as mitral regurgitation or rupture of the interventricular septum. In addition, appropriate noninvasive investigations that compliment clinical and hemodynamic evaluations of complications of acute myocardial infarction should be considered. Two-dimensional echocardiography is particularly useful for the differential diagnosis of right ventricular infarction and cardiac tamponade. Doppler flow studies are helpful to assess mitral regurgitation, ventricular septal rupture and pulmonary hypertension. Radionuclide scintigraphy may provide information regarding ventricular size and function, and the extent of myocardial injury.

Pulmonary congestion without hypoperfusion (Subset II, table 9–3)

Mild pulmonary congestion is common, particularly at the onset of myocardial infarction, and may be accompanied by mild dyspnea and orthopnea,

tachypnea, bibasilar posttussive pulmonary rales, an S_3 gallop, mild-to-moderate hypoxemia, and radiologic evidence of mild-to-moderate pulmonary venous hypertension. Arterial pressure is usually normal or modestly elevated, and there is no clinical evidence of hypoperfusion. Invasive hemodynamic monitoring is usually not required in these patients, and symptoms of pulmonary congestion are relieved fairly rapidly following administration of diuretics and/or venodilators (nitroglycerin and nitrates).

Supplemental oxygen should be administered to ensure adequate arterial oxygenation. Intravenous furosemide (20 mg–40 mg) may cause prompt reduction in pulmonary venous pressure, even before diuresis starts, and results from the increased peripheral venous capacitance and increased venous pooling, and consequent reduction of left ventricular preload [38]. In patients with chronic congestive heart failure, however, a vasoconstrictor response, associated with a transient increase in pulmonary capillary wedge pressure, decreased cardiac output, and increased systemic vascular resistance, has been observed following larger doses of furosemide [39]. Increased peripheral vascular tone in response to furosemide in these patients has been thought to be mediated by the activation of the renin-angiotensin system and vasopressin release. However, such adverse effects of furosemide have not been documented in patients with acute myocardial infarction.

Nitroglycerin and nitrates are also effective in reducing pulmonary venous pressure. Initially, sublingual nitroglycerin followed by topical nitroglycerin or oral isosorbide dinitrate frequently relieve the symptoms of pulmonary congestion, and usually no further therapy is required. It needs to be emphasized that aggressive and repeated diuretic and venodilator therapy should be avoided, since hypotension and a low output state may result from excessive reduction of left ventricular preload.

Acute pulmonary edema without hypoperfusion and shock require prompt, aggressive therapy. These patients present with acute respiratory distress, sometimes accompanied by expectoration of a pink, frothy sputum; tachycardia, and hypertension; and cool, clammy, and diaphoretic skin. Tachypnea; orthopnea; extensive bilateral pulmonary rales, occasionally accompanies by wheezing (cardiac asthma); an S_3 gallop; and frank pulmonary edema on chest x-ray are present.

The immediate therapeutic objectives are maintenance of adequate gas exchange and rapid reduction of pulmonary capillary wedge pressure. High concentrations of oxygen (60%–100%) should be administered via a face mask, and arterial blood gases should be determined. Endotrachael intubation should be considered in patients who are unable to maintain an arterial p_{O^2} of at least 60 mmHg with a face mask and who develop a progressively rising p_{CO^2} or a declining arterial pH. The addition of positive end-expiratory pressure during mechanical ventilation may be required to maintain adequate systemic oxygenation and to allow the use of a relatively safe oxygen concentration ($FI_{O^2} \leqslant 60\%$). Positive end-expiratory pressure (PEEP) exceeding

5 cm, however, may decrease cardiac output due to decreased left ventricular preload and increased right ventricular afterload.

Rapid reduction of pulmonary capillary wedge pressure can be achieved by the administration of nitroglycerin and nitrates. Nitroglycerin and nitrates are predominantly venodilators and cause a significant reduction of pulmonary capillary wedge pressure by venous pooling and by decreasing venous return to the heart. Initially, nitroglycerin or isosorbide dinitrate should be administered sublingually until the hemodynamics are determined. Although intravenous diuretics (furosemide) are also used concomitantly, it should be realized that the effects of diuretics are slower than those of nitrates. Intravenous morphine sulphate should be used and can be helpful in calming an agitated patient; it also possesses a modest venodilatory effect.

After initial therapy, hemodynamics should be determined and subsequent treatment should be tailored to the hemodynamic abnormalities. If cardiac output and oxygen delivery are adequate, and metabolic acidosis is absent, nitroglycerin therapy may be continued (preferably intravenously), provided pulmonary capillary wedge pressure is elevated. In patients who remain hypertensive (e.g., arterial pressure exceeding 160/90 mmHg), sodium nitroprussiode appears to be the more effective than nitroglycerin in reducing arterial pressure as well as pulmonary venous pressure. Nitroprusside is also preferable in patients who develop pulmonary edema due to mitral regurgitation. Digitalis, aminophylline, and positive pressure ventilation are generally not effective in the management of acute pulmonary edema following myocardial infarction.

After recovery from pulmonary edema and stabilization of hemodynamics, these patients require evaluation of cardiac function, the severity of the coronary artery disease, and the extent of their myocardial ischemia.

Hypoperfusion without pulmonary congestion (subset III, table 9–3)

Invasive hemodynamic monitoring, in addition to clinical and noninvasive assessment, is required in patients with hypoperfusion without pulmonary congestion to detemine the underlying mechanism of hypoperfusion. As both right ventricular infarction and hypovolemic shock can be associated with low cardiac output without pulmonary venous hypertension, the precise diagnosis should be established. The management of low-output state following right ventricular infarction has already been outlined.

Hypovolemic shock is characterized by hypotension, low cardiac output, and decreased right and pulmonary capillary wedge pressures. Initial therapy for hypovolemic shock consists of rapid administration of fluids intravenously to increase cardiac output by increasing right and left ventricular preload. The choice of intravenous fluids is less important in these patients, as prolonged therapy is usually not necessary. Initially, 100 cc–200 cc of intravenous fluid should be administered fairly rapidly, and the changes in right atrial and pulmonary capillary wedge pressures and cardiac output should be monitored.

If cardiac output increases appreciably, with a modest increase in right atrial and pulmonary capillary wedge pressures, fluid therapy is continued and the rate of fluid administration is adjusted to maintain a pulmonary capillary wedge pressure between 14 mmHg and 18 mmHg. The *optimum filling pressure* to increase stroke volume has been determined in patients with acute myocardial infarction. When mean pulmonary capillary wedge or pulmonary artery diastolic pressures are used as the left ventricular filling pressure, in most patients, the optimal range of filling pressure appears to be between 14 mmHg and 18 mmHg [40]. When left ventricular end-diastolic pressure is used instead of pulmonary capillary wedge pressure, the optimal filling pressure is between 20 mmHg and 25 mmHg.

If, during initial intravenous fluid therapy, pulmonary capillary wedge pressure increases rapidly and exceeds 20–25 mmHg, fluid administration should be discontinued because of the potential risk of precipitating pulmonary edema.

In some patients, there is an inadequate increase in cardiac output, despite an optimal filling pressure during intravenous fluid therapy. In these patients, appropriate therapy for pump failure should be instituted, maintaining an adequate filling pressure with intravenous fluids.

Hypoperfusion and pulmonary congestion (subset IV, table 9–3)

A marked reduction in cardiac output and elevated pulmonary capillary wedge pressure causes hypoperfusion and pulmonary congestion, and results from marked depression of cardiac function. Other hemodynamic changes are frequently observed and are significant tachycardia and elevated right atrial and pulmonary arterial pressures. Systemic vascular resistance is also increased, and left ventricular stroke work index is markedly reduced. Although the mean arterial pressure may be normal, it is usually lower than in patients with and without mild pump failure. The hemodynamic profiles of uncompliated patients and of patients with mild and severe pump failure are summarized in table 9–4. When the clinical features of shock are present, hypotension and lower cardiac output and evidence of diminished organ perfusion can accompany. Cardiogenic shock results from extensive myocardial damage. Autopsy studies have demonstrated involvement of more than 40% of the left ventricular myocardium in patients dying of cariogenic shock [41]. It should be recognized that the cumulative loss of previously functioning myocardium determines the degree of depression of cardiac function and the hemodynamic impairment. Cardiogenic shock may occur due to a relatively small, recent infarct in a patient with prior myocardial infarction. The extension of an initially small infarct may also precipitate severe pump failure with or without the syndrome of cardiogenic shock. The presence of both a recent and an old myocardial infarction and extension of a recent infarction are common autopsy findings in patients who succumb from cardiogenic shock [28, 29]. Complicating mechanical defects, such as mitral regurgitation and rupture of the

Table 9–4. Hemodynamic abnormalities in patients with uncomplicated infarction, mild pump failure, and severe pump failure

	Uncomplicated	Mild pump failure	Severe pump failure
No. of patients	6	9	12
Heart rate (beats/min)	89 ± 7	91 ± 4	100 ± 4
Mean arterial pressure (mmHg)	91 ± 3	101 ± 5	82 ± 2
Mean pulmonary artery pressure (mmHg)	17 ± 2	32 ± 2	37 ± 2
Mean right atrial pressure (mmHg)	5 ± 1	10 ± 2	13 ± 1
Pulmonary artery wedge pressure (mmHg)	11 ± 5	24 ± 1	29 ± 2
Cardiac index ($L/min/m^2$)	2.9 ± .2	2.6 ± .1	1.8 ± .1
Stroke work index ($gm\text{-}m/m^2$)	39 ± 8	34 ± 3	14 ± 1
Systemic vascular resistance (dynes. sec. cm^{-5})	1383 ± 148	1577 ± 141	1908 ± 260

interventricular septum, may also precipitate severe pump failure and the hemodynamic profile of cardiogenic shock.

The major objectives of therapy of severe pump failure with or without the clinical syndrome of cardiogenic shock are: 1) to improve cardiac performance, 2) to normalize hemodynamic abnormalities, and 3) to maintain the viability of ischemic myocardium and to limit the extent of myocardial damage.

General supportive therapy is similar to that employed for other subsets of patients with acute mycoardial infarction. Maintenance of adequate oxygenation, correction of electrolyte imbalance and acid-base abnormalities, and relief of pain and control of dysrhythmias are essential. Hemodynamic monitoring is required to determine the severity of hemodynamic abnormalities and to assess the response to therapy.

Pharmacotherapy to improve cardiac performance of patients with severe left ventricular failure is based on two physiologic principles: 1) reduction of left ventricular ejection impedance with vasodilator therapy and 2) enhancement of contractile function with positive inotropic agents. In many patients, a combination of vasodilator and intropic therapies is required to optimize improvement in cardiac function and hemodynamics.

Various vasodilator drugs have been used for the treatment of pump failure complicating myocardial infarction, and their expected hemodynamic effects have been determined in a number of studies (table 9–5) [37]. The most commonly used vasodilators are sodium nitroprusside and nitroglycerin. Although both of these agents produce qualitatively similar hemodynamic effects, some differences are apparent that should be considered during the institution of vasodilation therapy in a given patient.

Nitroglycerin and nitrates are predominantly venodilators, and their prin-

Table 9–5. Expected systemic hemodynamic effects of vasodilator therapy used for treatment of pump failure in acute myocardial infarction

Vasodilator	Heart rate	Mean blood pressure	Right atrial pressure	Pulmonary capillary wedge pressure	Cardiac output	Systemic vascular resistance
Nitroprusside	No change or increase	Decrease or no change	Decrease	Decrease	Increase	Decrease
Nitroglycerin	No change or increase	Decrease or no change	Decrease	Decrease	No change or increase	No change or decrease
Phentolamine	Increase or no change	Decrease or no change	Decrease	Decrease	Increase	Decrease

cipal hemodynamic effects are decreased systemic and pulmonary venous pressures; systemic vascular resistance may not decrease substantially, and, therefore, cardiac output either remains unchanged or increases slightly. Nitroglycerin, however, may occasionally increase stroke volume and cardiac compliance [37]. Nitroglycerin-induced reduction of segmental myocardial ischemia may also be associated with improvement in the overall cardiac performance and increased cardiac output [37]. Nitroglycerin has been shown to increase collateral blood flow. In experimental myocardial infarction, subendocardial perfusion also improves.

Sodium nitroprusside appears to have balanced effects in arteriolar and venous beds; thus, there is usually a significant decrease in systemic vascular resistance and an increase in cardiac output [42]. Pulmonary capillary wedge and right atrial pressures decrease significantly. Nitroprusside also increases left ventricular diastolic compliance, and, in some patients, cardiac output may increase substantially, even when pulmonary capillary wedge pressure decreases markedly [42]. In patients with pump failure with elevated left ventricular end-diastolic pressure, nitroprusside usually improves myocardial metabolic function. In experimental myocardial infarction in dogs, nitroprusside improves subendocardial perfusion if left ventricular end-diastolic pressure is elevated prior to nitroprusside therapy. In the absence of left ventricular failure, subendocardial perfusion declines with nitroprusside [37].

Controversy exists regarding the relative advantages and disadvantages of nitroglycerin and sodium nitroprusside in relation to their effect on the extent of myocardial injury [43]. Although in experimental animals nitroglycerin has been shown to decreases infarct size, and nitroprusside to increase the extent of myocardial injury, there is no convincing data available to suggest that either nitroglycerin or nitroprusside produce any beneficial or deleterious effects. Both nitroglycerin and nitroprusside dilate the human epicardial coronary arteries and have the potential to increase coronary blood flow [44].

The choice between nitroglycerin and nitroprusside in the treatment of pump failure complicating myocardial infarction should depend on the hemodynamic profile in an individual patient. When systemic vascular resistance is elevated, and cardiac output and pulmonary capillary pressure are increased, sodium nitroprusside is the drug of choice. When pulmonary capillary wedge pressure is elevated, but the cardiac output is inadequate, nitroglycerin can be used effectively to lower pulmonary capillary wedge pressure. In some patients, nitroglycerin and nitroprusside can be combined to optimize the hemodynamic changes. In some patients with severe pump failure, an increase in cardiac output with sodium nitroprusside is not associated with a significant decrease in pulmonary capillary wedge pressure; the addition of nitroglycerin may cause a further decrease in pulmonary capillary wedge pressure.

The adverse effects of nitroprusside therapy include excessive hypotension, reflex tachycardia, thiocyante and cyanide toxicity, and methemoglobinemia. Worsening of arterial hypoxemia due to an increased ventilation-perfusion mismatch may also occur during nitroprusside therapy.

The adverse effects of nitroglycerin are hypotension, headache, and, rarely, methomoglobinemia. Arterial hypoxemia due to ventilation-perfusion mismatch may also occur during nitroglycerin treatment [37].

The major disadvantage of vasodilator therapy, irrespective of the vasodilator agent used, is hypotension, which may compromise myocardial perfusion and may enhance ischemia. Coronary blood flow is more likely to decrease in the presence of ischemia because of metabolically mediated coronary vasodilatation and decreased coronary vascular resistance. In these circumstances, coronary blood flow depends on perfusion pressure, and decreased arterial pressure during vasodilator therapy may compromise myocardial perfusion. Thus, when hypotension occurs without any increase in cardiac output or with a decrease in pulmonary capillary wedge pressure, vasodilator therapy should be discontinued. In hypotensive patients (arterial pressure $<90/60$ mmHg), vasodilator therapy cannot be initiated. Inotropic and vasopressor agents should be started to maintain adequate arterial pressure before vasodilator therapy can be added.

Inotropic and vasopressor agents (table 9–6)

The major objective of inotropic therapy is to increase cardiac output, and the major objective of vasopressor therapy is to increase arterial pressure. It should be recognized that all inotropic agents do not elevate arterial pressures and all vasopressor agents do not increase cardiac output. In the treatment of acute pump failure, such as following myocardial infarction and in cardiogenic shock, the most frequently used inotropic and vasopressor agents are catecholamines. Dobutamine, dopamine, and norepinephrine are the sympathomimetic amines that are more frequently employed.

Dobutamine is predominantly a $beta_1$ receptor agonist, although it exhibits some $beta_2$ and $alpha_1$ adrenergic receptor agonist effects. The usual systemic

Table 9–6. Expected systemic hemodynamic effects of inotrope-vaospressors used for treatment of pump failure in acute myocardial infarction

Agent	Heart rate	Mean blood pressure	Right atrial pressure	Pulmonary capillary wedge pressure	Cardiac output	Systemic vascular resistance
Dobutamine	No change or decrease	No change or decrease	Decrease	Decrease	Increase	Decrease
Dopamine	Increase	Increase	No change or increase	No change or increase	Increase	Decrease
Norepinephrine	Increase	Increase	Increase	Increase or no change	No change or increase	Increase
Amrinone	Increase	No change or decrease	Decrease	Decrease	Increase	Decrease
Enoximone	Increase	No change or decrease	Decrease	Decrease	Increase	Decrease

hemodynamic effects are an increase in cardiac output and stroke volume, and a decrease in systemic vascular resistance, pulmonary vascular resistance, and pulmonary capillary wedge and right atrial pressures [46]. Although systolic arterial pressure may increase along with increased cardiac output, mean arterial pressures usually do not change. Indeed, with relatively larger doses of dobutamine, mean arterial pressure may fall. Heart rate also does not change significantly with usual doses, but with larger doses, tachycardia may develop. Increased myocardial oxygen requirements, resulting from its positive inotropic effect, may also enhance myocardial oxygen consumption [46]. It is apparent that dobutamine is not the drug of choice for treating hypotension. The usual dose of dobutamine is 5–10 μg/kg/min.

Dopamine, a naturally occurring precursor of norepinephrine, produces pharmacologic and hemodynamic effects by activating dopamine and alpha and beta receptors, as well as by releasing norepinephrine [47–50]. The cardiovascular effects of dopamine are related to its dose. With low doses (2–5 μg/kg/min), dopamine receptors are activated: Postsynaptic dopamine$_1$ receptor stimulation causes vasodilation of renal, mesenteric, coronary, and cerebrovascular beds, and presynaptic dopamine$_2$ receptor activation is associated with decreased neuronal release of norepinephrine, which may also contribute to peripheral vasodilation. In higher doses [6–15 μg/kg/min), it increases contractility and cardiac output through stimulation of the myocardial beta$_1$ receptors. In larger doses (15–20 μg/kg/min), generalized vasoconstriction predominates because of alpha-receptor stimulation. The usual hemodynamic effects of dopamine, when used for pump failure, are increased cardiac output and arterial pressure, with a modest decrease in systemic vascular resistance. Heart rate and pulmonary capillary wedge pressure may not change or increase. The hemodynamic effects of dopamine and dobutamine have been compared in patients with severe pump failure, and some

differences in response have been observed [51–52]. For a similar increase in cardiac outaput, dopamine produced a greater increase in cardiac output and a smaller decrease in systemic vascular resistance. Dopamine tended to increase pulmonary capillary wedge and pulmonary artery pressures, as well as total pulmonary resistance; whereas with dobutamine, pulmonary capillary wedge pressure and pulmonary resistance decreased.

The magnitude of increase in cardiac output with dopamine appears to depend on the initial level of cardiac function. The more severe the pump failure, the less is the response. In patients with severe pump failure and shock, the increase in cardiac output may be entirely due to an increase in heart rate [53]. As with other inotropic agents, dopamine may cause deterioration of myocardial metabolic function and may enhance myocardial ischemia.

The combination of dopamine and dobutamine have been used in some patients with cardiogenic shock [54]; with smaller doses of each agent, combined therapy caused a substantial increase in cardiac output without increasing pulmonary capillary wedge pressure. Low-dose dopamine is frequently added during inotropic or vasodilator therapy to improve renal function and urinary output.

Norepinephrine causes arteriolar and venous constriction by stimulating vascular alpha receptors and by increasing systemic vascular resistance. It can also increase cardiac output by stimulating cardiac $beta_1$ receptors [55–57]. However, because of the concomitant increase in sytemic vascular resistance (left ventricular afterload), the net increase in cardiac output is usually small. Not infrequently, there is no increase, or there may even be a decrease, in cardiac output. Norepinephrine is thus used for temporary support of arterial pressure in patients with severe hypotension. The addition of the alpha blocking agent, phentolamine, or of direct-acting vasodilators, such as nitroglycerin or sodium nitroprusside, may be helpful to counteract extreme vasoconstriction and to unmask the inotropic effect of norepinephrine [58]. Dopamine, norepinephrine, and dobutamine all cause tachycardia and may induce ventricular tachyarrhythmias, particularly in patients with acute myocardial infarction. Tachyarrhythmias appear to be more common with norepinephrine and dopamine than with dobutamine.

New phosphodiesterase inhibitors, such as amrinone, milrinone, and enoximone, possess both inotropic and vasodilatory properties and their beneficial hemodynamic effects have been documented in patients with severe pump failure [59–61]. The hemodynamic effects of the drugs are characterized by a marked increase in cardiac output and stroke volume, and a significant decrease in systemic and pulmonary venous pressures, and in systemic and pulmonary vascular resistances. Heart rate may increase slightly and arterial pressures may remain unchanged. With larger doses of these agents, hypotension may occur. The mechanism of the positive inotropic effect of these agents is not related to inhibition of Na-K ATPase activity, like digitalis, or to activating beta receptors, like catecholamines. Phosphodiesterase III inhibition

is associated with increased intracellular concentration of 3′5′ cyclic AMP, resulting from its decreased degradation. As the mechanism of action of the phosphodiesterase inhibitors is different from that of digitalis or catecholamines, these agents can be used in combination with digitalis glycosides or catecholamines to enhance contractile function. Amrinone is the only drug of this class that has been approved by the United States Food and Drug Administration for intravenous use in the treatment of severe low output state. Amrinone has been used in patients with acute myocardial infarction and has been shown, in rather modest doses, to significantly increase cardiac output and to decrease pulmonary capillary wedge pressure [62]. However, the relative advantages and disadvantages of amrinone in the treatment of severe pump failure and cardiogenic shock following acute myocardial infarction have not been defined.

Digitalis, as an inotropic agent, is seldom used for treating pump failure complicating myocardial infarction. The magnitude of increase in cardiac output and decrease in pulmonary capillary wedge pressure in response to intravenous digoxin or ouabain in patients with pump failure in sinus rhythm is usually minimal [63]. Studies comparing the hemodynamic effects of digitalis to those of dobutamine have demonstrated the superiority of dobutamine to digitalis in increasing cardiac output and in decreasing pulmonary capillary wedge pressure [64]. Digitalis may also increase myocardial oxygen consumption and may enhance myocardial ischemia. Ischemic myocardium also appears to be more susceptible to the arrhythmogenic effects of digitalis, and the coronary as well as the peripheral vasoconstrictor effects of rapid intravenous administration of digitalis may produce deleterious effects [65]. Thus, digitalis has very limited use in the treatment of left ventricular failure complicating myocardial infarction. It is, however, useful in the management of atrial arrhythmias (i.e., supraventricular tachycardia and atrial fibrillation or flutter).

The choice of inotropic agents in the treatment of pump failure should depend on the associated hemodynamic abnormalities and on the response to a given agent. In patients with markedly elevated pulmonary capillary wedge pressure, low cardiac output, and adequate arterial pressure, dobutamine or amrinone are preferred to dopamine or norepinephrine. In the presence of moderate hypotension, dopamine is the drug of choice. When marked hypotension is present (e.g., systolic arterial pressure is 80 mmHg or less), or when arterial pressure remains low despite dopamine, norepinephrine infusion may be used for temporary support of arterial pressure.

The combination of vasodilator and inotropic vasopressor agents may produce superior hemodynamic effects in patients with acute and chronic congestive heart failure with low cardiac output [66–67]. Vasodilators increase cardiac output and lower filling pressures, but systemic arterial hypotension may result. Concomitant use of inotropic and vasopressor agents may be useful to maintain arterial pressure and also to cause a further increase in

cardiac output. Using lower doses of more than one agent (combined therapy) may offset one another's adverse effects while augmenting overall left ventricular function. The most commonly used vasodilators for combined therapy are nitroglycerin and nitroprusside, and the inotropic agents, dobutamine or dopamine. The principal advantage of adding a vasodilator to dobutamine or dopamine is that increments in cardiac output are achieved at lower left ventricular filling pressures and systemic vascular resistances.

Intraaortic balloon counterpulsation

Intraaortic balloon counterpulsation (IABP) is the most commonly used mechanical circulatory assist device in the management of hypotension and cardiogenic shock. The advent of the percutaneous insertion technique has increased the frequency of its use; however, insertion of the balloon catheter through a surgical femoral arteriotomy is still required in a small number of patients [68]. Balloon inflation and deflation are triggered by the electrocardiogram. Balloon inflation is sychronized with aortic valve closure to increase diastolic arterial pressure (diastolic augmentation) and deflation just prior to the onset of systole to decrease systolic arterial pressure (systolic unloading). Diastolic augmentation is associated with an increase in peak and mean arterial diastolic pressures. Systolic unloading decreases peak systolic arterial pressure and frequently left ventricular isovolumic pressure. Systolic unloading is also associated with decreased left ventricular end-diastolic volume and pressure, and pulmonary capillary wedge pressure, and increased cardiac output and stroke volume. In patients with mitral regurgitation, the regurgitant volume decreases and the forward stroke volume increases. In the presence of ventricular septal rupture, the magnitude of left-to-right shunt decreases as the ratio of systemic vascular resistance to pulmonary vascular resistance decreases. Intraaortic balloon counterpulsation also produces beneficial effects on coronary hemodynamics [69]. Myocardial oxygen consumption decreases as left ventricular systolic pressure and left ventricular volume (wall stress) decreases. Regional myocardial perfusion may also increase due to increased diastolic perfusion pressure, increased transmyocardial pressure gradient, and increased collateral flow. In the presence of ischemia, the increase in regional blood flow is proportional to the magnitude of diastolic augmentation. However, the net effect of intraaortic balloon counterpulsation is usually a decrease in global coronary blood flow [70].

Although intraaortic balloon pumping is frequently associated with temporary hemodynamic and clinical improvement in patients with cardiogenic shock, the short-term and long-term prognoses remain poor until revascularization surgery or corrective surgery for mechanical complications can be performed [69, 71]. Intraaortic balloon pumping is least likely to be effective in patients with multiple previous infarctions, in those with large areas of myocardial scarring with massive irreversible necrosis, and in patients with late and advanced stages of cardiogenic shock. Elderly patients with severe

peripheral vascular disease are more likely to experience the complications and morbidity of balloon insertion. Early institution of balloon counterpulsation, within a few hours of the onset of the syndrome, evidence of ischemic but viable myocardium, and the presence of mechanical complications offer the best prospects of benefit from intraaortic balloon counterpulsation until subsequent surgical therapy can be performed [69, 72]. Balloon counterpulsation should be instituted promptly in appropriate patients who fail to improve with a trial of pharmacotherapy given for 30–60 minutes. Appropriate investigations should be performed to determine the presence of surgically remediable lesions. How long counterpulsation should be continued prior to cardiac catheterization and surgery remains controversial. Although it has been reported that balloon counterpulsation for 10–14 days followed by corrective surgery decreases mortality [73], prolonged counterpulsation is usually not feasible in most patients because of the increasing frequency of complications with longer counterpulsation. The usual practice is to use balloon counterpulsation for 48–96 hours followed by cardiac catheterization and surgery in suitable patients. Intraaortic balloon counterpulsation without surgery has been reported to improve the prognosis in patients with severe left ventricular failure without shock [74]. However, these studies were not controlled, and the number of patients treated was too small to assess the value of counterpulsation for treatment of left venticular failure without hypotension or cardiogenic shock.

The incidence of complications from intraaortic balloon counterpulsation, regardless of whether percutaneous or surgical techniques of insertions are employed, is approximately 30% [69, 71, 75]. Ischemia of the inferior extremities, hemolysis, thrombocytopenia, sepsis, gas leak, and embolism are the observed complications. Complications are prone to occur in elderly patients with aortoiliac disease and also in females.

Severe mitral regurgitation and ventricular septal rupture

Infarction of the left ventricular papillary muscle with or without rupture, along with infarction of the adjacent left ventricular free wall, produce severe mitral regurgitation in approximately 1% of patients with acute myocardial infarction and accounts for the up to 5% of infarcts resulting in death [76, 77]. Most frequently, papillary muscle rupture occurs between 2 and 7 days after infarction, but approximately 20% of cases occur within 24 hours of the onset of infarction. The majority of ruptures involve the posteromedial papillary muscle, a complication of inferior or posterior myocardial infarction resulting from the occlusive disease of the right or the circumflex coronary arteries. In approximately 50% of patients, the degree of myocardial necrosis is relatively small [77]. The extent of coronary artery disease is also variable, and single-vessel disease is present in approximately 50% of patients [76].

Sudden, excessive volume overload causes a marked and rapid deterioration of already compromised left ventricular function. Cardiac output rapidly

declines and pulmonary venous and arterial pressures increase, which also precipitate right ventricular failure. If these hemodynamic abnormalities are not promptly corrected, *shock syndrome* supervenes. The sudden onset of severe pulmonary edema, along with symptoms and signs of low cardiac output, dominate the clinical picture. Systolic murmur of mitral regurgitation is usually detected, but it can be absent in some patients with cardiogenic shock [78]. The diagnosis is confirmed by demonstrating a tall peaked v wave in the wedge pressure tracing or a large transmitted v wave in the pulmonary artery presure tracing without a step-up in oxygen saturation in the pulmonary arterial blood, compared to that of right atrial blood. Two-dimensional echocardiography and Doppler flow studies are also helpful in making the diagnosis.

The prognosis of patients with acute severe mitral regurgitation complicating myocardial infarction is poor, with a 50% mortality within 24 hours and 94% mortality within 8 weeks [76, 77, 79]. Initially, vasodilator therapy, particularly sodium nitroprusside, should be considered, as it can decrease regurgitant volume and increase forward stroke volume [80]. Left ventricular end-diastolic pressure, the magnitude of the regurgitant v wave, and mean pulmonary capillary wedge pressure decrease. The addition of inotropic therapy, particularly dobutamine, may cause a further increase in cardiac output. In hypotensive patients, intraaortic balloon counterpulsation should be employed prior to vasodilator therapy. Although drug therapy and intraaortic balloon pumping produce beneficial effects, such therapy should be regarded as supportive, rather than definitive treatment. Surgical correction should be considered as soon as hemodynamic and clinical stabilization are activated. Early surgical correction has been reported to salvage 60%–70% of patients, which provides the rationale for early recognition and early surgery in papillary muscle rupture [81–83].

Rupture of the interventricular septum, another catastrophic complication of acute myocardial infarction, occurs in 0.5%–2% of infarct cases, and accounts for 1%–5% of all infarct-related deaths [84]. The incidence of septal rupture is approximately equal in patients with anterior and inferior, or posterior, myocardial infarction. Single-vessel coronary artery disease is present in some patients, although multivessel disease is more common. This complication most frequently occurs between 3 and 7 days after infarction, although it can occur within 24 hours or as late as 2 weeks after infarction. Ventricular septal defect, resulting from septal rupture, causes a left-to-right shunt, producing increased pulmonary flow and decreased systemic output. Volume overload is imposed on both the right and left ventricles, and worsening right and left ventricular function precipitates the low output state and the shock syndrome.

Usually a loud, pansystolic murmur over the precordium with widespread radiation, often accompanied by a palpable thrill (approximately 50% of

patients), is detected in patients wth septal rupture. Recurrence of chest pain, worsening dyspnea, the signs and symptoms of a low output state, hypotension, or shock are other frequent clinical manifestations. The diagnosis can be confirmed rapidly at the bedside using two-dimensional echocardiography, which demonstrates the site and approximate size of the septal rupture [85, 86]. Doppler echocardiography is also helpful to establish the diagnosis. Radionuclide ventriculography may demonstrate intracardiac left-to-right shunt. A step-up in oxygen saturation ($\geqslant$ 10%) from the right atrium to the right ventricle, or proximal pulmonary artery, confirms the diagnosis of left-to-right shunt.

The prognosis of septal rupture is poor, with a 24% mortality within 24 hours, 46% mortality at 1 week, and 67%–82% mortality at 2 months [84, 87]. Like patients with papillary muscle rupture, prompt and aggressive therapy is required to improve the prognosis of these patients. Vasodilator therapy, in general, is less effective in patients with ventricular septal rupture than in patients with mitral regurgitation. The magnitude of the left-to-right shunt in patients with septal rupture is primarily determined by the ratio of the pulmonary to systemic vascular resistance, as the size of the ventricular septal defect is usually large and the defect itself offers little resistance to left-to-right shunt. A greater decrease in systemic vascular resistance than in pulmonary vascular resistance is associated with a decreased left-to-right shunt and with increased systemic output. This is the rationale for the use of vasodilators in patients with ventricular septal defect, and, indeed, in occasional patients, sodium nitroprusside and isosorbide dinitrate produce beneficial hemodynamic effects [88]. However, vasodilator drugs also decrease pulmonary vascular resistance and, when the ratio of pulmonary to systemic vascular resistance decreases during vasodilator therapy, the magnitude of the left-to-right shunt increases. Intraaortic balloon counterpulsation decreases selectivity to the ejection impedance of the left ventricle, and, thus the magnitude of the left-to-right shunt is likely to decrease. Thus, the use of intraaortic balloon pumping is the preferred initial therapy for ventricular septal rupture. It needs to be recognized that intraaortic balloon counterpulsation with vasodilator and intropic therapy only stabilizes the patient, and corrective surgery should be performed as soon as feasible. Aggressive surgical therapy may be associated with 48%–75% short-term survival and a late mortality of 5%–14% during long-term followup (17–91 months) [87].

Surgery

As discussed above, corrective surgery is required in almost all patients who develop papillary muscle infarction or ventricular septal rupture. An acceptable low mortality has been reported following early repair in hemodynamically stable patients. Controversy exists regarding the indications for concomitant

coronary artery bypass graft surgery. Some studies suggest that coronary artery bypass graft surgery may improve the long-term survival, although it may not influence acute surgical mortality [89, 90].

Resection of the acute left ventricular aneurysm has been attempted, based on experimental studies that suggest infarctectomy may improve left ventricular function [91]. However, surgical mortality for infarctectomy with or without revascularization in patients without mechanical defects remains very high. Cardiac transplantation has been performed in some patients with intractable cardiogenic shock with occasional success.

Ventricular free-wall rupture is almost always fatal until emergency surgical repair can be performed. Free-wall rupture occurs in approximately 3% of patients with acute myocardial infarction, and it is the third most common cause of infarct-related early death [92]. Survival depends on prompt diagnosis and surgical repair. However, diagnosis of free-wall rupture is seldom possible before tamponade, and surgical therapy can be rarely offered.

Acute reperfusion therapy

As severe pump failure and cardiogenic shock result primarily from large areas of nonfunctioning left ventricular myocardium, which has been deprived of perfusion because of thrombolytic occlusion of the infarct-related artery, restoration of function of ischemic but viable myocardial segments with reperfusion therapy can potentially improve prognosis. Early reperfusion therapy and thrombolytic agents, primary transluminal percutaneous coronary angioplasty or coronary artery bypass graft surgery, have been shown to improve left ventricular function, sometimes immediately and more often over time. Some preliminary and mostly uncontrolled studies have reported encouraging results in selected patients with cardiogenic shock [93–95]. However, in a randomized trial, intravenous streptokinase was shown to have no beneficial effect on the prognosis of patients in Killip classes III and IV [96]. Thus, further studies will be required to establish the value of acute perfusion therapy in the management of severe pump failure and shock complicating acute myocardial infarction.

SUMMARY

A low output state following myocardial infarction may result from different pathophysiologic mechanisms. Invasive hemodynamic monitoring is required for the diagnosis of a persistent low output state and pump failure. Determination of hemodynamics is also required to institute pharmacotherapy and to assess the response to therapy. Depending on the hemodynamic profile of a given patient, and the hemodynamic response to a given therapy, a therapeutic strategy can be developed, as illustrated in figure 9–3. Prompt assessment of the response to therapy and appropriate changes in interventions according to the response are essential in the management of critically ill patients.

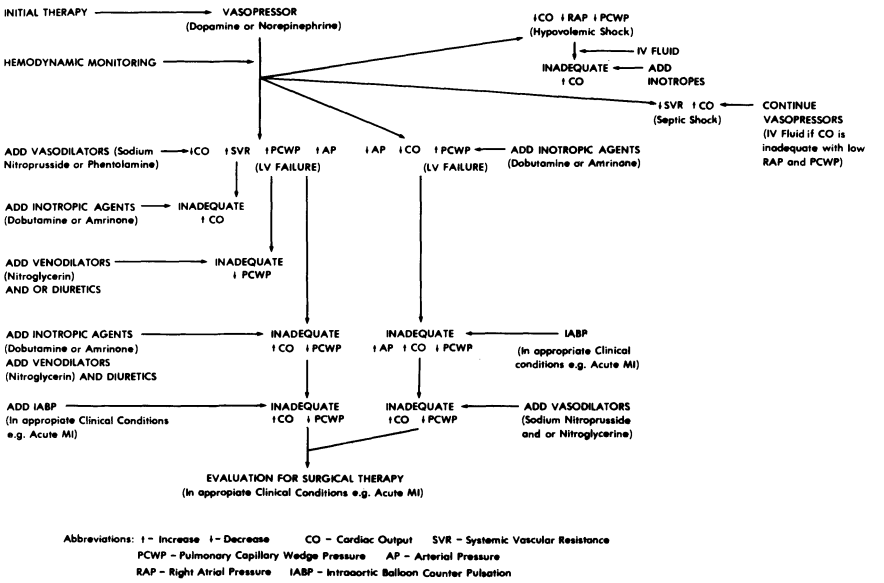

Figure 9–3. Hypotension in critically ill patients — stepwise therapeutic approach based on hemodynamic response.

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10. THE ROLE OF NUCLEAR CARDIOLOGY IN THE ASSESSMENT OF MYOCARDIAL INFARCTION AND THE EVALUATION OF EARLY INTERVENTIONS

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Management of patients with infarction has now become actively interventional, with strategies directed at early reperfusion of occluded vessels in the hope of salvaging ischemic myocardium. In this light, the role of nuclear cardiology in the past ten years has expanded from its use primarily as a diagnostic tool for coronary artery disease to that of defining and quantifying functional characteristics of myocardium in patients with acute and stable coronary artery disease. Myocardial infarction can be divided functionally into two phases: the acute phase of infarction when myocardial damage is evolving, and the convalescent phase, after the completed infarct. In each phase, there are several questions that require immediate answers; in both phases, nuclear techniques can play an important role in providing these answers. Acutely, one wishes to know how much myocardium remains at risk, how much is permanently damaged, how much potentially reversibly damaged myocardium is present, the level of ventricular function, the patient's prognosis, and the efficacy of any intervention employed in the early hours of the infarct. In the convalescent phase, one wishes to define and determine myocardial functional reserve, the presence of ischemia, and the future risk and prognosis. Based on these data, an appropriate management strategy can be developed.

The use of nuclear techniques in the convalescent phase for functional characterization and risk stratification has become routine; the value of newer nuclear techniques for acutely distinguishing reversibly from irreversibly damaged myocardium and assessing the efficacy of intervention is currently

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under active investigation. This chapter will review the current state of the art and will point to potential future directions for the application of nuclear techniques for the study of the infarct patient.

ACUTE PHASE OF MYOCARDIAL INFARCTION

Ventricular function

Equilibrium radionuclide angiocardiography or first-pass radionuclide angiocardiography provides information concerning global left ventricular performance and regional wall motion abnormalities. Global measures of ventricular function represent a summing of several factors: the amount of myocardium that is irreversibly damaged; the functional status of the residual myocardium which includes irreversibly dysfunctional myocardium; and normal and compensatory hyperkinetic regions. During the course of evolving myocardial infarction, there may be an improvement in performance in some areas and a reduction of compensatory hyperkinesis in others, with the net result being little change in overall global performance. For this reason, the measurement of regional left ventricular function may provide a more direct assessment of the efficacy of intervention. Nevertheless, global measures such as ejection fraction reflect overall global function, correlate well with clinical status, and, at the time of discharge, provide highly relevant prognostic information.

Several studies have related left ventricular ejection fraction to patient prognosis; currently, left ventricular ejection fraction is the best single prognostic index in the postinfarction patient [1–7]. In the largest study in this area, involving 799 patients, the Multicenter Postinfarction Research Group reported that patients with ejection fractions greater than 40% had less than a 5% 1-year cardiac mortality [7]. As left ventricular ejection fraction progressively decreased, there was an exponential increase in mortality, such that patients with ejection fractions less than 20% experienced a 1-year mortality of approximately 50% (figure 10–1). These results parallel those of Ritchie et al., who reported that by using a stepwise regression analysis, radionuclide left ventricular fraction at rest was the best predictor of death in patients resuscitated from out-of-hospital ventricular fibrillation [8]. Clear-cut major differences in survival were identified in groups of patients with normal or near-normal function, moderate depression in ejection fraction, and severe depression in ejection fraction. Such studies, obtained in varying groups of patients, suggest a rationale for reducing infarct size such that left ventricular function will be preserved and prognosis thereby improved [9].

Natural history studies of left ventricular function during acute myocardial infarction have demonstrated that left ventricular ejection fraction during the early phase of myocardial infarction may spontaneously vary. Wackers et al. [10] and Nemerovski et al. [5] found that while mean left ventricular ejection fraction for a group of prethrombolytic era patients with acute myocardial infarction did not change significantly over time, ejection fraction in individual

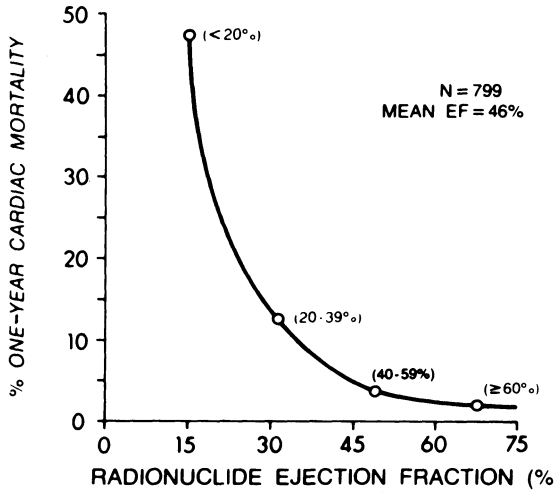

Figure 10–1. Relation of predischarge left ventricular ejection fraction to 1-year cardiac mortality in 799 patients with acute myocardial infarction. From The Multicenter Post-infarction Research Group: *N Engl J Med* 309:331, 1983, with permission.

patients changed significantly over the first 24 hours in over half of the group. These changes far exceeded the intrinsic variability of the measurement in stable patients. Ong et al. correlated changes in left ventircular ejection fraction obtained by radionuclide angiocardiography acutely and at discharge with serial creatine kinase MB determinations in 52 infarct patients treated in a routine manner [11]. Twenty-four patients had a rapid rate of early creatine kinase MB serum peak, and this group also had a significant increase in left ventricular ejection fraction from 38% to 48%. In contrast, patients with a more usual late creatine kinase peak had no significant change in ejection fraction (figure 10–2). In parallel fashion, regional ejection fraction within the infarct area improved significantly in the early creatine kinase peak group, but there was no regional improvement in patients with the late creatine kinase peak. Rapid rise of creatine kinase MB suggests spontaneous reperfusion of the occluded infarct vessel with resultant fast washout of creatine kinase. The improvement in ejection fraction seen in this group presumably reflects the functional correlate of salvaged ischemic myocardium following spontaneous reperfusion. Thus, although variations in global ejection fraction may occur due to a change in volume status, hemodynamic status, or loading conditions, it may also reflect an improvement in left ventricular function as a result of reperfusion of ischemic tissue.

Such natural history studies underscore the potential difficulty in assessing the efficacy of interventions by using a change in ejection fraction when the baseline value is obtained very early in the course of infarction. Sine left

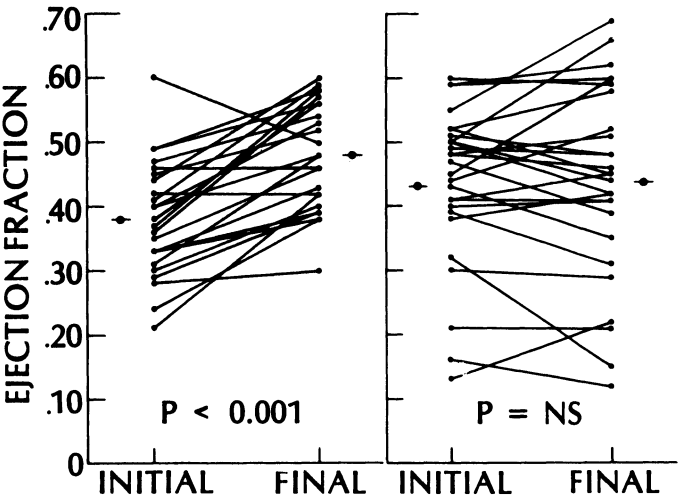

Figure 10–2. Acute (initial) and prehospital discharge (final) global left ventricular ejection fraction in patients with rapid (*left panel*) and slow (*right panel*) release of creatine kinase MB. The ejection fraction of patients with rapid release of creatine kinase increased significantly, presumably reflecting salvage of ischemic myocardium following spontaneous reperfusion. From Ong et al.: *N Engl J Med* 309:1, 1983, with permission.

ventricular ejection fraction is dependent on many factors and can vary spontaneously during the earliest hours of infarction in the absence of intervention, demonstrating a causal relationship between improved left ventricular function and successful reperfusion may be difficult unless large numbers of patients are studied and experiments are carefully controlled. In addition, if improvement in a hypokinetic region is accompanied by decreased contractility in a segment of previously hyperkinetic myocardium, the global ejection fraction may remain unchanged, despite improvement in function of the depressed region. Early studies using radionuclide angiocardiography to evaluate the efficacy of streptokinase therapy during acute myocardial infarction failed to demonstrate a difference in ejection fraction between the treated group and the control group [12–15]. Some of these studies have been criticized because the time to the onset of therapy was greater than 6 hours from the onset of symptoms, and thus was too late to demonstrate a beneficial effect of reperfusion.

However, in one study, the ejection fraction in the treated group at day 10 was 47% ± 9% versus 39% ± 12% for the control group ($p < .05$) [15]. Koren et al. similarly demonstrated that the ejection fraction determined angiographically 4–9 days after myocardial infarction was significantly higher in 38 patients treated with streptokinase within 1.5 hours from the onset of chest pain than in 23 patients treated 1.5–4 hours after the onset of symptoms [16]. Raizner et al. reported that the ejection fraction in patients successfully re-

canalized with streptokinase improved from 42% to 49%; this improvement was not seen in patients in whom reperfusion was not successful, nor in patients not treated with streptokinase [17]. This improvement was primarily seen in patients presenting with an ejection fraction lower than 45%.

The regional ejection fraction was also seen to improve, with the most marked improvement seen in patients who were successfully recanalized. Stack et al. used quantitative angiographic techniques to analyze sequential changes in regional wall motion of ischemic and uninvolved left ventricular segments following intracoronary streptokinase infusion in patients with acute myocardial infarction [18]. They found that all of the patients who reperfused within 6 hours of infarction had improvement in contractility of the involved segment, but only 44% of these patients demonstrated either no improvement or a decline in the left ventricular ejection fraction. In a larger Dutch trial of 533 patients, the global ejection fraction in patients treated with streptokinase was higher than in patients not treated [19]. Regional wall motion in both the infarct zone and in the noninfarct zone, acutely and at followup, was significantly better in the group treated with thrombolytic therapy than in the group that was not treated. More recently, Mathey et al. [20] usd a centerline method to angiographically analyze changes in regional contractility following thrombolytic therapy within 3 hours of symptoms. In patients successfully reperfused within 2 hours of symptoms, hypokinesis within the infarct area improved significantly after thrombolysis. In contrast, in patients in whom treatment was either successful but was initiated after 2 hours from the onset of symptoms, or was unsuccessful, there was no improvement in regional wall motion.

Using a similar centerline approach, as part of the Thrombolysis in Myocardial Infarction trial (TIMI), we have developed a quantitative technique to assess regional wall motion determined from radionuclide angiocardiography in the left anterior oblique and left lateral/left posterior oblique views [21–22]. Quantitative analysis of radionuclide angiocardiograms is performed using a newly developed edge detection algorithm, which first finds proper left ventricular boundaries and then links the boundary elements to form the left ventricular outline. The computer-generated boundary is then traced with a joystick-operated cursor in both end-systolic and end-diastolic frames. Regional wall motion is assessed in five equally sized left ventricular segments, as well as in both the infarct and noninfarct regions, using a centerline method, and data are expressed as standard deviations from a normal data base (figure 10–3). With this technique, quantitative changes in regional wall motion may be assessed reproducibly. Thus, this technique may be able to noninvasively identify changes in regional function after thrombolytic therapy in a manner that will complement global analysis [23].

A newer, more aggressive approach to acute myocardial infarction involves percutaneous transluminal angioplasty performed in the initial hours after infarct onset [24–29]. Although early studies noted some modest improvement

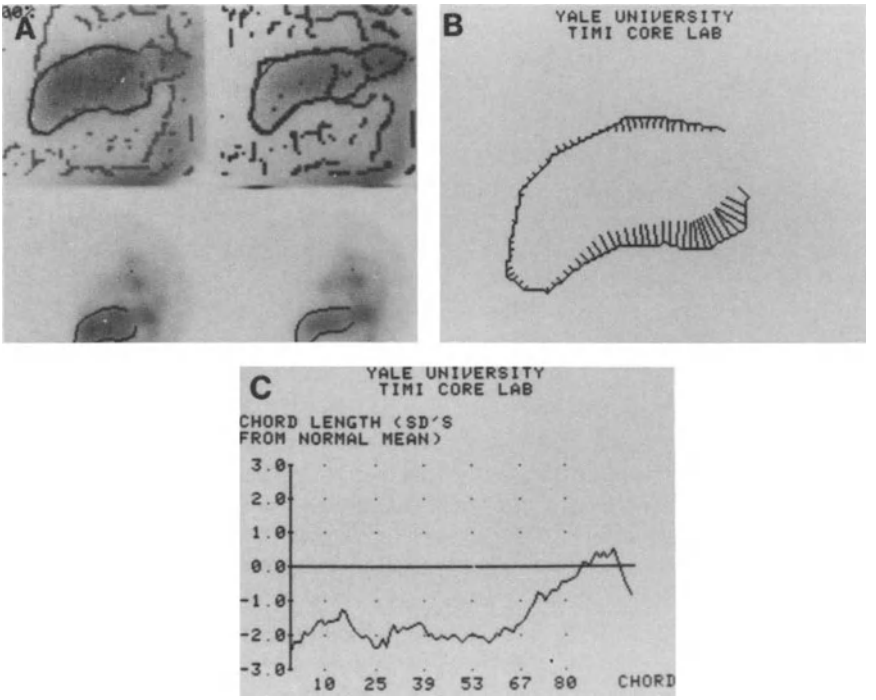

Figure 10–3. Quantitative analysis of equilibrium radionuclide angiocardiogram in left lateral view in a patient with an acute anterior-wall myocardial infarction. **Panel A**: Upper panels show computer-generated left ventricular edges with superimposed operator tracing. Upper left is end-diastolic frame; upper right is end-systolic frame. Lower panels show operator tracings superimposed on end-diastolic image (lower left) and end-systolic image (lower right). **Panel B**: Computer-generated left ventricular chord model in end diastole and in end systole. The solid outline represents the left ventricular perimeter in end diastole; chords represent fractional shortening to end systole. There is akinesis of the anterior wall and apex, and normal motion of the inferior wall. **Panel C**: Graphic representation of fractional shortening, expressed as the standard deviation from normal mean. Chords are numbered consecutively counterclockwise from 0 to 80, starting from the high anterior wall and ending at the posterobasal segment. Anterapical abnormality is seen in chords 1–70, which are greater than one standard deviation below the normal mean.

in global and regional function in patients treated with coronary angioplasty as compared to patients treated with streptokinase, recent trials comparing rt-PA therapy and early versus later angioplasty have shown no significant improvement in left ventricular performance with angioplasty performed acutely. Furthermore, combined thrombolytic therapy and early angioplasty appears to be associated with increased morbidity and does not improve global left ventricular function as compared with elective angioplasty following thrombolytic therapy [28, 29].

Regional functional analysis may also have independent prognostic value.

Meizlish et al. have demonstrated the prognostic importance of abnormal regional left ventricular wall motion in a manner distinct from global ejection fraction [30]. In this study, regional ventricular dilation associated with regional akinesis or dyskinesis, considered a functional aneurysm, was present in 18 patients with initial anterior myocardial infarction and was absent in 33. While the ejection fraction was comparable in both groups of patients, the mortality in the group with functional aneurysms was 61%, as compared with 9% in the group without this severe regional wall motion abnormality ($p < .001$). Thus, this extreme regional wall motion abnormality carries with it a very poor prognosis, independent of ejection fraction. The impact of thrombolytic therapy on the formation of a left ventricular aneurysm is still being investigated. Preliminary data reported by our laboratory based on TIMI patients suggested that left ventricular aneurysms are associated with poorer global and regional function, and an increased incidence of congestive heart failure [31]. A newer quantitative approach using computer application of diastolic shape analysis is being developed to further define this phenomenon of diastolic expansion [32].

Finally, the use of radionuclide angiocardiography, particularly first-pass studies, provides the best noninvasive assessment of right ventricular function. Recognition of right ventricular infarction in the setting of acute myocardial infarction is important, because the hemodynamics and consequently the management of these patients is different than the management of patients with primary left ventricular infarction. Changes in right ventricular function have been observed following successful thrombolysis in patients with initial complicating ischemic right ventricular dysfunction [33].

In summary, analysis of the resting left ventricular ejection fraction and regional wall motion after myocardial infarction provides important prognostic information. Left ventricular ejection fraction obtained early in the course of acute myocardial infarction reflects the function of both viable and nonviable myocardium and thus may not necessarily predict whether reperfusion will improve function. Analysis of regional left ventricular function may be a more direct means of assessing the efficacy of thrombolytic therapy than global ejection fraction, but global ejection fraction remains the most important measurable prognostic endpoint following infarction.

Perfusion imaging

Thallium-201 perfusion imaging, when combined with exercise testing, is well established as a technique for diagnosis and characterization of patients with stable coronary artery disease. With exercise, ischemic myocardium shows decreased initial uptake of thallium and abnormally slow washout of thallium over time when compared to normal myocardium; thus serial imaging demonstrates a defect that, when compared with normal myocardium, may resolve subsequently. Thallium perfusion imaging may also be used in the acute phase of myocardial infarction to estimate infarct and ischemic zone size. Thallium

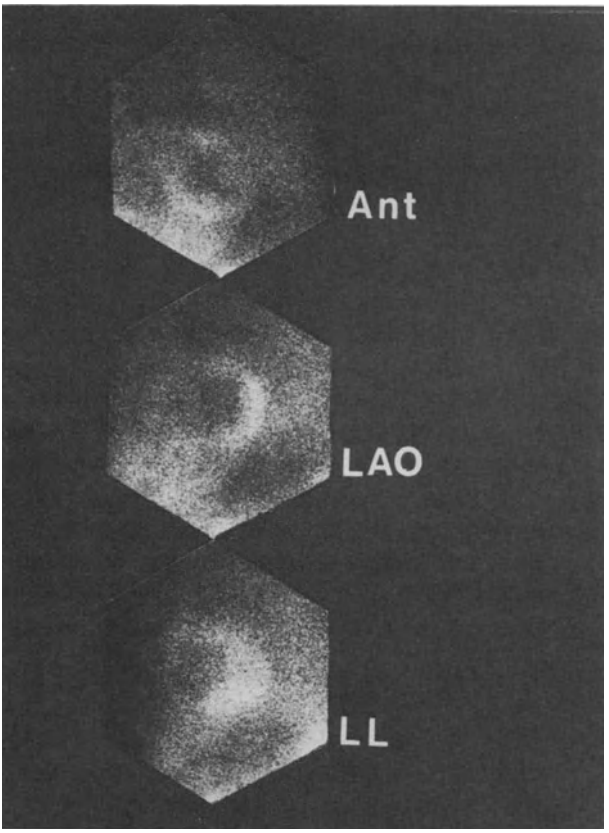

Figure 10–4. Resting thallium-201 scintigram of a patient with an acute anterseptal myocardial infarction. There is a defect in the anterior wall seen in the anterior (Ant) and left lateral (LL) views, and a defect in the septum seen in the left anterior oblique (LAO) view.

perfusion imaging may also be employed to demonstrate establishment of reperfusion to a previously nonperfused region following successful thrombolytic therapy. Thallium-201 imaging defines differences in perfusion between vascular beds; normal ventricles demonstrate a homogenous distribution of thallium, whereas ventricles with infarcted or ischemic myocardium show a comparative decrease in regional thallium uptake.

Wackers et al. first reported the clinical use of thallium-201 imaging to identify patients with acute myocardial infarction in 1976 (figure 10–4) [34]. They reported that greater than 90% of patients with transmural infarction, and 67% of patients with nontransmural infarction could be identified if imaged within the first 6 hours of infarction. This sensitivity decreased significantly over the first 24 hours, and the technique became less useful clinically after this time. Serial imaging tended to show a decrease in the size of the defect that was thought to represent regression of ischemia.

Since this initial report, techniques have been developed to quantitate and localize the amount of infarcted myocardium. These parameters have been related to prognosis, independent of clinical assessment. This is particularly useful for patients who do not appear clinically to be at high risk. Silverman et al. and Becker et al. used computer techniques to develop a thallium defect score to assess patients with acute myocardial infarction [35, 36]. With this objective method, patients with a defect score corresponding to a reduction of activity involving 40% of the left ventricular circumference identified a patient subgroup with 62% mortality at 6 months [35]. Patients with lower scores had a 6-month mortality of 7%. When compared with the ejection fraction, the thallium defect score was more sensitive for predicting nonsurvivors at a similar level of specificity [26]. This may be because the thallium score reflects a summation of irreversible ischemic damage (both old and new), as well as potentially reversible damage. In contrast, global ejection fraction, while reflecting myocardial damage, may be influenced by other factors such as preload, afterload, left ventricular geometry, and the level of intrinsic sympathetic tone. Similarly, Perez-Gonzalez et al. found in a study of 62 patients, perfusion abnormalities greater than 35% of projected left ventricular area as determined by thallium-201 scintigraphy, or scintigraphic infarct size greater than 25 cm^2 as determined from technetium-99m pyrophosphate scans, identified a group with 61% mortality at 16 months followup; those patients under these limits had a mortality of 7% [37]. Gibson et al. found that resting thallium scans performed 7–35 days after admission for acute inferior myocardial infarction identified a subset of patients with anterior perfusion defects who were at higher risk for subsequent coronary events, presumably because of stenosis of the left anterior descending coronary artery [38].

With thrombolytic therapy and percutaneous transluminal coronary angiography now frequently employed as a means of therapy for acute myocardial infarction, several groups have investigated the use of planar thallium-201 imaging for assessing reperfusion and salvage of ischemic myocardium. Since thallium-201 uptake is based on both flow and regional extraction, new uptake following injection of thallium-201 occurring in areas not reperfused on baseline studies may represent both successful reperfusion as well as salvage of nonreperfused but viable myocardium. Early studies involved acquisition of a baseline thallium-201 perfusion image following injection of intravenous thallium-201 prior to intervention so as to identify nonperfused myocardium [39–41]. Following intervention, a large dose of intracoronary thallium-201 was injected and uptake of thallium-201 occurring in areas that previously showed no uptake demonstrated successful reperfusion, and presumably salvage of nonperfused viable myocardium. However, several groups now have demonstrated in the canine model that immediately following reperfusion there is hyperemic flow, and the distribution of thallium-201 following injection during this period primarily parallels flow and is independent of extraction by viable cells [42–44]. Thus, a defect represents nonperfused tissue; new uptake indicates successful reestablishment of flow, but does not

necessarily indicate that tissue is viable. However, Schofer et al. [41] did find clinically that patients who demonstrated improvement in regional wall motion in the infarct zone following successful thrombolysis had new thallium-201 uptake, and in patients in whom thrombolysis failed, there was no change in either regional ejection fraction or thallium-201 uptake.

Granato et al., in an elegant experimental study, demonstrated that in the canine model, if thallium-201 is injected intravenously and baseline imaging is performed prior to intervention, delayed imaging peformed 2 hours after reperfusion (without reinjection of thallium-201) can demonstrate differences in thallium-201 washout between reperfused and nonreperfused myocardium [44]. In this setting, increased thallium-201 uptake in a previously nonreperfused area only occurred in areas of both improved flow and residual viable myocardium. De Coster et al. assessed whether imaging could be used in patients to determine whether reperfusion occurred and to assess whether jeopardized (ischemic) myocardium was salvaged in patients undergoing acute reperfusion [45]. In this study, 44 patients with acute myocardial infarction were randomized to therapy with either intracoronary streptokinase or placebo. Thallium-201 was injected prior to therapy, and imaging was performed prior to the onset of therapy, and again 2–4 hours after completion of the therapy. Qualitative assessment of the thallium perfusion defect remained unchanged in patients who demonstrated no reperfusion by coronary angiography, but patients in whom reperfusion occurred (independent of therapy) had a decrease in the size of the thallium defect (figure 10–5). Although this study can be criticized because 1) thallium analysis was not quantitative, and 2) there were no data provided on correlation with other functional information, it does demonstrate that perfusion imaging can identify successful reperfusion and appears to demonstrate salvage of previously nonperfused viable myocardium.

Weiss et al. reported the phenomenon of *reverse redistribution* at rest: That is, a defect that appears or is more evident on the delayed image than on the initial image in reperfused patients [46]. They found that this pattern observed on resting thallium imaging performed 10 days after intracoronary thrombolytic therapy (within 3 hours of the onset of symptoms) correlated with the presence of a nontransmural infarct zone subtended by a patent coronary artery (i.e., successful reperfusion). This phenomenon is thought to be due to faster than normal thallium washout in the reperfused area, due to the presence of both viable tissue and necrotic tissue in this region. In addition, there was improvement in regional wall motion in the segments demonstrating reverse redistribution, suggesting the regional occurrence of at least some viable myocardium with near-normal function. This type of analysis has an advantage in that a study prior to therapy is not needed. In general, obtaining a baseline thallium scan prior to the onset of thrombolytic therapy is not practical because the time needed to obtain the study will delay the onset of treatment.

A more practical approach to this type of imaging may be afforded by a new class of technetium-labeled myocardial perfusion imaging agents, the isoni-

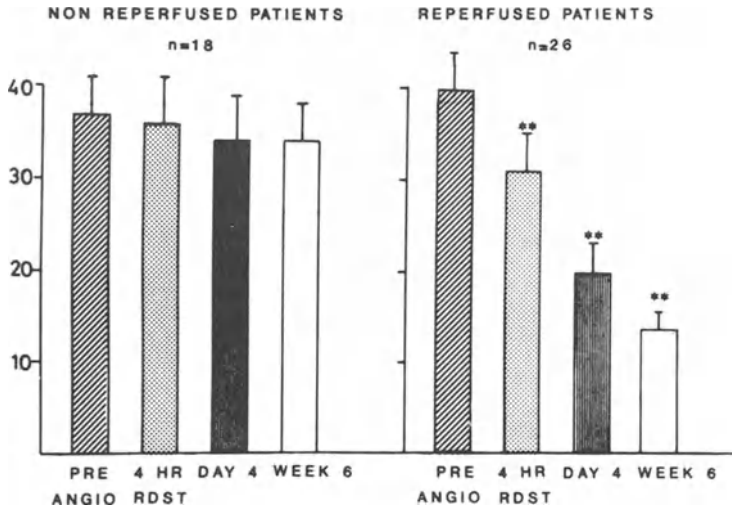

Figure 10–5. Sequential thallium defect scores of nonreperfused (**left panel**) and reperfused (**right panel**) patients, expressed as mean values ± standard deviations of the mean. Reperfused patients show a significant improvement in thallium defect size over time. From De Coster PM et al.: *Am J Cardiol* 55:889, 1985, with permission.

triles. The most widely used of these agents is Tc-99m hexakis-methoxy-isobutyl-isonitrile (Tc-99m MIBI), which accumulates in the myocardium in proportion to blood flow [47–50]. The tracer then remains bound to cytosolic proteins, does not demonstrate significant redistribution over time, and is unaffected by subsequent alterations in regional myocardial blood flow. These unique characteristics make it possible to inject this tracer immediately prior to the initiation of thrombolytic therapy, without causing a delay in the administration of therapy, and to image the patient several hours later, after the patient has been stabilized and effectively treated. The images obtained at that time would presumably reflect perfusion at the time of injection, i.e., the risk zone. The final infarct area is defined at a second study performed several days later after a repeat injection, and any improvement between the two sets of images would presumably reflect reestablishment of flow and salvaged myocardium. This approach has been used successfully in our laboratory [51] and is currently being evaluated prospectively using both planar and single-photon-emission computed tomographic techniques in patients receiving rt-PA for acute myocardial infarction.

Myocardial metabolic imaging

The use of nuclear techniques to image metabolic events and regional substrate utilization offers a new dimension to the assessment of myocardial tissue characterization in both normal and pathologic states. By labeling cell sub-

strates, it is possible to measure myocardial-cell fuel uptake and utilization, and therefore obtain a more accurate indication of regional viability and metabolism. Abnormalities in metabolism may be used to identify areas of myocardium that are necrotic or ischemic prior to intervention and may help to direct intervention. In addition, identification and quantification of regional myocardial metabolic function may identify areas of myocardium that are dysfunctional because of repeated ischemic events, so-called "stunned myocardium" [52], or may identify myocardium with altered metabolic and contractile function that may represent a protective response to prolonged ischemic injury, but that might recover function gradually or with revascularization, so-called "hibernating"myocardium. The development of positron-emission tomography has permitted initial study of these phenomena.

Positron-emission imaging detects radioactive decay that results from annihilation of a positron (positive electron) and an electron. This produces two photons simultaneously, which are emitted 180° apart with an energy of 511 keV. This photon pair can be recorded by detectors aligned 180° apart, and recording occurs only if a photon pair strikes both detectors of the pair simultaneously. This type of imaging has several advantages over single-detector imaging systems employed for routine planar imaging. There are few random counts (since they would have to hit detectors 180° apart simultaneously); there is no loss of positional data due to attenuation (a source distant from one detector is close to the other detector of the pair); tomographic techniques using several detector pairs allows for three-dimensional reconstruction; the half-lives of the isotopes are short, permitting serial assessment. A major disadvantage of this technique is that most positron isotopes are cyclotron produced, necessitating an on-site cyclotron. The cost of a positron unit including an imaging device and a cyclotron is substantial.

In the normal heart, 40%–80% of the energy requirements are met by beta oxidation of free fatty acids, although the heart is also able to utilize other substrates such as glucose and amino acids. In ischemic myocardium, beta oxidation and utilization of fatty acids are impaired. Ischemic myocardial cells metabolize glucose anaerobically, and the net result of ischemia is decreased fatty acid utilization and increased glucose utilization. Fatty acid metabolism has been characterized by positron-emission tomography utilizing C-11-palmitate as a substrate [53, 54]. When compared with normal myocardium, ischemic myocardium has decreased initial uptake of fatty acid and no rapid turnover of fatty acid (representing beta oxidation).

Glucose metabolism has been assessed by F-18-deoxyglucose (FDG), a glucose analogue [55]. This substrate diffuses into myocardial cells and is phosphorylated with the same kinetics as glucose. However, FDG is not a substrate for either glycolysis or glycogen synthesis, and it becomes trapped in the cell. Since ischemic myocardial cells show increased utilization of glucose, PET scanning should be able to identify ischemic myocardium [56]. In patients with recent myocardial infarction, Marshall et al. were able to demonstrate increased

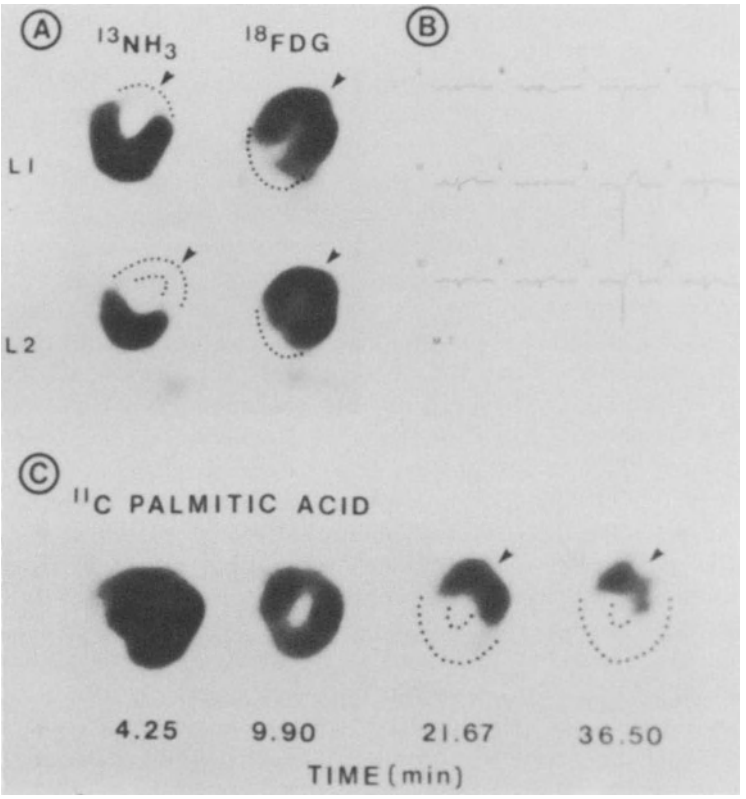

Figure 10–6. Positron emission tomographic images in a patient with acute anterior-wall myocardial infarction. **Panel A**: Decreased blood flow to the anterior wall (arrow) as assessed by 13-N-ammonia. 18-fluorodeoxyglucose (18-FDG) imaging shows increased uptake into same region, indicating enhanced glucose utilization. **Panel B**: Electrocardiogram of the same patient showing transmural anteroseptal infarction. **Panel C**: Serial C-11-palmitate images in the same patient, demonstrating prolonged clearance of activity matching the region with increased glucose utilization and decreased blood flow. From Schwaiger M, Schelbert HR: *New Concepts in Cardiac Imaging*. In Pohost, et al., eds. Chicago: Year Book Medical Publishers, 1986, with permission.

glucose utilization in ischemic tissue with little or no flow as assessed by N-13-ammonia imaging, and were able to identify infarcted tissue by demonstrating no flow and no glucose utilization (figure 10–6) [57]. Schwaiger et al. studied seven patients with PET and serial echocardiograms during acute myocardial infarction [58]. They found that myocardial blood flow was reduced in 13 left ventricular segments, and 9 of these 13 segments showed increased FDG utilization. Five of these nine segments showed improvement in regional function; in 2 of 9 regional function was unchanged, and in one patient with infarct expansion, regional function deteriorated in two segments. This study

suggests that PET scanning can differentiate infarcted from ischemic tissue in the setting of an acute infarction and should also be able to assess the success of reperfusion by demonstrating normal metabolism in areas of myocardium exhibiting abnormal metabolism prior to intervention. Tillisch et al. have used this technique to predict the reversibility of preoperative wall motion abnormalities following successful coronary artery bypass surgery [59].

Using positron techniques, N-13-ammonia has been used as a tracer to assess myocardial blood flow and perfusion. At normal body pH, ammonia exists primarily as NH_4^+, but the fast equilibrium constant favors formation of NH_3. NH_3 can diffuse into myocardial cells, where it is converted to NH_4^+ and becomes trapped as glutamine in a reaction catalyzed by glutamine synthetase. Generally, tracer uptake is proportional to flow and tissue extraction. However, Rauch et al. point out that the use of ^{13}N-ammonia as a tracer may also depend on cell-membrane integrity, pH gradient, and normal function of glutamine synethetase [60]. Schelbert et al. and Shah et al. have extensively characterized ^{13}N ammonia kinetics in the canine model and have been able to calculate myocardial blood flow in ml/min/100 grams with a good correlation with microsphere-dervived myocardial blood flow ($r = 0.94$) [61, 62]. Since extraction and kinetics of ^{13}N ammonia has not been extensively characterized in humans, and because of limitations in resolution, blood flow is reported as counts/region of interest.

Rubidium-82 has also been used to assess myocardial blood flow. This isotope can be obtained from an ^{82}Sr-^{82}Rb generator, rather than for a cyclotron and therefore obviates a major logistic problem of positron technology, namely, having an on-site cyclotron. Mullani et al. and Goldstein et al. have demonstrated that rubidium-82 can be used to generate gated first-pass blood-pool images as well as perfusion images, and theoretically, absolute blood flow expressed in ml/min/g can be determined [63–65]. Rubidium kinetics can also be used to identify viable but ischemic myocardium [66]. Recently, Gould et al. reported the use of rubidium-82 or ^{13}N ammonia following administration of intravenous dipyridamole combined with handgrip exercise to identify coronary stenoses [67].

Myocardial blood flow can be assessed with labeled albumin microspheres, but since these need to be injected in the left side of the heart (i.e., left atrium), their use is limited to invasive techniques [68].

Metabolic imaging has also been performed with single-photon radiopharmaceuticals using radioiodinated free fatty acids. These can be imaged by both planar and tomographic techniques. Van der Wall et al. demonstrated regionally decreased uptake of I–123 labeled heptadecanoic in patients with angina pectoris [69]. Hoeck et al. demonstrated abnormalities in patients with idiopathic congestive cardiomyopathy with SPECT imaging using 17-I-123 iodoheptadecanoic acid [70]. Myocardial perfusion was normal, suggesting that cardiomyopathy is associated with focal alterations in metabolism despite normal perfusion. However, the measured half-life of these iodine-labeled free

fatty acids is not the same as that of ^{11}C palmitate. It has been suggested that the regional myocardial half-life of this type of iodinated free fatty acid does not correlate with beta oxidation of fatty acid, but rather is a function of diffusion of free iodine label from the mitochondria into the coronary circulation [71]. In order to overcome this problem, iodine has been introduced into the fatty-acid molecule in a different location and via a phenyl group addition. In addition, beta methyl substitution also has been employed to increase the amount of time the isotope remains in the myocardium, and thereby to improve imaging. Livni et al. have reported on 14-(p-iodophenyl) beta methyletradecanoic acid as an imaging agent [72]. Although this compound does show some clearance from myocardial tissue, it does demonstrate prolonged myocardial residence time, permitting high-quality planar and SPECT imaging. Yoshiharu et al. demonstrated focally decreased fatty-acid uptake and a concomitant increase in glucose utilization in the left ventricular free wall of hypertensive rats [73].

Infarct avid imaging

Technetium-99m pyrophosphate (Tc-PYP) imaging was first introduced as a means of diagnosing acute myocardial infarction in 1974. However, because images are not positive until 24–48 hours after infarction, a time frame within which one can diagnose acute myocardial infarction reliably by other means, this technique has been largely abandoned clinically. Parkey et al. first reported clinical use of Tc-PYP as an infarct avid imaging agent in 1974 [74]. This technique was able to visualize areas of transmural infarction with a sensitivity exceeding 90%, but at 24–48 hours after the initial event [75]. Patterns of uptake demonstrating large areas of uptake with a donut appearance, or persistently positive areas of uptake indicate either a large infarct, or expansion or reinfarction, and predict a poorer prognosis. However, with the advent of thrombolysis as a treatment for acute infarction, a somewhat renewed interest has developed in this imaging technique as a possible means of assessing the efficacy of therapy. Since only necrotic myocardium takes up pyrophosphate, the technique may be able to distinguish between salvaged and infarcted myocardium after therapy.

Relevant to the issue of thrombolysis is the critical dependence of regional uptake of Tc-PYP on blood flow to the infarcted area, as well as the degree of myocardial necrosis, infarct age, and regional calcium concentration. Zaret et al. demonstrated that Tc-PYP uptake is maximal at flows of 30%–40% of normal, and at lower flow Tc-PYP uptake tends to decrease dramatically [76]. This is actually intuitive: At very low flow there is little delivery of tracer to necrotic tissue. Uptake of isotope begins to increase 4 hours after permanent occlusion and peaks approximately 48 hours after infarction [77]. Larger infarcts may attain maximal increased uptake later because of decreased delivery of the isotope [78]. Thus, in addition to necrosis, delivery of the isotope is

critical. This whole time sequence is altered by reestablishment of flow to the infarct zone.

Wheelan et al. used Tc-PYP imaging to identify successful reperfusion after intravenous streptokinase therapy for acute myocardial infarction [79]. Generally, there is no uptake of intravenously injected Tc-PYP in the early hours of myocardial infarction; focal uptake in the area of infarct following thrombolytic therapy presumably represents establishment of flow to infarcted tissue. They found that all patients with patent infarct arteries following acute infarction had early 3+ or 4+ Tc-PYP uptake, and 10 to 11 patients who demonstrated 3+ or 4+ uptake had a patent infarct artery. The patient with 3+ uptake but an occluded infarct artery had early peaking of creatine kinase MB and was thought to have a late reocclusion. This study demonstrates that successful reperfusion can be identified with Tc-PYP imaging.

Use of radiolabeled antibody fragments against cardiac myosin represents a biological approach to imaging acute necrosis [80]. The tracer is specific for infarcted cardiac tissue and therefore should provide most accurate information. In addition, uptake of the tracer is inversely proportional to blood flow, and little flow is needed for imaging (much less than for Tc-PYP imaging) [81]. Thus, scans using this technique should be diagnostic for acute infarction and may be suitable for sizing infarction in the immediate acute phase. This work is still quite experimental, with relatively little data in humans currently published. Studies to date are limited by the physical characteristics of the tracer, Indium-111, and the delayed clearance of the antibody.

With more interventional treatment of acute myocardial infarction, the effect of reperfusion at the cellular level is being investigated. Specifically, possible deleterious effects of reperfusion have been identified related to free-radical formation and neutrophil accumulation at the site of ischemic injury. Indium-labeled leukocytes as a means of imaging myocardial infarction was first reported by Thakur et al. [82]. More recently, investigators have used this technique to assess myocardial salvage by antiinflammatory agents given during acute infarction, as well as the effects of free-radical scavengers [83, 84]. Although these studies have been performed to date in animal models, this research is becoming particularly clinically relevent and will soon be extended to clinical situations.

Single-photon-emission computed tomography

Radionuclide techniques involving single-photon-emission computed tomography (SPECT) are being developed to quantitate infarct size and to determine left ventricular mass. With this technique, a scintillation detector rotates 180° around the patient, aquiring a two-dimensional image for 20–40 seconds every 5°. The information is then summed and reconstructed into a transaxial image in several planes. This technique may be of value in defining the border between normally perfused myocardium and the perfusion defect more effectively than conventional planar imaging, and may be able to delineate better

different vascular regions by virtue of elimination of overlapping structures. The three-dimensional reconstruction also permits quantitation of volume and correlation with ventricular mass. Corbett et al. found tomographic imaging with Tc-PYP superior to planar imaging for detection of acute nontransmural infarction, and Caldwell et al. and Corbett et al. were able to measure infarct size [85–87]. SPECT with thallium-201 has also been able to quantitate the mass of normally perfused myocardium in dogs, and recently, in the canine model, Wolfe et al. have combined these two techniques to express myocardial infarct size as a percent of total left ventricular mass [88, 89]. Although SPECT infarct studies currently are used in only in a few centers and must be considered experimental, combined SPECT imaging with thallium-201 and Tc-PYP may be an appropriate means of quantifying infarcted, ischemic, and salvaged myocardium.

CONVALESCENT PHASE RISK STRATIFICATION FOLLOWING ACUTE MYOCARDIAL INFARCTION

In the convalescent phase of myocardial infarction, it is important to identify the patient at high risk for reinfarction or death so that more aggressive therapy can be instituted. Several factors have been found to relate to risk stratification. Resting ejection fraction reflects left ventricular dysfunction related to the amount of damaged myocardium, and exercise studies reflect, in addition, the presence of residual ischemic myocardium, also important for assessing prognosis. Corbett et al. found that with submaximal exercise, failure to increase left ventricular ejection fraction by 5%, or an increase in left ventricular end-systolic volume by greater than 5%, had a sensitivity of 95% and a specificity of 96% for predicting important post-infarction complications in a series of 61 postinfarct patients [90]. Hung et al., in a study of 117 patients, found that the ejection fraction response during exercise radionuclide angiocardiography provided the best prognostic information when compared to several other variables, including exercise stress testing [91].

The importance of the role of these radionuclide techniques are emphasized by several studies that indicate this prognostic information is not available by either knowledge of coronary anatomy or assessment of various clinical parameters. Both Wasserman et al. and Nicod et al. found that the results of coronary angiography did not predict subsequent cardiac events as well as did left ventricular response to exercise [92, 93]. Nicod and coworkers found that of 16 patients with single-vessel disease, a group that on angiographic criteria would be considered benign, 11 had major cardiac complications. The failure to increase left ventricular ejection fraction by greater than 5% provided the best prognostic information by correctly identifying the course of 13 of 16 patients [94]. Similarly, Morris et al., using a statistical analysis in a prospective study of 106 consecutive survivors of acute myocardial infarction, found a significant association between the time to death and ejection fraction at rest and at exercise [94].

There are limited data reported on the left ventricular response to exercise following thrombolysis. Our laboratory reported the initial experience with exercise testing at hospital discharge in 149 patients in an open-label phase of the TIMI trial [95]. A fall in left ventricular ejection fraction with supine bicycle exercise testing was an uncommon event occurring in only 6% of patients. In contrast, the predominant response to exercise reported in the literature in the prethrombolytic era has been a fall in ejection fraction, occurring in 50% of these patients [96–99]. The fall in left ventricular ejection fraction in TIMI patients was associated with a poor prognosis. Guerci et al. reported the ejection fraction response of a group of patients receiving thrombolysis followed by elective angioplasty [100]. In this study, patients undergoing both thrombolysis and angioplasty demonstrated an improved left ventricular ejection fraction response to exercise as compared to control patients receiving only thrombolytic therapy, although the resting left ventricular ejection fraction was the same for both groups. This study supports the role of exercise radionuclide angiography for evaluation of this type of therapy. Several other large trials assessing the efficacy of thrombolysis and thrombolysis combined with angioplasty are currently evaluating the role of exercise radionuclide angiography in different patient subgroups.

Exercise thallium scintigraphy has also been widely used as a method for evaluating the presence of residual postinfarction left ventricular ischemia. Recent advances in the development of computer-determined quantitative analysis of myocardial thallium washout make this additional approach mandatory for accurate interpretation of perfusion data [101]. Gibson et al. found that 13 of 140 postinfarct patients who had subsequently developed reinfarction or severe angina had single-vessel disease by coronary angiography and would have been considered low risk on anatomic grounds [102]. However, 12 of these 13 patients had abnormal thallium scintigraphic studies. In addition, abnormal thallium scintigraphy demonstrating multiple defects, the presence of delayed redistribution, or increased lung uptake of thallium were more sensitive than the electrocardiographic response or the coronary anatomy for predicting subsequent cardiac events. In patients with non-Q-wave infarction, Varma and Gibson have shown that the results of thallium-201 imaging at predischarge exercise testing were useful in assessing the risk, whereas the results of exercise testing alone were not [103].

Pharmacologic stress in conjunction with thallium-201 scintigraphy is another means of evaluating post-myocardial-infarction risk, independent of patient effort. Leppo et al. found that 11 of 12 infarct patients who subsequently died or had reinfarction, and 22 of 24 patients who were readmitted for the management of angina had abnormal redistribution of thallium after dipyridamole infusion [104]. Twenty-six patients underwent both pharmacologic stress testing and exercise stress testing. Twelve of 13 patients with subsequent serious cardiac events had abnormal thallium resdistribution by dipyridamole study, while only 6 of 13 had abnormal exercise thallium redis-

tribution studies. Recently, it has been demonstrated that oral administration of dipyridamole may be a suitable replacement for the intravenous preparation [105].

In addition to evaluating left ventricular functional reserve and ischemia at exercise, recent attention has focused on the prognostic significance of silent ischemia occurring at rest — that is, electrocardiographic manifestation of ischemia (ST-segment changes) in the absence of pain [106]. However, electrocardiographic monitoring of ST segments is subject to false positives (as in exercise testing), and ECG changes may not necessarily reflect ongoing myocardial ischemia [107]. In several laboratories including our own, there is ongoing investigation of the use of a nonimaging radionuclide ventricular function monitoring detector (VEST), which may be worn by ambulatory patients [108]. This detector continuously records left ventricular ejection fraction and a two-channel electrocardiogram on a Holter tape, which is subsequently analyzed offline by computer. Using this technology, we have demonstrated that transient asymptomatic falls in left ventricular ejection fraction during monitoring of routine activity at the time of hospital discharge in patients treated with thrombolysis had an adverse prognostic significance [109]. Thus, transient left ventricular dysfunction occurring at rest, presumably because of decreased supply rather than increased demand, may be more common than appreciated and have major clinical and prognostic import.

Although radionuclide techniques provide much prognostic information for the post-myocardial-infarction patient, optimum strategies for determining the order or selection of tests have not been developed. Resting radionuclide angiocardiography provides crucial information on both global and regional left ventricular function and wall motion and perhaps is the single most important study to obtain. However, there is limited data comparing the value of exercise radionuclide angiocardiography, exercise thallium scintigraphy, and dipyridamole thallium scintigraphy for assessing residual left ventricular ischemia, particularly in the thrombolytic therapeutic era. The choice should in part depend on the expertise in the laboratory performing the study.

SUMMARY

In the assessment and management of the patient with acute myocardial infarction, nuclear studies have a role in both the acute and convalescent phase. In the acute phase, areas of decreased flow can be assessed by resting thallium-201 imaging, and assessment of reperfusion and potential salvage of myocardium can be made qualitatively with delayed imaging. SPECT may provide additional quantification of infarct size, and possible quantitation of salvaged myocardium if serial studies are performed. Further studies are necessary to determine its role. PET scanning is currently the only noninvasive technique that can identify and separate infarcted and ischemic myocardium on a metabolic basis. In the convalescent phase, global and regional left ventricular

function provide important prognostic information, and the results of exercise testing combined with either thallium perfusion imaging or ventricular function studies to assess myocardial reserve can be used for risk stratification and to determine the most appropriate management strategies.

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11. RISK STRATIFICATION AFTER ACUTE MYOCARDIAL INFARCTION: THEORY AND PRACTICE

ELIZABETH A. GILPIN AND JOHN ROSS, JR.

The natural history of the patient with acute myocardial infarction (AMI) has been thoroughly investigated. Studies have focused on establishing morbidity and mortality rates and have sought to identify factors that are associated with increased risk of death or other events. The ultimate aim of such work, of course, is to facilitate risk assessment in the individual patient, so that therapeutic management can be optimized. Much investigation in the field of risk stratification has involved the identification of important historical, laboratory, or clinical variables that either individually or together in a multivariate scheme allow definition of risk groups with varying event rates. In the past few years the utility of special procedures for this purpose has received considerable attention, and investigators have focused on the relative importance of known risk factors to prognosis and whether they provide "independent" prognostic information.

Cardiac mortality after AMI has been characterized in several large studies, and an exponential fall in mortality out to 6 or 8 months after AMI has been suggested [1–3]. More recently, in 2290 patients from three geographically distinct populations (figure 11–1), starting 24 hours after hospital admission, it was shown that 50% of all deaths in the first year occurred by day 19, and 75% of all deaths occurred by day 100 [1]. Overall, cardiac mortality between day 2 and 3 weeks was 11.4%, and for the remainder of the year it was 10.5%. It was found that separate exponential curves best describe the mortality distribution up to 3 weeks and for the remainder of the year. Studies of risk stratification

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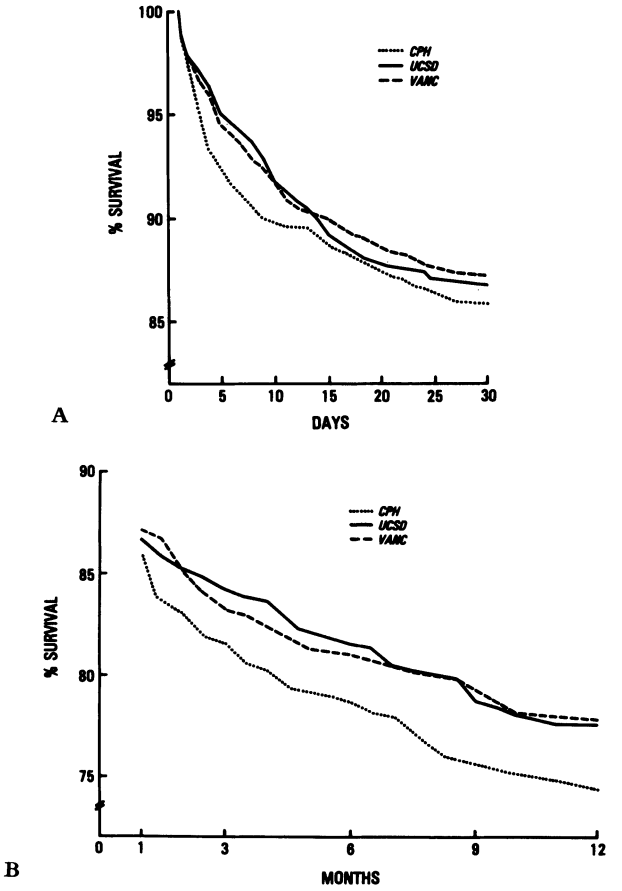

Figure 11–1. The percent of patients alive at the end of the first day following admission through day 30 is shown in the top panel. The bottom panel gives the extension of these curves from day 31 to 1 year on a different time scale. Abbreviations: CPH = Copenhagen, Denmark; UCSD = University of California, San Diego; VANC = Vancouver, British Columbia, Canada.

have often focused on one of several periods including the first day after admission [4], the hospital period, the interval ranging from 2 to 20 or 30 days [4–13], and the postdischarge period, ranging from several months [4, 6, 14–19] to several years [4, 12, 20–27]. These intervals, although not exact, have basis in both the observed mortality patterns and the time points at which theapeutic decisionmaking is most appropriate.

Shortly after hospital admission, information from the patient's history, initial physical examination, ECG, chest x-ray, and laboratory results, including the serum enzyme determination, is available. These admission findings have been used to identify patients at high risk of early death [4–5],

serious complications [28], and events such as ventricular fibrillation [29] or myocardial rupture [30]. Within the next few days, while the patient is in the coronary care unit (CCU), more clinical information of the same nature becomes available. Data from the history and the first 24–48 hours after admission have been used to identify a group of patients at risk of either early [4–6, 8, 11, 12] or late death [6, 18, 19]. Also, such data can identify low-risk subgroups for possible early hospital discharge [28].

In addition to historical and clinical data obtained throughout the hospital admission, predischarge evaluation by special studies such as an exercise test, radionuclide left ventriculography, 24-hour ambulatory ECG monitoring, and coronary angiography can provide additional prognostic information. With such data, it should be possible to make reasonable decisions regarding theraputic management, based on assessed risk of death or other coronary events in the individual patient. When the high incidence of events in the first few months after hospital discharge is considered, such predischarge evaluation beomes especially important.

Athough many approaches to the problem of risk stratification after AMI have been proposed and investigated, evaluation of the results of such investigations within the framework of patient management is not a trivial task. In this review, our goal will be to define and evaluate the main issues, both in theoretical and practical terms.

MULTIVARIATE METHODOLOGIES

Before reviewing investigations on risk stratification, it will be helpful to discuss briefly some of the main advantages and disadvantages of the major multivariate statistical methodologies used to develop risk stratification schemes and to consider certain issues concerning the interpretation of results from such analyses. Additional details concerning these methodologies are given in the appendix.

Advantages and disadvantages

There are basically two classes of multivariate methodologies. One class of methodologies is called *parametric* [31] and is based on computing the parameters or coefficients of a proposed mathematical model or equation that best describes or fits the observed data. The mathematical models underlying these methodologies require that certain assumptions regarding the nature of the outcome and predictor variables, and the nature of the relationship of the predictors to the outcome variable, be met in order for statistical tests regarding the significance of the computed parameters to be valid (see the appendix). However, these methodologies are robust to violations of these assumptions and have proved useful in risk stratification after AMI. Risk strata are formed by determining cutoff points on the scale of the predicted outcome variable that define groups with different observed incidences of endpoints.

Table 11–1. Comparison of multivariate methodologies

	Parametric				Nonparametric		
Characteristic	MLR	LDF	LR	COX	PS	AID	RP
Can accomodate different length followup in one analysis				X			
Can identify interactions among predictor variables					X	X	X
Accounts for costs of misclassification in variable selection							X
Can accommodate missing data without estimation							X
Easy to understand conceptually	X	X			X	X	X
Computer programs widely available	X	X	X	X			
Resulting scheme easy to use without calculator					X	X	X

Abbreviations: MLR = multiple linear regression; LDF = linear discriminant function; LR = logistic regression; COX = Cox regression; PS = prognostic stratification; AID = automatic interaction detection; RP = recursive partitioning.

Another class of methodologies, called *nonparametric* [31], requires no assumptions concerning the nature of the predictor or outcome variables and seeks to discover combinations of predictor variables that define groups of patients having very different incidences of endpoints.

Table 11–1 summarizes the positive features of four different parametic methodologies (multiple linear regression, linear discriminant function analysis, logistic regression, and Cox regression) and three nonparametric methodologies (prognostic stratification, automatic interaction detection (AID), and recursive partitioning). For all methodologies but Cox regression, followup to a given point in time must be complete for all patients used in the analysis. Input to Cox regression is the length of followup or time to an event, rather than whether or not an event took place by a particular point in time. Another feature of the Cox model allows relative risk ratios to be determined for patients with or without a given feature while adjusting for all other important factors. With these advantages comes a certain degree of conceptual complexity, which is greater than with the other parametric methodologies.

When using a parametric model, the investigator must hypothesize beforehand which factors' predictive powers might be enhanced by the presence or absence of other factors or must include many potentially unimportant interaction terms to ensure that relevant ones will be included. By automatically searching for combinations of factors that define high-risk groups, nonparametic methodologies identify important interactions.

The use of schemes derived from the parametric methodologies involves

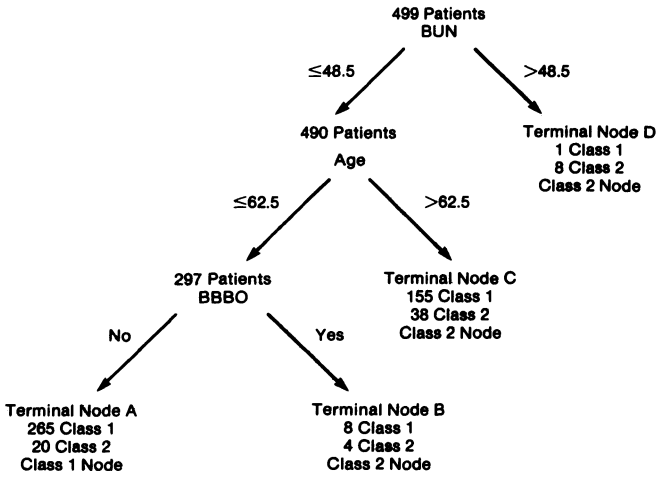

Figure 11–2. Classification tree derived by recursive partitioning applied to 499 patients from the University of California, San Diego. Abbreviations: BUN = blood urea nitrogen; BBBO = old bundle branch block.

enough computation that, to ensure accuracy, a computer or programmable calculator should be used. A patient's data can be keyed in and the resultant risk level or strata is the output. For prognostic stratification, only a few variables need to be examined. The schemes resulting from AID and recursive partitioning are easy-to-use classification trees (figure 11–2). A patient can be classified by simply inspecting a diagram.

In the tree-building process, at each step the variable is chosen that best discriminates between patients with and without certain events. The groups determined by the chosen variables are then analyzed again to find another split variable. The process continues until the group being considered is too small to subdivide further, contains all one class, or no variable proves adequately discriminating for another subdivision.

Recursive partitioning has several additional positive features. When choosing a split variable, the relative costs of misclassification (see the appendix) are considered for all possible cut-points for each continuous variable before it is evaluated with respect to all the other variables. For the parametric schemes, these relative costs of misclassification are not considered in the variable selection process, but only when the cut-point(s) for defining risk strata on the scale of the predicted outcome variable is chosen. Although some investigators substitute estimates for missing data in a multivariate analysis (usually mean values for the available data), recursive partitioning can directly accommodate missing data for some of the candidate variables in the tree-building process and provides alternative variables to use in the classification process if one of the selected split variables is not available for a given patient.

The main problem with nonparametric methods is that smaller and smaller groups of patients are being analyzed at each step. Therefore, the probabilities of selecting an unimportant factor within an idiosyncratic subgroup and missing an important one are both enhanced. If the patient population used to build the scheme is large to begin with, and the process is not carried too far, these problems can be minimized.

Finally, the choice of one methodology over another may depend on the availability of computer programs for building the schemes. So far, the parametric methodologies have been more widely disseminated, as they are part of standard statistical software packages. As the speed of computers has increased, the cost of analysis has ceased to be a major determining factor for even the more computationally complex methodologies.

Importance and independence of predictor variables

All of the parametric methodologies mentioned above are generally utilized in a stepwise mode. At the first step, all the variables in the analysis are examined, and the variable that provides the most prognostic information by a particular statistical criterion — which depends on the methodology — is selected. Then the remaining variables are examined to see whether they are able to provide additional prognostic information beyond that provided for by the first variable selected. In some procedures, each variable already in the model is examined to see if it still contributes significantly when adjustment (usually by regression techniques) is made for the other variables already in the model. If not, it is removed. Thus, it is entirely possible that the first variable to enter may eventually be discarded because several others account for the same prognostic information. The process is terminated when no more variables contribute additional information, while all the variables in the model contribute significantly.

The variables retained are called *independent* predictors and their *relative importance* can be assessed by examining the magnitude of the test statistic or its significance level for each variable at the final step. The test statistic or its significance level shows the importance of the variable, adjusting for all the other variables retained in the final model, and allows a ranking of the variables in order of importance rather than in order of selection. In many cases the order of selection and the final ranking are identical.

Although stepwise procedures usually come close, they do not necessarily identify the best set of predictors. To do that, all possible combinations of potential predictors would have to be utilized in separate nonstepwise analyses and the statistic that indicates overall model performance would have to be examined to identify the best model. The second best model may perform nearly as well as the best one, just as the model with a variable eventually discarded from a stepwise procedure might perform nearly as well as the final model. Thus, disregarding a predictor that is important in a slightly

suboptimal model is falacious, especially if the suboptimal model performs well and has fewer or more easily obtained variables.

RESULTS OF PROGNOSTIC STRATIFICATION

Use of historical, standard laboratory, and clinical data

The natural history following AMI and its relationship to historical and clinical factors has been widely investigated, beginning as early as 1941 [32–34]. Except for historical factors such as age, sex, previous AMI, and the presence of various preexisting diseases and conditions, most of the standard laboratory and clinical factors provide an indirect indication of the extent of cardiac damage and the resulting depression of cardiac performance.

Data from the physical examination, including heart rate, systolic blood pressure, respiration rate, temperature, peripheral hypoperfusion, shock, gallop rhythm, rales, and peripheral edema, have been related to outcome. The chest x-ray provides prognostic information by assessment of pulmonary congestion and cardiomegaly. Laboratory data such as the leukocyte count, blood urea nitrogen, uric acid, cholesterol, serum creatinine, and serum enzymes (CK, LDH, etc.) have also been related to prognosis. From the ECG, the site of infarction, QRS duration, QT interval, ST-segment changes, conduction defects, atrial and ventricular dysrhythmias, and sinus tachycardia have provided prognostic information [35].

More direct assessment of cardiac performance by hemodynamic indices such as left ventricular filling pressure, left ventricular stroke work index, stroke volume index, cardiac output, cardiac index, AVO_2 difference, and left ventricular ejection fraction has improved predictive accuracy compared to historical and clinical data alone [5, 26]. Even when overt clinical manifestations of pump failure are absent, hemodynamic indices or left ventricular ejection fraction can be abnormal [36–38]. Conversely, severe congestive heart failure does not inevitabley presage a poor immediate prognosis, and occasionally such patients survive for years beyond the acute event.

As early as 1953, one researcher endeavored to use simultaneously a wide spectrum of factors that were known to be individually related to prognosis. Schnur devised a *pathologic index* rating system that summed weights assigned to various factors observed from the history or during the first 24 hours postadmission according to the strength of their association to prognosis in the population studied [39]. The index included 19 separate factors, some with fixed weights and others with a range from which the clinician could choose, depending on the severity of the finding. The index was applied to 230 patients surviving the first 24 hours of hospitalization. Five groups were defined by dividing the score scale into 20-point intervals. Ten-year mortality in the lowest group was 8% compared to 95% for the highest group.

The well-known Peel Index was published in 1962 [40]. The number of

factors was limited, so that only six numbers had to be summed to obtain a patient's score. The factors included age, sex, previous history, shock, heart failure, the electrocardiogram, and rhythm disturbances observed during the first 24 hours after admission. An attempt was made to limit observer latitude by carefully defining each factor and its rating. The index was initially applied to 628 patients. Again, the range of scores was divided into five intervals, producing groups of patients with mortality at 30 days ranging from 2.5% to 88.5%. This index has been tested widely by other investigators [9, 41–43], and it has even been used as a single "composite" clinical variable in other multivariate schemes [9, 23, 44].

The advent of the high-speed computer allowed the application of statistical approaches for constructing various indices. Two studies published in 1963 were among the first to take advantage of this technology [8, 13]. Lemlish applied multiple linear regression to 371 patients in an attempt to rank nine univariately important factors for 30-day death or survival [13]. All factors were scaled to standardized units, and the resulting magnitudes of the regression coefficients were noted. Blood pressure, a history of a previous myocardial infarction, age, temperature, and duration of elevated temperature were identified in the order listed as the most important factors. Hughes examined over 20 historical, admission, and early postadmission variables in 445 patients in a discriminant analysis to predict in-hospital mortality [8]. Ten variables contributed significantly, including age, white blood cell count, temperature, systolic blood pressure, presence of a conduction defect, pulmonary infarction, congestive heart failure, and shock. Overall 97% of survivors and 80% of deaths were classified correctly. Two much smaller studies appeared in 1968, one predicted outcome for 20 shock patients using discriminant analysis on hemodynamic data obtained up to 80 hours postadmission [10], and the other used admission hemodynamic data and evidence of ventricular failure from the initial chest x-ray, together with the Peel Index, to predict in-hospital mortality using multiple linear regression in 42 patients [9].

Norris and associates in 1969 and 1970 applied discriminant analysis in a novel way to historical and admission data from a large patient population to develop indicies for in-hospital and 3-year mortality [11, 22]. Instead of using raw data, all univariately significant variables were scaled between 0 and 1 based on the proportion of deaths observed in the various category intervals. The discriminant weights were then computed using the scaled variables. The resulting index scores were again divided into strata that exhibited increasing mortality rates. For in-hospital outcome, age, location of infarct, admission systolic blood pressure, heart size, the presence of congestive failure from the chest x-ray, and a history of infarction or angina were utilized [11]. For late outcome only age, the data from the chest x-ray, and previous AMI or angina were utilized [22]. The selection of variables was made by the investigator rather than by a stepwise procedure. The Norris indices, like the Peel Index,

have been tested by a number of investigators [41–43, 45–47]. Since the publication of the Norris indices, many other investigators have developed indices based on the statistical analysis of historical and clinical data from various patient populations [4–8, 11, 12, 14–16, 18–22].

Most of the relevant historical and clinical data are available no later than the time of discharge from the CCU, so a patient can be stratified according to risk (even late risk) fairly soon in the hospital course [12, 18, 22]. However, for most studies of late outcome, variables from the entire hospital course are used [4, 14–16, 20, 21]. The only variables from later in the hospital period that have proved consistently useful are pulmonary congestion on the chest x-ray [12, 14, 15] and some arrhythmias [4, 18, 20, 21, 23, 24].

At least three studies have shown that data from the first 24–48 hours allow risk prediction from 6–36 months following the acute event [12, 18, 22]. In a study from our group (n = 818), data from the first 24 hours, together with historical data, predicted 1-year outcome for hospital survivors using discriminant analysis nearly as well as data from the entire hospital course [18]. The three most important variables were maximum blood urea nitrogen level (obtained on admission and 24 hours later in our protocol), a history of previous infarction, and age. These same factors were still important when data from throughout the hospital stay were added, but additional variables did enter the analysis (maximum heart rate in the CCU, extension of MI, and S_3 gallop at discharge). Overall correct prediction and prediction of death or survival was improved less than 2% by the inclusion of the other factors.

In another study, linear regression selected age, female sex, diabetes, previous angina, blood pressure, clinical and radiologic left ventricular failure, high LDH, high blood urea nitrogen, and high leukocyte count from among 42 different factors from the history and first 48 hours postadmission [12]. Survival both at 1 and 6 months was predicted using different cutoff points on the scale of the prognostic score. This scheme correctly classified 90% of patients (alive at 48 hours) at 1 month and 86% at 6 months. These results reflect the fact that most deaths resulting from AMI occur within this time period, and they indicate that patients who will die because of their AMI can be identified early in the hospital course.

Patients identified as being at high risk might benefit most if this designation could be made within the first 3–5 days. Additional tests could then be scheduled while the patient is still in the hospital or therapeutic measures could be instituted early. Also, patients identified at an early time as being at very low risk could be mobilized early and prepared for early hospital discharge as part of an overall management policy.

Early hospital discharge for low-risk patients

Several small, controlled studies of early hospital discharge in selected patients have not detected any difference in event rates during 1.5–8 months of

followup between patients in the control group and those discharged early [49–54]. The main weakness of these studies was their small size. Since not all of the patients were eligible to participate, the overall number of patients followed ranged from 66 to 253. It would take much larger samples to detect an event rate significantly greater than the 4%–6% event rate that can be expected to be obtained for low-risk patients.

Other uncontrolled studies with well-defined criteria for selecting patients for early discharge have also shown very low event rates (0% to 2.7%) during the early postdischarge period (2–6 months) [28, 55–57]. In a large (n = 1140), retrospective study in which patients were evaluated daily using a methodology for risk assessment based on Cox regression, patients were considered discharged when their risk of events (death, cardiac arrest, or shock) was less than 2% [28]. However, all patients were actually kept in the hospital until at least day 18 and were observed for events until day 30. Altogether, 47% of the patients could have been discharged early at or below the 2% risk level after day 5. This policy would have resulted in only one death outside the hospital (soon after day 5), but four patients experienced cardiac arrest and there were seven nonfatal infarct extensions. Still, these 12 events represented only a 2.6% event rate for the group which could have been discharged early. The same center has prospectively discharged 67% of 169 consecutive patients surviving at day 5 as early as day 6 with only two unexpected deaths (1.7%), at days 12 and 24, in the first 2 months postdischarge [28].

Only one additional study computed risk level based on a multivariate risk assessment scheme [57]. This center used seven prognostic variables from the first 48 hours selected by a discriminant analysis. These factors were: age greater than 65, blood urea nitrogen greater than 12 mol/l, ST depression greater than 2mm, ventricular ectopic beats greater than 40 in any hour after 6 hours postonset, any R on T beats after 6 hours, persistent sinus tachycardia (>100 beats/min), and pulmonary venous congestion on the chest x-ray. The low-risk group had only two deaths (1.2%) in the 3-month prediction period.

In the other studies, the investigators relied on a set of exclusion criteria. The following set of criteria has been proposed and is fairly typical of those used in most of the studies [58]. A patient should *not* be discharged early if during the first 5 days there is infarct extension, persistent chest pain, signs of congestive heart failure, hypotension or cardiogenic shock, or severe dysrhythmias (cardiac arrest, ventricular tachycardia, supraventricular tachycardia, atrial fibrillation, heart block, nodal rhythm, or frequent or complex ventricular premature beats). In addition, very elderly patients, and those with a previous myocardial infarction or serious disease of other organ systems, should not be considered for early discharge. Another report required uncomplicated patients to have a negative submaximal exercise stress test to be discharged early [54].

It is not surprising that most of the investigations in this area have been

conducted in Europe [49, 51, 53–57], where health care costs are of major governmental concern. As DRG reimbursement procedures are applied in this country, it seems likely that an upsurge of interest will occur here, too, in identifying low-risk patients for early hospital discharge.

Behavioral factors

The status of the left venticle is the main determinant of prognosis, at least for the first few months following AMI, but later the rate of disease progression may better relate to outcome. Several studies have addressed this issue in terms of behavioral and psychosocial influences [44, 59, 60].

In a study of 118 nonsmoking males, the ability to predict events using physiologic factors only, behavioral factors only, and a combination of these factors was investigated [44]. The study group consisted of 40 patients who had experienced a cardiac event by the end of year 2 after the index AMI and 80 others randomly selected from the remainder of the population. The only important physiological variable among the six investigated (Peel Index, cholesterol level, age, systolic and diastolic blood pressures, and body mass index) was the Peel Index, which achieved 70% predictive accuracy. Among 49 behavioral variables related to a lifestyle characterized by chronic struggle, 15 were univariately predictive and four had independent importance in a discriminant analysis. Again, overall predictive accuracy was 70%. When both sets of variables were combined, predictive accuracy increased to 75%. The authors concluded that living a lifestyle of chronic struggle increases the risk of recurrent MI.

Psychosocial factors contributing to risk during the 3 years following AMI were examined after adjusting for other important prognostic factors in the 2320 male participants of the Beta Blocker Heart Attack Trial [59]. Although type A behavior was considered, the variables with independent prognostic value were measures of social isolation and life stress. Adjusting for other factors in a Cox regression showed patients who were socially isolated and who had a high degree of life stress to be at four times the risk of death compared to patients without these characteristics. Type A behavior also showed no statistical relationship to mortality at 2 years after AMI in another study of 545 patients [60].

Radionuclide angiography

The functional status of the left ventricle is known to be a strong predictor for cardiac death after AMI [11, 15, 16, 23, 61, 62]. However, in only 50% of patients can the presence of a depressed left ventricular ejection fraction (LVEF) be predicted correctly from an abnormal chest x-ray alone [37]. Therefore, direct measurement of LVEF by radionuclide angiography or at cardiac catheterization can provide important prognostic information.

LVEF within the first 24 hours of admission has been univariately related to short-term mortality [64]. After the first 24–48 hours, LVEF stabilizes [65] and LVEF assessed late in the hospital stay has been shown to be related to mortality postdischarge for up to 2 years [25–27, 66–72]. Although many studies have used the value 0.30 [27, 66] or 0.40 [25, 26, 67] as a break point to demarcate a high-risk group, there is recent evidence that a break point of 0.45 can provide optimal sensitively and specificity for cardiac death up to 1 year [68]. In 750 patients followed 1 year, an LVEF less than 0.45 classified 62% of deaths correctly with 64% of survivors having an LVEF greater than or equal to 0.45. Only 19% of deaths within the first year had an LVEF less than 0.30, but 90% of survivors had an LVEF greater than or equal to 0.30.

The role of LVEF combined with other variables in a multivariate analysis has been the subject of several large multicenter investigations [25–27, 67–72]. All these studies found LVEF to be an independent predictor of outcome post hospital discarge. In the Multicenter Post-Infarction Research Group, 866 patients had an LVEF prior to discharge. Two other markers of left ventricular dysfunction, a history of previous AMI, and rales (diffuse rales or pulmonary edema) in the coronary care unit were analyzed together with LVEF in a logistic regression analysis of 2-year mortality [67]. Both rales and LVEF had independent prognostic importance. The authors presented tables showing the relationship of each variable to the other and to mortality. It is interesting to note that, taken together, rales and LVEF less than 0.40 identified a group of 63 patients with a 2-year mortality of 38.1%. Mortality for the remaining patients was 8.9%. A history of a previous AMI and rales defined a group of 33 patients with 39.4% mortality. In this case mortality for the remaining patients was 11.6%. Although rales and LVEF less than 0.40 perform well together, rales and a history of a previous AMI appear to be as effective.

In a multicenter study from our group (n = 750), LVEF was analyzed together with many other factors from the history, physical examination, ECG, chest x-ray, and laboratory findings from both the CCU period and at discharge [68]. In a discriminant analysis of 1-year mortality, LVEF ranked as an independent predictor behind pulmonary congestion on the chest x-ray, history of previous congestive heart failure, and age. Correct prediction of death was essentially unchanged using LVEF alone dichotomized at 0.45, and correct prediction of survivors increased from 64% to 80%. However, when LVEF was excluded from the analysis, the correct classification rates using historical and clinical factors alone remained unchanged.

In the Multicenter Investigation of the Limitation of Infarct Size (MILIS), an LVEF less than 0.40 was used together with 15 other variables, including ventricular premature beats greater than or equal to 10/hour from a 24-hour Holter monitor in a Cox regression analysis [25]. An LVEF less than 0.40 ranked second behind ventricular premature beats greater than or equal to 10/hour and was followed by use of digitalis at discharge and a history of a previous AMI.

Ambulatory electrocardiographic monitoring

Sudden cardiac death accounts for about half of all cardiac mortality following discharge for AMI [27, 73]. Investigators have long sought a method of identifying patients at high risk of sudden death so that prophylactic antiarrhythmic therapy can be undertaken. Many studies concerned with predicting sudden death (presumably arrhythmic death) have focused on the occurrence of frequent and/or complex ventricular arrhythmias during the recovery phase from AMI [24, 72–79]. Ventricular arrhythmias have also been related to total cardiac mortality [27, 69, 71]. Investigators have been able to define risk strata with statistically different rates of cardiac death [24, 73–75], but by itself this factor had not proved to be adequately sensitive or specific for therapeutic decisionmaking in the clinical environment [76]. It was suggested that if analysis of dysrhythmias were combined with other factors, prediction might be improved [76], and several recent studies have substantiated this approach [71, 72].

Several early studies used the occurrence of ventricular arrhythmias on an electrocardiogram to predict outcome [20, 77]. A continuous 1-hour electrocardiogram in the CCU of 1739 men showed that ventricular ectopic activity and either congestive heart failure or shock in the CCU carried a seven fold risk of sudden death compared to the absence of both findings [20]. A similar result was observed in 940 patients using a 6-hour Holter ECG tracing [77]. Both these studies, although large, have been criticized for the definition (or method of determination) of congestive heart failure and the brief period of monitoring.

A much smaller study using 24-hour ambulatory ECG monitoring and a radionuclide determination of LVEF as the measure of left ventricular dysfunction has been widely quoted [78]. In 81 patients, all eight patients who died suddenly were in the subgroup of patients with an LVEF less than 0.40 and complicated ventricular arrhythmias. This study has elicited controversy regarding the relationship of these factors to each other and to prognosis. Do patients die suddenly due to ventricular arrhythmias triggered by poor ventricular function, or does ventricular ectopic activity independently contribute to the risk of death?

In addition, controversy exists concerning whether it is the frequency or complexity of ventricular ectopy that is related to prognosis, especially using the Lown [79] classification system [80]. Two recent, large, multicenter studies have addressed these issues [25, 27]. The Multicenter Investigation of the Limitation of Infarct Size (MILIS) with 533 patients showed ventricular premature beats greater than or equal to 10/hour to not only provide the most predictive characterization of ventricular ectopy, but also to be the number one predictor of sudden death [27]. Using this variable in a Cox regression, the next most important predictor was an LVEF less than or equal to 0.40, after adjusting for 14 other historical and clinical variables. Patients with both

ventricular premature beats greater than or equal to 10/hour and an LVEF less than or equal to 0.40 (7.5% of the study population) had a sudden-death mortality during a mean followup period of 18 months of 18% compared to only 2% for patients with neither of these findings.

The Multicenter Post-Infarction Research Group studied 766 patients with both an LVEF and a 24-hour Holter monitor and found that although an LVEF less than 0.30 was considerably more important for predicting total cardiac mortality, runs of ventricular ectopic beats and ventricular ectopic beats greater than or equal to 3/hour were also both independently predictive [25]. No adjustment was made for other clinical and historical factors in this analysis. (In another report by this group, LVEF less than or equal to 0.40, ventricular ectopy greater than or equal to 10/hour, a history of congestive heart failure, and pulmonary rales in the CCU were all independently important for mortality [26].) Of patients with an LVEF less than 0.30, runs of ventricular ectopic beats, and at least 3 ventricular ectopic beats/hour (2.6% of the study population), 50% died compared to 6% of patients with none of these findings.

Both studies concluded that both LVEF and ventricular ectopy were independently related to the risk of death or sudden death. Although the MILIS study identified ventricular premature beat frequency greater than or equal to 10/hour to be the most predictive feature from 24-hour monitoring, complex features such as R on T, couplets, runs, or multiform ventricular premature beats also were significantly related to sudden death [27]. They noted that 78% of patients with frequent ventricular premature beats also had these complex features. In the Multicenter Post-Infarction Research Group study, both complexity and frequency were independently important [25]. It was suggested that in a clinical setting it is easier to recognize complexity than to determine frequency for the 24-hour period [27].

In both of the above studies, the high-risk group defined by combining low LVEF and ventricular ectopy was a very small fraction of the population. In the MILIS study, 24% of all sudden deaths were in the high-risk group, and in the Multicenter Post-Infarction Research Group, only 12% of all cardiac deaths (some may not have been sudden) were in the high-risk group. Thus, the goal of achieving a more sensitive and specific method to determine a high-risk group for sudden death has not been realized by this approach.

Instead of examining specifically the relationship of heart failure and ventricular ectopic activity, a recent study from our group investigated the relationship of complex premature ventricular contractions (multiform, couplets, and ventricular tachycardia) to infarct location. Complex premature ventricular contractions were shown to be independently important for predicting survival in non-Q-wave infarction patients but not for Q-wave infarction [81]. Not only was survival the same for patients with and without complex ectopic activity in the Q-wave group, but the incidence of complex ectopic activity was equally divided among patients with LVEF above and below 0.45. In a

multivariate analysis, LVEF was the most important predictor of 1-year cardiac mortality for Q-wave infarction. For the non-Q-wave patients dying within 1 year, 69% had complex ectopic activity compared to only 39% of survivors. In this subgroup, a low LVEF was highly associated with the occurrence of complex ventricular ectopy and was not independently important in multivariate analysis. It was concluded that these patients might be a logical subgroup in whom to test the efficacy of antiarrhythmic drugs.

Exercise testing

Submaximal or symptom-limited exercise testing at the time of hospital discharge has become established as a safe and useful test, both for patient management and for prognostic evaluation. The exercise test demonstrates the patient's cardiac functional capacity, so that appropriate activity level and rehabilitation can be prescribed. Also variables from the exercise test have been related to coronary events for up to 6 years after AMI. Finally, it can be useful for identifying patients for more aggressive management (i.e., coronary arteriography and possible coronary artery bypass surgery or percutaneous transluminal angioplasty).

It has been suggested that in uncomplicated patients prognosis is primarily dictated by coronary anatomy [82]. Exercise testing has been shown to have considerable potential for the early identification by exercise-induced, ST-segment changes due to coronary disease additional to that in or adjacent to the recently infarcted area [83].

In a series of 119 carefully selected, uncomplicated patients, both a symptom-limited exercise test and coronary angiography were performed within 6 weeks of AMI. Based on ST-segment depression greater than 1 mm, 84 patients had a positive test for additional disease in vessels not adjacent to the recent infarct. This finding was confirmed in 82 (98%) of the patients by coronary angiography [82]. In two other studies, the results of a similar comparison were less impressive [84, 85]; however, these studies used a submaximal exercise test protocol and included patients on drugs that can affect the ST segment.

In general, exercise-induced ST-segment changes are related to the extent of coronary disease, and it is not surprising that abnormalities have been shown by many investigators to be related to morbidity and mortality [70, 86–91]. Other exercise test variables that have been related to coronary events include the occurrence of angina pectoris [70, 86–89, 91–93], complex ventricular premature beats [70, 86, 94–96], and hypotension as reflected in the systolic blood pressure response [69, 91, 97–99] or rate pressure product [95], and the heart rate response [97]. Also important is the exercise functional capacity as measured by duration of exercise [96, 100, 101], early stopping of exercise [97], the maximum workload achieved in watts [69, 99], and the total METs achieved (1 MET = 3.5 ml 0_2/kg-min) [87, 94, 98, 102].

The results from these studies are varied, and considerable controversy exists concering which factors are most important for predicting coronary events, largely because of differences in patient selection, varying exercise test protocols, and different definitions of predictor variables [103]. A recent survey article employing meta-analytic techniques concluded that among exercise test response variables, only an abnormal blood-pressure response and poor exercise capacity predicted risk more frequently than chance for all patients when results from 24 studies were pooled. Exercise-induced, ST-segment depression was predictive only in the subset of patients with inferior-posterior MI[103].

In a recent study from our group, patients achieving less than or equal to 4 METs had an 18% rate of new events (death or new MI) within 1 year. Patients achieving more than 4 METs had less than a 2% event rate [102]. In this study, good functional capacity (>4 METS) could be predicted in a multivariate analysis using clinical findings, age, and resting ST-segment changes. Among the 67% of patients predicted to have good functional capacity (224/374), only 34 (15%) were unable to achieve at least 4 METS on the exercise test. Other studies have also emphasized the importance of a maximal workload less than or equal to 4 METS as an indicator of future events [87, 98].

Not all patients are able to perform an exercise test. Some are too old or are in poor general condition, others have severe cardiac dysfunction or diseases of other organs that preclude adequate exercise, and the proportion of patients in various study populations who have undergone exercise testing has ranged from 32% to 78% [95, 96, 102, 104]. Also, patients selected for exercise testing generally have a more favorable prognosis compared to those not tested [95, 96, 101, 104]. In one study, the ability to perform an exercise test was used as a variable in a multivariate analysis with other clinical factors [99], and it proved to be the number one predictor of outcome.

Whether exercise test variables are more useful for predicting outcome than historical and clinical variables has also been investigated [69, 87, 93, 101, 105–108]. Several of these studies attempted to rank variables by univariate significance and concluded that clinical data such as congestive heart failure in the CCU, history of congestive heart failure or angina, and ventricular premature beats, as well as exercise test variables, were important for prognosis [93, 105, 106]. When clinical and exercise test variables have been compared in separate multivariate analyses, clinical data performed better than exercise test data [69, 101, 107]. However, another study that looked at survival in subgroups defined by combinations of either clinical or exercise test data concluded that exercise test variables performed better [108]. But all studies [69, 101, 107, 108] report that a combination of clinical and exercise test variables produces a more powerful scheme than either set alone.

Since not all patients can exercise, it is important to define the role of exercise testing for risk stratification after AMI. In the most recent and largest

study from the Multicenter Post-Infarction Research Group, the role of exercise testing was to identify a very-low-risk group rather than a high-risk group [101]. Patients who were exercised and achieved a blood pressure greater than 110 mmHg, and who had no evidence of pulmonary congestion on a chest x-ray, constituted a group (70% of patients exercised) with a 1-year cardiac mortality of only 1%. Cardiac mortality in patients not exercised was 14%, and in the remaining 30% who were exercised it was 13%.

Another study has also addressed this issue in a large investigation of 702 patients [90]. Historical factors (history of previous AMI or angina) and recurrent angina in the CCU identified a high-risk group (10% of the population) with an 18% death or new AMI rate during the first 6 months. Among the remaining patients, ineligibility for an exercise test identified another 40% of patients with a 6.4% event rate. The combined rate for patients not exercised tested was 8.6%. Finally, among patients who underwent an exercise test, the event rate was 9.7% in those with a positive test ($\geq$2 mV ST-segment depression) and 3.9% for those with a negative test, for a combined event rate of 4.4%. These two studies demonstrate that once patients not able to exercise or at high risk based on clinical factors are excluded, exercise testing can play an important role in defining low- and high-risk subgroups for the remaining patients.

Exercise during other test procedures

Exercise testing has been combined with radionuclide ventriculography or thallium perfusion scintigraphy, and data derived from these studies has proved useful for prognostic purposes after AMI [85, 98, 109, 110]. Failure to increase LVEF by 5% was the most sensitive and specific (both >95%) for cardiac events (death, new AMI, unstable or limiting angina, and severe congestive heart failure) in 61 patients during a 6-month followup period compared to other clinical, exercise test, and resting or exercise radionuclide ventriculography data [85]. Exercise ECG variables performed less well, with the most specific ECG variable being ST-segment depression greater than or equal to 0.1 mV, which had 92% specificity but only 35% sensitivity. After multivariate adjustment for clinical variables, failure of LVEF to increase was independently important for distinguishing patients with and without events. Over half the events were limiting angina.

In another recent study of 106 patients, the change in LVEF from rest to peak exercise predicted medically refractory angina but not death or new AMI, after adjustment for clinical variables in a Cox analysis [109]. Both resting and exercise LVEF had independent importance for death. The authors concluded that measures of poor ventricular function were more predictive of death, whereas measures that reflect residual ischemic myocardium, such as the change in LVEF from rest to exercise, were predictive of nonfatal ischemic events.

The same conclusion can be stated concerning the ability of exercise thallium

scintigraphy for predicting events. In 140 patients followed for a mean of 15 months who underwent an exercise ECG test, exercise thallium scintigraphy, and coronary angiography, high risk as defined by more than one region with a defect, redistribution, or an increased lung uptake on exercise thallium scintigraphy, was more sensitive (>95%) for predicting nonfatal events or limiting angina than a positive exercise ECG (ST-segment depression >1 mm or angina) or multivessel disease determined by coronary angiography [110]. However, for predicting death, multivessel disease determined by coronary angiography performed best. Thallium test criteria were also more specific for predicting all events combined than the other procedures. The authors attributed the advantage of exercise thallium scintigraphy to its ability to detect resdistribution problems in patients with single-vessel disease.

Another study compared variables from maximal exercise ECG testing, exercise thallium scintigraphy, and radionuclide angiography in 117 men followed for a mean of 12 months [98]. Cox regression was used on these variables, together with some clinical data. The thallium variables considered were an exercise perfusion score and a reversible perfusion score, which both failed to enter the analysis after an exercise test workload less than or equal to 4METs and a decrease (>.05) in LVEF with exercise for predicting death, nonfatal ventricular fibrillation, or nonfatal new AMI. When other events, including hospitalization for unstable angina, congestive heart failure, or coronary arter bypass surgery were included, recurrent ischemic pain in the CCU also entered the analysis.

Coronary angiography

Cardiac catheterization has been performed relatively early after myocardial infarction in consecutive series of patients who met various criteria in an attempt to describe proportions of patients with single-, double-, or triple-vessel disease and to identify clinical traits that characterize these patients and their prognosis [66, 111–121]. The prevalence of left main coronary disease has ranged from 1.1% to 13.3% [115, 116, 120, 121] and of three-vessel disease from 9% to 53%, with a median of 33% [66, 111–115, 117–119, 121]. These wide ranges reflect both differences in patient selection criteria and in definitions of significant coronary stenosis.

Clinical characteristics prevalent in patients with multivessel disease have included advanced age [66, 113], post-infarction angina [111, 113, 115, 116, 119], ventricular tachycardia or ventricular fibrillation in the CCU [120], complex arrhythmias during 24-hour Holter monitoring [66, 114], advanced Killip class [66, 120], weight, systolic blood pressure, serum cholesterol [116], and infarct location [113, 116]. Patients with an anterior infarct had more coronary disease in one study [113], but in another study patients with an inferior infarct location had more disease [116]. In other reports, no difference could be found [115, 120]. A history of previous AMI was related strongly to

extent of disease in several studies [66, 115, 119, 120], as was a history of angina [115, 116, 120] or changing angina prior to infarction [111]. Also, a family history of coronary disease [116] and a history of hypertension [66] have been related to the extent of the disease. LVEF from the angiogram was inversely related to the number of involved vessels, and the left ventricular end-diastolic pressure, stroke work index, and end-diastolic volume were directly related [118].

In one study (n = 100) restricted to men under age 45, linear discriminant analysis classified 75% of patients correctly with respect to single-vessel or multivessel disease [116]. Variables selected were residual angina, family history of coronary disease, inferior infarct location, and serum cholesterol level. In the group predicted to have two- or three-vessel disease, 73% actually did. Other studies identified functional anginal class, age, and resting ECG anterior ST and T abnormalities [113] or a positive treadmill test [121] as the most important predictors of multivessel disease.

Several studies have evaluated variables from coronary arteriography multivariately with respect to outcome [66, 113, 117, 119]. Based on Cox regression, LVEF, the number of diseased vessels, and the occurrence of congestive heart failure in the CCU were independently important for survival during a mean 34-month followup period after AMI [117]. A large number of clinical and angiographic predictors were included in the analysis. In another smaller study, LVEF less than 0.40 and a history of previous AMI were the only independent predictors of 30-month death or survival in a discriminant analysis [66]. All 13 deaths were correctly identified. Another study using various combinations of variables from coronary arteriography identified a subgroup of patients (LVEF <0.30 or three-vessel disease) with 22% mortality during a mean followup of 28 months [119]. This study was small (n = 179, including 13 deaths), and followup was not complete to a fixed time.

Recently, the prognostic value of a coronary artery jeopardy score was evaluated, but in the Cox regression analysis, LVEF again proved to be the most important predictor, followed by the jeopardy score and the maximal percent stenosis observed in the left anterior decending and right coronary arteries [122].

Whether or not all patients should undergo cardiac catherization for the purpose of risk assessment is debatable. The study cited above, which correctly identified 75% of patients with multivessel disease using a discriminant function, nevertheless recommended that all patients undergo cardiac catherization [116]. Another study recommended that patients with radionuclide LVEF between .21 and .49 be so studied, because this group yields a high proportion of patients with three-vessel disease [117]. Still another center concluded that only patients with a positive treadmill test be studied, since in 91 patients under age 60, 8 of 9 patients with left main disease, three-vessel disease, or disease of the proximal LAD had positive treadmill tests [121].

The studies that have related variables from cardiac catheterization to

outcome all found LVEF to be a major determinant. Since LVEF can be assessed noninvasively, the need for cardiac catherization for risk stratification purposes is diminished. However, cardiac catherization has an important role as part of an aggressive policy for the managment of patients identified by other factors as being at high risk, since it is necessary to confirm suspected multivessel disease in such patients and to assess operability.

Two recent consensus-based reports have suggested that coronary angiography be performed in certain subsets of patients [123, 124]. In one set of recommendations, patients surviving until hospital discharge are divided into three groups based on observation during the first 5 days after admission [123]. Those with severe myocardial ischemia on days 2–5 are considered to be at increased risk and early angiography is recommended. Among the remaining patients, those with severe pump failure (Killip class III or IV) are also identified as being at very high risk and medical therapy is recommended. Other patients are assessed near the time of hospital discharge, and those with an infarction estimated to be more than 35% of the left ventricle or with a radionuclide LVEF less than .35 are also designated as high risk and are treated medically. In the remaining patients, a submaximal exercise test is recommended prior to discharge (days 7–14), and coronary angiography is recommended if positive for ischemia (≥2 mm ST-segment depression or failure of systolic blood pressure to rise at least 10 mmHg).

A subcommittee of the Task Force on Cardiovascular Procedures and Therapy of the American College of Cardiology and the American Heart Association has provided guidelines for subgroups on which there is considered to be general agreement that coronary angiography is appropriate in the convalescent phase of acute MI[124]. These subgroups include: patients with resting ischemic pain, especially late in the hospital stay, patients with early signs of left ventricular failure, patients with LVEF less than .45, especially those with severe ventricular arrhythmias, patients with exercise-induced ischemia, and patients with non-Q-wave MI.

We assessed these published quidelines and performed additional analyses in our database of 1848 patients. This experience led to the development of a modified scheme for selection of patients for coronary angiography in the convalescent phase of acute MI, which was then tested in an additional 780 patients admitted later[125]. In the new scheme, patients over age 75 years (22% 1-year mortality) are considered separately, and those with severe resting ischemia beyond day 1 (18% 1-year mortality) or a history of previous MI plus clinical or radiographic signs of left ventricular failure (25% 1-year mortality) are recommended for coronary angiography. Among patients who perform an exercise test, those with a positive test (≥2 mm ST-segment depression or drop in systolic blood pressure, or failure to achieve at least 4 METS; 10% 1-year mortality) are recommended for coronary angiography. When an exercise test is not performed, a radionuclide LVEF is obtained and if the LVEF is between .20 and .44 (11% 1-year mortality), coronary angio-

graphy is recommended. This relatively simple scheme excludes the elderly, who are not in general candidates for revascularization, considers patients with in-hospital left ventricular failure and/or reduced left ventricular function in whom another event would be likely to prove fatal, and approaches the problem of patients who do not perform an exercise test. It would avoid early coronary angiography in patients under age 75 with an average 1-year mortality after discharge of 3% and recommends coronary angiography in those at increased risk (average mortality rate 16%), who comprised about 55% of the population under age 75 [125].

Two-dimensional echocardiography at rest

Two-dimensional echocardiography has been investigated as a means for quantification of regional wall-motion abnormalities [126–129]. Two-dimensional echocardiography during exercise has been investigated for its utility in diagnosing coronary artery disease [130, 131] or in quantifying left ventricular function [132], and one study has related changes in wall motion with exercise to outcome [133]. Various derived wall-motion indices at rest have been investigated for their prognostic value in predicting events both in the hospital [127, 128, 134, 135] and after hospital discharge [135–137]. Interobserver variability in the interpretation of wall-motion abnormalities has been minimal [138, 139], and correlation with radionuclide ventriculography [135] or coronary angiography has been good [136].

In 61 consecutive patients, two-dimensional echocardiography was performed within 12 hours of admission for AMI [134]. From the echo, 14 segments were assigned a wall-motion score and the results were summed to obtain an index. Patients with an index score greater than or equal to 2 were determined to be at high risk for pump failure, malignant ventricular arrhythmias, or death during the hospital stay. Of 27 high-risk patients, 24 (89%) suffered one of these events, compared to an event rate of 18% for the low-risk group. The in-hospital mortality alone was 37% for patients with an index greater than or equal to 2 and only 6% for patients with an index less than 2, confirming results regarding the application of such indices in other studies [126, 134]. The ability to predict hemodynamic deterioration in patients who show no outward clinical indications of poor function has also been reported previously [126–129].

Another study showed two-dimensional echocardiography to be comparable to radionuclide ventriculography for the assessment of wall-motion abnormalities in anterior infarction, and it appeared to be superior for the detection of inferoposterior wall-motion abnormalities [135]. In 93 patients with both two-dimensional echocardiography and radionuclide ventriculography performed within 48 hours of hospital admission, LVEF correlated well ($r = 0.82$) and wall-motion indices correlated reasonably well ($r = 0.66$), which allowed the definition of groups at comparable high or low risk of in-hospital death. A

second pair of studies was performed at 10 days in the 81 survivors and, again, risk groups determined by each technology had similar-1 year mortality rates.

In 50 patients, a wall-motion score derived by averaging the individual grades for 14 segments was related to 3-year survival [136]. Segment grades were: 1 = normal, 2 = mild-to-moderate hypokinesia, 3 = severe hypokinesia or akinesia, 4 = diskinesia, and 5 = aneurysmal. Patients with an index greater than 2.5 had worse 3-year survival. These results confirmed an earlier similar study where the threshold for this same index was set at 2.0[137]. In this study (n = 46), 15/17 patients with events during a mean followup of 21 months had an index score of 2.0 or greater. Another study of 40 patients showed that changes in wall motion with exercise related to cardiac events during 6–10 months of followup[133]. A positive exercise echocardiogram was defined as the appearance of new wall-motion abnormalities or marked worsening of existing abnormalities in at least two segments in the same area. In the 20 patients with cardiac events, 16 had a positive test (80% sensitivity), and 19/20 had a negative test (95% specificity).

Programmed electrical stimulation

The role of programmed electrical stimulation in identifying patients at high risk of late sudden death has been controversial [140, 141]. Identifying patients who are electrically unstable by the response to programmed electrical stimulation could allow a group at high risk for sudden death to be determined. Several studies have produced mixed results, probably due to different protocols involving small, selected patient groups and different numbers and intensities for the applied extrastimuli. Two positive studies used a maximum of two extrastimuli at two right ventricular sites of 1 V to 10 V [142, 143]. The smaller study (n = 37) observed sudden death in the first year in 4 out of 12 patients responding with more than five repetitive complexes, versus 1 out of 25 for nonresponders. In another somewhat larger study (n = 165), among 38 patients in which 10 seconds or more of ventricular tachycardia or ventricular fibrillation were induced, the rate of sudden death within 8 months was 32%, compared to 2% for nonresponders. However, in another small study (n = 46), using extrastumuli at only one site at two times end-diastolic threshold, 10 patients responded with sustained or nonsustained ($\geq$4 beats) ventricular tachcardia with only one sudden death during 18 months [144]. For nonresponders, 5 of 36 experienced sudden death. Another relatively large study of 150 patients showed no difference between patients with or without inducible ventricular tachyarrhythmias with respect to the occurrence of cardiac events (two sudden deaths, three other cardiac deaths, and two patients with new episodes of sustained ventricular tachcardia).

Fifty preselected hospital survivors who were already at high risk of death (total observed cardiac mortality of 24%), by virtue of having one of a number of clinical features shown associated with sudden death in other studies were recently studied using an aggressive protocol [140]. It was necessary to use up

to three extrastimuli of four times end-diastolic threshold at a maximum of two right ventricular sites to define a high-risk group of responders with sustained (>15 seconds) or nonsustained (>7 beats but less than or equal to 15 seconds) ventricular tachycardia. Sudden death was 7/17 (41%) in the responder group, and no sudden deaths occurred among the nonresponders. The authors concluded that the technique was highly sensitive but relatively nonspecific for sudden death.

Programmed electrical stimulation and the exercise test have been combined to define low- and high-risk groups for 138 patients followed 1 year [146]. A moderate programmed electrical stimulation protocol (double extra stimuli at two sites first at twice end-diastolic threshold and then at 20 mA) was used followed by a symptom-limited exercise test. Among 53 patients with inducible ventricular tachycardia or ventricular fibrillation and/or ST-segment depression greater than or equal to 2 mm, 7 died (13%) within 1 year, compared to only 1 death (<1%) among patients with neither of these findings. Disregarding the exercise test results, 10/27 responders (37%) died within 1 year of cardiac cause compared to 4/111 nonresponders (<4%). In this relatively uncomplicated group of patients able to exercise, response to extra stimuli in a more moderate protocol defined a group of patients with nearly the same mortality as in the study of relatively high-risk patients cited above [140]. Another later study from this group with 306 patients studied both by programmed stimulation and serial averaged electrocardiograms showed the ability to induce sustained tachyarrhythmias and the presence of delayed potentials to be correlated, and results from both techniques related equally well to cardiac death by 1 year [147]. It has been suggested that further investigation is needed into the importance of intercardiac electrophysiologic testing to further define risk in patients known to be at high risk for sudden death due to congestive heart failure, ventricular arrhythmias, or bundle branch block and that it is not indicated in uncomplicated patients.

SOME POINTS OF INTERPRETATION

Many of the studies discussed above have compared the ability of different factors in multivariate analyses to predict events or have claimed that a given factor was or was not an independent predictor [25–27, 69–72, 98, 146]. It is difficult to interpret these claims for several reasons, especially in small studies [70–72]. In particular, not all studies included the same set of candidate variables in their stepwise multivariate analyses or the same set of endpoints or length of follow-up. Also, definitions of variables and procedures for data gathering may have been different. Finally, different multivariate methodologies were used.

There are some more subtle but perhaps even more important reasons why such claims may be presumptuous. Selected data from a recent study by our group will be used to illustrate these problems [19].

Relative importance and independence of predictors

In multivariate procedures, the variables demonstrating a significant contribution can depend on the patient sample used for the analysis. Removing or adding patients (especially patients with endpoints) can change the correlations among the variables slightly, and in stepwise procedures this can affect the order of variable selection and the number of variables retained in the model or sheme.

To investigate these problems, a patient population (499, including 70 deaths) was divided into ten subsamples of 50 patients each (except for one subsample with 49). Then, omitting one subsample at a time, the other nine were pooled and used in multivariate analyses to predict cardiac death or 1-year survival in patients with AMI discharged from the hospital. This procedure is called cross validation and is useful for obtaining realistic estimates for classification error rates [147]. The variables used included features of the history and data observed during the first 24 hours after admission (physical, laboratory, ECG, x-ray). Three different multivariate methodologies were used: stepwise linear discriminant analysis, a logistic regression procedure, and recursive partitioning. In table 11–2, the variables and their ranking are shown for each of the ten analyses performed leaving out one tenth of the population.

For stepwise linear discrimination, the F ratio for each variable is shown, which indicates the contribution of that variable, adjusting for all the other variables finally included in the model. In all ten analyses, blood urea nitrogen (BUN) was the most important variable, with history of previous AMI second in 5 out of 10 analyses. Age was second in three analyses, with sinus bradycardia and evidence of an old bundle branch block each second in one analysis. Three additional variables were important in at least two analyses, but another three appeared in only one analysis each, but with low rank.

For the logistic regression procedure used, the ratio of the computed coefficient to its standard error, adjusting for all the other seven variables included in the analysis, gives an indication of the relative ranking among the variables. Only ratios above 1.5 are shown in table 11–2B. The procedure was not stepwise, and the eight variables used were selected based on some preliminary analyses carried out to discover what factors seemed important to all of the methodologies for this population and another population from Vancouver, British Columbia. BUN ranked first in 9 out of 10 of the analyses. Age and sinus bradycardia each ranked second in four analyses. A history of a previous AMI most often ranked third or fourth. It is probably safe to say that most of the prognostic information is present in these four variables for this multivariate methodology.

For recursive partitioning, the level of the split for each variable within each tree is given. In some cases a variable will appear again at a lower level in the same branch or at the same level in a different branch. In table 11–2C, only levels up to five are shown; however, the ten trees constructed ranged in depth from five to nine levels. All ten trees had the same first-level split on BUN.

Table 11–2. Relative importance of variables selected by multivariate methodologies

	Replication									
	1	2	3	4	5	6	7	8	9	10
A: LINEAR DISCRIMINANT ANALYSIS										
Variable										
Age	8 (2)		5 (5)	8 (2)		8 (3)	7 (4)	5 (5)		10 (2)
Hx prev AMI	7 (3)	9 (3)	8 (2)	5 (4)	6 (2)	9 (2)	8 (3)	9 (2)	11 (2)	7 (4)
BUN	17 (1)	24 (1)	22 (1)	27 (1)	35 (1)	26 (1)	33 (1)	21 (1)	27 (1)	23 (1)
Abnormal apex	5 (4)							7 (3)	7 (3)	
Max HR		5 (5)	8 (3)	6 (3)				7 (4)		
Systolic murmur		6 (4)			5 (4)					
Old BBB		10 (2)	7 (4)							
Sinus bradycardia						4 (3)	5 (5)	9 (2)		8 (3)
Min SBP							6 (4)			
Peripheral edema										6 (5)
VBP > 6/min										5 (6)
B. LOGISTIC REGRESSION										
Variable										
Age	−3.1	−2.3	−3.1	−1.9	−2.2	−2.8	−2.5	−1.7	−2.6	−2.0
Hx prev AMI	−1.9	−2.0		−1.6	−2.0	−2.2	−2.3	−2.3	−1.6	−2.0
BUN	−2.8	−3.5	−3.5	−3.8	−3.5	−4.1	−3.6	−3.5	−3.3	−3.4
Sinus bradycardia	1.7	2.0	2.1	2.1	2.0	2.9	2.4	2.0	2.8	2.1
Abnormal apex							−1.8	−1.8		
C. RECURSIVE PARTITIONING										
Variable										
BUN	1	1	1	1	1, 2	1, 3	1, 2	1, 4	1, 4, 3	1, 3, 5
Hx prev MI		2	2			4	3	2	2	2
Old BBB	3	3	4	4	4		3		3	4
Max PR	2							3, 3		4
Max CK	5	4	5		4	4, 3	4, 4	4, 5	4	5
Age		4, 5	3, 5	2	3, 5	2	4			
Max HR		3, 5	3	5	3	5	5, 4		5	
Min SBP						5				
Max grade PC			4							
Loc AMI 4	4			3	5		5	4		
Bibasilar rales						4				
Max QRS						6				
Systolic murmur									5	3
Rales > scapulae							5			4

Abbreviations: Prev = previous; BUN = blood urea nitrogen; Abnormal apex = apex outside the midclavicular line; Max = maximum; Min = minimum; HR = heart rate; BBB = Bundle branch block; PR = PR interval; QRS = QRS duration; CK = creatine kinase; LOC = location of infarct; PC = pulmonary congestion on x-ray; VPB = ventricular premature beat.

Only five trees had the same level two split on history of previous AMI, and only two of these had the same third level split on evidence of an old bundle branch block. The trees differ even more at lower levels. When the entire population was analyzed, the first split was on BUN, followed by age (only level two in two subsamples) and evidence of an old bundle branch block (figure 11–2).

Considering the results from all three methodologies, it is evident for this population and the stated endpoint that BUN is the most important predictor. It would be safe to say that history of previous AMI and age also have independent prognostic importance. However, to draw conclusions beyond these regarding the importance of additional variables, let alone their relative importance, would be unwarranted, and yet such statements make their way into the popular press [149].

This study involved 499 patients from four hospitals in San Diego, all of which are participants in a prospective multicenter study designed to address issues in the field of risk prediction. Smaller populations from only one center would be subject to even more variability if analyzed in a similar manner. On the other hand, large multicenter studies might be expected to yield more stable findings. It is important to recognize that there is no one best way to predict outcome. Any subset of a number of univariately important prognostic factors, when combined in a multivariate scheme, can probably achieve reasonably similar predictive power.

Comparison of multivariate methodologies

The main purpose of the study just described was to compare the performance of the three multivariate methodologies. The schemes constructed from each analysis using nine tenths of the population were used to predict death or survival in the remaining one tenth of the population. The classification results were then averaged over the ten analyses. The cross validation procedure provides an alternative less biased than resubstitution (classifiying the original patient population using the scheme developed on it) for estimating scheme performance when an independent test set is not available [148]

Table 11–3 gives both the resubstitution and cross validation error rates for this study. The column labeled *ER* for *error risk* is a weighted average of the individual errors for both survivors and deaths. The weights were based on the stipulated relative cost of misclassifying deaths and survivors, and the prevalence of deaths within this population (see the appendix). The error rates for survivors and deaths differ somewhat among the methodologies. For stepwise linear discrimination and logistic regression, the resubstitution error rates for

Table 11–3. Within population comparison of multivariate methodologies

	Resubstitution			Cross validation		
	ER	SUR	DTH	ER	SUR	DTH
Linear discriminant function	.29	.21	.36	.40	.26	.54
Logistic regression	.34	.22	.47	.38	.24	.51
Recursive partitioning	.33	.38	.29	.37	.32	.43

Abbreviations: ER = error risk; SUR = survivors; DTH = deaths

survivors were just over .20, but for deaths they were .36 and .47, respectively. For recursive partitioning the error rate for survivors was .38, and for deaths it was only .29. Although the cross-validated error rates were generally higher than those obtained by resubstitution, they were more consistent among the methodologies, and the overall error risk is very similar for the three methodologies, ranging from .37 to .40.

This same result was observed in another earlier study by our group involving prediction of 30-day mortality [150]. In that study, the error risk also differed at most by only .04 for both resubstitution and cross validation among the same three methodologies.

The best way to compare schemes is to apply them to an entirely new patient population, provided the new and old patient groups are comparable. The schemes developed on the San Diego population (499 patients) were applied to 646 patients (including 69 deaths) from Vancouver General Hospital in British Columbia, Canada. Comparing table 11–4 with table 11–3 indicates that the schemes based on logistic regression and stepwise linear discrimination generalized very well, achieving an error risk even lower than predicted by the cross-validation procedure. Recursive partitioning generalized less well. This was also the case in the study on 30-day mortality.

Another investigator working with our group compared linear discriminant analysis, Cox regression, and recursive partitioning [7, 16]. Schemes were developed in a base population from Copenhagen, Denmark and were tested on a population from Vancouver for both short-term (36-day) and long-term (1-year) mortality. In the study on short-term mortality, each scheme was forced to achieve approximately 90% correct classification of deaths by resubstitution in the base population by selecting appropriate cut-points for the predicted outcome variable [7]. In the test population, correct classification of deaths was 87% for discriminant analysis and 89% for the other two methodologies. Correct classification for survivors was 57% for discriminant analysis and 54% for the other methods, yielding a total correct classification within 3% for all three methodologies, which is probably within the noise level. For 1-year mortality, recursive partitioning actually did slightly better than the other methods on the test population, but the tree only branched on one variable (heart failure in the CCU) [16].

It can be concluded from these studies that the choice of multivariate statistical methodology is not crucial in terms of ultimate expected perfor-

Table 11–4. Comparison of multivariate methodologies applied to a different population from Vancouver, British Columbia, Canada

	Error risk	Survivors	Deaths
Linear discriminant function	.32	.21	.44
Logistic regression	.34	.18	.49
Recursive partitioning	.39	.27	.51

mance. Although different methodologies make use of the information contained in a set of prognostic variables in a different manner, similar performance is achieved. Therefore, the choice of technique can depend on factors such as availability of software or ease of use.

Other validation studies of risk prediction schemes

As indicated above, a risk prediction scheme will generally perform better in the population used to develop it than in an independent test sample. The necessity for validating a risk stratification scheme was recognized by Peel et al., who tested the Peel Index on a separate group of patients, including some from other hospitals [40]. Subsequently, other investigators have applied the Peel Index to their own patient populations as well [9, 41, 42]. These validation studies were relatively small, ranging from 65 to 153 patients. If the high-risk group or the group predicted to die is defined as patients with an index score greater than or equal to 13, in two studies the overall error rates were 23% and 29%, with error rates for survivors of 37% and 31%, and for deaths of 4% and 21% [9, 41]. The error rates on the base population used to construct the index were 28% overall, 31% for survivors and 18% for deaths.

The Norris Index for in-hospital mortality [11] has also been widely tested by other investigators. Using an index cut-point greater than or equal to 9 to predict death, in the base population of 757 patients the overall error rate was 37%, with a 40% error rate for survivors and a 29% error rate for deaths. The error rates in the much smaller (largest = 153) test populations were less than those for the base population [41, 45, 46], ranging from 4% to 19% for deaths and from 12% to 22% for survivors.

In some more recent studies, risk assessment schemes have been applied to independent test samples, either a second, usually chronologically later series of patients from the same population [4–6, 57, 151, 152] or to patients from another population [7, 16, 153]. In general, schemes applied to a later group of patients from the same hospital have performed well. Some of these studies are summarized in table 11–5. The error rates for deaths and survivors reflect the investigators' relative costs of misclassification; in some of the studies the error rates for survivors are low and in others the error rates are low for deaths. The important thing to compare is how well the schemes perform in the base (B) versus test (T) population. Five schemes for various prediction periods (2 weeks to 2 years) based on linear discriminant function analysis yielded overall error rates within 6% of those obtained in the base samples [5, 6, 21, 57, 151]. When schemes have been applied to different hospitals, the results have been more variable. Habib [45], applying the scheme based on logistic regression developed by Chapman [153] for in-hospital death or survival, obtained results that were 2% better overall than in the base population. Bigger et al. [15] were concerned that application of prognostic stratification techniques in their population did not yield results at all similar to those reported by Moss et al. [14]. Mortality for patients in the population reported by Bigger using the set

Table 11–5. Validation results for various risk-stratifications schemes

Study	Prediction methodology period			Error rates TOT	%ERR	SUR	%ERR	DTH	%ERR
Willems [6]	CCU	LDF	B	1724	(.15)	1456	(.11)	268	(.32)
			T	588	(.13)	494	(.12)	94	(.27)
Chapelle [151]	2 weeks	LDF	B	159	(.18)	142	(.18)	17	(.18)
			T	201	(.16)	176	(.15)	25	(.24)
Henning [5]	30 days	LDF	B	177	(.07)	143	(.03)	33	(.27)
			T	150	(.12)	123	(.04)	27	(.48)
Evans [57]	3 months	LDF	B	298	(.29)	249	(.33)	49	(.04)
			T	437	(.35)	362	(.44)	95	(.04)
Moss [14]	4 months	PS	B	269	(.13)	258	(.12)	11	(.36)
			T	234	(.16)	223	(.14)	11	(.55)
Helmers [4]	1 year	AID	B	308	(.24)	255	(.21)	53	(.38)
			T	163	(.21)	141	(.20)	22	(.32)
Luria [21]	2 years	LDF	B	137	(.17)	110	(.06)	27	(.59)
			T	105	(.14)	91	(.08)	22	(.57)
Vedin [152]	2 years	MLR	B	292	(.40)	262	(.44)	30	(.03)
			T	195	(.34)	178	(.36)	17	(.16)

Abbreviations: TOT = number for all patients; SUR = number of survivors; DTH = number of deaths; %ERR = percent of group incorrectly classified; LDF = linear discriminant function analysis PS = prognostic stratification; AID = automatic interaction detection; MLR = multiple linear regression; B = base sample; T = test sample.

of predictors identified by Moss (20 or more ventricular premature depolarizations per hour, history of angina on moderate activity or at rest, and hypotension or heart failure in the CCU) was not significantly different than for patients in their population without these predictors. However, both studies were small and Bigger attributed the discrepancy to differences in age, cardiac status, and urban versus suburban locale for the two populations.

Only one of the studies in table 11–5 involved a base sample of more than 1000 patients [6]. All the others were considerably smaller. A much larger study of the placebo group of the Multicenter Coronary Drug Project (2789 patients) achieved good results when data from various subsets of clinics were used to develop schemes that were then tested on another subset of clinics [20]. The clinic subsets were determined in one analysis by geographical location and in another by university versus community hospitals. Logistic regression incorporating the ten best variables in the base sample was used to construct schemes to predict death or survival at 3 years. Even though very different variables proved important for a given subset of clinics, acceptable prediction was achieved in each analysis on the test set. Our experience supports these observations [19, 150].

Cross-population testing of various schemes by our group (table 11–4) has convinced us that risk stratification schemes can produce acceptable results when applied to a new population. It appears that each population, or more likely the level of noise due to data collection practices within the population,

allows for a certain degree of predictive accuracy. This degree of accuracy can be achieved by schemes developed in that population or elsewhere. However, it is essential that, before clinical decisionmaking is based on computed risk, careful testing be carried out. It is possible that if the target population is too dissimilar from the base population, a scheme will not generalize.

For the most part, the issue of validation has been ignored in the large multicenter studies [25–27]. Although the nature of these studies should lead to generally applicable results, some effort should be made to test the more important findings in independent samples.

THE PRACTICE OF RISK STRATIFICATION

Nearly every report in this field (including this one) holds out the promise of *aggressive theraputic management for high-risk patients* or *individualized management of patients based on assessed risk* such as *early discharge for low-risk patients*. In practice, this goal has yet to be realized, except perhaps for a few studies in the last category.

Clinicians do make therapeutic decisions based on their own judgement of risk in an individual patient. But the basis of this judgement is their own personal knowledge and experience, rather than a formalized risk-stratification scheme. For instance, it is common practice today to do a treadmill test on post AMI patients deemed able to exercise. Those with "positive" tests or other alarming signs are then referred for cardiac catheterization. Among patients unable to exercise, those with residual and/or limiting angina, but otherwise without contraindication to possible coronary artery bypass surgery or angioplasty, are also referred. Then, depending on the angiographic results, a patient may or may not be recommended for surgery or angioplasty. This strategy applied by different clinicians would probably result in different patients being referred for cardiac catheterization, depending on the physician's criteria for who should have an exercise test, what exercise test protocol is used, and what criteria are used for a "postive" test.

There have been only a few studies reporting the prospective clinical application of a formalized risk assessment scheme [28, 30]. One center was able to reduce the rate of myocardial rupture observed in autopsied patients drastically by identifying patients at high risk of rupture and by aggressively modifying factors that were associated with rupture [30]. In a consecutive series of autopsied patients, those with evidence of rupture were compared to those without and the following potentially alterable factors were different between the groups: high blood pressure on admission, persistent or recurrent chest pain, and level of agitation. Other unalterable factors were also different between the groups: age, sex, history of angina or AMI, and time since infarct. In a prospective series of patients, hypertension was treated by sublingual nifedipine or nitroprusside infusion; chest pain was treated by nitrates or morphine sulfate, and a relative was allowed to remain with the patient in an effort to reduce stress. Before the aggressive elimination of risk factors (prior

to 1977), the rate of myocardial rupture in autopsied cases was 31%, and afterwards it declined steadily to only 5.6% in 1982.

In one other report, it was implied that the results in a test sample for a scheme for identifying very-low-risk patients for early hospital discharge was successful enough that the former research program would be continued clinically [28].

Although many approaches to risk stratification have been proposed, none has provided highly accurate prediction, but it should be clear from this review that it is possible to identify groups of patients with either a very low or a very high risk of future cardiac events. Exactly what management strategies should be implemented for various groups identified may present more of a challenge to researchers than the identification of such groups. It has been suggested that antiarrhythmic therapy be given to patients at high risk of sudden death, but the efficacy of such therapy is still subject to considerable controversy [154]. Implantable defibrillators may provide an alternative strategy [155]. Although the results of recent controlled clinical trials indicate that beta blockade reduces the incidence of future events, for very-low-risk patients the potential side effects may outweigh the therapeutic benefit [156, 157]. This therapeutic modality might be best confined to a "medium"-risk group. Because of the problems associated with the interpretation of the results of recent large-scale secondary prevention trials, it has been suggested that if prospective risk stratification were used, it might at least define which strata were most likely to benefit from therapy [156]. This has been done retrospectively in at least two studies [158, 159].

The next step in the field of risk stratification might be to survey potential therapies and to characterize the patients most likely to benefit from each one, so that risk prediction schemes can be targeted to specifically identify such patients. Identifying patients with multivessel disease for cardiac catheterization is an example of this approach [117, 118].

APPENDIX — MULTIVARIATE METHODOLOGIES

A variety of methodologies have been applied to the problem of risk stratification after AMI. These include parametric methodologies [31] such as multiple linear regression [9, 12, 13, 152], linear discriminant function analysis [5, 6, 8, 10, 11, 21, 22, 44, 55, 68, 117, 118, 151], logistic regression [19, 67, 150, 153], and Cox regression [7, 16, 25, 28, 98, 127], all of which involve fitting the parameters of a mathematical model, and prognostic stratification [14, 15, 23], automatic interaction detection [4], and recursive partitioning [7, 16, 19, 150] which do not. The latter methodologies are called *nonparametric* [31].

Relative cost of misclassification

Once the parameters of the mathematical model have been determined, the investigator typically chooses one (or more) cutoff values on the scale of the

dependent variable to define prognostic strata. The choice of a cutoff value either consciously or subconsciously is based on how many patients without events the investigator is willing to tolerate in the high-risk stratum in order to include as many of the patients with events as possible. This decision represents a choice regarding the relative costs of misclassification and also depends on the frequency of events within the population. Mathematically, this concept has been formalized in the following manner. The *error risk* (ER) is defined as a weighted function of the error rates resulting from the cutoff value used.

$$\text{ER} = w_1 e_1 + w_2 e_2,$$

where e_1 and e_2 are the error rates for groups 1 and 2, and w_1 and w_2 are the associated weights, which are constrained to sum to 1 and are defined as

$$w_i = p_i c_i \quad \text{for} \quad i = 1, 2,$$

where p_i is the proportion of patients in group i and c_i is the cost of mistakenly classifying a patient in group i.

Thus, if it is decided that it is 10 times more important to correctly identify a group 1 patient than a group 2 patient, and the proportion of patients in group 1 is .20, the weights can be determined as follows:

$$w_1 = p_1 c_1 = (.2)(10c_2) = 2c_2 \quad \text{and} \quad w_2 = (1-p_1)c_2 = .8c_2.$$

Since $w_1 + w_2 = 1$,

$$2c_2 + .8c_2 = 1.$$

Solving for c_2 yields $c_2 = .36$, so that $w_1 = .72$ and $w_2 = .28$.

Parametric models

The use of a mathematical model involves the willingness on the investigator's part to assume that the data conform to various sets of assumptions. The first step in any multivariate analysis is, of course, a thorough univariate examination of the candidate variables. Both the nature of their distributions and the relationship to the dependent or outcome variable should be examined thoroughly. It can also be instructive to examine their relationships to each other. Once this preliminary step is completed, the investigator is in a better position to evaluate which model to use or whether a method not based on a mathematical model is more appropriate. A brief description of each mathematical model and its underlying assumptions is given below.

Multiple linear regression [160, 161]

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n$$

Both the dependent variable, Y, and the independent variables, $X_1, \ldots, X_n$, are assumed continuous. The relationship between the dependent and independent variables is linear and additive. However, if the linearity is known not to hold, the model can be modified (in some cases) to account for the known relationship (i.e., $y = \beta_0 + \beta_1 X_1^2 + \beta_2 X_2$). Also, if the impact on prognosis of two variables is more than the sum of each factor individually, the model can include a multiplicative or interaction term (i.e., $y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2$). The least squares method of estimating the coefficients of parameters minimizes the overall sum of the difference between the actual and predicted values squared [i.e., Σ (actual−predicted)^2]. Since the actual value is either 0 for no endpoint or 1 for an endpoint, the method is not truly appropriate to the problem. Also, many of the prognostic variables are coded 1 for the presence of a finding and 0 for its absence.

Linear discriminant function analysis [162]

$$\text{Score} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n.$$

Here a score is related to the independent variables according to the same assumptions outlined above for multiple linear regression. The same modifications to the model can also be made, if appropriate. However, the computational procedure differs. Instead of minimizing the sum of squared differences between the predicted and actual values, the procedure computes estimates for the coefficients of the X_i that determine the equation of a hyperplane perpendicular to the line determined by the centroids (the point in space representing the mean value of each variable) of the two groups of patients with and without an endpoint. This procedure is illustrated graphically in figure 11A–1 for the case of the two predictors X_1 and X_2. The closed circles represent patients with events or endpoints and the open circles represent those without. The open and closed squares represent the centroids of the two classes. The discriminant analysis procedure computes the equation of a line, in this two-dimensional case, perpendicular to that determined by the centroids. The procedure can be extended to discriminate between more than two groups by computing additional hyperplanes to divide the variable space.

The score cutoff point is a function of the proportion of patients in each group within the population and the specified relative cost of misclassification. Geometrically, the cutoff point simply determines how close to one centroid or the other the perpendicular hyperplane will be.

There are several additional assumptions that underlie this methodology.

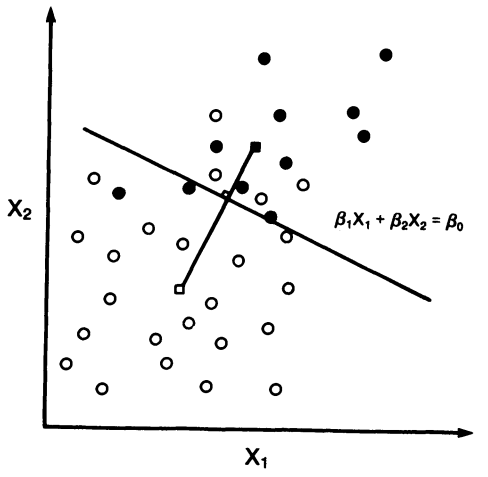

Figure 11A-1. Graphical representation of linear discriminant function in two dimensions. Closed circles represent patients without endpoints and open circles represent those with endpoints. Squares represent group centroids.

One is that the X_i have a joint multivariate normal probability distribution, and the other is that the groups have a common variance-covariance matrix. Since variables indicating the presence or absence of a factor are almost always included for predicting risk after AMI, the first assumption is violated. However, many investigators have found that, in practice, the procedure performs well, even when such variables are included [163, 164]. The main problem with noncommon variance-covariance matrices is that cases are more likely to be classified into the group with the most dispersion. This problem is minimized if both groups are assumed to have a variance-covariance matrix equal to that for the entire population, and most computer programs allow this option. One theoretician suggested that transforming all predictor variables to the same scale might improve homogeneity [164]. Some investigators have tried this approach [5, 11, 22, 57]. In one case even continuous factors were transformed into binary variables by defining appropriate cut-points. However, the results did not differ from those obtained when the factors were analyzed on a continuous scale [5].

Logistic regression [165, 166]

$$\log [(P/(1 - P)] = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n.$$

In this model the independent variables need not be continuous, and their relationship to P, the probability of an endpoint, is assumed to be logarithmic instead of linear. The model can include multiplicative or interaction terms. In

linear discrimination the best hyperplane that can divide the variable space into two regions is found. For logistic regression, this surface can be curved instead of planar. The computational procedure involves maximizing a likelihood function, which is accomplished by an iterative, hill-climbing procedure. The advent of high-speed computers has made this method feasible, since the computational procedure is considerably more complex than that for multiple linear regression or linear discrimination.

Cox regression [167]

$$h(t) = h_o(t) \exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n).$$

The hazard, $h(t)$, is the probability a patient who is without an event at time t will have one within a short period of time after time t. An underlying constant but unknown hazard function, $h_o(t)$, and a log linear relationship among the independent variables determine $h(t)$. As for logistic regression, the idependent variables can be categorical. It is assumed that the relationship between $h_o(t)$ and $\exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n)$ is multiplicative, which means that the ratio of the hazard functions for two individuals with different sets of covariates does not depend on time. Graphic techniques exist that can be used to test these assumptions. Both the regression coefficients, $\beta_0 \ldots \beta_n$ and $h_o(t)$ are estimated from the data. Modifications of the Cox model can accommodate competing hazards (more than one endpoint) and violations of the constancy of $h_o(t)$. As for logistic regression, the model parameters are estimated by maximizing a likelihood function by iterative, hill-climbing techniques.

One major advantage of Cox regression over the other mathematical models is that variable-length followup periods can be accommodated. Input to the procedure is either the time to an event or the time to when the patient is last known to be alive and well. The risk of an endpoint, hazard, at a certain point in time, for instance, $t = 365$ days, is computed by first evaluating $h_o(365)$, so the same model can be used for prognostication at different times. Another feature of the Cox regression model allows $\exp(\beta_i)$ to be interpreted as the relative risk of an event for patients with factor i, compared to those without this finding, while adjusting for all the other variables by holding them constant at their mean values.

Stepwise procedures

All of the models discussed above can be built in a stepwise fashion. At each step all candidate variables not already included in the model are evaluated to determine which contains the most prognostic information. The criterion for variable evaluation differs depending on the model. For linear discrimination, the variable is selected that increases the distance of the class centroids the greatest amount. After a new variable is added to the model, each variable

already in the model is reevaluated to determine whether removing it would significantly decrease the distance between group centroids. If not, it is removed. It is entirely possible that the strongest univariate predictor, after entering the model on the first step, is eventually discarded, because several others entering later render it superfluous. When a variable is retained in the model, it is said to be independently important. The final set of variables in the model can depend greatly on the patient sample used to construct it. Removing or adding patients (especially patients with endpoints, since this is usually the smaller group) can change the correlations among the variables slightly and can influence the order of variable selection and which variables are ultimately retained in the model.

Stepwise procedures do not guarantee that the resultant model will be the optimal one that can be constructed from a given set of predictors. To identify the optimal model, all possible combinations of predictors would have to be evaluated in separate analyses, and the overall "goodness of fit" criterion would have to be examined to select the best one. A slightly suboptimal model may be preferable if it includes fewer or more easily obtained variables.

Nonparametric models

The methods described above have been criticized because the resulting functions are difficult and are tedious to apply without the aid of a computer and do not demarcate logical categories or groups of patients. Also, problems concerning violations of underlying assumptions have made some investigators seek alternative approaches. Methodologies not based on a mathematical model are used less frequently, since they are not part of standard statistical software packages.

Some investigators have examined subsets of patients defined by various combinations of variables until they find a group with a high incidence of events [14, 15, 23]. Before the search can begin, continuous variables are converted into binary type variables. One such procedure, called *prognostic stratification* [168], automates this approach by exhaustively examining all possible combinations of the candidate variables taken 1, 2, 3, etc. at a time, flagging the combinations defining groups with a high proportion of endpoints. In one study all pairs and triples among eight candidate prognostic factors were examined to predict 6-month mortality in 100 patients surviving at least 12 days post AMI [15]. The best combination was trivariate and was defined by a peak CK greater than 585 IU, BUN greater than 20 mg/dl, and the presence of left ventricular failure in the CCU. The mortality in this group was 55%, compared to only 5% for patients having none, one, or two of the factors.

Other approaches that avoid the problems associated with mathematical models build classification trees. The entire population is examined to select the variable that best divides it according to endpoint status. Optimal cutoff points are first determined for continuous variables before they are evaluated

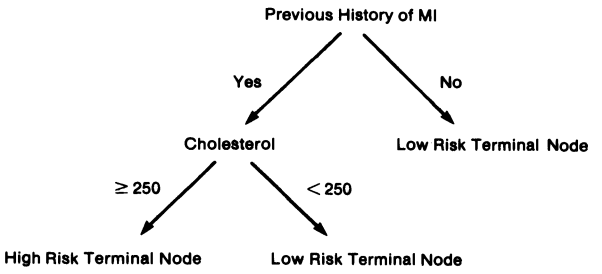

Figure 11A-2. Hypothetical classification tree showing interaction between two factors: a history of previous AMI and cholesterol level.

with respect to all the other factors, which may not utilize all the information contained in continuous variables fully. Within each of the groups defined by the selected variables, the process is repeated, resulting in a classification tree.

In the parametric case, the investigator had to hypothesis which interaction terms needed to be included in the model. In the tree construction methods, after the initial split variable is chosen, each further subdivision is performed on a subgroup of patients defined by the presence or absence of a given characteristic. The next variable selected interacts with the first to further define a group of patients with higher or lower risk. The hypothetical tree of figure 11A–2 indicates that patients with a history of a previous AMI and an elevated cholesterol level are at greatest risk of new events.

Another advantage of nonparametric methods is that nonlinearities in the predictor variables can be handled. For instance, heart rate above 110 beats/min might be selected to define a group of patients with high mortality. Then later in the remaining group, heart rate less than 50 beats/min might enter to define another high-risk group.

Several methods have been proposed for building the trees, and they differ mainly in the criteria used to select the best variables at each branch and when to terminate the process. The AID (automatic interaction detector) computer program uses a variance reduction score [169]. The variance of a parent group is NPQ where N is the group size, P is the proportion of the group with an endpoint, and Q is the proportion without. Each candidate variable defines two offspring groups with variances $n_1p_1q_1$ and $n_2p_2q_2$, respectively. The variable that maximizes the variance reduction score, $(NPQ - n_1p_1q_1 - n_2p_2q_2)/NPQ$, is selected, and the process continues until the variance reduction achieved by any variable is less than a threshold amount. This methodology was used extensively by one investigator to define groups at risk of death for time periods ranging from 24 hours to 2 years [4]. A separate analysis was performed for each time period.

Another approach chooses the variable that maximizes at each step the ratio of true positives to false positives in one of the offspring groups [170]. This results in extremely homogeneous subgroups being stripped off. The process

is terminated when the residual group is itself homogenous or is too small to divide further. This procedure has not been applied to risk stratification after AMI.

An approach that has been investigated recently, both in the area of diagnosis of AMI [171] and in risk stratification after AMI [7, 16, 19, 150], is called *recursive partitioning* [172]. The criterion for variable selection is based on maximizing the reduction in a diversity index, which takes into account the proportion of endpoints in the population and the relative cost of misclassification. The diversity index is computed for the parent group and the offspring groups defined by each candidate variable. The diversities for the offspring groups are summed and then are subtracted from the diversity for the parent group. The variable that causes the greatest reduction is selected. A stopping rule is applied that limits both the total number of end categories and the cost of misclassification incurred by not subdividing further. An example of a tree produced by this procedure is given in figure 11–2.

The main advantage of recursive partioning over the other methods is that the variable selection process incorporates the endpoint frequency and the relative cost of misclassification in the variable selection process via appropriate weights for the errors, as described above. Some of the approaches based on mathematical models incorporated these weights into the selection of a cutoff point for the score or risk probability, but this is done after the model is determined (after the variables are selected).

Modifications to the recursive partitioning process allow cases to be included in the analysis, even if data are missing for some of the candidate variables. The variables are selected based on all available data, but at each step the variable(s) that perform nearly as well as the selected variable are noted, so that if a case has missing data for the best variable, another can be used to decide offspring group membership.

Disadvantages of tree-building procedures arise from the smaller and smaller subgroups with which the procedures work. Important variables may be missed altogether, and idiosyncratic groups may result in the selection of counterintuitive variables. Thus, the resulting tree may not generalize well to other patient populations. Also, more statistical tests based on fewer and fewer patients are performed than for stepwise building of mathematical models. All variables are tested at each step, not just variables not already in the model. This multiple testing increases the probability of a significant relationship being detected when it really does not exist (type I error).

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