ACUTE CORONARY CARE 1986

To Lydia Califf
for her many and varied contributions
to the work in acute coronary care by
both Drs. Califf and Wagner.

ACUTE CORONARY CARE 1986

edited by
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PREFACE

The concepts of acute coronary care are changing so rapidly that it is appropriate that the volume ACUTE CORONARY CARE: PRINCIPLES AND PRACTICE, published early in 1985, would have yearly updates. The process of rapid production of camera-ready manuscripts has added new capability to the exchange of information. ACUTE CORONARY CARE 1986 is the first of a series of yearly updates in this important area of cardiology.

Materials published during the fall of 1984, including abstracts for the November American Heart Association meetings were reviewed by the editors to identify the areas of new information and the authors making important contributions. Manuscripts were completed and edited during the spring of 1985 and the final camera-ready versions were delivered to Martinus Nijhoff by mid-July.

The broad area of coronary care is divided into its five time sectors: Pre-hospital, Post-admission, Coronary Care Unit, Pre-discharge, and Convalescent. As patients are more frequently encountered in the pre-hospital phase, it has become evident that alterations in the autonomic nervous system have a great impact on the clinical situation. The chapter by Ron Victor emphasizes the important interactions between the nervous system and the cardiovascular system in this critical situation.

Immediately post-admission in a setting where acute coronary care is available, a most important decision regards initiation of aggressive attempts at coronary reperfusion. This places additional responsibility on optimal interpretation of the standard 12-lead electrocardiogram, which is the only universally available diagnostic technique with potential for indicating the presence and, possibly, extent of the ischemic myocardium. Tom Hinohara discusses our current level of understanding of quantitative changes in the admission electrocardiogram. He stresses the importance of careful electrocardiographic evaluation of patients receiving acute interventional therapy to improve understanding of the capabilities and limitations of this simple technique. There is a great deal of new information available about several interventions which might potentially have profound effects on the process of acute myocardial ischemia and infarction. Peer Grande and Anne-Marie Grauholt discuss the role of antiplatelet agents for preventing an acute infarction in

patients with unstable angina pectoris. Gene Passamani reviews the clinical trials of thrombolytic agents which have been completed and also indicates those still in progress. Newer thrombolytic agents are also on the horizon, as discussed in the chapter by Elliott Grossbard. Richard Stack presents the rationale for combining angioplasty with acute attempts at thrombolysis in the modern interventional cardiac catheterization laboratory.

All of these interventions are aimed at restoration of coronary blood flow and thereby improving myocardial nutrient supply. The other aspect of the equation is decrease in myocardial metabolic demand. Salim Yusuf reviews the clinical trials which have evaluated acute use of intravenous beta-adrenergic blocking agents in patients with acute myocardial infarction.

Since many patients are treated with strategies designed to achieve reperfusion prior to arrival on the CCU, the early aspect of the CCU phase is often dominated by "post thrombolytic care" as is discussed by David Harrison. With all of the attempts at limitation of infarct size, it is important to develop improved methods of accurate infarct size measurement. Four such methods are covered in detail: Bob Roberts and Peter Puleo review the status of enzymatic studies, Bruce Brundage discusses rapid computerized tomography, Rick White et al. present nuclear magnetic resonance, and Rick Goldstein reviews positron emission tomography.

Since an important consequence of myocardial infarction is limitation of cardiac function, it is important to consider new diagnostic and therapeutic aspects of hemodynamics. Bob Lester points out the limitations of the bedside evaluation of cardiac function and indicates the importance of developing new non-invasive methods of estimating the status of peripheral perfusion. Both pharmacologic and mechanical methods have been available for several years which are capable of improving coronary and/or peripheral blood flow. Jose Martin compares the effects of the intravenous administration of nitroglycerin and nitroprusside.

A discussion of acute coronary care in 1986 would not be complete without a consideration of the medical economics involved. Phyllis Ellenbogen and Andy Wallace review cost-benefit considerations in the chapter on acute coronary care and diagnosis related groups.

Optimal post-discharge management requires consideration of the complications which often are encountered by the individual patient. Jim Heinsimer reviews the use of ultrasound to detect infarct expansion and mural thrombi, findings which are associated with an adverse prognosis. It is important to evaluate the role of invasive as well as non-invasive studies immediately post infarction and Phil Harris presents lessons from an extensive experience with predischarge cardiac catheterization. Seth Worley considers the relationship between the processes of identifying the patients at high risk of sudden death and selection of the optimal antiarrhythmic therapy. Now that several large studies have documented decreased post infarct mortality in patients receiving beta adrenergic blockade, it is important to optimize the selection of patients as reviewed by Bill Friedewald.

David Waters reviews the various techniques for characterizing the patient entering the convalescent phase following acute myocardial infarction. Many of these patients will have chronic cardiac failure and Chuck Simonton and Kanu Chatterjee summarize the current status of new inotropic agents. Since a smooth transition between the acute and convalescent phases is critical, Steve Roark discusses the common problems encountered in patient management during this period.

Few areas of medical care are in so great a state of uncertainty as acute coronary care. The brief chapters in this book are designed to provide easy access to the literature available during 1985 in a relatively few areas of acute coronary care.

Robert M. Califf, M.D.
Galen S. Wagner, M.D.

I. CORONARY CARE: THE PRE-HOSPITAL PHASE

1

AUTONOMIC CHANGES DURING THE ACUTE PHASE OF ACUTE MYOCARDIAL INFARCTION AND ISCHEMIA

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INTRODUCTION

Most deaths from acute myocardial infarction occur within one hour of the onset of symptoms (1-3). There is now substantial evidence that the autonomic nervous system plays a major role in the high mortality during the acute phase of myocardial infarction (4-6). For example, sympathetic neural activation can precipitate sudden death in the early stage of myocardial infarction by decreasing the threshold for ventricular fibrillation (7,8). In addition to ventricular arrhythmias, profound changes in peripheral vascular resistance and ventricular performance can be triggered by autonomic influences during coronary occlusion (9).

Autonomic changes can also accompany sudden alterations in myocardial perfusion during coronary vasospasm (10) and following coronary thrombolysis (11,12). Thus, most acute ischemic events (and even interventions which relieve ischemia) are accompanied by autonomic changes which have important effects on circulatory control and on survival.

This chapter will review the autonomic responses to acute myocardial infarction and ischemia, their determinants, mechanisms, and management. The major purpose of this review is to present a conceptual framework for the role played by neurogenic reflexes in the regulation of the circulation during acute myocardial infarction and ischemia.

Three concepts will be presented. First, anterior myocardial infarction engages predominately "excitatory" neural reflexes which promote increased neurohumoral drive to the circulation (13). This leads to hypertension and tachycardia. Second, inferoposterior infarction engages an "inhibitory" reflex (Bezold-Jarisch reflex) which promotes decreased neurohumoral drive to the circulation (14). This leads to hypotension and bradycardia as well as gastric dysmotility with nausea and vomiting. Third, acute myocardial infarction with hypotension and cardiogenic shock

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engages both excitatory and inhibitory reflexes. The interaction of these reflexes determines the overall pattern of neurocirculatory adjustments to the development of hypotension and cardiogenic shock (15).

IMPORTANCE OF INFARCT SITE ON AUTONOMIC INPUTS AND CIRCULATORY RESPONSES TO ACUTE CORONARY OCCLUSION.

Studies utilizing mobile intensive care units have shown that the overwhelming majority of patients with acute myocardial infarcts have evidence of autonomic disturbances during the first hour of the attack (4-6). These disturbances produce hypertension and tachycardia in over 30% of these patients and hypotension and bradycardia in over 50% of patients with acute infarcts.

Webb and colleagues (5) have demonstrated convincingly that the pattern of autonomic disturbance during the initial phase of myocardial infarction is related to the site of the infarct. As shown in Figure 1, hypertension and tachycardia occur more commonly in patients with anterior infarcts, whereas hypotension and bradycardia occur much more commonly in patients with inferoposterior infarcts. These findings are not explained by differences in pain, anxiety, or infarct size.

Thus, autonomic responses are predominately "excitatory" during anterior infarction but predominately "inhibitory" during inferoposterior infarction. Considerable experimental evidence indicates that these two distinct patterns of neurocirculatory responses are governed by different mechanisms. In other words, anterior and inferoposterior infarcts tend to produce different autonomic responses at the onset of infarction because they engage different neural reflexes.

"Excitatory" Neural Reflexes in Acute Anterior Myocardial Infarction.

Over 50% of patients during the hyperacute phase of anterior myocardial infarction have hypertension and/or sinus tachycardia (Figure 1). Moreover, the vast majority of these patients have elevated levels of plasma catecholamines which peak within the first hour of the attack (16-18). These observations indicate that acute anterior infarction causes prompt stimulation of sympathetic outflow.

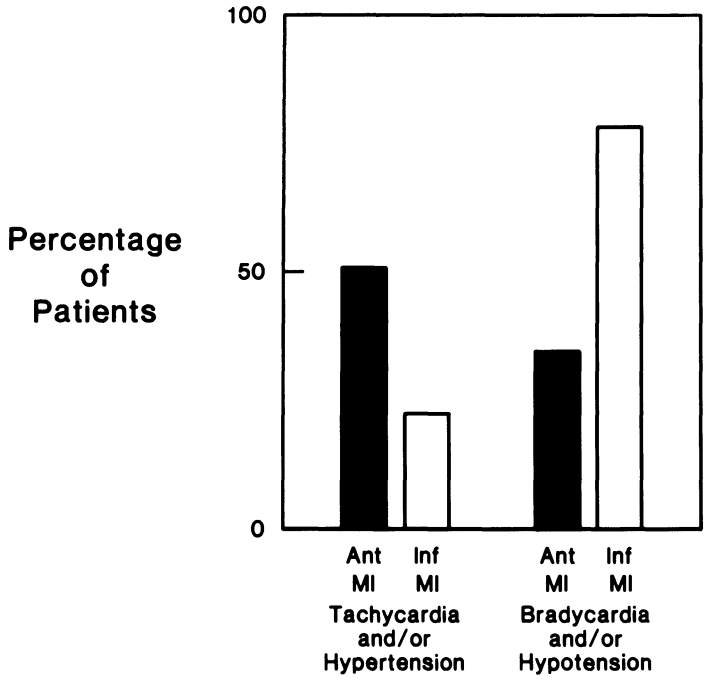

Fig. 1. Relative frequency of tachycardia/hypertension vs. bradycardia/hypotension during the first 30 minutes of anterior (Ant) and inferoposterior (Inf) myocardial infarction (MI). Tachycardia and hypertension were more common in patients with anterior infarcts whereas bradycardia and hypotension were much more frequent in patients with inferoposterior infarcts. (Adapted from Webb, S.A., Adgey, A.A.J., and Pantridge, J.F. [5], with permission).

Mechanisms. Sympathetic neural activation at the onset of anterior myocardial infarction has been attributed to several reflex mechanisms.

1. Arterial Baroreflexes. Changes in arterial pressure alter the discharge of the aortic and carotid sinus baroreceptors and thus their influence on sympathetic outflow (19). Since large infarcts generally promote a decrease in systemic blood pressure, arterial baroreflexes should trigger sympathetic excitation with vasoconstriction and tachycardia. However, anterior infarction commonly increases arterial pressure (4-6). So, mechanisms which do not directly involve arterial baroreceptors also must be involved.

2. Pressor Reflexes Produced by Stimulation of Cardiac Sympathetic Afferents. In experimental animals, coronary occlusion has been shown to activate sensory endings throughout the heart (9). One group of these nerve endings triggers a pressor reflex which is mediated by afferent (sensory) nerve fibers that enter the upper thoracic spinal cord via the cardiac sympathetic nerves (20). During coronary occlusion, stimulation of these sensory endings produces reflex efferent sympathetic activation with tachycardia, hypertension and increased ventricular contractility (9,21,22).

Two mechanisms have been implicated in this excitatory reflex. The first is that the sympathetic afferents transmit the sensation of pain during myocardial ischemia and infarction to higher brain centers (23,24). Therefore, the pain of myocardial ischemia can be eliminated in patients by removal of the stellate ganglion and the first through fifth thoracic ganglia (25). In other words, sympathetic excitation during anterior infarction is in part a response to cardiac pain.

The second mechanism is a spinal sympathetic reflex. The excitatory neural response to stimulation of these cardiac sensory endings is present in spinal animals and is abolished by section of the dorsal roots where the afferent fibers enter the spinal cord (26). Thus, the afferent sympathetic fibers may produce efferent sympathetic discharge during coronary occlusion by either central or peripheral (spinal) mechanisms, or both.

This conclusion is consistent with the clinical observation that acute hypertension in patients can precede or coincide with the onset of chest pain during spontaneous episodes of angina (27,28). However, the actual importance of afferent sympathetic fibers in the integrated control of the circulation during anterior myocardial infarction in patients remains to be determined.

3. Cardiogenic Hypertensive Chemoreflex. It has been postulated that platelet aggregation during acute coronary thrombosis can reflexly increase sympathetic outflow and arterial pressure because serotonin, which is released by platelets in the thrombus, activates a "cardiogenic hypertensive chemoreflex" (29). This pressor reflex is thought to originate in chemoreceptor tissue which is located near the origin of the aorta and main pulmonary artery. Although this chemoreceptor tissue resembles the carotid body histologically, the cardiogenic chemoreceptors are acti-

vated by serotonin and not by arterial hypoxemia, hypercapnia, or acidemia. The afferent fibers travel to the brainstem in the vagus nerve.

It has been determined that the cardiogenic chemoreceptors almost always receive their arterial blood supply from a small branch of the left main or proximal left anterior descending coronary artery (30). Based on these anatomical findings, James and colleagues (29) have suggested that the cardiogenic hypertensive chemoreflex may be activated only when acute coronary thrombosis involves the proximal left coronary circulation. Thus, the cardiogenic hypertensive chemoreflex might contribute to greater sympathetic excitation in anterior vs. inferoposterior infarction. For now, this should be considered a provocative hypothesis that needs to be tested in both experimental animals and patients.

Significance. Activation of the sympathetic nervous system causes increased secretion of catecholamines and produces many of the characteristic clinical features of acute anterior wall infarction (3). Plasma catecholamine levels in patients peak in the first hour after the onset of infarction, rise in proportion to infarct size, and correlate with the incidence of heart failure and ventricular arrhythmias (16-18,31). These clinical observations are consistent with experimental models of myocardial infarction in which the threshold for ventricular fibrillation is decreased by sympathetic excitation and increased by sympathectomy and adrenergic blockers (7,8,32-33). In addition, secretion of catecholamines stimulates myocardial oxygen consumption (3). Thus, excessive sympathetic outflow during myocardial infarction is usually deleterious.

Therapeutic Considerations. Reduction of augmented sympathetic drive is therefore an important therapeutic goal in some patients with acute anterior infarcts. Several factors should be considered. First, the ideal approach would be prompt restoration of coronary blood flow since myocardial ischemia is the underlying stimulus to sympathetic activation in this setting. The development of effective thrombolytic agents that can be administered by paramedics would come close to accomplishing this goal. Second, hypovolemia and hypotension should be corrected promptly to prevent baroreflex-mediated vasoconstriction and tachycardia. Third, administration of opiates and tranquilizers to relieve pain and anxiety should help to decrease sympathetic drive in some patients. Fourth, administration of beta-receptor antagonists to patients during acute infarction

can block many of the deleterious effects of catecholamines (33-34). In addition, beta-blockers have been shown to decrease plasma catecholamine levels significantly in patients with acute infarcts (35), although the mechanism of this effect has not been determined. Nevertheless, beta-receptor blockers obviously must be used judiciously in patients with acute anterior infarcts and clearly are contraindicated in patients with severe bradyarrhythmias and evidence of pump failure.

"Inhibitory" Reflexes in Acute Inferoposterior Infarction and Ischemia. About 80% of patients during the hyperacute phase of inferoposterior myocardial infarction have evidence of decreased neurohumoral drive to the circulation with bradycardia and hypotension (Figure 1). This results from increased parasympathetic drive to the heart (bradycardia) or from decreased sympathetic drive to the peripheral vessels (vasodilatation), or both (14). In addition, inferoposterior infarction is often accompanied by nausea and vomiting which indicates excessive parasympathetic influence on gastric motility (13).

Mechanisms. "Bezold-Jarisch Reflex". In experimental animals, infusion of veratrum alkaloids (previously used as antihypertensive drugs) into the left ventricle elicits a potent inhibitory reflex, the "Bezold-Jarisch" reflex (36,37). The reflex response is characterized by intense peripheral vasodilatation from sympathetic inhibition plus marked bradycardia from parasympathetic activation (9). This combination of autonomic influences produces a powerful depressor response. The afferent limb of this inhibitory Bezold-Jarisch reflex originates in sensory nerve endings which are located primarily in the inferoposterior wall of the left ventricle. These endings send unmyelinated afferent fibers to the brainstem via the vagus nerve.

There is now overwhelming evidence from animal experiments that the characteristic bradycardia and hypotension seen in patients at the onset of acute inferoposterior myocardial infarction is a clinical counterpart of the Bezold-Jarisch reflex. In the dog, for example, veratrum alkaloids cause much greater reflex vasodilatation and bradycardia when injected into the circumflex artery than into the left anterior descending artery (38). In addition, reflex bradycardia, hypotension, and sympathoinhibition are much more common with inferoposterior than with anterior wall

ischemia in dogs (39,40). These findings indicate that the sensory endings which give rise to the inhibitory Bezold-Jarisch reflex are preferentially distributed in the inferoposterior wall of the canine left ventricle (41). The high incidence of bradycardia and hypotension in patients during inferoposterior infarction suggests a similar anatomic distribution of these inhibitory cardiac receptors in humans.

An understanding of the afferent and efferent limbs of Bezold-Jarisch reflex helps to explain several clinical features of acute inferoposterior infarction in patients.

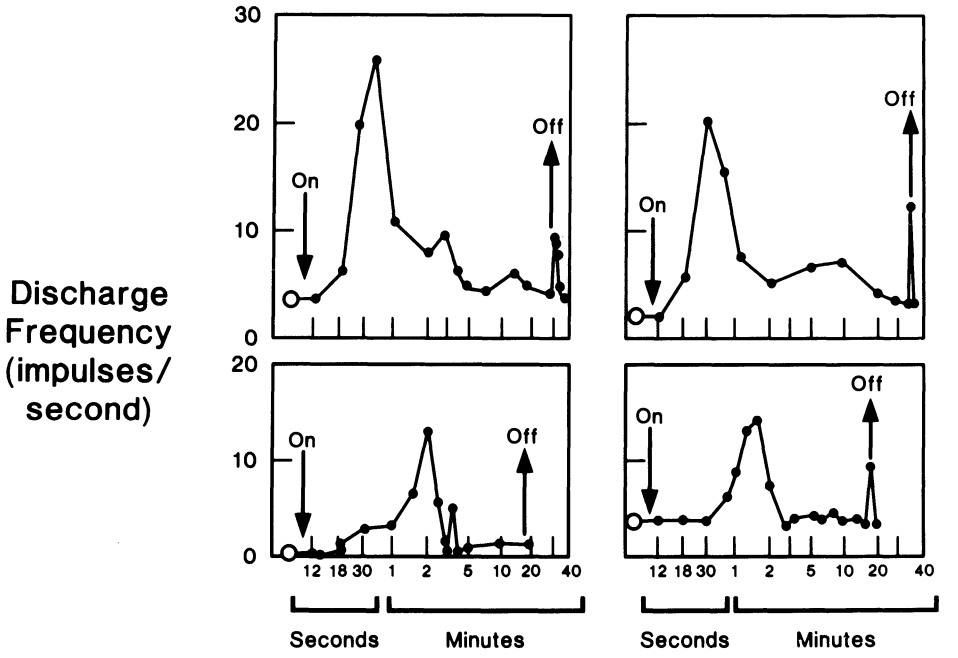

Fig. 2. Discharge frequency of four left ventricular receptors with vagal afferents during and immediately after occlusion of the coronary artery which supplied the receptor area. "On" refers to the onset of coronary occlusion. "Off" refers to release of occlusion. Note: 1) that discharge frequency increases almost immediately with the onset of coronary occlusion; 2) that afferent neural discharge peaks rapidly within 2 minutes of coronary occlusion but is not sustained when occlusion is maintained for several minutes; 3) that there is a transient "paradoxical" increase in discharge frequency upon release of coronary occlusion in 3 of 4 experiments. (Adapted from Thorén, P.N. [11], with permission).

Activation of Ventricular Receptors with Unmyelinated Vagal Afferents During Myocardial Ischemia. Figure 2 (11) shows the effects of experimental coronary occlusion on the discharge frequency of left ventricular receptors with unmyelinated vagal afferents. Discharge frequency increases almost immediately with the onset of coronary occlusion and peaks rapidly within two minutes.

The exact mechanism whereby myocardial ischemia activates these sensory nerves is not known; however, mechanical distortion of the receptors is probably involved since the neural firing coincides with systolic bulging of the myocardium (11).

Note also that the initial increase in afferent neural discharge is followed by a decrease in discharge frequency when the coronary occlusion is maintained for several minutes (Figure 2). So, although myocardial ischemia is a potent stimulus to these ventricular sensory endings, the impulse activity is not sustained. This observation may explain why the incidence of bradycardia and hypotension is greatest in patients at the onset of acute inferoposterior infarction and declines rapidly thereafter.

Coronary Reperfusion. Figure 2 also demonstrates that coronary reperfusion upon release of coronary occlusion frequently produces "paradoxical" activation of ventricular receptors with unmyelinated vagal afferents. The mechanism is unknown. Nevertheless, this phenomenon may also occur in patients who undergo successful thrombolytic therapy for coronary thrombosis. In a study by Wei and colleagues (12), transient bradycardia and hypotension occurred in up to 87% of patients who underwent successful reperfusion following infusion of streptokinase into the right coronary artery. In contrast, only 14% of patients with successful reperfusion involving the left anterior descending artery developed bradycardia and hypotension. Thus, paradoxical activation of the Bezold-Jarisch reflex appears to be particularly common in patients with right coronary artery occlusions who undergo successful thrombolysis.

Coronary Vasospasm. There is also evidence that the Bezold-Jarisch reflex can be engaged during coronary vasospasm. For example, in a study of patients with Prinzmetal's angina (10), heart rate decreased significantly during pain associated with inferior ischemia but increased significantly during pain associated with anterior ischemia. This is summarized in Figure 3.

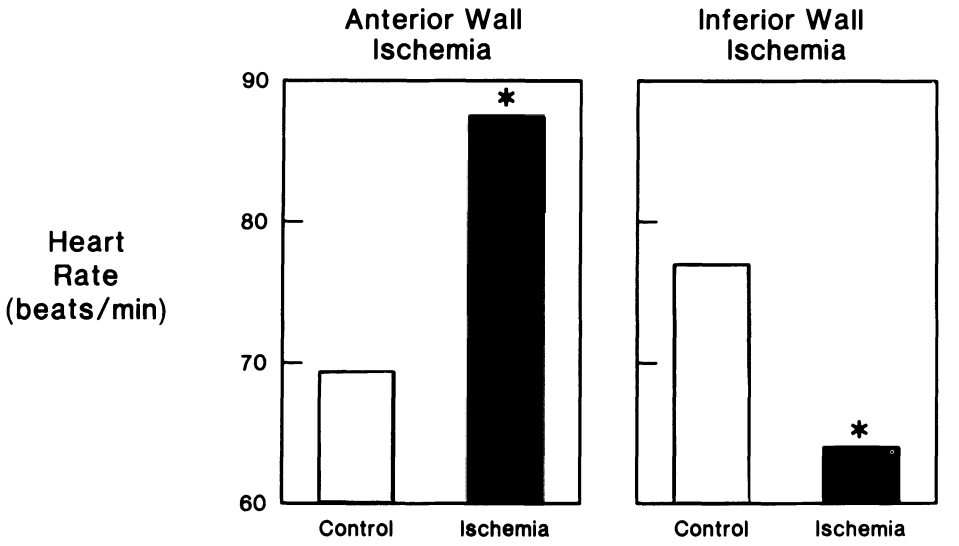

Fig. 3. Heart rate changes during chest pain produced by coronary artery spasm in patients with Prinzmetal's angina. Heart rate increased significantly during pain associated with anterior wall ischemia but decreased significantly during pain associated with inferior wall ischemia. (Adapted from Perez-Gomez, F., DeDios, R.M., Rey, M., and Aguado, A.G. [10], with permission).

Furthermore, transient A-V block was more common during inferior ischemia, whereas ventricular tachycardia and fibrillation were much more common during anterior ischemia. These observations are consistent with the view that anterior wall ischemia or infarction predominately activates "excitatory" neural reflexes whereas inferoposterior ischemia or infarction engages a powerful inhibitory reflex, the Bezold-Jarisch reflex.

Nausea and Vomiting during Inferoposterior Infarction. Nausea and vomiting during acute myocardial infarction are frequent side effects of opiate administration. However, when this factor is eliminated, nausea and vomiting are more than twice as common in patients with inferoposterior than anterior infarcts (42). This observation is almost certainly

explained by preferential stimulation of the Bezold-Jarisch reflex during inferoposterior infarction since gastric relaxation and retching frequently accompany bradycardia and hypotension during stimulation of the Bezold-Jarisch reflex in animals (43,44). In addition, gastric relaxation in dogs is much greater when veratrum alkaloids are infused into the circumflex coronary artery than into the left anterior descending artery (45). This reflex response in gastric motility is mediated by a non-cholinergic vagal pathway (9). In other words, the response is abolished by vagotomy but not by atropine.

Significance. Activation of the Bezold-Jarisch reflex therefore explains many of the clinical features of acute inferoposterior myocardial infarcts. These include the high incidence of bradycardia, hypotension, and gastrointestinal symptoms. In addition, the combination of severe bradycardia and widespread vasodilatation in patients with inferoposterior infarcts can produce circulatory failure and death (4-6). Thus, the Bezold-Jarisch reflex plays a major role in the pathophysiology of acute inferoposterior myocardial infarction.

The importance of this reflex in causing vasodilatation and hypotension during acute infarction should be emphasized. In the absence of serious arrhythmias, hypotension during myocardial infarction usually has been attributed to a primary dysfunction in ventricular performance (i.e., "pump failure"), and the importance of the peripheral vasculature has received relatively little attention (3). Therefore, it is important for cardiologists to recognize that inhibitory reflexes during acute myocardial infarction, particularly infarction involving the inferoposterior wall, can cause severe hypotension even in the absence of primary pump failure. This hypotension is due not only to bradycardia but also to profound reflex vasodilatation in many peripheral vascular beds.

Therapeutic Considerations. The bradycardic and hypotensive responses to the onset of inferoposterior infarction are characteristically transient (4-6). These autonomic disturbances therefore may resolve spontaneously, sometimes by the time that the patient is admitted to the coronary care unit. However, in a significant proportion of patients, reflex bradycardia and vasodilatation produce acute circulatory failure which requires emergent treatment.

The conventional approach to this problem is prompt administration of atropine (46). The rationale for atropine, a muscarinic blocker, is that the inhibitory cardiovascular responses during acute inferoposterior infarction are generally considered to reflect "parasympathetic overactivity" (4-6). However, this is an oversimplification of the efferent components of the Bezold-Jarisch reflex (9,14). Although the bradyarrhythmias result from excessive parasympathetic drive to the heart, the peripheral vasodilation results from withdrawal of sympathetic vasoconstrictor tone. In addition, the associated changes in gastric motility with nausea and vomiting are produced by non-cholinergic vagal fibers. Thus, peripheral vasodilatation and gastric symptoms in patients with acute inferoposterior infarcts should not be expected to respond to atropine (14).

Another drug which may eventually prove to be beneficial in this setting is lidocaine. In experimental animals, intravenous administration of lidocaine in doses of 3-4 mg/kg has been shown to abolish the Bezold-Jarisch reflex during coronary occlusion (47). The mechanism is thought to involve "endoanesthesia" of inhibitory cardiac sensory receptors by lidocaine. This is an exciting concept that needs to be tested in carefully selected patients. Parenthetically, lidocaine has been reported to increase heart rate during acute myocardial infarction in some patients with sinus bradycardia (48).

INTERACTIONS BETWEEN EXCITATORY AND INHIBITORY NEURAL REFLEXES IN ACUTE MYOCARDIAL INFARCTION: AUTONOMIC CHANGES IN PATIENTS WITH HYPOTENSION OR CARDIOGENIC SHOCK.

In general, autonomic responses are initially excitatory in anterior myocardial infarcts and inhibitory in inferoposterior infarcts. However, this is not a strict dichotomy since multiple reflex mechanisms undoubtedly are engaged in most, if not all, ischemic events.

Furthermore, there is substantial evidence that the various excitatory and inhibitory autonomic inputs are interactive (15). This means that the net pattern of autonomic change during acute myocardial infarction is influenced by the interplay between various neural reflexes.

For example, an important interaction between the Bezold-Jarisch reflex and the arterial baroreflex occurs during inferoposterior infarc-

tion (15,40,49). When coronary occlusion causes hypotension, arterial baroreflexes should trigger sympathetic excitation with vasoconstriction and tachycardia. However, the hypotension during inferoposterior myocardial infarction is usually accompanied by vasodilatation and bradycardia (4-6,39). These observations indicate that the excitatory neural influence produced by the arterial baroreceptors in this setting is obscured by a stronger inhibitory influence from the Bezold-Jarisch reflex. Thus, the Bezold-Jarisch reflex inhibits the arterial baroreflex.

This inhibitory reflex interaction also plays an important role in the pathophysiology of cardiogenic shock.

Inhibition of Arterial Baroreflexes by the Bezold-Jarisch Reflex During Cardiogenic Shock. Both clinical and experimental studies indicate that reflex peripheral vasoconstriction is often impaired during acute myocardial infarction with cardiogenic shock. For example, Ramo and colleagues (50) examined systemic hemodynamic changes during acute myocardial infarction in 123 patients upon admission to the Duke Coronary Care Unit. These investigators could not separate patients into those with and without shock on the basis of calculated total peripheral resistance. Thus, systemic vascular resistance was not consistently elevated in the presence of cardiogenic shock.

This finding has been confirmed repeatedly in animal experiments (51-54) and is demonstrated most clearly in studies which have compared renal vascular responses to cardiogenic vs. hemorrhagic shock (52,53). Figure 4 demonstrates that systemic hypotension produced much less renal vasoconstriction during coronary occlusion than during hemorrhage, even though blood pressures were reduced to comparable levels in both groups of experimental animals (53). In several animals, renal vascular resistance actually decreased during hypotension produced by coronary occlusion.

During myocardial infarction with cardiogenic shock, the Bezold-Jarisch reflex is engaged because of extensive myocardial ischemia and because increased left ventricular end diastolic pressure promotes mechanical distortion of the inhibitory cardiac sensory receptors (9,15). In contrast, the Bezold-Jarisch reflex is usually not engaged during the development of hemorrhagic shock when cardiac filling pressures are low. Thus, arterial baroreceptors produce greater vasoconstriction when inhibitory cardiac receptors are not activated (hemorrhage) than when cardiac

receptors are activated (myocardial infarction). In other words, the Bezold-Jarisch reflex inhibits arterial baroreflex control of vascular resistance during the development of cardiogenic shock.

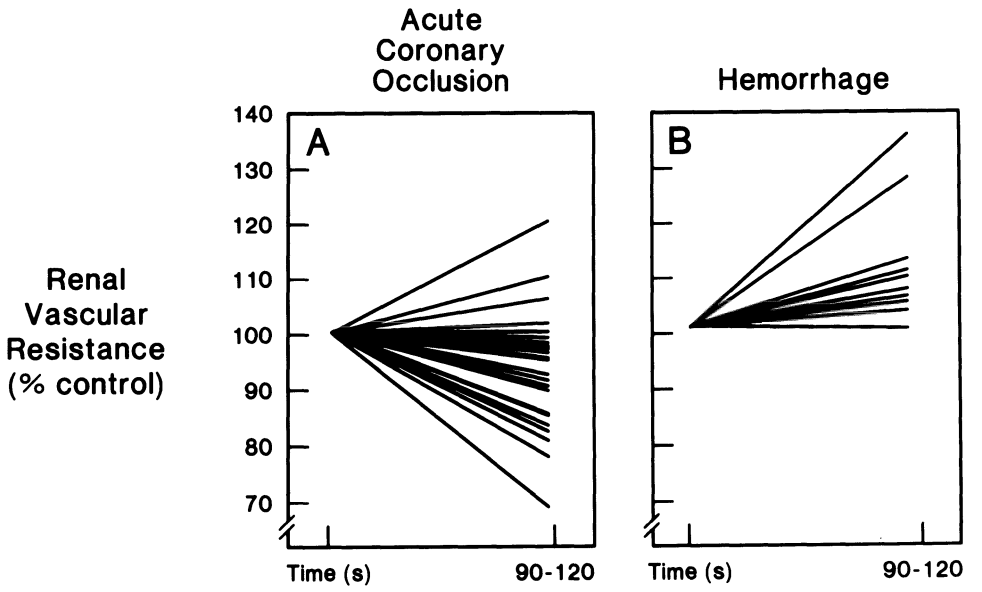

Fig. 4. Changes in renal vascular resistance (expressed as a percentage of the control values) during A) acute coronary occlusion and B) brief hemorrhage in dogs. Blood pressures were reduced to comparable levels in both groups of animals. Nevertheless, systemic hypotension produced much less vasoconstriction during coronary occlusion than during hemorrhage. In several experiments, renal vascular resistance actually decreased during hypotension produced by coronary occlusion. (Adapted from Hanley, H.G., Raizner, A.E., Englesby, T.V., and Skinner, N.S., Jr. [53]), with permission.

Significance and Clinical Implications: Based on these findings, one might speculate that an inhibitory interaction between the Bezold-Jarisch reflex and the arterial baroreflex is important teleologically. For example, reduction in neurogenic vasoconstriction during cardiogenic shock could provide a mechanism for minimizing deleterious elevations in left ventricular afterload.

In addition, it should be emphasized that many of the traditional clinical hallmarks of "shock" such as cold extremities and oligoanuria reflect reflex vasoconstriction (55). In marked contrast to the intense vasoconstriction which characterizes the initial phase of hemorrhagic shock, reflex neurogenic vasoconstriction is initially impaired in a substantial proportion of patients who develop pump failure. Such patients therefore can develop cardiogenic shock without displaying cold extremities, oliguria, or increases in total peripheral resistance. Thus, the early clinical recognition of shock in the acute phase of myocardial infarction cannot be based upon evidence of peripheral vasoconstriction.

CONCLUSIONS

In this chapter, I have presented an overview of the autonomic changes during acute myocardial infarction. Autonomic mechanisms were emphasized to develop a conceptual framework for the role played by neurogenic reflexes in the control of the circulation during acute myocardial infarction and ischemia.

Most of what we know about neurocirculatory control during coronary occlusion has come, and will come, from research on animals. Even with the development of highly sophisticated approaches for studying autonomic mechanisms in human subjects, it will be difficult, but not impossible, to directly test concepts about neurogenic reflexes in patients with acute myocardial infarcts. For now, it is appropriate to be cautious in drawing firm conclusions about autonomic influences during ischemic events in patients based upon findings in experimental animals. Nevertheless, there is a striking similarity in the patterns of autonomic response to experimental coronary occlusion in animals and to acute myocardial infarction in patients. This similarity in the responses of animals and patients strongly suggests that the autonomic changes observed in the experimental and clinical settings are governed by very similar mechanisms.

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II. CORONARY CARE: THE POST-ADMISSION PHASE

2

USE OF THE INITIAL ELECTROCARDIOGRAM DURING ACUTE MYOCARDIAL INFARCTION TO ESTIMATE THE EXTENT OF THE JEOPARDIZED MYOCARDIUM AND GUIDE THE DETERMINATION OF THERAPY

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INTRODUCTION

During the initial assessment of a patient with suspected acute myocardial infarction (MI), few diagnostic tests are immediately available. A standard 12-lead electrocardiogram (ECG) remains the most useful method to assess the clinical situation and to guide the determination of therapy. The ECG is almost always immediately available at the site of patient presentation and is inexpensive and easy to perform. Although a normal ECG does not eliminate the possibility of an acute coronary event, the patient's position along the spectrum from entirely normal to marked epicardial injury should guide the intensity of the acute intervention. Such information is particularly important in an era when limitation of infarct size has become an important goal of acute coronary care. Should a patient be managed "conservatively" with little or no effort aimed at size limitation, or managed "aggressively" with every effort exerted to optimize coronary blood flow? It is important for clinicians to understand the capability and limitation of the ECG as a diagnostic aid for the assessment of patients with suspected acute MI.

DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION

ECG changes during acute MI have been recognized for over 60 years. Although certain changes strongly suggest the presence of acute MI, it is important to note that none of these "diagnostic" changes are either 100% sensitive or 100% specific. Despite a totally normal ECG, it is possible that an acute MI could be in progress or, more likely, that acute ischemia had been present but had remitted prior to the time of the tracing. A previously chronically abnormal ECG is much more likely to hide the acute ischemic or infarction process. Previous infarction, bundle branch block, or ventricular hypertrophy mimic the ECG changes of acute ischemia or infarction. Also, ST segment and T wave abnormalities may be caused by electrolyte disturbances, various medications, noncoronary myocardial or pericardial conditions, and the

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normal variation of "early repolarization." Therefore, the ECG obtained at the time of patient presentation with suspected acute coronary insufficiency should always be interpreted in conjunction with other clinical information. A previous ECG, if available, should be examined to determine if changes are related to the acute clinical event.

Changes in repolarization (T wave) have been considered to indicate "ischemia" and changes in the period between depolarization and repolarization (the ST segment) have been termed "injury." Both "ischemia" and "injury" are potentially reversible conditions and their T wave and ST segment alterations may occur either in the presence or absence of accompanying infarction. T wave and ST segment changes will therefore precede the changes in depolarization (the QRS complex) which require the development of irreversible change: infarction.

Two general patterns of ST segment and T wave changes may be observed during an acute ischemic event: 1) the epicardial injury pattern characterized by ST segment elevation, and 2) the endocardial injury and/or ischemic pattern indicated by ST segment depression and/or T wave inversion. Concepts based on both systolic and diastolic phenomena have been suggested for the explanation of the ST segment deviation resulting from "myocardial injury." The systolic concept considers that there is true ST segment elevation caused by early repolarization of the injured area compared to the normal myocardium. The diastolic concept considers that the ST segment appears to be elevated because of the downward displacement of the TQ segment. Depolarization persists in the injured area and it is, therefore, negative relative to the normal myocardium. With completion of depolarization of the injured area, the potential becomes isoelectric relative to that in the normal myocardium. Thus, although the ST segment during the systolic phase is isoelectric, there is relative ST segment elevation because of the TQ segment depression (1).

Epicardial injury, which usually represents transmural myocardial involvement, is most often caused by an acute occlusion of a major coronary artery. DeWood et al. (2) documented the very high incidence (87%) of total occlusion of epicardial arteries by thrombus during acute MI in patients who had duration of chest pain less than 4 hours and ST segment elevation. Although 13% of patients had only subtotal stenosis at the time of cardiac catheterization, it is likely that these patients previously had total occlusion with subsequent spontaneous reperfusion. Yasue et al. (3) demonstrated the relationships between ST segments or T waves changes and the degree of stenosis

documented by coronary angiograms during episodes of spontaneous or induced angina. Transient total occlusions of epicardial arteries during episodes of angina in the absence of significant collateral vessels were associated with ST segment elevation in ECG leads corresponding to the area of myocardium involved. Subtotal occlusion of the epicardial arteries or total occlusion with good collateralization were associated with ST segment depression or T wave changes.

ST segment depression is generally termed the "subendocardial injury pattern." This is a less specific indication of true myocardial injury than is ST segment elevation. Other conditions such as electrolyte imbalance, medications, noncoronary myocardial disease, conduction disturbances, and ventricular hypertrophy with "strain" may cause ST segment depression which mimics the "subendocardial injury pattern." Also, ST segment depression in one lead may be reciprocal to the changes of ST segment elevation in a lead with opposite orientation to the myocardium. The MILIS (Multicenter Investigation of the Limitation of Infarct Size) study (4) included 3697 patients with more than 30 minutes of chest pain considered to indicate probable acute MI. Patients with only ST segment depression without ST segment elevation or new Q waves had only a 52% incidence of subsequent documentation of acute MI.

The MILIS study (4) also provided insight into the sensitivity of acute electrocardiographic changes. In all patients who were subsequently proven to have an acute MI, only 65% had "diagnostic changes" on the admission ECG. Diagnostic changes were considered to be "the presence of new or presumably new ST segment deviation of $\geq$0.10 mv, or new or presumably new Q waves of at least 30 msec in duration and 0.2 mv in depth in at least 2 leads". Brush et al. (5) evaluated the initial ECG in 469 patients with suspected acute MI. Among 167 patients whose initial ECGs revealed normal or nonspecific ST changes, 24 patients (15%) proved to have MI. Among 302 patients whose initial ECGs revealed positive changes (pathologic Q wave, ST segment elevation, ST segment depression or T wave inversion), 171 patients (57%) proved to have MI. Thus, it should be emphasized that a normal or near normal ECG does not rule out acute myocardial infarction. A normal or near normal ECG in a patient with evolving acute coronary event may be due to several factors: 1) no significant ischemia or injury at the time of the ECG tracing, 2) delay of electrocardiographic change despite ischemia, 3) only a small area with myocardial ischemia, 4) pseudonormalization of previously abnormal changes (6) (Figure 1), and 5) ischemia in an electrocardiographically silent area.

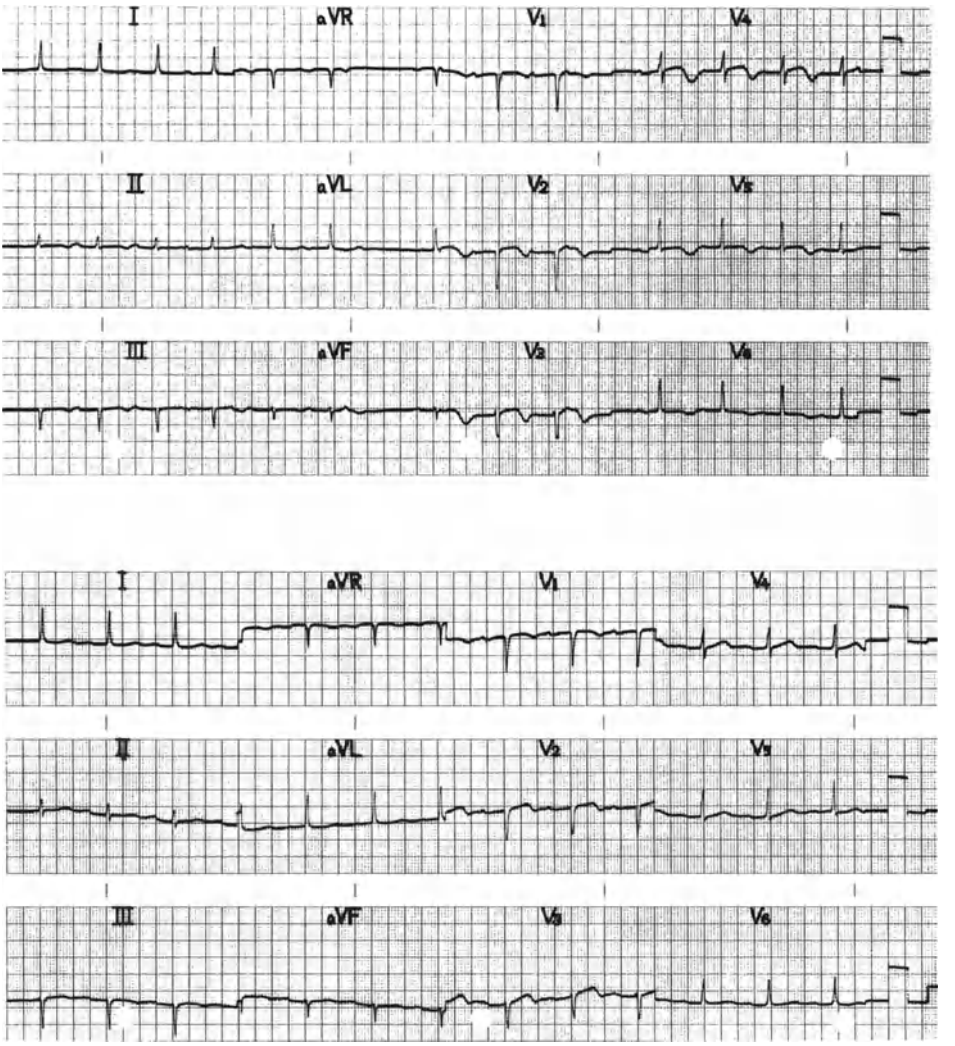

Figure 1. Pseudonormalization of T waves. Panel A: An ECG obtained prior to an episode of chest pain. Note the marked T wave inversions in precordial leads. Also Q waves in V_1 and V_2 indicate previous anteroseptal MI. Panel B: An ECG obtained during an episode of prolonged chest pain. The emergency cardiac catheterization during this episode revealed a total occlusion of the left anterior descending artery. Note the normalization of T wave in precordial leads - "pseudonormalization."

LOCATION OF ACUTE ISCHEMIA AND THE INVOLVED CORONARY ARTERY

The standard 12-lead ECG also contributes information regarding the area of myocardium where the acute ischemic process is occurring. Previous studies (7) have indicated that ST segment depression is much less location specific than QRS changes, ST segment elevation, or T wave changes. The epicardial injury pattern almost always indicates the location of the myocardial involvement, but the subendocardial injury pattern is markedly less specific. Recently, more information has become available through acute intervention studies (8).

Left Anterior Descending Artery Occlusion.

Most patients with an acute MI caused by a total occlusion of the left anterior descending (LAD) manifest classical ST segment elevation in the precordial leads. These changes occur most commonly in lead V_2 (83%) and least commonly in leads V_5 and V_6 (8). ST segment elevation in leads I and aVL occurs less frequently, and is almost always associated with concurrent precordial lead changes. ST segment elevation in the inferiorly oriented leads (II, III, and aVF) may occur when a large LAD extends to the inferior wall. These changes are very infrequent and are always associated with precordial lead ST segment elevation.

Right Coronary Artery Occlusion.

A total occlusion of the right coronary artery usually results in ST segment elevations in leads II, III, and aVF; the most common occurrence is in lead III (59%) (8). It is generally considered that ST segment elevation in leads V_5 and V_6 in the presence of elevation in the inferiorly oriented leads indicates involvement of the apical area. However, this relationship has not been well established. The concomitant ST segment depression in leads V_1-V_3 has been extensively investigated and probably indicates involvement extending laterally into the posterior aspect of the left ventricular free wall.

Right coronary artery occlusion also often results in right ventricular infarction. The standard 12-lead ECG is less able to indicate right than left ventricular involvement. Unless the right ventricle is hypertrophied, it contributes relatively little to activity on the standard 12-lead ECG. However, recently, the diagnostic capability of the ECG for right ventricular involvement has been emphasized. The right precordial leads (V_{3R}-V_{6R}) have been shown to be more sensitive than the standard leads for detection of right ventricular involvement. Erhardt et al. (9) observed frequent incidence of ST elevation in V_{4R} among patients who had autopsy proven right ventricular MI.

Croft et al. (10) examined the right precordial ST segment changes and compared them with radionuclide ventriculography and Technetium^{99} scanning among patients with acute MI. Those with ST segment elevation had right ventricular wall motion abnormality and low right ventricular ejection fraction. ST segment elevation of 0.1 mv or greater in one or more of leads V_{4R} to V_{6R} is both highly sensitive (90%) and specific (91%) in identifying acute right ventricular MI. Right ventricular MI may also cause significant ST segment elevation in the left precordial leads. Geft et al. (11) reported that 5 of 69 patients (7%) who underwent attempted thrombolytic therapy had ST segment elevation in leads V_1-V_5 caused by right coronary occlusion and right ventricular MI. Often, this was not associated with ST segment elevation in the inferiorly oriented leads. These changes would therefore mimic those of acute anterior MI. Some clues to differentiation would be: 1) in those with right ventricular involvement, ST segment elevation would be highest in lead V_1 or V_2 and decrease with more leftward oriented leads; 2) in those with anterior left ventricular involvement, the elevation is usually less prominent in lead V_1 and increases in leads V_2 and V_3. The right precordial leads (V_{4R} to V_{6R}) will be helpful to differentiate these two conditions. An example of the changes in acute right ventricular infarction due to total occlusion of the proximal right coronary artery is shown in Figure 2.

Left Circumflex Artery Occlusion.

Patients with circumflex artery occlusion manifest more variable acute ECG changes when compared with the other vascular supplies. When the left system is dominant (the circumflex supplies the posterior descending artery), the changes may mimic those of right coronary occlusion. When the circumflex is nondominant, only the posterolateral free wall of the left ventricle is involved. These patients may have ST segment elevation in leads I and aVL, elevation in leads V_5 or V_6, or ST segment depression in leads V_1 and V_2. This area of myocardium appears to be more "electrically silent" resulting either in nonspecific changes on ECG or in no changes at all (12).

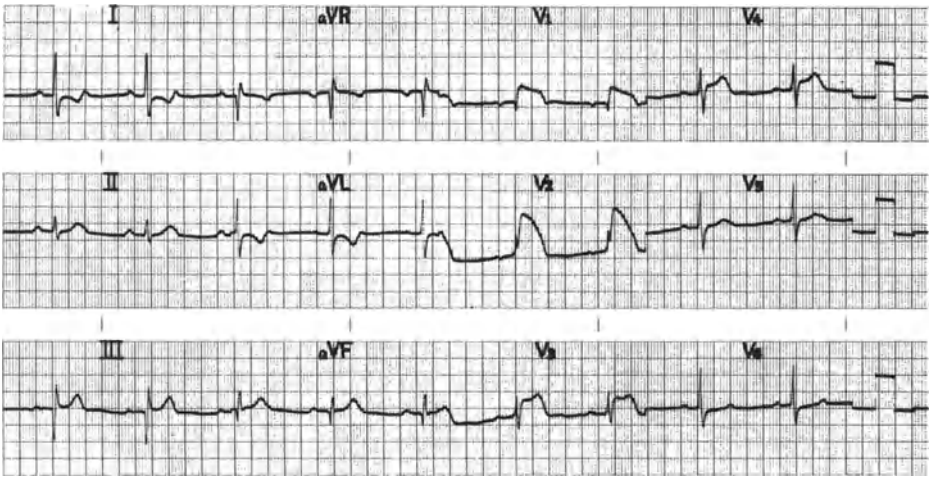

Figure 2. An ECG obtained from a patient with right ventricular MI, initially misdiagnosed as an acute anterior MI. The emergency cardiac catheterization during this episode revealed a total occlusion of the proximal right coronary artery proximal to a right ventricular branch. The left coronary artery contained only insignificant disease. Note marked ST elevation in V_1 to V_3 without any ST elevation in the inferiorly oriented leads (II, III, and aVF). These changes mimic those of acute anterior MI.

PREDICTION OF INFARCT SIZE AND PROGNOSIS

The prediction of infarct size and prognosis from the 12-lead ECG at the time of initial assessment could be very important for individualization of patient management. Various ECG changes are important for such prediction: presence of atrioventricular and intraventricular conduction disturbances, presence of premature beats and tachyarrhythmias, indications of infarct location or locations, and the extent of ST segment and T wave abnormalities in individual leads.

Brush et al. (5) studied the use of the initial ECG to predict in-hospital complications of suspected acute MI among 469 patients. Forty-two (14%) of 302 patients with positive ECG changes (evidence of ischemia, infarction, left ventricular hypertrophy, left bundle branch block or paced rhythm) had "life-threatening" complications (ventricular fibrillation, sustained ventricular tachycardia or heart block). In contrast, only 1 (0.6%) of 167 patients with

negative initial ECG changes had "life-threatening" complications. Other in-hospital complications such as nonsustained ventricular tachycardia, pump failure and recurrent chest pain were 3 to 10 times more frequent among patients with positive ECG changes. In-hospital mortality was 9.9% in patients with positive ECG changes and 0.6% in patients with negative ECG changes. Thus a normal ECG is one of the strong predictors for a very benign hospital course among patients wtih suspected acute MI.

The prediction of the extent of myocardial infarct size by attempts to quantify the amount of jeopardized myocardium at the time of initial assessment would add important information for patient management. The extensiveness of the injured area might be manifested by the number of the leads indicating acute epicardial injury and/or by the amplitude of the ST segment deviation. Generally, in LAD occlusion if ST segment elevation in leads V_1-V_4 is accompanied by elevation in either leads V_5 and V_6 or leads I and aVL there is occlusion of the proximal aspect of a very large vessel. Such assertions are only speculative at present, but current common practice of attempted reperfusion should facilitate correlational studies which will document the capabilities and limitations of the 12-lead ECG.

Many studies have investigated the controversy involving significance of ST segment depression in the precordial leads in the presence of acute inferior epicardial injury. Is the ST segment depression a) the reciprocal of the inferior changes, b) indicative of involvement of the posterolateral wall, or c) indicative of anterior wall ischemia? Studies have considered angiographic, radionuclide, enzymatic, and clinical observations. Croft et al. (13) suggested that ST segment depressions in precordial leads were simple reciprocal changes and therefore not indicative of involvement in other areas. However, both Gibson et al. (14) and Shah et al. (15) demonstrated more extensive inferior left ventricular involvement when precordial ST segment depression was present. There was more involvement of the posterolateral wall, lower left ventricular ejection fraction, higher levels of myocardial specific enzymes, and poorer prognosis. Hlatky et al. (16) confirmed the poor prognosis among patients with these changes and demonstrated that the ST segment depression in precordial leads was an independent predictor of prognosis in a large number of patients with acute inferior MI. Studies have tended to refute the earlier concept that precordial ST segment depression in the presence of inferior MI indicated anterior ischemia or "ischemia at a distance" (17). It is likely that both more extensive left ventricular involvement and reciprocal

change share responsibility for the ST segment depression in the precordial leads.

The amount of ST segment elevation may provide information regarding the extent of myocardium involved. Various factors may alter the degree of the ST segment elevation: the duration of the injury, the amount of the injury, the location of the electrode, and other pre-existing ST segment abnormalities. Many studies have been performed on experimental animals to compare quantitative ECG changes with infarct size, coronary blood flow, and metabolic changes. These have generally indicated (18) good correlations between the extent of the ST segment elevation and independent indicators of the extent of the ischemic process. Studies in man have also been performed to determine the relationship between ST segment changes in precordial maps and infarct size estimated by various methods. Some of these studies (19) have indicated good correlations between the sum of ST segment elevations and eventual infarct size in those with anterior involvement. However, precordial mapping is relatively complex and not readily available during the time required for initial clinical decisions. Lux et al. (20) demonstrated an excellent correlation between changes in six precordial leads and changes in more extensive precordial maps. Nielsen (21) demonstrated the relationship between the degree of ST segment elevation in standard 12-lead ECGs and the prognosis during acute MI. Patients with significant ST elevation had higher incidences of various serious complications and mortality during the acute phase.

The value of observation of the quantitative aspects of acute ST segment change is not yet known. Previous investigators have not had the ability to relate the changes on the ECG to either the coronary artery anatomy or the extent of myocardial dysfunction. Currently, many patients are undergoing acute interventional studies and such correlations should be forthcoming. A continuing limitation is the inability of any available clinical method to accurately measure the size of the eventual amount of infarction which occurs. It would be hoped that use of combinations of available techniques such as QRS complex changes, quantitative enzymatic determinations, or extent of wall motion abnormality might provide such information. Alternatively, information from newer techniques such as nuclear magnetic resonance (see White chapter), rapid CT scanning (see Brundage chapter), or PET scanning (see Goldstein chapter), could provide accurate methods of infarct sizing against which to evaluate the acute electrocardiographic changes.

USE OF THE 12-LEAD ECG TO IDENTIFY A CANDIDATE FOR ACUTE REPERFUSION THERAPY

Recently, more aggressive interventions using thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA) have been used in patients with acute infarction. The decision for the intervention is mainly based on clinical history and the initial 12-lead ECG. When acute intervention is considered, the information from the ECG should be maximally utilized. Unfortunately, the studies are not yet available which would optimally guide the clinician in this process. In general, presence of Q waves or diminution in R waves in precordial leads indicates myocardial necrosis rather than reversible injury. Presence of such changes might indicate that the process of infarction is nearing completion. Therefore, patients with already significant QRS changes would be considered poorer candidates for acute interventions. However, some recent observations have indicated that even QRS changes might be reversed by acute reperfusion (22). The marked ST segment elevation indicating epicardial injury in the absence of QRS changes would suggest that significant areas of myocardium might still be salvaged through reperfusion. However, recent observations have also indicated the prompt occurrence of Q waves at the time of reperfusion (23). Perhaps acute epicardial injury can mask the QRS changes that would otherwise indicate that necrosis had already occurred (Figure 3).

Generally, acute interventions are attempted if the duration of chest pain is less than 6 hours. This is based on experimental studies which indicate that most of the myocardium in jeopardized areas becomes irreversibly damaged following more than 6 hours of total occlusion. However, the onset of chest pain does not necessarily indiate the time of total occlusion. The initial chest pain may have been caused by subtotal stenosis which was then followed by a total occlusion (Figure 4). Also, the pain is often intermittent and it is difficult to identify the precise time of the onset of the pain which led to the acute patient presentation. Also, the presence of collateral flow may alter the progression of the epicardial injury. There may be significant amounts of jeopardized but not yet infarcted muscle remaining after prolonged periods of pain. This might be indicated by electrocardiographic appearance of marked ST segment elevation without new Q wave development.

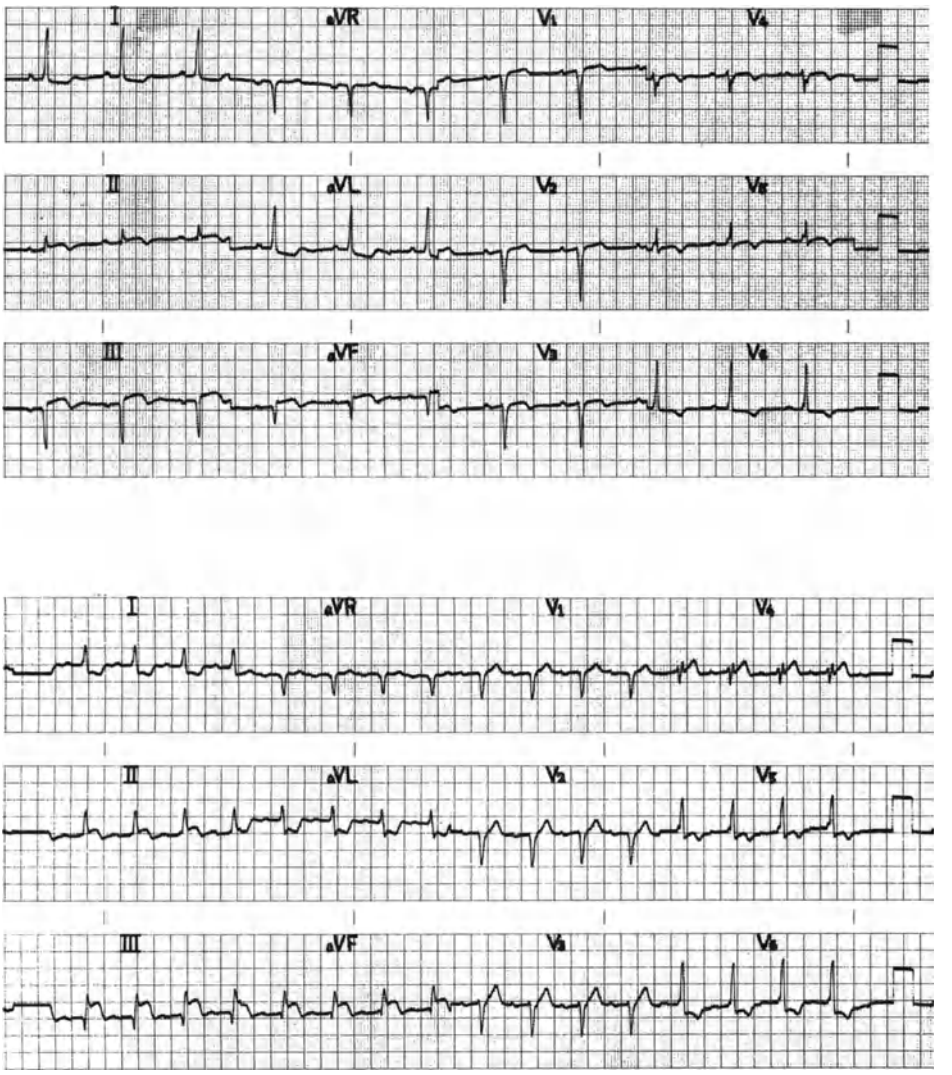

Figure 3. Disappearance of Q waves during significant acute epicardial injury. Panel A: An ECG obtained from a patient who had a recent inferior MI. Note a pathologic Q wave in lead aVF indicating previous inferior MI. Panel B: An ECG obtained from the same patient two days later during a prolonged episode of chest pain. Note the significant difference in Q wave morphology in lead aVF compared with the previous ECG. Only an insignificant Q wave in lead aVF was present during an episode of epicardial injury despite a previously documented significant Q wave.

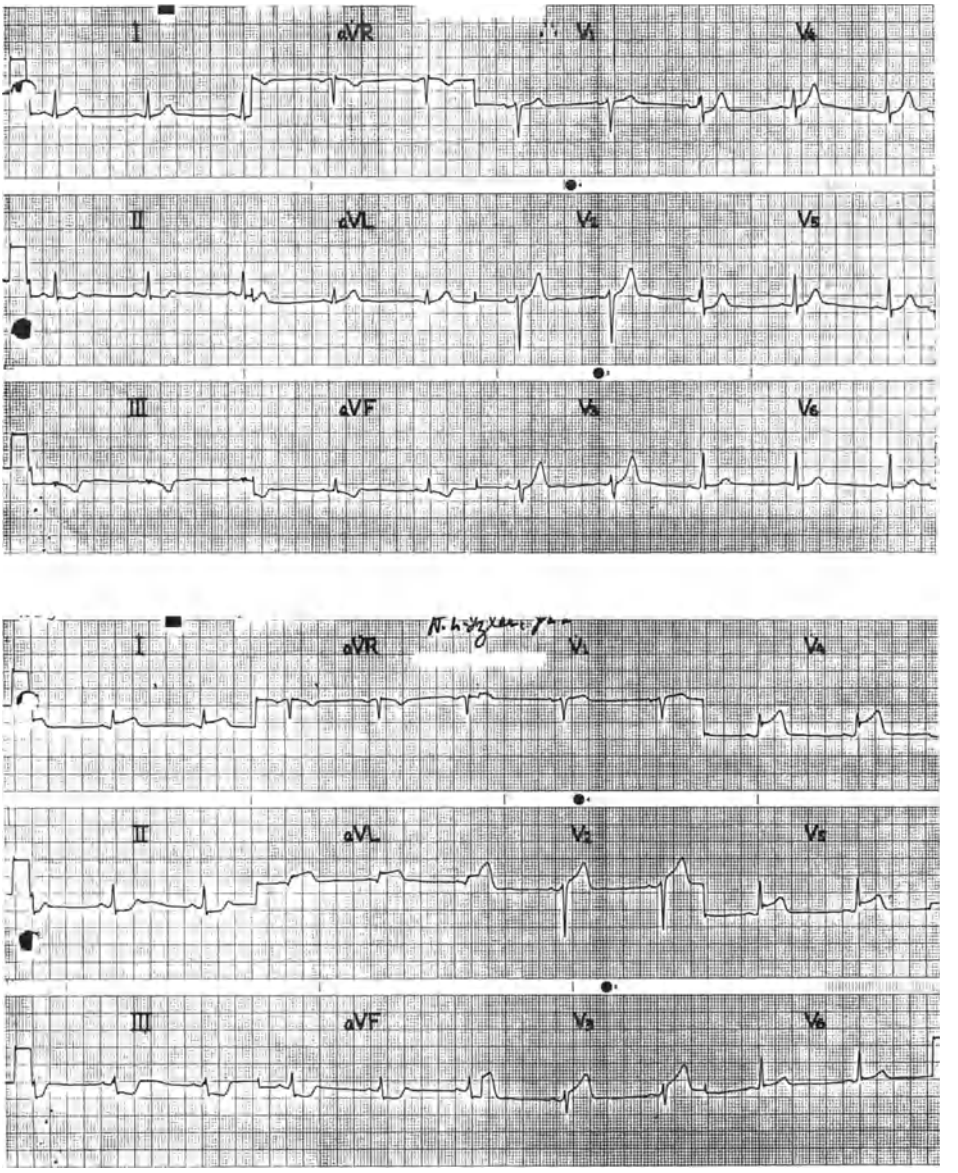

Figure 4. Delayed ST segment changes: an ECG obtained from a patient who had a prolonged episode of chest pain. Panel A: An initial ECG obtained at 30 minutes after the onset of chest pain. Note T wave inversions in II and aVF without significant changes in precordial leads. Panel B: A follow-up ECG obtained one hour later while the patient continued to have chest pain. Note the marked new ST elevations in precordial leads.

The long accepted concept that presence of Q waves indicates irreversible change has been challenged by some recent observations that Q waves may disappear following reperfusion. Blanke et al. (22) showed gradual improvement in R wave size or Q waves in precordial leads following successful reperfusion. Serial ECG changes were studied in patients who had total occlusion of the anterior descending artery. In patients with successful reperfusion by intracoronary streptokinase, significant increases in the sum of R wave amplitudes and decreases in the number of Q waves during hospitalization were observed. In patients with documented total occlusion without attempted reperfusion (conventional treatment), no significant serial changes in R wave amplitudes or Q wave appearance occurred. Such resolution suggests that QRS changes may have been caused by transient absence of electrical activity in the severely injured myocardium. Reperfusion may prevent irreversible damage and lead to reappearance of a normal QRS pattern. In contrast, the marked Q waves which have been observed following acute reperfusion could be "artifact" resulting from the reperfusion process and not from actual myocardial necrosis.

CONCLUSION

The standard 12-lead ECG is a very important tool for the assessment of patients with suspected acute MI. Further information is needed to establish the value of observations of quantitative changes and their relationship to the amount of jeopardized myocardium and to final patient prognosis. In patients receiving acute interventional therapy, a strict protocol for obtaining ECG information should be instituted. Only such careful analysis of serial ECG changes and their relationships to other indicators of both the extent of the amount of initial myocardium in jeopardy and the final myocardium infarcted, can allow optimal use of this inexpensive, easy to obtain, and universally available method.

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3

USE OF ANTIPLATELET AGENTS IN PATIENTS WITH UNSTABLE ANGINA PECTORIS

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INTRODUCTION

Patients with unstable angina pectoris are at high risk of developing acute myocardial infarction (MI). Coronary angiography has revealed that these patients often have significant coronary artery stenosis, with or without a partially occluding thrombus (1,2). Completion of the occlusion by additional thrombosis would likely precipitate an MI (3). Prevention of MI in patients with unstable angina may be accomplished by acute coronary bypass grafting or by percutaneous transluminal coronary angioplasty; however, this is not always possible. Therefore, antithrombotic therapy may have a place in the treatment of patients with threatening MI due to unstable angina.

THROMBUS AND PLATELETS

Platelets have a primary role in hemostasis. Platelets may adhere to the atherosclerotic vessel wall but not to the normal endothelium. Among others, adherent platelets release ADP, S-hydroxytryptamine, platelet factor 4, and thromboxane A_2 (TXA_2), which promote local vascular contraction and further platelet adhesion, thus continuing the cycle of development of a platelet thrombus. Some of these substances also initiate fibrin and thrombin deposition, the clotting mechanism. In the thrombus, red and white blood cells and other blood components are incorporated, depending largely on the rate of blood flow. In the arteries, the thrombus is generally pale, consisting mainly of platelet aggregates with some fibrin.

THE PROSTAGLANDIN BALANCE

Arachidonic acid (AA), a constituent of the phospholipid of cell membranes, is the precursor of major prostaglandins in man (Figure 1). All cells possess in their membranes prostaglandin synthetase (cyclo-oxygenase), which converts AA into unstable cyclic endoperoxides. In turn, these can be converted into prostacyclin (PGI_2), TXA_2 and stable prostaglandins. Platelets

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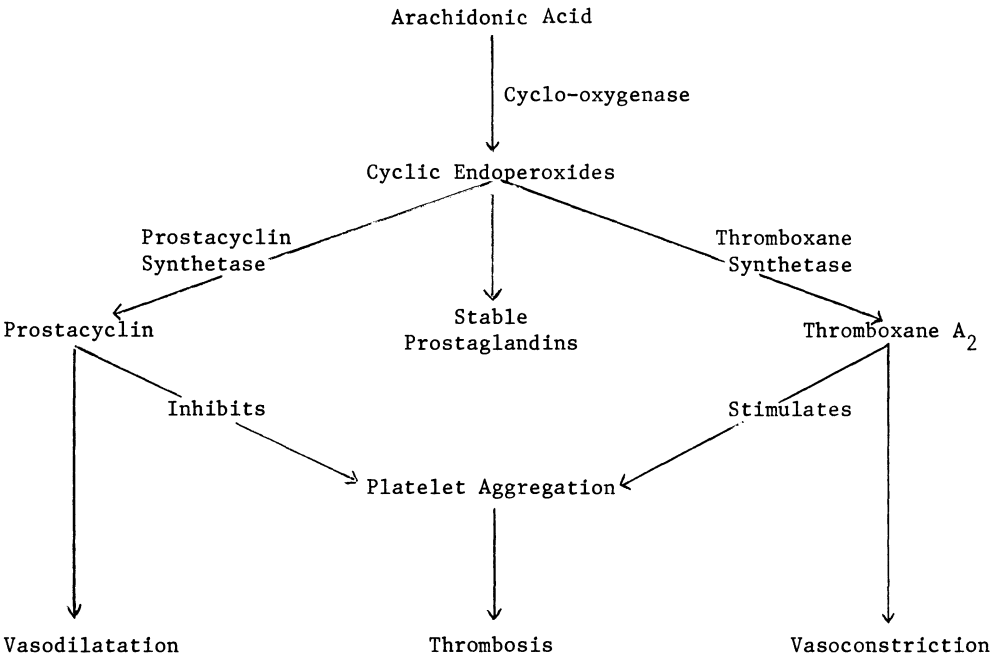

Figure 1. The interrelationships between the various prostaglandins and their effects on both the vessels and platelets are indicated.

convert the endoperoxides mainly into TXA_2 by the enzyme thromboxane synthetase; the vascular endothelium, rich in prostacyclin synthetase, produces mainly PGI_2. TXA_2 is a potent vasoconstrictor and proaggregatory agent. Conversely, prostacyclin has the antagonistic effects of causing both vasodilatation and the dispersement of preformed aggregates, which inhibits platelet aggregation and thrombosis, respectively. Prostacyclin has a half-life of 2 to 3 minutes at body temperature and pH, then spontaneously degrades to 6-ketoprostaglandin $F1_\alpha$ (6-keto-$PGF_{1\alpha}$), a stable and physiologically inert compound. TXA_2 also is rapidly hydrolyzed to the stable, but physiologically inert, thromboxane B_2 (TXB_2). Balance between TXA_2 and PGI_2 is essential for the healthy regulation of vascular tone and platelet homeostasis. An overbalance of TXA_2 would promote platelet aggregation, coronary vasoconstriction, further platelet aggregation and the tendency to thrombus formation. Therefore, efforts altering the balance between PGI_2 and TXA_2 in attempts to prevent platelet aggregation, thrombus formation, or infarction should be a relevant therapeutic approach in patients at risk.

PROSTAGLANDINS IN ISCHEMIC HEART DISEASE

Several studies have shown unfavorable changes in the prostaglandin metabolites, platelet proteins and platelet aggregation in patients with ischemic heart disease. TXB_2 levels are increased in patients with stable angina pectoris at rest (4), during pacing (5), and in exercise-induced chest pain (6). Patients with unstable angina and unprovoked pain seem to have even higher TXB_2 levels (7) and decreased levels of PGI_2 in their blood (8). Levels of 6-keto-$PGF_{1\alpha}$ are normal at rest, but increase less with exercise in patients with angina pectoris than in normal controls (6). The platelet proteins, platelet factor 4 (PF4) and β-thromboglobulin, are increased in venous blood from patients with induced angina attacks (9,10) and in patients with unstable angina pectoris (10,11). Furthermore, patients with either stable or unstable angina have hyper-aggregable platelets (12,13).

Patients admitted to the hospital with acute MIs have increased blood levels of TXA_2 (14), although there is conflicting information concerning the levels of PF4 (15,16). In the very early phase of acute infarction, platelets seem to be hyper-aggregable (17) and, thereafter, become hypo-aggregable (18). This may reflect excessive aggregation during the evolution of the infarct formation.

It is difficult to prove whether the platelet dysfunctions described precede myocardial ischemia or occur secondary to the ischemic event. The documentation of a fresh occlusive thrombus in acute MI suggests that platelets and prostaglandins may have an important primary role. However, if the platelet hyperactivity and TXA_2 release are not the primary phenomena, the presence of the myocardial ischemia may activate platelets and increase TXA_2, which would lead to propagation of the ischemic lesion. Therefore, whether platelet hyperactivity is primary, or occurs secondary to ischemia, platelet dysfunction and TXA_2 release extend and reinforce the ischemic lesion.

ANTIPLATELET THERAPY IN UNSTABLE ANGINA PECTORIS

Antiplatelet therapy as secondary prevention after acute MI has been studied (19,20). Because these studies suggested negative results, antiplatelet therapy has not gained widespread use in such patients. Only a few studies of antiplatelet therapy have been performed in patients with unstable angina pectoris.

Aspirin

Aspirin is probably the first drug recognized to have important platelet-inhibitory effects. Aspirin irreversibly inhibits the enzyme cyclo-oxygenase, thus blocking the synthesis of both the pro-aggregatory TXA_2 and the anti-aggregatory PGI_2. The inhibition of TXA_2 synthesis in platelets lasts for the entire life of the platelets, since the ability of platelets to synthesize proteins is very limited. However, as vascular endothelial cells can synthesize new enzyme, exposure to aspirin renders them unable to synthesize PGI_2 only for several hours. Thus, platelet cyclo-oxygenase may be more sensitive than that of vascular tissue to aspirin and, with appropriate dosing intervals and amounts, aspirin may selectively inhibit platelet TXA_2 production with preservation of some endothelial PGI_2 production (20-22).

The question of aspirin quantity for the prevention of thrombosis remains unclear. It is possible that all studies performed have used an excessive dosage. Eighty mg a day, or 200 mg every three days may be optimal (22,23).

In a multicenter, double blind, placebo-controlled randomized trial of aspirin treatment using 324 mg daily (24), 1266 men with unstable angina were randomized to aspirin or placebo for 3 months. The incidence of acute MI during the study period was 7.8% in the placebo group and 3.5% in the aspirin group ($p < 0.001$). The mortality was 51% lower in the aspirin group (1.6% vs 3.3%), although the difference did not achieve statistical significance ($p = 0.054$). The incidence of either death or acute MI was 10.1% in the placebo compared to 5.0% in the aspirin group ($p = 0.001$). Since aspirin was given in a buffered solution, no difference in gastrointestinal symptoms or signs of blood loss appeared. Thus, of the 625 men taking aspirin for 3 months, an additional 11 survived (95% confidence limits 5-19 men), and 23 more may have avoided nonfatal MI (95% confidence limits 14-33 men). If these results can be confirmed by other studies, this simple and inexpensive treatment may be indicated for the treatment of patients with unstable angina pectoris.

Sulfinpyrazone

Sulfinpyrazone has also been shown to prevent TXA_2 synthesis by inhibition of cyclo-oxygenase. In contrast to the effects of aspirin on platelets, sulfinpyrazone effects are reversible and last only as long as the drug is in the circulation. Sulfinpyrazone is also a much weaker inhibitor of platelet aggregation than is aspirin.

Cairns et al. (25) recently performed a double blind, placebo-controlled, randomized trial of aspirin, 325 mg q.i.d. and/or sulfinpyrazone in 555

patients with unstable angina. The patients were followed for a mean of 19 months. The primary end points were cardiac death or nonfatal acute MI. No difference was seen when the patients were divided into those given and not given sulfinpyrazone. Comparing patients with and without aspirin therapy revealed that the aspirin group had fewer nonfatal MI/cardiac deaths (16, 6%, vs 37, 13%; p = 0.004) and lower total mortality (6, 2%, vs 22, 8%; p = 0.005). Thus, although the dose of aspirin given in this study was most likely excessive, these results support the beneficial effect of treating patients with unstable angina with aspirin.

Dipyridamole

Dipyridamole is an inhibitor of phosphodiesterase, which decreases platelet TXA_2 production and stimulates PGI_2 formation (26,27). Dipyridamole has not been studied in patients with unstable angina pectoris.

Prostacyclin

Prostacyclin is synthesized in the vascular endothelium and is a potent coronary vasodilatator and inhibitor of platelet aggregation. It stimulates adenylate cyclase, and thereby increases cyclic AMP which in turn decreases TXA_2 production. Because prostacyclin is very unstable at the physiological pH, it must be kept at an alkaline pH until administration. Also, its half-life is very short. No controlled studies of prostacyclin in unstable angina have been published. The uncontrolled studies have shown less consistent results than would be expected based on the initial animal studies and studies in normal persons (28-31).

Although pain relief in patients with spontaneous angina has been indicated, most studies fail to show a uniform effect. Prostacyclin is a powerful vasodilator, and increases cardiac output and myocardial oxygen demand. A coronary steal phenomenon may be the explanation for the lack of effect. A controlled study of prostacyclin infusion in patients with acute MI has shown lower serum enzyme estimated infarct size in the treated group (32). However, the conflicting results, the instability of the PGI_2 salt, and the difficulty in administration are major limitations for further investigations.

Dazoxiben

Dazoxiben is a thromboxane synthetase inhibitor which decreases TXA_2 production, and should cause a shift in arachidonic acid metabolism such that synthesis of PGI_2 increases (33). Recently a study was performed comparing 200 mg dazoxiben and 250 mg aspirin in 25 patients with pacing-induced angina (34). The ischemic response, quantified by measuring lactate levels and ST

depression, was significantly reduced after dazoxiben, but not after aspirin (34). Dazoxiben is currently being evaluated in patients with unstable angina pectoris in a multicenter trial.

CONCLUSION

During recent years, much evidence has appeared that suggests a primary thrombus has an important etiologic role in the development of acute MI and sudden death (2,35). Because ischemic heart disease is responsible for millions of deaths every year, there is a great need for drugs which interfere with the development of its fatal manifestations. Drugs which prevent coronary thrombus formation may therefore be clinically important.

Such drugs should primarily be evaluated in high risk groups; that is, in patients with unstable angina pectoris. So far, however, no drug has been fully evaluated. Aspirin is the oldest and most widely studied drug. In addition to the need for further support for the efficacy of aspirin in preventing thrombosis, questions remain concerning its optimal dosage and time of treatment. Theoretically, however, aspirin is not the drug of choice. A new generation of drugs synthesized as platelet suppressive agents is now appearing from the research laboratories. Thus, a more effective strategy against coronary artery thrombosis must await further basic and clinical investigations.

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4

THROMBOLYTIC THERAPY IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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Coronary artery disease is a major public health problem in the United States, resulting in 550,000 deaths annually.(1) A similar number of patients who survive myocardial infarction vary in disease severity and prognosis and require application of a wide variety of therapeutic maneuvers ranging in cost and complexity from risk factor modification through antianginal medication, percutaneous transluminal coronary angioplasty, and coronary artery bypass graft surgery.(2) About a quarter million Americans underwent PTCA or CABG in 1984. It is estimated that approximately 10% of the $1 billion per day expended for health care in the United States is applied to patients with cardiovascular diseases, and patients with myocardial infarction require a substantial part of this large sum.

Acute non-fatal myocardial infarction first described by Herrick in 1912 is a painful, life-threatening syndrome.(3) The pathophysiology of this disorder has been debated since Herrick's initial description.(4) Thrombus superimposed upon high grade coronary arterial narrowing appears to be the direct cause of subsequent ischemic myocardial necrosis in most patients. The size of myocardial infarction is directly related to both in-hospital and subsequent mortality and morbidity.(5) Infarction involving more than 40% of the left ventricular mass often results in death. Patients with large infarctions or multiple small infarctions leading to substantial loss of myocardial pumping capacity as measured by reduced left ventricular global ejection fraction are at high risk of subsequent death and more likely to develop symptoms of congestive heart failure. Nearly one-half of patients currently chosen for

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cardiac transplantation develop congestive heart failure secondary to loss of myocardium due to infarction.

The size of myocardial infarction is not initially fixed but dependent upon myocardial oxygen supply and demand over the next several hours. Over the past decade, careful and extensive laboratory and clinical research has explored whether modification of both supply and/or demand will limit infarct size. Although promising results have issued from the laboratory, there has been no conclusive demonstration of benefit in patients.(5) Limitation of infarct size by early coronary recanalization is at present the most promising means available.(6)

Laboratory investigation of the time course of myocardial necrosis by means of placement and removal of a coronary ligature has revealed that complete coronary occlusion for 20 minutes with subsequent reperfusion results in no discernible myocardial necrosis. Removal of the coronary ligature after six hours results in no myocardial salvage in the dog whatsoever.(7) Thus, the temporal window for myocardial salvage by reperfusion in the dog is less than six hours; the likelihood of salvage of a substantial amount of myocardium decreases rapidly after two hours. The time course of myocardial necrosis in most patients probably follows a similar pattern.

The development of streptokinase and, later, urokinase and the suspected relationship between coronary thrombosis and myocardial infarction led to gargantuan clinical trial efforts in the 1960's and early 1970's to test whether these thrombolytic agents would change the acute or chronic outcome in patients with acute myocardial infarction.(8,9) The observed effect of thrombolytic therapy on subsequent mortality in these trials is mixed with some trials showing a trend in favor of thrombolytic therapy, others a suggestion of toxicity, and most no difference.(10,11) Careful review of the design of these trials reveals an innocence of modern understanding of the pathophysiology of acute infarction. For example, patients were often entered into trials many hours after the point at which myocardial necrosis should have been complete; the rate of infusion of thrombolytic therapy was also leisurely. In addition, concomitant

therapy was often poorly standardized, and, in some cases, thrombolytic therapy was not followed by attempts to sustain recanalization by medical or surgical means.

Rentrop (12), Ganz (13), and others, in the early 1980's, reported series of patients with acute infarction who were immediately taken to the cardiac catheterization laboratory, coronary anatomy defined, and streptokinase delivered by intracoronary administration; coronary recanalization with intracoronary streptokinase was observed in 60 to 90% of patients.(14) Following U.S. Food and Drug Administration approval of intracoronary streptokinase (May 1982) and intracoronary urokinase (October 1983) for selected patients with acute myocardial infarction, substantial numbers of patients have been treated in this fashion in hopes of improving quality and quantity of life. The requirement for specialized personnel and the catheterization laboratory, as well as the discomfort, cost, and delay imposed by intracoronary delivery, has led to a new generation of clinical trials and to rather widespread clinical use of intravenous thrombolytic therapy as a potential means for improving outcome in patients with acute infarction.

Clinical Trial Design Issues

It is clear from many reported series that intracoronary streptokinase and probably urokinase result in recanalization of two-thirds to three-quarters of closed coronary arteries.(14) The likelihood of sustained patency, the effect of coronary recanalization on infarct size and subsequent quality and quantity of life have not been conclusively demonstrated, though a number of carefully executed investigations have revealed promising findings.

There is no presently available validated measure for directly determining the size of myocardial infarction in humans given thrombolytic therapy. Moreover, even with an accurate method of measuring infarct size, and a successful therapy, the effect of reduction in infarct size upon long-term outcome of patients with acute myocardial infarction so treated would have to be charted prior to general acceptance. For example, the risk of subsequent catastrophic reocclusion of a recanalized artery in a convalescent

patient at home out of the reach of immediate expert care would have to be defined. Thus, in the absence of a means to measure infarct size directly, and given the problem of long-term outcome, most investigators have chosen to measure the effect of thrombolytic therapy upon indirect measures of infarct size, such as global or regional left ventricular function and have also gathered survival data.

Intracoronary Thrombolytic Therapy

Design features and outcome of recently published trials of intracoronary thrombolytic therapy are summarized in Table 1.(15-19) The Western Washington Intracoronary Streptokinase Trial randomized 250 patients with chest pain and electrocardiographic evidence of infarction within 12 hours of the onset of chest pain.(15) After definition of coronary anatomy by acute coronary arteriography, patients were treated with intracoronary streptokinase or were returned to the coronary care unit for conventional treatment. The mean interval from onset of chest pain to initiation of intracoronary streptokinase infusion was 4.6 hours. The primary endpoint for which the trial was designed, ventricular function at day 14 compared with ventricular function during the first 48 hours, revealed no difference between treatment and control groups. However, a substantial and statistically significant difference in 30-day mortality was noted; 3.7% of SK treated patients and 11.2% of controls were dead by 30 days. This mortality difference became more impressive by six months with 3.7% of SK treated patients and 14.7% of controls dead by this time. The difference at one year was attenuated and no longer statistically significant, with 8.2% of streptokinase treated patients and 14.7% of controls dead. The lack of ventricular function difference by hospital discharge, the late delivery of therapy when most or all of jeopardized myocardium would have been expected to be already necrotic, coupled with the impressive two-thirds reduction in 30-day mortality, has made interpretation of this study difficult. There is a lack of cohesiveness to these findings, and several other trials of intracoronary streptokinase have been reported which do not confirm these findings.

Rentrop and colleagues randomized 124 patients to conventional coronary care without acute catheterization (31), intracoronary nitroglycerin (30), intracoronary streptokinase (31), and intracoronary streptokinase and nitroglycerin (32).(16) The interval from onset of chest pain to initiation of intracoronary streptokinase infusion averaged 5.9 hours. At 6 months, 21% of streptokinase treated patients were dead, compared with 10% of those not so treated, a result which is close to statistical significance ($p = 0.08$), but which becomes less marked after adjustment for baseline covariates ($p = 0.29$). Paired (Day 0 - Day 10-14) left ventricular ejection fraction data on 47 of the 124 patients revealed a mean increase of 2.1 ejection fraction units in streptokinase treated patients and a decrease in the remainder of 1.4 ejection fraction units. This result is not statistically significant and difficult to interpret, given missing data on 77 or 62% of randomized patients.

Khaja, Anderson, and Leiboff have reported small randomized, controlled trials (40, 50 and 43 patients randomized respectively) which were designed to test the effect of intracoronary streptokinase upon change in left ventricular function between baseline and a convalescent study 10-14 days later.(17-19) The length of time between onset of symptoms and initiation of intracoronary SK infusion differed (5.4, 4, and 4 hours respectively), as did the results. Anderson, in one of the earliest treatment delivery trials, noted a substantial, statistically significant improvement in left ventricular ejection fraction in streptokinase treated patients (net differences of 6.9 to 9.7 ejection fraction units, depending upon correction used for dead patients not having a convalescent value).(18) Ross, who initiated therapy at a mean of 4 hours, and Khaja, who initiated treatment at 5.4 hours, reported no net improvement in left ventricular ejection function.(17,19)

Table 1

REPORTED THROMBOLYTIC TRIALS
(INTRACORONARY)

TRIAL	CONTROL	BLIND	ENTRY (HOURS)	ONSET TO INFUSION (HOURS)	SAMPLE SIZE	MORTALITY T	MORTALITY C	CHANGE IN LVEF CONVALESCENT - ACUTE T	CHANGE IN LVEF CONVALESCENT - ACUTE C
WWIS	Acute Catheterization Followed by CCU Care	Open	≤ 12 Included Subtotal Occlusion	4.6	250	5/134(3.7%) (30-day) 5/134(3.7%) (6 month) 11/134(8.2%) (1 year)	13/116(11.2%)* 17/116(14.7%)* 17/116(14.7%)	+0.01	+0.01
Mt. Sinai	No Catheterization CCU Care	Open	≤ 12 Included Subtotal Occlusion	5.9	124	13/63(21%) (6 month)	6/61(10%)	+0.021	+0.014
Henry Ford/ U. of M.	Intracoronary D5W Platelet-Active Drugs	Double Blind	≤ 6 Only Total	5.4	40	1/20(5%) (Mean F/U 9.6 months)	4/20(20%)	0	-0.01
Utah	No Catheterization CCU Care Platelet-Active Drugs	Open	≤ 4 Included Subtotal	4.0	50	1/24(4%) (in hospital)	4/24(17%)	+0.04	-0.01*
George Washington	Acute Catheterization IC TNG q 15 min X 5	Open	≤ 4 Only Total Occlusion	4.0	43	4/22(18%) (Mean F/U 11 months)	2/18(11%)	-0.03	0
Baylor	No Catheterization (16) I.C. and I.V. TNG (19)	Open	≤ 6 Included Subtotal	5.6	64	4/29(14%)	2/19(11%)TNG 0/16 No Cath.	+0.03	+0.02

* $p \leq 0.05$

All 5 reported randomized controlled trials of intracoronary streptokinase yield one trial with an improvement in left ventricular function (Anderson) and one with a major reduction in mortality (Kennedy). Delivery of therapy in all 5 trials was very late, ranging from 4 to 5.9 hours after chest pain onset because of the requirement for cardiac catheterization. It is quite likely that most of these patients had nearly completed infarcts by the time reperfusion was established an average of 30-60 minutes after initiation of streptokinase infusion. It is difficult to explain a salutary influence upon function or mortality deriving from limitation of infarct size. Perhaps other mechanisms such as the play of chance or infarct healing are important in these results.

The obligatory delay imposed by cardiac catheterization has led to efforts to evaluate systemic administration of thrombolytic agents. Intravenous thrombolytic therapy must effectively recanalize

most closed coronaries and must be delivered very early, probably within 2-4 hours, if significant myocardium is to be salvaged.

Intravenous Thrombolytic Therapy

Intravenous thrombolytic therapy offers the advantage of being widely available, relatively inexpensive, and has the potential for speedy delivery during the very early minutes and hours of acute infarction. A number of relatively large, randomized, controlled trials carried out in the 1960's and 1970's have revealed inconclusive results as noted above.(10,11)

Given the success of recanalization with intracoronary streptokinase, a strategy of high dose streptokinase infusion has been investigated as a means to induce recanalization rapidly.(20-24) Estimates of the proportion of patients with successful recanalization given this short-term, high-dose infusion regimen have varied widely, ranging from 10% to 96%.(14) Recanalization rates noted in case series in which a pre-intervention angiogram was performed ranged from 10% to 62%, averaging 45% over 144 patients. Investigators who did not perform pre-intervention angiography report patency rates from arteriography done several days after high-dose intravenous streptokinase, range from 73% to 96%, with an average of 84% over 289 patients. It is likely that the major difference between these two sets of findings relates to the presence of incomplete obstruction of the infarct related vessel at baseline which has been observed in as many as one-third of patients. The explanation of inconsistent results observed in the many previously reported large, long-term thrombolytic trials may lie in this relatively low recanalization rate, the late delivery of treatment, and perhaps in the lack of sustained coronary patency.

New Thrombolytic Agents

There is a new generation of thrombolytic agents being developed which includes tissue-type plasminogen activator, prourokinase, and acylated streptokinase-plasmin.(6) A theoretical advantage of these agents is activation of plasminogen on the surface of a clot rather than diffuse generation of plasmin noted with streptokinase. One of

these agents, tissue-type plasminogen activator (rt-PA), is now available in sufficient quantities for a clinical trial.(25,26) Collen and colleagues reported a 75% recanalization rate in patients with given intravenous tissue-type plasminogen activator.(27)

Thrombolysis in Myocardial Infarction (TIMI)

The National Heart, Lung, and Blood Institute established the Thrombolysis in Myocardial Infarction, or TIMI, Study Group in 1983. During protocol design, it became apparent that intracoronary thrombolytic therapy requires conditions which make it unattractive or impossible for general use and imposes an unacceptable delay during which much myocardium withers. Thus, TIMI investigators chose to study the effect of intravenous thrombolytic therapy. Since estimates regarding recanalization rates for high-dose, short-term streptokinase varied widely, and since tissue-type plasminogen activator had become available in sufficient quantities for a clinical trial, TIMI investigators chose to conduct TIMI in two phase; Phase I was designed to compare coronary recanalization rates observed 90 minutes after initiation of intravenous infusion of streptokinase or tissue-type plasminogen activator. In 240 patients with acute myocardial infarction and a closed infarct-related coronary artery, 66% of rt-PA treated patients and 36% of SK treated patients were observed to have an open coronary artery 90 minutes after the onset of the infusion.(28) Similar results were observed in an open-label phase performed as a prelude to the randomized Phase I TIMI Trial. Thus, infusion of 80 mg. of rt-PA over three hours opens closed coronary arteries in about two-thirds of patients, while streptokinase 1.5 million units infused over one hour opens closed coronary arteries in about one-third of patients. Tissue-type plasminogen activator given intravenously appears to be as effective as intracoronary streptokinase without the obligatory 1-2 hour delay imposed by catheterization and, thus, may represent a major advance in thrombolytic therapy for patients with acute infarction. A European study with a design similar to TIMI has recently been published and reveals similar results.(29)

Future Directions

A number of extremely large intravenous streptokinase trials are being planned, and several are nearing completion as summarized in Table 2. The protocol details have been gathered by personal communication with the trial leadership and reflect the protocols as constituted in mid 1985.

Table 2

ONGOING TRIALS - THROMBOLYTIC AGENTS
(INTRAVENOUS)

TRIAL	ISAM	WWIS	Oxford-Pilot	Oxford - Full-Scale	GISSI
INVESTIGATOR	R. Schroder Berlin	J. W. Kennedy Seattle	P. Sleight	P. Sleight	G. Tognoni Milan
CENTERS	26 German and Swiss Hospitals	28 Hospitals in Western Washington	10 Hospitals in UK	500!	100
POPULATION	MI Symptoms ECG Changes (ST Elevation) ≤ 75 Years	MI Symptoms ECG Changes (ST Elevation) ≤ 75 Years	MI Symptoms ECG Changes (ST Elevation and Depression)	MI Symptoms ECG Changes	MI Symptoms ECG Changes
ENTRY WINDOW	≤ 6 Hours	≤ 6 Hours	≤ 24 Hours	≤ 24 Hours	≤ 24 Hours
SAMPLE SIZE	860 Initially Revised to 1500	660	600	20,000	12,000
RECRUITMENT	3/82-8/83 Initially Revised-3/82-3/85	11/83-11/86	7/83-7/85	4/85-6/87	1/84-6/85
DRUG/DOSE	SK - 1.5M	SK - 1.5M	SK - 1.5M	SK 1.5M	SK 1.5M
CONTROL	Placebo Heparin and Oral Anticoagulants X 3 wks	Conventional Therapy No Anticoagulants	Placebo Heparin in 1/2 ASA in 1/2	Placebo	Placebo
BLIND	Double Blind	Open	Double Blind - SK and ASA Open - Heparin	Double Blind	Double Blind
ENDPOINT	Total Mortality	14-Day Mortality	ECG Changes	Mortality	Mortality

Schroeder and colleagues have randomized about 1,500 patients to high dose, short-term streptokinase infusion of 1.5 million units over one hour versus a conventionally treated control group; Tognoni and colleagues have randomized 12,000 patients to a similar regimen of streptokinase versus conventionally treated patients. Results from both of these trials and the Oxford Pilot should be available in early 1986. The Western Washington Intravenous Streptokinase Trial and the full-scale Oxford Study will be completed in late 1986 and 1987 respectively. These trials should clarify many questions

surrounding the use of thrombolytic therapy in patients with acute myocardial infarction.

There are two major, unsolved problems which must be resolved prior to general application of thrombolytic therapy for patients with acute infarction. The first relates to whether it is possible to recanalize closed coronary arteries in practical circumstances sufficiently early to limit infarct size. Given an affirmative answer to this question, a second, perhaps more important, question follows, whether a recanalized coronary artery with stunned but not yet necrotic myocardium dependent on sustained patency can be kept open by medical means such as antiplatelet drugs. It is apparent that in a portion of patients recanalized coronary arteries will close, most likely those with residual high-grade lesions. Given myocardial salvage, the definition and selection of patients requiring mechanical therapy such as PTCA or bypass surgery to sustain patency and salvaged myocardium will be most important.

Intravenous thrombolytic therapy for patients with acute myocardial infarction may be a major advance in the treatment of patients with acute myocardial infarction. General use of this therapy awaits careful definition of subgroups most likely to benefit, clarification of potential toxicity or side effects of effective intravenous thrombolytic drugs, and definition of subgroups requiring appropriate concomitant therapies such as PTCA or bypass surgery in the hours and days following thrombolytic therapy.

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5

NOVEL THROMBOLYTIC DRUGS

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INTRODUCTION

The demonstration by Rentrop in 1979 (1) of the feasibility of intracoronary thrombolysis and by DeWood in 1980 (2) of a high incidence of complete coronary occlusion early in the course of acute transmural myocardial infarction produced a surge of interest in thrombolytic drugs. Streptokinase and Urokinase have been widely available for years and will not be discussed here. Major efforts have been focused in the past five years in developing thrombolytic drugs which have a greater specificity for the fibrin thrombus than for normal coagulation proteins. Such drugs might produce thrombolysis without systemic fibrinogen breakdown, or clot-specific lysis, reducing susceptibility to iatrogenic hemorrhagic complications.

Biology of Fibrinolysis (3)

The fibrinolytic system, which participates in the physiologic dissolution of clots and which may be exploited for more rapid pharmacologic thrombolysis, centers around the conversion of a proenzyme, plasminogen, to the active enzyme plasmin. Plasmin is a non-specific protease and will degrade not only the fibrin thrombus, but also fibrinogen, Factor V and Factor VIII producing a bleeding diathesis secondary to coagulation factor depletion and the anticoagulant properties of fibrinogen degradation products (FDPs). Extensive conversion of plasminogen to plasmin overwhelms the (plasmin) inhibitory proteins (α_2-antiplasmin, α_2-macroglobulin) and a systemic (proteo)lytic state is produced. The new thrombolytic drugs under development seek to localize the generation of plasmin to the thrombus by modification of existing compounds or by exploitation of pharmacologic doses of physiologically more specific proteins.

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Acyl-Enzymes

The active site of plasmin or plasminogen can be acylated with a number of different side chains which render the plasmin(ogen) molecules catalytically inert thus unable to degrade systemic plasma proteins. The acyl enzymes may still bind to a fibrin clot because the lysine binding sites of the plasmin(ogen) are discrete from the catalytic site. The fibrin bound acyl-enzyme might then undergo slow deacylation at the fibrin clot yielding a locally active enzyme with clot specific fibrinolysis (4). A number of compounds were prepared based on known deacylation half-lives and some understanding of the kinetics of fibrin binding of plasminogen and α_2-antiplasmin neutralization of free plasmin. In a rabbit model it was demonstrated that these acyl-enzymes could induce extensive thrombolysis (based on liberation of labeled fibrinogen from a clot) with minimal fibrinogen breakdown (4,5). BRL 26921, a p-anisoyl human plasminogen-streptokinase complex proved to be the most attractive of the early derivatives studied. In studies in rabbit and dog venous thrombosis models significant thrombolysis was achieved at doses that did not deplete fibrinogen or α_2-antiplasmin (4-6). Others, however, using closed-system experiments with human plasma in vitro questioned whether BRL 26921 was indeed fibrinolytic without being fibrinogenolytic (7).

Walker et. al. (8) used BRL 26921 in doses ranging from 5 to 25 mg in 12 patients with acute myocardial infarction. The complex was well tolerated but in contrast to the preclinical studies, measurements of fibrinogen, plasminogen, α_2-antiplasmin and fibrinogen degradation products demonstrated systemic fibrinolytic activation, which was variable but profound in some.

Marder et. al. (9) reported a dose response study of BRL 26921 in coronary artery thrombosis which indicated that a dose of 30 mg administered intravenously over two to four minutes was effective in recanalizing the majority of occluded vessels, but systemic fibrinolytic activation was the rule.

Other studies (10,11) indicated that BRL 26921 was an effective thrombolytic but aside from the practical advantage of bolus administration, it appears to offer no significant advantage over streptokinase with regard to clot selectivity.

Other acylated modifications of the active site of plasmin(ogen) are under investigation (12), but no product has yet emerged into clinical trial with the desired profile of thrombolysis without fibrinogenolysis.

Pro-Urokinase

A single chain 55,000 molecular weight (MW) form of urokinase was purified from human urine (13). Subsequently a transformed human kidney cell line was identified which produced sufficient quantities of the material, called pro-urokinase (Pro-UK), for clinical evaluation (14). Pro-UK proved to be a zymogen precursor of the 55,000 MW two-chain urokinase.

A mechanism of action for Pro-UK has been proposed. Plasmin can activate Pro-UK to urokinase. In blood traces of plasmin are rapidly inactivated by α_2-antiplasmin, thus preventing the activation of Pro-UK. In contrast, at the fibrin clot plasmin which is formed is bound to fibrin (by its lysine binding site) and is relatively unavailable to α_2-antiplasmin neutralization which occurs at the same lysine binding site. The localized plasmin can convert Pro-UK to urokinase which in turn locally induces fibrinolysis. Details of the nature of the clot specificity of Pro-UK remain to be elucidated, both with regard to mechanism and dose dependence.

Pro-UK incubated in plasma without a clot causes no fibrinogenolysis at doses which, in the presence of a clot, are thrombolytic. Urokinase in contrast causes fibrinogenolysis whether or not a clot is present when incubated at concentrations that cause clot lysis comparable to that seen with Pro-UK.

When clot lysis experiments are performed in a plasma-free buffer, Pro-UK produces plasminogen activation indistinguishable from urokinase suggesting that plasma may contain inhibitors of Pro-UK, in addition to inhibitors of plasmin.

Since greater concentrations of Pro-UK than needed for clot lysis, when studied in the plasma clot lysis model, produce fibrinogen degradation, it is possible that pharmacologic doses of Pro-UK may cause systemic plasminogen activation.

In vivo experiments performed with embolized clots in rabbits and dogs demonstrated that appropriate dosages and regimens could be defined so that significant thrombolysis (as measured by release of radiolabeled fibrinogen) could be obtained with minimal fibrinogenolysis. The time to 100 percent lysis as measured by release of radiolabeled fibrinogen in the dogs was on the order of 5-6 hours.

Studies have been performed with a recombinant form of Pro-UK both in vitro and in vivo (15). The major difference between the recombinant and tissue culture Pro-UK is the glycosylation which is absent in the former. Comparisons were made among recombinant urokinase, recombinant Pro-UK and tissue plasminogen activator (derived from melanoma cells). The studies suggested that both with regard to potency (as a fibrinolytic) and clot-specificity that recombinant Pro-UK was superior to recombinant urokinase and inferior to t-PA.

There have been no reported clinical trials of Pro-UK in myocardial infarction, venous thrombosis or pulmonary embolism to date.

Tissue-Type Plasminogen Activator

Tissue-type Plasminogen Activator (t-PA) has been partially purified from uterine tissue and in much larger quantities more completely purified from the culture fluid of a stable melanoma cell line (16,17). It is a serine protease with a molecular weight of approximatley 65,000. It may exist as a one-chain form or upon limited plasmic action become a two-chain protein linked by one bisulfide bond. The one-chain and two-chain forms have virtually the same fibrinolytic and plasminogen activating properties (18). The one-chain form is likely converted at the fibrin surface to the two-chain form. In addition to heterogeneity related to "chainedness", there appears to be heterogeneity with regard to glycosylation of the protein as well, with one form being somewhat more glycosylated than the other, although again the biologic activities are indistinguishable (19).

t-PA is a poor enzyme in the absence of fibrin, but fibrin markedly enhances the activation of plasminogen to plasmin by t-PA. Thus in plasma circulating t-PA does not convert significant amounts of plasminogen to plasmin; at the clot site however, substantial amounts of fibrin bound

plasmin (relatively unavailable to α_2-antiplasmin) are generated resulting in thrombolysis (20). It is however reasonable to expect that pharmacologic doses of t-PA might cause free plasminogen activation depending on the plasma concentration of the t-PA and duration of exposure to it (21).

t-PA from "natural" sources is quite scarce but techniques of molecular biology and recombinant DNA technology have allowed the production of a recombinant t-PA (rt-PA) which is biologically indistinguishable from "natural" t-PA (19). This t-PA has been used in a variety of preclinical models including rabbit jugular vein thrombosis (19), canine femoral vein thrombosis (22), and canine (23,24) and primate coronary thrombosis (25). These studies have demonstrated a number of salient points: a) rt-PA can reliably induce thrombolysis without significant fibrinogenolysis (19,23-25); b) early thrombolysis can salvage jeopardized myocardium (24); c) the presence of rt-PA in pharmacologic concentrations in plasma can produce an artifact in the measurement of fibrinogen and fibrinogen degradation products (24).

The half-life of rt-PA is quite short, on the order of five to ten minutes in patients in whom it has been measured (26), confirming results of pre-clinical studies (19). The peak concentration of t-PA in plasma following rt-PA therapy for acute coronary occlusion is on the order of several thousand nanograms/ml of plasma. Resting t-PA blood levels are 2-5 ng/ml. Therapy with rt-PA thus produces a thousandfold increase in rt-PA concentration and this excess may, if present for sufficient duration, produce a loss in the clot-selectivity with some fibrinogen degradation ensuing (21).

Clinical trials with rt-PA in myocardial infarction have progressed rapidly. The first reported study demonstrated that 40-60 mg of rt-PA infused over 60-120 minutes intravenously could elicit angiographically proven thrombolysis in 80 percent of cases (27,28). Fibrinogen in rt-PA treated patients was generally spared although 15 percent of patients showed changes in coagulation studies suggesting some degree of systemic fibrinogenolysis. A subsequent study of 45 patients by the National Heart, Lung and Blood Institute Thrombolysis in Myocardial Infarction (NHLBI TIMI) investigators using 80 mg of rt-PA over three hours confirmed the efficacy seen in the first study, estimated a clinical reocclusion rate

of 20 percent and found a fibrinogen decrease of 25-30 percent consistent with what might be expected from a higher dose and longer duration of therapy (29).

A double-blind randomized trial conducted by the NHLBI (TIMI) comparing intravenous rt-PA to intravenous streptokinase demonstrated that rt-PA was statistically significantly superior to streptokinase ($p < 0.001$) in recanalizing angiographically proven complete coronary occlusion within 90 minutes (30). A randomized trial conducted in Europe comparing rt-PA and streptokinase gave comparable results and demonstrated that rt-PA was significantly more fibrinogen sparing than streptokinase (31). Nevertheless, the doses of rt-PA administered in the NHLBI (80 mg over three hours) and European (0.75 mg/kg over 90 minutes) trials produced a 30-50 percent decrease of fibrinogen from baseline.

Conclusion

Thrombolytic drugs offer the opportunity for relatively rapid restoration of blood flow to ischemic myocardium. A relatively high success rate when the intravenous route is used makes this mode of therapy widely available. Means of preventing coronary reocclusion must be developed. Subtleties in doses and durations of drug administration must be understood. Among the new thrombolytic drugs rt-PA appears to most approximate the goal of reliable thrombolysis with reduced fibrinogenolysis. It is likely that further research will see the development of even more potent, perhaps more specific thrombolytics. Concurrent efforts with the early application of coronary angioplasty following intravenous thrombolytic therapy will likely lead to clear and convincing demonstration of infarct size reduction, and possibly improvements in mortality as well.

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6

ACUTE INTERVENTIONAL CARDIAC CATHETERIZATION

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In the past, cardiac catheterization has been used primarily as a method for providing diagnostic information in patients with cardiac disease. Recently, it has become clear that these same techniques can be modified to allow direct therapeutic intervention for the definitive treatment of cardiac disorders. Since the original description of percutaneous transluminal coronary angioplasty (PTCA) in 1977 by Andreas Gruentzig, the technique has become well recognized as a safe and effective treatment for selected patients with single or multivessel coronary artery disease. The term interventional cardiac catheterization is now used to describe a variety of direct therapeutic procedures performed with catheterization techniques. Yet PTCA is by far the most common application of interventional cardiac catheterization. When PTCA was first described, it was applied only to patients who were in stable condition without evidence of myocardial infarction. In recent years however, several investigators have begun to apply these same techniques on a emergency basis on patients with acute myocardial infarction (1-3).

Salvage of jeopardized myocardium during an acute myocardial infarction has been the subject of extensive investigation in recent years. Much of this interest stems from evidence (4,5) indicating that infarct size is a major determinate of both early and late morbidity or mortality. Early clinical studies (6,7) were directed at reducing myocardial oxygen demand during acute myocardial infarction to limit infarct size. These attempts met with little success because of the inability to restore adequate blood flow to the ischemic region.

Experimental studies in dogs have shown that reperfusion of an occluded coronary artery can effectively reduce infarct size in the region of the jeopardized myocardium. Reimer, et al (8,9) demonstrated the area of necrosis begins in the subendocardium and expands outward

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toward the epicardium. Within three hours of occlusion the area of necrosis involves approximately two-thirds of the jeopardized myocardium and by six hours myocardial necrosis is essentially complete in the area served by the occluded vessel. Coronary reperfusion within forty minutes of coronary occlusion resulted in major salvage of the ischemic myocardium and the percentage of salvage decreased as the period of ischemia continued toward six hours. Experimental studies have also documented functional improvement after reperfusion within the borders of jeopardized myocardium. Theroux, et al (10) studied segmental function using ultrasonic crystals in awake dogs following a two hour temporary occlusion. These investigators show that there is a delayed functional improvement after two to four weeks at the center and even greater improvement at the margins of the ischemic zone. Puri (11) found a 60% recovery of segmental function in dogs two weeks after a three hour occlusion.

Recently several studies have shown that coronary recanalization can be accomplished in a majority of patients with acute myocardial infarction by the use of intracoronary streptokinase (12-16). Initial reports in 1976 by Chazov, et al (17) and in 1979 by Rentrop, et al (18) introduced the concept of clinical reperfusion of acute infarcts in man using intracoronary thrombolytic agents. Since that time the use of thrombolytic agents alone or in combination with PTCA for the treatment of acute myocardial infarction has been extensively investigated. The ability to salvage significant amounts of jeopardized myocardium using this technique, however, has only recently been established. Most clinical studies have relied on analysis of the global left ventricular ejection fraction to assess myocardial function following reperfusion. However, the global ejection fraction represents an average of the contractile performance of all segments of the left ventricular myocardium. Although diminished contractile performance in the ischemic area may be reflected in a diminished global ejection fraction, early hyperdynamic compensatory changes in the uninvolved regions could influence ejection fractions in the opposite direction. If a significant improvement occurred in the contractile function of the jeopardized region following recovery of the reperfused myocardium, it is likely that the hyperdynamic compensatory wall motion of the uninfarcted myocardium would return toward normal. This could result in an unchanged or even

decreased global ejection fraction following reperfusion despite significant functional improvement in the region of the jeopardized myocardium.

In a previous study from our laboratory, 24 consecutive patients with acute myocardial infarction were treated with intracoronary streptokinase within six hours of the onset of chest pain (19). Biplane left ventriculograms were obtained acutely, at 24 hours and at one week following reperfusion. Regional wall motion analysis was performed using a quantitative radial axis technique developed in our laboratory (20). Results from infarct patients were compared with normal values for percent radial shortening in each of 23 radial axes derived from 58 normal patients (21). Abnormal radial shortening in this study group was defined quantitatively as percent shortening greater than two standard deviations below the normal mean.

Fifteen patients (62%) were reperfused within six hours of the onset of symptoms. Figure 1 shows results of patients in all three studies who were successfully reperfused. Panel A shows those patients who demonstrated a greater than 5% increase in global ejection fraction at the time of the one week restudy. Panel B shows those patients who were successfully reperfused but showed no improvement in ejection fraction. Each patient who was successfully reperfused showed a delayed but significant regional functional improvement in the jeopardized myocardium regardless of the effect on the overall global ejection fraction. Most patients who were reperfused returned to the low normal range of regional function following reperfusion. Patients who failed to demonstrate significant improvement in ejection fraction showed a significant decrease in the initial hyperdynamic wall motion of the uninvolved normal myocardium between the acute and chronic studies.

In contrast, Figure 2 shows the results in patients who were not initially reperfused. None of these patients showed improvement in either the jeopardized myocardium or the overall ejection fraction despite the presence of late recanalization at 24 hours in most patients. These data illustrate the complexity of evaluating the effects of reperfusion therapy in acute myocardial infarction. Several days or more may be required for transiently ischemic myocardium to regain function. Meanwhile, compensation by nonischemic myocardium may invalidate global measurements for estimating either damage or recovery. Despite the fact

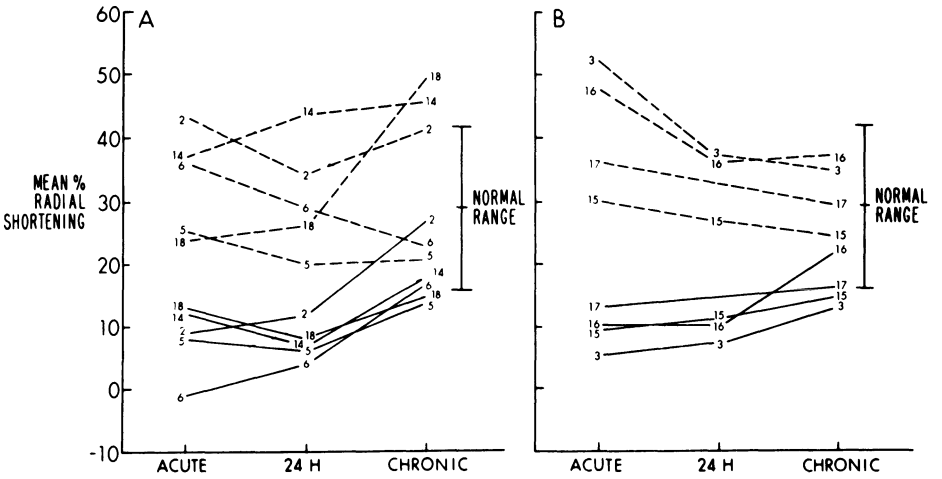

Fig. 1. A) Percent radial shortening (RS) in all patients with acute and chronic catheterization studies who were initially reperfused and who showed a significant (greater than 5%) improvement in angiographic ejection fraction between the acute and chronic study. Changes in the %RS in the jeopardized region are shown using solid lines while changes in the compensatory region are shown using interrupted lines. The normal range (mean $\pm$ 2SD) for %RS in 58 normal patients is shown on the right. B) %RS in patients with acute and chronic catheterization studies who were initially reperfused and who showed no change or a decrease in the ejection fraction between the acute and chronic studies.

that intracoronary streptokinase may improve regional function in patients who are successfully reperfused, two major limitations of thrombolytic therapy alone for coronary reperfusion remain. First, there is a relatively low reperfusion rate (62%). Although intravenous streptokinase therapy has become quite popular, the incidence of successful persistent reperfusion may be even lower than intracoronary

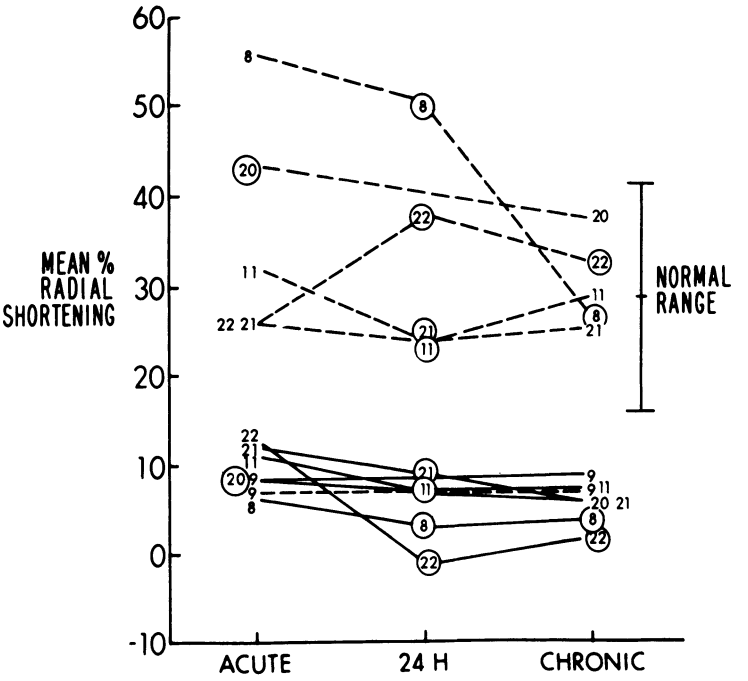

Fig. 2. Percent RS in all patients with acute and chronic catheterization studies who were not reperfused during the acute study or who later reoccluded after initial recanalization. A circle around the patient number indicates that the infarct-related vessel was open at the end of that study. Changes in the %RS in the jeopardized region are shown using solid lines while changes in the compensatory region are shown using interrupted lines.

streptokinase. The results of the recent Thrombolysis in Myocardial Infarction (TIMI) trial (22) showed that only one-third of patients who received high dose intravenous streptokinase therapy showed persistent reperfusion at catheterization. In addition, successful reperfusion with intravenous or intracoronary streptokinase does not affect the underlying atheromatous obstruction. The residual stenosis following intracoronary streptokinase among the patients described above was 85%. This degree of

stenosis may well be flow-limiting at rest and is frequently associated with early reclosure after a successful initial reperfusion. On the basis of these limitations, we and others have applied immediate PTCA techniques for the emergency management of patients with acute myocardial infarction (1-3). At the present time, 44% of the patients undergoing PTCA at Duke University Medical Center are within six hours of the onset of acute myocardial infarction. The protocol presently used in our laboratory includes a combination of thrombolytic therapy and PTCA.

Patients with acute myocardial infarction documented by a typical clinical pain syndrome and persistent ST segment elevation in two or more leads are considered candidates for the reperfusion protocol. In patients referred from outside hospitals, helicopter transport service has become a major adjunct for the safe and rapid transport of patients with acute myocardial infarction. An infusion of 1.5 million units of intravenous streptokinase is started at the local hospital or on the helicopter if there is no contraindication to thrombolytic therapy. Each patient is treated with lidocaine prior to transport. Patients with acute myocardial infarction of less than six hours duration before reaching the Interventional Cardiac Catheterization Laboratory are considered candidates for the protocol. However, patients who have persistent ST segment elevation and pain between six and eighteen hours following the onset of discomfort may also be considered as potential candidates.

The patient is prepped and draped in the usual manner. An 8 French right femoral arterial and 6 French right venous sheath are inserted. Each patient undergoes left venticulography prior to coronary arteriography. Following completion of the ventriculogram, the uninvolved coronary artery is injected first to assess the degree of collateral flow to the obstructed vessel. This catheter is then exchanged for the opposite coronary catheter to cannulate the involved coronary artery. Following an injection of intracoronary nitroglycerin, a repeat cineangiogram is performed.

If there is total occlusion, intracoronary infusion of 300,000 units of streptokinase may be started. If this is ineffective in reestablishing flow in five to ten minutes, the vessel is crossed directly with an angioplasty guidewire and catheter. Despite the liberal use of streptokinase in patients transported to the Interventional

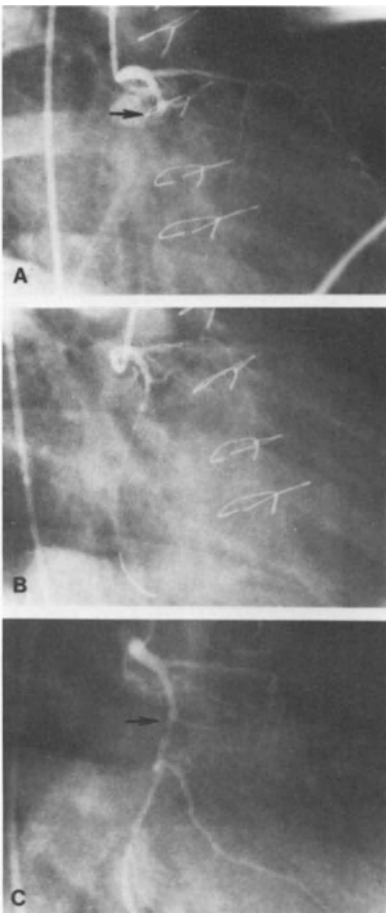

Fig. 3. A) Right anterior oblique view of a totally occluded left circumflex artery (arrow) in a patient with an acute myocardial infarction. B) PTCA guidewire across the total occlusion in the distal left circumflex with the balloon catheter positioned at the site of the occlusion. C) After PTCA, flow to the distal left circumflex is restored with only a minimal residual stenosis at the site of the previous occlusion (arrow).

Cardiac Catheterization Laboratory, 52% have total obstruction at the time of initial coronary arteriography. Immediate angioplasty is performed in all patients with acute myocardial infarction if there is greater than 75% luminal diameter narrowing following an infusion of streptokinase. Fifty-two percent of patients have complete obstruction of the coronary artery at the time of PTCA. Despite this, a PTCA guidewire and balloon catheter are able to cross the blind obstruction in 99% of cases (see Figure 3).

Among 50 patients who were first treated with this protocol, one patient died during the procedure. The overall in-hospital mortality rate was 10%. The overall hospital mortality among the patients in the streptokinase study (19) was 17%.

Persistent reperfusion rate among patients treated with both steptokinase and PTCA was 96% compared with 62% in the intracoronary streptokinase study. The mean residual stenosis in the patients successfully treated with streptokinase alone was 86%. The mean residual stenosis among the patients treated with combined thrombolytic therapy and PTCA was 34%. At the present time, further studies are underway to evaluate long-term regional and global left ventricular performance in patients treated with both thrombolytic therapy and PTCA.

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7

THE USE OF BETA-BLOCKERS IN THE ACUTE PHASE OF MYOCARDIAL INFARCTION

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In the early hours following a coronary attack, some 30% to 50% of subjects die from ventricular fibrillation. For the survivors who reach the hospital, the amount of viable myocardium that remains is an important determinant of short and long term mortality and morbidity. Patients with large areas of infarction tend (especially if there has been previous damage) to demonstrate poor left ventricular function and to develop cardiogenic shock, late ventricular arrhythmias, or secondary ventricular fibrillation. Although coronary care units may well have considerably decreased in-hospital mortality from arrhythmias, there has been little reduction in hospital deaths from the other principal causes, such as reinfarction, heart failure, or cardiogenic shock.

Consequently efforts at preventing even a small proportion of the early deaths either by preventing ventricular fibrillation or by reducing the extent of myocardial damage are likely to be worthwhile, especially if such treatments are simple and widely practicable. A number of pharmacological interventions have been shown to be useful in experimental infarction but few have been of proven clinical efficacy. The group of beta-adrenoceptor blocking agents have been the subject of intensive experimental and clinical investigation in myocardial infarction (MI) since 1965. In experimental MI, a variety of beta-blockers have been shown to reduce the extent of myocardial damage measured both directly at post-mortem and indirectly by enzyme or ECG indices of cell necrosis.[1] In addition, pre-treatment of animals

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with beta-blockers reduces the incidence of ventricular fibrillation following coronary artery ligation.[2] In this chapter, I shall not deal with the effect of beta-blockers in experimental (MI) as they have been extensively reviewed elsewhere; instead, I shall summarize the evidence on the use of short term beta-blocker treatment instituted in the early hours of MI with respect to their potentially beneficial effects on infarct size, arrhythmias, reinfarction and mortality; and any adverse effects from all available randomized trials on a total of about 30,000 patients.

THE NEED TO DIFFERENTIATE BETWEEN INITIATION OF TREATMENT ORALLY OR INTRAVENOUSLY IN THE EARLY HOURS OF MYOCARDIAL INFARCTION

Although the process of infarction during which ischemic myocardium progresses to necrotic tissue is thought to typically spread out over a period of several hours from the onset of pain, most of this damage is likely to occur in the first few hours--except, of course, for patients who suffer reinfarction. About 50% of ECG signs of necrosis (e.g. Q wave development) is complete within 6 hours, 75% by 12 hours, and nearly all complete by 18 to 24 hours after the onset of pain.[3] Similarly, dangerous ventricular arrhythmias such as ventricular fibrillation (VF) are common only in the early hours, and their frequency then decreases rapidly with the passage of time.[4] Consequently, a critical period during which beta-blockade should be tested is the first few hours after chest pain. This can be achieved only with an initial intravenous (IV) dose, however, because the use of purely oral treatment leads to a considerable delay in achieving full blockade. Figure 1 suggests that adequate beta blockade is not usually achieved until about 12 hours after the administration of an oral betablocker, such as atenolol to patients with acute MI. By contrast, if an initial IV dose is given prior to oral medication, within 15 minutes there is a marked and sustained reduction in heart rate. Further, in some of the trials of purely oral treatment, many patients were not entered until 24, 48, or even 72 hours after the onset of chest pain, at which times myocardial damage is largely complete and

the incidence of ventricular arrhythmias has spontaneously decreased. Both individually and collectively, therefore, these randomized trials, where treatment was started orally, provide little useful information about the effects of early beta-blockade on mortality, on arrhythmias, or even on the limitation of infarct size in humans. Such effects, therefore, can be assessed satisfactorily only by adequate-sized, randomized trials of early intravenous beta-blockade.

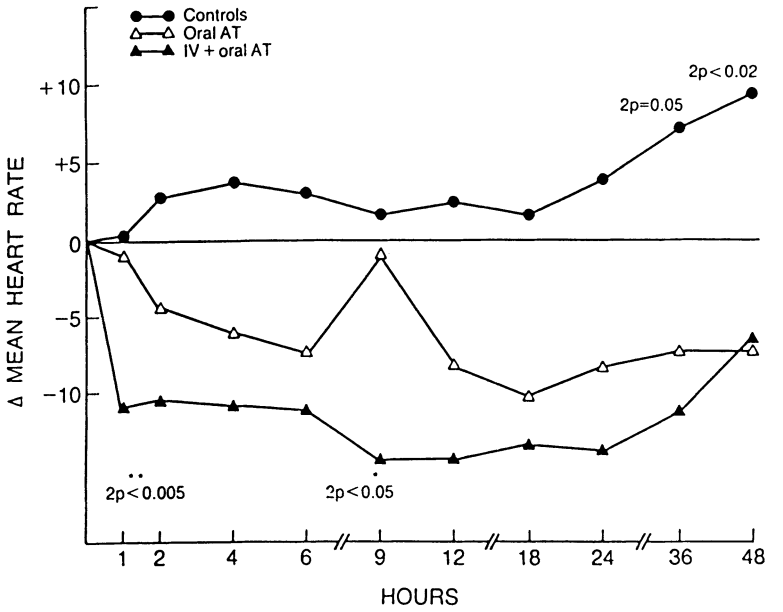

Figure 1 demonstrates the change in heart rate in patients randomized to receive placebo, oral atenolol or intravenous atenolol in patients with suspected acute MI. The reduction in HR is quickest and most marked with intravenous atenolol and much slower with oral treatment (Reproduced from Beta-Adrenergic blockade in Acute Myocardial infarction, Yusuf S, D.Phil thesis 1980, University of Oxford)

TRIALS OF IV USE OF BETA-BLOCKERS IN ACUTE MI

Early IV beta-blockade might affect infarct size, arrhythmias, reinfarction chest pain, and even mortality; these will be discussed separately. The design of all available short-term trials that began

with an early intravenous dose of beta blocker, are reviewed in an extensive overview.[5]

Typically all these trials commenced treatment within 24 hours of the onset of chest pain. Among the larger trials, the studies by Norris et al[6] (735 patients) and Salathia et al[7] (800 patients) started treatment in all patients within 4 hours of pain; the studies by Yusuf et al[8] (477 patients) and the International Study of Infarct Survival; ISIS (16,105 patients)[9] both evaluating atenolol with 12 hours of pain, and the Goteborg study[10] (1395 patients) and Metoprolol in Acute Myocardial Infarction; MIAMI[11] (5778 patients) both evaluating metoprolol within 24 hours of pain. The initial intravenous dose varied from 5 to 10 mg of IV propranolol, 5 to 10 mg of IV atenolol or about 10 to 15 mg of IV metoprolol. This was followed by oral treatment for varying intervals. In 24 trials the evaluation period during which treatment or placebo were administered varied from 24 hours to 2 weeks (median of about 7 to 10 days). After this period, all patients either received standard treatment or both groups received long term oral beta-blocker treatment. In 3 trials,[7,10,12] in which a total of about 2,500 patients were randomized, oral beta-blockers or placebo were continued for 3 months to 1 year.

Infarct size

Infarct size cannot, of course, be measured directly in humans, and since indirect techniques such as enzyme release or ECG changes have their limitations, evidence from more than one such technique may be necessary before it can be inferred that infarct size is truly reduced. Most studies entered all their patients within about 12 hours of the onset of pain (and, in fact, entered most within 6 hours). Data from some trials are missing, and this may, of course, to some extent be because the effect of treatment on infarct size in those trials appeared unpromising or was not measured. Despite this, however, examination of the available data provides reasonably consistent evidence of a moderate effect on enzyme levels of early IV treatment, though not of treatment that was started 12 or more hours after the onset of pain. Efficacy has been demonstrated with a variety of beta

blockers[5]: atenolol, propranolol, metoprolol, sotalol, timolol, and perhaps alprenolol. This suggests that the effect is chiefly due to beta (or beta-one) blockade per se and that it is largely unrelated to ancillary properties such as cardioselectivity (atenolol and metoprolol are cardioselective, whereas propranolol and alprenolol are not), membrane-stabilizing activity (propranolol possesses this; the other three do not), or intrinsic sympathomimetic activity (which alprenolol possesses but the other three do not). Typical reductions in cumulative enzyme output appear to be around 20%, at least for patients who are entered within the first few hours of the onset of pain. The significant results are sufficient for it to be almost certain that some effect exists, but so many results are unavailable (and there is so much variation in time from entry to randomization) that it is difficult to estimate the magnitude of this effect reliably.

Electrocardiographic evidence that is also indirectly but independently suggestive of limitation of infarct size is provided by the highly significant (P <.001) preservation of R waves observed in trials with atenolol[8] (Fig 2) and by the significant reduction in the development of Q waves in trials with propranolol[13] and with timolol.[14] These favorable electrocardiographic changes, taken in conjunction with the demonstrated reduction in enzyme levels and with the experimental animal data, strongly suggest that a true reduction in infarct size can be produced by early intravenous beta blockade.

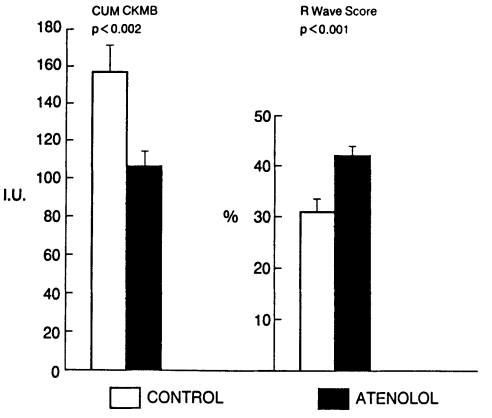

Figure 2 demonstrates the reduction in enzyme release and preservation of R waves in atenolol treated patients in the Oxford-Wythemshawe randomized trial.[8] (Reproduced with permission of the American Heart Association)

Prevention of infarction (Table I)

Patients who present with characteristic chest pain suggestive of a recent MI but who do not as yet have diagnostic ECG changes may be described as having "threatened infarction." Data from only three* of the randomized controlled studies of such patients, where serial enzyme changes were measured, are available, one each testing propranolol, atenolol and metoprolol. In the small propranolol[13] study only 55% of the treated patients developed myocardial infarction, compared to 96% of the controls. The corresponding percentages from the larger atenolol study are 49% and 66%.[8] In the MIAMI trial[11], among those randomized within 7 hours who had a normal ECG at entry, only 26% of the treated patients developed an MI compared to 31% in the control group. Pooling the information from all 3 studies suggests that beta blockade can average reduce the odds of full development of MI by approximately one-sixth ($P < .001$). This conclusion is supported by data on patients with abnormal ECG on admission from the Goteborg[10] and the MIAMI[11] trials of metoprolol. In the former study, the number of patients randomized within 12 hours developing a confirmed MI in the first 4 days (irrespective of their initial ECG) was 55% in those allocated metoprolol compared to 61% in those allocated control. Similar differences were obtained in the MIAMI trial among patients with an initial abnormal ECG, where 80% of the treated patients and 86% of the control patients developed an MI. These data, together with the observations among patients with an initially normal ECG strongly suggests that early IV betablocker treatment prevents the progression to infarction in some patients (although for the reasons stated earlier, the exact magnitude of benefit is subject to some uncertainty).

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*In the ISIS trial, enzymes were not measured serially. Instead, elevation of "routine enzyme" levels above "twice normal" was used to assess the presence of MI. In this trial, the prevention of the evolution to "definite" infarction was small. This may be partly due to the crude measures used, but this also suggests that the real effect may be somewhat smaller than that suggested by the 3 studies that chose to report it separately.

Table I Summary of Results on Development of Myocardial Infarction, Nonfatal Reinfarction and Nonfatal Cardiac Arrest

	Allocated Beta-blocker	Allocated Control	Odds Ratio	95% Confidence Interval	P
1. Proven MI among those with initial "threatened" MI Norris 79, Yusuf 83, MIAMI 85, ISIS 85	312/1110(28.4%)	401/1236(32.4%)	0.83	0.69-0.98	0.04*
2. Proven MI among those with an initial ECG that was abnormal/data from trials where no ECG classification was available. Hjalmarsson 83, Norris 85, MIAMI 85, Salathia 85, ISIS 85	6096/9439(64.6%)	6083/9256(65.7%)	0.95	0.89-1.01	0.10*
3. Nonfatal Reinfarction: Hjalmarson 83, Yusuf 83, ICSG 84, MIAMI 85, ISIS 85	263/11,970(2.2%)	315/11,906(2.6%)	0.83	0.70-0.98	0.03*
4. Nonfatal Cardiac arrest: Ryden 83, Yusuf 83, Rasmussen 84, ICSG 84, Roberts 84, Norris 84, MIAMI 85, Salathia 85, ISIS 85	275/13,133(2.1%)	323/13,050(2.5%)	0.84	0.71-0.98	0.03

* Since these three effects reinforce each other, there is no significant heterogeneity and suggests that treatment is likely to prevent the development of an MI or a further one in approximately 5 to 15% of patients.

Arrhythmias

Two randomized studies have been reported that involved analysis of continuous tape recordings to assess the effects on arrhythmias of the use of IV beta-blockers early in infarction. In the study of Rossi et al[15], 182 patients were recorded, each for a period of about 24 hours, early in their clinical course, and the treatment began with IV atenolol at a mean of 5 hours after the onset of pain. There was a three-fold ($P < .001$) reduction both in the frequency of isolated ventricular ectopic beats and in the percentage of patients with (R-on-T) ectopics (Fig 3), together with lesser reductions in various other types of arrhythmia. A smaller study in 49 patients using IV propranolol did not report any significant benefit, but treatment was started late after pain, the numbers studied were small, many arrhythmias may have been undetected as continuous tape recordings were not available, and propranolol was combined with atropine, which may have reduced any beneficial effects.[16] There are as yet few data on the prevention of supraventricular arrhythmias, but three studies with other principal end points mentioned incidentally a reduction of atrial fibrillation with practolol[17], metoprolol[10] and atenolol[8]. The latter study also observed a promising reduction in nonfatal cardiac arrest of 4% in control patients (10/233) to 1% in atenolol-treated patients (3/244). Ryden et al[18] have reported a similar, and significant, reduction in ventricular fibrillation during hospitalization in their study of IV metoprolol (17/698 control patients v 6/697 treated patients), as did Norris et al[6] in their final report from the PREMIS study (14/371 controls v 2/364 propranolol-allocated). This reduction in VF presumably reflects an antiarrhythmic property of beta-blockers, but in addition, late VF may be prevented by a reduction in infarct size. Favorable results have been reported with both selective and non-selective beta-blockers and currently there is uncertainity whether beta-2 receptor blockade is additionally beneficial. However, the results on cardiac arrest in some of the smaller trials have probably been exaggerated by chance as in the two large studies (ISIS and MIAMI) only small differences were observed. Nevertheless, combining data from all the trials that

included over 100 patients (i.e. on a total of 24,000 patients) suggests a 15% reduction which is statistically significant. In almost all the trials, the reduction in arrhythmias was reflected in a lower requirement for other antiarrhythmic drug treatments such as lignocaine.

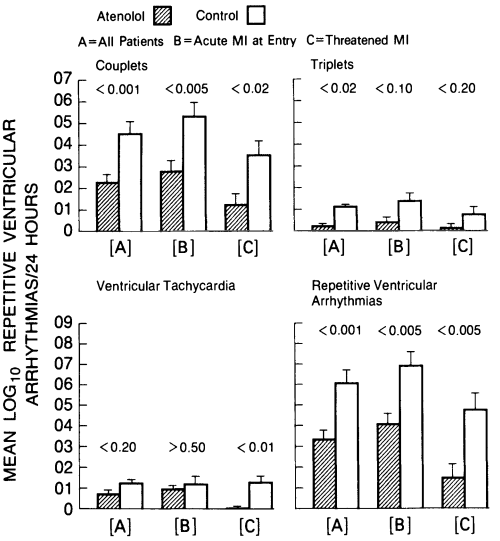

Figure 3 demonstrates the reduction in various forms of repetitive ventricular arrhythmia in patients treated with IV atenolol in the study of Rossi et al (15) (Reproduced with permission of the British Medical Journal)

Prevention of Reinfarction

Longer term beta-blocker treatment has been shown to clearly reduce the incidence of subsequent reinfarction in several trials.[5] Evaluating this in the short term studies is difficult as the distinction between the initial MI, an extension or a subsequent MI is often not clear. Several studies arbitrarily classified MI developing after 4 days as being due to reinfarction. Bearing these limitations in mind, it may nevertheless be useful to review whether the data from

the short term studies demonstrate a reduction in nonfatal reinfarction.[8] Only one trial demonstrated a significant reduction in reinfarction. However a favorable trend was observed in several studies, including the 2 larger ones (ISIS and MIAMI). Table I summarizes the information from 5 trials on a total of about 24,000 patients. This suggests that beta blocker treatment reduces the risk of nonfatal reinfarction by about 17%. Although there may be some uncertainty regarding the magnitude of benefit (as the 95% confidence limits are wide), the direction of effect (i.e. benefit) is likely to be true since similar effects were observed in the longer term trials. This is supported by the earlier observations of prevention of a "definite" first MI and a reduction in the "extent" of the initial MI by early intravenous beta-blocker treatment.

Chest pain

Beta-blockers are useful agents in the prevention and relief of anginal pain. A logical extension would be the demonstration of similar benefits in patients with myocardial infarction. At least three studies have reported relief of chest pain, two with metoprolol[10,19] and one with atenolol.[20] In this last study, the reduction in pain paralleled the reduction in cardiac work, suggesting that the decrease in oxygen demand led to a decrease in ischemia that resulted in relief of pain. In addition, in several studies the need for subsequent treatment with opiate analgesics, calcium blockers and nitrates was significantly reduced in the beta- blocker treated group.

Effect of IV Beta Blockers on One-week Mortality

In general, most short-term trials involving initial IV treatment were designed to provide reliable information not about mortality, but rather about other endpoints like infarct size. Only 2 of the 27 trials, ISIS which randomized 16,105 patients and MIAMI which randomized 5778 patients, are of reasonable size. Almost all the other studies were so small that even a 50% reduction in mortality might have been missed. The two larger studies were of sufficient size to detect about a 15% (ISIS) or a 35% (MIAMI) reduction in mortality reliably. In ISIS there was a 15% reduction in cardiovascular and total mortality at the end of 7 days (the treatment period)--304/8090 cardiovascular

deaths (3.76%) among those allocated atenolol compared to 355/8015 (4.43%) among those allocated control (p=0.03). A similar difference in mortality was observed in the MIAMI trial**, which evaluated metoprolol, but this trial failed to reach statistical significance on its own, perhaps due to inadequate numbers of patients (7 day mortality: 74/2877 (2.6%) in the treated group versus 87/2901 (3.0%) in the control group; p=0.30). These two trials on a total of about 22,000 patients provide fairly persuasive evidence that in patients with myocardial infarction early intravenous beta blocker treatment followed by oral treatment for about a week reduces the risk of death by about one-sixth. Further analyses in both trials did not detect any particular subgroup defined by baseline characteristics (e.g. heart rate, delay from pain, risk category, site of MI etc.) where treatment effect was consistently concentrated. Although the relative risk reduction appears to be similar in patients at low and high risk, of course, the absolute benefit is likely to be higher among those at greatest risk of death. In both trials, the entire reduction in mortality was observed within the first 48 hours, with apparently similar number of deaths in both groups thereafter. This does not mean that it would be safe to stop treatment after 48 hours as the treated group contains patients who were "saved" and it is not known whether these "salvaged" patients would be lost or not, if treatment were discontinued. After 7 days (i.e., the post-treatment period), there was a further small difference in favor of the treated patients in the ISIS trial, but this trend was nowhere near conventional levels of statistical significance. These data indicate that the early benefit observed is at least not lost in the subsequent year or two.

Adverse Effects

Table II summarizes the available data from all trials on the incidence of heart failure and heart block. There was a small,

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**The study period was 14 days, but analysis of the 7 day data for comparison with ISIS is presented. However, there did not appear to be any further benefit from treatment in MIAMI from 7 to 14 days.

Table II Major Adverse Effects in the Randomized Trials of Early IV Beta-blocker Treatment

	Allocated Betablocker	Allocated Control	Odds Ratio	95% Confidence Interval	P
1. Heart Failure	1067/6645(16.1%)	1024/6436(15.9%)	1.01	0.92-1.11	N.S.
2. 2nd or 3rd degree AV Block	433/14,215(3.0%)	401/13,988(2.9%)	1.06	0.93-1.27	N.S.

non-significant excess of second or third degree A-V block (433/14,215, 3.0% in the treated patients versus 401/13,988, 2.9% in the control patients). This difference was due to the small excess of reversible III° atrio-ventricular block observed in ISIS. It is reasonably reassuring that the incidence of heart failure in the treated and control group were identical. However, data on heart failure was not separately available in the ISIS trial although the use of diuretics was similar in both groups and the use of digitalis and nitrates was significantly lower among the treated patients. This does not, of course, mean that the chances of precipitating these adverse outcomes are absolutely zero, but instead, are likely to be small (probably no more than 0.5%). But most patients entering these trials have been those least prone to developing adverse effects, so that these expectations of little harm are largely applicable to this select group of patients who have no contraindications to beta- blockers. The incidence of "cardiogenic shock" appears to be about 1 to 2% higher among those allocated treatment but this is readily reversible on cessation of the beta-blocker or use of the inotropic agent. These patients do not appear to have suffered any lasting adverse effects as the total number of deaths due to cardiogenic shock were similar in patients in the beta blockers and control groups in the two large studies. This suggests that a few unusual patients will suffer an over-response to intravenous beta blockade and the physician may either need to discontinue such treatment or occasionally intervene with atropine or an inotropic agent.

IMPLICATIONS FOR CLINICAL PRACTICE

Early intravenous beta blockade followed by oral treatment for a week:

(i) reduces various indirect measures of infarct size by about 20%

(ii) prevents the progression to an infarction in about 15 to

20% of patients with "threatened infarction"

(iii) reduces the incidence of nonfatal reinfarction by about 15%

(iv) reduces various supraventricular and ventricular arrhythmias. In addition such treatment probably reduces nonfatal cardiac arrest by about 15%.

(v) reduces mortality at 7 days by about 15%.

The "price" that one pays for these benefits is relatively small, as major adverse effects are easily reversible.

These data suggest that for about 150 patients treated, one premature death is likely to be prevented. Comparisons with other more established treatments is somewhat artificial, but since treatment is simple, widely practicable and of short duration, the "yield" is relatively impressive. For example, treating 75 patients with severe hypertension (diastolic over 115 mm Hg) for one year is necessary to prevent one death compared to IV beta-blockers in acute MI where treating 150 patients for one week saves one life. In addition, one or two patients may be spared a nonfatal reinfarction or cardiac arrest. Further, some reduction in "infarct size" and arrhythmia can be demonstrated in the rest of the patients. These rather small reductions in mortality and major morbidity may superficially appear to be negligible, but they may nevertheless be worthwhile in public health terms for they could potentially prevent some tens of thousands of deaths per year in the well doctored Western World. Further, since long term beta blocker treatment has been shown to be beneficial, the practical question on when (rather than simply whether) to start beta blockade has been addressed by these short-term IV trials. Data from the few long-term trials of beta blockade that started treatment within the early hours of infarction, on a total of about 4000 patients, suggest that the "long-term" (i.e. deaths after 7 days) benefits on their own are at least as good as a delay of a few days indicating that early treatment does not negate the benefits of long term treatment.

Therefore, the combined use of early IV beta blocker treatment followed by long-term oral treatment is likely to be more beneficial than either treatment alone. If about 150 patients were treated with an initial intravenous injection followed by oral treatment with beta-blockers for about a year, then one might expect preventing about 3 to 4 deaths and a similar additional number of patients developing nonfatal reinfarction or cardiac arrest (an absolute total of 6 to 8 major events prevented). Of course, several patients who are not suitable for early IV treatment, may be eligible for long term treatment. Conversely patients who are given early IV treatment may develop clinical complications that might be a contraindication to further beta-blockade. Therefore, if a policy of using beta-blocker treatment were to be adopted, patients should be evaluated at entry and later during their hospital stay for eligibility and contraindications.

IMPLICATIONS FOR CLINICAL RESEARCH

It has taken almost 20 years since Snow's initial publication to demonstrate that early beta-blocker treatment is of benefit in reducing mortality in the "acute" phase of MI. This is perhaps because the treatment has only a modest (although worthwhile) effect of preventing some 15% of deaths, so that clear evidence had to wait until much larger trials than are currently usual were completed. It is possible that several other promising acute interventions such as thrombolytic therapy which are currently available will also be useful in preventing some deaths. But it is also likely that each of these treatments on their own may have only a modest effect on mortality (of about 15 or 20%), even if they have larger effects on intermediate endpoints such as coronary recanalization or ventricular function.[21] Therefore, if we are to reliably and quickly evaluate the effects of such promising treatments on mortality, randomized trials of several thousands of patients in which about a thousand deaths occur are more commonly needed.

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III. CORONARY CARE: THE CORONARY CARE UNIT PHASE

8

POST THROMBOLYTIC CARE

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The administration of streptokinase following acute myocardial infarction effectively lyses occlusive thrombi superimposed on atherosclerotic lesions and thereby allows for reperfusion of a previously occluded vessel. When given early in the course of myocardial infarction either intravenous or intracoronary streptokinase may have a favorable effect on both subsequent mortality and the extent of myocardial dysfunction. However, the clinical course following the administration of streptokinase for myocardial infarction is not only influenced by the presence and extent of myocardial necrosis but also by factors related to thrombolytic therapy. Thus the patient who has received thrombolytic therapy after myocardial infarction is exposed to several additional risks. In this review we will discuss these additional factors that influence the clinical course of these patients. Much of the data that we will present has been derived from patients who have received intracoronary streptokinase, yet are relevant to patients who have received intravenous streptokinase.

Mechanism of Action of Streptokinase

A detailed description of the myriad of effects of streptokinase is beyond the scope of this chapter. An extensive review of this subject is published by Brogden et al (1). Briefly, streptokinase is a proteolytic enzyme which interacts with human plasminogen to form plasmin. This occurs both in circulating blood and within the thrombus where plasminogen is contained within fibrin strands. Plasmin, a trypsin like enzyme, hydrolyzes fibrin into a number of soluble peptide fragments. Additionally, plasmin is capable of hydrolyzing a number of other proteins including fibrinogen, prothrombin, and factors V and VIII.

In addition to the thrombolytic effect of streptokinase, several reactions occur which induce an anticoagulant effect. When large doses of streptokinase are administered, similar to that given for intravenous

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streptokinase, almost complete activation of circulating plasminogen occurs and this may result in the formation of plasmin in excess of the ability of antiplasmins to neutralize plasmin. This leads to an increased proteolysis of fibrinogen, factor V, and factor VIII. In addition, degradation products of fibrinogen are known to exert an anticoagulant effect through the inhibition of several phases of the coagulation mechanism (1). The duration of each of these effects is variable. Following the administration of 600,000 units of i.v. streptokinase, plasminogen levels and fibrinogen levels are diminished by less than 20% of their pretreatment values at 3 hours and remain depressed for 24 hours. The thrombin time is markedly elevated to values greater than 100 seconds within 2 hours of streptokinase administration and returns to normal approximately 48 hours following administration (2).

Hemorrhagic Complications Following Streptokinase

In view of the coagulation abnormalities described above and the need for systemic anticoagulation with heparin, it is not surprising that patients who have received streptokinase are predisposed to bleeding complications.

Although smaller doses of streptokinase are used for myocardial infarction when the drug is administered directly into the occluded artery, systemic fibrinolysis frequently results after intracoronary streptokinase. Cowley et al. (3) showed that following an average of 201,000 units of intracoronary streptokinase, a systemic fibrinolytic effect was present as evidenced by reduced fibrinogen levels and plasminogen levels. The prothrombin time and partial thromboplastin time are also prolonged. Failure to achieve recannalization after streptokinase administration does not indicate failure to achieve a systemic fibrinolytic effect. Recently White et al. showed that patients who were given intracoronary streptokinase without successful recanalization had serum fibrinogen levels that were as reduced as in patients with successful recannalization of the occluded vessel (4).

The incidence of bleeding complications following either intravenous or intracoronary streptokinase have been reported by several groups (Table 1). Two studies have compared the efficacy of intracoronary versus intravenous streptokinase and have compared bleeding complications resulting from both modes of therapy. In the study by Alderman et al.(5), 28 patients received either intravenous or intracoronary streptokinase. The frequency of bleeding

complications were not different between the two groups. Bleeding episodes seemed to develop in the second or third day after streptokinase administration, well after the peak fibrinolytic effect and during heparin infusion. The authors attributed these bleeding episodes primarily to the anticoagulation effects of heparin rather than to the effects of the thrombolytic agent. Valentine et al. (6) compared the efficacy of intracoronary streptokinase in 98 patients to intravenous streptokinase in 66 patients. Both groups underwent coronary angiography. Bleeding of sufficient magnitude to necessitate transfusion occurred in 5% of the patients receiving intravenous intracoronary streptokinase and 3% of the patients receiving intravenous streptokinase. When bleeding occurred, it was always at the site of arterial catheter insertion and usually more than 24 hours after streptokinase administration, well beyond the peak thrombolytic effect.

TABLE 1 Hemorrhagic Complications After Streptokinase

Authors	Route of Administration	Hemorrhagic Complications	
		Minor	Major*
Alderman et al.[5]	i.v. and i.c.	7/28 (25%)	4/28 (14%)
Valentine et al.[6]	i.v.	+	2/66 (3%)
	i.c.	+	5/98 (5%)
Mathews et al.[7]	i.c.	20/155 (14.2%)	2/155 (1.3%)
Ganz et al.[8]	i.v.	+	10/81 (12%)
Merx et al.[9]	i.c.		15/204 (7%)

*Major hemorrhagic complications were considered those requiring transfusion or associated with intracerebral hemorrhage.
+Data not provided in the manuscript.

Thus it would appear that hemorrhagic tendencies related to streptokinase therapy occur with equal frequency in patients given streptokinase either by the intravenous or intracoronary route. Bleeding complications can be reduced by not removing the arterial sheath through which the catheterization is performed for at least 24 hours following the cardiac catheterization and by not administering streptokinase to patients with a recent history of gastrointestinal bleeding or cerebrovascular accident. If the arterial sheath must be removed while a fibrinolytic effect is present, we recommend removal by a vascular surgeon after the vessel is exposed by cutdown. Using

this approach, hemostasis may be obtained while the puncture site is observed and if necessary the puncture site can be repaired.

In all series, bleeding episodes seldom have required multiple transfusions. At the University of Iowa, in over 175 patients treated with either intracoronary or intravenous streptokinase we have not had an episode of bleeding that was not controlled by transfusion and discontinuing heparin therapy. Although very rarely necessary, the activation of plasminogen by streptokinase may be inhibited by epsilon-aminocaproic acid (Amicar). The administration of such an agent should be reserved for only the most severe bleeding episodes refractory to other measures. If rethrombosis of the residual coronary stenosis were to occur following administration of epsilon-aminocaproic acid, the administration of additional streptokinase would be ineffective (1).

Anticoagulation Following Streptokinase

Following successful thrombolysis with streptokinase, there is always an atherosclerotic lesion present at the site of the previous occlusion. These lesions are quite different than other atherosclerotic lesions found in patients with stable angina pectoris. A large majority of these contain ulcerated plaque and the overlying endothelium is often damaged or absent, predisposing to platelet aggregation, fibrin deposition, and rethrombosis. The incidence of rethrombosis has been reported to range from 7% (8) to 29% (10). While a randomized study comparing the effects of anticoagulation to no anticoagulation following streptokinase reperfusion has not been performed, most physicians feel systemic anticoagulation is warranted following streptokinase. After plasminogen has been depleted, streptokinase has no further substrate upon which to act. At this point, in the absence of adequate systemic anticoagulation, it is possible to form new clots which cannot be dissolved by administering more streptokinase (1). Because the systemic anticoagulation that results from streptokinase is somewhat variable, many physicians recommend administering heparin immediately after beginning streptokinase therapy. This is currently the practice at the University of Iowa. Another approach would be to monitor the partial thromboplastin time or activated clotting time and institute heparin therapy when these return to levels less than twice normal values.

Following acute anticoagulation with heparin long term anticoagulation with Warfarin is generally employed unless the patient undergoes either coronary bypass graft surgery or percutaneous angioplasty.

Because there is a significant incidence of rethrombosis following initially successful streptokinase therapy, several issues should be considered regarding the care of these patients. Some of these considerations are:

1. Are certain lesions particularly predisposed to rethrombosis while others are unlikely to reocclude?
2. Is the size of the residual lesion different several weeks following successful streptokinase reperfusion than immediately thereafter? This is particularly relevant to immediate decisions about further interventions after recannalization.
3. Should percutaneous transluminal angioplasty be performed in all patients shortly after streptokinase reperfusion?
4. If the patient has three-vessel coronary artery disease, or if percutaneous transluminal angioplasty cannot be performed for technical reasons, should the patient undergo coronary artery bypass surgery shortly following recannalization of the vessel?

Predictors of Rethrombosis

We have recently examined the quantitative characteristics of residual lesions following streptokinase reperfusion in an attempt to identify factors that predispose these lesions to rethrombosis and thus to identify a group of patients who may benefit from immediate intervention (10).

In these studies we employed computer-assisted quantitative coronary angiography similar to that described by Brown and Dodge in 24 patients who had undergone successful streptokinase reperfusion. The coronary angiograms analyzed were those obtained immediately following the discontinuation of streptokinase and similar views of the vessel obtained at recatheterization 8-14 days later. An average of 177,000±13,000 units of intracoronary streptokinase was administered. A constant infusion of intravenous heparin was instituted at the time of cardiac catheterization and continued until repeat catheterization, the goal being to maintain the partial thromboplastin time greater than 60 seconds. In general all patients received 10-20 mg of Nifedipine orally every 8 hours and received some form of long-acting nitroglycerin between the catheterizations.

Two important observations were made in this study regarding the residual lesion after successful intracoronary streptokinase reperfusion.

1. Among the 13 patients with very high grade stenoses after

streptokinase reperfusion (residual lumen area less than 0.4mm^2, area stenosis greater than 90%), seven had vessel rethrombosis. In contrast, none of the 11 patients with residual lumens greater than 0.4mm^2 had vessel rethrombosis (Figure 1). The likelihood that rethrombosis was related to residual lumen size was confirmed using an independent method of angiogram analysis, computer-assisted videodensitometry. Lesion rethrombosis was not related to patient age, initial hemodynamics, or adequacy of anticoagulation. Thus, we feel these data support the notion that lesion rethrombosis is strongly influenced by the size of the residual lesion. Brown and co-workers have recently confirmed that lesion rethrombosis is more likely to occur in patients with lesions less than 0.5mm in diameter following streptokinase reperfusion (11).

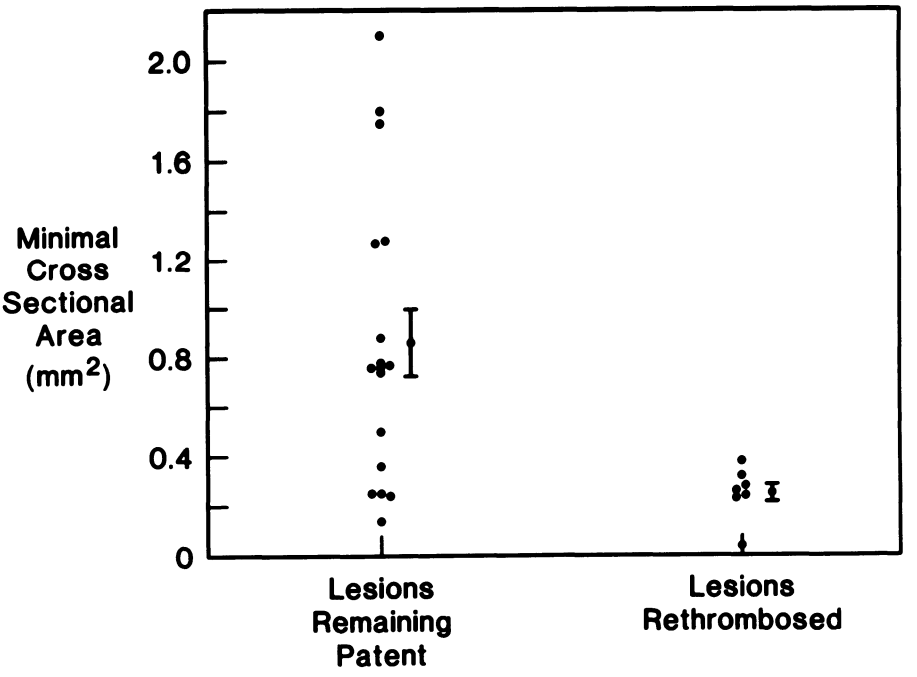

Fig. 1. The distribution of minimal cross-sectional areas in patients with lesions that rethrombosed versus those with lesions that remained patent. Seven of 12 patients with minimal cross-sectional areas less than 0.4 mm^2 had rethrombosis. In contrast, none of 12 patients with minimal cross-sectional areas greater than 0.4 mm^2 had rethrombosis. This difference was significant by Chi square analysis ($p < .005$). (Reprinted with permission from the American Heart Association.)

2. Among those lesions that remained patent, an increase in residual lumen size occurred in all but two during the 8-14 days after streptokinase administration. In seven, residual lumen size more than doubled (Figure 2A). The average percent increase in minimal cross-sectional area for all lesions was 116±34%. This was associated with a similar decrease in percent stenosis (Figure 2B). An example of this late change in lesion size is shown in Figure 3.

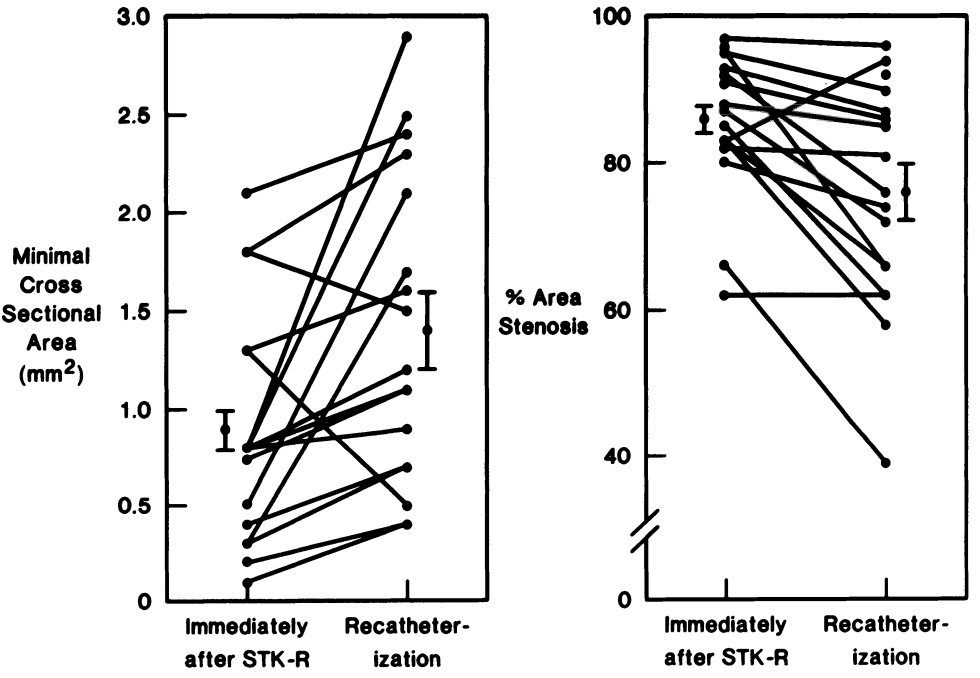

Fig. 2. Shown are changes in minimal cross-sectional area (A) and percent area stenosis (B) from immediately following streptokinase infusion to recatherization 8 to 14 days later. (Reprinted with permission from the American Heart Association.

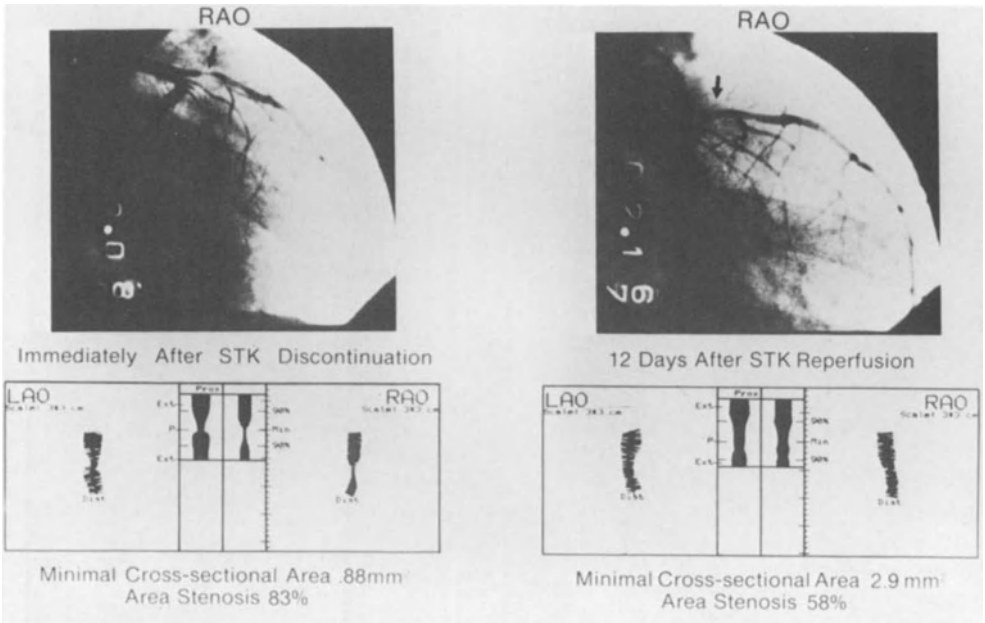

Fig. 3. Example of a late change in lesion size that occurred after reperfusion with streptokinase. Left: RAO angiogram of a stenosis of the left anterior descending coronary artery immediately after infusion of streptokinase. Right: The patient underwent recatheterization 12 days later and minimal cross-sectional area of the lesion has increased from 0.9 mm^2 to 2.9 mm^2 during the interval. (Reprinted with permission from the American Heart Association.

At least three mechanisms may play a role in the late change in lesion size after reperfusion with streptokinase. All of these relate to factors that prevent the vessel from opening to its fullest extent immediately after streptokinase administration. One of these is acute plaque rupture which undergoes remodeling during the ensuing 8-14 days. Several postmortem studies have shown that acute plaque rupture is a common predisposing event associated with acute coronary occlusion (12-14). After streptokinase the ruptured plaque persists and may require several days or months for

re-endothelialization and resorption of associated hemorrhage. Second, vasospasm superimposed upon the residual stenosis may be present despite therapy with intracoronary nitroglycerin and sublingual nifedipine. This may particularly be true for eccentric lesions in which some portion of the circumference of the stenotic segment is not diseased and therefore capable of active vasomotion. Lastly, unlysed thrombi that persist after administration of seemingly adequate doses of streptokinase may not allow the lesion to open to its fullest extent. Endogenous thrombolysins may continue to remove any persistent thrombi over the ensuing days and result in the late increases in lesion size seen in our study and in others (15). Under these circumstances larger initial doses of streptokinase might result in a more complete opening of the stenosis. This possibility is in part supported by a separate analysis of a subgroup of eight patients treated late in our series who received a higher dose of streptokinase (240,000±16,700 versus 140,000±9,000 units for the earlier patients). In this high dose subgroup, a minimal lumen cross-sectional area was 1.0±0.3mm^2 immediately after streptokinase compared with 0.6±0.1mm^2 in the remaining patients ($p<.05$). Among the vessels that remained patent, the average increase in minimal cross-sectional areas during the 8-14 days after streptokinase was 40±23% in this high dose subgroup compared with 127±47% in the earlier patients ($p<.05$). Thus in both groups there was a late change in lesion size, however this was more striking in the group given the lower dose of streptokinase.

What is the Role of Percutaneous Angioplasty Following Streptokinase Thrombolytic Therapy?

Because there is a substantial incidence of lesion rethrombosis after streptokinase reperfusion, particularly when the residual stenosis is severe, several groups have examined the efficacy of percutaneous transluminal angioplasty in treating residual stenoses shortly after streptokinase reperfusion. Meyer et al. (16) performed percutaneous transluminal

angioplasty 20-60 minutes after streptokinase reperfusion in 19 patients and within 31 hours of streptokinase reperfusion in an additional 2 patients. In 17 of these 21 patients, successful dilation of the residual stenosis was achieved. During follow-up, only 1 patient died, 2 patients had reinfarction, and 1 patient was found to have asymptomatic reocclusion at recatheterization. Not all patients underwent repeat angiography in this series. These results were compared to a separate group of 18 patients who received streptokinase alone. Four of these 18 had reinfarction during the hospital stay and 3 died during a 2-8 month follow-up period.

Gold et al. (17) performed percutaneous transluminal angioplasty in 28 patients immediately after streptokinase reperfusion. In 16 of these cases, the indication for percutaneous transluminal angioplasty was failure to achieve successful reperfusion after streptokinase. In 11 of these 16 cases, percutaneous transluminal angioplasty successfully opened the vessel. In 12, percutaneous transluminal angioplasty was performed because the residual lesion was greater than 90%. When percutaneous transluminal angioplasty reduced the residual stenosis to less than 90%, the recurrence of ischemic events was substantially lower than if the original stenosis was greater than 90%.

These studies and others (18), have shown that percutaneous transluminal angioplasty can be performed in the setting of acute myocardial infarction and with relative safety. Although many of these studies have examined relatively small numbers of patients, and none have been performed in a prospective randomized fashion, they would suggest that percutaneous transluminal angioplasty may have a salutary effect on the clinical course following streptokinase administration.

Potential Role of Coronary Bypass Surgery After Streptokinase Infusion

Emergent coronary artery bypass surgery has been performed by several groups as a treatment for acute myocardial infarction. While no study has shown such therapy to be beneficial to the outcome of acute myocardial infarction, surgical revascularization may have a place in the treatment of patients with high grade coronary stenoses following thrombolytic therapy. In this setting, coronary artery revascularization may obviate the consequences of vessel rethrombosis. Whether or not the outcome would be significantly altered remains unclear.

The additional surgical risk imposed by the presence of acute infarction has been reported by several groups. DeWood et al. (19) have shown that when surgery was performed within the first 18 hours from the onset of pain, the overall mortality rate was 4.1%. Patients operated on within the first six hours of an infarction suffered a 2.1% mortality rate compared to a slightly higher mortality rate for patients operated on later than 6 hours. These results have been confirmed by other investigators (20,21).

Two preliminary reports have described successful coronary artery bypass surgery performed within 24 hours of the administration of either intracoronary or intravenous streptokinase, without excessive mortality or transfusion requirements (22,23). These studies involve small numbers of patients and no controlled trials have been performed. Whether or not coronary artery bypass surgery in this setting is truly efficacious remains unclear.

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9

DETERMINING REPERFUSION AND MYOCARDIAL INFARCT SIZE USING SERUM ENZYMES

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INTRODUCTION

Interventions implemented to date in the clinical setting of acute myocardial infarction to salvage ischemic myocardium were aimed primarily at decreasing myocardial oxygen demands. Attempts to increase coronary flow have been relatively unsuccessful with drug therapy. Reperfusion, although shown in experimental infarction to be the most effective means of increasing coronary flow, was until recently not feasible in man. The recent demonstration that transmural myocardial infarction is associated with a coronary thrombus (1) which can be lysed with thrombolytic therapy (2) has drastically changed our thinking in both the assessment and treatment of acute myocardial infarction. Intracoronary streptokinase was very quickly approved by the Food and Drug Administration for routine use in acute myocardial infarction, perhaps too quickly. The impetus for this therapy has been enhanced by the recent demonstration that coronary thrombolysis could be achieved by the intravenous administration of streptokinase and, more recently, the relatively clot-selective, naturally occurring tissue plasminogen activator (rt-PA) (3). Given the safety and ease whereby the recombinant form of rt-PA can be given, it is conceivable that it could be administered to patients with suspected acute myocardial infarction at home or in transit to the hospital. Documentation of coronary thrombolysis is exciting, but should the present, ongoing, multicentered trial show coronary lysis with rt-PA to be effective in salvaging myocardium and reducing mortality, it could indeed revolutionize the care of the patient with acute myocardial infarction and change the overall thrust in the coronary care unit (4). The more widespread clinical implementation of reperfusion will require improvement in existing techniques as well as new and more rapid means of diagnosing

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and assessing myocardial infarction. Just as thrombolytic therapy has become feasible, other options to induce reperfusion in the setting of acute myocardial infarction have also become available, as well as means to maintain coronary patency. Coronary angioplasty is now undergoing trials as sole therapy and in combination with thrombolytic therapy in acute myocardial infarction, as well as following thrombolytic therapy as a means to maintain long-term coronary patency. Acute coronary bypass surgery has been implemented and shown to be feasible in the setting of acute myocardial infarction. Given these options, there is a great need to diagnose myocardial infarction within hours and to assess rapidly and noninvasively at the time of intervention whether perfusion has been effectively restored.

To understand the effect of early reperfusion on enzymatic assessment of infarction, it is necessary to review the experimental and clinical data on enzymatic estimation of infarct size and plasma creatine kinase (CK) release. We will review how early reperfusion is likely to influence the enzymatic diagnosis and assessment of myocardial infarction based on the conventional plasma CK isoenzymes, as well as the role of the recently discovered plasma CK isoforms and their limitations in assessing reperfusion under the following headings: 1) CK and the diagnosis of infarction; 2) CK to date the onset of infarction; 3) Infarct size and early reperfusion; 4) CK as a marker of reperfusion; 5) CK and spontaneous reperfusion; and 6) CK and reocclusion.

Reliability and Feasibility of Enzymatic Estimation of Infarct Size in Man

It is over a decade since the first estimates of infarct size based on serial changes in plasma CK were performed in man (5). Infarct size has now been estimated in a large number of patients in a variety of situations, either as an endpoint in assessing interventions designed to limit infarct size or to predict acute and long-term prognosis. In calculating infarct size in man, we assumed the ratio of CK released to that of CK depleted from the myocardium to be the same as determined in experimental infarction (0.15), and the distribution volume to be that of plasma (4.5% of body weight) (6). The k_d, determined from the downslope of the plasma CK time-activity curve corresponds to a

monoexponential function. However, if one uses a k_d derived from multicompartment analysis, one obtains a CK release ratio of 0.30. Compared to 0.15 with single compartment analysis, however, estimates of infarct size remain the same since it influences similarly both the numerator and denominator (7,8). Estimates of normal myocardial CK activity (1,600 IU/g) were obtained from hearts removed at necropsy within one hour of death (9). Although 75% of myocardial CK is depleted as a result of necrosis only 15% is released into the plasma; thus, 180 units in the plasma would correspond to one gram of necrosis. Thus, the total CK released into the plasma divided by 180 units represents an estimate of infarct size referred to as CK-g-Eq. In assessing infarct size in man, blood samples should be collected every four hours, preferably for 72 hours, but a compromise would be 48 hours followed by every six hours for another 24 hours. In man, although one could derive the original K_d from the original plasma CK time-activity curve, because of variation and possible interference from small amounts of CK released during the declining plasma CK activity, we recommend using a mean value for K_d of 0.001 for total CK and 0.0015 for MB CK (10). The computer program for estimating infarct size is quite simple, to the extent that a hand calculator is adequate.

Enzymatic estimates of infarct size from plasma CK were validated in relation to anatomical estimates and estimates of myocardial CK depletion in the animal. Since this is not feasible in man and would require some time to acquire such data at postmortem, we initially evaluated enzymatic estimates of infarct size in relation to clinical parameters known to reflect the severity of myocardial infarction. Numerous studies have shown a close correlation between infarct size by the plasma CK method and that of acute and long-term mortality and morbidity. In addition to our own studies (11,12), enzymatic estimates of infarct size have been related to mortality by Cairns et al (13) in Canada, Norris et al (14) in New Zealand, Thompson et al (15) in Australia, Kahn et al (16) in France, and Bleifeld et al (17) in Germany. In all studies to date, there has been a close correlation between enzymatic estimates of infarct size and that of acute or long-term mortality. Infarct size also correlates closely with the degree of regional impairment of left ventricular function as shown by Rogers et al (18), Hori et al (19), and Morrison et al (20). Mathey et

al (21) found a good correlation between infarct size, left ventricular hemodynamics and changes in ventricular compliance. Kahn et al (16) in France showed a very close correlation between enzymatic estimates of infarct size and the incidence and severity of ventricular failure. Thompson et al (15), as did Geltman et al (11), found a close correlation between infarct size and long-term mortality. The correlation between infarct size and mortality is much closer in patients without prior infarction, indicating that there is a cummulative effect (11). We have also observed a close correlation between enzymatic estimates of infarct size and the incidence and severity of ventricular arrhythmias, both during the acute phase of myocardial infarction and also with long-term Holter follow-up studies (11).

The ultimate validation of enzymatic estimates of infarct size in man awaited documentation in comparison to histological estimates performed at postmortem. Bleifeld (17) observed a close correlation of 0.93 between enzymatic and anatomical estimates of infarct size in 15 patients in whom anatomical infarct size was estimated after identification of the area of infarction with nitro blue tetrazolium (NBT). The time of death in this study ranged from one to 29 days after infarction, but 12 of the 15 patients died within two weeks of onset of infarction. More recently, Grande et al (22) observed a close correlation of 0.89 between enzymatic and anatomic estimates of infarct size in 22 patients who subsequently succumbed to myocardial infarction. As in the study by Bleifeld et al, infarct size was estimated following identification of infarction at postmortem using the NBT staining. However, identification and quantification would be preferred on the basis of histology rather than the NBT stain since there is some concern of the accuracy of the latter method in man. Such a study comparing histological estimates of infarct size with that derived from plasma CK has now been completed. In a large multicentered study (23) of over 900 patients designed to assess limitation of infarct size by hyaluronidase and propranolol, hearts from patients who succumbed were sent to a Pathology Core Laboratory at Duke University for quantitative estimates of infarct size. Histological estimates of infarct size were performed quantitatively by Hackel et al (23) by techniques previously published by the group. Enzymatic estimates of infarct size were performed by

the Core CK Laboratory and neither laboratory had any knowledge of clinical data or of the results of the other laboratory. The data from both laboratories were analyzed by a third party, the Central Data Coordinating Center. In brief, it consisted of cross-sectioning the heart into five or more slices of approximately one cm thick, and from photographs using a computerized X-Y digitizer the borders of infarction were planimetered in the left and right ventricles. The total volume of each infarct was then calculated and expressed in cubic centimeters. A total of 49 patients were analyzed; however, in only 25 patients were there adequate histological and enzymatic data to calculate infarct size. In this study, the correlation between histological and enzymatic estimates of infarct size was shown to be 0.87 and 0.86 for total and plasma MB CK, respectively.

One concern over the years from studies in the experimental animal (24-26) has related to the possible inaccuracy of estimates by the CK method in patients with extensive myocardial infarction. It was postulated in patients with extensive damage, where there is also extensive microvascular damage and markedly decreased flow in the central area of the damage, there would be underestimation of infarct size due to less CK released into the blood. In the three studies to date comparing enzymatic to postmortem estimates, enzymatic underestimation of large infarcts has not been observed. In the postmortem studies, despite a wide range from small to large infarcts, there was a consistent tendency for enzymatic estimates to be greater than those of histological estimates (23). The difference between infarction in man and that of the experimental dog may be that collateral blood flow, the long-standing coronary atherosclerosis, or the microvascular damage is less in the dogs with sudden, sustained coronary occlusion. Thus, the postmortem correlations together with the clinical correlations and its widespread clinical use indicate it is a valid and feasible endpoint for assessment of infarct size in clinical trials. Enzymatic estimates of infarct size have now been employed to assess a variety of drug therapies including nitroglycerin (27-29), beta-blockers (30-33), calcium blockers (34-36), nitroprusside (37,38) and hyaluronidase (39,40). However, one must be sure the various parameters are not influenced by the intervention per se. Secondly, several of these parameters were derived from studies

performed in the experimental animal in a model of sustained coronary occlusion and do not necessarily apply to that of patients who undergo early reperfusion. With onset of reperfusion, there is a more rapid washout of plasma CK and the overall plasma CK kinetics are changed markedly, as will be discussed.

Myocardial CK Depletion

To understand the basis and limitations of enzymatic estimation of infarct size, one must understand myocardial CK depletion and its relation to histological estimates of infarct size. Creatine kinase activity is uniformly distributed throughout the myocardium of the right and left ventricles, with average values of 2024±65 IU/g in the dog and 1600±110 IU/g in man (41,42). Following experimental coronary artery occlusion, regions undergoing necrosis assessed directly 24 to 48 hours later consistently show 75% of the myocardial CK activity depleted (43,44). The initial assumption that estimates of the accumulated CK released into the plasma would reflect infarct size stemmed from the observation that myocardial CK depletion quantitatively reflected infarct size assessed histologically in experimental infarction (43,45). Recently, it was shown that depletion of myocardial MB CK correlates closely with morphometric estimates of infarct size determined at necropsy in patients dying early after acute myocardial infarction (22). In the experimental animal, estimates of infarct size based on myocardial CK depletion have been shown to correlate closely with histological estimates of infarct size despite a variety of interventions including early reperfusion (46-48), administration of verapamil (49,50), nifedipine (51), nitroglycerin (41), propranolol (52,53), anesthesia (54,55), hyperbaric oxygen (56), or hyaluronidase (57). Myocardial CK depletion following coronary artery occlusion is independent of interventions that decrease demand, such as beta-blockers, or increase coronary flow, such as calcium antagonists, including early reperfusion and, thus, the close correlation between infarct size estimated morphometrically and that by myocardial CK depletion is retained. Studies performed in the experimental animal with sustained coronary occlusion showed that estimates of infarct size from plasma CK release correlated closely with estimates based on myocardial CK depletion and anatomical estimates of infarct size (58).

The good correlation referred to earlier between enzymatic estimates of infarct size and that of histological estimates at postmortem and other clinical parameters suggest a similar relationship in man. However, as pointed out earlier, the amount of CK recovered from the plasma using either monocompartmental or multicompartmental analysis accounts for only a fraction of the CK activity depleted from the myocardium, suggesting a significant amount of the CK is inactivated locally or is released into lymph (59) and does not gain access to the blood. Early reperfusion, while it does not influence myocardial CK depletion, is known to be associated with more rapid release of plasma CK and may increase the net amount of CK released and, thus, without a correction for our present CK release ratio, estimates of infarct size from plasma CK would lead to overestimation of infarct size.

Reperfusion and Plasma CK Release

The ratio of CK depleted from the myocardium to that released into the plasma was determined in the conscious animal with sustained coronary occlusion. Estimates of plasma CK release are based on the assumption that the rate of change of plasma CK activity (dE/dt) reflects two competing processes; namely, the rate of release from the myocardium [f(t)] and elimination from the plasma (k_d). Thus, CK release rate is calculated from the following equation: $dE/dt = f(t)-(k_d x E)$; where E = plasma CK activity, t = time, and k_d = the fractional disappearance rate of plasma CK. Assuming a disappearance rate in dog of 0.0048 or in man of 0.001 and a distribution volume of 4.5% of body weight, the total CK released (CK_r) is calculated from the following equation:

$$CK_r = \int_0^t f(t)dt = E(t) + k_d \int_0^t E(t)dt$$

Early reperfusion in man such as induced by intracoronary intravenous streptokinase or intravenous rt-PA produces a plasma CK time-activity curve quite distinct from that observed after sustained coronary occlusion. The peak plasma CK values occur much earlier (12 hours versus 24 hours) and are of greater magnitude with earlier return to normal levels (60,61). A similar phenomenon is observed after bypass surgery where with restoration of perfusion, one sees a more rapid

release of CK into the plasma resulting in peak levels of six to 12 hours with return to normal levels often within 36 to 48 hours (62,63). The effect of early reperfusion on plasma CK in experimental infarction is illustrated in Fig. 1 from the studies of Vatner et al (64). Peak

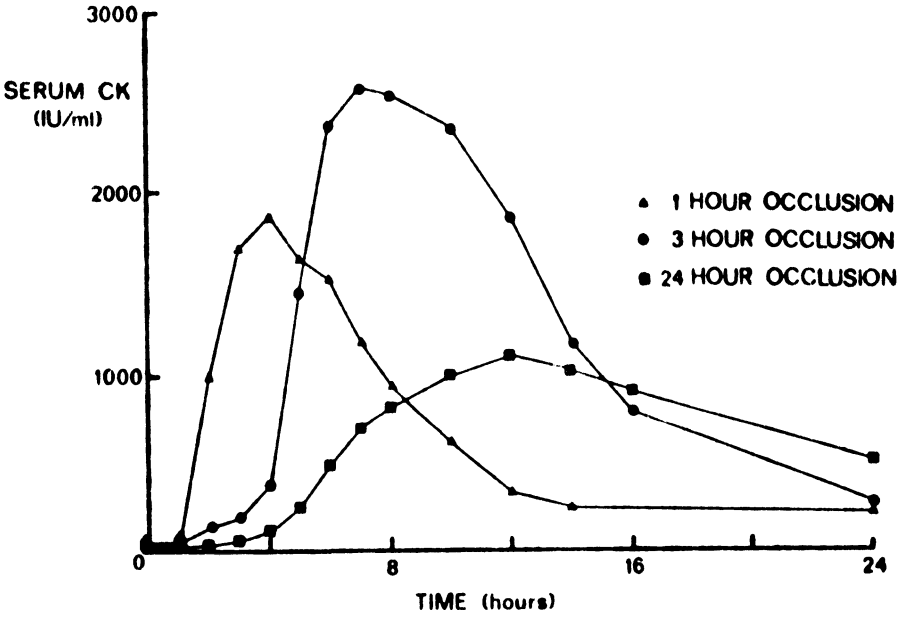

Fig. 1. Serum creatine kinase (CK) time-activity curves associated with reperfusion in the conscious dog after one hour and three hours of coronary occlusion. The third curve represents release of CK associated with sustained coronary occlusion. Serum CK peaks 12 hours after occlusion in the absence of reperfusion. Reperfusion after one hour or three hours of occlusion resulted in peak serum CK activity at four hours and eight hours, respectively. These results indicate that the rate of release is flow-dependent. However, whether more CK is released as opposed to the same amount released more rapidly cannot be determined from the serum CK time-activity curves. (Reprinted with permission from J. Clin. Invest. 61: 1048, 1978.)

plasma CK activity after sustained occlusion in the conscious dog occurs about 12 hours after initiating the occlusion. In contrast, transient occlusion followed by reperfusion for one or three hours was associated with peak plasma CK activity at four and seven hours, respectively. Restoration of flow after only 60 minutes of coronary occlusion resulted in peak activity four hours later which was much higher than with sustained occlusion. Thus, the same amount of CK released during sustained occlusion would, with early reperfusion, lead to much higher plasma levels due to release over a shorter interval. The higher plasma levels observed after early reperfusion led to the suggestion that values for infarct size estimated by the CK method in this setting represent an overerstimation due to the greater net release of CK per gram of necrosis. As stated earlier, only a fraction of CK depleted from the myocardium is released into the plasma, with the remainder presumably denatured locally. With more rapid release, there is less time for local denaturation leading to more being released into the blood and a greater myocardial CK release ratio. Other possibilities have been excluded, such as an effect of streptokinase on the CK assay or the plasma CK disappearance rate.

Plasma samples containing activity of 100 to 5,000 IU/l assayed before and after incubation with streptokinase (5,000 IU/ml for 30 minutes at 37°C), showed less than 5% variation, indicating streptokinase has no effect per se on the CK assay (65). The plasma disappearance ratio (k_d) was determined using purified CK from canine myocardium, as previously described (66). Boluses of purified CK were injected intravenously into conscious dogs and a control k_d was determined and compared to k_d determined one day later during continuous infusion of streptokinase. The dose consisted of an initial 50,000 IU given over 30 minutes followed by 20,000 IU per hour for 4.5 hours. The lack of effect of streptokinase on k_d is shown in a representative example in Fig. 2. We have also shown that tissue plasminogen activator exerts no effect on the CK assay, and multiple studies performed to date with this agent have shown no difference in the plasma CK disappearance rate between the patients receiving rt-PA and placebo.

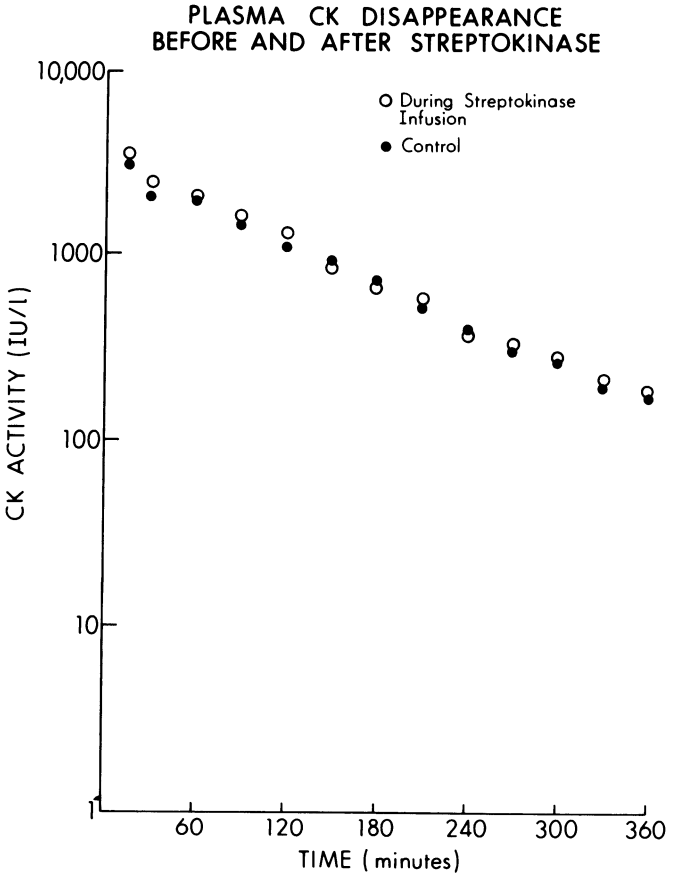

Fig. 2. The disappearance of creatine kinase (CK) from the plasma of a conscious dog after a bolus injection of purified canine myocardial MMCK. The CK disappearance was assessed in the same animal separated by an interval of 48 hours.

Infarct Size and Early Reperfusion

The rate at which CK is released into the plasma is clearly dependent on coronary flow with improved perfusion leading to more rapid release, but whether there is an increase in the net amount of CK released into the plasma during early reperfusion in man remains unknown.

Late reperfusion, five to seven hours after coronary occlusion, in the conscious dog is associated with more rapid release of CK, but the CK release ratio, the net amount of CK released and, thus, enzymatic estimates of infarct size were similar to that of sustained occlusion

(67). Early reperfusion performed within two hours of coronary occlusion during experimental infarction in the conscious dog, however, does affect enzymatic estimates of infarct size. Although the plasma CK release ratio was not determined directly, the estimates of infarct size from both morphometric analysis and myocardial CK depletion were less than those from plasma CK. The overestimation was assumed due to greater washout of CK, implying a greater ratio of CK released to that depleted. Preliminary studies (68) in our laboratory in the experimental animal showed reperfusion initiated within the first two hours after onset of occlusion is associated with a greater CK release ratio and a net increase in the amount of CK released into the circulation. Animals reperfused after one or two hours exhibited a CK release ratio of 47±5% and 51±5%, respectively, using the two-compartment analysis, as opposed to only 28±1% with sustained occlusion. In contrast, reperfusion after four hours was associated with a release ratio of 29±6%, similar to that of sustained occlusion. Thus, these studies confirm previous suspicions that reperfusion performed within the first two hours after coronary artery occlusion during experimental infarction is associated with an increase in the net amount of CK released due to a greater CK release ratio. Presumably, some of the CK which with sustained occlusion would have been denatured locally and/or destroyed in the lymph is with early reperfusion released into the plasma. These results on early reperfusion suggest the release ratio is similar whether performed at one or two hours, whereas at four hours it is similar to sustained occlusion. It remains to be determined what happens to the release ratio between two and four hours. Further studies are necessary to determine the consistency of the CK release ratio during the early hours; however, based on this preliminary data, it does appear to be fairly consistent. These studies performed in the conscious dog indicate enzymatic estimates of infarct size to be accurate despite reperfusion if performed four or more hours after occlusion, but earlier reperfusion is associated with overestimation of infarct size requiring an appropriate correction of the release ratio.

Careful analysis of the studies of Vatner et al (46) indicate the potential for accurate estimates of infarct size during reperfusion. Morphometric estimates of infarct size were compared with those from plasma CK in animals during early reperfusion performed 60 minutes and

three hours after coronary occlusion. Despite enzymatic estimates of infarct size in this study being much greater than the morphological estimates, results of the two methods correlated closely with an r value of 0.90. This close correlation would indicate a consistent relationship between reperfusion and increased CK release. This is illustrated in Fig. 3 where the line of identity between morphological and enzymatic estimates is consistently shifted to the left in keeping with overestimation. This consistent relationship is also in keeping with the CK release ratio of 0.47 and 0.51 observed when reperfusion was performed one and two hours after coronary occlusion, respectively. The appropriate correction in the release ratio would be expected to shift the line to the right, and the absolute values would be similar by both techniques. Further studies are needed to confirm whether, in fact, this is the case and also to confirm the consistency of this

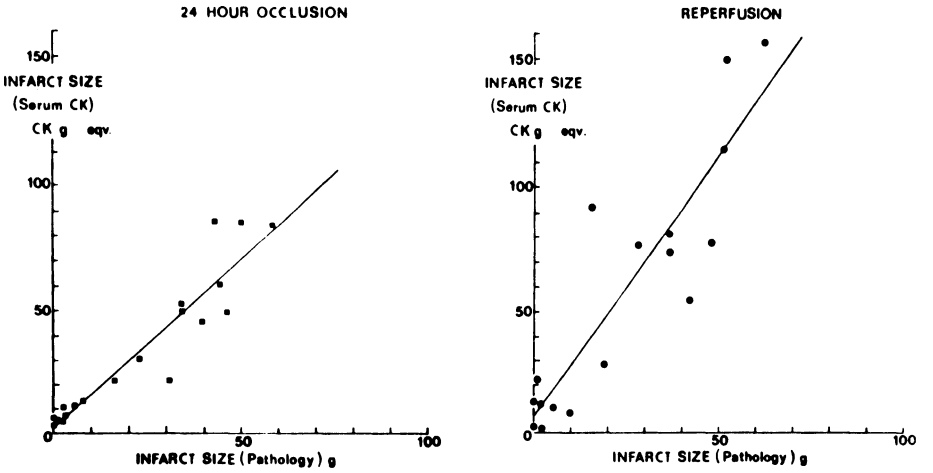

Fig. 3. (Left) The close correlation between infarct size determined by morphology (abscissa) and infarct size estimated from serum creatine kinase (CK) (ordinate, r = .94) after sustained coronary occlusion in the conscious dog. (Right) A similar close correlation between infarct size estimated from morphology (abscissa) and infarct size estimated from serum CK (ordinate, r = .90) in the conscious dog after coronary occlusion, but associated with early reperfusion. However, there is a difference in the dogs that underwent reperfusion in that the regression line is shifted to the left. In view of the close correlation despite the overestimation, it should be feasible to experimentally determine a correction factor that would shift the regression line to the right and correct for the degree of overestimation. (Reprinted with permission from J. Clin. Invest. 61: 1048, 1978.)

relationship. In man, this relationship will have to be confirmed by some independent technique. This is probably only possible by three-dimensional analysis using radioisotope technique such as is possible with short-lived positron-emitting isotopes, but possibly with single photon-emitting isotopes using tomographic imaging. Theoretically, reperfusion is advantageous since with a greater amount of CK released into the plasma more rapidly, estimates can be obtained earlier and more accurately since the effect of any error on estimates of infarct size will be attenuated. The potential for obtaining accurate estimates of infarct size during early reperfusion has just recently been enhanced by the recent documentation and quantification of MMCK isoforms. Following release of tissue MMCK into the circulation, its C-terminal lysine amino acid undergoes proteolytic hydrolysis resulting in an alteration in the isoelectric point and development of isoforms which will be discussed in the next section.

Isolation and Characterization of Plasma CK Isoforms

For some time, it has been known that plasma MMCK would occasionally on electrophoresis exhibit many forms, but until recently was discarded as artifact. Smith (69) speculated that the multiple forms were due to confirmational changes in a subunit. Others have proposed that the various isoforms were due to complexes with IgG or the BB isoenzyme (70,71). We showed several years ago that creatine kinase purified from canine myocardium had a much shorter plasma half-life than creatine kinase recovered from plasma (8). Nevertheless, we were unable to observe any difference in molecular weight, electrophoretic mobility on cellulose acetate or antigenic properties between MMCK recovered in the plasma and that purified from the myocardium of the same animal. In the meantime, Wevers et al (72,73) had shown that plasma MMCK, despite showing a single form after electrophoresis on cellulose acetate, exhibits three different forms on isoelectric focusing. In subsequent studies (74,75), it was shown that creatine kinase exists as a single form in tissue, which upon release into the plasma, is converted into three forms separable by their different electric charges. Existence of the three forms of plasma MMCK has now been confirmed by several investigators (76-79).

In an attempt to clarify the mechanism responsible for this conversion and to assess their physiological significance, we used chromatofocusing to isolate and purify each of the three forms of MMCK and to compare them with that of tissue MMCK (78). Results of these and subsequent studies (79,80) showed a single form of MMCK present in the tissue, whether myocardial or skeletal muscle, which upon release into the plasma, is sequentially converted into first MM-2, a more negatively charged molecule, and MM-1 which is the most negatively charged. This nomenclature was adopted to comply with international recommendations that the more cathodic form have the lowest number. The conversion to more negatively charged forms is due to carboxypeptidase-N induced hydrolysis of the C-terminal lysine of the tissue MMCK. Carboxypeptidase-N is a ubiquitous enzyme found in the plasma of all mammals and vertebrates. Based on C-terminal analysis of MMCK, it was shown that lysine is the C-terminal amino acid which is a specific substrate for carboxypeptidase-N or B. From hybridization experiments and peptide mapping, we showed that MM-2 results from removal of lysine, a positively charged amino acid from a single M subunit, whereas MM-1 results when lysine is removed from both subunits. This mechanism has been shown to present in several species, and incubation in vitro of tissue CK with carboxypeptidase-B or N produces the other two forms, as shown in Fig. 4. The reaction is inhibited by GEMSA, a specific inhibitor for carboxypeptidase-N, and also by removal of calcium by EGTA. To date, we have analyzed the C-terminus of tissue MMCK from human, dog, rabbit, rat and the electric eel and found lysine to be the C-terminal amino acid in each species (79). Thus, it would appear to be universal that a single tissue form of MMCK, upon release into the plasma, is converted into more negatively charged forms by carboxypeptidase-N. Billadello et al recently in a preliminary study (81) confirmed that MM-2 and MM-1 have their C-terminal lysine removed.

In the isolation and characterization of the CK isoforms, we relied on their separation by chromatofocusing, as shown in Fig. 5. While this method (78) is sensitive and precise, it is tedious and probably not applicable for routine clinical use. Using high resolution agarose, we

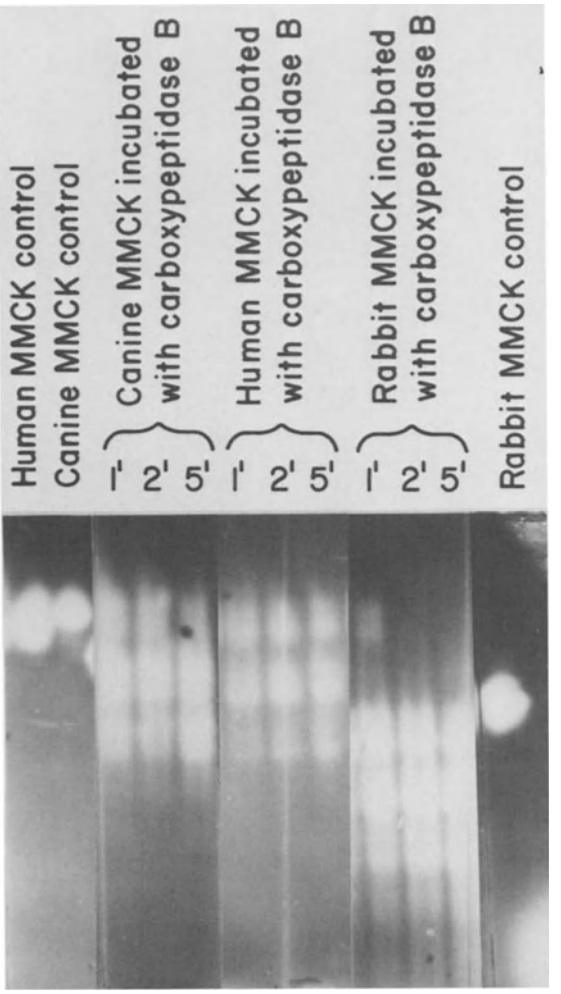

Fig. 4. Effect of incubation of tissue MM creatine kinase (CK) with carboxypeptidase-B. Incubation of human, canine, or rabbit tissue MMCK with carboxypeptidase-B for one to five minutes resulted in the production of two additional CK isoforms. The cathode is at the top.

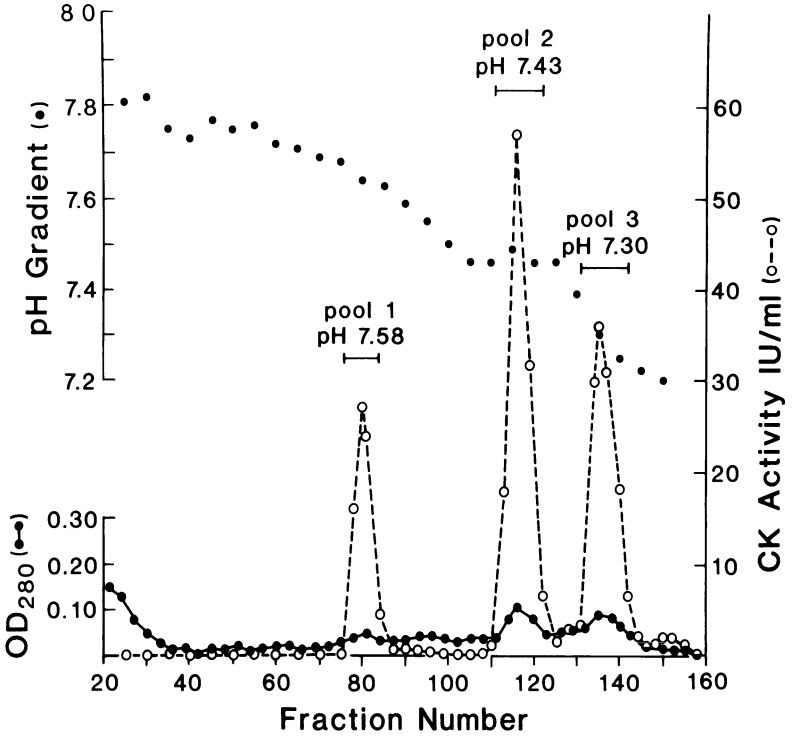

Fig. 5. Elution profile of plasma creatine kinase following chromatofocusing. Activity pools I to III correspond to creatine kinase MM-3, MM-2 and MM-1, respectively. OD - optical density; CK = creatine kinase.

obtained good separation of the plasma MM isoforms by electrophoresis (Fig. 6). A densitometric recording of each form was made and the integrated area, expressed as a percentage of the plasma total CK activity, provided an estimate of the activity for MM-3, MM-2 and MM-1. This method (82) is less sensitive than chromatofocusing but provides highly reproducible results which can be utilized in the clinical assessment of myocardial infarction. The technique is convenient, simple and routinely available to the clinical laboratories. Morelli et al (83) have utilized isoelectric focusing which, while more convenient than chromatofocusing, is unlikely to be implied for routine clinical use. Using the clinical data so far available, we will now discuss the role of the isoforms in the diagnosis and assessment of myocardial infarction. The data on reperfusion in the setting of acute myocardial infarction obtained using these techniques must be regarded as

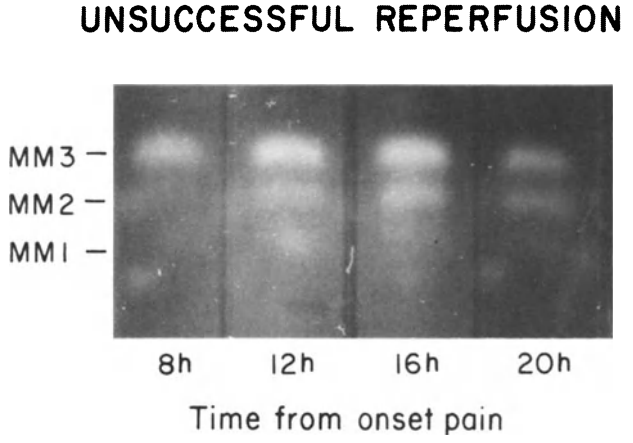

FIGURE 6: Shown here are the isoforms separated on high-resolution agarose following electrophoresis. The patterns are representative of the changes that occur over the interval of six to 20 hours from onset of infarction. The upper panel is for a patient in whom thrombolytic therapy was unsuccessful. MM-3 is still evident as a bright band at 20 hours with only faint evidence for MM-2 and MM-1. In contrast, the lower panel is from a patient with successful reperfusion, MM-3 has all but disappeared at 20 hours and the prominent bands, even at 16 hours, are MM-2 and MM-1. This difference reflects the rapid bolus release and conversion of MM-3 associated with successful reperfusion.

preliminary and further confirmation is required before we can make definitive conclusions.

Enzymatic Diagnosis of Infarction following Reperfusion

Elevated plasma MB CK remains the most sensitive and specific diagnostic marker for acute myocardial infarction, as well as the most cost-effective (84,85). Plasma MB CK activity, as detected by a sensitive quantitative assay, is elevated on the average four to eight hours after the onset of symptoms. In the case of reperfusion, due to more rapid release of a larger amount of CK analogous to a bolus infusion, reliable diagnosis can be made much earlier (60,61). The earlier the reperfusion, the earlier it is possible to confirm the diagnosis from plasma MB CK. With the recent data showing coronary thrombolysis can be achieved with intravenous therapy, it is conceivable in the future that rt-PA, given its present safety record, could be given intravenously or even intramuscularly to induce reperfusion within an hour of onset of symptoms. It is expected that within minutes of reperfusion induced even after an hour of symptoms, plasma MB CK activity would be adequately elevated to provide a reliable diagnosis. Reliable diagnosis of infarction on the basis of elevated plasma MB CK within one hour of symptoms with implementation of reperfusion remains to be determined in man, since experience to date has been restricted to reperfusion performed within three to six hours from onset of symptoms. Studies by Ganz et al (61) have shown plasma MB CK levels significantly elevated within minutes of reperfusion performed within four hours of onset of symptoms. Trials now in progress should adequately test this hypothesis.

Detection of an elevation in the plasma of the tissue form of MMCK (MM-3) reflects newly released CK indicative of new injury. In experimental infarction in the dog without reperfusion, this was detected within one hour (86) of coronary occlusion, which with reperfusion should be detected within minutes. In the clinical setting of chest pain, an elevation in plasma MM-3 may be adequate for implementing treatment, but confirmation of infarction will still be required with plasma MB CK since MM-3 is nonspecific and could be released from injury to tissue other than the heart. Nevertheless, with the development of a simple and convenient assay for the isoforms, it

should be possible to diagnose infarction within minutes of onset of symptoms. In experimental infarction, it has been shown that an increase in the tissue form of MM occurs before there is an elevation in the total plasma CK activity. Widespread clinical use of reperfusion and the recent concurrent detection of the CK isoforms combine to provide both the necessity and the means for an early diagnosis of acute myocardial infarction. The limitation in the setting of reperfusion to early diagnosis of infarction will probably relate more to the time required to perform the assay than the elapsed interval from onset of symptoms.

Plasma CK as a Marker of Reperfusion

With the advent of intravenous thrombolytic therapy, there is a great need for a noninvasive marker of reperfusion. This is particularly so in view of other options for definitive therapy which are now being exercised such as PTCA or acute bypass surgery. While several factors are influenced by successful reperfusion, such as relief of pain, appearance of transient arrhythmias and rapid evolution of electrocardiographic changes, they are relatively insensitive and, at best, extremely unreliable.

With the introduction of intracoronary streptokinase, results of several studies suggested that time to peak plasma CK may differentiate between successful and unsuccessful reperfusion (60,61). Further studies indicated there was considerable overlap if one depended solely on early peaking of total CK or plasma MB CK (3,87). The following guidelines are put forth based on results of the TIMI trial and several other studies in which reperfusion was documented by cardiac catheterization.

1) If the infarct related artery is completely occluded and adequate reperfusion is initiated within the first six hours from onset of symptoms, plasma CK peaks within the subsequent six hours;

2) Incomplete coronary occlusion with or without further lysis, leads to earlier peaking of plasma CK and this makes it difficult to determine if reperfusion has occurred;

3) Late reperfusion (greater than eight hours) after complete or incomplete occlusion may exhibit earlier peaking of CK than on the average without thrombolysis but there is extensive overlap.

There are several factors influencing the time to peak plasma CK such as infarct size, plasma CK disappearance rate, early reinfarction, and the extent to which reperfusion is established and maintained. Extensive ischemic injury is associated with a longer interval of CK release and delayed peaking of plasma CK activity. Based on the results in over 900 patients, the time to peak CK averaged 28 hours; however, the average time in patients with Q-wave infarction was 27 hours, and infarct size averaged 25 CK-g-Eq. In patients with non-Q-wave infarction, infarct size averaged 11 CK-g-Eq, and the time to peak CK was only 15 hours (88). If, as happens at least occasionally, early reinfarction occurs within the initial 24 hours, then, of course, the time to peak CK is markedly increased. In an attempt to improve on the inadequacy of total or plasma MB CK as markers of early reperfusion, we explored the potential of the CK isoforms.

As noted above, MMCK in cardiac or skeletal muscle is homogeneously present as MM-3, undergoing irreversible sequential conversion to MM-2 and MM-1 only after tissue release. The kinetics of this conversion to the modified isoforms is relatively rapid, so that a bolus of purified MM-3 injected intravenously into a dog is more than 50% converted to the modified forms within two to three hours. By four to six hours after injection, less than 10% of the MM activity is present as MM-3, the unmodified tissue form (89). A similar rate of conversion is observed when canine (87) or human (74) MM-3 is incubated in serum in vitro at physiologic temperatures. In contrast, in the setting of acute myocardial infarction, the observed shift in predominance from MM-3 to the other isoforms is significantly slower, both in the experimental preparation (86) and in man (90,91). The reason for this difference in MM-3 conversion rates between the bolus injection and myocardial infarction is that in the former, as MM-3 is rapidly and irreversibly converted to the modified forms, it is depleted from the serum. The same is true when MM-3 is incubated in serum in vitro. On the other hand, in myocardial infarction, as MM-3 is converted to MM-2 and MM-1, it is replaced in the serum with more MM-3 from necrotic myocardium, thus maintaining MM-3 at elevated levels until CK release is complete; generally, 16 to 24 hours after the onset of infarction. With the cessation of release, circulating MM-3 is quickly modified, and MM-3 levels drop toward baseline. Thus, sustained elevation of MM-3 suggests

persistent release of tissue MM and, conversely, rapid decrease of MM-3 suggests that release of tissue MM has ceased. The kinetics of the isoforms after infarction in man is illustrated by the results from a representative patient in Fig. 7.

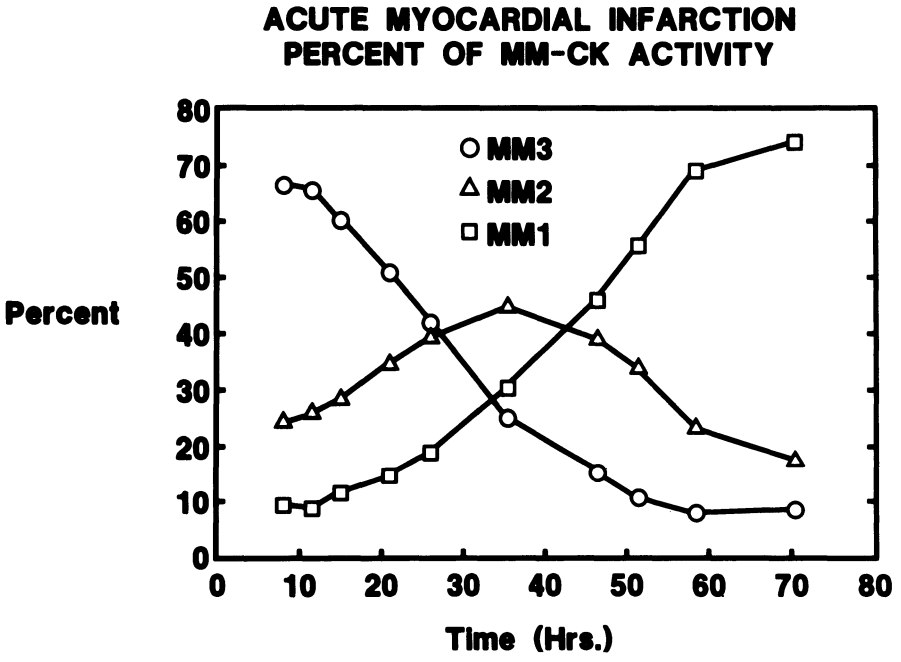

Fig. 7. Shown here are the changes in the three isoforms following acute myocardial infarction. MM-3, the tissue form, peaks immediately after onset of release, representing about 68% of the total activity, and declines rapidly to about 20% at 35 hours. Corresponding with this rapid decline in MM-3, one sees a corresponding increase in MM-2 and MM-1, with MM-2 making up about 75% of the total activity by 70 hours which is similar to baseline. These curves illustrate the rapid conversion of tissue MM-3 to MM-1 and MM-2 and how release of MM-3 reflects new tissue injury, reaching a peak very early after onset of symptoms.

Since CK washout is rapid in experimental and clinical reperfusion, it was reasonable to assume that MM-3 would decline rapidly in the setting of reperfused infarction, but remained elevated for a much longer period with non-reperfused infarction. Accordingly, we explored this hypothesis in 45 patients who underwent thrombolytic therapy (91). Blood samples were collected every four hours for 48 hours for MMCK isoform analysis. All patients underwent acute cardiac angiography to determine the success of therapy. The mean decline of MM-3 in the reperfused group was significantly more rapid than in the unsuccessful reperfusion group (-4.5%/hour versus -1.9%/hour; $p<0.001$). A cutoff point of -3.3%/hour provided good separation of the reperfused from the non-reperfused patients, so that 24 of 26 reperfused patients had a rate of decline faster than the 3.3%/hour, and 18 of 19 non-reperfused patients had a slower rate of decline, yielding a sensitivity of 92% and a specificity of 95%. These results are preliminary, and further prospective confirmation of these findings in a larger number of patients is necessary. In a preliminary study by Morelli et al (83) in a smaller number of patients, it was shown the CK isoforms can be used to detect reperfusion.

Spontaneous Reperfusion and the CK Isoforms

The role of MMCK isoform analysis in establishing the presence or absence of spontaneous reperfusion is relatively unexplored. The data of DeWood et al (1) strongly suggested that most, if not all, Q-wave infarctions are initiated by complete coronary occlusion. He also noted the incidence of complete coronary occlusion on coronary angiography decreased as the time from onset of symptoms increased and, thus, postulated spontaneous reperfusion had occurred. However, it should be kept in mind that in patients with Q-wave infarction, incomplete occlusion was seldom present on cardiac catheterization in the initial interval of six hours. In a group of patients with early peak of plasma MB CK, Ong et al (92) noted an increase in the left ventricular ejection fraction which was significantly greater than that observed in patients

exhibiting late peaking of the plasma CK activity and postulated that this was due to spontaneous reperfusion resulting in more rapid washout of CK. However, in this study, no attempt was made to document spontaneous reperfusion on coronary angiography.

There is considerable anecdotal data to suggest spontaneous reperfusion occurs, but most of it is based on the high incidence of incomplete occlusion of the coronary artery related to the area of infarction noted in patients studied several hours to weeks after onset of the infarction (1,93-95). The studies in the TIMI trial in which cardiac catheterization was performed acutely and eight to 10 days later showed late spontaneous reperfusion may occur, but of course those patients did receive heparin therapy. There is yet no angiographically documented case of early spontaneous reperfusion (88). Whether or not early spontaneous reperfusion occurs, say within the first four to six hours, has important implications for enzymatic estimation of infarct size as well as for etiology and management. Early spontaneous reperfusion would be expected to distort total and plasma MB CK curves as well as the isoforms, and one would expect overestimation of infarct size based on CK in this setting. Late reperfusion after six hours may distort the plasma CK isoform curves but have less effect on total or plasma MB CK curves, and although more rapid washout occurs, enzymatic estimates of infarct size is likely to remain accurate. Most of the myocardial injury has evolved by six hours, if not by four hours, and proteolytic activity which may account for some of the depletion of myocardial CK is also probably completed by six to eight hours. Thus, enzymatic estimates may remain valid if perfusion occurs after eight hours, even if peak activity does occur somewhat earlier. Consequently, whether spontaneous reperfusion does occur, its functional significance in attentuating infarct size and the degree to which spontaneous reperfusion can be detected by enzymatic analysis remains uncertain.

Recent studies have also shown that the incidence of late spontaneous reperfusion may not be as high as originally claimed (95-98), and patients who within the first three to six hours have an incomplete coronary artery obstruction may indeed have had an initial partial occlusion as the precipitating event for their infarction (87). In preliminary studies from our laboratory, results suggest that, as for total and plasma MB CK, the CK isoform time-activity curves are not

significantly different whether the patient has total or subtotal coronary stenosis. The reason for the lack of rapid washout of CK with incomplete occlusion is not clear. It may reflect a more gradual physiological process rather than the sudden rapid induction of reperfusion as observed with thrombolytic therapy, or it may again reflect better perfusion throughout the course of the infarction without any spontaneous reperfusion. Recent studies from Blanke et al (99) and Rogers (100) also suggest that patients with incomplete occlusion and acute infarction do not exhibit significantly different plasma total and MB CK time-activity curves than those of patients with complete obstruction. If, in fact, spontaneous reperfusion occurs after one to two hours of symptoms, one would not likely detect a difference in total or plasma MB CK, and indeed it may be difficult even with the CK isoforms unless multiple early samples are obtained. Full elucidation of the nature and incidence of spontaneous reperfusion and its effect on release of plasma creatine kinase awaits further investigation.

Even less clear is the pathophysiology of nontransmural, or non-Q-wave infarction. The non-Q-wave infarction generally involves less acute loss of myocardium than transmural, or Q-wave, infarction and, consequently, is associated with a lower acute mortality. However, subsequent angina and reinfarction occur at a much greater rate resulting in a long-term mortality similar to Q-wave infarction (101,102). Arteriographic studies have demonstrated a significantly higher incidence of incomplete occlusion in non-Q-wave infarction than in Q-wave infarction (103). Therefore, the difference in acute survival might be on the basis of spontaneous reperfusion with a higher incidence of late events due to subsequent reocclusion. The other definite possibility, as suggested by Ganz et al (104), is these patients have an initial incomplete occlusion which may completely occlude later or they simply undergo repeated attacks of incomplete occlusion. The role of CK isoforms in this setting has yet to be elucidated. It is conceivable that isoform analysis might identify patients with non-Q-wave infarction who indeed undergo spontaneous reperfusion. If, indeed, such a group can be identified at risk for late events, as opposed to those with non-Q-wave infarction but with complete occlusion, the former group would indeed benefit from more intensive medical therapy or some form of revascularization.

Detection of Coronary Reocclusion and Reinfarction

We and others have shown previously that plasma MB CK is an effective means of detecting early reinfarction (101,105-107). These studies, however, refer to a secondary elevation in plasma MB CK which occurs 48 hours or later after the onset of the initial infarction after MB CK has returned to baseline. The detection of extension or reinfarction within the first 24 to 48 hours, however, has not been reliable with the use of total of plasma MB CK. The recent introduction of convenient clinical assays for plasma CK isoforms may also improve our ability to detect reinfarction within the first 24 hours. Dating the onset of extension or reinfarction, whether it occurs after 48 hours or several days later, should be possible with the CK isoforms, and one should detect reinfarction or extension much earlier than with total or plasma MB CK.

Follow-up studies have shown a substantial portion of patients who undergo successful reperfusion with thrombolytic therapy subsequently develop coronary reocclusion and reinfarction. The use of plasma MB CK and the CK isoforms should also be of significant benefit in early detection of such reocclusion when associated with myocardial damage. Early coronary reocclusion within hours of successful thrombolysis may in part account for that subset of patients who despite successful reperfusion fail to exhibit improved ventricular function or survival. Preliminary data (108) from our laboratory have shown that successfully reperfused patients who had significant improvement in the left ventricular ejection fraction have a single peak in their plasma MB CK curve with a rapid decrease. In contrast, patients whose left ventricular ejection fraction failed to improve despite successful reperfusion had multiple peaks of plasma MB CK activity with a secondary rise in MB CK eight to 16 hours after the initial peak. These results suggest that in such patients, early reocclusion could be responsible both for the failure to improve left ventricular function as well as the secondary release of myocardial MB CK. The CK isoforms should be even more sensitive in detecting new tissue injury and, thus, is an exciting potential area in which not only may the CK isoforms provide a marker for successful reperfusion, but may also attest as to whether perfusion is adequate and sustained. It is clear that overall the CK isoforms

have a tremendous potential in the noninvasive assessment of patients with acute myocardial infarction with or without reperfusion.

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10

THE MEASUREMENT OF ACUTE MYOCARDIAL INFARCT SIZE BY CT

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INTRODUCTION

Over the past 15 years clinicians have been challenged by the idea that patients with acute myocardial infarction could have myocardium saved if treatment was initiated soon enough.(1) This concept that myocardium destined to become necrotic could be salvaged is still controversial.(2) Many reports have suggested a variety of medications to reduce myocardial oxygen consumption or increase coronary perfusion at the borders of the evolving infarction.(3-6) More recently, the rediscovery that myocardial infarction is often precipitated by an acute thrombosis of a coronary artery has stimulated the use of thrombolytic agents to dissolve the thrombus and reestablish perfusion in the occluded vessel.(7) However, in spite of more than a decade of investigations evaluating the effects of these many therapies, there is still significant controversy about the effectiveness of any of these agents.(8) A major reason for the continuing confusion is the lack of a satisfactory method for accurately measuring the amount of infarcted myocardium and judging the quantity of jeopardized myocardium that is potentially salvageable. In a recent review of infarct limiting therapy, Mueller and Braunwald state "the assessment of the efficacy of therapeutic intervention has been greatly hampered by the absence of a direct method of determining infarct size in patients with nonfatal myocardial infarction. In addition to identifying salvage of myocardium, it is helpful not only to measure but also to predict how large the infarction would have been had the intervention not been applied. Such predictions are difficult, if not impossible, in the clinical situation at the present time."(9)

X-ray transmission computed tomography (CT) is capable of imaging acute myocardial infarction in both animals and man.(10-12) With the recent development of ultrafast CT which provides high resolution images of the infarcted myocardium and simultaneous assessment of regional ventricular function by defining wall motion and wall thickening, CT may well be the diagnostic tool for which Mueller and Braunwald and others have been searching.(13,14)

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Animal Experience

In 1976, CT imaging of acute myocardial infarcts was first reported using a head scanner.(15) Because this scanner was so slow, infarcts could only be visualized in the nonbeating heart. The infarction was detected by its decreased x-ray attenuation compared to normal myocardium. The low CT density of infarcted myocardium has been attributed to increased water content (edema). Infarcted myocardium could not be detected in the beating heart until faster scanners were developed and contrast enhancement was employed.(16) Higgins and co-workers, have extensively studied the use of contrast medium to delineate experimental infarcts in dogs.(17) They described two methods of defining acute myocardial infarction. Immediately following the administration of contrast medium, an area of low density compared to normal myocardium defines the infarct. After 10 to 180 minutes post contrast administration the infarcted myocardium develops increased enhancement compared to normal myocardium. Higgins defined three types of contrast enhancement: Global enhancement, where the entire infarct becomes more dense than normal myocardium and this was observed in 40% of animals. Partial enhancement of the epicardial periphery of the infarct and this was observed in 30% of the animals. No delayed enhancement was seen in the remaining 30% of animals. Abraham and Higgins demonstrated increased iodine concentration in necrotic myocardial cells after the intravenous injection of contrast medium by a scanning electron microscropic technique.(18) This work suggests there is loss of myocardial cell membrane integrity following ischemic injury which permits the iodinated contrast accumulation. Normally contrast agents remain in the extravascular space and do not enter living myocardial cells. The movement of iodine into non-viable myocardial cells is similar to the shift of sodium and chloride ions observed after infarction. Others have observed that delayed contrast enhancement most frequently occurs in the epicardial portion of the infarct.(19) This region also develops the greatest collateral blood flow in experimental dog infarcts. This coincidence suggests that delayed enhancement of infarcts is dependent on collateral blood flow to deliver iodinated contrast to the dead myocardial cells, therefore those in contact with the greatest collateral flow show the greatest enhancement. Delayed contrast enhancement has been demonstated to occur as long as two months after infarction. This finding is consistent with histologic data that indicates that necrotic cells persist for 6 to 8 weeks or longer after infarction. Carlsson and co-workers also suggest that neovascularization of the infarct may be another mechanism that causes delayed contrast enhancement several weeks after infarction.(20)

Several investigators have correlated CT and post-mortem measurements of infarct size in dogs. The first studies were done in excised non-beating hearts.(16) The correlation was high but infarct size was underestimated. Subsequent studies of beating dog hearts found an excellent correlation between CT and post-mortem infarct size.(10)

Myocardial infarction has been shown to progressively increase in size in dogs during the initial 4 days, probably because of edema of the infarcted myocardium.(21) This initial increase is followed by a gradual reduction in infarct size over the next month as the necrotic myocardium is replaced by fibrous tissue.(20) Another interesting observation in one dog study is the increase in mass of the normal myocardium over the first 30 days, indicating that hypertrophy may occur to compensate for muscle lost to infarction. If similar changes follow acute

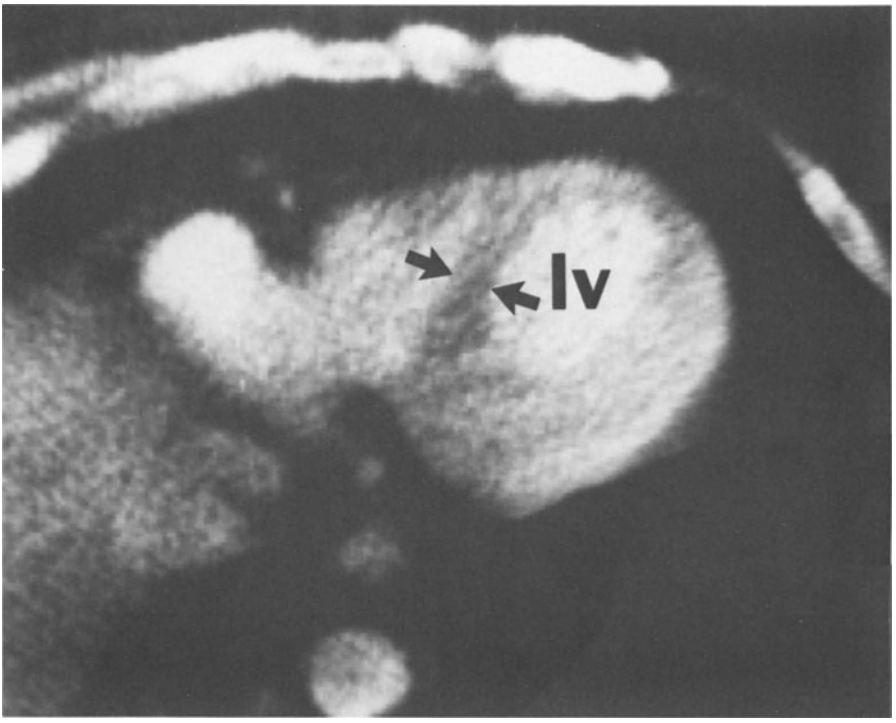

Fig. 1 A transmural (arrows) septal infarction is delineated by contrast enhancement. Note the infarction becomes subendocardial anteriorly and then again transmural. LV = left ventricle, RV = right ventricle.

infarction in humans then care must be taken interpreting the effects of therapies thought to limit infarct size.

Human Infarct Experience

Building on the experience with animals, we have imaged acute myocardial infarcts in 19 humans.(11) Using a conventional body scanner with a 2.4 second scan time and contrast enhancement, infarction was identified as a region of low density (Figure 1). Evidence of infarction was seen in all 13 patients with anterior infarcts but detection of inferior wall infarcts was difficult. This problem is primarily due to the orientation of the inferior wall to the scanning beam and movement of the inferior wall in and out of the scanning plane. Initial experience with the new ultrafast CT scanner indicates that inferior wall infarcts can be imaged with greater frequency because motion artifact has been eliminated.(13) However, axial anglelation of the scanning beam needs to be further increased so it will strike the inferior wall more perpendicularly. When the scanning beam is at right angles to the area of infarction it significantly increases CT's sensitivity for

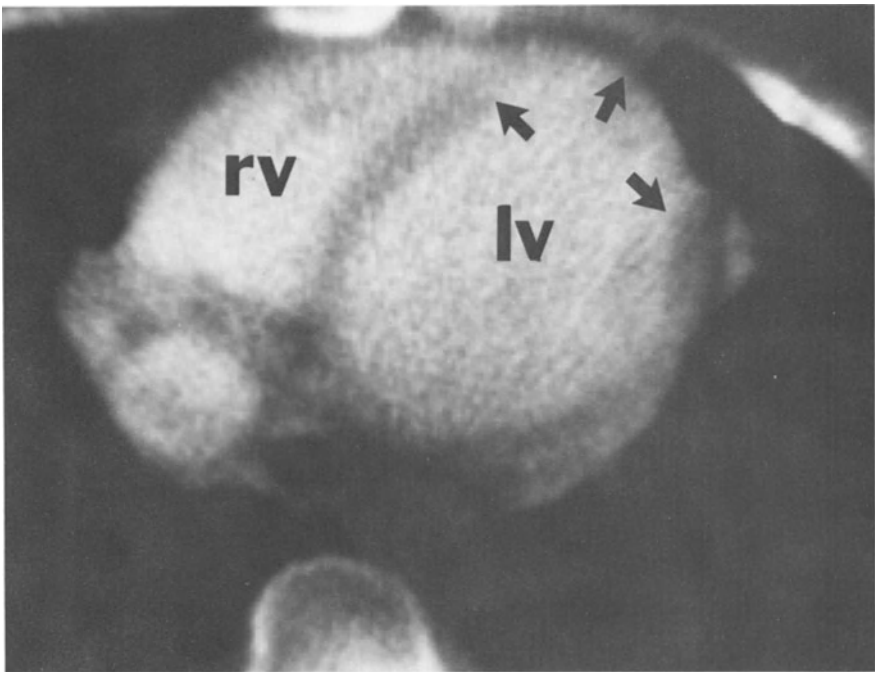

Fig. 2 A healed transmural infarction is identified as a region of thinned ventricular wall (arrows). Note the abrupt change in wall thickness. LV = left ventricle, RV = right ventricle.

detecting infarction. Others have recently reported the same difficulty in imaging inferior wall infarcts with 2 seconds body scanners.(12)

We observed that after 2 weeks, infarcts are noticeably thinned.(11) Masuda and co-workers also observed this change in wall thickness and documented a progressive decrease over the first 30 days after infarction.(12) Minimal thinning continues over the next two months (Figure 2).

Delayed contrast enhancement of myocardial infarction is frequent in dogs but we observed it in only 5% of our patients. Masuda et al, reported a higher incidence in their patients but they included patients far beyond the acute phase of infarction. They observed a 30% incidence in patients scanned within 1 month of infarction. They found as we, that the low density perfusion defect seen at the termination of the contrast medium injection best defines the infarct. We administered contrast by infusion and they used a bolus technique. Now with the availability of ultrafast CT,

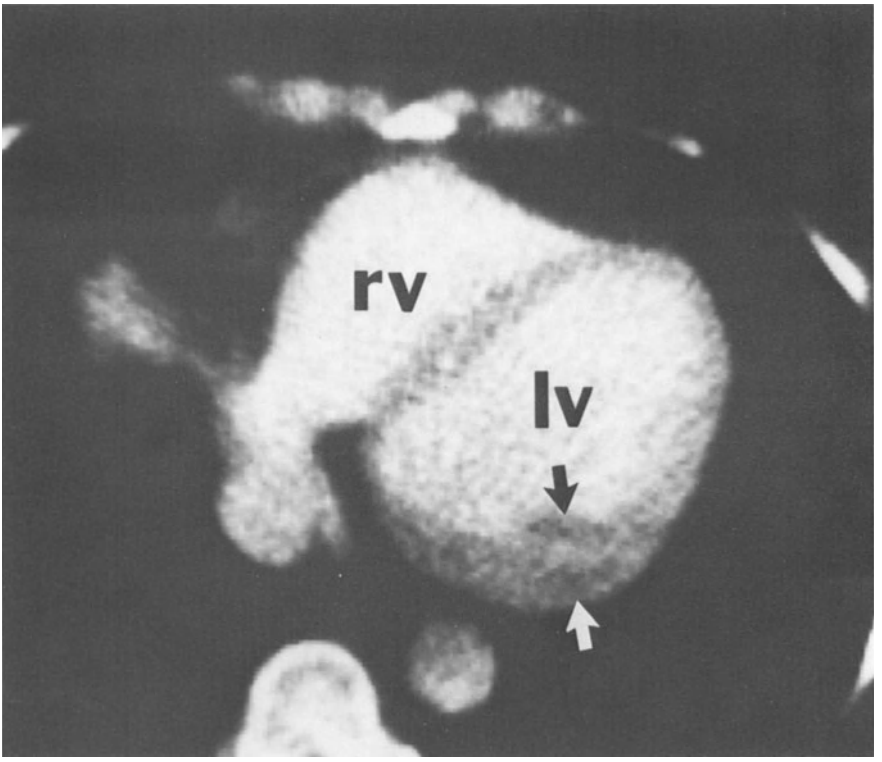

Fig. 3 A small subendocardial posterolateral wall myocardial infarction is seen on this CT scan (white arrow). A portion of the lateral papillary muscle is also infarcted (black arrow). LV = left ventricle, RV = right ventricle.

bolus injection is probably the best method for imaging infarcts because this method not only defines the extent and spatial distribution of the infarction but permits estimation of the regional myocardial blood flow as well.(22)

Imaging acute myocardial infarction by CT provides a 3 dimensional analysis of the distribution of the infarct. This feature may improve our understanding of such clinical entities as transmural and subendocardial myocardial infarction (Figure 3).

We measured acute infarct size in 11 patients with a 2.4 second body scanner. Infarct images were obtained by infusing 1.5 ml/kg body weight of contrast in approximately 10 minutes. At the end of the infusion adjacent one cm single scans were obtained from the base to the apex of the heart. As already described, the infarcted myocardium was recognized by its characteristic low density compared to normally enhanced myocardium. The infarct volume was measured by tracing the margins of the low density myocardium and computing the area by planimetry. Since each slice is 1 cm thick, the area represents the volume in cubic cm. The total volume of infarction was then computed by summing the measured volumes from all scans where infarction was identified. The total CK was determined every 6 hours after the patient's admission to the coronary care unit for 3 consecutive days. The CT volume was then compared to the area under the total CK curve by linear regression (Figure 4).

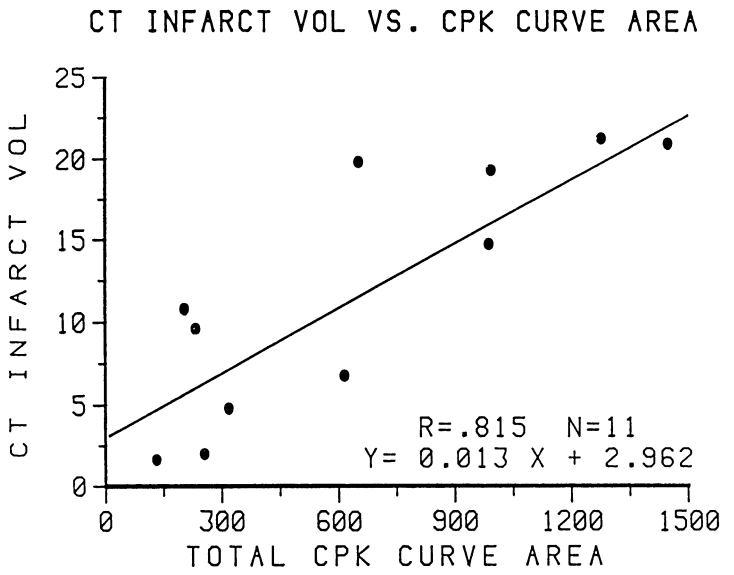

Fig. 4 The linear regression comparing infarct volume measure by CT with area under the total CPK curve for 11 acute myocardial infarctions.

The correlation was highly significant ($p < 0.01$) with an r value of 0.81. The 11 patients were scanned from 3 to 11 days after the acute infarction. The patients were divided into two groups, those scanned less than one week after infarction and those scanned 1 week or more after infarction. The infarct volumes of the 7 patients scanned 7 or more days after acute infarction correlated even better with total CK curve area ($r=0.98$, $p<0.001$) (Figure 5).

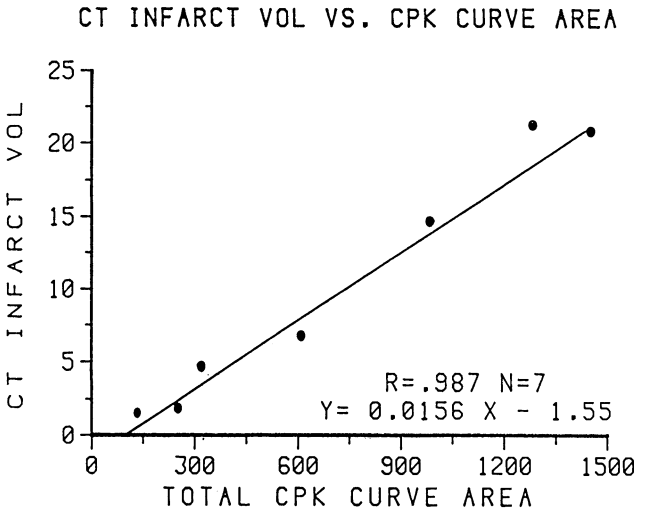

Fig. 5 The linear regression for 7 acute infarcts in Figure 4 imaged by CT 7 or more days after onset.

Note the intercept of the regression line in Figure 5 is shifted downward compared to that in Figure 4, indicating there was infarct shrinkage with time. These findings are consistent with the animal data showing that infarcts increase in size for about 4 days and then gradually shrink the first month after infarction.(21) These infarct sizing data obtained in humans using a conventional body scanner indicate there is real promise that CT may provide an accurate measurement of infarct size. Indeed, more recent experience with the ultrafast CT scanner, suggests that the quantitation of infarct size with this imaging modality is going to be clinically useful.(13)

Infarct Sizing By Other Methods

The most frequently used method for estimating infarct size has been the analysis of CK or CK MB time activity curves. Shell, Sobel and Roberts popularized this method for estimating infarct size in the early 1970's and several refinements have subsequently been reported.(23-25) Review of many clinical

studies reported using this method, clearly indicates there is a correlation between infarct size and the amount of CK enzyme released. Recently an autopsy study demonstrated a good correlation between CK-MB release and infarct size measured at autopsy.(26) However, a comparison of values for human infarcts reported in the literature ranges from greater than 100 gm. equivalents to less than 20 gm. equivalents. This five fold difference in estimation of infarct size can in part be explained by differences in patient population; however, the wide range raises questions about the accuracy of this technique for estimating infarct size.

Early reperfusion of an infarct, after successful thrombolytic therapy, causes greater release of CK and enzymatic analysis often overestimates infarct size.(27) Furthermore, investigators have suggested the technique may overestimate the size of small infarcts.(28) If true, this fact would limit the use of enzymatic estimations of infarct size to evaluate infarct limiting therapies most often employed in patients with small to moderate size infarctions. Indeed the excellent correlation between CK estimate of infarct size and autopsy measurement has to be biased by patients with large infarcts which caused their death.

Enzyme techniques for quantifying infarct size require at least 9 hours of enzyme release in order to reasonably estimate infarct size.(29) Therefore, this technique can not be used to evaluate infarct limiting therapies by projection of the early levels because 9 hours is too late to institute infarct limiting therapy and expect a significant beneficial effect. In order to evaluate infarct limiting therapy with the enzymatic method, patients must be divided into a control and treatment group, then the effect of therapy can only be judged by any enzyme release difference between the two groups. Therefore, an infarct sizing technique that would permit estimation of infarct size before and after therapy in the same patient would be highly desirable.

The great variability of infarct size among the reports in the literature may be partially explained by the different values employed to gauge enzyme clearance from the plasma. This constant (Kd) is determined for the individual patient in some studies while in others it is assumed using values reported in the literature. However, these Kd values range from .001 to 0.086 IU/min, and depending on the constant used a marked difference in the estimated size of infarction can be obtained.

Planar imaging of infarcts with the radioisotopes technetium 99m pyrophosphate and thallium 201 have shown a correlation between the hotspot or coldspot and infarct size.(30,31) However, the spatial resolution of these

techniques is poor and they are hampered by overlap of the infarct by other structures. They have not received wide clinical acceptance as useful tools for measuring infarct size. More recently, several reports using single photon emission computed tomography with the same two isotopes have reported better correlations with infarct size.(30-33) However, the spatial resolution of these images is still relatively poor and better methods for sizing acute myocardial infarction continue to be sought.

Positron emission tomography is a new radioisotope imaging technique which is providing valuable information about cardiac metabolism in ischemic heart disease and acute myocardial infarction.(34) The method however has the same spatial resolution limitations as any isotope technique and it is unlikely it will become the preferred method for sizing acute myocardial infarction.

Improvements in echocardiographic imaging continue with the development of better transducers and computer enhancement of images. Experimental work indicates that the echogenisity of infarcted myocardium is different than normal myocardium and acute myocardial infarcts have been identified in animal models.(35) However, at the present time this method usually requires direct application of the echotransducer to the external surface of the heart, something which is obviously not clinically feasible. Contrast agents for echocardiography that can be used to evaluate myocardial perfusion are under development.(36) Currently, these agents have to be injected directly into the coronary arteries or proximal aorta in order to achieve a concentration adequate to be detected by echocardiography. If these agents can be developed to the point where intravenous injection will produce adequate contrast enhancement of the myocardium, then acute myocardial infarction could be detected by echocardiography.

The most exciting new imaging technique is nuclear magnetic resonance (NMR) and several reports have already appeared in the literature indicating that detection of experimentally produced myocardial infarction is possible with this technique.(37) There is some indication that contrast enhancement will be necessary to image myocardial infarction in vivo. Recent reports suggest further development of contrast agents will be necessary before acute myocardial infarction can be satisfactorily imaged by NMR.(38)

Future of CT

The brief review of other methods employed to quantify infarct size emphasizes the need for an accurate clinically applicable technique. With the development of ultrafast computed tomography, which produces motion artifact

free images of the heart,such a technique may now be available. Using contrast media, acute myocardial infarction can be detected as a region of low x-ray attenuation. The clarity with which the infarction can be seen allows easy measurement of the volume of myocardium involved. Further improvement in the image quality of this new scanning technology can be expected and should enhance the ability of CT to detect even very small infarcts.

The cause of delayed contrast enhancement of infarcts is unknown as are the incidence differences between dog and man. Further investigation of this phenomenon is required and may lead to a better understanding of the pathogenesis of acute myocardial infarction and indeed even improve the accuracy of measurement.

At the present time, based on the very limited data available, CT may underestimate infarct size. Creatinine phosphokinase enzyme techniques give average infarct sizes in the range of 30 to 40 grams and SPECT imaging with technetium or thallium report average sizes between 20 and 30 grams. The experience with CT, although very limited, indicates that average infarct sizes are between 10 and 20 grams. Further elucidation of the differences among these techniques is necessary. Possibly, the margins of human infarcts may develop enough contrast enhancement which at the present time is not being distinguished from normal myocardium so it is not included in the infarct measurement and causes underestimation.

Probably the most exciting development with the advent of ultrafast computed tomography is the possibility of employing this technique to measure regional myocardial blood flow.(22) Any technique used to measure myocardial infarct size would be greatly enhanced by the ability to determine regional myocardial blood flow at the same time. Continued controversy over the value of a wide variety of therapies to limit infarct size requires a method that can measure regional blood flow before and after therapy. In a recent review of thrombolytic therapy Sobel stated "to define the possible benefit of thrombolysis, we need to know the status of nutritional perfusion". He observed that "we do not know the magnitude of the no reflow phenomenon in man and that we need to be able to evaluate nutritional perfusion in an area where we have increased supply as with thrombolysis not only immediately but after 24 hours and even after a week in order to judge whether the patient has truely benefited". Ultrafast computed tomography shows real promise as a tool that can provide such information.

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11

MAGNETIC RESONANCE IMAGING FOR EVALUATION OF MYOCARDIAL ISCHEMIA AND INFARCTION

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INTRODUCTION

Magnetic Resonance (MR) is a completely noninvasive modality, which employs high-strength static magnetic fields, low-strength changing magnetic fields, and radio-frequency (RF) pulses to generate tomographic images with high soft-tissue contrast (1, 2). Because of the abundance of hydrogen in biologic tissues and its efficiency (maximum number of nuclei per atomic number) for MR, hydrogen (proton) resonance has, in general, been used for imaging various regions of the body, including the cardiovascular system (3-5).

BASIC PHYSICAL PRINCIPLES OF MRI

Physics

The fundamental physics of Magnetic Resonance Imaging (MRI) are described in great detail elsewhere (6, 7). Atomic nuclei with an odd number of protons and/or neutrons have a magnetic moment which causes them to align with (parallel or antiparallel) the lines of force of the static magnetic field. With the application of RF pulses of a specific frequency characteristic of the nuclei (Larmor frequency), these nuclei will realign away (nonparallel) from the magnetic field. After cessation of RF transmission, the displaced nuclei will resonate at a specific frequency during their return to equilibrium. During this process, called relaxation, the nuclei emit the previously absorbed RF energy that can be utilized to generate images.

Monitoring of the distribution (concentration and location) of the resonant nuclei within the body is the basis for MRI. However, the intensity of the signal at any site, and consequently the image contrast between tissues, is not dependent only on the density of the nuclei. Intensity is also influenced by rates of magnetic relaxation by the nuclei, temperature, viscosity, and blood flow.

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The magnetic relaxation times, which are themselves affected by a variety of physical and chemical factors, are described in detail elsewhere (8, 9). Briefly, T1 (spin-lattice or longitudinal relaxation time) is an estimate of the rate at which nuclei realign with the static magnetic field after the RF perturbation, and T2 (spin-spin or transverse relaxation time) is an estimate of the rate of loss of coherence amongst the nuclei after the pertubation. The relaxation times are parameters used to characterize tissue of various organs in healthy and diseased states.

Of the variety of MRI techniques available to generate images, saturation recovery, inversion recovery, and spin echo technique (a special type of saturation recovery) have been most frequently employed. These techniques vary in the type of RF pulses applied, the time between the initiating RF pulse and the sampling of the signal, and the time between each set of pulses (repetition time, TR). Image contrast can be altered by a change from one technique to another or, within a particular technique, by variations in the interval between pulse sequences (i.e. TR)(10). Some techniques, such as saturation recovery and inversion recovery, provide contrast emphasizing T1 differences between tissues. Other techniques, such as spin echo, evaluate both T1 and T2.

Shortening the interval between pulse sequences (each consisting of only a 90-degree RF perturbation pulse in saturation recovery and both a 90-degree initiating perturbation followed by a 180-degree refocusing pulse in spin echo) will generally enhance tissue contrast according to T1 differences. This is because tissues with longer T1 will realign less with the static magnetic field before a new RF excitation is initiated, and thus yield less signal than those with shorter T1. Varying the signal sampling time (echo delay time, TE) within a spin echo sequence will selectively enhance contrast according to T2 differences. Tissues with longer T2, indicating a slower loss of internuclear coherence, provide greater intensity. Each organ exhibits its own characteristic range of values for T1 and T2, and pathologically damaged organs frequently exhibit relaxation values outside normal range.

Importantly for MRI of the cardiovascular system, motion of nuclei through the region being imaged will influence signal intensity (3-5, 11-16). Although the influence of blood flow in MRI is complex, and depends somewhat on the technique used, the motion of the excited nuclei during the MRI sequence generally causes a decrease in signal intensity with higher rates of flow.

Instrumentation

MRI requires strong, homogenous, and stable magnetic fields. The field strength of most current proton MR imagers ranges from 1 kG (0.1 tesla) to 5 kG (0.5 tesla). A number of different types of magnets, which have been described elsewhere (2), are now available.

The technology has focused on the use of superconducting magnets for both proton imaging and spectroscopy of other nuclei. These electromagnets, responsible for the static magnetic fields, consist of niobium-titanium coils, which are made essentially nonresistant to current flow by extreme cooling (negative 40 degrees Kelvin by liquid helium and liquid nitrogen). The superimposed weak magnetic field gradients are supplied along each of the three main planes of the imager by gradient coils during each RF excitation sequence. These field gradients define the plane thickness and encode spatial identity to the image acquisition and reconstruction processes.

The MRI process also requires the repetitive application of RF pulses. RF transmitter and receiver are located at 90 degrees to the main magnetic field for production of RF pulses and reception of the MR signal from the imaged volume, respectively.

Spectroscopy

The nondestructive in vivo monitoring of metabolism by the MR process requires the evaluation of elements of biologic interest other than hydrogen. Because of the lesser abundance and lower efficiency of nonhydrogen species, such as carbon 13, sodium 23, and phosphorus 31, imaging with these elements is much more difficult than with hydrogen (17). Distributions of these elements in metabolically important compounds can be investigated by high-resolution MR spectroscopy.

In vivo spectroscopy of nuclei other than hydrogen requires field strengths of 15 kG (1.5 tesla) or more. Surface coils are placed over the region of interest on the body, resulting in the large signal-to-noise level required for sampling nonhydrogen nuclei which are far less abundant than hydrogen.

TECHNICAL ASPECTS OF CARDIAC IMAGING BY MRI

General

The cross-sectional imaging format is generally used for cardiac MRI studies, although alternative imaging planes have been described (18-20). In

contradistinction to computed tomography, but similar to echocardiography, the walls of the heart and vascular structures are clearly distinguished without need for contrast media (3-5, 11, 12). The inherent sharp interface in contrast between flowing blood in the cardiac chamber and the cardiac walls results in clear discrimination of the inside and outside of all walls of the heart.

Physiologic Gating

Due to deterioration of images from the loss of signal associated with moving structures and the variable position of cardiac structure relative to imaging pixels when data is acquired indiscriminately throughout the cardiac cycle, physiologic gating of the image sequence is usually necessary. Three devices for gating the MRI sequences to a fixed segment of the cardiac cycle have been employed (21-23). They include a sphygmomanometer plethysmograph which detects changes in limb distention with arterial pulsation, a laser-Doppler velocimeter that detects the cyclic changes in capillary blood volume of a superficial capillary bed (tongue or ear lobe) beneath a 1 mm^3 light probe, and an electronically isolated electrocardiogram (ECG) electrode-lead circuit.

In the setting of MR, gating is associated with unique problems since sensors, wire leads, and transducers are, in general, composed of ferromagnetic materials. When situated within the RF shield room, containing the MR imager, they may generate considerable noise or distortion in the images (24). Consequently, the gating devices have been designed to include a nonferromagnetic circuit for sensing of the physiologic signal.

Although adequate images have been obtained from each of the gating systems, more precise timing of the acquisition to a fixed segment of the cardiac cycle has been obtained with the ECG gating technique (Figure 1). With this technique, the TR is defined by the R-R interval of the ECG. Thus, with a heart rate of 60 beats/minute, the TR is 1.0 second. The TR is 2.0 seconds if gating utilizes every second beat.

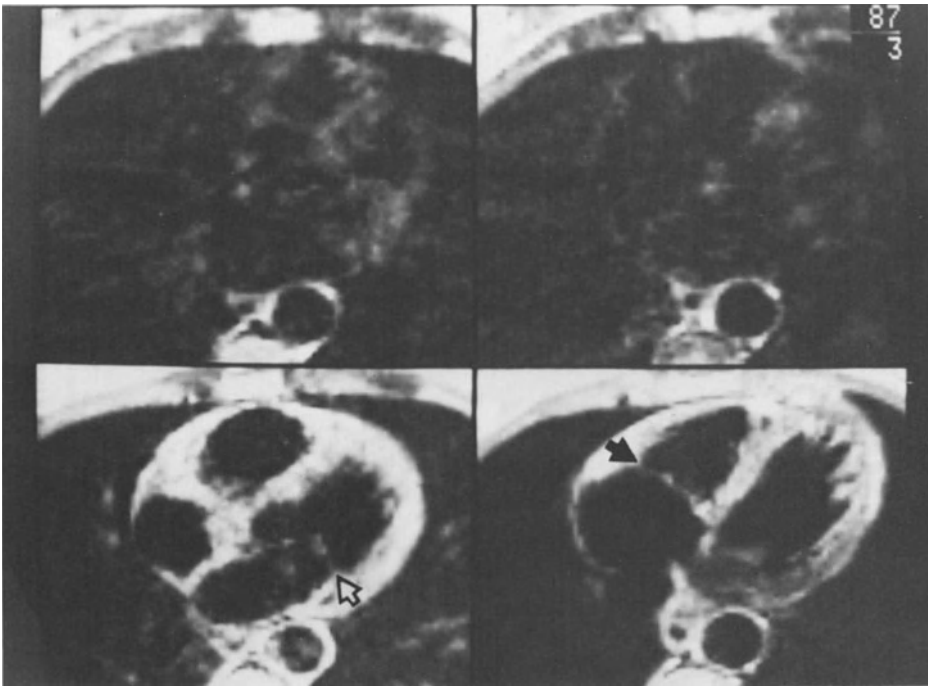

Fig. 1. Cross-sectional nongated (upper) and ECG-gated (lower) MRI images at two transverse levels of the heart of a normal volunteer. Nongated images show inadequate cardiac definition due to cardiac motion during the MRI sequence. On gated images, natural contrast from rapidly flowing blood results in excellent delineation of the myocardial walls. Parts of the mitral valve (white arrow), tricuspid valve or annulus (black arrow), and trabecular pattern of both ventricles are demonstrated. (Reprinted with permission from the Am J of Roentgenol 142:661-667, 1984.)

Because the phase of the cardiac cycle for acquisition of imaging data is short (5-10% of the cycle), it is possible to sequentially image multiple (usually five) consecutive axial sections of the heart during the same cardiac cycle (19). The inherent delay in the imaging (usually 100 msec) of consecutive cardiac levels is manifested in the corresponding images, which represent consecutively later (by 100 msec) stages of the cardiac cycle. With this multisectional technique, gated axial images encompassing most of the left ventricle (LV) can be obtained in an imaging time of approximately 6 to 10 minutes. Multisection imaging can be implemented so as to allow the imaging of

each of 5 levels of the heart at different points in the cardiac cycle (19). Volume (three-dimensional) data acquisition has also been achieved using an ECG-gated sequence (19, 26). With this technique, images in any desired plane can be reconstructed at a later time. As opposed to the multisection technique, all reconstructed planes should be in the same phase of the cardiac cycle for volume imaging. Gated cardiac images in man, which have been generated using a gated saturation recovery or spin echo sequence, tend to highlight proton density.

Although inferior to those produced by gated systems, images produced by nongated MRI employing a pulse sequence with short TR and TE to reduce degradation may be sufficient to provide qualitative diagnostic information (27). A newer method known as echo planar imaging may ultimately permit cardiac MRI in near real-time (28). With this method, images may eventually be produced in less than 50 msec without need for gating.

Safety Considerations

MRI at current field strengths are very safe. No genetic or mutagenic effects of MRI have been demonstrated at the magnetic field strengths, RF pulses, or switching magnetic fields currently employed for hydrogen imaging (29-31). On the other hand, the alterations of magnetic fields may disrupt the operation of cardiac pacemakers even at fringe field strength of 10 G (32). Therefore, to maintain a conservative margin of safety, patients with pacemakers should be excluded from areas with field strengths of 5 G or more.

Another concern has been the production of ventricular fibrillation due to induction of a current into the patient by the rapidly changing magnetic field. A threshold rate of change of magnetic field of approximately 500 tesla/second was necessary to produce ventricular fibrillation in canine experiments (24). With the currently employed proton MR imagers (rate of change of 2 tesla/second for a 0.35 tesla system (25)), there is a large safety margin for the production of ventricular fibrillation.

The strong magnetic fields involved with MRI can displace and/or heat large ferromagnetic prosthetic devices (24). A recent study demonstrated no displacement of prosthetic heart valves when placed in the bore of a 0.35 tesla MR system (33). However, with increasing availability of higher field strength systems, such valves need to be further tested for movement in the higher field strengths. While hemostatic clips in most regions of the body are not a

contraindication to MRI, patients with intracranial aneurysm clips must be excluded from this environment.

Contrast Enhancement

Although contrast enhancement is not needed to delineate the blood-tissue interface of the cardiovascular system, it may prove useful for evaluating myocardial ischemic changes and perfusion. Paramagnetic substances, by accelerating the relaxation process, can shorten T1 and T2 differentially in normal and ischemically damaged myocardium. Consequently, such substances, including manganese compounds (34, 35) and gadolinium-DTPA (36-38), have been used as contrast agents in the evaluation of myocardial ischemia and acute myocardial infarction (AMI) by MRI. Attempts have been made to attach paramagnetic agents to antimyosin antibody in an effort to produce "hot spot" imaging of myocardial infarction (38).

MRI OF VARIOUS ISCHEMIC EVENTS

Acute Myocardial Ischemia and Acute Myocardial Infarction

Initial reports on MRI of excised hearts with AMI (34) suggested that MRI could not distinguish acutely infarcted from normal myocardium without paramagnetic contrast media. However, other studies employing hydrogen spectrometry of tissue samples demonstrated significant prolongation of T1 relaxation time associated with acute ischemia (39-41). More recently, MRI techniques (22, 43-46) have been used successfully to image acute infarction of the myocardium without use of contrast enhancement.

Variable prolongation of T1 relaxation time in AMI has been noted in excised (39-44) and beating (22, 46) canine hearts. More notable is the significant prolongation of T2 relaxation time of ischemically damaged myocardium relative to normal myocardium (22, 43-45). These alterations tend to increase with duration of acute ischemia and are most pronounced in subendocardial regions. Considering that increasing intensity of signal on spin echo images results from decreases in T1 and prolongation of T2, it is apparent that prolongation of both of these parameters, as found in AMI, have opposing contributions to signal intensity. It is most likely that the contribution of T2 prolongation predominates in spin echo MRI, especially when the more T2-weighted second spin echo is employed. Because there is a significant increase in percent water content of infarcted myocardium over that of normal myocardium, with a strong linear relationship between T2 relaxation

time and water content (44), it appears that findings of prolongation of T1 and T2 in AMI are related to these local changes in tissue water (22, 44). In addition, an increase in water content, resulting from edema, increases local spin density which contributes to local increase in signal intensity within AMI. It is likely that alterations in biochemical environment of ischemic cells also contribute to rise in relaxation times (47). In keeping with this hypothesis, T1 prolongation has been demonstrated only 30 minutes after coronary occlusion (39-41), despite evidence that only intracellular and not total tissue water content increases during early occlusion (48). Marked increases in total water content after reflow into an ischemic zone have been noted (49).

Gated MRI performed in vivo experimentally (22, 46) or clinically (45) has demonstrated that acutely infarcted myocardium can be distinguished from normal myocardium without contrast enhancement. The infarcted myocardium, especially the more susceptible subendocardial regions (22, 43), has high signal intensity compared to normal myocardium. Using the spin echo technique (22, 45, 46), substantially greater absolute intensity and contrast with adjacent normal myocardium was obtained in AMI imaged with the second versus the first spin echo (Figure 2).

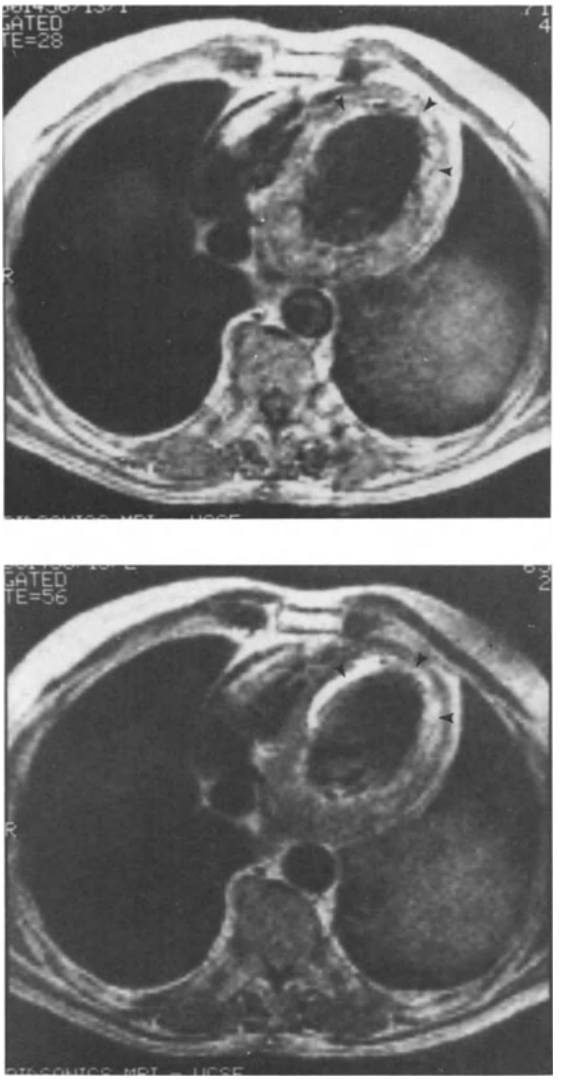

Fig. 2. Cross-sectional ECG-gated MRI images through the middle of the LV in a patient with an acute subendocardial myocardial infarction. Note the high signal intensity in the subendocardium of the intraventricular septum anteriorly and the anterolateral wall of the LV (arrowheads), corresponding to the area of infarcted myocardium. The relative intensity of the infarct is greater on the second spin echo (lower; TE = 56 msec) versus the first spin echo (upper; TE = 28 msec).

The presence and location of AMI has been confirmed at postmortem examination of canine hearts in which coronary occlusion was experimentally induced and resulting AMI imaged in vivo by MRI (22, 46). In patients with AMI confirmed clinically by diagnostic ECG and enzyme/isoenzyme changes, the extent and location of AMI, as determined by MRI, corresponds with that determined by ECG (45). LV wall thinning and chamber dilatation during periods of acute ischemia, which revert toward normal with reperfusion, have also been observed experimentally (50).

While magnetic relaxation times and images have successfully characterized the advanced stages of acute ischemic changes in myocardium (i.e. AMI), hydrogen MRI of early ischemia prior to the onset of myocardial edema or infarction has not been achieved readily. The differentiation of ischemic, but not yet infarcted, myocardium from normal myocardium has not been achieved without contrast enhancement (22, 42-46). No significant differences in either T1 or T2 relaxation times between acutely ischemic (less than 2 minutes of coronary occlusion) and normal myocardium have been noted without the use of paramagnetic contrast agents as perfusion markers (34-36). Significant reduction in T1 and T2 relaxation times have been demonstrated experimentally in normal (34-37) and acutely ischemic (34-36) myocardium following the in vivo intravenous administration of such agents. Because of their differential and time-varying effects on relaxation times in normal versus acutely ischemic myocardium, contrast between normal and jeopardized myocardium can be accentuated by varying the MRI sequence (Figure 3). For example, under the influence of gadolinium-DTPA, normal myocardium undergoes a more rapid decay in transverse magnetization (i.e. T2) than ischemic myocardium, resulting in a relatively greater signal intensity from the ischemic myocardium on the second spin echo (36). Consequently, paramagnetic agents have been used to enhance the contrast between infarcted and normal myocardium on MRI (37).

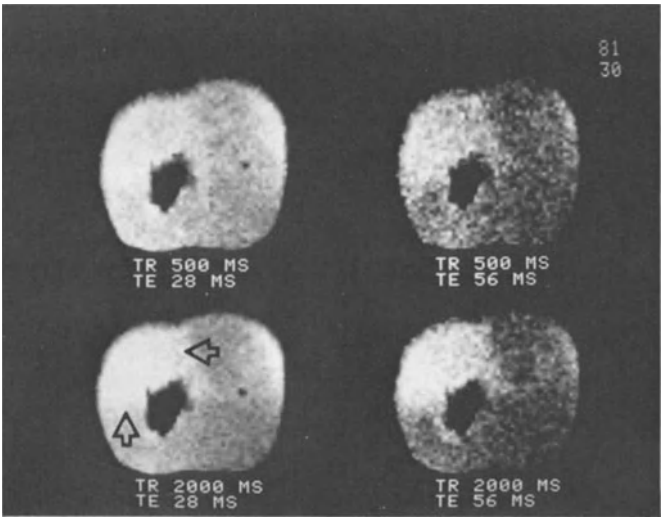

Fig. 3. Cross-sectional spin echo images of the same level of the LV in an excised heart from a dog that received gadolinium-DTPA one minute after acute occlusion of the left anterior descending artery. The TR and TE imaging parameters are shown with each image. The ischemic anterior wall of the LV appears as a high intensity region (arrows) due to relatively more negative enhancement of adjacent normal myocardium by gadolinium-DTPA. Contrast between normal and ischemic myocardium is greatest with increased T2 weighting (lower right; TR = 2000 msec, TE = 56 msec). Ischemic myocardium was not distinguished from normal myocardium in the hearts of control dogs with the same method for induction of ischemia, but without the administration of gadolinium-DTPA. (Reprinted with permission from Radiology 153:157-163, 1984.)

Chronic Myocardial Infarction

MRI techniques can differentiate both AMI and chronic myocardial infarction (CMI) from normal myocardium, and can distinguish AMI from CMI. The AMI can be recognized by high signal intensity of the myocardium, while the CMI has decreased signal intensity in comparison to normal myocardium. A CMI in various locations of the heart can be demonstrated on gated MRI by its regions of wall thinning (3, 51). The transition from normal myocardial wall thickness to regions of CMI is sharply defined, providing an estimate of the extent of involvement of the LV (Figure 4). These MRI findings have been correlated with LV angiogram and/or echocardiogram.

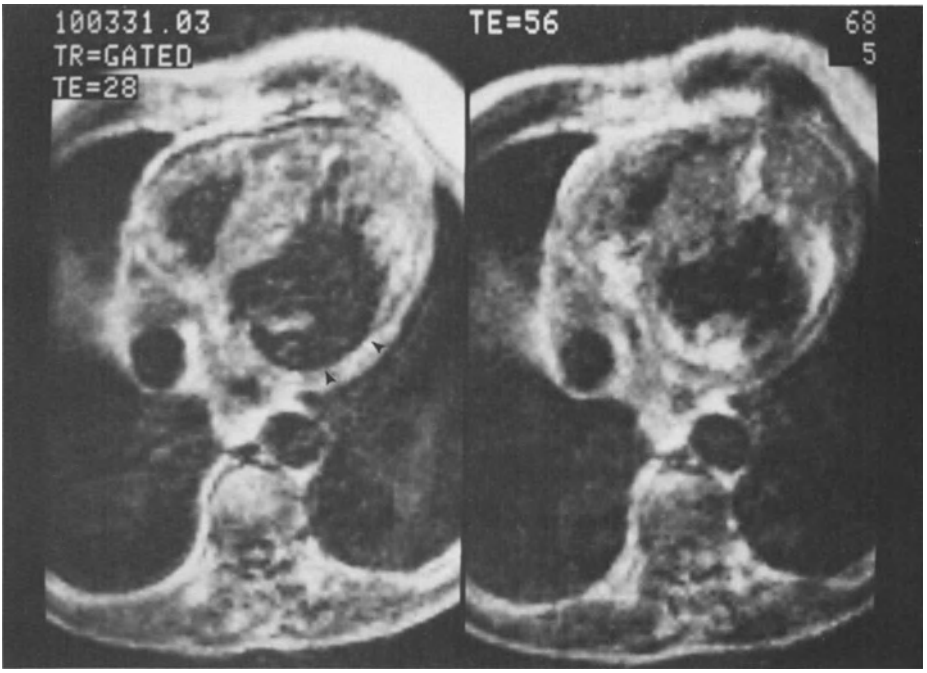

Fig. 4. Cross-sectional ECG-gated MRI images through the LV in a patient with a chronic transmural posterolateral myocardial infarct, manifested as regional wall thinning (arrowheads). The image produced from the first spin echo (left; TE = 28 msec) shows essentially no intraluminal signal, while the second spin echo image (right; TE = 56 msec) shows an area of high intensity adjacent to the area of infarction. The pattern indicates blood flow stasis in a region of dyskinesis.

In addition to wall thinning, gated MRI has displayed regions of bulging in the LV wall corresponding to post-infarction aneurysm (51). Only the images generated from the second spin echo show areas of anomalous signal intensity within the region of the LV aneurysm, representing blood flow stasis due to regional akinesis or dyskinesis (Figure 5).

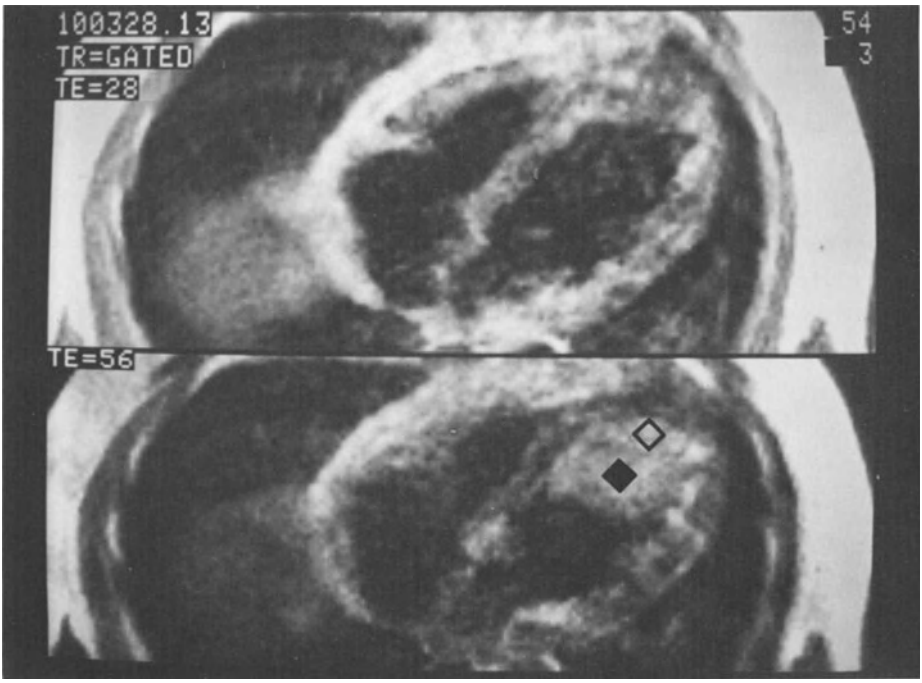

Fig. 5. Cross-sectional ECG-gated MRI images through the LV in a patient with a chronic myocardial infarct of the anterior interventricular septum and anterior LV wall. The image produced from the first spin echo (upper; TE = 28 msec) shows a high-intensity region adjacent to the thinned anterior wall, representing thrombus, which results in a "square" contour to the anterior portion of the LV lumen. The image produced from the second spin echo discriminates better the interface between the thrombus (white diamond) and the myocardial wall. The area of the LV lumen from which the signal is generated is increased on the second spin echo image. This additional area of signal generation (black diamond) represents slow moving blood or relative stasis of blood flow adjacent to the thrombus. (Reprinted by permission of the American Heart Association, Inc. and Circulation 69:523-531, 1984.)

MRI has also been able to detect the presence of LV thrombus confirmed by computed tomography or echocardiography (51). Mural thrombus is noted on MRI as areas of medium signal intensity projecting into the signal void of the LV chamber. The signal intensity of thrombus characteristically increases when changing from first to second spin echo images. This increase accentuates the interface between thrombus and myocardial wall. In addition, the presence of signal on both spin echo images helps to differentiate thrombus from static blood (signal on second spin echo only).

FUTURE PERSPECTIVES

Cardiovascular MRI offers several unique potential insights into the assessment of cardiac disease processes and their response to therapeutic interventions: direct tissue characterization with (3, 22, 23, 40, 42-45, 50, 51) or without (34-38) contrast enhancing agents affecting the relaxation times (currently T1 and T2), noninvasive measurement of hemodynamics (28, 52) and regional blood flow (3, 11-16, 37, 42), and metabolic imaging. If MRI can characterize myocardium by quantitation of water content, which has been shown to correlate with myocardial cell survival (53), it may serve as a useful predictor of future cardiac events. The advantages of producing real-time MR images are obvious, especially for time-dependent processes, such as blood flow and cardiac function. The study of regional myocardial blood flow will probably be aided by further advancement in the use of contrast agents. Of the potential insights, perhaps the most promising is metabolic imaging. This capability exploits another parameter of MR, the ability to measure chemical shifts. The chemical nuclei that seem most attractive for in vivo metabolic studies are sodium 23, carbon 13, and phosphorus 31 (17).

MRI of nuclei other than hydrogen has considerable appeal as a method for studying pathophysiologic processes. Since a unique ionic composition is characteristic of normal myocardial cells, and a reversal of the sodium/potassium ratio characterizes myocardial cells that have lost membrane integrity after an ischemic insult (54, 55), MRI of sodium 23 (56) should identify and provide quantitation of the mass of irreversibility damaged myocardium. Regions of AMI produce high signal intensity by MRI of sodium 23 in the excised heart (57). This is presumably due to increased intracellular sodium content from loss of membrane integrity.

Other nuclei also hold considerable interest for the study of cardiac physiology. These include phosphorus 31 for high-energy phosphate metabolism (58-61) and carbon 13 for fatty acid (62) and glycogen metabolism (63, 64). MRI studies of high-energy phosphate metabolism in isolated and intact hearts have demonstrated cyclical changes in the concentration of these compounds (e.g. ATP, phosphocreatine) during the cardiac cycle (59), alterations in the intracellular pH and in various phosphorous moieties during myocardial ischemia (58, 60, 61), and the temporal sequence of replenishment of high-energy phosphate compounds with the resolution of ischemia without or with therapeutic intervention (58, 60). Topical magnetic resonance, the name given to techniques for MR spectroscopy on internal organs in living subjects, has permitted in vivo monitoring of regional myocardial metabolism during myocardial ischemia (60).

An optimistic projection for the future is metabolic imaging based on the distribution and concentration of metabolically important nuclei within myocardium. This may come about through the tandem use of hydrogen MR along with spectroscopic sampling from regions of interest within the gated hydrogen image (65). Work in this aspect of MRI is preliminary at the present time.

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12

POSITRON IMAGING IN THE EVALUATION OF ISCHEMIA AND MYOCARDIAL INFARCTION

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One of the longstanding goals in the treatment of acute myocardial infarction has been to limit infarct size using interventions that improve myocardial perfusion, reduce oxygen demands, or decrease inflammation in the infarct.(1) Unfortunately, there have not been diagnostic modalities for the rapid differentiation of reversible from irreversible ischemic injury.(2) Radionuclide imaging with thallium-201 can be used to assess relative perfusion of the myocardium. Redistribution images obtained 3-4 hours after initial images are related to viability of the myocardium but a delay of several hours is required to determine whether there is reversible ischemic injury. Thus, it does not provide a suitable guide for clinical therapy in an individual patient.(3,4) Tc-99m pyrophosphate can be used to localize a zone of necrosis and thus has prognostic implications in patients with acute myocardial infarction. However, it cannot identify the region of myocardium at risk for subsequent damage.(5,6,7)

Positron emission tomography (PET) is a unique imaging approach since it allows quantification of regional myocardial radioactivity by virtue of its decay characteristics.(8) Studies of regional myocardial metabolism are possible since there are positron emitting isotopes of carbon, oxygen and nitrogen that can be used to synthesize labeled fatty acids, amino acids or carbohydrate. Recent studies from our group have focused on Rb-82, a diffusible cation with a short half-life that is obtained from a generator and thus, has the potential for routine clinical use without a cyclotron. In this chapter, the basic principles of positron imaging and their application to imaging of acute myocardial infarction will be reviewed.(8,9)

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PHYSICS

Most isotopes used for cardiac imaging decay by emission of a single packet of energy (i.e. photon) whose direction is random. These photons are then detected by a camera placed over the chest. The amount of radioactive events recorded will be adversely influenced by factors such as scatter of radiation, the distance of detector from the tracer and attenuation from overlying tissue. These physical effects will produce a loss of position information and prevent the accurate measurement of regional concentrations of radioactivity. These problems are worse in patients with obesity, chronic lung disease and breast tissue.

Positron tracers emit a particle that has the mass of an electron but a positive rather than a negative charge. This particle known as a positron ($\beta+$) travels a few millimeters in tissue and then annihilates with an electron after which it releases two high energy photons (511 KeV each) 180 degrees apart. Thus, rather than using a single planar camera, positron emitters can be detected by a pair of detectors aligned 180 degrees from each other. Only counts that reach both detectors at virtually the same time are included as true counts and thus activity from outside the field of interest is electronically excluded. In state-of-the-art positron cameras hundreds of pairs of detectors arranged in multiple rings about the patient portal can be used to reconstruct regional tracer counts into tomographic and three-dimensional images. Detailed reviews on the characteristics of cameras, radiation doses and physics are available.(8,9,10)

Table 1 lists positron tracers that have been used for infarct imaging. Of particular importance is the very short half-life of each tracer which permits serial imaging with minimal background - a property of great potential for the evaluation of an evolving infarct.

Table 1. Positron Emitters Used for Myocardial Ischemia and Infarction

CYCLOTRON-PRODUCED

Isotope	Half-Life	Compound	Uses
N-13	10 min	N-13 ammonia	Perfusion
C-11	20 min	C-11 carbon monoxide	Blood pool
		C-11 palmitate	Fatty acid
		C-11 glucose, pyruvate, acetate	Carbohydrate metabolism
F-18	108 min	F-18 2-deoxyglucose	Carbohydrate metabolism

GENERATOR PRODUCED

Isotope	Half-Life	Compound	Uses
Rb-82	75 sec	Rb-82 chloride	Perfusion
Ga-68	68 min	Ga-68 red blood cells	Blood pool
		Ga-68 platelets	Thrombus formation

SPECIFIC APPLICATIONS

Fatty Acid metabolism

Beta oxidation of fatty acids constitutes one of the major energy sources to the normal myocardium. Under ischemic conditions, fatty acid oxidation is minimal and the tissue consumes primarily glucose.(11) Early studies by Weiss et al demonstrated that the uptake of C-11 palmitic acid was decreased in ischemia in isolated heart preparations.(12) These studies were then extended to intact dogs with experimental infarction using PET.(13) The regional decrease in concentration of C-11 counts derived from labeled palmitate correlated with local depletion of creatine kinase and histologic evidence of infarction. In patients with remote infarction, the location of the infarct by PET with C-11 palmitate corresponded to the electrocardiogram and the estimated size of the infarct was linearly related to infarct size by plasma creatine kinase.(14,15) PET imaging with C-11 palmitate has been found to have a good sensitivity for the diagnosis of both transmural and subendocardial infarction.(16)

Subsequently PET imaging has been performed in dogs and in man before and after thrombolytic therapy with either streptokinase or tissue

plasminogen activating factor. These studies demonstrate improved uptake of palmitate following restoration of flow within the first few hours of infarction.(17,18) If reperfusion was delayed, the ischemic region did not normalize palmitate uptake implying that salvage of tissue did not occur. Other experimental studies suggest that the actual rate of fatty acid oxidation can be measured regionally in μmols/g/min if appropriate models are developed.(11,19,20,21)

Carbohydrate metabolism

Another attractive tracer for the study of myocardial infarction utilizes 2-fluoro-2-deoxyglucose (FDG). This tracer gets taken up in proportion to glucose but is incompletely metabolized and thus is essentially trapped during the imaging period.(22,23) Since glucose is used in preference to fatty acids during ischemia, uptake of glucose out of proportion to flow can be used to localize sites of anaerobic metabolism in potentially viable myocardium. Delivery of tracer is decreased during ischemia and thus, studies with FDG must include a second injection of a flow tracer to determine perfusion. Glucose uptake is then normalized for perfusion in each region. Using this approach, Schelbert's group has demonstrated areas of increased uptake of FDG in patients with post infarction angina.(24)

Another potential method that may obviate the need for a separate flow tracer is with the use of C-11 pyruvic acid.(25) Pyruvate is rapidly metabolized by normal tissue but accumulates as lactic acid in ischemic regions. Thus, early images after labeled pyruvate should indicate delivery of tracer whereas late images will reflect ischemic regions producing lactate. Additional studies are needed to validate this approach.

Rubidium-82

Rubidium-82 (Rb-82) is a positron emitting cation ($T_{\frac{1}{2}}$ = 75 sec) that is taken up and distributed in a manner similar to potassium. Unlike the tracers listed above, it can be obtained using a simple generator system with a shelf-life of 4-6 weeks. In an initial series of studies from our group we developed a model for the quantification of regional myocardial flow over a wide range and under a variety of conditions.(26,27)

In open chested dogs with experimental infarction, Rb-82 was injected as an intravenous bolus and myocardial and arterial positron counts were recorded at the epicardium overlying the infarct with a beta probe. Unlike

a PET camera, beta counts rather than annihilation photons were collected.(28) Thus, recorded activity reflects a well localized region and excludes counts from areas outside the probe including the ventricular blood pool. Time-activity curves of Rb-82 (corrected for physical decay of the isotope) obtained with the beta probe were used to determine the net rate constant for transfer of rubidium across the cell membrane, k_T, Figure 1A. Positive values indicate that after first pass extraction by the myocardial cells, there is more uptake of Rb-82 (from re-circulation) than egress. Under control conditions, k_T averaged $+1.22 \times 10^{-3}$ sec^{-1} and was not significantly changed during occlusion in viable myocardium ($+1.41 \times 10^{-3}$ sec^{-1}) (Figure 1B). Thirty-six percent of irreversibly injured tissue samples had a negative k_T indicating net leakage due to membrane damage. However, there was no significant difference between irreversibly injured tissue k_T's ($+0.93 \times 10^{-3}$ sec^{-1}) and either control or viable samples. Following reperfusion, all viable samples had a positive k_T (mean = $+1.26 \times 10^{-3}$ sec^{-1}) whereas all non-viable regions had a negative k_T (-1.51×10^{-3} sec^{-1}, $p<.001$, Figure 2A and 3). Additionally, patency of the artery could be determined based on measurements of flow with Rb-82 (Figure 4).

These results suggest that Rb-82 could be useful in the diagnosis of myocardial infarction to assess both patency of the artery on admission and after either spontaneous or pharmacologically induced reperfusion. The changes in membrane transport of Rb-82 may provide a way for determining whether there has been salvage of myocardium. Imaging with Rb-82 has the potential for a major impact on acute coronary care since it does not require either a cyclotron or a radiochemistry lab for on-site use - a property that is unique from the positron emitters discussed earlier.

Our group recently performed Rb-82 PET imaging in 14 patients with acute myocardial infarction.(29) Patients were given 30-60 mCi of the tracer and PET imaging was done within 96 hours of the onset of pain and within 24 hours of coronary catheterization. Ten normal patients were also studied. The infarct related artery was correctly identified in all patients. No defects were observed in normals or in non-infarcted regions. This study demonstrated the feasibility of clinical PET imaging in a critically ill population of patients. Additional studies to ascertain

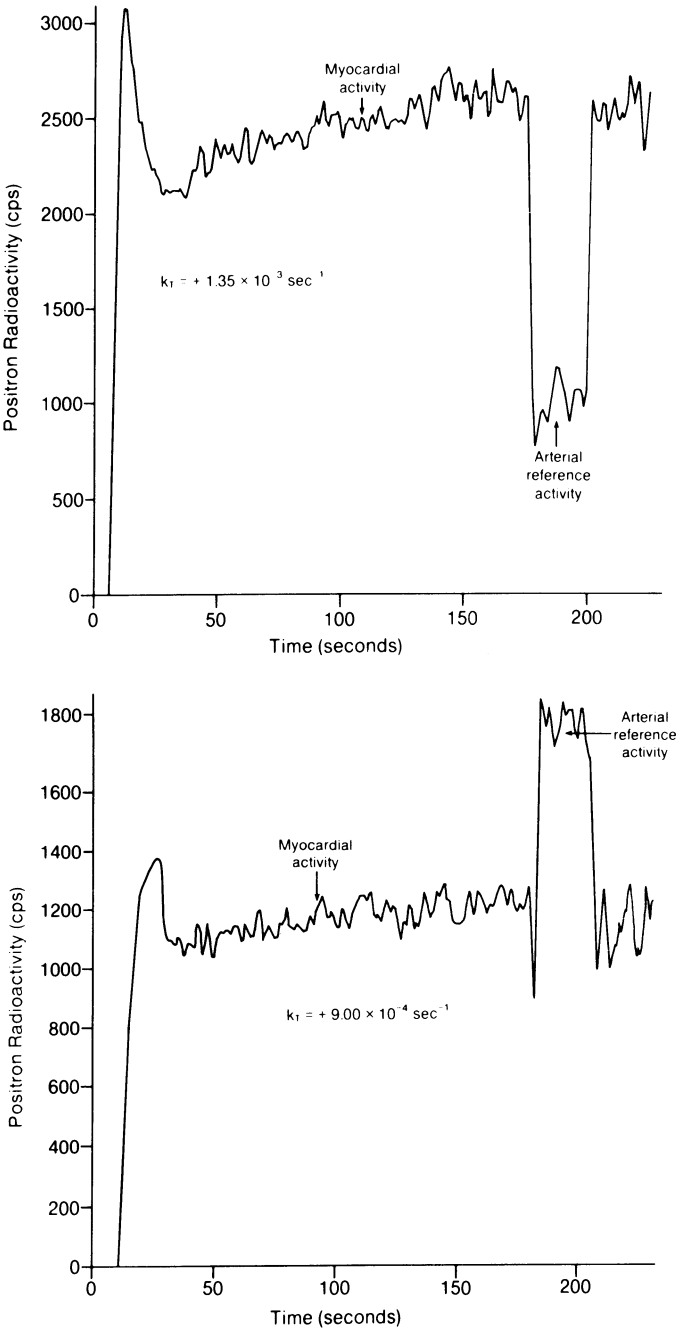

Figure 1. Epicardial time-activity curves of Rb-82 in a control (A) and following coronary occlusion (B). (Reprinted with permission from ref. 28)

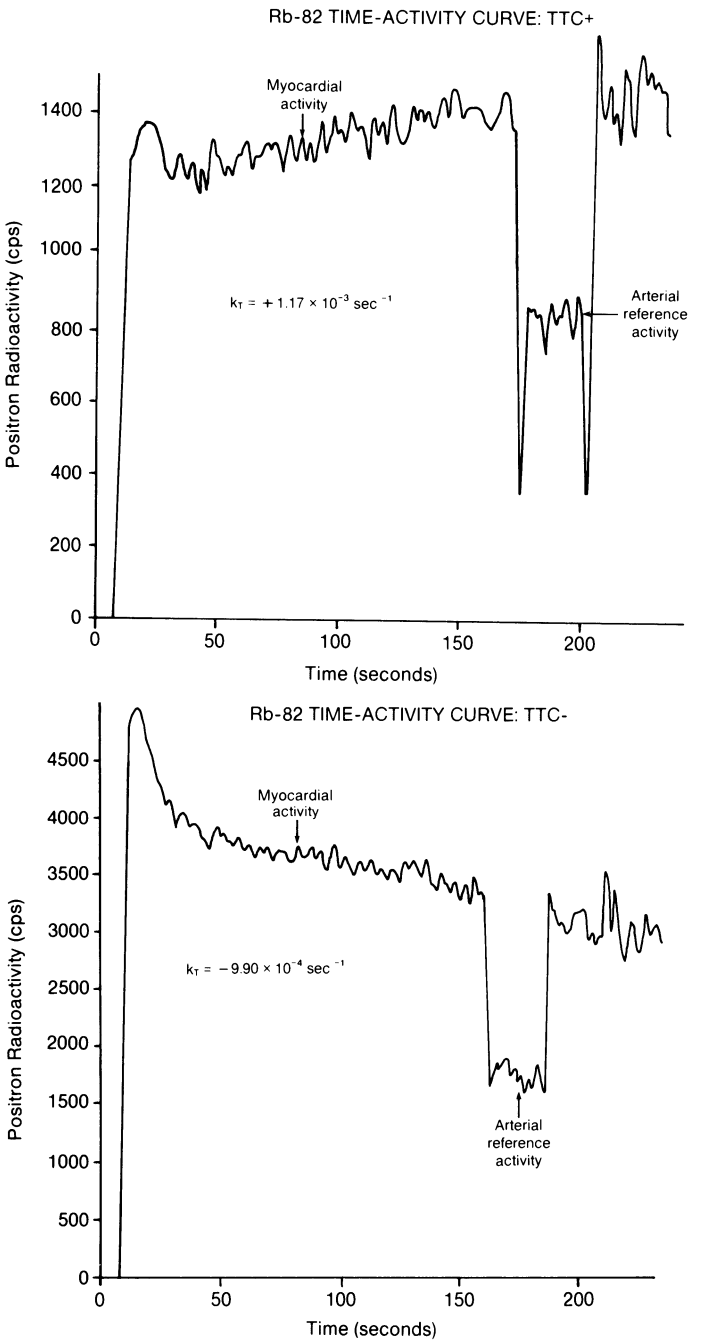

Figure 2. Epicardial time-activity curves of Rb-82 after reperfusion in viable (A) and irreversibly injured samples (B). (Reprinted with permission from ref. 28)

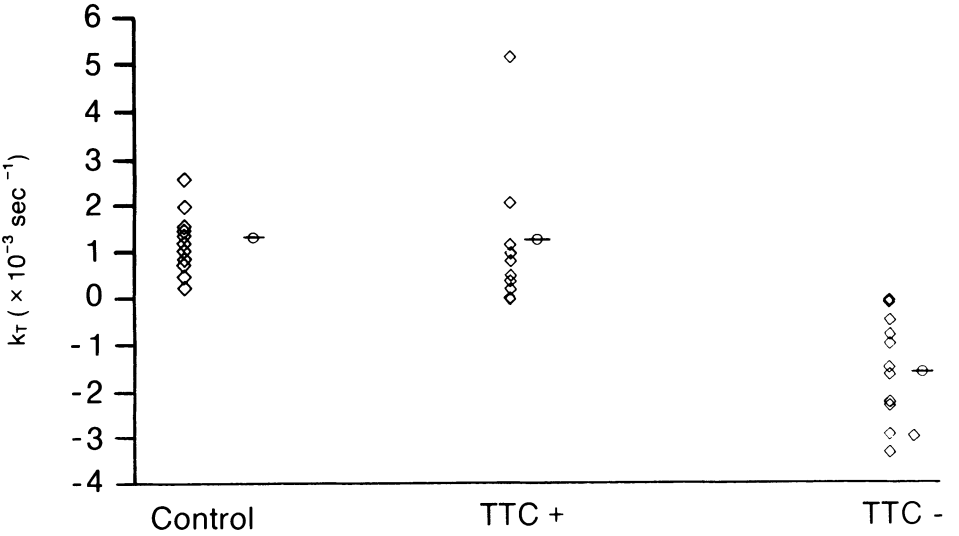

Figure 3. Rb-82 transfer rate constant at baseline and after reperfusion in viable (TTC +) and irreversibly injured samples (TTC -). (Reprinted with permission from ref. 28)

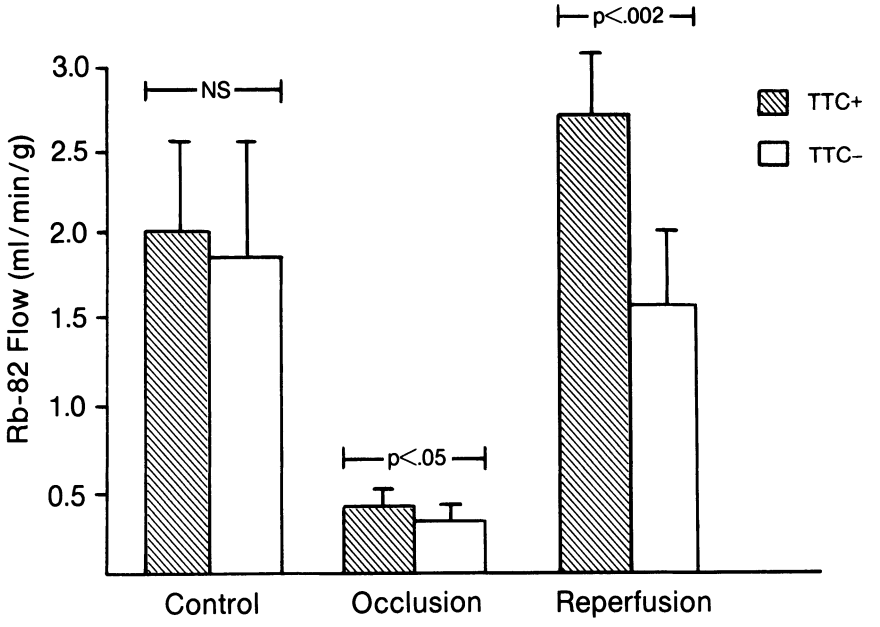

Figure 4. Epicardial flow measured by Rb-82 at baseline, following occlusion and reperfusion for potentially viable (TTC +) and irreversibly injured samples (TTC -). (Reprinted with permission from ref. 28)

whether Rb-82 can predict reperfusion and subsequent improvement in function are underway.

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13

HEMODYNAMIC CONSIDERATIONS IN ACUTE INFARCTION

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INTRODUCTION:

Some degree of hemodynamic dysfunction occurs in most patients with acute myocardial infarction. The level of dysfunction is directly correlated with the extent of myocardial damage and is the principal factor governing in-hospital mortality. As such, the process of hemodynamic evaluation and recognition of disturbances is critically important in diagnostic assessment, prognosis and treatment of patients with acute infarction.

Most of the clinical signs of hemodynamic dysfunction during acute myocardial infarction denote varying degrees of congestive heart failure and selective peripheral organ perfusion. These signs are a consequence of impaired left ventricular performance. As such, the conventional approach to subgroup classification has employed either a clinical or hemodynamic algorithm to assess cardiac status. The former is based upon physical findings of pulmonary congestion and hypoperfusion, whereas the latter relies on contractile measures of pump function including mean diastolic ventricular pressure, effective systolic arterial pressure and cardiac output. However, neither of these schemes directly addresses the physiologic function of the circulation, namely the adequacy of oxygen delivery at the tissue level. This shortcoming is overcome, however, by analysis of bulk oxygen transport variables.

In light of this observation, the understanding and routine assessment of perfusion related parameters is crucial to hemodynamic subgroup analysis and conveys prognostic and

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therapeutic information. Therefore, the purpose of this chapter is to review the fundamentals of cardiovascular physiology as it pertains to hemodynamic evaluation; trace the evolution of subgroup classification schemes; and finally, to propose a new stratification strategy which integrates indices of peripheral perfusion and oxygen transport with cardiac mechanics.

CARDIOVASCULAR PHYSIOLOGY

Myocardial Oxygen Balance:

Acute myocardial infarction may be conceptualized as a disruption in cardiac oxygen balance secondary to a reduction in oxygen supply. When the amount of damaged tissue significantly compromises the heart's systolic performance, peripheral organ perfusion and steady-state metabolism may be altered. Therefore, the hemodynamic goals of management during acute myocardial infarction are to limit the extent of myocardial necrosis either by augmenting coronary blood flow or reducing cardiac metabolic requirement; and to insure that cardiac performance is sufficient to maintain adequate tissue perfusion and aerobic metabolism. In order to achieve these objectives, myocardial oxygen supply must be balanced with oxygen demand by manipulating one or more of the determinants of oxygen availability and oxygen consumption.

Myocardial oxygen supply is governed by coronary blood flow, the oxygen carrying capacity of arterial blood and the amount of oxygen extracted from the blood by the heart. Since both the oxygen content of arterial blood and the myocardial oxygen extraction ratio are generally fixed, the primary mechanism whereby oxygen availability can satisfy need is through an increase in coronary blood flow. This may be accomplished by coronary dilatation, collateral formation or measures to eliminate the stenosis and establish reperfusion.

An alternative approach to restoring myocardial oxygen balance during acute infarction is to lower cardiac oxidative need. The utilization of oxygen by the myocardium is primarily determined by heart rate, contractility and systolic wall stress. The latter varies directly with changes in ventricular mass, ventricular diameter and aortic impedance. As such, in the

presence of tachycardia, increased afterload, ventricular dilatation or enhanced contractility, myocardial oxygen consumption increases. In order to lower cardiac work, one or more of these variables must be favorably altered. Steady-state oxygen equilibrium will therefore be restored if compensatory mechanisms and pharmacologic interventions succeed in bringing oxygen need into balance with oxygen supply. Inability to restore metabolic hemostasis, on the other hand, will eventuate in anaerobic metabolism and possible enhancement of myocardial ischemia.

VENTRICULAR FUNCTION CURVES:

Ventricular contractility is an index of the mechanical performance of the heart and is described by the Frank-Starling principle. [1-2] This principle is usually illustrated by a ventricular function curve which relates systolic performance of the ventricle to end diastolic fiber length at a constant heart rate. (Figure 1) Most commonly, stroke work or cardiac index is plotted against left ventricular end diastolic pressure or pulmonary capillary wedge pressure. An upward shift of the curve may result from an increase in venous return, improved ventricular compliance, positive inotropic influences, or vasodilator therapy. Conversely, decreases in preload, compliance, or contractile state, or an increase in afterload will shift the curve downward thereby lowering cardiac output and minute work.

At the bedside, diastolic fiber length or end diastolic volume of the left ventricle can not be readily measured. As a substitute, pulmonary wedge pressure, due to its ease of recording, has been utilized to represent left ventricular preload. However, the relationship between end diastolic volume and pressure is not linear but curvilinear and concave upward. (Figure 2) Moreover, the pressure-volume plot is a function of ventricular compliance rather than contractility. [3] For example, a large increment in wedge pressure in response to a small volume challenge suggests the ventricle is non-compliant and on the steep ascending limb of the pressure volume curve.

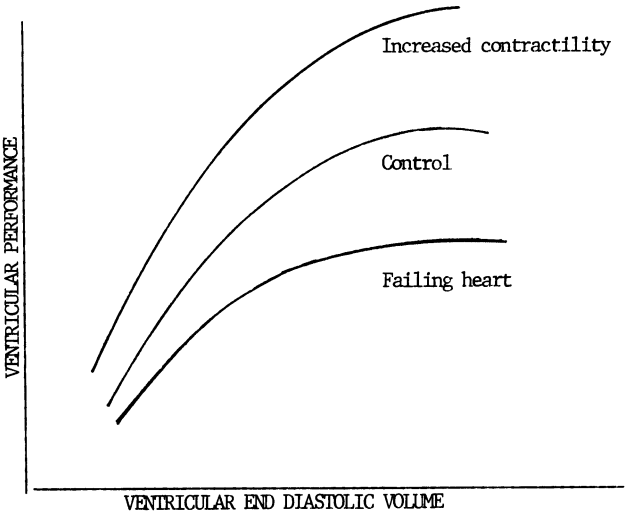

Figure 1. Left Ventricular Function Curve. The effect of alterations in the contractile state of the myocardium on the level of ventricular performance at any given level of end diastolic volume.

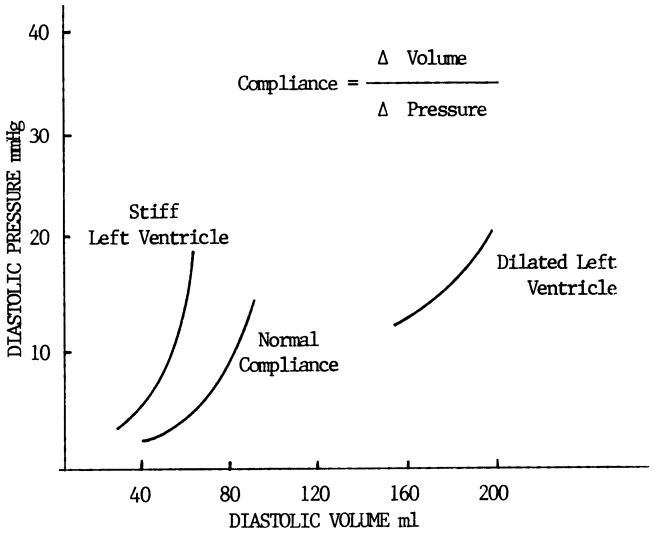

Figure 2. The relationship between diastolic pressure and diastolic volume expresses the stiffness/elasticity of the ventricle. Greater volume for a given pressure change means increased compliance or elasticity; conversely, greater pressure for a given volume change means increased stiffness. The dilated ventricle is more compliant and less stiff. (Reprinted with permission from Shoemaker WC, Thompson WL, Holbrook PR (eds). Textbook of Critical Care Medicine, Philadelphia: WB Saunders, 1984, p. 336.)

Alternatively, a negligible or small increase in wedge pressure in the face of a volume challenge is consistent with a compliant ventricle. Thus, tracking wedge pressure against cardiac output can be misleading since shifts of the ventricular function curve may be secondary to alterations in compliance rather than contractility.

A final consideration is that in acute myocardial infarction, ventricular function is dynamic and modulated by physiologic and pharmacologic stimuli. Thus, by constructing serial ventricular function curves in the same patient, the adaptive response of the ventricle to either myocardial damage or therapeutic interventions can be studied.

COMPENSATORY MECHANISMS:

In an effort to restore myocardial oxygen balance, a series of intrinsic adaptive responses is triggered during acute infarction to reduce the imbalance between myocardial oxygen supply and demand. These responses are seen both centrally and peripherally and reinforce one another. The degree of cardiac dysfunction and magnitude of circulatory impairment is intimately related to the success of these compensatory mechanisms in restoring metabolic equilibrium.

With respect to central mechanisms, a reduction in ventricular contractility is present in most individuals with acute infarction. As a result, there is a rise in end diastolic volume and pressure and the ventricle dilates. This engenders an increase in stroke volume due to the Frank-Starling relationship. Left ventricular filling is further enhanced by more vigorous atrial contraction which promotes venous return and regulates mean atrial pressure. [5] Finally, when sufficient contractile reserve is present, endogenous catecholamines liberated by stress may directly augment contractility. This produces a shift to a higher and less depressed ventricular function curve. Sympathetic neurotransmitters may also augment cardiac output by accelerating heart rate.

A series of peripheral compensatory mechanisms during acute infarction is also encountered in the setting of

circulatory impairment. [5] As nutrient flow and oxygen delivery declines, tissue extraction of oxygen increases by a factor up to three times the baseline amount. [6] A second mechanism to maintain regional homeostasis involves a fall in arteriolar resistance due to byproducts of anaerobic metabolism. This reduction in afterload may directly improve cardiac function by an upward shift of the ventricular function plot and a lowering of cardiac work. Thirdly, neurohumoral responses are posited to augment venomotor tone and foster filling of the ventricles. Additionally, activation of baroreceptors secondary to decreased blood pressure serves to blunt vagal efferent nerve activity. The consequent increase in sympathetic tone may produce a rise in stroke volume by boosting contractility and chronotropy. Moreover, blood pressure may also be supported by sympathetic mediated arteriolar vasoconstriction although increased systemic vascular resistance is a later response to more advanced levels of hypoperfusion. Lastly, in the setting where renal blood flow is compromised, a series of endocrine and humoral alterations lead to salt and water retention, expansion of blood volume, and an increase in capillary pressure.

Many of these adaptive mechanisms may, paradoxically, either directly or indirectly contribute to hemodynamic deterioration. Myocardial metabolic requirements are augmented by tachycardia, inotropic stimulation and increased wall stress related to cardiac dilatation and an elevated systemic vascular resistance. This, in turn, may exacerbate the imbalance in cardiac oxygen availability and lead to further depression of pump activity. Additional compensatory responses would then be called into play and unless equilibrium is restored, a progressive downhill cascade of events ensues in which circulatory failure begets further failure. Thus, limitation of myocardial necrosis, in-hospital morbidity and ultimate survival is correlated with the effectiveness of these compensatory mechanisms in preserving hemodynamic stability and oxygen balance.

NORMAL HEMODYNAMIC VALUES: (Table 1)

Table 1

Variable	Formula	Normal Value	Units
Cardiac index	CI = cardiac output/BSA	3.2 ± 0.2	$L/min \cdot m^2$
Systemic vascular resistance index	SVRI = 79.92* + (MAP-CVP)/CI	2180 ± 210	$dyne \cdot sec/cm^5 \cdot m^2$
Pulmonary vascular resistance index	PVRI = 79.92* ± (MPAP-WP)	270 ± 15	$dyne \cdot sec/cm^5 \cdot m^2$
Mean transit time	Direct measurement	15 ± 1.4	sec
Central blood volume index	CBVI = MTT x CI x 16.7	830 ± 86	ml/m^2
Stroke index	SI = CI/HR	46 ± 5	ml/m^2
Left ventricular stroke work index	LVSWI = SI x MAP x .0144*	56 ± 6	$g \cdot m/m^2$
Right ventricular stroke work index	RVSWI = SI x MPAP x .0144*	8.8 ± 0.9	$g \cdot m/m^2$
Left cardiac work index	LCWI = CI x MAP x .0144*	3.8 ± 0.4	$kg \cdot m/m^2$
Right cardiac work index	RCWI = CI x MPAP x .0144*	0.6 ± 0.06	$kg \cdot m/m^2$

*Conversion term to equalize the units.
(Reprinted with permission from Shoemaker WC, et al. (eds). Textbook of Critical Care Medicine, Philadelphia: WB Saunders, 1984, p. 119.)

As outlined by Baker, the interpretation of cardiac output and pulmonary wedge pressure data requires an appreciation of a) normal values, b) appropriate values, c) adequate values and d) inadequate values. [4] Normal measurements are determined by statistical pooling of data in a normal population, calculating a mean value, and then defining a normal range as two standard deviations above and below this mean figure.

An appropriate value is that level of cardiac output or left ventricular filling pressure which has occurred by an intrinsic response to physiologic or pharmacologic stimuli. The magnitude of this response is a function of the heart's adaptive ability such that cardiac performance will be commensurate with physiologic need. For example, a supernormal output is an obligatory requirement in hypermetabolic states such as strenuous exercise, fever, anemia or hyperthyroidism. This is an appropriate circumstance in which higher than normal values of cardiac output are essential to provide sufficient oxygen delivery to the tissues.

An adequate cardiac output value is that which permits aerobic metabolism to continue whereas an inadequate value is indicative of a hypoperfusion state in which anaerobic metabolism will likely eventuate in metabolic acidosis.

The aforementioned nomenclature has greatest meaning when cardiac output and other hemodynamic variables are followed by serial determinations and trending of values. A single measurement of output or wedge pressure in the absence of other perfusion related variables is difficult to interpret as adequate or inadequate. Moreover, a normal value may be inappropriate for

the patient's physiologic state and anaerobic metabolism may be present due to impaired oxygen delivery. Alternatively, a subnormal value may be sufficient for tissue perfusion and aerobic metabolism will be present. Thus, cardiac performance indices by themselves do not always permit identification of patients who have tissue hypoperfusion and are at higher risk during the course of their infarction.

SUBGROUP CLASSIFICATION SCHEMES

Clinical Subset Classification:

The recognition of cardiac dysfunction, pulmonary congestion and hypoperfusion is essential to the management of patients with acute myocardial infarction. Early detection of significant cardiac depression may lead to myocardial salvage and limitation of infarct size. Later in the hospital course, the finding of cardiac failure and decreased oxygen delivery states may lower morbidity and mortality by identifying patients at high risk for infarct extension and shock. Hence, risk stratification of patients with acute myocardial necrosis is prognostically and therapeutically beneficial.

The most commonly employed clinical classification in patients with acute infarction is that of Kilip and Kimball. [7-8] They developed a scheme based upon clinical descriptors of heart failure and pulmonary congestion.

Class I - uncomplicated without clinical features of left ventricular failure
Class II - generally asymptomatic but manifesting a ventricular third sound, basilar post-tussive rales or venous hypertension
Class III- clinical evidence of pulmonary edema
Class IV - cardiogenic shock indicated by a systolic blood pressure less than 90 mm. Hg. and at least one of a) oliguria less than 20 cc./hour, b) low skin temperature, c) mental confusion

In their series of 250 patients the distribution and corresponding in-hospital mortality of the various cohorts are shown below. [7]

	Total cases	(Percent)	Mortality
Class I	81	(33%)	6%
Class II	96	(38%)	17%
Class III	26	(10%)	38%
Class IV	47	(19%)	81%

This study is weighted in favor of patients with left ventricular dysfunction and reveals that only one third of the population was entirely uncomplicated. Furthermore, total mortality for the group is exceedingly high. Finally, it is evident that mortality increases with clinical class and is correlated with the severity of cardiac failure. These figures are representative of other similar investigations and support the view that prognostic information is derived from subset analysis.

HEMODYNAMIC SUBSET CLASSIFICATION:

The major advance to our understanding of hemodynamics in patients with acute myocardial infarction is attributed to the balloon-tipped flow-directed pulmonary artery catheter. [9] The relative ease of insertion and safety of this instrument has made it a routine bedside procedure when knowledge of right heart pressures, central venous saturation or cardiac output is desired. Moreover, data from this catheter characterizing left ventricular function has fostered numerous classification schemes. [10-14] Each of these is predicated on the observation that an increase in pulmonary capillary wedge pressure or a reduction in cardiac contractile performance is the substrate for clinical signs and symptoms of congestive heart failure.

The most widely known subset categorization is that of Forrester and coworkers. [10] They used wedge pressure as a marker for pulmonary congestion and cardiac index as a guide to peripheral perfusion. Employing these parameters, four hemodynamic subgroups were defined. (Table 2)

A wedge pressure of 18 mm. Hg. was chosen as a pivotal value since pulmonary vascular congestion is usually not seen below this level while values greater than 18 mm. Hg. may precipitate interstitial edema. [15] By the time a pressure of

TABLE 2

HEMODYNAMIC SUBSETS IN ACUTE MYOCARDIAL INFARCTION

	Clinical Subset	Number of Patients	Cardiac Index (liter/min/sq meter)	Pulmonary Capillary Wedge Pressure (mm Hg)	Mortality (%)
I.	No pulmonary congestion or peripheral hypoperfusion	75	2.7 ± 0.5	12 ± 7	2.2
II.	Isolated pulmonary congestion	36	2.3 ± 0.4	23 ± 5	10.1
III.	Isolated peripheral hypoperfusion	22	1.9 ± 0.4	12 ± 5	22.4
IV.	Both pulmonary congestive and hypoperfusion	67	1.6 ± 0.6	27 ± 8	55.5

30 mm. Hg. is recorded, alveolar pulmonary edema and clinical signs of heart failure are usually apparent. This hydrostatic conceptual approach assumes a normal oncotic pressure, normal capillary and lymphatic function and no underlying cause for a chronic basal elevation in left ventricular end diastolic pressure. With respect to the cardiac index selected, they felt that clinical evidence of hypoperfusion, reflecting depressed cardiac function, was associated with values less than 2.2 liters/minute/meter^2.

Forrester recognized that a hemodynamic classification scheme permitted risk stratification into high and low risk cohorts and provided useful guidelines for intervention. In his series of 200 patients, the mortality was 5% in the subgroup with a cardiac index greater than 2.2 liter/min./m^2 as opposed to a 44% mortality in the subgroup with a depressed cardiac index less than 2.2 liter/min./m^2. The highest risk (51%) was observed in patients with pulmonary congestion and significantly compromised cardiac systolic function. Hypoperfusions with or without pulmonary congestion also adversely affected survival with at least a fourfold increase in mortality. [10]

Similar findings have been reported by other investigators confirming that in-hospital mortality is a function of left ventricular mean diastolic pressure and cardiac contractile function. [11-14] As the level of cardiac performance declines, or if wedge pressure rises or hypoperfusion supervenes, the probability of survival during acute myocardial infarction decreases. Thus, anticipation and recognition of the high-risk patient is essential for improving short-term prognosis in this population.

LIMITATIONS OF CLASSIFICATION SCHEMES:

The Kilip clinical classification scheme has several shortcomings which limit its relevance to therapeutic decision-making. Chief amongst these is the underdiagnosis of depressed cardiac function as judged by wedge pressure and cardiac output data. Forrester and colleagues noted that 33% of their uncomplicated patients had either a depressed cardiac index

less than 2.2 liter/min./m^2 or an elevated pulmonary wedge pressure greater than 18 mm. Hg. [10] Failure to identify high risk patients by the clinical exam has important prognostic implications since all deaths recorded in their subset H2 occurred in patients with unrecognized reduction in cardiac index. [11]

The lack of correlation between the physical exam and wedge pressure values was studied by Rotman and coworkers. [16] They found that 47% of patients in whom rales were absent had an elevated wedge pressure. High left ventricular filling pressures were also seen in 52% without a third heart sound and 40% in the absence of radiographic congestion. Rales were found to be neither a specific nor sensitive marker of left ventricular dysfunction whereas a ventricular gallop and abnormal chest x-ray were relatively specific but insensitive indices of an abnormal wedge pressure.

Similar findings of a discrepancy between the physical exam and hemodynamic data are commonplace, especially in the failure to detect impaired peripheral organ perfusion. [16-19] This limitation fostered the development of hemodynamic algorithms to better assess left ventricular performance and tissue perfusion. [10-13] However, deficiencies in hemodynamic subset analysis are also apparent. As with the clinical scheme, underdiagnosis of hypoperfusion may occur. A cardiac index over 2.2 liter/min./m^2 does not exclude impaired oxygen transport. Pulmonary wedge pressure may be elevated secondary to decreased left ventricular compliance, afterload stress or valvular dysfunction in the absence of cardiac failure. Compensatory mechanisms may mask hypoperfusion, and older patients and those on beta adrenergic blockers may not manifest a tachycardia despite compromised ventricular function. Finally, single measurements of filling pressure and cardiac output do not address whether circulatory transport is adequate nor do they answer the question of what is the optimal value for these measurements in any given patient. [20]

Thus, there is a need to further refine our hemodynamic categorization of patients with acute myocardial infarction. To

this end, a paradigm which focuses on peripheral oxygenation is suggested since the presence of hypoperfusion is associated with a substantial increase in mortality. [10,11] By understanding bulk oxygen transport variables and incorporating these parameters into a classification scheme, patients at high risk may be identified earlier and therapeutic decision-making will be facilitated.

PERFUSION RELATED VARIABLES

Oxygen Transport:

The measurement of cardiac output and pulmonary capillary wedge pressure provide prognostic and therapeutic guidelines in patients with acute myocardial infarction. These parameters do not, however, furnish precise data regarding the physiologic function of the circulation, namely tissue perfusion. [4,6,19,21]

It is not readily possible to ascertain tissue perfusion directly. Nonetheless, circulatory competence may be assessed by consideration of bulk oxygen transport parameters. [6,17,19] Of all circulatory components, oxygen is the most flow-dependent, has the highest percentage of extraction, and is easily measured. Satisfactory tissue perfusion involves a complex interplay of events related to oxygen transport. Review of these reveals that, in theory, oxygen is delivered to the tissues through two principal processes: conventional transport in the vascular tree and diffusional transport. [22] The former is dependent upon the level of oxyhemoglobin, cardiac output and arterial flow whereas once the capillary level is reached, diffusional transport predominates. Diffusion, in turn, is governed by the geometry of the microvasculature and target tissues surrounding the capillary network.

The components of capillary blood flow include nutritional flow or that required to transport consumed oxygen; and reserve flow defined as that in excess of basal physiologic need. In the situation of hypoperfusion, nutritional and reserve flow decreases while non-nutritional shunt flow increases. Moreover, in low flow states, blood viscosity will rise since viscosity is inversely related to the velocity of flow. This factor has

greatest impact in post-capillary venules where cross-sectional area is larger than pre-capillary arterioles and flow velocity is lower at rest. As systemic perfusion is reduced, post-capillary venular flow is significantly slower and may lead to red blood cell rouleaux formation.

In addition to these geometric-flow considerations, a mathematical appreciation of oxygen transport physiology is crucial for evaluating organ perfusion. [6] Oxygen transport refers to the amount of oxygen which is delivered by the heart to the tissues each minute. It is calculated by the following expression:

$$\text{Arterial } O_2 \text{ transport (ml } O_2\text{/minute)} = C.O. \times CaO_2 \times 10$$

In a parallel manner, venous oxygen delivery can also be estimated:

$$\text{Venous } O_2 \text{ transport} = C.O. \times CVO_2 \times 10$$

Therefore, if the amount of oxygen transported away from and that returning to the heart are known, the difference represents oxygen consumed by the tissues.

$$O_2 \text{ consumption } (VO_2) = \text{Arterial } O_2 \text{ transport} - \text{Venous } O_2 \text{ transport}$$

$$= 10 \times C.O. \times CaO_2 - 10 \times C.O. \times CVO_2$$
$$= 10 \times C.O. \times CaO_2 - CVO_2$$
$$= C.O. \times Hb \times 13.8 \ (SaO_2 - SVO_2)$$

This expression depicts the steady-state balance between tissue oxygen need and oxygen availability as originally described by Fick in 1887. Any factor which produces a decline in oxygen supply or an increase in demand will disrupt this balance and result in a shift to anaerobic metabolism unless compensatory mechanisms correct the disturbance.

A decrease in VO_2 may be caused by several mechanisms. [6] Chief amongst these are inadequate oxygen transport across the lungs, poor tissue perfusion due to maldistribution of flow or

decreased metabolic turnover as seen in hypothyroidism, hypothermia and terminal disease states. Conversely, increased VO_2 reflects a high rate of tissue metabolism and may be found with sepsis, hyperthermia, fever, drugs, and anesthetics that stimulate metabolism and catecholamine excess.

The absolute value of VO_2 does not, by itself, indicate circulatory competence and oxygen balance. Supernormal values, for example, may be observed in the setting of unusually high states of oxidative stress including sepsis or major trauma. More predictive of an adequate circulation and peripheral perfusion is the response of VO_2 to therapy. If VO_2 is normal or greater than normal before an intervention and does not rise, then tissue oxygen delivery is probably adequate. However, if VO_2 is normal or low before treatment and improves after therapy, then either the circulation has spontaneously improved or therapy has been beneficial. When VO_2 does not increase or falls with treatment, then either the therapy has been ineffective or hypoperfusion has progressed.

In addition to VO_2, there are numerous measured and derived values of bulk oxygen transport. [17] (Table 3) These perfusion related variables are the best physiologic predictors of clinical course and therapeutic need since they describe the relationship between tissue oxygen utilization, blood flow and cardiac contractile function.

Mixed venous oxygen saturation is the most widely employed index of tissue oxygen delivery. [6,23-25] Fiberoptic catheters have heightened its popularity by enabling reliable, real-time determinations which are more accurate than derived values from blood gases. The normal mixed venous saturation is 75%. Values below this level are noted with anemia, arterial oxygen desaturation, low cardiac output and conditions of increased oxidative metabolism. Providing that these non-cardiac disorders can be excluded, mixed venous oxygen saturation directly correlates with cardiac performance and may be useful in trending a patient's clinical course. A rise in saturation is consistent with increased blood flow and less tissue need whereas a decline in saturation suggests a reduced cardiac output and greater

TABLE 3

OXYGEN TRANSPORT VARIABLES

Variable	Formula	Normal Value
Fraction of inspired oxygen	FIO_2	20-30
Oxyhemoglobin saturation	$SaO_2=HbO_2/Hb+HbO_2x100$	95
Mixed venous oxygen tension	PvO_2 = direct measurement	75
Alveolar-arterial oxygen tension gradient	$P(A-a)O_2$	20 torr (room air)
Alveolar-arterial oxygen tension gradient	$P(A-a)O_2$	560-670 torr (100%)
Arterial oxygen content	$CaO_2=.0031xPaO_2+1.38xHbxSaO_2$	20.4
Venous oxygen content	$C\bar{v}O_2=.0031xP\bar{v}O_2+1.38xHbxS\bar{v}O_2$	15.8
Arteriovenous oxygen content difference	$C(a-v)O_2=CaO_2-CvO_2$	5.5
Oxygen consumption	$VO_2=CIxC(a-v)O_2$	120-160
Oxygen delivery	$DO_2=CIxCaO_2$	550-650
Oxygen extraction rate	$O_2ext=C(a-v)O_2/CaO_2$	20-30
Red cell mass	RCM-direct measurement	
Oxygen transport/RCM	$OTR=VO_2/RCM$	.12
Red cell flow rate	$RCFR=CIxHct$	1.2
Tissue oxygen extraction	$TOEI=C(a-v)O_2/RCFR$	40
Oxygen transport/RCFR	$OTRF=VO_2/RCFR$	.12
Coefficient of oxygen delivery	$COD=COxCaO_2/VO_2$	4

tissue extraction of oxygen.

The coefficient of oxygen delivery has been suggested by Kawakami and coworkers as the most sensitive measure of convectional oxygen transport to peripheral tissues. [22] It relates oxygen delivery as calculated by cardiac output times arterial oxygen content to tissue oxygen uptake.

$$\text{Coefficient of Oxygen Delivery (COD)} = \frac{CAO_2 \times C.O.}{VO_2}$$

$$= CaO_2/CaO_2 - CVO_2$$

By simultaneously determining mixed venous oxygen tension and the coefficient of oxygen delivery, one can define whether oxygen supply to tissues is primarily limited by impaired convectional transport or a diffusion abnormality. This latter disturbance may be overcome by oxygen inhalation whereas if oxygen delivery is compromised, then an augmentation in forward flow is necessary. Moreover, in low flow states, both a transport and diffusion problem may coexist.

Shoemaker and colleagues have suggested that the efficiency of tissue oxygen extraction ($CaO_2 - CVO_2$/red cell mass =ECOE) has the greatest predictive power regarding survival of patients with varying degrees of hypoperfusion. [17] The rate of oxygen uptake by the tissues per liter of red cell flow (VO_2/red cell mass) was similarly a sensitive and specific marker for perfusion and clinical outcome whereas cardiac index, pulmonary wedge pressure and mixed venous saturation did not readily identify hypoperfusion and distinguish survivors from non-survivors in their study. [17]

At present, no single oxygen transport variable can accurately segregate individuals with acute infarction into low and high-risk cohorts. Rather, a multivariate analysis of these variables is proposed from which a predictive algorithm may be derived. This scheme can then be utilized to monitor cardiorespiratory status and evaluate the efficacy of therapeutic interventions.

CONCLUSION:

There has not been a prospective study demonstrating the benefit of hemodynamic monitoring on mortality in patients with acute myocardial infarction. As such, routine pulmonary artery catheterization in the uncomplicated individual who may be at higher risk is not generally recommended. Nonetheless, the underdiagnosis of hypoperfusion using only clinical markers coupled with the increased complication rate in those with impaired perfusion is a compelling argument in support of routine hemodynamic assessment in all patients with acute myocardial necrosis.

Emerging technology has expanded our ability to measure central and peripheral circulatory dynamics. Fiberoptic reflectance oximetry incorporated into the balloon-tipped thermodilution catheter has provided a reliable on-line recording system for mixed venous oxygen saturation.[6] Transcutaneous oxygen measurement using a miniature heated polarographic electrode is a non-invasive method of evaluating the cutaneous circulation. [26] This technique may be more sensitive to changes in oxygen delivery compared to conventional hemodynamic variables and also aids in differentiating circulatory from respiratory impairment. Finally, the most promising technology appears to be non-sensitive field-effect transistors and other biochemical semiconductor sensors which can be inserted into either the arterial or venous system. [27] They are designed to furnish continuous information pertaining to electrolyte and blood gas status and may therefore yield valuable data concerning the patient's metabolic status.

In summary, the optimal hemodynamic classification scheme will require consideration of traditional indices of left ventricular performance along with bulk oxygen transport variables. By combining these measurements, a more complete and accurate profile of circulatory competence, prognosis and therapeutic options will emerge.

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14

COMPARATIVE EFFECTS OF INTRAVENOUS NITROGLYCERIN AND SODIUM NITROPRUSSIDE IN CARDIAC INTENSIVE CARE

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INTRODUCTION

Since the report of Burton (1) in 1867 describing the relief of anginal pain with amyl nitrite, nitrates have gained widespread acceptance as primary therapeutic agents in the treatment of patients with angina. The use of nitrates has now been extended to the treatment of congestive heart failure and acute myocardial infarction (AMI). However, commercially available nitroglycerin (NTG) preparations (sublingual, oral and paste) presented several important pharmacokinetic problems in predicting therapeutic response because of unpredictable absorption and metabolism. The intravenous form of NTG, introduced in the mid 1970's, enabled the clinician to titrate the dose to the desired clinical or hemodynamic effect. Intravenous NTG has led to widespread use of the compound in the production of controlled hypotension during surgery and blood pressure control in perioperative hypertension.

Thus, commercial formulations of the IV preparation have made it possible for clinicians to use IV NTG in clinical situations where Sodium Nitroprusside (SNP) has been previously used. The clinician is now faced with the choice between IV NTG and SNP in cases of overlapping indications, since they exert similar changes on many hemodynamic parameters. However, important differences exist between them that may make IV NTG the preferrable agent in the treatment of patients with an acute manifestation of ischemic heart disease. This chapter will review the comparative effects of IV NTG and SNP, contrasting their similarities and differences, hopefully allowing the clinician to make a more rational choice.

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PHARMACOLOGY

Although the clinically desirable effect of nitrates is to relax vascular smooth muscle, NTG also relaxes virtually all smooth muscle tissue, including the uterus, gastrointestinal tract, ureteral and bronchial smooth muscle (2). It's precise mechanism of action is incompletely understood, but studies suggest that NTG reacts with sulfhydryl groups on a "nitrate receptor" to stimulate guanylate cyclase, and thereby increase concentrations of cyclic 3', 5' guanosine monophasphate (cGMP) which appears to be tightly coupled to the relaxation process (3).

Intravenous NTG has an onset of action of 1.5 to 2 minutes. It is rapidly metabolized in the liver and red blood cells to dinitrates, mononitrates and inorganic nitrites by the enzyme glutathione-organic nitrate reductase (4,5). These metabolites possess approximately one tenth the vasodilating strength of the parent compound. The elimination half life of IV NTG is around 1.9 to 2.8 minutes (6,7). After discontinuation of the infusion, the hemodynamic profile usually returns to baseline within 10 minutes (8).

Sodium nitroprusside (SNP) has a unique chemical structure, containing five cyanide ions and a nitroso group attached to a ferrous ion. The compound is a reddish-brown water soluble powder to which 5% dextrose must be added in order to prepare a fresh solution for slow IV infusion. The aqueous solution must be protected from light by being wrapped in opaque material such as aluminum foil because of photosensitivity.

SNP also relaxes smooth muscle, but in contrast with NTG, its effect is remarkably specific for vascular smooth muscle (9). Its precise mechanism of action remains unknown but it does not seem to exert its effect via any known receptor system. Postulated mechanisms of vasodilatation include inhibition of calcium transport, interaction with intracellular sulfhydryl groups and an effect on cyclic nucleotides (cGMP) (9).

SNP acts within seconds of administration. It is metabolized nonenzymatically in the blood to cyanide. Cyanide is converted to thiocyanate by a hepatic mitochondrial rhodanase enzyme system that facilitates the transfer of sulfur to the cyanide molecule in the presence

of a sulfur donor (thiosulfate) (10,11). Once the infusion is stopped, hemodynamic alterations return to pretreatment levels in 1 to 10 minutes.

The therapeutic response to both agents is best determined by titrating the dose to the desired clinical or hemodynamic end point rather than by following pharmacokinetic parameters.

PHARMACODYNAMIC STUDIES

Both IV NTG and SNP effect similar changes on many hemodynamic parameters, however, major differences may exist between the two vasodilators with respect to the balance between venodilation and arterial dilation. Furthermore, different actions of these two agents on regional myocardial blood flow (anti-ischemic effect) may make IV NTG the drug of choice in patients with coronary artery disease.

NTG dilates both the venous and arterial systems in a dose related fashion (12). Flaherty and colleagues showed that at lower infusion rates (average 37 mcg/min) venous pooling predominates over arteriolar vasodilation (12). As a result, IV NTG significantly decreased central venous pressure, right atrial pressure and pulmonary capillary wedge pressure (45% reduction), while only minimally lowering mean arterial pressure (7% reduction) and avoiding reflex tachycardia. At higher infusion rates (mean 57 mcg/min), mixed venous and arterial dilating effect were evident by a 9 mm Hg (52% reduction) lowering of filling pressure and a 21 mm Hg (20% reduction) lowering of mean arterial pressure (13). In several series, IV NTG has been reported to produce approximately a 30% reduction in systemic vascular resistance (afterload) (14,15). Interestingly, IV NTG lowers systolic blood pressure more than diastolic blood pressure (16). This preserves the coronary perfusion gradient while decreasing myocardial oxygen demand. The IV administration of NTG does not usually cause significant changes in heart rate (12), as opposed to other nitrate preparations, possibly the result of a gradual lowering rather than a precipitous decrease in blood pressure. IV NTG has been found to decrease pulmonary artery pressure and pulmonary vascular resistance, presumably by pulmonary vasodilation. In addition, after abrupt withdrawal of NTG infusion, there does not appear to be rebound pulmonary hypertension (17). Intrapulmonary shunting has been reported either to be not affected (18), or to increase (19), leading to a widening of the alveolar-arterial oxygen gradient (A-a gradient).

It appears that the effect of NTG on cardiac hemodynamics depends on the underlying status of the left ventricle. Indices of cardiac function - stroke work, stroke volume and cardiac output, are usually unchanged or decreased in patients with normal ventricular function, perhaps because the reduction in afterload may be offset by simultaneous significant reductions in preload. In patients with initially elevated filling pressures, afterload reduction predominates and stroke volume and cardiac output increase. Patients with the most depressed LV function appear to receive the greatest hemodynamic benefit (13).

The effect of IV NTG on coronary blood flow in humans has been variable, with some studies reporting no change and others indicating a decrease in coronary blood flow accompanying the reduction in preload and afterload. However, regional myocardial blood flow, especially to jeopardized myocardium, appears to be beneficially augmented by IV NTG in patients with coronary artery disease, independent of changes in hemodynamic status (13).

NTG has long been known to decrease myocardial ischemia, but the precise mechanism by which NTG exerts its anti-ischemic effect has been debated. Several mechanisms (20) have been postulated:

(1) NTG is a coronary vasodilator. It may increase coronary blood flow by reducing coronary arteriolar resistance.

(2) NTG has a specific vasodilator effect on the large epicardial conductance vessels.

(3) NTG increases collateral circulation to ischemic myocardium.

The coronary arteries can be divided into two functionally different types of vessels (Figure 1). The first type, the large epicardial conductance vessels, serve primarily a conduit role. Their tone is markedly diminished by nitrates. The second type, the precapillary arterioles (resistance vessels), are more influenced by local metabolic factors such as ischemia of downstream myocardium. These resistance vessels are little affected by nitrates. When these arterioles are maximally dilated by ischemia, changes in large vessel resistance can increase coronary blood flow. Nitrate mediated dilatation of collaterals or conductance vessels from which they arise probably contributes to the beneficial results observed. In addition, NTG relieves coronary artery

spasm which usually occurs at the site of atherosclerotic plaques in the large conduit arteries.

Nitroglycerin has beneficial noncoronary effects on the ischemic myocardium. By reducing left ventricular filling pressure (preload) and lowering mean arterial pressure (afterload), left ventricular (LV) end-diastolic volume and therefore LV end-diastolic pressure is reduced, decreasing the compressive forces on the coronary vessels in diastole. Also, the reduction in LV volume leads to a reduction in myocardial wall tension, a major determinant of myocardial O_2 demand. Thus, IV NTG appears to improve regional ischemia despite modest lowering coronary perfusion pressure. However, aggressive lowering of mean arterial pressure below a critical level required to maintain coronary perfusion may offset any potential for beneficial effect, as recently shown by Jugdutt (21) in an experimental conscious open-chest dog model.

Partial tolerance to the circulatory and anti-anginal effects of nitrates has been described in angina pectoris (22,23). There is some attenuation of the effects of nitrates on headaches, systolic blood pressure and heart rate after long-term use. However, the efficacy of sublingual NTG for the management of an acute anginal attack remains unimpaired. Needleman and Johnson have postulated that the responsiveness of the nitrate receptor is decreased when sulfhydryl groups are oxidized. Responsiveness to nitrates has been restored by administration of disulfide reducing agents like diothiothreitol and N-acetyl cysteine, a sulfhydryl donor (23). In the chronic heart failure population, tolerance may occur to the hypotensive response of nitrates, however there is sustained reduction in pulmonary capillary wedge pressure (PCWP) (22).

Like NTG, SNP dilates both the venous and the arterial system (24). It produces similar hemodynamic effects in many measured parameters, such as LV filling pressure, systemic vascular resistance, MAP, heart rate, cardiac output, stroke volume and stroke work indexes (Table 4). However, SNP produces a greater hypotensive response than IV NTG and decreases diastolic blood pressure more than systolic blood pressure (8,16). Unlike NTG which produces prolonged vasodilatation of the pulmonary vasculature, rebound pulmonary hypertension has been reported after abrupt discontinuation of SNP (17). Similar to NTG, SNP has been noted to increase intrapulmonary shunting and widening of the A-a gradient (15). In contrast to NTG, tolerance to SNP is unusual despite the fact that both

the effects of NTG and SNP may be mediated by cGMP. Significant rebound hemodynamic deterioration has been reported after abrupt withdrawal of SNP (31) but not with NTG. This may relate to differences in catecholamine or other neurohumeral responses to these drugs.

Comparative Effects on Myocardial Blood Flow

A major difference between IV NTG and SNP may be their potentially different effects on the coronary perfusion gradient and on regional myocardial blood flow in patients with ischemic heart disease:

(1) Unlike NTG, SNP appears to decrease diastolic blood pressure to a greater extent than systolic blood pressure (8, 16). Decreased diastolic blood pressure may compromise coronary perfusion, since most coronary blood flow occurs in diastole.

(2) SNP may reduce regional myocardial perfusion, although this effect is controversial.

Chiariello et al. (25) in 1976 reported that IV NTG and SNP exhibited dramatically different effects upon ischemic injury (precordial ST segments) and regional myocardial blood flow (RMBF). In 10 patients with acute anterior myocardial infarction, they titrated SNP and sublingual NTG to achieve comparable reduction in MAP. Despite similar hemodynamic effects, SNP increased the average ST segment elevation ($\overline{ST}$) while NTG reduced it. To clarify this disparity, SNP and IV NTG were administered to reduce MAP by 20 mm Hg from control values to 7 open chested dogs after acute coronary occlusion. Regional myocardial blood flow was determined by the microsphere technique. SNP increased ST segment elevation and reduced RMBF; in contrast IV NTG reduced ST segment elevation while increasing RMBF. Mann et al. (26) also demonstrated a potentially different effect of these agents on collateral blood flow in patients with coronary artery disease, using the Xenon washout technique to study regional myocardial blood flow. NTG increased collateral blood flow to areas of myocardium served by coronary arteries with subtotal obstructions whereas SNP reduced collateral blood flow. The differences between the two drugs effect on RMBF cannot be explained by their systemic hemodynamic effects since both drugs exerted similar actions.

It has been proposed that SNP's potentially deleterious effect on RMBF is secondary to a "coronary steal" phenomenon (25,26). As previously mentioned, it has been suggested that NTG acts in the coronary circulation primarily by dilating the large conductance vessels while its action in

the small resistance vessels is of a small magnitude and transient (Figure 1) (20,27). This effect on the conductance vessels may account for the increase and the redistribution of flow to ischemic areas despite a fall in coronary perfusion pressure. In contrast, SNP's main effect on the coronary circulation is to dilate the smaller resistance vessels (20,27). Since the resistance vessels in an area of ischemic myocardium are already under maximum dilating stimulus, SNP may shunt blood to non-ischemic myocardium, where the vascular resistance can still be lowered by the drug. In 1977, Capurro et al. (28) also found that intravenous NTG was a more potent dilator of intercoronary collaterals than SNP.

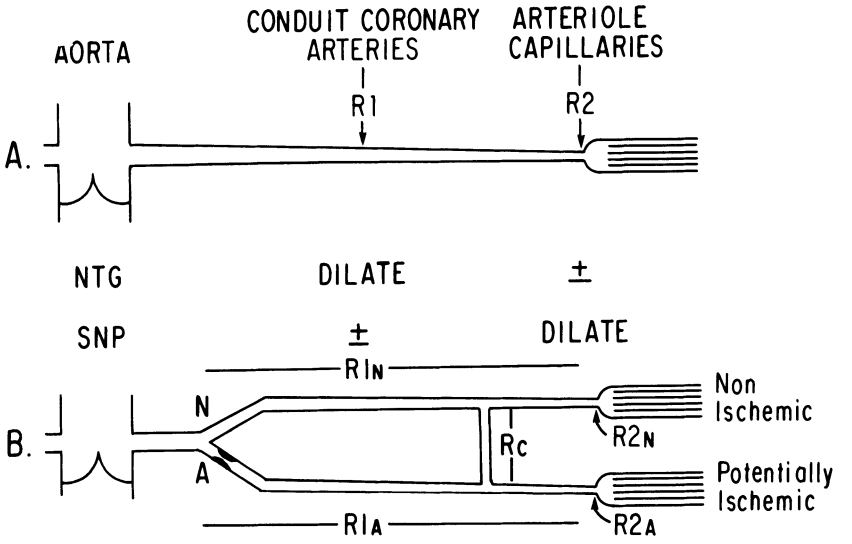

Figure 1. Models of (A) normal coronary circulation and (B) a circulation in which one branch is the site of atherosclerotic narrowing. R1 = resistance of conduit arteries; R2 = resistance of arterioles; N = normal conduit artery offering resistance R/N; A = abnormal narrowed conduit artery offering resistance R/A; R/c = resistance of collateral pathways; R2N = arteriolar resistance in territory of normal coronary artery ("nonischemic"); R2A = arteriolar resistance in territory of abnormal coronary artery ("potentially ischemic"). Sites of vasodilatation for NTG and SNP are also indicated. (Reprinted with permission from ref. 20).

Because of continued controversy over the effects of both NTG and SNP on myocardial ischemia, Hillis and Khuri (29) in 1980 studied their effects on RMBF and severity of regional ischemia in a controlled trial of open chest dogs with normal LV filling pressure. RMBF was quantitated by the radioactive microsphere technique; myocardial CO_2 tension provided an index of the severity of regional myocardial ischemia after transient coronary ligation. Infusions of IV NTG and SNP were titrated to produce a 20 mm Hg decline in MAP. When NTG was administered before coronary occlusion, it caused significantly smaller elevation in myocardial CO_2 tension than that which occurred during control occlusion. RMBF to the ischemic region was not altered. In contrast, SNP caused no change in myocardial CO_2 tension and a significant decrease of RMBF to the ischemic region.

Contrary to these studies, da Luz et al. (30) found SNP to improve overall cardiac performance and mechanical performance of regional ischemic myocardium in an open chest dog model. Importantly, SNP in their study was titrated to produce a significant reduction in peripheral resistance while MAP was maintained within the physiologic range, thus avoiding a detrimental reduction in coronary perfusion pressure.

Thus, although IV NTG and SNP exert similar hemodynamic effects, their effects on the coronary circulation may be substantially different. IV NTG exerts salutary effects on the coronary circulation and regional myocardial blood flow. NTG improves regional ischemia and maintains coronary blood flow despite lowering coronary perfusion pressure. On the other hand, SNP may aggravate myocardial ischemia and decrease coronary blood flow by shunting blood away from ischemic myocardium and lowering coronary perfusion pressure. However, care must be taken when extrapolating data from animal studies and studies containing small numbers of patients to clinical practice.

IV NTG AND SNP IN AMI

The beneficial hemodynamic effects of vasodilators in patients with acute myocardial infarction (AMI) complicated by pump failure have been satisfactorily documented (32,33). Although once thought to be contraindicated in the management of patients with AMI, IV NTG and SNP have been used in this clinical setting with the hope of limiting infarct size and favorably influencing long term survival and functional capacity.

Tables 1, 2 and 3, summarize the results of clinical trials of these vasodilators in patients with acute myocardial infarction.

Several points about research methodology deserve emphasis before reviewing the specific studies. Most of the studies assessing the efficacy of these agents in AMI have been conducted on relatively small numbers of patients. In addition, the critical time lapse for myocardial salvage (time from onset of symptoms to institution of therapy) in these studies has varied widely (mean 4.2 hours to 12 hours). The duration of treatment also has not been uniform with some patients treated for 2 hours while others were treated for 5-7 days. Most of the studies used indirect techniques to quantitate the effect on myocardial salvage, such as ST segment mapping, CK-MB enzyme curves, or radionuclide scans. Only the most recent studies (34,35) have included sufficiently large numbers of patients to use patient survival, the ultimate goal of therapy, as the primary end point. In addition, those studies have avoided potential hidden biases by randomizing patients to treatment either with IV NTG, SNP or placebo.

Many studies performed subgroup analyses in an attempt to discover those few patients who might receive the most benefit from therapy. Interpretation of these studies must be performed with caution, as retrospective subgroup analysis can lead to spurious results when no overall treatment benefit is seen. Any subdivision is arbitrary, breaks the randomization process and introduces bias. This bias may be exaggerated when there are small numbers of patients within each subgroup.

Clinical Trials of IV NTG in AMI

Table 1 summarizes the clinical trials of IV NTG in AMI. Several observational studies by Flaherty and co-workers (12,13) demonstrated improvement in LV function and the ability of IV NTG to decrease the extent of myocardial ischemia assessed by precordial ST segment mapping studies in patients with AMI treated within approximately 8 hours after the onset of symptoms. Although the improvement in LV function appeared to be greatest in those patients with the most severe LV dysfunction, the extent of myocardial ischemia was decreased irrespective of the presence or absence of LV failure. Most importantly, these studies showed that IV NTG could be safely administered to patients with evolving MI with only a minimal drop in mean arterial pressure and with no significant change in

TABLE 1

Summary of Clinical Trials of IV NTG AMI

AUTHOR - (YEAR)	STUDY DESIGN	SAMPLE SIZE	DURATION OF Rx	DURATION OF Sx PRIOR TO RANDOM OR Rx (HRS)	CHF (KILLIP CLASS)	END POINT	RESULTS
FLAHERTY (1975)	OBSERVATIONAL	20	2 HRS	8.7	60% II 5% III	ST SEGMENTS	NTG > C
FLAHERTY (1976)	OBSERVATIONAL	47	2 HRS	< 24 (MEAN ≈ 8)	74% II 4% III	ST SEGMENTS	NTG > C
DERRIDA (1977)	RANDOMIZED CONTROLLED	74	5-7 DAYS	< 24 (MEAN 10.1)	NOT STATED	MORTALITY ST SEGMENTS VT/VF	NTG > C
BUSSMAN (1977)	RANDOMIZED CONTROLLED	31	48 HRS	12	% NOT STATED	CK-MB	NTG = C
BUSSMAN (1981)	OBSERVATIONAL	60	48 HRS	< 8 (MEAN 4.5) > 8 (MEAN 12.8)	PCWP > 15 mmHg KILLIP CLASS NOT STATED	CK-MB	NTG > C NTG > C
FLAHERTY (1981)	RANDOMIZED PLACEBO CONTROLLED	104	48 HRS	< 12	≈ 60% II	MORTALITY NEW CHF INFARCT EXTENSION CK-MB ST SEGMENTS THALLIUM 201 TEC P_yPO_4 SCANS 2-D ECHO	NTG = C
JAFFEE (1981)	RANDOMIZED PLACEBO CONTROLLED	85	24 HRS	< 12 (MEAN 6.2)	32% II 7% III	CK-MB	NTG = C

Abbreviations: NTG=nitroglycerin; C=control; NTG>control=effect of nitroglycerin greater than control; Rx=treatment; Sx=symptoms; CHF=congestive heart failure; PCWP=pulmonary capillary wedge pressure; TEC P_yPO_4=technetium pyrophosphate.

heart rate. These observations helped dispell the old belief that NTG was contraindicated in this clinical setting.

Bussman and co-workers reported conflicting results on the effect of IV NTG on infarct size calculated from CK-MB enzyme curves (36,37). In a randomized study of 31 patients treated 12 hours after the onset of symptoms, infarct sizes were the same in both NTG and control groups regardless of the status of LV function and despite beneficial hemodynamic effects (36). In a later observational study of 60 patients with PCWP > 15 mm Hg, it appeared that NTG reduced CK-MB release and thus calculated infarct size in both early and late intervention groups (37).

Derrida and co-workers (38) reported the first study to use mortality as an end point. They randomized 74 patients within 24 hours of AMI (mean 10.1 hours) to prolonged NTG infusion (5-7 days) or control. The effect on ST segments and on the frequency of ventricular arrhythmias was also recorded, although the status of LV function was not reported. Treatment with IV NTG significantly reduced in-hospital mortality, decreased the incidence of ventricular tachycardia and ventricular fibrillation and aborted the appearance of Q waves at "vulnerable sites", defined as sites with ST segment elevation $\geq$ 1.5 mm and persistent R wave on initial maps.

Jaffe (39), in 1981, reported similar findings to Bussman's initial study in 1977. In a randomized placebo controlled trial of 85 patients, IV NTG was administered within 10 hours of the onset of symptoms (mean 6.2 hours) of AMI. There was no significant difference in infarct size index calculated from CK-MB enzyme curves between control and NTG treated patients. It was only after <u>retrospectively</u> stratifying patients into subgroups according to locus of infarction that a benefit was demonstrated in IV NTG treated patients with inferior infarction. A similar but statistically insignificant trend was observed for non-Q wave infarction, but no difference was observed for anterior infarction.

Flaherty and coworkers (40) enrolled the largest number of patients reported to date. One hundred and four patients were randomized to either IV NTG or placebo treatment within 12 hours of onset of symptoms. They reasoned that with a sample size of approximately 100 patients, mortality alone would not be an adequate end point for the trial. Therefore, other clinical variables (infarct extension, new CHF, ventricular arrhythmias) in addition to laboratory parameters (CK-MB, radionuclide scans) were

measured as end points which might indicate the salvage of ischemic myocardium. When all NTG and placebo treated patients were compared, no significant differences in clinical or laboratory outcomes could be demonstrated. NTG and placebo treated patients were then retrospectively subdivided into early and late treatment groups (treatment begun < 10 hr vs > 10 hr after onset of symptoms). A significant reduction in the combined frequency of new CHF, infarct extension, or early cardiac death was demonstrated in those treated early (< 10 hrs), although reductions in each individual complication was not significant when tested separately.

Clinical Trials of SNP in AMI

Table 2 summarizes the clinical trials of SNP in AMI. The initial studies of SNP in AMI focused primarily on the drug's effect on cardiac hemodynamics. Franciosa et al. (32) in 1972, reported the beneficial effect of SNP on LV function. In 15 patients treated within 24 hours of symptoms of AMI, SNP decreased PCWP by 50% and increased cardiac output in patients with elevated LV filling pressures. Awan and co-workers (41) in 1976, infused SNP in 12 patients within 6 hours (mean 4.2 hours) of onset of symptoms. Precordial ST segment maps were used to asses the effect on myocardial injury, in addition to conventional hemodynamic measures of myocardial O_2 consumption. Evidence of myocardial ischemic injury, as assessed by ST segment mapping, decreased in association with reduction of myocardial O_2 demand. Although encouraging, these initial studies suffered from faulty study design (lack of a control group, lack of randomization); and, in addition, involved very few patients. Therefore, a meaningful conclusion can not be derived from these studies.

Hemodynamic changes and mortality were compared in a randomized controlled trial by Hockings et al. (42) in 1981. Fifty patients with a mean PCWP > 20 mm Hg with AMI were assigned to SNP or furosemide within 24 hours (mean 11.2 hours) after onset of symptoms. Although beneficial acute hemodynamic effects of SNP were demonstrated, there was no difference in mortality or in serum level of CK-MB (as an estimate of infarct size).

In 1982, Cohn (34) and Durrer (35) each reported prospective, randomized, and placebo controlled trials of SNP in AMI. Both studies included substantial numbers of patients, both used mortality as their primary end point, yet the results were quite different.

TABLE 2

Summary of Clinical Trials Using SNP in AMI

AUTHOR - (YEAR)	STUDY DESIGN	SAMPLE SIZE (PATIENTS)	DURATION OF Rx MIN/HRS	DURATION OF Sx PRIOR TO RANDOM/Rx (HRS)	CHF	END POINT	RESULTS
FRANCIOSA (1972)	OBSERVATIONAL	15	NOT STATED	< 24	80% FCII-IV CHF	HEMODYNAMIC EFFECTS	50% ↓ PCWP ↑ CO IN PATIENTS WITH ↑ LVFP
AWAN (1976)	OBSERVATIONAL	12	10-15 MIN	4.2	NONE	ST SEGMENTS	↓ ΣST: ↓ $\overline{ST}$ ↓ NST
HOCKINGS (1981)	RANDOMIZED CONTROLLED	50	48 HRS	11.2	100%	HEMODYNAMIC EFFECTS MORTALITY CPK - MB	↑CO ↓ SVR SNP = CONTROL
COHN (1982)	RANDOMIZED PLACEBO CONTROLLED	812	48 HRS	17	100% PCWP > 12 mmHg	MORTALITY	SNP = P
DURRER (1982)	RANDOMIZED PLACEBO CONTROLLED	328	24 HRS	5	11.6%	MORTALITY CARDIOGENIC SHOCK CLINICAL CHF CK - MB	SNP > P

Abbreviations: SNP=sodium nitroprusside; P=placebo; C=control; S-T=ST segment; ΣST=total ST elevation in all EKG leads; ST=average ST elevation; NST=number of EKG leads with ST elevation greater than 1 mm; SNP>C indicates that sodium nitroprusside was superior to control with respect to end point; SNP=C indicates that sodium nitroprusside was equal to control with respect to end point; Rx=treatment; CHF=congestive heart failure; PCWP=pulmonary capillary wedge pressure; CO=cardiac output; SVR=systemic vascular resistance.

Cohn and colleagues (34) (Veterans Administration trial) randomized 812 male patients with elevated LV filling pressure (> 12 mm Hg) to placebo or SNP infusion within approximately 16 hours from onset of symptoms. Importantly, patients likely to receive anti-hypertensive therapy were excluded from the study. The treatment and control groups were closely matched, particularly for variables used to stratify randomization (age, systolic pressure, LV filling pressure). Mortality rates at 21 days and at 13 weeks were not significantly different between treatment and control groups. Although there was no favorable overall treatment effect, retrospective subdivision into early and late treatment groups (< 9 hours vs $\geq$ 9 hours) showed that early treatment with SNP had a deleterious effect on mortality at 13 weeks (24.2% SNP vs 12.7% placebo) and that later treatment had a beneficial effect (14.4% SNP vs 22.3% placebo).

Durrer and colleagues (35) (European Study) randomized 328 patients within approximately 5 hours from onset of symptoms to treatment with SNP or placebo. These investigators did not exclude hypertensive patients requiring specific therapy. They studied the effect of SNP on mortality at one week; on the incidence of cardiogenic shock, clinical signs of CHF and on peak levels of CK-MB. They reported a favorable treatment effect large enough to warrant early termination of the study. A significant reduction in mortality and in the other parameters measured was observed.

There are several major differences between the Veterans Administration trial and Durrer's European Study that may account for the divergent results:

1. The VA Study included only male patients; European Study included both male and female patients.
2. The time from onset of symptoms of infarction to the initiation of treatment was approximately 16 hours in the VA Study but only 5 hours in the European Study.
3. The VA study included only patients with hemodynamically documented elevated LV filling pressures whereas only 11.2% of the patients enrolled in the European Study manifested clinical CHF on admission.
4. The VA Study excluded patients requiring anti-hypertensive treatment in the peri-infarction period. These patients were not excluded from the European Study.

5. The VA Study enrolled only patients with ST segment elevation or significant (0.04 second) Q waves on the EKG. In contrast, the European Study included patients with ST segment depression or T wave inversion, thereby including subendocardial as well as transmural infarction.

As Flaherty (43) points out, the cause of death in the European Study in nine placebo-treated patients was free wall rupture, papillary muscle rupture or rupture of the ventricular septum. This relatively high incidence (7%) of myocardial rupture in a population of patients with an apparent low risk of death (ie., subendocardial infarction, absence of LV dysfunction) seems higher than expected. Since hypertensive patients were not excluded from this study, the beneficial effects of SNP could therefore be interpreted as reflecting the ability of SNP to prevent myocardial rupture by lowering excessively elevated blood pressure during AMI. However, SNP did lead to a significant reduction in peak CK-MB blood levels and a reduction in the incidence of CHF during the hospital period.

Comparative Trials of IV NTG and SNP in AMI

There are only two clinical studies directly comparing the effects of IV NTG and SNP in the setting of AMI (Table 3) (25,44). Both are cross-over studies, and enrolled very few patients, most of whom had documented elevated LV filling pressures. However they differ in the time interval elapsed from onset of symptoms to initiation of therapy and the measured end point. Armstrong's study (44) addressed only the hemodynamic effect of these two agents. IV NTG exhibited a greater effect on venous pooling (greater fall in PCWP) than SNP despite comparable infusion doses (63 mcg/min NTG vs 76 mcg/min SNP), and comparable reductions in mean arterial pressure and total peripheral resistance. The study by Chiariello and associates (25) has already been referred to in the previous section on pharmacodynamics. They demonstrated dramatically different effects on ischemic injury (ST segment maps) and regional myocardial blood flow (radioactive microsphere technique). IV NTG reduced ST segment elevation and increased regional blood flow; in contrast, SNP increased ST segment elevation and reduced regional blood flow. The detrimental effects of SNP were postulated to be secondary to the "coronary steal phenomenon".

At the present time, neither IV NTG nor SNP can be recommended for routine use in patients with AMI in an attempt to decrease infarct size.

TABLE 3 Direct Comparative Trials of SNP and IV NTG in AMI

AUTHOR - (YEAR)	STUDY DESIGN	SAMPLE SIZE	DURATION OF Rx	DURATION OF Sx	PCWP > 12	END POINT	RESULT
ARMSTRONG (1975)	CROSS-OVER	18	10-15 MIN AFTER NORMALIZING MAP OR PCWP	< 24 HRS	100%	HEMODYNAMIC EFFECTS	IV NTG > SNP ON PRELOAD
CHIARIELLO (1976)	CROSS-OVER	10	10 MIN AFTER STEADY - STATE ACHIEVED	6.4 HRS	90%	ST SEGMENTS	SNP: ↑ $\overline{ST}$ IV NTG: ↓ $\overline{ST}$

ABBREVIATIONS: NTG=nitroglycerin; IV=intravenous; SNP=sodium nitroprusside; Rx=treatment; Sx=symptoms; PCWP=pulmonary capillary wedge pressure; MAP=mean arterial pressure; ST=average ST-segment elevation; NTG>SNP=nitroglycerin effect greater than sodium nitroprusside.

Although either agent can be used to treat congestive heart failure or hypertension complicating AMI, suggestions that SNP may exacerbate myocardial ischemia through a coronary steal phenomenom support a preference for NTG over SNP. Future studies using these agents with the hope of decreasing infarct size should take into account the time interval between onset of symptoms and initiation of therapy. Patients should be randomized preferably within 4 hours of onset of symptoms. In addition to proper study design, large numbers of patients need to be enrolled in order to avoid bias and reach a meaningful conclusion. The role of these agents as adjuncts to thrombolytic therapy or PTCA in the setting of AMI remains to be determined.

IV NTG AND SNP IN CHF WITH OR WITHOUT AMI

Vasodilators have gained widespread acceptance for the management of patients with CHF with or without associated AMI (32,22,45). Studies in the early 1960's established the importance of afterload as a major determinant of cardiac output in the presence of LV dysfunction. The term afterload refers to the hydraulic forces (impedance) opposing the left ventricle as it ejects blood. The determinants of impedance in the human circulation are complex, difficult to measure and require sophisticated analysis. Therefore, although not entirely correct, clinicians use systemic vascular resistance synonymously with afterload. Acute unloading of the severely failing LV results in improvement in the extent of fiber shortening with a resultant increase in stroke volume. Afterload reduction also leads to lower filling pressures, since with improved systolic pump function, the heart is less reliant upon compensatory mechanisms provided by the Frank-Starling relationship. The improved cardiac performance is accomplished with little changes in arterial pressure and without a reflex tachycardia. Patients having the most depressed LV function appear to receive the greatest hemodynamic benefit from vasodilator therapy.

In patients with ischemic heart disease in addition to improving forward cardiac output and alleviating symptoms of dyspnea, vasodilator induced decreases in LV end-diastolic volume (chamber size) and LV systolic pressure decrease myocardial O_2 demand. In addition, vasodilators may also increase coronary perfusion and regional blood flow as previously alluded to.

Intravenous NTG and SNP have the capacity to improve the performance of the failing left ventricle. These agents have been shown to effect equivalent increases in stroke volume when systemic vascular resistance is lowered and LV filling pressures are maintained above 15 mm Hg (45). Both are beneficial as single agents, however when combined with ionotropic agents (Dobutamine or Dopamine), the Frank-Starling relationship can be shifted even further upwards and to the left. In cases of valvular regurgitation, NTG and SNP decrease regurgitant volume and heart size in addition to uniformly lowering elevated LV filling pressures.

In patients with underlying coronary artery disease, initial therapy with IV NTG may be preferable to SNP because of its uniformly beneficial effect on regional myocardial blood flow and the relative preservation of coronary perfusion pressure.

CLINICAL TRIALS OF IV NTG AND SNP DURING AND AFTER CARDIAC SURGERY

Vasodilators are commonly used during and after cardiac surgery. Intraoperative arterial hypertension is a frequent occurrence in patients undergoing coronary artery bypass grafting (CABG) despite adequate anesthesia. Stimulation of the sympathetic nervous system during median sternotomy may cause tachycardia and an increase in systemic vascular resistance (afterload). Also, increases in pulmonary capillary wedge pressure (preload) have been noted in patients with or without chronic LV dysfunction. The resultant increase in myocardial wall tension and O_2 demand exposes the cardiac patient to the danger of a perioperative infarct. Both IV NTG and SNP have been evaluated in clinical trials which compared their effects in patients during and after cardiac surgery (Table 4) (14,15,16,46).

From the available studies, it appears that IV NTG and SNP are equally effective in most patients for the treatment of intraoperative and post-operative hypertensive episodes. Both agents lower myocardial O_2 demand and improve LV performance in patients with LV dysfunction. IV NTG may be preferrable to SNP in this setting in view of its more gradual lowering effect on arterial blood pressure; less tendency to lower coronary perfusion pressure and its uniformly beneficial effect on myocardial ischemia. In a minority (about 15%) of patients "NTG resistance" is observed; with doses up to 1,100 mcg/min only 20-50% of the

TABLE 4 Clinical Trials of IV NTG and SNP During and After Cardiac Surgery

AUTHOR - (YEAR)	NO OF PATIENT	STUDY DESIGN		DOSAGE (ug/min)	HEMODYNAMIC EFFECT MAP	SBP	DBP	SVR	HR	PCWP	CI
STINSON (1975)	25	OBSERVATIONAL		NTG:MEAN 59	-9			±	±	-13	-7
				SNP:MEAN 77	-23			-34	+6	-27	+19
KAPLAN AND JONES (1979)	20	OBSERVATIONAL		NTG:32	-5	-6	-4		±	-24	
				SNP:20	-13	-10	-15		±	-24	
				NTG:64	-15	-17	-13		±	-29	
				SNP:40	-20	-18	-22		±	-41	
				NTG:96	-21	-24	-18		± 14	-35	
				SNP:60	-24	-21	-27		± 11	-47	
TOBIAS (1981)	22	RANDOMIZED CONTROLLED	NTG	BOTH STARTED AT 20 TITRATED TO MAP	-30			-30	±	-62	±
			SNP	70-80 mm Hg	-38			-38	±	-60	±
FLAHERTY (1982)	17	RANDOMIZED CROSSOVER		NTG:MEAN 111	-22			-30	±	±	+21
				SNP:MEAN 95	-22			-30	±	±	±

Abbreviations: NTG=nitroglycerin; SNP=sodium nitroprusside; MAP=mean arterial pressure; SBP=systolic blood pressure; DBP=diastolic blood pressure; SVR=systemic vascular resistance; HR=heart rate; PCWP=pulmonary capillary wedge pressure; CI=cardiac index

All values reported are in percentages, and are reported as significant changes from control values; ± = no significant change. (Reprinted with permission from ref. 5).

response seen with SNP is observed. In these patients, SNP should be substituted.

SIDE EFFECTS AND DRUG INTERACTIONS

Intravenous NTG

IV NTG is usually well tolerated with relatively few side effects. Hypotension, the most common side effect, has been reported to occur in approximately 18% of patients (5). Hypotension can be counteracted by slowing the infusion rate or stopping the infusion altogether, placing the patient in the Trendelenburg position and administering IV fluids if necessary. Although sinus tachycardia occurs very infrequently (< 1%), vagally mediated sinus bradycardia is occasionally seen (4%) (5) and usually responds to atropine . Headache, nausea and vomiting appear to be dose related side effects treated by decreasing the infusion rate. Although rare, methemoglobinemia has been reported to occur with administration of IV NTG in association with high infusion rates (> 7 mcg/kg/min). Methemoglobin levels > 3% signal toxicity.

Several drug interactions have been noted: IV NTG infusion has been reported to potentiate the hypotensive effects of tricyclic anti-depressants. In addition, IV NTG may prolong pancuronium-induced neuromuscular blockade. This may be a selective pancuronium-NTG drug interaction. IV NTG has been noted to possibly slow catabolism of narcotics. IV NTG should not be administered to patients with increased intracranial pressure, which may be raised even further after NTG. NTG is to be avoided in patients suspected of pericardial constriction or cardiac tamponade. It should also not be administered to patients with known hypersensitivity or idiosyncratic reactions to IV NTG or to other nitrates.

SNP

Like NTG, hypotension is the most common side effect noted and can be treated in a similar fashion. Like NTG, many of the symptoms noted are secondary to excessive vasodilation. These include nausea, vomiting, sweating, restlessness, headache and palpitations. These symptoms disappear promptly when the infusion is stopped or the rate is reduced.

Thiocyanate levels should be monitored in patients treated with SNP for longer than 72 hours to avoid thiocyanate toxicity especially in the

setting of renal disease (9). Cyanide toxicity, although a theoretical possibility, occurs rarely in clinical practice because of its rapid conversion to thiocyanate in the liver. Plasma thiocyanate levels < 10 mg/dl are usually well tolerated; however many patients tolerate levels ≥ 20 mg/dl without clinical evidence of toxicity (9). Toxic manifestations include metabolic acidosis, nausea, epigastric pain, confusion, hyperreflexia, seizures, cyanosis secondary to methemoglobinemia and death. Infusions of thiosulfate, hydroxycobalamin and sodium nitrate are indicated when stopping the infusion appears to be inadequate (9). Thiocyanate toxicity can be treated with emergent hemodialysis which easily removes the thiocyanate ion.

DOSAGE AND ADMINISTRATION

Intravenous NTG is usually diluted in glass or polyolefin containers to a final concentration of 100 to 400 mcg/ml with either D5W, normal saline, or lactated Ringers solution. Infusion of NTG is usually started at 5-10 mcg/min and the dose titrated upwards by 10 mcg every 5-15 minutes until the desired clinical effect is achieved. Blood pressure and heart rate are recorded with each increment in dosage and every hour after reaching a stable dose. The infusion rate is not increased further if there is a drop in blood pressure or increase in heart rate greater than 20% of baseline values. If the desired clinical end point has not been achieved (relief or prevention of recurrent angina), intravenous fluids can be administered to allow increases in the infusion rate. No recommendations can be made as to an optimum dose range as there is marked interpatient variability. Therefore for each individual patient, the dose of IV NTG is tailored to the desired clinical effect. To insure uniform NTG delivery, polyvinyl chloride administration sets and tubing must be avoided. Multiple studies have documented their capacity to absorb NTG limiting the concentrations of NTG that eventually reach the patient. Low absorption sets constructed from polyethylene-polypropylene have minimized the loss of NTG potency and are recommended for administration.

Similarly, SNP can be diluted to a final concentration of 100 to 400 mcg/ml. The solution must be protected from light by wrapping in an opaque material like aluminum foil. Like NTG, the starting dose of SNP is usually 10 mcg/min, the infusion rate is increased by 10 mcg/min every 5-15 minutes until the desired end point is achieved. Similar emphasis is

placed on recording blood pressure and heart rate with each dose increment to avoid excessive lowering of the blood pressure and reflex tachycardia.

HEMODYNAMIC MONITORING

In many patients, intravenous NTG and SNP can be used safely without need for invasive hemodynamic monitoring. The extensiveness of hemodynamic monitoring required depends on the severity of the patients illness, the status of left ventricular function, and the end point of the therapeutic trial. When one wishes to obtain precise assessment of the clinical problem at hand and maximally optimize the dose-response effect of therapy, then continuous monitoring of left ventricular filling pressure, cardiac output and arterial pressure is recommended.

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ACUTE CORONARY CARE AND DIAGNOSIS RELATED GROUPS

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INTRODUCTION

In 1983 the United States Congress amended the Social Security Act to include a new and prospectively determined payment system for in-hospital services for Medicare beneficiaries. This new Prospective Payment System (PPS) was government's principal strategy for slowing the rapid rate of increase of Medicare expenditures and for at least delaying the forecasted insolvency of the Medicare trust fund. Bankruptcy of this fund was predicted from calculations based on two assumptions: (1) annual payments would continue to increase on behalf of an increasingly large number of individuals over age 65, and (2) these payments would not be offset by tax revenues from those entering the work force because they were entering at a slower rate than those attaining the age of 65 and leaving the work force.

Prior to 1983 hospitals were reimbursed for the reasonable cost of the services they rendered to Medicare patients. The rising cost of most services and the increasing number of services compounded the problem created by an increasing number of people over age 65. The new PPS addresses a part of this problem, by setting a reimbursement rate for an episode of illness that requires hospitalization based on the nature of the illness - the diagnosis related group (DRG) into which the illness falls. The concept was that the payment would be the same for all patients within the same DRG at any given hospital: for some patients reimbursement would exceed cost and for others reimbursement would be below cost, but on balance reimbursement should equal cost. Once the reimbursement rate was set, payment

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could be adjusted each year based upon some inflation factor such as the CPI or the medical market basket index.

These changes are of major significance to hospitals and to physicians because of the large and growing number of Medicare patients. The issue is especially significant to those engaged in coronary care because of the proportion of patients who are sponsored by Medicare and because of the rapidly changing concepts of their appropriate and optimal care. In short, if reimbursement is less than cost, or if the rate reimbursement increases is slower than the rate costs increase, the practice of cardiology on a coronary care unit presents a potential financial problem for the hospital and its cardiologists.

This chapter describes the DRG-based prospective payment system and its effects on the coronary care unit. If the system is understood and if patient care is managed appropriately, the potential financial problem can be avoided or lessened without compromising quality patient care.

THE DRG SYSTEM

Diagnosis Related Groups or DRGs are nothing more than a patient classification scheme. The scheme was developed in the late 1960s and further refined during the 1970s. The system is designed to place each discharged patient first into one of 23 clinically coherent groups or major diagnostic categories (MDCs). Patients are assigned to one of these groups based upon the ICD-9-CM codes corresponding to the principal diagnosis. These 23 groups or MDCs are basically the major organ systems affected by disease: For example MDC-01 refers to Diseases and Disorders of the Nervous System, MDC-05 to Diseases and Disorders of the Circulatory System, and MDC-22 to Burns. Each principal diagnosis in the ICD-9-CM code leads to one and only one MDC.

Most MDCs are then partitioned into a medical and a surgical subset based upon whether or not a procedure requiring the use of an operating room is carried out. For

example, MDC 05, Diseases and Disorders of the Circulatory System, subdivides into 25 medical DRGs and 18 surgical DRGs. Within the surgical subset of any given MDC an episode of illness is further classified based on the specific operative procedure. For example, a closed mitral valvulotomy leads to a different DRG than an open heart procedure for valve replacement. Within the medical partition of MDC-05, patients are first subdivided on the basis of the presence or absence of acute myocardial infarction. For those with infarction further subsetting is employed on the basis of discharge status (alive or dead). For those without infarction, further subdivision is based upon whether or not a catheterization was done. Finally, in both the medical and surgical partitions, factors such as age, other complex diagnoses and co-morbid conditions are considered if they were found to increase length of hospital stay significantly. The final result is that each patient is assigned to one of 468 DRGs. A statistical process was used to select and weigh variables that lead to DRG assignment, such that DRG assignment was designed to predict typical resource consumption. (1) The application of the assignment logic for selected cardiovascular diagnoses is illustrated in Figure 1.

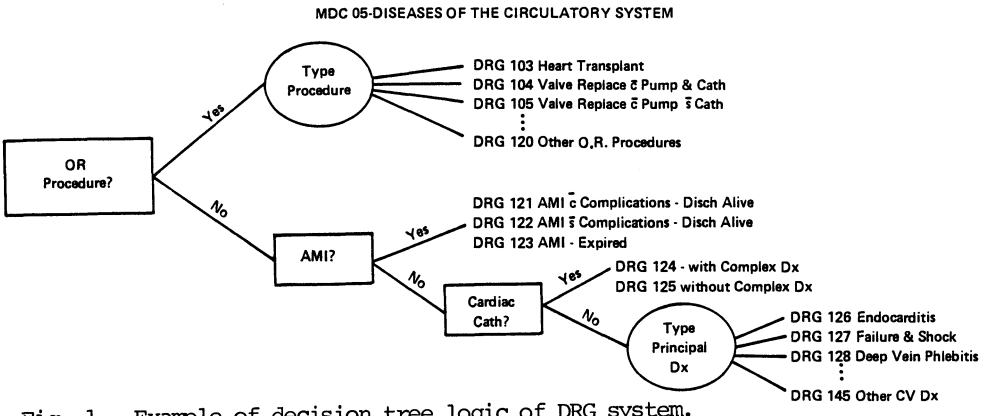

Fig. 1. Example of decision tree logic of DRG system.

PAYMENT BY DRG

Payment under the DRG system is intended to cover all typical hospital operating costs. It includes the usual Part A costs for routine services, intensive care and ancillary services. In deriving the actual payment, capital related costs and the cost of direct medical education were initially excluded. Using this definition a 20% sample of all Medicare discharges in 1981 was selected to compute a national representative average cost for all Medicare discharges in the sample. Patients within the sample were then classified into each DRG and the average cost by DRG was computed. By dividing the average cost per DRG by the national representative average cost, a relative weight was derived for each DRG. For example:

Table 1

DRG	Title	Relative Weight
121	AMI with Complications - alive	1.8648
122	AMI without Complications - alive	1.3651
123	AMI expired	1.1200
126	Infectious Endocarditis	2.6645
140	Angina pectoris without Catheterization	0.7548
143	Chest pain	0.6814

The reimbursement rate for each DRG is the product of two factors (a) the DRG relative weight and (b) the national representative cost per discharge. The labor component of cost is adjusted for differing wage levels by MSA* region. Also, for each teaching hospital, the rate is adjusted to reflect the indirect cost of medical education based on the resident to bed ratio.

Finally, medicare pays each hospital a series of "pass throughs" to cover depreciation of capital, specific costs such as kidney acquisitions (in proportion to their allowable costs) and the direct costs related to house staff education.

* MSA = Medical Service Area.

These federal payments, as well as relative weights, were based on a 1981 sample. Actual payments in 1983, 1984, 1985 were elevated by an inflation factor which has varied from year to year and which is subject to regulatory constraints we will not address here. In addition, actual payments in 1983 and subsequent years were calculated to allow for a four-year transition from a predominant hospital-specific rate in 1983 to a single national average rate four years later.

The central message in the above analysis is that under the fully developed DRG system a hospital will be paid a specific amount per discharge for rendering inpatient service to a Medicare patient. This amount is intended to be fair and to cover the cost of a typical patient within that DRG, after accounting for certain differences related principally to the cost of educating house staff and of wages. The hospital is given an incentive to achieve average costs that are less than the average payment. Conversely, the hospital is at risk if cost exceeds reimbursement.

POTENTIAL PROBLEM(S)

To appreciate potential problems created by the DRG prospective payment system on a typical CCU it is important to approach the situation from several points of view. From a financial point of view we would start by defining a problem as any consistent pattern of coronary care utilization or patient management that leads to a situation where reimbursement is less than cost. The words consistent and pattern are chosen carefully to highlight that the PPS is based on averages. No single patient or episode of illness necessarily presents a problem. However, if the pattern by which a physician or group of physicians manages most patients leads to costs in excess of reimbursement then a problem will exist. For patients with acute myocardial infarction (DRGs 121, 122, 123) such patterns might include: consistently long hospital stays that exceed the national

average for the DRG, consistent retention of patients on an expensive CCU beyond the typical period of transfer to a routine care unit, monitoring of variables that are not standard, or even of standard variables for atypically long periods of time.

Another potential problem on the CCU relates to its utilization. Under PPS reimbursement is based on diagnosis, rather than the setting in which care is rendered. Recall that reimbursement is proportional to the DRG weighting factors. DRGs 121, 122 and 123, which include all patients with established acute myocardial infarction, have DRG weights of 1.86, 1.36 and 1.12 respectively. Alternatively, DRG 140 (angina pectoris without catheterization) has a weight of 0.75 and DRG 143 (chest pain without catheterization) has a weight of 0.68.(2) Thus, when a coronary care unit is used to rule out myocardial infarction in patients who subsequently prove to have non-anginal chest pain or angina without infarction, reimbursement will be less than when infarction is proven. It can be reasonably assumed that days spent on the CCU for such patients will be at a cost significantly greater than the cost of routine care and especially if prolonged, will result in aggregate costs greatly in excess of reimbursement. The potential magnitude of this problem can be appreciated when we recall that many coronary care units, including our own, admit two patients with chest pain who prove not to have infarction for every one who does have infarction.(3)

We have discovered a third potential problem in analyzing our own data. The problem is probably not unique to Duke and we would speculate that it may occur at other relatively large tertiary care facilities. The DRG weighting factors assign a weight of 1.86 to DRG 121 (AMI with complications discharged alive), 1.36 to DRG 122 (AMI without complications discharged alive) and 1.12 to DRG 123 (AMI expired). The relatively low weight for DRG 123 reflects the national average length of stay before death of 3.1 days. At

Duke, the average patient cost in DRG 123 is twice that of DRG 122 (opposite to their relative weights) and the average length of stay before death is 8.0 days versus the national average of 3.1 days. We learned that more than 50% of our patients in DRG 123 had been transferred from another hospital. This problem can only be resolved by some future modification of the DRG system which takes into account the unique features and costs of complicated patients transferred from one hospital to another.

Another potential problem results from the fact that PPS does not presently take into account the rapidly changing patterns of care in acute myocardial infarction or of clinical research which heretofore has been covered at least in part by the patient care dollar. Recall that the DRG weights which determine reimbursement were developed based on 1981 data; although some of these weights have been adjusted slightly, there has been no significant change in those DRGs related to infarction. During this same period of time we have moved from a management strategy in which less than 10% of our patients with AMI underwent cardiac catheterization with coronary thrombolysis in 1981 to over 60% in 1984. In the absence of angioplasty, these patients remain in the medical partition and they are assigned to a DRG that does not reflect catheterization in the reimbursement rate.

Still another aspect of this problem relates to clinical research. One has only to read the abstracts of the annual meetings of cardiac societies, or the listing of published articles dealing with AMI in the Cumulative Index, to appreciate the magnitude of research on coronary care units. Who pays for serial echocardiograms to evaluate LV ejection fraction, continuous precordial mapping, sequential technetium 99m pyrophosphate scans, serum myoglobin levels, exercise testing at discharge, etc.? To whatever extent these studies are charged to patient care and to whatever extent these studies began since the DRG weights were created, they may be contributing to a financial problem defined as cost in

excess of reimbursement. Whatever the level of these activities, they probably predominate at university medical centers and will contribute to costs at these centers in excess of the national average and hence in excess of reimbursement.

HOW TO DECIDE IF YOU HAVE A PROBLEM

We have previously defined a potential problem under PPS as one in which the average cost for patients within a DRG is significantly more than the federal payment for that DRG. To illustrate this approach, Table 2 compares the actual costs at Duke in 1983 for the three DRGs that include all patients with documented infarction and the federal payment Duke would have received in 1983 had the DRG reimbursement scheme been in its mature form. In this analysis, total reimbursement includes the area specific payment for the DRG, inflated by the Duke specific indirect medical education adjustment, plus appropriately allocated shares of the pass-throughs.

Table 2

	Cost	Payment
DRG 121 (AMI, complicated, alive)	$ 7,905	$ 8,507
DRG 122 (AMI, uncomplicated, alive)	$ 6,123	$ 6,262
DRG 123 (AMI, expired)	$10,709	$ 6,090

With the practice patterns that prevailed in 1983, Duke would have been reimbursed approximately 7% more than cost for DRG 121, nearly equal to cost for DRG 122, and $4,619 or 43% less than cost for DRG 123. When the number of Medicare cases in each DRG is considered, the total shortfall would have been approximately $150,000 or $1,272 per Medicare patient. Clearly a problem exists, it is of moderate proportion and is attributable, at least at this institution, to DRG 123. As noted previously, for this DRG our average

length of stay was 8.0 days whereas the national average is 3.1 days. For the typical hospital, DRG 123 is dominated by patients with acute MI who die within the first 48 hours of the admission. For this institution, over 50% of the patients in DRG 123 were transferred to the CCU because of complications, and were supported for an average of 8 days before dying. From our point of view the DRG weight of 1.12 is inappropriately low for the patients in our case mix.

Using this approach, one can easily identify the DRG classification of the remaining non-infarction patients admitted to any CCU and determine their actual cost and expected reimbursement within the DRG system. As a first approximation, however, remember that the DRG weights for angina pectoris without catheterization and for chest pain without catheterization are 0.75 and 0.68 respectively or about ½ of that for uncomplicated acute MI. Correspondingly the reimbursement will be about ½ that for an uncomplicated acute MI. These patients are likely to present a financial problem especially if they are retained on the CCU for more than 24-36 hours.

HOW TO APPROACH THE PROBLEM

We would submit that even if reimbursement were not in question, the medical profession must address the fundamental issue of re-evaluating the value of what we do. Does a diagnostic procedure or therapeutic strategy favorably affect the outcome of a patient, which outcomes, what is the degree of effectiveness, for whom and when, and how certain are we?(4) Cost has traditionally been a minor and later consideration, but constraints on reimbursement have brought the issue of value into sharper focus. The coronary care unit is not immune to such scrutiny, nor should it be.

Several recent reviews have concluded that despite the absence of appropriate and adequately designed clinical trials, coronary care as it was introduced in the early and mid 1960s probably reduced the case fatality rate of

hospitalized patients with acute myocardial infarction by as much as one third.(5) The evidence was based largely on historical controls and attributed primarily to treatment or prevention of life threatening arrhythmias. The greatest degree of effectiveness seems to be in those admitted early and in those without serious complications. In such patients the length of stay on the CCU has been shortened progressively to as low as 24 hours and the total length of hospital stay has been shortened progressively to as low as 6-7 days without apparent adverse effect.(6-8) No one would seriously question that the CCU is the optimal environment for treating patients with severe infarction and pump failure, but the evidence for efficacy is debatable.

The period between 1970 and 1980 brought forth a host of strategies, pharmacological and others such as balloon assist devices, designed to reduce infarct size and the consequences of infarction to left ventricular function. Hemodynamic monitoring, serial enzymes and serial imaging or electrocardiographic techniques were used to estimate infarct size and ventricular function. Many of these studies have appeared to show promising results with regard to intermediate outcomes, but the evidence for any further reduction in hospital case fatality rate was marginal and controversial.(9)

The last 5-7 years have witnessed two important new trends relative to the care of acute ischemic heart disease. First, in patients with early infarction or impending infarction, there is overwhelming evidence for acute coronary thrombosis in a very distinct majority, thrombi that can be lysed with restoration of coronary blood flow, but often requiring early subsequent coronary angioplasty or coronary artery bypass surgery to maintain patency of the artery. The physiologic appeal of these approaches is beyond debate, but the evidence for effectiveness beyond restoring coronary arterial patency remains to be established.(10) The other trend of significance is the increasing use of coronary care

units and even of early catheterization to rule out infarction. Several studies suggest that the CCU is overutilized for this purpose and that rather simple strategies can be used to stratify patients, even in the emergency room, into those at high risk and very low risk of acute ischemia.(11-14)

With these considerations in mind let us address the question of costs significantly in excess of reimbursement. The CCU is an expensive resource. Our first obligation is to be certain that this resource is not any larger than is needed to meet appropriate demands for its use. Once the optimal size of the unit has been determined, the next step is to look at its direct expense budget. About 90% of the direct expense budget of a CCU is payroll and 90% of payroll is for nursing. How many nurses are required? The nursing leadership will have strong views on this question. They will tell you the number is influenced in part by their views of optimal nursing care, but adjusted significantly by the turnover rate of patients on the unit and by the demands placed on nursing that flow directly from the doctor's order sheet. The principal economic dividend of an experienced senior attending physician, and prudent ordering of monitoring and tests, is <u>not</u> the decreased cost of these tests, but rather the opportunity to limit the direct expense budget of the unit, namely payroll.

In hospital management it is useful to view the budget of any unit or program in terms of a fixed component, a relatively fixed component and a variable component. The latter are those expenses such as consumable supplies, drugs, etc. where cost varies directly with use or volume. The former are costs such as payroll, space and its maintenance, unit support, business office expenses, etc. which either are independent of census or vary only slightly with census. As a practical matter about 75-80% of the expense budget of a CCU is fixed or relatively fixed. These costs do not vary significantly with variations in occupancy in the range of

70-90%. Thus, cost per case or cost per patient day is directly related to occupancy. This fact again highlights the need to have a unit of appropriate size. Especially for an expensive unit such as a CCU it must be used at near capacity to be efficient and to minimize cost per patient day. If other units are full, it may be better to have a patient on the CCU who doesn't have infarction, even if he/she is charged a rate equivalent to routine care, than to have empty beds that are staffed.

About fifty percent of the total cost of a hospital stay for acute myocardial infarction can be attributed to resources used by and for the patient on the unit, but provided to the patient by other hospital units. Included in these allocated costs are diagnostic and therapeutic ancillaries such as radiology, respiratory therapy, laboratory services such as EKG and blood gases, and supplies (drugs, catheters, solutions, etc.). At first glance it might seem that a 10% or 20% reduction in the orders for x-rays, blood gases, enzymes, etc. would produce a proportional decrease in charges and cost per patient. However, this is not the case because like the CCU, a high proportion of the costs of an x-ray department or a hospital laboratory are also relatively fixed and vary little or not at all with use. Thus, a modest and random reduction in requests for service from only one unit such as the CCU does not reduce the cost to run the x-ray department and the cost per service goes up. The most effective way for the CCU director to influence the cost of x-rays or laboratory tests is to influence the cost per unit of service provided by these units. He can do this only by joining with other users either to identify new activities which increase use and decrease unit cost of the existing capacity of the laboratory, or by helping to define reductions of demand on the laboratory so that its capacity and fixed costs can be reduced.

Duke University operates a coronary care unit that was 16 beds in size in 1983 and maintained an average daily occupancy of 83%. The cost of services provided to all Medicare patients on the unit which would not have been reimbursed under PPS was about 7% of total cost. This is an important figure because it suggests the following: the combination of (a) a very modest increase in occupancy to perhaps 85%, (b) a very modest decrease of 1-2% in direct expenses related to payroll and (c) a very modest decrease of 1-2% in the cost per unit of service provided through departments such as radiology, laboratory, etc. could correct the shortfall. We believe that changes of this magnitude are achievable without compromise to the quality of patient care or to the basic style of clinical practice on the CCU. However, they will not happen without conscious efforts to efficiently use CCU capacity, to understand and modify the relationship between physician orders and nursing requirements, and a coordinated effort to increase the efficiency of other departments that provide services to patients on the CCU.

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IV. CORONARY CARE: THE PRE-DISCHARGE PHASE

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THE USE OF ULTRASOUND TO DETECT INFARCTION EXPANSION AND MURAL THROMBI

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INTRODUCTION

With the widespread availability of two-dimensional (2-D) echocardiography and, more recently, of Doppler echocardiography, ultrasonic methods for the evaluation of ischemic heart disease have greatly improved. Whereas time-motion ("M-Mode") echocardiography allowed only an ice pick view of a small (and possibly nonrepresentative) portion of the heart, 2-D echo allows a much broader field of view, as well as the potential to obtain views in various planes at multiple tomographic levels. In addition, significant improvements in image quality now allow excellent definition of ventricular wall motion, wall thickening, and chamber size in most patients (1).

These technical achievements have made it possible to echocardiographically diagnose myocardial infarction within hours in humans (2) and within minutes of coronary occlusion in animal models of acute infarction. Similarly, 2-D echo can be used to evaluate and serially follow segmental and global ventricular function noninvasively (1,3). Echocardiography is particularly useful in the evaluation of certain complications of myocardial infarction including the development of pericardial effusion, the detection of mural thrombus formation, and in the estimation of the size and functional significance of left ventricular aneurysms and pseudoaneurysms. The purpose of this chapter is to review the echocardiographic diagnosis of thrombi and aneurysms with particular attention to the sensitivity and specificity and therapeutic implications of these echocardiographic diagnoses.

THE DETECTION OF INFARCT EXPANSION BY ECHOCARDIOGRAPHY

Because echocardiography can be done repeatedly without exposure

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to ionizing radiation or invasive techniques, it is well suited to the detection of infarct expansion in patients and in experimental models. Such expansion--a disproportionate dilatation and transmural thinning in the infarcted zone--was studied using computer processing of two-dimensional echo images by Eaton and found to occur in 29% of patients with acute MI (myocardial infarction)(4). In this series, infarction expansion was first apparent at 3-4 days post MI with continued expansion occurring during the 2 ensuing weeks and was most common in large anterior transmural infarctions.

Although many infarcts probably undergo some degree of expansion asymptomatically (5), a subset of these infarcts develop localized, well demarcated thinning with protrusion of the infarcted wall during both ventricular systole and diastole ("true anatomic aneurysm" formation as defined by Cabin and Roberts (6)). In order to ascertain the ability of echocardiography to detect the incidence of such aneurysms, Visser and co-workers studied 422 consecutive patients coming to catheterization for the usual variety of clinical indications (7). Adequate quality 2-D echocardiograms were obtained in 386 patients (91%) in whom a 29% and 31% incidence of LV (left ventricular) aneurysms was found by catheterization and echocardiography, respectively. Using the cineangiogram as the gold standard, ultrasound examination for the presence of LV aneurysm yielded a sensitivity of 93% with a specificity of 94%. Similarly, other series demonstrate 90-100% sensitivity and 70-100% specificity of 2-D echo for detection of LV aneurysms in comparison to catheterization studies (8-11). In one of these studies (11), 2-D echo and equilibrium radionuclide angiography were compared to catheterization ventriculography in 24 patients. Radionuclide angiography had a sensitivity of 88% and specificity of 91% whereas 2-D echo had a sensitivity of 92% with a specificity of 73% when both techniques were compared to catheterization. In all these series, aneurysms were most commonly apical and anterior. False negative 2-D echo studies were due to aneurysms that were either very small or very large (and, hence, in the latter case, difficult to distinguish from diffuse dilatation of the left ventricle)(12). Other aneurysms were missed due to technical factors such as reverberations from the transducer causing poor

visualization of the apex. Since aneurysms tend to occur at the apex, additional apical two-dimensional echocardiographic views, separated by 45° rather than the more conventional 90°, may have a higher diagnostic yield (13). By contrast, M-Mode echocardiography has a very low yield by itself and rarely adds to the 2-D echo examination for the detection of aneurysms or infarct expansion.

In addition to the ability of echocardiography to diagnose aneurysms accurately, cardiac ultrasound also has an important role in the assessment of the residual myocardium that is left after aneurysmectomy. Using long axis views of the ventricle taken from two-dimensional echocardiograms and catheterization ventriculograms, Barrett showed that a larger index of the residual myocardium predicted favorable surgical and medical outcomes (14).

Echocardiography may be especially useful for the discovery of LV aneurysms when such aneurysms are filled with thrombus. Under such circumstances, contrast ventriculography and radionuclide angiography may miss an aneurysm whereas echocardiography might be able to detect the thrombus and the aneurysm.

MURAL THROMBUS DETECTION BY ECHOCARDIOGRAPHY

The incidence of mural thrombi in patients with myocardial infarction depends upon the population studied. Since autopsy series are biased in the direction of patients with more extensive infarction, it is not surprising that the reported incidence of mural thrombi in patients with myocardial infarction coming to necropsy is high--on the order of 17-66% (15). Similarly, systemic arterial occlusions are found at autopsy in approximately 30% of patients with LV mural thrombi, however, only 4% were clinically apparent in life.

The antemortem diagnosis of mural thrombus also depends on the infarction population studied and on the method and timing of study. For example, Arvan (15) performed multiple echocardiographic studies on 25 patients with acute MI and found a 24% incidence of left ventricular mural thrombus. However, Arvan also noted that when he studied a population at high risk for mural thrombi due to the presence of a recent large transmural anterior wall MI with significant LV dysfunction and with an akinetic or dyskinetic wall,

the incidence of left ventricular thrombus rose to 60%. Likewise, repeated frequent studies tend to bias the results of studies towards higher mural thrombus detection rates.

Mural thrombi are present in approximately 18% (range = 9-32%) of acute myocardial infarctions by echocardiography (Table 1).

Table 1: Summary of echocardiographic studies on the incidence of mural thrombi and systemic emboli after a myocardial infarction (MI)

Ref.	Acute or Healed MI	No. of cases	% LV thrombi	(thrombus by echo) % embolize	(No thrombus by echo) % embolize
15	Acute	25	24 (6 cases)	---	---
16	Acute	70	17 (12 cases)	0*	---
17	---	1000	9 (89 cases)	12%	5%
18	Acute	50	14 (7 cases)	24%	0
19	Acute	261	17 (46 cases)	0 (0/25)* 39 (7/18)#	---
20	Acute	54	32 (17 cases)	0 (0/10)* 86 (6/7)#	0
21	---	129	12 (15 cases)	---	---
22	Acute	96	19 (18 cases)	0*	0
			Avg. = 18%		

* = anticoagulated
\# = not anticoagulated
--- = information not available

Stagnant blood flow and decreased wall motion combine in the setting of myocardial infarction to significantly increase the risk of mural thrombus formation. Numerous studies have shown that larger anterior and apical infarctions have a significantly higher incidence of thrombi than are seen with inferior infarctions (15-19,23,24). Other risk factors for thrombus formation include: 1) akinetic or dyskinetic wall segments, 2) significant left ventricular dysfunction, and 3) acute transmural myocardial infarction (15,23).

The echocardiographic detection of mural thrombi is based on the presence of a mass with one or more of the following criteria: 1) a margin that is acoustically distinct from the underlying myocardium, 2) decreased wall motion at the site of the presumed thrombus, 3) central lucency due to liquefaction necrosis, 4) apical location, 5) free motion of an intracavitary thrombus margin, and 6) variation noted on serial examinations (23). Thrombi can usually be differentiated from other intracardiac masses such as tumors because tumors often involve walls having normal motion whereas thrombi almost always occur in a region of hypokinesis.

False positive diagnoses of mural thrombi by echocardiography are usually due to technical factors such as reverberation artefacts (23) or to the misinterpretation of unusually prominent normal anatomy (15). Thus, left ventricular hypertrophy with thickened left ventricular trabeculae, ectopic chordae tendinae, and prominent papillary muscles can occasionally be mistaken for thrombus. By insisting that the thrombus is viewed from multiple imaging planes (particularly emphasizing apical views) and by requiring that the examination is technically adequate, one can largely avoid overdiagnosis and false-positive diagnosis of mural thrombus.

False negative diagnosis of mural thrombus by echo is unavoidable since the resolution of current 2-D instrumentation does not allow definition in the clinical setting of very small but potentially significant thrombi. By placing clots on the endocardial surface of a motionless heart in a water bath, Drobac was able to demonstrate that clots as small as 2 mm could be visualized (25). In actual clinical practice however, thrombi must usually be 1 cm or larger in order to be distinctive enough to be recognized as thrombi (23). Thus,

echocardiographic methods currently allow only moderately-large to large clots to be detected (Figure 1). Furthermore, it is possible to miss even fairly large thrombi if the acoustic impedance of the thrombus is not sufficiently different from that of the surrounding normal structures to allow detection.

Despite the potential for false positive and negative studies, echocardiography has been found to be 70-80% sensitive and 80-100% specific using pathologic, angiographic, intraoperative, or indium-111 platelet imaging for comparison (24,26-28). Because indium-111 platelet scanning is a marker of the hematologic activity of the

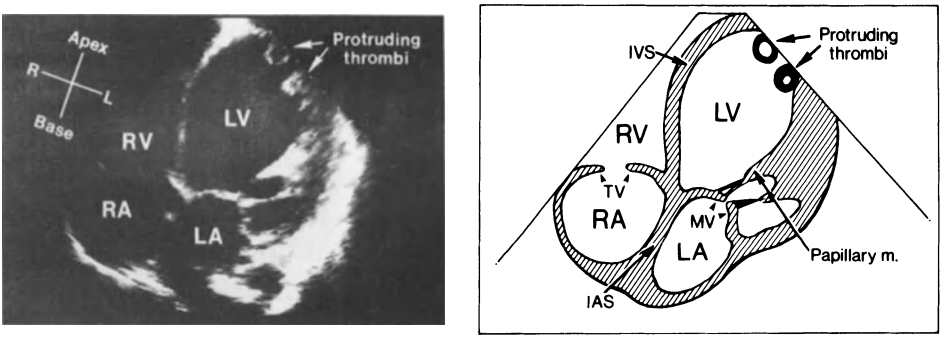


Figure 1: Left hand panel: Still frame of two-dimensional echocardiogram taken in the apical 4-chamber view. Right hand panel: schematic of top panel.

Two protruding 1½-2 centimeter round thrombi with shaggy borders and central lucency suggesting liquefaction necrosis, are seen near the apex in this patient with apical akinesis. The thrombi were mobile when viewed in real-time and suggest a high embolic potential.

Abbreviations: IVS = interventricular septum. RV = right ventricle. RA = right atrium. LV = left ventricle. LA = left atrium. TV = tricuspid valve. MV = mitral valve. Mod. Band = moderator band (a particularly prominent RV trabeculation). IAS = interatrial septum.

thrombus, whereas the echo shows the anatomic features of the thrombus, it is likely that the particular attributes of the two techniques might yield higher sensitivity and specificity when combined than by either method alone (29,30).

As shown in Table 1, most studies demonstrate an increase in the risk of systemic emboli if a mural thrombus is found by echocardiography in a patient with an acute MI, particularly if the patient is not anticoagulated. DeMaria has suggested that the actual configuration of the thrombus on two-dimensional echocardiography has additional implications for embolic risk due to these thrombi (31) (Figures 1 and 2). It has now been shown in several centers that increased embolic potential exists with: 1) larger thrombi, 2) greater thrombus protrusion into the LV cavity, 3) shaggy borders of the thrombus, 4) marked mobility of the thrombus, and 5) with thrombi that have a central lucency (32,33,34).

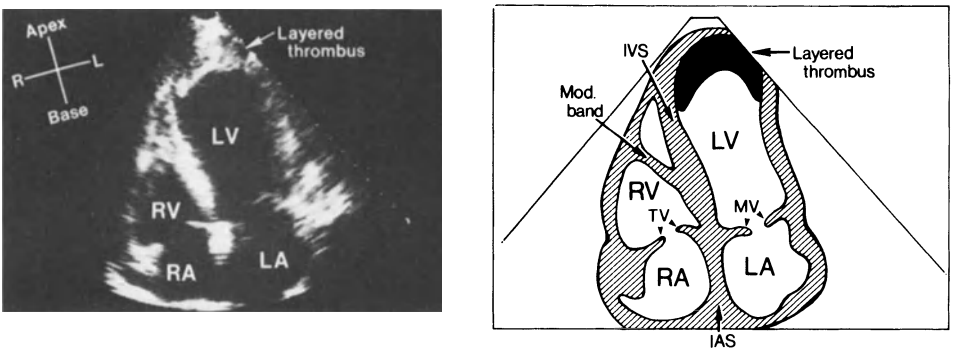


Figure 2: Left hand panel: Still frame of two-dimensional echocardiogram taken in the apical 4-chamber view. Right hand panel: schematic of top panel.

A layered thrombus occupies the aneurysmally dilated apex of the left ventricle. Because the thrombus is relatively flat and broad based, such a thrombus is believed to have lower embolic potential than protruding thrombi. Because the apex is largely filled with clot, the aneurysm could be missed by angiography or echocardiography.

Abbreviations: Same as Figure 1.

Figure 1 shows a dilated left ventricle containing 2 thrombi that protrude, have a central lucency, and during real-time video display, had marked mobility within the LV cavity. In contrast, Figure 2 shows a flat, layered, thrombus with a broad attachment to an aneurysmal apex. From the preceding discussion, it might be anticipated that such a thrombus would have a low embolic potential. A large body of evidence exists to support the idea that, although mural thrombi are found in 40-70% of left ventricular aneurysms, clinically apparent embolism occurs in only 3-5% (6,35,36). Cabin and Roberts suggested that mural thrombi located in an LV aneurysm tend to have a very low embolic potential because they are typically located in a non-contracting recess of the LV apex--well away from the LV inflow and outflow and thus, are relatively unlikely to have a portion of the thrombus break off.

CONCLUSION

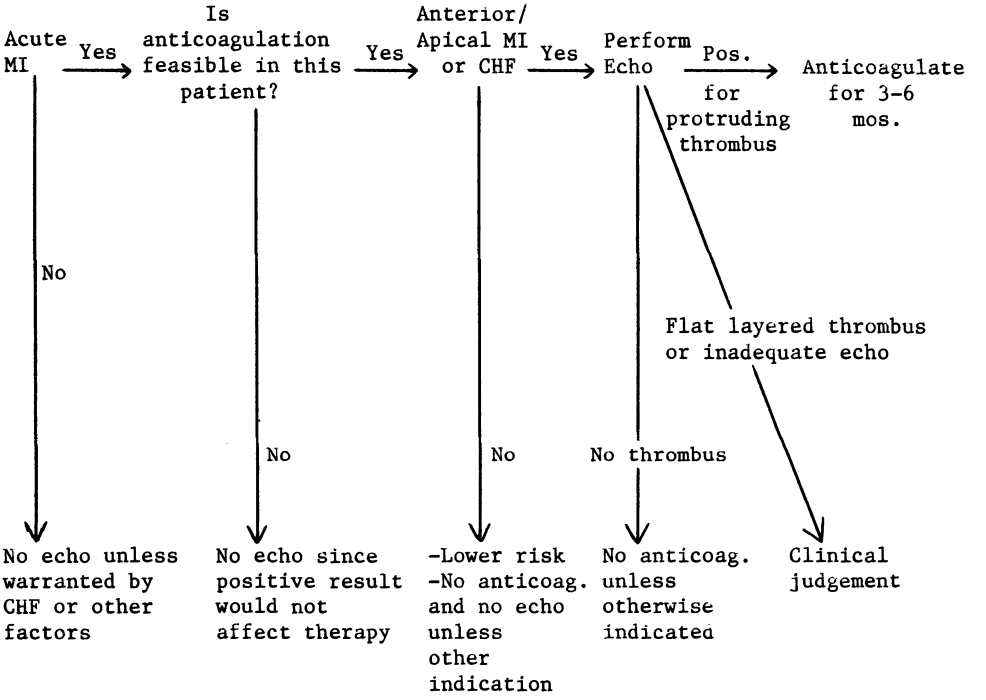
Given the large number of patients who present with myocardial infarction annually and the cost of an echocardiogram (estimated conservatively at $200/study), it is clear that a strategy that employs echocardiography routinely to look for mural thrombus in order to lower embolic complications would prove to be very expensive and of doubtful value. Similarly, a strategy that employs routine anticoagulation in all myocardial infarctions in order to prevent emboli has been shown to decrease emboli complications but without a decrease in mortality and with the side effect of increased propensity to hemorrhage (37).

From the previous discussion, it is clear that patients with an acute MI can be stratified into high and low risk groups for systemic embolic complications. High risk patients include those with large, anterior infarctions with depressed LV function. Unless there is a contraindication to anticoagulation, it would seem reasonable to obtain two-dimensional echocardiographic assessment of such patients.

The timing of the echo examination should probably be between 3 and 5 days after admission (38) since many embolic events occur early in the hospital course (19) and since many series show that thrombus often is recognizable by echo within the first 3-5 days post MI

(16,22). If a large pedunculated thrombus is seen, anticoagulation would seem to be advisable (Fig. 3). Hopefully, this strategy would be cost-effective and provide anticoagulation therapy for a group at high risk of embolization.

Figure 3: Possible cost-effective algorithm for use of echocardiography to diagnose thrombi in MI patients in order to decide regarding anticoagulation



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LESSONS FROM PREDISCHARGE CARDIAC CATHETERIZATION

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INTRODUCTION

The extent of coronary disease and its relationship to prognosis has been well documented in patients with angina pectoris (1). Acute myocardial infarction is generally an earlier manifestation of coronary artery disease (CAD) than angina (2). Therefore it cannot be assumed that patients with acute myocardial infarction have the same spectrum of coronary disease with the same prognostic significance as patients with angina.

Because of early concern about the safety of cardiac catheterization in post-infarct patients, initial information about coronary anatomy in myocardial infarction was derived from retrospective studies of post-infarct patients undergoing routine cardiac catheterization (3,4). These studies reported a high prevalence of multivessel disease, particularly three vessel disease.

Once the safety of catheterization in post-infarct patients was established, several series in which a high proportion of the patients admitted with acute myocardial infarction were prospectively catheterized before or just after discharge (5-14) were published.

From October 1976 to December 1983 we catheterized survivors of acute myocardial infarction aged 60 years or less prior to discharge. We excluded patients who had been transferred from other hospitals, patients who had undergone previous bypass surgery, requiring early catheterization for complications of myocardial infarction and those with severe life threatening diseases or significant valvular disease. Of 392 eligible patients 327 (83%) underwent coronary angiography and are followed annually.

THE SEVERITY OF CORONARY DISEASE IN POST-INFARCT PATIENTS

In our series only 3 patients had 50% or greater left main stenosis. Using 70% luminal diameter narrowing as the definition of significant stenosis in the other vessels, 30 (9%) of patients had insignificant disease. One

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hundred eighty-five patients (57%) had single vessel disease, 81 (25%) had two vessel disease and only 28 (9%) had three vessel disease.

A small but significant proportion of patients with insignificant coronary disease has been found in all studies. The actual proportion of patients with insignificant disease is related to the age of the population. The highest prevalence of insignificant disease has been found in the studies with the youngest patients (13,14,15).

In general, significant left main coronary stenosis is uncommon in uncomplicated post-infarct patients. Two studies (6,7) found that up to 10% of post-infarct patients had left main stenosis but the majority of studies contain no reference to left main stenosis or report a prevalence of only 1-2% (8,10,13,11). This is consistent with the finding that the majority of ischemic events in post-infarct patients are fatal and that non-fatal infarction is a relatively rare event (16).

The relative frequency of one, two and three vessel disease reported in post-infarct patients is so variable that on first analysis it appears that few conclusions can be drawn. For example, the reported prevalence of three vessel disease varies from 45% (3) to 9% (10). However, a number of factors related to patient selection determines the severity of coronary disease found at pre-discharge catheterization and when these are taken into account important lessons do emerge.

FACTORS RELATED TO THE SEVERITY OF CORONARY DISEASE

Our study (10) contained the highest proportion of patients with single vessel disease (57%) and the lowest proportion of patients with three vessel disease (7%). Studies published earlier (3-7) found higher prevalences of three vessel disease and lower prevalences of single vessel disease whereas more recent studies (8,9,11,12,14) have been more consistent with our findings.

The relationship of several clinical factors to the severity of coronary disease in our study is shown in Table 1. Increasing age, previous myocardial infarction and the occurrence of complications such as left ventricular failure are associated with an increased prevalence of multivessel disease.

All our patients were aged 60 or less. Several studies had a higher maximum age limit. Among patients aged less than 40, 64% had single vessel disease but none had three vessel disease. Among patients aged 51-60, 52% had single vessel disease and only 11% had three vessel disease. Roskmann et al.,

Table 1. The relationship of age, previous myocardial infarction (MI) and Killip Class to severity of coronary disease in post-infarct patients. The number of patients in each subset is shown in parentheses.

	# of Vessels with Significant Stenosis		
	1	2	3
Total Group (327)	57%	25%	9%
Age (years)			
Less than 40 (36)	64%	17%	0
41-50 (114)	61%	19%	7%
51-60 (177)	52%	30%	11%
First MI (285)	61%	22%	7%
Previous MI (42)	26%	45%	19%
Killip Class			
I (238)	60%	23%	6%
II-IV (86)	48%	29%	16%

who studied 679 patients less than 40 years old, found single vessel disease in 51%.

Previous myocardial infarction is also an important predictor of multivessel disease. In our study only 13% of the patients had a history of previous myocardial infarction. In these patients single vessel disease was only half as likely and three vessel disease nearly three times more likely than in patients with their first infarction. Two studies (6,7) in which a higher proportion of patients than ours had three vessel disease also contained a higher proportion of patients with a history of myocardial infarction (27% and 26% respectively).

We excluded patients transferred from other hospitals because they were usually referred for management of complications of infarction and we wished to avoid introducing a selection bias. Most studies have demonstrated that both early and late complications are associated with an increased likelihood of multivessel disease. Studies which have included patients referred because of complications are likely to have an increased prevalence of three vessel disease.

No consistent relationship has been found between the severity of coronary disease and the site of infarction or whether the infarct was a Q wave or non Q wave infarct.

CORONARY ANATOMY AND PROGNOSIS

The severity of coronary disease is one of many characteristics which have a univariate relationship to post infarct survival. Consequently the survival rates of groups which have undergone pre-discharge catheterization reflect the spectrum of underlying coronary disease. In our group with a high prevalence of single vessel disease the one, five and seven year survival rates were 96%, 86% and 85% respectively.

The important question is whether coronary anatomy contributes independent prognostic information, after adjustment for other important prognostic characteristics such as left ventricular function and age.

The question remains unanswered. Four studies (7,8,14,17) have included coronary anatomy in multivariable analyses of post infarct survival. Two (7,17) found that coronary anatomy was not a significant independent factor, one (8) found that it was, and one found only a marginally significant effect. In our study (10), among patients with ejection fraction less than 50% those with multivessel disease carried a significantly worse prognosis than single vessel disease (Figure 1).

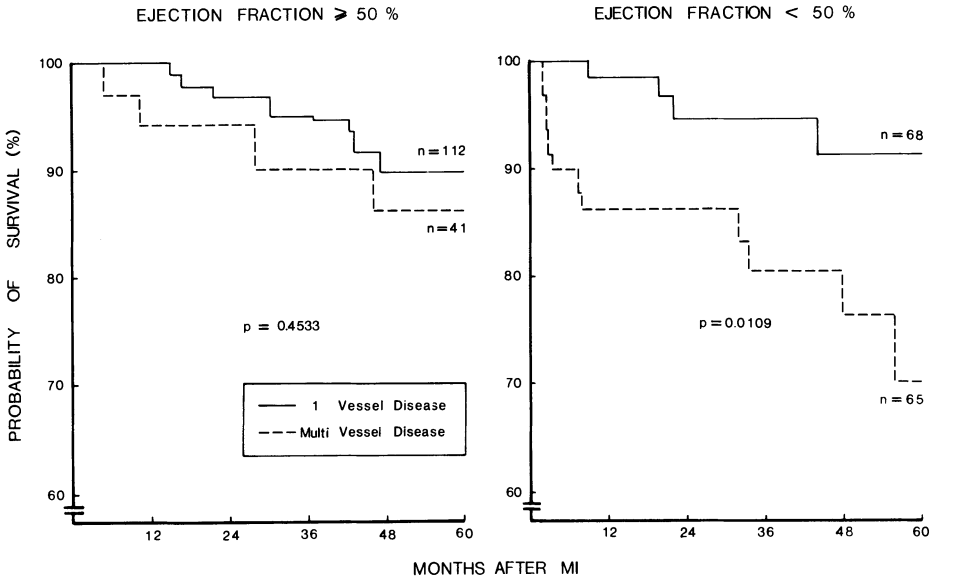

Figure 1. Comparison of survival curves for post-infarct patients with single and multivessel disease within subgroups based on left ventricular ejection fraction.

De Feyter et al. (9) found that the combination of EF <30% and three vessel disease was the best predictor of post-infarct events, and in a comparison with other prognostic factors, found that coronary anatomy was a better predictor of outcome than exercise test variables. Gibson et al. (11) also found that coronary anatomy was a better predictor than exercise variables but found that thallium scintigraphy was a better predictor than coronary anatomy.

CONCLUSIONS

Pre-discharge catheterization can be performed with safety. The probability of finding multivessel disease is closely related to the patient's age, whether there is a history of previous infarction and whether any complications have occurred. A young patient with a first, uncomplicated myocardial infarction is most likely to have single vessel disease.

Since left ventricular function can now be measured by radionuclide angiography, the only indication for pre-discharge catheterization is to determine coronary anatomy.

Routine pre-discharge catheterization following myocardial infarction cannot be justified on a cost benefit basis at the present time. However, post infarct patients with three vessel disease and reduced LV ejection fraction have a poor prognosis. Attempts to identify these patients should be pursued by non-invasive evaluation. A history of previous myocardial infarction, early or late complications, a reduced ejection fraction, or an abnormal exercise test (18) should lead to consideration of early post-infarct cardiac catheterization.

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THE PROCESS OF SELECTING THE PROPER ANTIARRHYTHMIC TREATMENT FOR PATIENTS AT HIGH RISK OF SUDDEN DEATH FOLLOWING MYOCARDIAL INFARCTION

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INTRODUCTION

Post infarction sudden death, defined as death less than one hour from the onset of symptoms, is usually due either to primary ventricular fibrillation or fibrillation following unstable ventricular tachycardia. The majority of these sudden deaths occur within one year of the presenting infarction (1,2). Analysis of clinical variables and selected test data gathered at the time of admission for myocardial infarction easily identifies patients at high risk of sudden death (3-13). Recognizing this, the clinician is faced with selecting an antiarrhythmic agent for the post infarction patient prior to hospital discharge. The purpose of this chapter is to outline the process of selecting the proper antiarrhythmic agent for patients at high risk of sudden death following myocardial infarction.

THE NATURE OF POST INFARCTION SUDDEN DEATH

Post infarction cardiac mortality is typically divided into sudden death and death from other cardiac causes, such as progressive congestive heart failure or reinfarction. Sudden deaths are presumed to be on the basis of a ventricular arrhythmia, and thus be amenable to antiarrhythmic therapy. More careful analysis of post infarction arrhythmic sudden death reveals that it contains two groups. The first group includes patients with recurrent myocardial infarction who develop primary ventricular fibrillation. Mortality will be decreased in this group by an antiarrhythmic agent that prevents primary ventricular fibrillation in the setting of acute infarction. A more desirable goal is to prevent reinfarction and as a result the need for antiarrhythmic therapy. Thus, part of the process of selecting the proper antiarrhythmic agent is to identify patients at high risk of reinfarction and prevent reinfarction if possible, rather than prescribe an antiarrhythmic agent. The second group includes patients who develop unstable ventricular tachycardia that degenerates into ventricular fibrillation. Mortality in the second group will be decreased by an antiarrhythmic agent that prevents unstable ventricular tachycardia. The ideal agent to prevent sudden death in the

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post infarction period will prevent unstable ventricular tachycardia as well as recurrent myocardial infarction (and thus the primary VF associated with acute infarction).

IDENTIFICATION OF PATIENTS AT HIGH RISK OF POST INFARCTION DEATH

With the recognition that the majority of post infarction sudden deaths occur within the first year of hospital discharge, risk stratification studies were undertaken to identify associations between clinical variables and sudden death. The initial studies revealed several variables associated with an increased risk of sudden death. More recent studies are directed at evaluating which of the known potent risk variables contain independent risk stratification information and which are different ways of looking at the same factor. For example, previous myocardial infarction, post infarction congestive heart failure, low ejection fraction, inability to exercise more than 2 mets and failure to elevate systolic blood pressure to 110 during exercise testing are all associated with increased post infarction risk. Each of these clinical variables characterizes the extent of myocardial damage. The extent of myocardial dysfunction can be regarded as the physiologic parameter common to the clinical variables. Other groups of risk factors suggesting a common physiologic parameter have been observed. Unfortunately, the proposed physiologic categories do not act independently, complicating precise risk stratification. Currently, the goal is to determine which methods of evaluating risk yield the most information for the least time, money and risk to the patient.

CLINICAL USE OF RISK STRATIFICATION

The first consideration for the clinician is to separate post infarction patients into a medical or surgical management category (14). Patients with clinical variables suggestive of additional myocardium at continued risk of infarction are at high risk of sudden death or death due to extensive reinfarction. Even if a patient survives reinfarction, and thereafter has no additional myocardium at risk, the risk of post infarction sudden death is increased in proportion to the extent of additional myocardial necrosis. The first goal then is to identify patients with additional myocardium at risk and prevent reinfarction rather than prescribe an antiarrhythmic agent.

Identification of Patients with Additional Myocardium at Risk. Several clinical variables suggest additional myocardium is at risk. These include a non Q wave infarction in the setting of previous infarction or abnormal EKG, post

infarction angina, a positive exercise tolerance test as well as evidence of deterioration of left ventricular function with exertion or stress (15,16). Clinical variables suggestive of myocardium at risk may co-exist and improve the ability to identify patients. For example Marmor et al., using multiple logistic regression analysis of 14 clinical variables, found that non Q wave infarction as well as obesity, female gender, and recurrent chest pain were associated with increased risk of early recurrent myocardial infarction (17). Another important group of patients with additional myocardium at risk was identified by Warnowicz et al. (18). They found that patients who developed pulmonary edema in the cardiac care unit at the time of acute infarction and had an ejection fraction of >0.45 near the time of hospital discharge had an exceedingly high risk of sudden death, reinfarction and unstable angina due to left main or 3 vessel coronary artery disease.

High mortality and failure to respond to conventional medical therapy is typical of patients with additional myocardium at risk of infarction. Marmor et al. found that patients with early recurrent infarction in the setting of a non Q wave infarction more than quadripuled their in hospital mortality (8% to 34%) as well as increasing their post infarction follow up mortality (23% to 34%) when compared to a group of patients with non Q wave infarctions without early recurrent infarction. As already noted, the patients identified by Warnowicz et al. with early pulmonary edema and an ejection fraction > 0.45 had an exceedingly high risk of recurrent infarction and sudden death (18). Schuster and Bulkley identified 70 patients with angina and ST/T changes that began less than 10 days after infarction. The overall mortality was 56% at 6 months; 72% if the ST/T changes with angina were outside the infarct and 33% if the ST/T changes were limited to the infarct zone (16). Thus, when the clinical variables and test data point to additional myocardium at risk of infarction, accelerated mortality and failure to respond to medical therapy is the rule.

Although a randomized study is not available to document the efficacy of revascularization in post infarction patients with additional myocardium at risk, it is generally agreed that, "either bypass surgery or balloon angioplasty is a reasonable therapeutic alternative for a subset of patients who have a poor prognosis when treated by conventional medical means" (14). One major objection to bypass grafting early after infarction is an anticipated high operative mortality. Several studies have looked at the mortality of cardiac surgery early post infarction. Levine et al. surgically revascularized 80 patients less than 30 days post infarction who developed unstable angina resistant to medical therapy.

Their operative mortality was 9% with one late death and one late infarction for a total 33 month mean follow up mortality of 11% (19). Roberts et al. reported 20 patients who had surgery less than 4 weeks following infarction for unstable angina and residual stenosis. No patient died and the 12 patients with preceding subendocardial infarction had a mean increase in ejection fraction of .08 (20). These data compare favorably to the 56% 6 month mortality reported by Schuster and Bulkley in patients with post infarction angina (16).

Partial support for early post infarction revascularization can be found by extrapolating from the randomized studies on stable angina where selected patients with 3 vessel coronary artery disease and all patients with left main disease benefit from revascularization (21). A significant percent of post infarction patients identified clinically as having additional myocardium at risk have either 3 vessel coronary artery disease and/or left main disease. Additional support for aggressive intervention comes from a study by Rogers et al in 1980. They retrospectively compared 43 patients who had coronary artery bypass grafting post infarction to 51 patients who were managed medically for post infarction angina. At mean follow-up of 23 months they found a 7% overall mortality in the surgical group vs. a 16% mortality in the medically treated group (P=NS). However, a significant difference was found in sudden death: 0% in surgical group vs 12% in the medical group. Also, improved survival ($p < 0.05$) was demonstrated in those patients of the surgical group who had 4 to 10 residual jeopardized segments when compared to those of the medical control group with a similar number of jeopardized segments (93% vs 64% survival) (22). Thus the goal is to identify patients with additional myocardium at risk of infarction and prevent reinfarction or infarct extension by revascularization.

CONTINUED RISK STRATIFICATION IN PATIENTS WITHOUT ADDITIONAL MYOCARDIUM AT RISK

Once patients with additional myocardium at risk are excluded the remaining patients are further subdivided. The next subgroup contains patients who developed sustained ventricular tachycardia or ventricular tachycardia degenerating into ventricular fibrillation before hospital discharge but greater than 48 hours after infarction. These patients are at extreme risk of sudden death due to recurrence of ventricular arrhythmias. The management of these patients should include electrophysiologic testing. A brief review of the concepts upon which electrophysiology testing is based is outlined below.

The role of electrophysiologic testing for the assessment of the arrhythmogenic potential of the heart. Recognizing that post infarction sudden death is due to a ventricular arrhythmia, one would like to have a method to estimate the vulnerability of the heart to these arrhythmias. The concept of using premature stimuli delivered to the heart to estimate electrical stability has its origin in the work of Wiggers and Wegria who demonstrated the vulnerable period in 1940 (23). They showed that PVCs induced near the apex of the T wave produced ventricular fibrillation in dogs. Subsequently, the use of fixed rate pacemakers demonstrated that premature stimuli delivered during the vulnerable period produced ventricular arrhythmias only in patients prone to arrhythmias (24). Currently premature stimuli are routinely used to induce ventricular tachycardia in patients with clinically documented arrhythmias to assess drug effect. The practice is referred to as programmed ventricular stimulation or, more loosely, as electrophysiologic testing. The number of sequentially induced premature beats required to fully assess cardiac electrical stability before and after drug therapy is best worked out for patients with documented sustained monomorphic ventricular tachycardia with onset remote from myocardial infarction.

Direction of therapy in patients at extremely high risk. Up to 10% of patients admitted to the Cardiac Care Unit with an acute myocardial infarction develop sustained ventricular arrhythmias within 24 hours of the onset of pain. These arrhythmias alone are not associated with a worsened prognosis. In contrast, those few patients who develop sustained ventricular tachyarrhythmias subsequent to 48 hours from the onset of pain are at extremely high risk, with an in hospital mortality as high as 60% (25). Electrophysiologically guided antiarrhythmic therapy for this group is currently being evaluated. Marchlinski et al. electrophysiologically studied 40 patients who developed ventricular tachycardia within 3 to 65 days from the onset of pain. Thirty three of forty had ventricular tachycardia induced similar to their clinical arrhythmia. Those whose VT remained inducible despite Type I antiarrhythmics were started on amiodarone. Two of seven patients whose inducible ventricular tachycardia was suppressed with type I agents died suddenly while 1/11 started on amiodarone died suddenly. In the 7 patients where ventricular tachycardia could not be induced, 4 died suddenly (57%), two were on empiric antiarrhythmic therapy and 2 were on no therapy (25). Unfortunately the numbers are too small to statistically document benefit from electrophysiologically guided antiarrhythmic therapy. However, given the extremely high risk conveyed by these symptomatic post

infarction ventricular arrhythmias, urgent referral for electrophysiologic evaluation is probably indicated. Antiarrhythmic therapy guided by electrophysiology study, empiric amiodarone therapy or an automatic implantable defibrillator are among the experimental treatments that may be instituted. The results of studies now in progress will hopefully document the best therapeutic approach to these difficult patients.

CONTINUED RISK STRATIFICATION IN PATIENTS WITHOUT ADDITIONAL MYOCARDIUM AT RISK AND WITHOUT EXTREME ELECTRICAL INSTABILITY

The remaining patients represent the majority of post infarction patients. As already mentioned, sudden death in these patients is due primarily to ventricular fibrillation following unstable ventricular tachycardia. Several lines of evidence support this belief. First, at least half of the early post infarction deaths are sudden, strongly implicating an arrhythmic cause. Second, a ventricular arrhythmia on 24 hour EKG recording prior to hospital discharge markedly increases the risk of sudden death (4,5,9). Third, in 1984 Goldstein et al. documented that a ventricular arrhythmia was the proximate cause of death in at least 83% of post infarction patients who died within 24 hours of recurrent symptoms (1). Finally, in 1985, Stevenson et al. compared patients more than 9 days post infarction presenting with aborted sudden death to those presenting with sustained ventricular tachycardia. During programmed ventricular stimulation, the group presenting with sudden death more frequently developed rapid polymorphic ventricular tachycardia or ventricular fibrillation than the group presenting with ventricular tachycardia. When monomorphic ventricular tachycardia was induced, the rate was faster (248 ± 32 vs 188 ± 27) in the sudden death group (2). Finding hemodynamically unstable monomorphic ventricular tachycardia supports the concept of sudden death resulting from ventricular tachycardia degenerating into ventricular fibrillation.

The appeal of the electrophysiology study for the identification of asymptomatic patients at high risk of sudden death. We saw earlier in the chapter than an electrophysiology study might someday be useful to document drug efficacy in patients who develop early (before discharge but $\geq$ 48 hours after the onset of pain) symptomatic post infarction ventricular tachycardia (25). Above we saw that many patients with aborted post infarction sudden death have rapid monomorphic ventricular tachycardia inducible with programmed ventricular stimulation (2). From this, the electrophysiology study is a logical test to identify patients at high risk of sudden death. However, the ability of programmed

ventricular stimulation to identify asymptomatic patients at high risk of sudden death in the post infarction period is controversial. Table 1 summarizes the electrophysiology studies that evaluated the risk of post infarction sudden death, usually in patients with congestive heart failure and/or ventricular arrhythmias (26-33). Several, but not all of the studies suggest that programmed stimulation is a sensitive but not specific method for the identification of patients at risk for the development of ventricular tachycardia or sudden death. It is difficult to compare these electrophysiology studies because of the wide variability of methods. However, the low sensitivity of the Marchlinski study appears to be due to the non aggressive stimulation protocol (only two extra stimuli of low amplitude and short duration at a single ventricular site). With regard to the aggressiveness of the stimulus protocol, Waspe et al. point out that 5 of 7 patients in their study who died suddenly required 3 extra stimuli to induce prognostically significant rhythms. However, because of the invasive nature of an electrophysiology study, even if the appropriate stimulation protocol demonstrates that programmed ventricular stimulation is a sensitive test for the identification of patients at high risk, it must identify patients at risk at least as well as other tests. In this regard, the ability of programmed ventricular stimulation to add prognostic information to the clinical data or to other less invasive studies such as ejection fraction and 24 hour EKG monitoring is just starting to be evaluated (Table 1). Further, it remains to be demonstrated that asymptomatic post infarction patients with a positive electrophysiology study can be converted to a low risk group by the use of programmed stimulation guided antiarrhythmic therapy. In summary, before programmed ventricular stimulation becomes a useful clinical tool in the asymptomatic post infarction patient, it must both identify patients at risk and accurately test the value of therapeutic interventions.

Currently available methods for the identification of asymptomatic patients at high risk of sudden death. The clinical data, estimates of left ventricular function, exercise capacity and 24 hour EKG monitoring can stratify the group without additional myocardium at risk and without extreme electrical instability into a spectrum from extremely low risk to high risk. However, given the limited therapeutic modalities available (to be discussed later), it is only useful to separate patients at extremely low risk from the rest of the group. A patient can be regarded as at extremely low risk of subsequent cardiac events if several criteria are fulfilled. For example one group of criteria that identifies the patient at extremely low risk requires that it be the first myocardial infarction in

Table 1. Electrophysiology Studies Evaluating the Risk of Post Infarction Sudden Death

Author Date	Rhythm Preceding Extrastimuli	Extra-stimuli Duration & Strength	Extra-stimuli Location	Extra-stimuli Number	Extra Response Criteria for a + Study	+Study Total Pts	SD or VT + Study	SD or VT - Study	Days After MI Before Study	Follow Up in Months	Comparison to Other Methods of Post MI Risk Eval
Greene[26] 1978	Atrial paced 86/min	0.9 msec 2X DT	RV apex	1	2 or more	19/48	15/19	4/29	8-85 (mean 24)	12	none
Hamer[27] 1982	NSR & Atrial paced 100/min & 120/min & 150/min	?msec 2 volts & 10 volts	RV apex & RVOT	2	6 or more	12/37	4/12	1/25	7-20 (median 11)	12	none
Marchlinski[28] 1983	NSR & RV paced 100/min &150/min	1 msec 2X DT	RV Apex	2	4 or more	10/46	1/10	5/36 (mean 22)	8-60 (mean)	18	SD5/16EF ≤ .40 vs 1/27EF >.40
Richards[29] 1983	RV paced 100/min	2 msec 2X DT & 20 mA	RV apex & RVOT	2	> 10 sec of VT or VF	38/165	13/38	3/127	6-28	8 (mean)	none
Santarelli[30] 1985	RV paced 100/min & 130/min	2 msec 2mA & 10 mA	RV apex & RVOT	2	10 or more	23/50	0/23	0/27	17-40 (mean 25)	11.2 (mean)	none
Waspe[31] 1985	NSR & RV paced 100/min & 141/min	1 msec & RVOT 4X DT	RV apex	3	7 or more	17/50	7/17	0/33	7-36 (mean 16)	23 (mean)	SD4/17EF≤.40 vs 2/33EF>.40

The studies of Kowey et al.[32], 1984 (57 patients 1 to 24 months from MI, mean 10 months) & Mason et al.[33], 1982 (28 patients 3 weeks to 3 years from MI, majority far greater than 3 weeks) are not included because the patients were remote from infarction.
RVOT = right ventricular outflow track; RV apex = right ventricular apex; EF = ejection fraction; NSR = normal sinus rhythm; msec = millisecond; mA = miliamp; Pts = patients; VT = ventricular tachycardia; VF = ventricular fibrillation; SD = sudden death; MI = myocardial infarction; DT = diastolic threshold; + study = a positive study; - study = a negative study.

a patient who was previously functionally normal. The first infarction must not be complicated by bundle branch block or congestive heart failure even transiently. In addition there must be less than 3 unifocal PVCs per hour on a predischarge 24 hour ambulatory EKG, a normal ejection fraction, and the ability to exercise to 5 mets with an increase in systolic blood pressure to >110 (11). Other groups of similar criteria can be used to identify extremely low risk patients. The utility of identifying the extremely low risk patient will be discussed later.

REDUCTION OF POST INFARCTION SUDDEN DEATH - DATA FROM SECONDARY PREVENTION STUDIES

Selecting the proper antiarrhythmic treatment for patients at high risk of sudden death following myocardial infarction is based on the results of secondary prevention trials. The goal of secondary prevention is to reduce the morbidity and mortality of patients with coronary artery disease as manifest by acute myocardial infarction. The secondary prevention approach developed because acute myocardial infarction or sudden death is frequently the first manifestation of coronary artery disease, thus primary prevention is not possible. Two factors helped to stimulate therapeutic trials aimed at secondary prevention of coronary artery disease. First, an acute myocardial infarction results in the logistics for study because the patients are collected at a central location (the cardiac care unit) with a disease process that is by definition severe in all the patients. Second, despite the fact that many of the patients are discharged from hospital post infarction without symptoms, most will eventually succumb to the disease. The secondary prevention approach is applied to post infarction patients like the subgroup we are considering, in whom no specific therapeutic intervention is dictated by the clinical symptoms/setting. Patients with additional myocardium at risk and patients with extreme electrical instability (those who develop symptomatic ventricular tachycardia greater than 48 hours post infarction) are not included in secondary prevention studies.

May et al. reviewed the various interventions aimed at secondary prevention of coronary artery disease and related each to the mechanism by which it would reduce morbidity and mortality (34). Anticoagulants, fibrinolytics and platelet-active agents are used with the intent of preventing recurrent coronary thrombosis. Diet, lipid lowering drugs, blood pressure reduction, cigarette cessation and exercise are aimed at preventing progressive coronary atherosclerosis. Calcium antagonists, beta blockers as well as platelet active

drugs and exercise are aimed at preventing recurrent ischemia. Inotropic agents and afterload reduction are used to treat congestive heart failure. Finally antiarrhythmic agents are used to prevent sudden death.

THE APPEAL OF ANTIARRHYTHMICS AS SECONDARY PREVENTION AGENTS

The use of antiarrhythmics for post infarction secondary prevention is supported by the fact that antiarrhythmics, particularly Type I agents, are effective in suppressing ventricular arrhythmias in the post infarction period. Based on the assumption that suppression of arrhythmias with Type I agents will reduce sudden death, it makes good sense to use antiarrhythmics for secondary prevention. However, no matter how reasonable the rationale for therapy, it is vital that clinical trials document efficacy. There is ample precedent for rational well considered therapy either resulting in no benefit or worsened morbidity and mortality.

Exacerbation of arrhythmias with antiarrhythmic drugs. It is important to recognize that drugs given in the hope of preventing serious arrhythmias, may actually make matters worse. A brief review of the proarrhythmic effects of antiarrhythmic agents is useful prior to discussing the specific agents evaluated for the prevention of post infarction sudden death. Since Selzer and Wray first described quinidine syncope in 1964, the potential for antiarrhythmic agents to cause or exacerbate ventricular arrhythmias has been recognized (35). Type I agents, such as quinidine, disopyramide and procainamide are most frequently associated with the exacerbation/induction of ventricular arrhythmias (36). The clinical arrhythmias associated with Type I agents may take a variety of forms, although classically the torsade de pointes morphology arises in the setting of marked QT prolongation and hypokalemia (37). Recently Winkle et al. reported that a new Type I antiarrhythmic agent, encainide, exacerbates severe arrhythmias in 12% of patients tested. More important they noted that the ventricular arrhythmias were not torsade-like and develop without associated QRS widening, QT prolongation, or R on T phenomenon (38). The Type III antiarrhythmic agent Amiodarone and the beta blocker/Type III agent sotalol have also been documented to induce/exacerbate ventricular tachyarrhythmias usually associated with prolongation of the QT interval. Even the beta blockers propranolol and metoprolol are reported to exacerbate arrhythmias (36).

The use of programmed ventricular stimulation has furthered our understanding of the ability of drugs to facilitate ventricular arrhythmias. With programmed ventricular stimulation, it is frequently observed that Type I agents

(procainamide and quinidine) and the Type III agent amiodarone make it easier to induce a patients clinical ventricular tachycardia, albeit at a slower rate. In some patients the agents convert non sustained to sustained ventricular tachycardia (39). Ruskin et al. reported 6 patients resuscitated from out of hospital cardiac arrest while taking quinidine or disopyramide with therapeutic levels and normal QT intervals. Subsequently no arrhythmias were induced by programmed stimulation until the drug was restarted (40). Thus, the lesson from programmed stimulation studies is that antiarrhythmic drugs may facilitate the appearance of a patient's underlying clinical arrhythmia without QRS widening or QT interval prolongation. Also, certain Type I antiarrhythmic agents facilitate the induction of arrhythmias in the setting of acute ischemia in the experimental animal (41). The clear ability of antiarrhythmic agents to exacerbate arrhythmias demands that they be proven effective prior to use as secondary prevention agents.

TRIALS OF ANTIARRHYTHMICS AS SECONDARY PREVENTION AGENTS

There are four types of antiarrhythmic agents. Type I includes lidocaine, procainamide, mexilitine, encainide, tocainide, phenytoin as well as numerous other agents. Type II refers to the beta blocks while Type III agents include amiodarone and bretylium as well as sotalol (which is also a beta blocker). Finally the Type IV agents include a variety of calcium blockers. The clinical trials of the antiarrhythmic agents used to prevent sudden death in the post infarction period are reviewed below by type. Keep in mind that in the post infarction situation a study that randomizes fewer than 250 patients will not show a statistically significant improvement or worsening of survival for the treated group unless the true difference is greater than 40%. For example, if the control mortality is 10%, the treatment mortality must be less than 6% or greater than 14% for the difference to be statistically significant (34).

Type I Agents. The Type I agents are the antiarrhythmics that first come to mind when the topic of arrhythmia suppression is mentioned. Until recently, review papers that discuss the use of antiarrhythmic agents in the prevention of sudden death in the post infarction period tacitly limit the review to the Type I agents. It is easy to see why. The ability of Type I agents to suppress ventricular arrhythmias is clearly documented, thus it is expected that the drugs will be effective. However, seven randomized trials, six of which were placebo controlled, failed to show a statistically significant improvement in total mortality or sudden death (42-48). In fact five of the seven trials demonstrated a trend toward worsened prognosis, and one absolutely no difference. These studies

are outlined in Table 2. The trend toward worsened prognosis seen with Type I antiarrhythmic agents is more compelling when other types of post infarction secondary prevention trials such as platelet agents, anticoagulants and exercise are considered. With the other types of secondary prevention agents, the majority of studies within a drug type demonstrate a statistically insignificant improvement in survival. Only the Type I antiarrhythmic agents and the lipid lowering agents demonstrate a trend toward impaired survival in the majority of studies (34). From the previous discussion on the proarrhythmic effects of antiarrhythmic agents and the results of the Type I antiarrhythmic trials it is clear that antiarrhythmic agents may worsen survival by promoting arrhythmias. It is particularly important to note that the trend toward worsened prognosis with the Type I antiarrhythmics is seen despite suppression of base line ventricular ectopy in the treated patients (Table 3). Thus, in those post infarction patients in whom ventricular ectopy is documented at base line, a Type I agent cannot be recommended, even if repeat 24 hour EKG monitoring demonstrates that the chosen agent has greatly reduced or eliminated the arrhythmias. In summary, Type I agents have no role in the post infarction patient except possibly as guided by programmed ventricular stimulation.

Type II agents. Beta blockers can function as antiarrhythmic agents either directly or indirectly. The antiischemic effects of beta blockers may have an indirect antiarrhythmic effect. The direct antiarrhythmic action of beta blockers can be attributed to one of two mechanisms. First, beta blockers inhibit the increased rate of diastolic depolarization in cells with pacemaker potentials produced by adrenergic stimulation. The antiadrenergic properties are likely to be particularly important when catecholamine excess is present such as in acute myocardial infarction. The antiadrenergic effects of beta blockers also inhibit the increased automaticity associated with glycoside excess. The second mechanism by which beta blockers may exert an antiarrhythmic effect is through a quinidine-like membrane stabilizing effect. That is, beta blockers can decrease the rate of maximum diastolic depolarization of the action potential resulting in decreased conduction velocity. Membrane stabilizing effects may also increase the refractory period and elevate the threshold of excitability. However, because the membrane stabilizing effects of beta blockers are observed only at supraphysiologic doses, they are not felt to be clinically relevant. Also, not all beta blockers have membrane stabilizing effects even at supraphysiologic doses (49,50). Clinically and in experimental animals, beta blockers without membrane stabilizing effects are just as effective antiarrhythmics as those with the effect.

Table 2. Secondary Prevention Trials with Type I Antiarrhythmic Agents

Medication	Author/ Date	Entry Time and Selection	Follow-Up	Patients in Study Pl/Rx	Overall Mortality Pl/Rx	Sudden Death Pl/Rx	Recurrent Infarction Pl/Rx
Phenytoin 300 to 400 mg/day vs 3 to 4 mg/day	Collaborative Group 1971[42]	Hospital discharge	12 mos (mean)	568 285/283	8.1%/9.2% (P = NS)	Data not given	Data not given
Phenytoin to level 10 to 20 ugm/ml vs open control	Peter, 1980[43]	Before CCU discharge	24 mos (mean)	150 76/74	18.4%/24.3% (P = NS)	16.9%/14.5% (P = NS)	1.8%/0% (P = NS)
Tocainide 750 mgIV + 1,200 mg/day vs placebo control	Ryden, 1980[44]	Within 2 days of infarct	6 mos (all patients)	112 56/56	8.9%/8.9% (P = NS)	Data not given	Data not given
Tocainide 1200 mg/day vs placebo control	Bastian, 1980[45]	Within 7 to 10 days of infarct	6 mos (all patients)	146 74/72	4.1%/5.6% (P = NS)	Data not given	Data not given
Mexiletine 600-750 mg/day vs placebo control	Chamberlain 1980[46]	Within 6 to 10 days of infarct (high risk patients)	4 mos (all patients)	344 163/181	11.7%/13.3% (P = NS)	9%/10.2% (P = NS)	Data not given
Mexiletine Perglongets 360 mg BID vs placebo control	Impact Research Group 1984[47]	Within 3 to 25 days (moderate risk patients)	9 mos (average)	630 313/317	4.8%/7.6% (P = NS)	1.3%/2.2% (P = NS)	4.1%/5.8% (P = NS)
Aprindine 100-200 mg/day vs placebo control	Hagemeijer 1982[48]	Within 14 days of infarct	12 mos (all patients)	305 152/153	12.5%/7.8% (P = NS)	8.0%/6.6% (P = NS)	Data not given

NS = Not significant; vs = versus; hr = hour; Pl = placebo; Rx = treatment; mos = months; CCU = cardiac care unit

Table 3. Antiarrhythmic Effects of Type I Agents in Secondary Prevention Trials

Medication Author/Date	Method of Evaluation	Arrhythmias; Placebo versus Treatment
Phenytoin Collaborative Group, 1971[42]	One minute rhythm strips were obtained at 6 week intervals	19% of the 109 placebo versus 7% of the 109 treated patients had frequent PVCs
Phenytoin Peter, 1980[43]	None	-------
Tocainide Ryden, 1980[44]	24 hour EKG baseline and at 1 and 6 months in 30 patients; bicycle exercise in 45 patients at 1, 3, and 6 months	The number of patients with >30 PVCs per hour or ventricular trachycardia were not significantly different when treatment was compared to control; significantly fewer treated patients had exercise arrhythmias
Tocainide Bastian, 1980[45]	24 hour EKG baseline and at 2, 8, 16, and 24 weeks after discharge	24/74 placebo versus 15/72 treated patients had unspecified significant arrhythmias
Mexiletine Chamberlain, 1980[46]	24 hour EKG baseline, and at 1 and 3 months after discharge	There was a significant reduction in treated versus control patients with couplets at 1 month (34% vs 48%) but not at 3 months. The hourly average PVCs were significantly reduced by treatment compared to placebo at 1 and 3 months.
Mexiletine Impact Research Group, 1984[47]	24 hour EKG baseline and at 1, 4 and 12 months after discharge	Placebo had significantly more patients with frequent or complex arrhythmias at 1 month (58% vs. 36.5%) and 4 months (59.9% vs. 41.7%)
Aprindine Hagenmeijer, 1982[48]	24 hour EKG baseline and at 1, 3, 6, and 12 months after discharge	75 to 83% of the placebo group vs. 47 to 51% of the treated group continued to have complex ventricular arrhythmias

For example, practolol, a beta blocker with no significant quinidine-like effect reduces post infarction sudden death in humans and raises the ventricular fibrillation threshold in dogs after coronary artery ligation (49). Thus beta blockers exert their direct antiarrhythmic action by inhibiting the effects of adrenergic stimulation, not by a membrane stabilizing effect.

Regardless of the mechanism, beta blockers clearly have a protective effect against ventricular fibrillation despite only a modest ability to suppress ventricular ectopy (49). Antifibrillatory effects of beta blockers are seen in experimental animals with occlusion, reperfusion, as well as electrically induced ventricular fibrillation (49,50). Also beta blockers prevent the decrease in ventricular fibrillation threshold produced by posterior hypothalamic stimulation or stress (49). When used in humans early in the course of acute infarction, metoprolol significantly decreased the number of patients with ventricular fibrillation compared to control (Table 5). In addition, there was a dramatic decrease in the number of episodes of ventricular fibrillation per patient when placebo was compared with metoprolol (from 2.4 to 1 per patient) (51). Paradoxically, by comparison to Type I antiarrhythmic agents (52), trials of beta blockers pay little attention to their effect on ventricular arrhythmias (53-60). Specifically, no 24 hour EKG monitoring was done in the Hjalmarson metoprolol, Hansteen propranolol, or the Taylor oxprenolol study. In the Norwegian timolol study only one of 20 centers did serial 24 hour EKGs (61). All four of these trials as well as the BHAT propranolol and the Olsson metoprolol trial demonstrated significantly improved overall mortality (Table 4). In addition, a significant reduction in postinfarction sudden death was observed in all the studies except the Hjalmarson metoprolol study which was unblinded after only 3 months. Further evidence that beta blockers function as antiarrhythmic agents is provided by the BHAT study. Twenty four hour ambulatory EKGs were obtained baseline and at 6 weeks in a random sample of 25% of the study population. The increase in ventricular arrhythmias seen after hospital discharge in the placebo group was attenuated by propranolol. As a result, significantly fewer propranolol patients were found in each of seven categories of ventricular arrhythmias (62). Almost identical results were observed in the Olsson metoprolol study (63). The fact that significantly fewer treated patients compared to control patients were withdrawn because of ventricular arrhythmias from the timolol, metoprolol and BHAT study is additional indirect evidence of the beta blockers antiarrhythmic efficacy. Table 5 outlines the data on the antiarrhythmic effects of beta blockers in these studies. In summary, beta blockers reduce post infarction sudden death probably

Table 4. Secondary Prevention Trials with Type II Antiarrhythmic Agents

Medication	Author/ Date	Entry Time and Selection	Follow-Up	Patients in Study Pl/Rx	Overall Mortality Pl/Rx	Sudden Death Pl/Rx	Recurrent Infarction Pl/Rx
Metoprolol (beta$_1$ selective no ISA) 100 mg BID vs placebo	Hjalmarson 1981[53]	Admission to CCU age < 75	3 mos (all pt)	1395 697/698	8.9%/5.7% (p < .03)	Study unblinded at 3 mos P = NS	7.8%/5.1% (P<.046) all infarcts
Metoprolol 100 mg BID vs placebo	Olsson 1984[54] 1985[55]	Before hospital hospital discharge age < 70	3 yrs (all pt)	311 147/154	21%/16% (P = NS)	14.7%/5.8% (P <.05)	21.1%/11.7% (p< .05) non-fatal
Timolol (non selective beta blocker no ISA) 10 m BID vs placebo	Norwegian Multicenter Study Group 1981[56]	7 to 28 days after infarction age ≤ 75	17 mos (mean)	1884 939/945	16.2%/10.4% (p < .001)	13.9%/7.7% (P <0.0001) no Rx> 28D assign to Pl	20.1%/14.4% (P <.0006) non fatal
Propranolol (non selective beta blocker no ISA) 60 to 80 mg TID vs placebo	Beta blocker Heart Attack Research Group 1982[57], 1983[58]	5 to 21 days after infarction age < 70	25 mos (mean)	3837 1916/1921	9.8%/7.2% (p < .005)	4.6%/3.3% (p < .05)	23%/13% (p < .01) all infarcts
Propranolol 40 mg QID vs placebo	Hansteen 1982[59]	4 to 6 days after infarction	12 mos (all pt)	560 282/278	13%/9% (P<.12)	8.2%/4% (P<.038)	7.4%/5.8% (P = NS) non-fatal
Oxprenolol (non selective beta blocker with ISA) 40 mg BID vs placebo	Taylor 1982[60]	<4 mo (mean) after infarct age <65	6 yrs (mean)	417 186/231	23%/5% (P<0.001)	7.5%/2.2% P = ?	13.4/10.4 (P = NS)

ISA = Intrinsic sympathomimetic activity; Pl = placebo; Rx = treatment; yrs = years mos = months; D = days; pt = patient(s)

Table 5. Antiarrhythmic Effects of Type II Agents in Secondary Prevention Trials

Medication Author/Date	Method of Evaluation	Arrhythmias; Placebo versus Treatment
Metoprolol Hjalmarson 1981[53] (Reported by Ryden et al 1983)[51]	No specific method of evaluation after discharge; only systematic reporting of the CCU phase arrhythmias	No report on effect of metoprolol vs control after discharge; in hospital (acute phase) results: metoprolol decreased the number of patients with VF from 17/691 to 6/694 ($P<0.05$). Also, metoprolol decreased the number of episodes of VF from 41 in 17 patients to 16 in 16 patients ($p<0.01$). The effect of metoprolol on VF was seen despite no difference in the % of patients with frequent PVCs (230/hour) or VT (<60sec) when compared to placebo in a subgroup of 145 pt who had intense arrhythmia analysis.
Metoprolol Olsson 1984[63]	All patients had a 6 hour EKG baseline 4 days before discharge, and after 3 days, 1, 6, and 12 months of therapy	Complex PVCs (multiform, paired, R on T PVCs and ventricular tachycardia) were found in 31% of the placebo group and in 41% of the metoprolol group at baseline. In the placebo group, the number of patients with complex PVCs increased after 6 (48%, $P<.05$) and 12 months (52% $P<.01$). In the metoprolol group, the percent of patients at 1 (36%), 6 (40%) and 12 months (49%) was not statistically different from baseline. A similar pattern was seen with total number of PVCs. Results were similar whether the data was analyzed by the on drug or intention to treat method.
Timolol Norwegian Group 1981[56] (Reported by von der Lippe et al 1981)[61]	Subpopulation at high risk in only 1/20 centers (44 placebo patients and 33 timolol patients) had 24 hr. EKG base line, then at 3 days 1 month and 6 months after initiation of therapy	The placebo but not the timolol group had a significant increase in the number of patients with complex ventricular arrhythmias (bigeminany, R on T, couplets, VT) at 6 months. Also the average number of PVCs per hour increased significantly in the placebo group at 6 months but not in the timolol group.
Propranolol BHAT 1981[57] (Reported by Lichstein et al 1983)[62]	85% of study population had 24 hr EKG base line. A random sample of 25% (1/2 propranolol 1/2 placebo) had a repeat 24 hr EKG at 6 weeks	The placebo group had a significantly greater increase in ventricular arrhythmias at 6 weeks compared to control ($Z=3.95$). Significantly fewer patients in the propranolol group were positive for any of seven categories of arrhythmias when compared to control.
Propranolol Hansteen 1982[59]	No specific method of evaluation	Not Reported.
Oxprenolol Taylor 1982[60]	No specific method of evaluation	Not Reported.

through their direct or antiischemic antiarrhythmic properties.

Type III agents. Type III agents have not been studied in secondary prevention trials.

Type IV agents. Calcium channel blockers have prominent electrophysiologic properties in addition to their effects on vascular smooth muscle. They are classified as Type IV antiarrhythmic agents with proven benefit in supraventricular as well as selected ventricular arrhythmias. Secondary prevention studies using calcium channel blockers have not been published. However, two studies evaluated calcium channel blockers for their ability to limit infarct size (64,65). The studies continued therapy after hospital discharge in those patients with documented infarction providing an opportunity to evaluate their effect on sudden death. The Danish Study Group evaluated verapamil 120 mg TID for 6 months following an initial 0.1 mg/kg loading dose at the time of cardiac care unit admission. They found no statistically significant difference in reinfarction or total mortality in the 717 verapamil treated patients compared to the 719 placebo treated patients (64). Sinnes et al. evaluated nifedipine 10 mg at the time of cardiac care unit admission followed by 10 mg QID for 6 weeks. There were 10 deaths in the 74 nifedipine and 10 deaths in the 83 placebo treated patients (65). Neither nifedipine nor verapamil seemed to reduce infarct size, total cardiac mortality, post infarction angina or recurrent infarction. Thus calcium channel blockers currently have no role as antiarrhythmic agents in the prevention of sudden death in the post infarction period.

HOW TO USE BETA BLOCKERS POST INFARCTION

Patients without additional myocardium at risk or symptomatic post infarction ventricular tachycardia, have a lower incidence of sudden death when treated with a beta blocker. There will also be a lower incidence of fatal and non fatal reinfarction in patients treated with beta blockade (Table 4). The other antiarrhythmic agents are either untested (Type III), ineffective (Type IV) or possibly harmful (Type I). The remainder of this chapter will deal with the practical aspects of using beta blockers in the post infarction patient. Table 6 gives the exclusion criteria and cause for withdrawal for patients treated with propranolol, metoprolol and timolol, the only agents available in the United States clearly documented to be effective. Table 7 outlines the suggested method of starting the proven beta blockers.

Table 6. Beta Blockers Available in the United States Documented to be Effective in the Reduction of Post Infarction Sudden Death

Medications, Exclusion Criteria, and Cause for Withdrawl

Medication Author/Date	Exclusion Criteria	Withdrawal;Comparison of Placebo to Medication
Propranolol BHAT 1981	Severe CHF, marked bradycardia, asthma as an adult, on beta blockers, age ≥70	9.3% placebo vs 12.8% propranolol withdrawn Hypotension (P< .005), reduced sexual activity (P < .05) and GI problems (P < .01) more frequently caused propranolol withdrawal; serious ventricular arrhythmias more frequently (P< .025) caused placebo withdrawal
Propranolol Hansteen 1982	Rest heart rate <50 BPM, 2nd or 3rd degree AV block, sinoatrial block, systolic pressure less than 100, unstable DM, COPD, uncontrolled congestive heart failure, need for antiarrhythmic agents or beta blockers, age < 35 or > 70	26% placebo vs 25% propranolol withdrawn Angina and serious arrhythmias more frequently (p< .05) caused placebo withdrawal; heart failure and symptomatic bradycardia more frequently (p<.05) caused placebo withdrawal
Timolol Norwegian Group 1981	Rest heart rate <50 BPM, 2nd or 3rd degree AV block, sinoatrial block, systolic blood pressure less than 100, unstable DM, COPD, severe claudication, uncontrolled congestive heart failure, need for beta blockers or antiarrhythmic agents, age > 75 years	23% placebo vs 29% timolol withdrawn Hypotension, (P <.001) sinus bradycardia <40 (P F.05) and dizziness (P < .01) more frequently caused timolol withdrawal; arrhythmias (P < .001) and, conditions requiring beta blockade (P < .001) were more likely to cause placebo withdrawal. In the first month after withdrawal from timolol, no excess in mortality or acute myocardial infarction was noted.
Metoprolol Olsson 1984 & 1985	BBB, AF, AV block Heart failure, Hypotension (<100 systolic) COPD, severe claudication, on beta blockers	23.8% placebo vs 24.7% metoprolol withdrawn Angina was a more frequent (p<.05) cause of placebo withdrawal; heart failure was a more frequent (p<.05) cause of metoprolol withdrawal

DM = Diabetes mellitus; COPD = chronic obstructive pulmonary disease; PO = oral; BBB = bundle branch block; AF = atrial fibrillation; AV = atrioventricular; BPM = beats per minute; CHF = congestive heart failure

Table 7. Beta Blockers Available in the United States Documented to Be Effective in the Reduction of Post Infarction Sudden Death

Dose and Time Table for Starting Therapy

Propranolol
1) Start 20 mg every 8 hours and evaluate for side effects
2) Increase to 40 mg every 8 hours and check a propranolol level 8 hours after 6 or more consecutive doses (steady state trough level)
3) Increase dose further based on level
   a) if > 20 ng/ml increase to 60 mg TID
   b) if ≤ 20 ng/ml increase to 80 mg TID

-or-

1) Start 40 mg QID before hospital discharge

Metoprolol
1) Start 50 mg, TID for three days in hospital and evaluate for side effects
2) Increase to 100 mg BID if tolerated, at or before hospital discharge

Timolol
1) Start 5 mg every 12 hours and evaluate for side effects
2) Increase to 10 mg every 12 hours before hospital discharge

IS THE DOSE OF BETA BLOCKER IMPORTANT

Beta blockers are beneficial in the prevention of post infarction mortality. The tendency is to assume that almost any dose is effective. However, the dose can be critical to the success of therapy. In 1982 the BHAT study demonstrated 180 to 240 mg per day (dose adjustment based on serum levels) of propranolol to be effective (57). Two years before, Barber et al. had published the results of a multicenter trial involving 49 hospitals in Italy, Yugoslavia and the United Kingdom where propranolol 120 mg per day resulted in no significant reduction in mortality (66). Conversely, oxprenolol 40 mg BID increased six year cumulative survival from 77% to 95% ($p < 0.001$) in a group of 417 patients entered within 4 months of infarction (60). In a separate study where patients were entered within 14 to 36 days of infarction, oxprenolol 160 mg BID decreased survival from 94.9% to 93.4% (P = NS) (67). Thus, when beta blockers are employed for the prevention of post infarction sudden death, the dose documented to be effective should be used. The starting dose and time table for beta blocker therapy of agents documented to be effective and available in the United States is shown in Table 7.

IS THE TYPE OF BETA BLOCKER IMPORTANT

Not only is the dose of beta blocker important, but the type is important as well. Sotalol, a beta blocker with Type III antiarrhythmic properties is an example. Julian et al. started treatment 5 to 14 after infarction in 1,456 patients, (60% randomized to sotalol 320 mg per day and 40% randomized to placebo) and followed all the patients for one year. There were 41 sudden (<24 hours) deaths in the 872 sotalol patients (4.7%) and 27 in the placebo group (4.6%). Also, although the rate of definite myocardial infarction was significantly lower ($p<.05$) in the sotalol group, the total mortality was not significantly different (68). One would expect sotalol, a beta blocker with Type III antiarrhythmic activity to be an ideal agent for the prevention of post infarction sudden death. However, the data do not support its use for this purpose. The experience with sotalol should be taken as a warning against the use of just any beta blocker for the prevention of post infarction sudden death.

WHEN TO START BETA BLOCKERS

Beta blockers should be started early, certainly within 3 to 4 weeks of the infarction. Early initiation of therapy is supported by the results of the timolol and propranolol studies. In these studies the beneficial effects were the most pronounced in the first 12 to 18 months after infarction (56,57). In the oxprenolol study, patients who started therapy more than 4 months after infarction showed no benefit while patients who started greater than a year after infarction actually had significantly worse mortality (60). The question of whether beta blockers should be started at the time of patient admission to the cardiac care unit with definite or suspected myocardial infarction is a separate issue. The use of any medication (including beta blockers) at the time of hospital admission with the intent of limiting infarct size is referred to as an acute intervention. Of all the acute intervention studies with beta blockers, only the Hjalmarson metoprolol study documented a benefit in survival. "Overall, there is only a slight, and non significant indication of benefit" (69). In general, beta blockers should be started several days before hospital discharge to monitor for side effects.

WHEN TO STOP BETA BLOCKERS

Most patients who sustain an acute myocardial infarction will eventually die from the effects of coronary artery disease. Several of the beta blockers used post infarction not only decrease the likelihood of sudden death but also reduce the likelihood of recurrent fatal and non fatal myocardial infarction (Table 4).

How long the protective effect is maintained is uncertain. In the oxprenolol study, survival curves for the two groups of patients (placebo and oxprenolol) entered less than 4 months after infarction were still diverging at six years (60). Continued analysis of the data from the timolol study reveals a statistically significant reduction in mortality for the treated group at 34 months (70). The side effects of the beta blockers at the doses documented to be effective in reducing post infarction mortality and morbidity are minimal. For example, in the BHAT study, many potential side effects were monitored, yet only bronchospasm, cold hands and feet and fatigue occurred more frequently in the propranolol group. Congestive heart failure was not more frequent in the propranolol treated group. Similar results were found in the timolol and metoprolol studies. Given the low incidence of side effects, the natural history of coronary artery disease and the uncertainty about when to stop beta blockers, the most prudent course of action is to continue therapy indefinitely. One can consider discontinuation of beta blockers in the extremely low risk subgroup after one to two years based on the low probability of improving an already excellent prognosis.

IS "BETA BLOCKADE" REQUIRED FOR BETA BLOCKS TO BE EFFECTIVE

The studies documenting beta blockers to be effective in the post infarction patient used either fixed dose schedules or dose adjustments based on serum levels. Dose adjustments were not made on the degree of beta blockade. The beta blocking effects of timolol 20 mg/day, metoprolol 200 mg/day and propranolol 160 to 240 mg/day are similar (71). In the BHAT study, the Inderal groups resting mean heart rate was 65 compared to a placebo group mean of 73. Systolic and diastolic blood pressures were nearly identical. Thus clinical evidence of profound beta blockade is not required for the beta blockers to be effective in the prevention of death in the post infarction period. The clinician should not dose adjust beta blockers for beta blockade when using them for post infarction mortality reduction.

DO SPECIAL PRECAUTIONS NEED TO BE TAKEN WHEN WITHDRAWING PATIENTS FROM BETA BLOCKERS

No excess in mortality or acute myocardial infarction was seen during the first month in patients withdrawn from timolol for side effects. The other studies report similar results. Thus patients who are withdrawn because of side effects from beta blockers used for the reduction of post infarction mortality do not

require special precautions. By comparison, termination of therapy in asymptomatic patients at an arbitrary point in time may result in the unmasking of ischemic symptoms. For example, at the end of 3 years of metoprolol therapy, Olsson et al. compared the withdrawal of placebo in 57 patients to the withdrawal of metoprolol in 58 patients. Disabling symptoms developed more frequently with metoprolol than placebo withdrawal (72). Depending on the nature and severity of the side effect, an appropriate alternate agent can be tried. For example, if a patient on propranolol develops mild to moderate bronchospasm a trial of metoprolol is justified. Conversely, if a patient complains of headache or nausea (which is just as likely to be seen with placebo), the alternative beta blocker choice is arbitrary. Clinicians may be less persistent in keeping their patients on a beta blocker if the patient is at extremely low risk.

CONCLUSIONS

The process of selecting the proper antiarrhythmic treatment for patients at high risk of sudden death following myocardial infarction centers primarily around selecting the right patient population for beta blockers. Specifically, patients with clinical variables indicating additional myocardium at risk should have cardiac catheterization with possible coronary artery bypass grafting or percutaneous transluminal coronary angioplasty. Patients with symptomatic ventricular tachycardia or ventricular fibrillation more than 48 hours after myocardial infarction have such extreme electrical instability that prompt referral for electrophysiology evaluation is indicated. The remaining patients should be placed on a beta blocker documented to reduce the risk of sudden death. One might argue that the subgroup at extremely low risk within this group may not be expected to benefit from beta blockers. However, given the high therapeutic index of the doses of beta blockers used, the author recommends treatment for all patients. The extremely low risk patients may have beta blockers discontinued after 2 to 3 uneventful years while the remaining risk patients should be continued indefinitely. The side effects versus therapeutic effects of metoprolol, timolol and propranolol are similar (73). Any of these drugs used at the dose documented to be effective, is equally acceptable. The beta one selectivity of metoprolol is well maintained at 100 mg BID and it should be the beta blocker of choice in patients with bronchospasm or a history of asthma.

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19

LESSONS FROM THE BHAT STUDY REGARDING SELECTION OF PATIENTS POST MYOCARDIAL INFARCTION FOR BETA BLOCKADE

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INTRODUCTION

By the mid-1970s, beta-blocking drugs had become common in the treatment of coronary heart disease, primarily for the symptomatic relief of angina pectoris. These agents had also been shown in experimental animal models to decrease myocardial ischemia and to limit infarct size. (1,2) Because of these and other potential reasons that beta-blockers might be beneficial, a number of clinical trials had been carried out by that time using these agents in the long-term treatment of survivors of myocardial infarction (MI). (3) Several of these studies showed trends favoring the use of beta-blockers; however, because of small sample size or other limitations in design and analysis, the results were inconclusive. Based on these studies and the advice from an expert committee, the National Heart, Lung, and Blood Institute (NHLBI) decided that a large clinical trial would be needed to address the question of benefit of beta-blockade in patients after myocardial infarction. To this end, in 1977 the NHLBI initiated the Beta-Blocker Heart Attack Trial (BHAT), a multicenter randomized, double-blind, placebo-controlled trial. The primary objective of the BHAT was to test whether the daily administration of propranolol hydrochloride initiated prior to hospital discharge in patients who had had at least one documented MI would result in a significant reduction in mortality from all causes during a two- to four-year follow-up period. Secondary objectives of the trial were to study the effect of chronic administration of propranolol on coronary heart disease (CHD) mortality; sudden cardiac death (death from arteriosclerotic heart disease, occurring within one hour of

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the onset of symptoms); and CHD mortality plus definite nonfatal MI.

Before the completion of BHAT, the results of additional clinical trials of beta-blockers in patients after MI were reported. One of these trials, which evaluated alprenolol hydrochloride, showed benefit with regard to total mortality in a subset of younger patients, but not in older patients (4); and one, reported earlier using practolol, also claimed benefit only in a subgroup of patients, namely those with anterior, but not posterior MI. (5) Two other trials, one of which studied timolol maleate and the other, metoprolol tartrate, demonstrated a statistically significant benefit from the use of beta-blockers. (6,7)

The results of the BHAT were first published in Nov. 1981, (8) and in more detail in March 1982. (9)

MATERIALS AND METHODS

Men and women from age 30 through 69 years who were hospitalized with an acute MI documented by appropriate symptoms, and ECG and enzymatic changes were candidates for enrollment in the trial. Patients were excluded from the study if they had medical contraindications to propranolol, a history of severe congestive heart failure or asthma as an adult; a life-threatening illness other than CHD; had or were likely to undergo cardiac surgery; or were already taking or were likely to have beta-blockers prescribed to them. Either propranolol or placebo was randomly assigned to eligible patients in a double-blind manner, five to 21 days after hospital admission and while the patient was still hospitalized.

A diagnosis of MI using BHAT criteria was made in about 16,400 patients who survived at least five days after admission and who were age eligible. Of these, 77% were not enrolled - 18% because of relative and absolute contraindications to propranolol, 18% because they were already receiving or were likely to have propranolol prescribed to them, 26% because of study design considerations, and 15% because they or their private physicians did not consent to participate. Approximately 23%, or 3,837

patients of the target population, were randomized (1,916 to propranolol and 1,921 to placebo).

Immediately after randomization, the patients began receiving a test dose of the assigned study medication (20 mg of propranolol hydrochloride or matching placebo). They were then given 40 mg of active drug or placebo every eight hours for 3 to 7 days and blood propranolol levels were determined. If the level in the propranolol-treated patients was less than 20 ng/ml, they were assigned 80 mg of propranolol three times a day; otherwise, they were assigned 60 mg three times a day. Dosage assignments were made randomly in the placebo group. However, both the patients and their physicians were blinded as to treatment group assignment. The dosage could be lowered during follow-up at the discretion of the clinic physician. Patients who were prescribed nonstudy beta-blockers by their physicians were instructed to discontinue use of the study medication. Of the 3,837 enrolled patients, 82% were assigned the 180-mg/day regimen and 18% were assigned the 240-mg/day regimen. Follow-up visits were scheduled at one month, six weeks, and three months after randomization. Subsequently, all scheduled follow-up visits occurred at three-month intervals. At each visit, the occurrence of morbid events was monitored as well as possible side effects, general health status, the use of nonstudy medication, and patient compliance with the treatment regimen.

For study purposes, a diagnosis of recurrent nonfatal MI could only be made if the patient was hospitalized and survived that hospitalization. Classification of suspected nonfatal MIs was done in a two-step process. In the first step, a computer algorithm determined whether the BHAT criteria for recurrent MI were met, using data from each clinic on the presence of typical chest pain and diagnostic elevations of cardiac enzyme values, and data from a centralized coding of ECG changes as defined by the Minnesota Code. In the second step, ECGs of patients who had events classified by the computer algorithm as MIs were reviewed in greater detail by cardiologist members of the Nonfatal Events subcommittee who were

blinded to the patients' treatment regimens. In this review, it was determined whether apparent ECG changes noted by categorical Minnesota Code rules were clinically important when ECGs around the event were examined serially. The adjudicated ECG findings, along with the original symptom and enzyme data, allowed the final classification to be made.

As done in other studies, patients were classified as having had an electrical (rhythm) complication defined as the reported, clinically determined occurrence of one of the following complications during the hospitalization of patients for the infarct: ventricular fibrillation or tachycardia (3 or more successive ventricular premature beats), complete or incomplete atrioventricular (AV) block (Mobitz Type I or II second-degree AV block), or "new" atrial fibrillation. A mechanical (pump) complication was considered to have occurred in patients who were reported to have suffered one of the following complications at the time of the infarct but before enrollment: pulmonary edema, cardiogenic shock (oliguria and systolic blood pressure below 90 mm Hg for 1 hour or more), basilar rales, or symptoms/signs of congestive heart failure (requiring therapy with digitalis and/or diuretics).

RESULTS

a) Overall

After an average follow-up period of 25.1 months, 138 patients in the propranolol group (7.2%) and 188 in the placebo group (9.8%) had died.(9) The survival curves are presented in Figure 1. Based on all randomized patients, the life-table z value for all-cause mortality is -2.90 (nominal $P < .005$; if repeated testing is taken into account, two-sided $P < .01$).

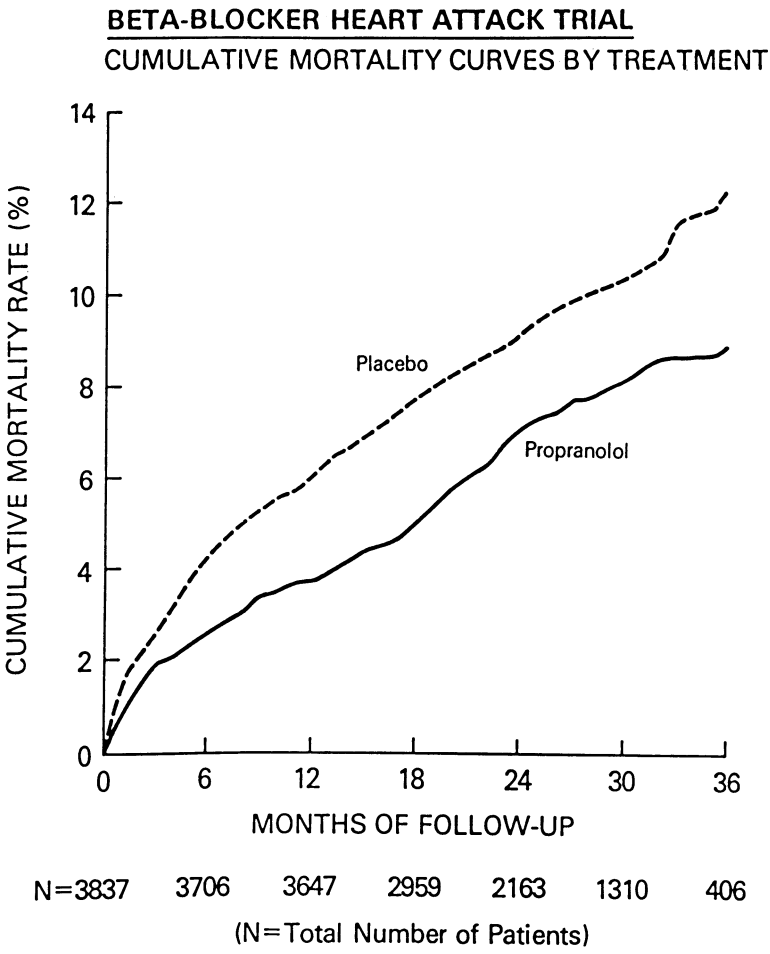

Figure 1

Cause-specific mortality results are presented in Table 1. Cardiovascular mortality was reduced in the propranolol group relative to the placebo group (6.6% v 8.9% respectively, $P < .01$). A subset of this category, arteriosclerotic heart disease (ASHD) mortality, was also reduced (6.2% propranolol v 8.5% placebo, $P < .01$). Sudden death, a subset of the ASHD category, was less frequent in the propranolol group (3.3% v 4.6% for placebo, $P < .05$).

Table 1 - Cause-Specific Mortality by Treatment Group

Cause of Death	Propranolol No.of Deaths	Propranolol Mortality %	Placebo No. of Deaths	Placebo Mortality %	p-value* (2-sided)
Total Mortality	138	7.2	188	9.8	.005
Cardiovascular Disease	127	6.6	171	8.9	.01
Arteriosclerotic Heart Disease	119	6.2	164	8.5	.01
Sudden+	64	3.3	89	4.6	.05
Nonsudden	55	2.9	75	3.9	NS
Other Cardiovascular Disease	8	0.4	7	0.4	NS
Noncardiovascular Disease	11	0.6	17	0.9	NS

*Because of the numerous statistical tests performed, the P values for cause-specific mortality should be interpreted cautiously.
NS=non-significant.
+Deaths occurring less than one hour from onset of symptoms.

Coronary incidence (recurrent nonfatal myocardial infarction or fatal atherosclerotic heart disease combined) and the occurrence of nonfatal reinfarction over the average 25-month follow-up period (10) are presented in Table 2. In the propranolol group, 192 (10.0%) of the participants had the combined endpoint of coronary incidence, compared with 249 (13.0%) in the placebo group, a reduction of 23% of events in the treatment group over the control group (relative risk, 0.77, $P < .01$). The incidence of definite nonfatal reinfarction was 4.4% in the propranolol group and 5.3% in the placebo group, or a 16% relative difference in incidence (relative risk, 0.84).

Table 2 - Incidence of Nonfatal Reinfarction and Coronary Incidence During Follow-Up Period, by Treatment Group

	Propranolol (n=1,916)		Placebo (n=1,921)		
	No. of Events	Rate/100	No. of Events	Rate/100	Relative** Risk
Definite nonfatal reinfarction	85	4.4	101	5.3	0.84
Definite or probable nonfatal reinfarction	103	5.4	121	6.3	0.85
Coronary incidence*	192	10.0	249	13.0	0.77

*Defined as recurrent nonfatal definite reinfarction plus fatal atherosclerotic heart disease (i.e. total fatal and nonfatal coronary heart disease).
**Rate for the propranolol group divided by the rate for the placebo group.

The number of persons experiencing a stroke during the study was small, and approximately the same in the two groups; 1.5% of the propranolol group compared with 1.6% in the placebo group.

b) Subgroups

Subsequent BHAT publications have looked at additional endpoints and several subgroups, categorized by variables measured at baseline. Before reviewing the data on subgroups, however, some cautionary statements are appropriate. Sample sizes clearly get smaller, and because the number of subgroups examined tends to be large, the opportunity to identify trends and even large differences that are not real, is greatly increased. Nonetheless such analyses are important in attempting to understand mechanisms of action and in potentially identifying subgroups where therapy may be especially beneficial or harmful.

One paper examined the relative efficacy of propranolol in younger compared to older participants.(11) In the age group 30-59

years, there were 78 deaths in the propranolol group and 95 deaths in the placebo group; these figures yield death rates of 6.0 and 7.4 per 100, respectively, and represent an 18.9% reduction in the mortality rate in the propranolol group. The mortality rates in the age group 60-69 years were 9.8 per 100 for the propranolol group and 14.7 per 100 for the placebo group. Thus in this age group, the propranolol-treated patients experienced a death rate 33.3% lower than that for the placebo group. Figure 2 shows the plot of the monthly cumulative percent mortality for each treatment group in the age groups 30-59 and 60-69 years. For the older group, there was a continuing benefit for the propranolol group up to 36 months of follow-up; while for the younger group, benefit seems to be confined to the first 6 months.

Cumulative Mortality Curves for the Placebo and Propranolol Groups By Age Group

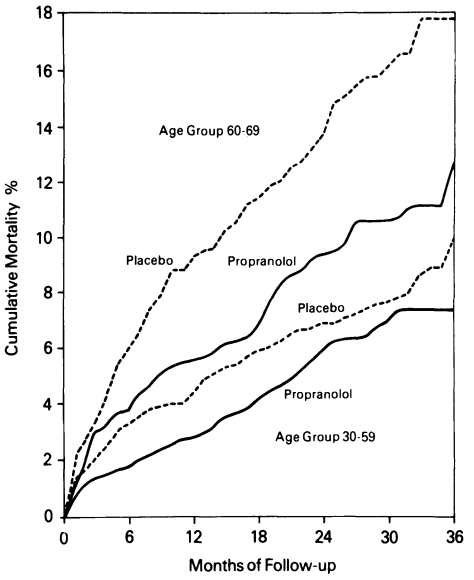

Figure 2

Table 3 shows the data for coronary incidence and recurrent nonfatal MI stratified by age and risk group; the event rates for the propranolol group were always less than the corresponding rates for the placebo group. As expected, lower placebo group event rates were seen in the younger cohort (aged 30 to 59 years) than in the older cohort (aged 60 to 69 years). Patients with uncomplicated MIs (risk group 3) also had lower rates than those with complicated MIs or multiple MIs (risk groups 1 and 2 respectively). The relative risks (propranolol rate/placebo rate) for the older cohort and the combined high-risk patients (risk groups 1 and 2) were consistently lower, although not statistically significantly, than those of their counterparts, suggesting, but not proving, a greater relative benefit in these two subgroups. Certainly the reported findings of the earlier alprenolol study (4) of a benefit from beta-blockers in the younger cohort (with a relative risk .46) and of possible harm in the older cohort (with a relative risk 1.46) were not confirmed by the BHAT.

Table 3 - Incidence of Nonfatal Reinfarction and Coronary Incidence During Follow-up Period, by Treatment Group, Age, and Risk Group

	Propranolol		Placebo		
	No. of Events	Rate/100	No. of Events	Rate/100	Relative Risk
Definite nonfatal Reinfarction					
Age, Year					
30-59	60	4.6	62	4.8	0.96
60-69	25	4.1	39	6.2	0.66
Risk Group*					
1 and 2	38	4.8	47	6.2	0.77
3	47	4.2	54	4.6	0.90
Coronary Incidence					
Age, Year					
30-59	122	9.4	137	10.6	0.88
60-69	70	11.4	112	17.7	0.64
Risk Group*					
1 and 2	98	12.3	133	17.6	0.70
3	94	8.4	116	9.9	0.84

*Group 1, patients who have had multiple myocardial infarctions (MIs);
Group 2, patients who have had a complicated first MI;
Group 3, patients who have had an uncomplicated first MI.

Table 4 presents the incidence of CHF during the study by history and treatment group. Of 345 patients in the propranolol group with a history of CHF, 51 (14.8%) experienced a recurrent episode of definite CHF during the study. This contrasts with 12.6% (46 of 365 patients with a history of CHF) in the placebo group. In patients without a history of CHF, the percentages experiencing CHF were 5.0% in the propranolol group and 5.3% in the placebo group. Overall, disregarding the history information, the percentages were the same in both treatment groups (6.7%).

Table 4 - Incidence of Congestive Heart Failure
During Follow-Up Period, By Treatment Group

	Propranolol			Placebo			
Relative Other Events Risk	No. of Patients	No. of Events	Rate/ 100	No. of Patients	No. of Events	Rate/ 100	
Congestive Heart Failure							
History	345	51	14.8	365	46	12.6	1.17
No History	1,571	78	5.0	1,556	82	5.3	0.94
Total	1,916	129	6.7	1,921	128	6.7	1.01

Patients were also classified on the basis of the presence or absence of findings indicative of electrical (rhythm) and/or mechanical (pump) complications early during hospitalization with their qualifying myocardial infarction and prior to randomization.(12) Approximately 55% of the patients in the BHAT study had no reported electrical or mechanical complication during their hospitalization prior to enrollment. Nearly one-fourth met the definition of having an electrical failure only. A total of 22% suffered a mechanical complication and approximately half of these had an electrical problem as well (Table 5).

The mortality from all causes for placebo patients with no complications was 6.6%. Patients with evidence of mechanical problems (either alone or in combination with electrical problems) were at the highest risk and in the control group had a mortality of approximately 17%. Those with only an electrical complication had a mortality of 10.9%. In the large subgroup with no complications, the observed benefit of propranolol treatment was only 6%; that is, the relative risk was .94. The most pronounced percentage difference in mortality between the two study groups was observed in the subgroup with electrical problems only. The mortality in the propranolol group was roughly half of that in the placebo group, the relative risk being .48. In the two risk groups with mechanical complications, the relative difference in mortality was 38% for mechanical only and 24% for combined mechanical and electrical. Statistical adjustment by logistic regression with the Walker-Duncan method for differences between treatment groups in baseline prognostic factors yielded only minor shifts in the relative risks.

Table 5 - All Cause Mortality by Risk Group and Treatment

	Propranolol		Placebo		Relative
Risk Group*	No. of Patients	Mortality %	No. of Patients	Mortality %	Risk
None	1,047	6.2	1,079	6.6	.94
Electrical Only	443	5.2	423	10.9	.48
Mechanical Only	201	10.4	202	16.8	.62
Electrical and Mechanical	225	12.9	217	17.1	.76

*Determined by pre-randomization presence or absence of complications

In the subgroup of patients with neither electrical nor mechanical complications, the numerical difference in the mortality for patients receiving propranolol and placebo was -.4/100 (6.6% minus 6.2%). The highest "absolute risk reduction" was found in the subgroups with either electrical or mechanical problems; between four and six lives were prolonged for every 100 patients treated. Although the relative benefit of propranolol treatment was intermediate in the two risk groups with pump complications, the high mortality for those

on placebo in these two groups explains why the absolute benefit is essentially the same as those with electrical complications only.

Of the patients receiving placebo who had mechanical problems in BHAT, 25 died instantaneously as compared with 13 of the patients receiving propranolol. In addition there were fewer nonfatal MIs in the actively treated group compared with the group receiving placebo (15 vs 24, respectively).

A more detailed analysis of the individual electrical and mechanical complications was performed. Patients who had suffered an episode of ventricular tachycardia during hospitalization made up the single largest subgroup. Among these patients, mortality was 44% lower in the propranolol group than in the control group. The lowest relative risk, which suggests the largest benefit from propranolol therapy, was observed in the small subgroup of patients experiencing ventricular fibrillation before randomization. The highest relative risk, which indicates little benefit from therapy, was seen in the small subgroup of patients who had episodes of pulmonary edema before enrolling in BHAT.

The occurrence of symptoms usually attributed to beta-blocker therapy was monitored in the trial. (12) Within the risk groups "none" and "electrical only", there were no major differences in the incidence of severe congestive heart failure between the propranolol and placebo groups. In the patients with initial mechanical problems, propranolol treatment seemed to cause an increased incidence of congestive heart failure.

DISCUSSION

The BHAT and other recent long-term controlled clinical trials of beta-blockers in survivors of myocardial infarction (MI) have convincingly demonstrated benefit of these drugs with respect to mortality from all causes, and other endpoints without generally unacceptable side effects or toxicity. (13) Nonetheless, these favorable results have raised additional questions. First, how do the beta-blockers exert their positive action? Although there is no certain answer, the data from BHAT suggest both an antiarrhythmic (with the significant reduction in sudden death) and an anti-ischemic

effect (with a statistically non-significant, but substantial reduction in non-sudden arteriosclerotic heart disease death and nonfatal reinfarction).(10) Second, should all patients with MI be treated with beta-blockers? Third, can beta-blockers be used safely in patients with MI who have been in congestive failure?

Secondary and subsequent analyses suggested that patients with MI who have an uncomplicated course during hospitalization benefit to a much smaller degree, if at all, from propranolol compared to those with complications. Patients with electrical complications seemed to benefit the most from propranolol treatment. This tends to imply that propranolol exerts its primary, favorable action through an antiarrhythmic effect. This view is supported by the earlier reported BHAT results on sudden death and other reports that beta-blockers reduce the incidence of ventricular fibrillation and tachycardia in patients with MI. The benefit of propranolol treatment on mortality from all causes in patients with mechanical problems appears paradoxic because congestive failure was seen more frequently in the propranolol group. However, it is well known that a large proportion of patients with congestive heart failure die suddenly, usually of ventricular fibrillation. In addition, the findings of BHAT suggest that propranolol exerts a beneficial anti-ischemic action (fewer nonfatal MIs) in patients with mechanical complications. In view of the benefit of propranolol in the risk groups with either electrical or mechanical complications, the expectation was that the same, or perhaps even larger, favorable outcome from treatment would be seen in the combined risk group. Two possible reasons may explain the observed smaller benefit in this subgroup. First, these patients experienced more cardiovascular side effects and the cardiodepressant action of the beta-blocker may have outweighed some of the favorable effects. Second, the numbers are small and therefore susceptible to chance variation, perhaps masking a truly larger effect.

Previous reports of beta-blocker trials have illustrated the potential problems with subgroup analyses. Subsets of patients have been identified in which treatment was claimed to be particularly beneficial or harmful. (4,5) None of these observations has been confirmed in subsequent beta-blocker trials. Thus, post hoc analyses

need to be interpreted with caution and it will be important to see if the BHAT subgroup findings are present in other completed trials. Although, these analyses should not be used to make definitive recommendations regarding the differential treatment of subgroups of postinfarction patients, a current rationale position regarding therapy is that post MI patients at relatively low risk, i.e. those who are young and who have had a relatively uncomplicated hospitalization, stand to gain little in absolute terms from routine treatment with beta-blockers.

However, those patients with the highest absolute risk stand to gain the most from treatment, as viewed from the perspective of the number of patients who must be treated for each life saved. An alternate approach to withholding treatment in low risk patients is to treat them for a shorter time, e.g. 6 months to 1 year, based on the observation that the maximum benefit overall occurred during this period. High risk patients would be treated for a longer period of time.

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V. CORONARY CARE: THE CONVALESCENT PHASE

20

THE PREHOSPITAL DISCHARGE EVALUATION OF THE PATIENT WITH ACUTE MYOCARDIAL INFARCTION

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INTRODUCTION

Survivors of myocardial infarction comprise a large, readily identifiable subset of patients with coronary artery disease with a relatively high short-term mortality rate. Approximately half a million patients are hospitalized annually in the United States with acute myocardial infarction and more than 400,000 survive to hospital discharge. Their subsequent mortality rate is at least 10% for the first year and averages 3% per year thereafter.

Beta-receptor blocking drugs reduce mortality after infarction (1). This reduction may be limited to patients with electrical or mechanical complications (2). As discussed below, a subgroup with a first year mortality of only 2%, consisting of more than half of post-infarction patients, can be identified before hospital discharge. Most patients in this subgroup require no treatment other than reassurance and rapid rehabilitation to facilitate an early return to normal activity. In contrast, high risk patients often benefit from further investigation and/or treatment specific to the underlying life-threatening abnormality.

Determinants of risk after infarction

The three major determinants of risk after myocardial infarction are (1) the degree of left ventricular dysfunction, (2) the presence and severity of electrical instability and (3) the potential for recurrent myocardial ischemia. The inter-relationships among these three variables are complex. Risk increases almost exponentially with increasing degrees of left ventricular dysfunction (3). Frequent and complex ventricular arrhythmias occur most frequently in post-infarction patients with severe left ventricular dysfunction.

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After hospital discharge most post-infarction deaths are sudden and relatively few are due to progressive heart failure.

Among the three major risk determinants post-infarction, myocardial ischemia is the most amenable to treatment. Ischemia at a distance is more dangerous than ischemia near the infarct zone (4) and ischemia at rest is more dangerous than exercise-induced ischemia. Angina accompanied by electrocardiographic evidence of transient ischemia is more serious than when electrocardiographic changes are absent (5). Organic stenoses likely cause exercise-induced myocardial ischemia after infarction, by limiting coronary flow when myocardial demand increases. On the other hand, angina at rest is more likely caused by changes in the artery itself with varying degrees of occlusion due to platelet deposition, thrombosis or vasoconstriction.

In our experience (6), post-infarction patients with myocardial ischemia tend to have had less extensive infarction and better residual left ventricular function than patients without evidence of myocardial ischemia. The correlation between ventricular arrhythmias post-infarction and myocardial ischemia is much weaker, if present at all, compared to the strong correlation between ventricular arrhythmias and left ventricular dysfunction.

The extent and severity of underlying coronary disease is the main determinant of the degree of left ventricular dysfunction and of the presence and severity of myocardial ischemia. The extent and severity of coronary disease also influences prognosis to a lesser extent independently of these two determinants. Progression of coronary disease (7) and new occlusion (8) are both more common in patients with extensive or severe coronary stenoses.

Clinical predictors of risk after infarction

The three major determinants of risk are expressed through a variety of clinical information that is already available before hospital discharge. Previous myocardial infarction presages a poor prognosis (6,9) presumably because two or more infarctions are likely to cause more left ventricular damage than one. Advanced age is a weaker predictor of poor outcome (9).

Left ventricular failure during the acute phase of infarction is a powerful predictor of increased risk after hospital discharge (9,11).

Transient hypotension, sinus tachycardia, basilar rales, a displaced apical impulse and a ventricular gallop reflect serious left ventricular dysfunction. Curiously, blood urea nitrogen levels emerge from multivariate analyses as one of the strongest predictors of late risk (9,11), probably because increased levels indicate a decrease or redistribution of cardiac output.

The electrocardiogram contains important prognostic information. Bundle branch block (9), anterior infarction (10) and ST depression (12) are associated with a worse prognosis. The QRS scoring system, as refined by Wagner et al (13), represents a rough index of infarct size and is a strong, independent predictor of prognosis (6). Similarly, infarct size as assessed by cardiac enzymes correlates with subsequent mortality (11). Patients with radiologic cardiomegaly also have a poor prognosis (9,11,14).

Angina during hospitalization signals the presence of residual myocardial ischemia and therefore, a poorer prognosis. For 1 year mortality, angina during hospitalization was associated with a relative risk of 3.4 in a series of patients from our institution (6).

Ventricular fibrillation during the acute phase of infarction increases late risk (15) but much of the increase may be due to coincident heart failure or previous infarction. Similarly, complex or frequent ventricular arrhythmias during the acute phase are markers of more extensive necrosis but do not predict long term outcome as well as arrhythmias assessed on a Holter recording before hospital discharge.

Ejection fraction

The single most important predictor of survival in post-myocardial infarction patients is ejection fraction. In 799 Multicenter Post infarction Research Group patients (3), one year cardiac mortality was 2% when ejection fraction was ≥60%, 4% with ejection fractions from 40 to 59%, 12% with ejection fractions from 20 to 39% and 47% with ejection fractions below 20%. The importance of ejection fraction has been confirmed in other studies (16-18).

Radioisotopic left ventricular angiography permits serial measurements to be obtained easily during acute and convalescent phases after infarction. During the first 2 weeks post-infarction, ejection fraction changes in most patients, often improving but sometimes

deteriorating (19). A decreasing ejection fraction suggests cardiac dilatation or extension of infarction and is a poor prognostic sign (19). On the other hand, an improvement in ejection fraction suggests that some residual flow may have been preserved to the infarct zone (20).

What should be done with the data obtained from radioisotopic left ventricular angiography in post-infarction patients? In selected cases segmental left ventricular function may be improved with bypass surgery or coronary angioplasty. However, in most patients medical or surgical treatment does not improve ejection fraction and most deaths in patients with low ejection fractions are sudden and not due to left ventricular dysfunction per se. Patients with low ejection fractions probably benefit from beta receptor blocking drugs because they decrease both arrhythmias and ischemia. Investigation in patients with low ejection fractions should be directed mainly toward the characterization and control of arrhythmias and ischemia.

Holter monitoring

Many studies have demonstrated that the frequency and complexity of ventricular arrhythmias recorded on a Holter monitor before hospital discharge are strongly predictive of subsequent mortality (9-11,21-24). For example, Moss et al (21) followed 940 patients for an average of 3 years after infarction. Half of the patients had no ventricular extrasystoles on a 6 hour Holter recording done before hospital discharge; their subsequent cardiac mortality was significantly less than the 254 patients with simple ventricular ectopy and less than half of the cardiac mortality rate among the 216 patients with complex ventricular ectopy.

In patients with chronic coronary disease referred for coronary arteriography, ventricular arrhythmias predict subsequent prognosis, as does ejection fraction; however, when adjustments are made for ejection fraction, ventricular arrhythmias no longer are predictive (25). In post myocardial infarction patients, ventricular arrhythmias are most commonly associated with low ejection fractions but also appear to be independent predictors of subsequent mortality (21,23,24).

Should ventricular arrhythmias be treated after hospital discharge? Beta-receptor blocking drugs reduce mortality and reduce

ventricular arrhythmias (26); however, these two findings may be unrelated. No other anti-arrhythmic drug has yet been shown to reduce mortality post infarction. Available anti-arrhythmic drugs frequently cause side effects and may worsen arrhythmias. For these reasons a sensible strategy would be to leave simple ventricular extrasystoles untreated but to treat ventricular tachycardia and possibly complex ventricular ectopy, with follow-up study to assess the efficacy of treatment.

Programmed ventricular stimulation induces ventricular arrhythmias in some survivors of myocardial infarction. Whether induced arrhythmias correlate with subsequent survival is controversial (27-30) and thus this technique is not routinely indicated after myocardial infarction.

Exercise testing

Most survivors of myocardial infarction can safely undergo a limited exercise test before hospital discharge (5,6,31) or a symptom-limited test shortly thereafter (32,33). ST depression (5,6,31,32), a poor exercise tolerance (33,34), exercise-induced ventricular arrhythmias (6,34) and an inadequate blood pressure response (6,31) have all been identified as predictors of increased mortality. In a series hospitalized in 1976-77, we found a 1 year mortality of 3% in 128 patients with no ST segment change during exercise compared to 23% in 69 patients with ST depression and 18% in 28 patients with ST elevation (6). The ST segment response during exercise testing was the strongest predictor of mortality during the first year, with a relative risk of 7.8, but no longer predicted mortality after one year (6). De Busk et al (32) found a cardiac death rate within 6 months of 9.7% in patients with positive tests compared to only 1.3% in patients with negative tests; 327 of 702 eligible patients were not tested because their risk was judged to be high and their 6 month cardiac death rate was 5.5%. In the study of Weld et al (34) exercise duration predicted subsequent mortality but ST depression did not attain statistical significance. DeFeyter et al (33) also found exercise duration to be a predictor of mortality but not ST depression; however, only 11 of their 179 patients died during follow-up.

Additional information can be obtained if Thallium-201 scintigraphy or radionuclide ventriculography is combined with exercise testing. In one study (35) exercise electrocardiography, exercise scintigraphy and coronary angiography predicted subsequent mortality equally well but exercise scintigraphy predicted cardiac events, usually severe angina, significantly better. An advantage of exercise Thallium scintigraphy is its ability to localize the ischemic area and to estimate its size.

Hung et al (36) found that peak workload and exercise-induced change in ejection fraction were predictors of hard cardiac events in 117 men tested 3 weeks after infarction and followed for a mean of 11.6 months. Corbett et al (37) reported that exercise-induced changes in ejection fraction were the best predictor of cardiac events in a series of 117 patients that they tested before hospital discharge.

Most of the abnormalities detected by post-infarction exercise testing indicate that residual myocardial ischemia is present. Detecting this condition is important clinically because surgical or medical treatment can often eliminate it. Whether such treatment improves survival in post-infarction patients with myocardial ischemia has not been proven. Nevertheless, coronary arteriography should be performed in nearly all patients who have a positive limited exercise test after myocardial infarction. Because risk is highest in the weeks immediately after infarction, doing arteriography before hospital discharge is wise.

Coronary arteriography

Some cardiologists recommend coronary arteriography after myocardial infarction in all patients without complications (38). The number of diseased vessels correlates with subsequent outcome but is a somewhat weaker predictor than ejection fraction (16,17). Depending upon the population studied, the prevalence of multivessel disease ranges from 30% (39) to 80% (40). If subsets of post-infarction patients with a very low risk can be identified non invasively with the tests discussed above, reserving coronary arteriography for high risk patients and patients who develop angina during subsequent follow-up would appear to be a reasonable strategy. The results of coronary arteriography should not be viewed in isolation but should be assessed

in conjunction with other available prognostic information.

Which tests for which patients?

A radioisotopic left ventriculogram and a limited exercise test are recommended before hospital discharge for all patients less than 70 years old with uncomplicated myocardial infarction. Unless contraindicated, coronary arteriography should be done in all patients who develop angina, ST depression or exertional hypotension during the limited exercise test. Patients with post-infarction angina in hospital should undergo arteriography as the first diagnostic step. Patients with persistent heart failure after infarction should have a radioisotopic left ventriculogram and Holter monitoring, since complex ventricular arrhythmias are frequently found in the absence of symptoms. Holter monitoring is also indicated for patients with low ejection fractions after uncomplicated infarctions.

Radionuclide ventriculography and Thallium scintigraphy both add additional prognostic information to post-infarction exercise testing, but also add substantially to costs. Whether the additional expense is worthwhile may vary from one institution to another and certainly varies from one patient to another.

A careful assessment of prognosis early after myocardial infarction permits the physician to recommend with greater precision subsequent treatment and the pace of rehabilitation, and to clarify the patient's long-term expectations.

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NEW INOTROPIC AGENTS

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INTRODUCTION

Left ventricular dysfunction after myocardial infarction has become widely recognized as the single most important determinant of survival in patients with coronary artery disease (1-4). Patients with chronic congestive heart failure (CHF) and coronary artery disease have a decidedly worse prognosis than patients without CHF, and mortality is greater in patients with severe symptoms (NYHA Class IV) than in those with mild or moderate symptoms (Class I, II, III) (1). In addition, prognosis can be further shown to be related to the severity of certain hemodynamic indexes of left ventricular function, including mean arterial pressure, left ventricular filling pressure, systemic vascular resistance, right atrial pressure, ejection fraction and stroke work index (2-4). Hence, any therapy directed at either improving the functional class or indexes of left ventricular function in patients with coronary artery disease and CHF has the potential to improve long-term prognosis.

At the present time several therapeutic strategies have evolved for the purpose of improving the symptomatic and hemodynamic profile of patients with CHF: (1) diuretics and salt restriction to decrease left ventricular filling pressure and systemic venous hypertension; (2) vasodilators and angiotensin-converting enzyme inhibitors (5) to reduce systemic and pulmonary venous congestion and to increase cardiac output by decreasing resistance to left ventricular ejection; and (3) inotropic agents to directly increase the contractile state of the left ventricle and thereby increase cardiac output.

Two new groups of positive inotropic agents have been developed for the treatment of patients with CHF: (1) sympathomimetic and (2) non-

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glycosidic, non-sympathomimetic agents (Table I).

Table I. New Inotropic Agents for the Treatment of Congestive Heart Failure

Sympathomimetic
Dopamine
Dobutamine
Butopamine
Levodopa
Salbutamol
Pirbuterol
Prenalterol
Corwin
Dibutinyl Cyclic AMP
Nonglycosidic, Nonsympathomimetic
Amrinone
Milrinone
MDL-17,043 (Fenoximone)
MDL-19,205 (Piroximone)
RO13-6438 (Posicor)
AR-L115BS (Sulmazol)

Other substances have been demonstrated to have positive inotropic effects (e.g. histamine, methyl xanthines, glucagon) but have been less extensively studied in patients with CHF (6-9). Although the intravenous sympathomimetic agents have been shown to have efficacy in the treatment of acute CHF secondary to myocardial infarction, the newer oral inotropic agents have presently been studied only in patients with decompensated chronic CHF. Clearly there is a need for testing the newer oral agents in the setting of acute myocardial infarction with CHF. The present discussion will review the hemodynamic and clinical effects of the newer sympathomimetic and non-glycosidic, non-sympathomimetic inotropic agents in chronic CHF.

SYMPATHOMIMETIC AGENTS

The sympathomimetic amines, epinephrine and norepinephrine, have potent positive inotropic effects, but are limited in their application to the treatment of CHF due to the fact that they produce excessive increases in myocardial oxygen demand, induce myocardial irritability and are limited to intravenous administration. As a result, several intravenous and oral analogues have been developed and tested clinically for both acute and chronic therapy of CHF.

Dopamine and dobutamine (10-15) are the two catecholamines most frequently used in the immediate treatment of severe heart failure. The physiologic effects of dopamine are mediated by activation of dopamine receptors, beta- and alpha-receptors and by the release of norepinephrines. The systemic hemodynamic effects of dopamine are partly dependent upon the dosage used. For instance, with 1-3 μg/kg/min only renal and no systemic hemodynamic effects are observed. With a dose of less than 10-15 μg/kg/min, beta-receptor effects are observed: namely, increased cardiac output resulting from both enhanced inotropic and chronotropic effects and decreased systemic vascular resistance. With larger doses (exceeding 10-15 μg/kg/min), the increased peripheral vascular tone that results from the activation of vascular alpha-receptors may produce adverse effects on cardiac function. In this instance, while arterial pressure may increase cardiac output may not change.

Dobutamine is primarily a $beta_1$-receptor agonist that also activates peripheral $beta_2$-receptors. In the majority of patients, it also increases cardiac output significantly, along with a significant reduction in systemic vascular resistance. Arterial pressure and heart rate may not change. With larger doses of dobutamine, however, tachycardia may develop due to a chronotropic effect, and arterial pressure may actually fall due to an excessive reduction in systemic vascular resistance. Pulmonary capillary wedge pressure, right atrial pressure, pulmonary artery pressure, as well as pulmonary vascular resistance tend to decrease.

In low doses, both agents tend to increase renal blood flow and renal sodium excretion. Myocardial oxygen consumption also increases in response to both dopamine and dobutamine. The two agents differ predominantly in their peripheral vascular effects, with dopamine having a greater pressor effect and thus being preferable in the setting of CHF associated with hypotension. The other major difference is that pulmonary capillary wedge pressure and pulmonary artery pressure may increase with dopamine while, in contrast, pulmonary capillary wedge pressure and pulmonary vascular resistance usually decrease with dobutamine. Both agents are limited to short-term intravenous use but are helpful for acute therapy of worsening left ventricular failure.

Recent evidence has suggested that short-term dobutamine infusions in CHF may confer a sustained beneficial hemodynamic and clinical effect lasting up to several months (13,14). A recent randomized, controlled study showed sustained improvement for four weeks in the functional status, left ventricular ejection fraction, and exercise tolerance of patients with CHF treated with a 72-hour infusion of dobutamine (14). The explanation for the sustained post-infusion benefits has not been established, but ventricular biopsy studies have shown improvement in myocardial ultrastructural morphology and high-energy phosphate content after intermittent inotropic therapy (15).

The search for an effective orally-active beta-adrenergic agonist has yielded a number of promising agents. Levodopa, administered orally in relatively large doses (1.5 - 2 gms every six hours) causes hemodynamic and clinical improvement in patients with chronic heart failure by elaborating dopamine in circulation. The hemodynamic effects consist of a significant increase in cardiac output and a decrease in systemic vascular resistance without any change in heart rate, blood pressure and pulmonary capillary wedge pressure. However, gastrointestinal and central nervous system side effects preclude the use of levodopa in many patients.

Butopamine is similar to dobutamine but can be administered both orally and intravenously. A slight structural change of the dobutamine molecule prevents deactivation after oral administration. Although beneficial hemodynamic effects have been observed after its intravenous administration, oral therapy has not been found effective because of side effects.

Dibutinyl cyclic AMP, given intravenously, increases the intracellular cyclic AMP level, increases contractility and promotes peripheral vasodilation. Its hemodynamic effects are similar to those of dobutamine. Clinical experience with this agent, however, is extremely limited.

Two other new agents, pirbuterol and prenalterol, appear to have beneficial acute hemodynamic effects in CHF but suffer from limited clinical efficacy due to attenuation of hemodynamic effects with chronic therapy (16-19). Pirbuterol, a selective $beta_2$ agonist, is predominantly a vasodilator but has been shown also to increase left

ventricular contractility in dogs. Acute oral administration of pirbuterol in patients with CHF produces marked decreases in systemic vascular resistance, also increases cardiac output, and has little effect on heart rate, left ventricular filling pressure or blood pressure (16). Prenalterol, a selective $beta_1$ agonist, acutely increases cardiac output (and in most studies, also heart rate), causes a mild-to-moderate decrease in systemic vascular resistance and left ventricular filling pressure, and has no significant effect on blood pressure (17). It has been used with modest success in the treatment of cardiogenic shock. Despite encouraging early results of short-term follow-up in patients with CHF treated with pirbuterol or prenalterol, several recent controlled studies have not shown sustained benefit by hemodynamic or clinical parameters after chronic therapy with these agents (17,18).

Thus, the currently studied, newer sympathomimetic amines show beneficial acute hemodynamic effects consistent with combined inotropic and vasodilator actions in patients with CHF. However, chronic therapy does not appear efficacious, possibly due to down-regulation of the beta receptors and the subresponsiveness of the failing heart secondary to high endogenous circulating catecholamines or sustained exposure to exogenous adrenergic agents (19).

NON-GLYCOSIDIC, NON-SYMPATHOMIMETIC AGENTS

In 1978 a new class of potent inotropic compounds was introduced that produced an increase in myocardial contractility without activating glycoside, beta and histamine receptors (20,21). The first of these was amrinone, a bipyridine derivative, which increased papillary muscle force of contraction in a dose-dependent fashion, not inhibited by ouabain (a digitalis glycoside), propranolol (a beta-adrenergic blocker), metiamide (histamine-2 receptor agonist), atropine or reserpine (21). In addition, amrinone produced a direct vasodilator effect on the animal hind limb. Hence, amrinone appeared to have the combined effects of positive inotropism and vasodilation, both theoretically beneficial effects for patients with CHF. Since 1980 several other agents in this class have been developed, including milrinone (an amrinone analogue with 20-30 times the *in vitro* potency of

amrinone), MDL 17,043 (fenoximone), MDL 19,205 (piroximone), RO13-6438 (posicor) and AR-L115BS (sulmazol) (Table I). These agents have now been shown to be inhibitors of phosphodiesterase associated with increased intracellular cyclic AMP and to increase calcium flux into myocardial cells during the plateau phase of the cardiac action potential (22-24), both potential mechanisms for their inotropic effects. Accumulation of cyclic AMP in smooth mucle cells explains this peripheral vasodilating effect.

Amrinone

Acute hemodynamic effects of intravenous amrinone in CHF include marked dose-dependent increases in cardiac index and stroke work index, marked decreases in mean pulmonary capillary wedge pressure and right atrial pressure with insignificant effects on mean arterial pressure or heart rate (25,26) (Figure 1). Peak hemodynamic effects of an intravenous bolus (0.75 - 3 mg/kg) occur within 10 minutes, can be sustained with infusions of 5-10 μg/kg/min, and last 30-120 minutes after discontinuation, depending on the loading dose. The beneficial hemodynamic changes reflect both inotropic and vasodilator effects, and can be produced even in patients with severe CHF who are refractory to maximum conventional vasodilator therapy. The myocardial metabolic effects have shown, in general, a reduction in myocardial oxygen consumption at rest. However, in some patients myocardial lactate production can occur despite decreased coronary vascular resistance. Currently amrinone lactate has been approved by the Food and Drug Administration for short-term (24 hour) IV infusion in patients with severely impaired left ventricular function who have failed digitalis, diuretics and/or vasodilators. Adverse side effects of IV amrinone include thrombocytopenia without spontaneous bleeding (2.4%), nausea (1.7%), vomiting (0.9%), arrhythmias (3%) and hypotension (1.3%).

Acute hemodynamic effects of oral amrinone are similar to those observed with IV administration except for slower kinetics due to less rapid increases in plasma drug levels via the oral route. Dose-related increases in cardiac index and decreases in pulmonary capillary wedge pressure are maintained with oral administration and are sustained after weeks of oral therapy (27,28). In addition, oral amrinone administration has been shown to acutely increase exercise tolerance

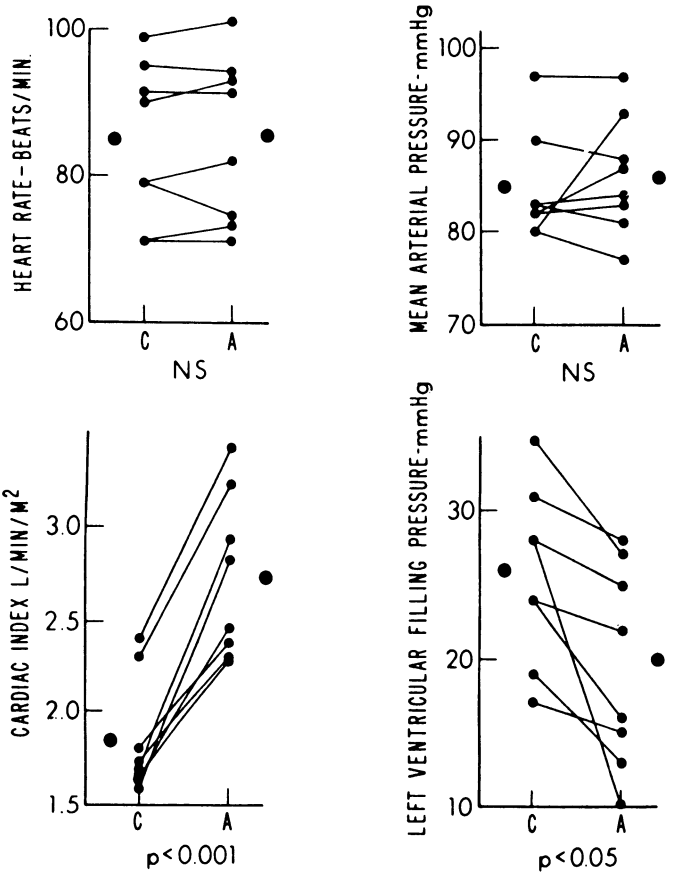

Fig. 1. Maximum acute hemodynamic effects (A) of an intravenous amrinone bolus on heart rate, mean arterial pressure, cardiac index and left ventricular filling pressure compared with control (C). (Reproduced with permission from American Heart Association and LeJemtel et al., Ref. 26).

measured as maximal oxygen consumption in patients with CHF (29), an effect not observed with acute oral vasodilator therapy with either hydralazine or captopril. This suggests that amrinone may have an advantage over conventional vasodilators in CHF by increasing blood flow to exercising skeletal muscles due to a combination of its direct

inotropic effect and perhaps a more selective vasodilator effect than that seen with other vasodilators.

Chronic therapy with oral amrinone has yielded discouraging results due to deterioration of baseline left ventricular hemodynamics after drug withdrawal when compared to pretreatment hemodynamic status (27), lack of clinical improvement in two recent multicenter controlled studies (30,31), and frequent adverse side effects. The largest multicenter, controlled study of long-term oral amrinone therapy involved 173 patients with predominantly NYHA functional class II and III CHF who had a mean left ventricular ejection fraction of 25 ± 15% (30). The first phase of the study involved oral amrinone therapy in all patients (113 ± 33 mg three times daily), 52 of whom (30%) showed a "response" to therapy defined as a maximal increase in treadmill exercise time exceeding two minutes. The remaining patients had a lesser increase in exercise time (42%), developed limiting adverse reactions (14%), died (12%) or dropped out (3%).

The 52 "responders" were randomized subsequently to either continue oral amrinone or switch to placebo. All patients continued standard treatment. Comparison of the patients receiving amrinone or placebo therapy for 12 weeks revealed no significant differences in NYHA functional class, left ventricular ejection fraction, resting heart rate or blood pressure, or exercise capacity. Adverse side effects were common in the amrinone-treated group and consisted mainly of gastrointestintal disturbances (27%) and central nervous system complaints (20%), limiting daily doses in general to 350 mg or less.

Milrinone

Milrinone has been shown to produce beneficial acute hemodynamic effects in patients with CHF similar to those seen with amrinone but with much greater potency (32,33). Dose-ranging studies with intravenous milrinone have shown peak hemodynamic effects similar to amrinone but with only 12.5-75.0 µg/kg boluses (34). Increases in cardiac index are maximal (40-45%) at 10 minutes and last for 30-60 minutes with IV boluses of 50-75 µg/kg. Pulmonary capillary wedge pressure and right atrial pressure decrease 45% and 37% respectively, and mean arterial pressure decreases 14% with the 75 µg/kg dose. Although there is a trend toward increasing heart rate, most studies

have shown the increase to be insignificant. Systemic vascular resistance is reduced in a dose-dependent fashion with a 42% decline after the 75 μg/kg dose, reflecting an important effect of milrinone in reducing left ventricular ejection impedance.

The hemodynamic data above are insufficient to determine how much of these beneficial hemodynamic changes are due to a positive inotropic effect versus peripheral vasodilation. However, recent reports have shown that milrinone has a direct vasodilator effect on the human forearm (35) and a direct inotropic effect with intracoronary infusion in patients with CHF (36), suggesting that both are important mechanisms of action. In addition to improving left ventricular systolic function, milrinone has also been shown to improve diastolic function reflected as a decrease in left ventricular end-diastolic pressure despite simultaneous increase in end-diastolic volume (37).

Oral milrinone therapy has revealed potent and strikingly dose-related beneficial hemodynamic effects in patients with severe CHF, even in patients refractory to maximum vasodilator agents (38,39). Acute oral dosing with milrinone causes increases in cardiac index and decreases in pulmonary capillary wedge pressure, systemic vascular resistance and mean arterial pressure which become progressively marked up to a maximal dose of 15 mg. The majority of patients show peak effects with a 10 mg dose, but some patients will require up to 15 mg. Peak effects include a 26% increase in cardiac index, 36% decrease in pulmonary capillary wedge pressure, 14% decrease in mean arterial pressure and 33% decrease in systemic vascular resistance, with a modest 7% increase in heart rate (39) (Figure 2). These beneficial changes are maintained with chronic therapy, although there is a trend toward reduced responses after an average of 37 days of therapy (39) (Figure 3).

Clinically, milrinone produces symptomatic improvement in approximately 50% of patients with severe CHF refractory to digitalis, diuretic and/or vasodilator therapy, although acute hemodynamic improvement occurs in virtually all patients (39). Of patients with NYHA class IV symptoms, we have observed initial clinical improvement in 13 of 24 patients which correlated with sustained hemodynamic improvement in 11 patients after an average of 37 days of therapy. The remaining 11 patients did not improve symptomatically, and only two were

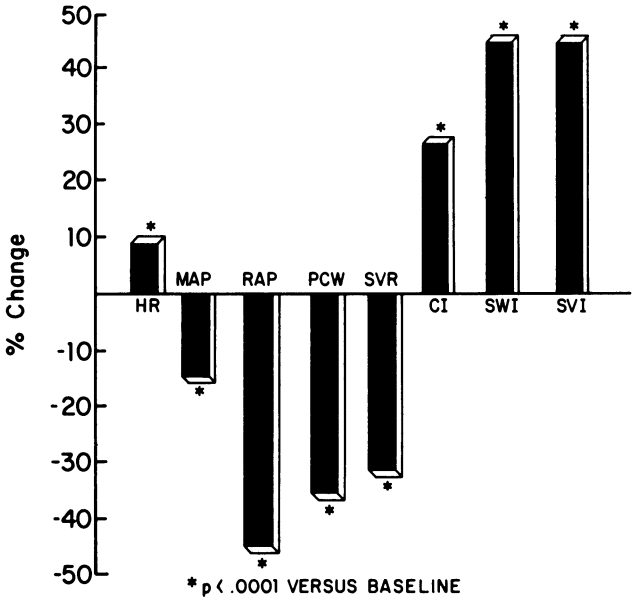

Fig. 2.
Peak hemodynamic effects of oral milrinone in 37 patients with severe CHF. Abbreviations: HR = heart rate; MAP = mean arterial pressure; RAP = right atrial pressure; PCW = pulmonary capillary wedge pressure; SVR = stroke work index; SVI = stroke volume index.

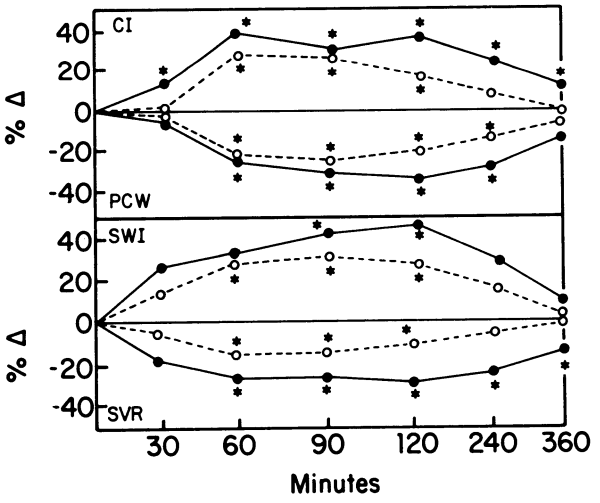

Fig. 3. Acute (•) and chronic (○) hemodynamic effects of oral milrinone in 25 patients with severe CHF. Percent change (% Δ) in each parameter is shown in relation to time after an oral dose (same dose with acute and chronic measurements). *p < .01 compared to baseline. Abbreviations same as Fig. 2.

able to be maintained on milrinone for repeat hemodynamic study. Eight of the 13 patients who improved initially had sustained clinical benefit at the time of last clinical follow-up (mean 165 days). Of patients with NYHA Class III CHF in our series, seven of 13 showed clinical improvement with chronic therapy; five patients had no clinical benefit; and one patient died suddenly soon after initiating therapy. It needs to be emphasized, however, that without controlled studies the potential beneficial effects of long-term milrinone therapy cannot be established.

Adverse side effects during chronic milrinone therapy have been minimal. We have observed mild diarrhea in one patient, which did not necessitate limitation in milrinone dose. One patient in our series had ventricular tachycardia during the acute oral dosing of milrinone which resulted in discontinuation of milrinone therapy due to persistent arrhythmia despite conventional antiarrhythmic agents.

Other Agents

MDL 17,043 (fenoximone) and MDL 19,205 (piroximone) are imidazole derivatives and also possess both inotropic and vasodilator properties, resulting from the inhibition of phosphodiesterase and the increase in intracellular cyclic AMP (40). In addition to inotropic and vasodilating mechanisms, fenoximone can increase left ventricular distensibility, which also contributes to improvement in left ventricular function (41). The hemodynamic effects are characterized by a marked increase in cardiac output and stroke volume and decreases in pulmonary capillary wedge, right atrial, and pulmonary arterial pressures and systemic and pulmonary vascular resistance, along with a modest decrease in blood pressure and a slight increase in heart rate (42,43). Fenoximone tends to increase myocardial oxygen delivery and myocardial oxygen consumption presumably due to increased myocardial oxygen requirements (44).

Posicor, another imidazole derivative and phosphodiesterase inhibitor, also produces similar systemic hemodynamic effects and improvement in left ventricular performance. However, it also decreases myocardial oxygen extraction and increases coronary sinus venous oxygen content, indicating primary coronary vasodilatation (45). In contrast to fenoximone, milrinone and posicor do not usually increase myocardial oxygen consumption. Following acute intravenous and short-term oral

therapy with fenoximone, piroximone and posicor, clinical improvement is noticed even in patients with severe heart failure (NYHA Class IV). Uncontrolled studies have failed to demonstrate sustained beneficial effects in terms of improvement in clinical class or in exercise tolerance in patients with chronic heart failure. It is clear that further controlled studies are needed to assess the value of long-term therapy with these agents in the management of patients with chronic heart failure.

Sulmazol produces systemic hemodynamic effects similar to those of other agents in this class. It has been suggested that in addition to inhibition of the enzyme phosphodiesterase, sulmazol enhances the responsiveness of the myofibrillar contractile proteins to calcium (10). Clinical trials of this agent, however, have been discontinued because of its potential carcinogenicity.

Reports on long-term survival in patients with severe CHF treated with the new nonglycosidic, nonsympathomimetic oral inotropic agents have shown that overall mortality remains high (42,43,46). Despite encouraging hemodynamic and symptomatic benefits in many patients refractory to vasodilators, mortality due to worsening left ventricular failure and sudden death during chronic therapy with these agents have been reported consistently as 60-65% at six months (39,42,46). In a retrospective review of 82 patients with NYHA class III and IV CHF treated with milrinone, MDL 17,043, RO13-6438 (posicor) and MDL 19,205, we have found a 64% mortality at 6 months (40) (Figure 4). This mortality rate is higher than any previously-reported mortality rates in CHF, including rates in subgroups of patients with NYHA class IV symptoms who are nonresponders to vasodilator therapy and have the poorest baseline hemodynamic indexes (4,47,48). In addition, we have reported a significantly greater incidence of sudden death during oral inotropic therapy for patients with an ischemic etiology of CHF when compared to patients with idiopathic, dilated CHF, and a trend toward reduced sudden death rates in patients treated with anti-arrhythmic agents concurrent with inotropic therapy (46) (Table II).

Multiple adverse side effects, including gastrointestinal symptoms, have been observed following fenoximone, piroximone, and posicor therapy in patients with chronic heart failure. Ventricular tachyarrhythmia, as

with amrinone or milrinone, remains a potentially life-threatening complication of these agents.

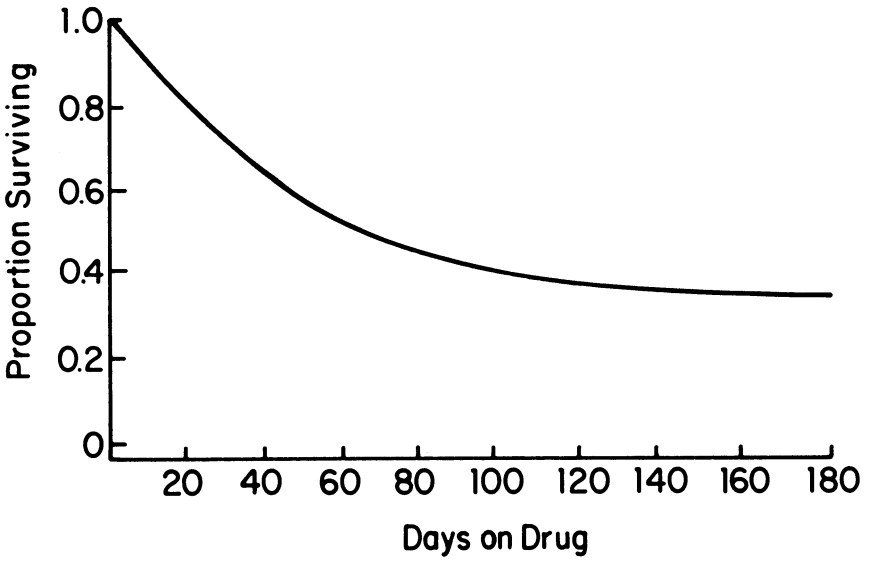

Fig. 4. Cumulative survival in 82 patients with severe CHF treated with the new nonglycosidic, nonsympathomimetic inotropic agents. Proportion surviving is shown in relation to time since beginning inotropic drug therapy.

Table II. Cumulative Mortality at Six Months for Severe CHF Treated With the New Inotropic Agents in Relation to Etiology of CHF and Anti-arrhythmic Therapy.

	OVERALL	SUDDEN DEATH	CHF DEATH
Etiology of CHF			
Ischemic (57)	68	28 **	56
Nonischemic (25)	52	5	49
Anti-arrhythmics			
Yes (39)	63	13 *	57
No (41)	63	29	47

Values are % mortality. Numbers in parentheses represent number of patients in each subgroup. **p < 0.05; *p = 0.06 (Ref 46)

CONCLUSIONS

The new inotropic agents developed for the acute and chronic management of CHF have been shown to produce hemodynamic and clinical improvement in many patients who are refractory to digitalis, diuretics and/or vasodilators. The sympathomimetic agents exert their effects by stimulating beta-adrenergic receptors. Their long-term application appears to be limited because of attenuation of their effects, possibly due to down regulation of the adrenergic receptors of the effector organs.

The nonglycosidic, nonsympathomimetic agents produce both positive inotropic and direct vasodilator effects. Their inotropic effects appear to be due to increases in calcium availability to the actin-myosin contractile elements secondary to inhibition of phosphodiesterase, which increases intracellular cyclic AMP. These newer inotropic-vasodilator agents appear to produce beneficial hemodynamic and clinical effects after acute intravenous and short-term oral therapy in patients with heart failure. However, further controlled studies will be required to establish their role in the long-term management of patients with chronic congestive heart failure.

Regardless of whether these agents prove to be clinically efficacious for the long-term therapy of CHF, future research must concentrate on a more definitive understanding of the underlying biochemical changes that occur in myocardial cells which result in a loss of contractility, depressed left ventricular performance, and the syndrome of congestive heart failure. Since the basic cellular defect which leads to a loss of contractility in the remaining normal myocardium following myocardial infarction is still unknown, future efforts to improve contractility with pharmacological agents that do not reverse this defect may result in only palliative effects while the underlying abnormality continues to progress.

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22

COMMON PROBLEMS IN PATIENT MANAGEMENT DURING THE TWO MONTHS FOLLOWING ACUTE MYOCARDIAL INFARCTION

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The first two months following an acute myocardial infarction are a time of change for the patient. This includes physiologic changes in endurance (1), changes in work status (2) and the resultant economic implications, changes in family and social roles, and acceptance of a modified lifestyle (3). Oftentimes, a myocardial infarction is the first clinical manifestation of coronary disease. In this setting a previously healthy person is suddenly labelled as a sick patient with serious heart disease. This psychosocial trauma is compounded by a hospitalization that frequently includes intensive care and the use of frighteningly complex technology. Current medical practice encourages the early discharge of patients with uncomplicated infarctions-as early as 7 days after the event (4). This short hospital stay means a brief period of time for acceptance of this new life situation, for education about potential beneficial changes in lifestyle, and for assessment and treatment of potential problems. Thus, the time after discharge is an important time that the physician and patient can utilize to alter medical regimens, deal with new problems, answer questions, and ensure the patient's return to a functional lifestyle (5). Frequent interactions with health care personnel can help to facilitate a successful outcome. This chapter will review several important common problems including recurrent

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chest pain, symptomatic premature beats, medication usage and psychosocial problems that occur following a myocardial infarction. The importance of close follow-up during this period of time will be emphasized.

RECURRENT CHEST PAIN

One of the most common problems facing the clinician in the post infarction period is the recurrence of chest pain. This represents both a diagnostic and therapeutic dilemma in the management of these patients. The three common causes of recurrent chest pain include non-anginal pain, postcardiac injury syndrome, and recurrent angina.

With the occurrence of a myocardial infarction, patients realize, perhaps for the first time, that good health cannot be taken for granted. Often they become overly concerned and sensitive about bodily discomforts. When faced with the possibility of death, minor symptoms become magnified and are dwelt upon. Somatic or non-anginal chest pain is a frequent source of concern to the patient. These discomforts are typically non-exertional, evanescent, of a sharp or pleuritic nature, and non-radiating. Likewise, they are not generally relieved with nitroglycerin nor associated with ECG changes. Typically the description of the pain suffices to allow the physician to conclude that this is not a serious problem. Reassurance and education following an office visit will usually help the patient understand the absence of significant potential harm from this type of discomfort.

Post cardiac injury syndrome (PCIS) or Dressler's syndrome occurs in less than 5% of patients following myocardial infarction. A recent report from the institution in which Dressler's syndrome was initially

described suggests that perhaps the syndrome has disappeared due to less anticoagulant use and more aggressive therapy of pericarditis during the acute phase (6). PCIS typically occurs 2-3 weeks after the infarct in contrast to the transient pericarditis often seen during acute infarctions. The signs and symptoms include pleuritic pain, fever, myalgias and a pericardial friction rub. The ECG may show new ST-segment or T-wave changes, making differentiation from recurrent ischemia difficult. Therapy to relieve pain is accomplished with anti-inflammatory agents and occasionally steroids. Relapse occurs in over 50% of cases and can occur as distantly as five years from the initial presentation. (7)

Recurrent angina following discharge is a common occurrence that often results in difficult diagnostic and therapeutic decisions. Waters et al followed 166 patients for one year post-MI and found that 59% had angina (8) (see Waters chapter). Surprisingly, only 27% of the patients reported angina consistently at three consecutive follow-up visits. Likewise, treadmill induced angina is not reproducible when comparing 2 and 6 week post MI tests (9). The strongest predictor of recurrent angina was angina prior to the infarct. When the results of predischarge exercise testing were combined with a history of pre-infarction angina, patients could be subgrouped for prediction of post infarct angina (Table 1). Patients with pre-infarct angina and an ischemic response of the ST segments on the exercise test had a very high incidence of post-infarction angina (90%). This compared with a very low incidence of angina in those patients with no prior history of angina and a negative exercise test (26%). Weiner reviewed recent trials of pre-discharge exercise testing (10). The occurrence of angina on the pre-discharge treadmill

increased the risk of a future cardiac event by 11% but was not nearly as strong a predictor of future events as an ischemic ST segment response. This emphasizes the importance of the peri-discharge exercise test in stratifying patients into risk groups for future cardiac events (11) (see Waters chapter). In one study of 338 patients undergoing exercise tests 3 weeks after infarction, those patients with non-ischemic (negative) tests had a one year mortality of less than 2%. This compared with a 6 month mortality of 10% in those with positive tests. Thus, patients that fall into low-risk groups (50 % of post MI patients) based on this evaluation subsequently developing recurrent angina can often be safely treated with a modification of their medical regimen to control these symptoms. These patients do not appear to be at increased risk for mortality or re-infarction.

TABLE I

	Positive Exercise Test	Negative Exercise Test	Total
Pre-Infarction Angina	96%	50%	70%
No Prior History of Angina	67%	26%	35%
Total	86%	36%	

Percentage of patients postinfarction with angina separated on the basis of preinfarction anginal history and pre-discharge exercise testing.

PVC's

Premature ventricular contractions (PVCs) are seen by ambulatory monitoring in 50% of the post MI population (12). Of the group with PVC's, roughly half have complex ventricular ectopy (couplets, runs,

bigeminy, R on T phenomenon or multiform beats). In the 1970's evidence from large groups of most MI patients indicated that complex ectopy was a predictor of subsequent cardiac death (12, 13). This led to recommendations for prophylactic anti-arrhythmic therapy for these patients with complex arrhythmias. Subsequently it was shown that coronary anatomy and left ventricular function were better predictors of survival than were ventricular arrhythmias and that the occurrence of more complex arrhythmias was related to ventricular function (14).

Furberg recently reviewed the six long term trials of antiarrhythmic agents post MI (15). Although they all have methodologic flaws, none showed a significant improvement in survival with therapy. By the time of termination of the trials, up to one-third of the patients were not taking the drugs due to side effects. In addition, recent evidence suggests that anti-arrhythmic drugs are also pro-arrhythmic (16). In up to 15% of patients given anti-arrhythmic agents for arrhythmia suppression, worsening of the arrhythmia is seen. This is not a predictable complication prior to the institution of these agents.

Confounding these data demonstrating the problems inherent in the use of anti-arrhythmic drugs is the observation that the first six months after an MI represents the period of greatest risk for sudden death. Sixty percent of the deaths that occur during this time occur during the first 2 months after infarction and two-thirds of these are arrhythmic in cause (with or without recurrent MI) (17). The management of patients with complex ectopy is discussed in an earlier chapter. In one quarter of patients post MI, however, simple ventricular ectopy can be documented. Once documented, should simple ectopy be treated? Moss et al recorded 6 hour ambulatory ECGs on 940

MI patients prior to hospital discharge (13). The life table curves for survival from sudden and non-sudden death show no difference in the patients with and without simple PVC's. Thus, in these patients with simple ventricular ectopy there is no indication for anti-arrhythmic therapy due to the low risk for sudden or non-sudden cardiac death, lack of demonstrated efficacy in prolonging survival, high incidence of side effects and possible pro-arrhythmic effects of the drugs.

DRUG THERAPY

Three classes of agents are currently available for the pharmacologic treatment of coronary disease. These drugs are utilized to improve survival, reduce the risk of re-infarction and decrease the occurrence of angina. These classes of drugs include the nitrates, the beta blockers and the calcium channel blockers; each class includes multiple different agents having varying pharmacokinetic and pharmacodynamic profiles. Frequently patients are discharged from the hospital after an acute infarction on "triple" therapy. Is all this medication necessary?

Various beta-blockers have been shown in well designed studies to reduce the risk of sudden death and re-infarction by 26% and 35%, respectively (18). There are now seven beta blockers released for use in this country. The physician's decision concerning whom to treat, with which agent, and in what dosage is not easily made. This problem is discussed in an earlier chapter. Compounding this dilemma is the frequent occurrence of side effects including fatigue, vivid dreams, dizziness, bronchospasm, impotence and cold extremities. Many of these side effects can be significantly decreased by dosage reduction

without a resultant increase in anginal frequency. The effect of decreased doses of beta blockers on secondary prevention benefits is not known.

The nitrates and calcium blockers have not been shown to play a role in secondary prevention but are used solely and widely for symptomatic purposes. Patients on one or a combination of these vasodilators at discharge frequently can have doses tapered (and often stopped) with close follow-up as an outpatient.

PSYCHOSOCIAL FACTORS

The occurrence of an acute myocardial infarction causes significant psychological stress. The concerns of the patient center on abilities to fulfill family roles, to resume economic responsibilites, and to re-evaluate life priorities (19). Coping with these problems begins on the CCU with support from hospital personnel. With shortened hospital stays, the burden for working through these dilemmas rests largely on the patient and family. Wishnie et al demonstrated in post MI patients after discharge that 83% complained of weakness, 88% were depressed or anxious, 60% had sleep disorders and 67% had family quarrels over matters concerned with convalescent care (20). Recent data from BHAT revealed that mortality post-infarction was related to social isolation and high life stress (21). These characteristics were more common in those patients with lower educational levels. The mechanisms within the individual, within the family and within society for coping with these problems of adjustment to a new life situation are complicated and well reviewed elsewhere (3, 19). The physician's role in this process must be combined with that of other health professionals and should include: time for

listening to the patient, providing support and reassurance, and education. The peri-discharge exercise test presents an opportunity for the physician to favorably influence the patient's course post-discharge. In studying post MI recovery, Ewart et al found increased activity levels and improved perception of health in individuals that completed the test without angina (22). Additional improvement was seen when a physician and nurse reviewed and explained the results of the testing for the patient. Thus, the ability to exercise vigorously without symptoms combined with education by medical personnel favorably influenced the patient's course.

Return to work after an MI is often used as a measure of the success of the rehabilitation process. There are numerous factors which influence return to work including the psychosocial make-up of the individual, physiologic characteristics, socioeconomic factors, individual perception of health status and risk, and the dynamics of family and community. This topic is well reviewed in a recent paper by Davidson (2). It is clear that the physician's perception of and advice on returning to work are important determinants of a successful outcome (23). The exercise test presents an opportunity to guide the physical activity of work based on safe limits determined by that test. Table 2 lists the MET expenditures of energy for various kinds of exertion. We set a training range for our patients from the exercise test (.7 x (maximum heart rate-resting heart rate) + resting heart rate), teach them to count their pulse rate, and suggest that they never exceed the lower end of this range in their activities of daily living. This gives the patient guidance and reassurance to gradually increase his activity level. In addition, participation in

a cardiac rehabilitation program provides professional advice on the safe limits of energy expenditure in a supervised setting.

TABLE 2

MET Expenditure for Common Activities

Activity	METS
Light housework	1.5
Dressing	2
Making beds	3
Walking 2.5 mph	3
Showering	3.5
Bicycling	3.5
Golf-pulling cart	4
Gardening	4.5
Tennis (doubles)	4.5
Walking 3.5 mph	5.0
Sexual Intercourse	5.0
Mowing the lawn	6.5
Shoveling	7.0
Walking 5 mph	7.0

Sexual dysfunction manifest as decreased frequency of intercourse or impotence following myocardial infarction occurs in up to 50% of patients (24). There are three major causes of sexual dysfunction including physiologic changes, psychosocial problems and drug side effects (25). From the cardiac standpoint there is rarely a physiologic reason to avoid sex. The average peak MET level of energy expenditure is 4.7-5.5 METS and maximal heart rate is 90-114 (26, 27). These levels of work are generally those of activities of daily living and less than the average patient can perform on the treadmill. There is often exagerated fear of the so-called coital coronary. Ueno investigated 5559 sudden deaths of which 18 (0.03%) were related to intercourse (28). Of these 18, fourteen were extramarital affairs occurring following heavy food and alcohol use. Thus, the coital coronary is a very uncommon event and seems to be more closely related to stress than exertion. The patient's performance on the peri-

discharge exercise test can be used to guide the patient's sexual and daily activities and reassure the patient of the safety of sexual performance.

The psychosocial problems of the post-infarct patient have been discussed briefly earlier and are well reviewed by McLane et al (25). These problems revolve around feelings of potential inadequacy due to illness, depression and anxiety following the infarct, and adequacy of information provided to the patient. It has been repeatedly shown that physician's tend to avoid educating the patient concerning resumption of sex and its safety (29). Perhaps this is due to the physicians lack of knowledge in these matters and discomfort in dealing with them.

Pharmacologically induced sexual dysfunction is uncommon but its occurrence must be aggressively sought by the physician. With recent trends toward increased use of beta blockade following infarction, this form of sexual dysfunction will likely increase. In one study of propranolol, 15% of patients developed impotence, 28% developed a decrease in potency and 4% had decreased libido (30). These side effects appeared to be dose related. If sexual dysfunction occurs, a trial of other beta blocking agents or reduction in dosage may be beneficial.

CONCLUSION

Frequent contact with medical personnel following an infarction can alleviate anxiety, answer questions, allow for appropriate alterations of medical regimens and allow further problems to be identified earlier. Traditional practice has the patient seen for an office visit 3-6 weeks after the event. This leaves long periods of

time with no medical follow-up. We have found that early enrollment (1-2 weeks after the infarct) in a cardiac rehabilitation program can facilitate a smooth transition from the hospital environment to an active lifestyle. Contact with health care personnel and even other patients several times per week in a rehabilitation setting provides reassurance and education as well as supervised activity. This setting also provides an ideal follow-up system for the physician. Recurrent angina, congestive failure and medication side effects can be detected and dealt with swiftly. In addition to the physiologic benefits of exercise, early cardiac rehabilitation can provide for more comprehensive care of the patient during a time of many changes.

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