PROTECTION OF ISCHEMIC MYOCARDIUM

RATIONALE AND CURRENT STATUS

MEDICAL GRAND ROUNDS
AUGUST 31, 1978

SOUTHWESTERN MEDICAL SCHOOL
THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER
AT DALLAS

THOMAS C. SMITHERMAN, M.D.

TABLE OF CONTENTS

CASE REPORT

(BBJ, 102304) was a 58 year old man who was admitted for the 6th time on July 7, 1978 and died the following day. His chief complaint was chest pain. Hypertension was discovered in 1950 and treated continuously since then. He was a smoker (90 "pack years") and had a remote history of syphilis in the 1940's which had been treated. He was otherwise generally well until he sustained an uncomplicated non-transmural myocardial infarction in March 1974. He was hospitalized in September of 1975 and December of 1976 for unstable angina pectoris which was successfully managed with an anti-anginal regimen. In March, 1978 he sustained an inferior wall MI. Subsequent to this he was managed on propranolol, isosorbide dinitrate, nitroglycerin, hydrochlorthiazide, and sustained-release quinidine sulfate. On this regimen he had moderate stable angina and one-mile exertional dyspnea. On the night of admission he awoke with severe chest heaviness that radiated into his left arm and was associated with diaphoresis. When seen in the emergency room, he was found to have ECG changes of an acute antero-lateral MI and admitted.

On examination he appeared well developed and nourished, in moderately severe distress with somewhat labored respirations. BP 120/94, HR 108-regular, R 12, afebrile. The jugular venous pressure was 5cm water and the carotid pulses were normal in volume and pulse contour. The chest had an increased antero-posterior diameter and was hyper-resonant to percussion. There were diffuse coarse rhonchi and minimal inspiratory basilar râles. Except for a non-palpable apex beat and the presence of a fourth heart sound, the cardiac exam was not remarkable.

The ECG showed changes consistent with an extensive, acute antero-lateral MI. Chest radiogram showed slight cardiomegaly without vascular redistribution or pulmonary congestion. Serum CK was 270 (upper limits of normal, 180) on admission but rose steadily being 748 at 1:00 am, 820 at 3:00 am, and 2020 at 8:00 am the following morning. He was treated with morphine sulfate, bedrest, oxygen administration, and ECG monitoring. At 5:00 am he developed clinical and radiographic signs of acute pulmonary edema. He responded initially to medical management including intravenous furosamide. At noon a thermistor-tipped Swan-Ganz catheter was positioned in the pulmonary artery. The mean pulmonary capillary wedge pressure was 27 mm Hg, cardiac output was 3 l/min. After 4:00 pm his blood pressure fell progressively and was unresponsive to dopamine and nor-epinephrine. Urine flow declined and his skin became cold and clammy. He developed a profound sense of impending doom. Cardiac output fell to about 1.5 l/min, the mean "wedge" pressure rose to 40mm Hg, the blood pressure declined to undetectably low levels and he died at 6:10 pm.

At autopsy, he was found to have extensive atherosclerotic disease of his entire coronary arterial tree, recent thrombosis of the anterior descending branch of the left coronary artery, healed postero-lateral and apical infarcts, widespread focal left and right ventricular interstitial fibrosis, and a recent massive antero-septal infarction. Both ventricles were hypertrophied and dilated and the lungs were severely edematous.

INTRODUCTION

The foregoing case report illustrates one of the major problems facing physicians treating patients following myocardial infarction (MI). There is a reasonable consensus that the advent of coronary care units decreased the in-hospital mortality from MI by about 15-20% by the early detection and treatment of potentially lethal arrhythmias and conduction defects. Death before patients with MI reach the health care delivery system and death from left ventricular "pump" failure are currently the greatest challenge to those who would try to further decrease the current nearly 700,000 annual death rate from MI. Dr. James Atkins discussed prehospital coronary care at these exercises 3 years ago (March 20, 1975). The amount of muscle lost in an infarct is a major determinant of the likelihood of "pump" failure (1,2) and of serious arrhythmias that occur in the period soon after infarction.(3) In recent years the hypothesis that an MI is a dynamic event that evolves for several hours or days has gained substantial credence, due especially to the work of Dr. Eugene Braunwald and his many associates. A wide variety of animal and some clinical experimentation have supported the notion that the eventual size of an MI and the likelihood of an extention of the MI can be modified by various interventions. The worst end of the spectrum of left ventricular pump failure after MI, cardiogenic shock, may be thought of as a vicious cycle (Figure 1) of progressive loss of ischemic muscle and progressively diminished left ventricular function, systemic blood pressure and myocardial perfusion.(4) With MI, there is usually a large zone of jeopardized ischemic heart both lateral to the center of the infarct and in adjacent subepicardial tissue. In large infarctions, this jeopardized zone tends to be particularly large. Successful limitation of the eventual size of the MI depends on protection of the jeopardized ischemic myocardium.

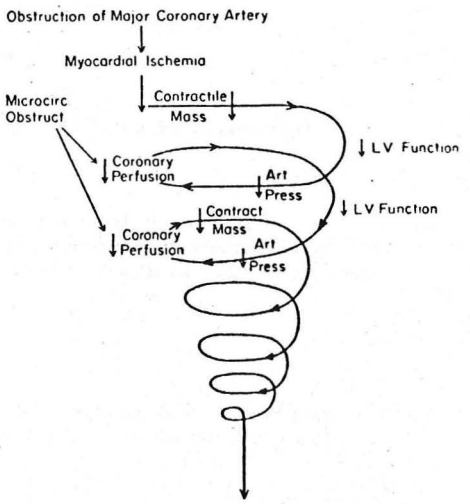


FIGURE 1. *Diagram depicting the sequence of events in the vicious cycle in which coronary artery obstruction leads to cardiogenic shock and progressive circulatory deterioration.*

From: E.Braunwald (Reference No.4)

Major amounts of research money and effort are being devoted to the endeavor to determine the effects of a number of interventions on limiting infarct size. In this review, I shall attempt to provide a broad overview of the rationale and current status of these interventions. I shall try to conclude [1] with some estimate of the efficacy, safety, and applicability of the interventions that have undergone substantial testing and [2] with some observations on how these investigations bear on the current routine management of patients with MI..

BASIC CONSIDERATIONS ON FACTORS INFLUENCING THE EXTENT OF INFARCTION

In approaching these topics, it is helpful to review some of the factors that are likely to be important in adversely affecting the extent of myocardial infarction once the process has begun. The eventual extent of myocardial infarction depends in part on the balance between oxygen supply and demand and on the intracellular accumulation of noxious substances. Some of these factors are outlined in Table I.

Table I

FACTORS THAT ARE LIKELY TO BE IMPORTANT IN ADVERSELY AFFECTING THE STATUS OF JEOPARDIZED MYOCARDIUM

I. Increased Myocardial Oxygen Demand ($M\dot{V}O_2$)
   - A. Tachycardia
     1. Sinus tachycardia
     2. Tachyarrhythmias
     3. Anxiety
     4. Congestive heart failure
     5. Fever
        - a. MI itself
        - b. Pericarditis
        - c. Infection
     6. Hypovolemia
     7. Drug-induced
   - B. Increased myocardial wall tension
     1. Hypertension (Increased "afterload")
        - a. Anxiety
        - b. Pre-existing hypertension
        - c. Drug-induced
     2. Hypervolemia (Increased "preload")
     3. Increased left-ventricular size (LaPlace Relationship) congestive heart failure
   - C. Increased contractile state
     1. Anxiety
     2. Increased catecholamines from stress of MI
     3. Drug-induced [Some β-adrenergic agonists, glucagon, digitalis in the non-failing heart, bretylium tosylate (Bretylol^{R}),etc.]

II. Decreased Myocardial Oxygen Supply
   - A. Decreased myocardial perfusion
     1. Coronary artery occlusion
     2. Swelling of myocytes
     3. Hypotension
     4. Profound hypertension (squeezing off nutrient vessels in the infarcted area with low arterial perfusion pressure)
   - B. Hypoxemia
   - C. Anemia

III. Accumulation of Noxious Substances
   - A. Results of shift from aerobic to anaerobic metabolism
     1. H^+
     2. Lactic Acid
   - B. Intracellular accumulation of fatty acids and/or intermediates in the oxidative pathway
   - C. Lysosomal enzyme release

CELLULAR ABNORMALITIES THAT ARE APT TO BE IMPORTANT IN ALTERING THE CONTRACTILE PERFORMANCE OF ISCHEMIC HEART AND IN LEADING TO IRREVERSIBLE DAMAGE TO MYOCYTES

Forty years ago Tennant and Wiggers (5) demonstrated that ligation of a coronary artery was attended by virtually immediate loss of contraction of the myocardium supplied by the ligated artery followed shortly by systolic bulging of that segment. In more recent years, it has also been found that the infarcted and ischemic zones also have alterations in relaxation as well as contraction. (Reviewed in 6).

In consideration of interventions that may limit infarction size, it is useful to review some of the cellular abnormalities accompanying myocardial ischemia that may be important in altering contractile performance and that may be important in causing injured myocytes to become irreversibly damaged. (Table II).

In normal individuals the first response to increased myocardial oxygen demand is an increased coronary artery blood flow. In patients with ischemic heart disease, increased flow rates may not suffice and an increased oxygen extraction occurs. If this also fails to yield sufficient oxygen, the metabolism of the cell can no longer remain completely aerobic. In addition, products of metabolism cannot be washed out of the cell because of the inadequate blood flow. Therefore, the primary events in the ischemic myocyte are due to deprivation of oxygen and nutrients and the inability to remove the products of metabolism. Following the onset of myocardial ischemia a rapid decline in aerobic metabolism is induced by cellular hypoxia. The rapidly falling levels of high energy phosphate compounds (ATP, ADP, and CP) leads to rapid enhancement of anaerobic metabolism. The increased glycolytic flux occurs because of enhanced glucose uptake due to increased hexokinase activity, acceleration of glycogenolysis by enhanced phosphorylase kinase activity, and by increased phosphofructokinase activity (Figure 2). The resulting accumulation of lactic acid and hydrogen ion which cannot be washed out of the ischemic cell leads rapidly to intracellular acidosis. (Reviewed in 6-8). Tennant suggested in 1935 that intracellular acidosis might be a major determinant of the precipitous decline in cardiac contractility following coronary obstruction.(9) Whether this acidosis is the only or the major cause in this decline in contractility is still unresolved. (10-13). The mechanism(s) responsible for the acidosis-mediated depression is unclear but the decreased contractility may be mediated through interference with the normal flux of calcium or the interaction of calcium with the contractile proteins. This may occur from interference with release of calcium from sarcoplasmic reticulum, (14) or with the "slow inward current" of calcium across the sarcolemma.(15) It was initially proposed by Katz and Hecht that hydrogen ions may interfere with calcium binding to troponin, but recent evidence with skeletal (16) and cardiac (17) troponin suggests this is not the case. A direct depressant effect of acidosis on the ATPase activity of actomyosin has proved difficult to study but there is suggestive evidence that such an effect occurs.(18-20) (All above also reviewed in 21).

Table II

SOME OF THE CELLULAR ABNORMALITIES OF IMPORTANCE IN THE ISCHEMIC HEART

I. Primary events are deprivation of oxygen and nutrients and inability to remove products of metabolism.

II. Rapid decline in aerobic metabolism induced by cellular hypoxia.

III. Rapid enhancement of anaerobic metabolism (glycolysis) induced by falling levels of ATP, ADP, and CP.

IV. Rapid development of intracellular acidosis due to buildup of lactic acid and H^+ which cannot be removed from the cells.

A. Acidosis likely responsible for the "early pump failure" of ischemic heart.

1. Interference with interaction of Ca^{++} and contractile proteins

a. ? affects release of Ca^{++} from sarcoplasmic reticulum
b. ?? affects the "slow inward current" of Ca^{++} across the sarcolemma
c. ??? affects Ca^{++} binding to troponin

2. ?? direct affect on actomyosin ATPase activity

B. Increased lactate has further deleterious effects.

1. Decreases anaerobic glycolysis by inhibition of activity of:

a. Phosphofructokinase
b. Hexokinase
c. Phosphorylase kinase
d. Glyceraldehyde-3-phosphate dehydrogenase

2. Inhibits utilization of free fatty acids and causes buildup of free fatty acids and/or intermediate products due to inhibition of carnitine palmityl CoA transferase

a. Increases $M\dot{V}O_2$
b. ? causes arrhythmias

3. The transfer of ATP and ADP between cytosol and mitochondria is inhibited by competitive inhibition of adenine nucleotide translocase by the increased concentration of fatty acid acyl-CoA esters

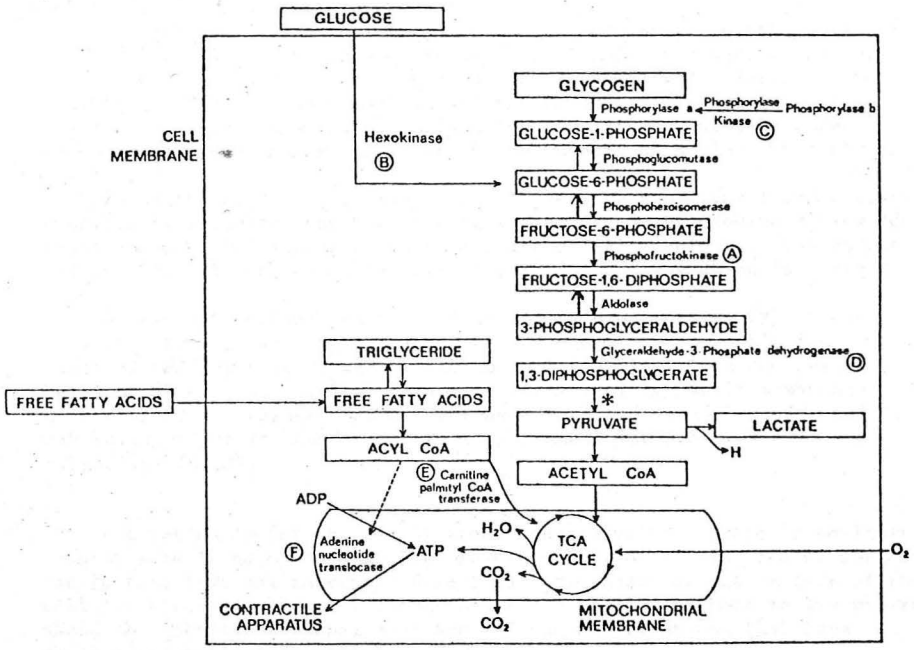
V. Loss of normal membrane functions.

A. Loss of potassium and magnesium, gain of sodium, chloride, and calcium

B. Net gain of water leading to cell swelling which compresses nutrient vessels

C. Loss of integrity of lysosomal membranes with leakage of acid proteases into cytosol.

Figure 2.



Schematic Representation of the Effects of Ischemia on Glycolysis and Free Fatty Acid Metabolism.

Ischemia increases the intracellular lactate concentration; in turn, the accumulation of lactate inhibits several enzymes in the glycolytic pathway. Phosphofructokinase (A) and hexokinase (B) are inhibited. Phosphorylase kinase (C) is also inhibited, thus preventing the activation of phosphorylase *b* to phosphorylase *a* and, therefore, suppressing the conversion of glycogen to glusose-1-phosphate. Glyceraldehyde-3-phosphate dehydrogenase (D) is suppressed by an elevation of intracellular lactate (* denotes that the glycolytic pathway has been condensed at this point).

With ischemia, the intracellular concentration of acyl CoA esters increases, in part because the intracellular accumulation of lactate inhibits carnitine palmityl coenzyme A transferase (E), the enzyme that catalyzes the transfer of acyl CoA from the cell cytoplasm to the mitochondria. The acyl CoA esters inhibit the effective exchange of ADP and ATP between the cytoplasm of the cell and the mitochondria by suppressing the activity of adenine nucleotide translocase (F). The antilipolytic agents are effective because they prevent a buildup of acyl CoA esters within the cytoplasm, and l-carnitine exerts a salutary effect on ischemic myocardium by reversing the inhibition of adenine nucleotide translocase, thus allowing continued movement of ADP and ATP between the cell cytoplasm and the mitochondria. (TCA denotes tricarboxylic acid.)

Modified from: Hillis LD, Braunwald E: (Ref. 6)

The increased rate of glycolysis of ischemic muscle is short-lived. The raised lactate level depresses anerobic glycolysis through inhibition of the activity of phosphofructokinase, hexokinase, phophorylase kinase, and glyceraldehyde-3-phosphate dehydrogenase (Figure 2), (22, 23 and reviewed in 6-8). Consequently, the ability of the ischemic heart to utilize the glycolytic pathway is limited.

Furthermore, the high intracellular lactate level inhibits utilization of fatty acids, which are the heart's normal major energy source, and causes an accumulation of them and/or intermediate products due to inhibition of carnitine palmityl CoA transferase (Figure 2).(23) This intracellular accumulation of fatty acids augments myocardial oxygen needs (24,25) and may be important in the genesis of serious arrhythmias. (26)

In addition, transfer of ATP and ADP between the cytosol and mitochondria is inhibited due to competitive inhibition of adenine nucleotide translocase by the increased concentration of fatty acid acyl-CoA esters (Figure 2).(27) Consequently, cytoplasmic ATP concentration is further reduced.(28)

Membrane functions are altered in the ischemic heart.(29) A net loss of potassium and magnesium and a net gain of sodium, chloride, calcium, and water occur which lead to cell swelling which compresses nutrient blood vessels.(30) Loss of integrity of lysosomal membranes with consequent leakage of acid proteases into the cytosol occurs and may be important in causing damage to intracellular proteins and organelles.(31,32)

The rationale for the use of agents that have been proposed to limit infarct size is based on avoiding, reversing, or mitigating one or more of the factors that may adversely affect ischemic heart or one or more of the cellular abnormalities of ischemic heart. I shall have more to say presently about the specific rationales of some of the interventions that have undergone substantial testing.

MEASURING INFARCT SIZE

In order to accurately assess the effect of interventions designed to limit infarct size in either experimentally - induced infarcts or acute MI in man, it is necessary to have methods for quantification of infarct size. Substantial effort has gone into the search for such efforts.

Measuring Infarct Size - A "Gold Standard"

No completely satistory means exists for sizing experimentally-induced MI short of killing the laboratory animal and examining the heart. In making the step from animal to clinical investigation, even more formidable barriers have been encountered in trying to assess the efficacy of limiting infarct size by various manipulations because of the lack of ideal methods for sizing infarctions. While an in depth discussion of estimating infarct size is beyond the scope of my presentation, it is useful to briefly review some of the values and limitations of the major methods for estimating the extent of myocardial necrosis that are currently in use.

Drs. Braunwald and Maroko have suggested (33) that an ideal method for assessing infarct size would be:

1. Safe and noninvasive
2. Simple, easy to apply, and inexpensive.
3. Capable of predicting the extent of necrosis to be expected if no interventions were employed.
4. Capable of assessing the extent of necrosis that actually develops.
5. Capable of providing data on potential and actual infarct size in absolute quantitative terms, e.g. grams of muscle.
6. Useful when applied immediately after the patient's admission.
7. Applicable to all patients with MI.

Note that if criteria number 3 and 4 are fulfilled, the patient could be utilized in an investigation as his own control which greatly simplifies the process of assessing interventions to reduce infarct size. The currently available methods should be compared to this ideal technique.

There are four major ways by which the extent of infarction has been estimated:

1. Hemodynamic evaluation of left ventricular function.
2. Electrocardiographic and vectorcardiographic evaluation of the ST segment and QRS complex.
3. Estimation of the quantity of enzymes released from the heart by measurement of the appearance and disappearance of these enzymes from the serum.
4. Myocardial scintigraphy.

Hemodynamic Evaluation Of Left Ventricular Function

When myocardial infarction is complicated by impairment of the circulation, hemodynamic evaluation of left ventricular function is extremely valuable to stratify patients into different groups and to direct specific therapeutic interventions. Alterations in left ventricular function can be determined by measurement of "left-sided filling pressure" and cardiac output (34-35) which requires placing a catheter in the pulmonary artery. Substantial information regarding left ventricular performance can also be gained with recently developed non-invasive techniques, e.g. radionuclide angiography (36), gated blood

pool scintigraphy (37-39), and echocardiography.(40-42) Even newer developments in gated blood pool scintigraphy with multiple images of the heart during the cardiac cycle instead of a single end-diastolic and end-systolic view (43) and the recent development of two-dimensional echocardiography are apt to add considerably to the noninvasive evaluation of left ventricular function of patients during the acute phase of MI. However, evaluation of ventricular function does not provide a direct quantitative measure of infarct size.

Electrocardiographic And Vectorcardiographic Evaluation Of The ST Segment And QRS Complex

ST-segment elevation as an electrocardiographic sign of obstruction of a coronary artery was first made in 1920.(44) Yet, the electrophysiological basis for this still remains uncertain.(45) After analysis of ST-segments at a number of epicardial sites was found to be useful in assessing myocardial injury in dogs,(46) it was determined that interventions that caused epicardial ST changes produced directionally similar changes at multiple precordial sites.(47) Subsequently, precordial ST-segment mapping techniques have been applied in studying patients. (Reviewed in 48). Use of vectorcardiographic analysis of ST-segments has also been utilized and may be somewhat simpler to interpret although more difficult to obtain, (49) and maybe more useful for inferior MI than precordial mapping. The principal values of ST segment analysis are that the information is available virtually immediately after the patient's admission to the CCU and can be repeated often so that a patient can serve as his own control in investigation designed to test the efficacy of an intervention to reduce myocardial injury. The chief limitations are that: (1) many other coexisting problems also affect the ST segment such as pericarditis, drugs (viz. digitalis and type I antiarrhythmics), electrolyte abnormalities, and interventricular conduction abnormalities, (2) the technique is fairly tedious to perform and interpret, (3) it is less useful for infarctions of the inferior and posterior wall than for the anterior wall, and (4) it does not give an estimate of the amount of infarction in absolute terms. Use of ST segment mapping has stirred up a fair amount of discussion and controversy regarding its clinical utility. (48,50-53) However, it seems that if one does not expect ST-segment mapping to yield absolute quantification of infarct size and recognizes its capacity to yield important, rapidly obtained information in a given patient which can be compared to repeated evaluations in the same patient to estimate the degree of change in myocardial injury, then much of the controversy is resolved.

Dr. David Hillis, who has recently returned to Southwestern from the Peter Bent Brigham Hospital in Boston, recently described with his colleagues at the Brigham an additional means of using the electrocardiogram for estimation of myocardial injury.(54). They determined that early ST-segment elevation in experimentally induced MI predicated subsequent loss of R wave forces and development of Q waves. The QRS changes correlated with development of enzymic (creatine kinase depletion) and histologic evidence for necrosis. While this refinement still does not allow absolute quantification of infarction size with electrocardio-

graphic techniques, it has an additional potential value in that evaluation of how many sites with initial ST-segment elevation eventually progress to QRS changes can be made in treated and untreated patients, as well as being useful in the presence of other abnormalities that affect the ST-segment later in their hospital course.

Estimation Of Depletion Of Creatine Kinase (CK)
From The Heart By Analysis Of Serum CK

The finding in 1954 that SGOT is released into the circulation after MI has had an enormous impact on the diagnosis of MI.(55) Since that time, dozens of enzymes that are present in myocardium and are released into the circulation have been evaluated for their sensitivity and specificity in diagnosing MI. By the early part of this decade, only three, creatine kinase (CK), glutamic oxaloacetic transaminase (SGOT), lactic acid dehydrogenase (LDH), and α-hydroxybutyric acid dehydrogenase [(α-HBD), which is also a measure of LDH, chiefly the two rapidly migrating isoenzymes, of which the heart is rich] were in common use. It was obviously attractive to question if the levels of these enzymes correlated closely with infarct size. In a large number of studies it was found that there was a general, but imprecise, correlation.

Dr. Burton Sobel and his many co-workers determined that the amount of CK depletion from the heart of an animal with an experimental infarct correlated very closely with the amount of the muscle that was infarcted.(56) They further reasoned that the appearance of CK in the serum might have a definable relationship to CK depletion from the heart and proposed a mathematical model relating serum CK to experimental infarct size. The model depicts serum CK activity as a function of myocardial release and first order decay, assuming that the releasing function was an unknown function of time. They considered as parameters the decay rate, the fraction of CK actually released from the necrotic heart, the fraction of body weight in which CK was distributed, and the amount of CK depleted per gram of myocardium. This model was successfully applied to both experimental animals (57) and patients with acute MI.(58)

The major value of this technique is that it appears to give an estimate of infarct size in absolute terms. Some have felt that it is only semi-quantitative (59,155c) and that interventions to reduce infarct size might change some of the above parameters and thereby change the calculated infarct size.(154) The major limitation is that determination of infarct size requires serum CK measurements for 36-48 hours which precludes early intervention to limit MI using the patient as his own control. Additional limitations include [1] the necessity of multiple, frequently-drawn blood samples and the somewhat complicated mathematical handling of the data that make this technique cumbersome to apply in the usual clinical setting, [2] that it is useful only for patients who get to the hospital promptly after MI, and [3] other problems

or complications (viz. liver disease, muscle disease or trauma, strokes, etc.) that lead to elevation of serum CK diminish the usefulness of the technique.

Dr. Sobel and his associates have recently utilized the early rate of appearance of CK in the serum for the first 7 hours after initial CK elevation to predict the eventual serum CK "curve".(60-61) If this observation proves to be true, the major limitation to this technique will be obviated. Modifications of the technique, using the myocardial specific isoenzyme CK-MB (155a) and using a fractional decay rate calculated for each individual patient, may improve accuracy. (155b, 155d).

Scintigraphic Techniques

Scintigraphy with myocardial infarct-avid radionuclides provides a "hot spot" image of the infarct and with radionuclides that are not taken up by ischemic or infarcted heart provides a "cold spot" image. Such graphic representation of the heart obviously provides an attractive possibility for infarct sizing.

"Hot Spot" Imaging"

Several types of radionuclides that are infarct-avid have been utilized for imaging myocardial infarction. Agents that have been used for bone scanning have proved to be particularly useful, especially technecium-labelled phosphates. Most in attendance at this exercise are aware of the pioneering work in this area done here by Drs. Willerson, Parkey, Buja, Bonte and their many associates.(62-63) Myocardial scintigrams with ^{99m}Tc-pyrophosphate (PYP) become positive 12-24 hours after the onset of MI and remain positive for about 5 days, but revert to negative after about one week. Recently PYP scans (64-65) and scanning with ^{99m}Tc-labelled tetracycline (66) have been used to assess infarct size.

The major value of PYP scanning to size MI is its specificity for identifying infarction. The major limitations are that [1] current technology does not have the capability to sufficiently resolve the infarct to allow quantification in absolute terms, [2] the scans cannot be carried out until 12-24 hours after the infarct precluding early intervention to limit ultimate infarct size utilizing the patient as his own control, and [3] uptake of PYP is minimal in areas of extremely reduced blood flow such as the central portion of a large MI.

"Cold Spot Imaging"

Several radionuclides are available for the evaluation of myocardial perfusion. Among the most useful of these are radioactive isotopes of potassium (^{43}K) and the physiological analogues of potassium (^{129}Cs, ^{81}Rb, ^{201}Tl). Thallium-201 is the agent most commonly used currently because it has the most advantageous properties for imaging with a gamma camera. Uptake of these agents is dependent on the perfusion and an intact Na-K ATPase of a given region of heart muscle. Areas of new or old infarction and transient ischemia are visualized as cold spots. Since the normal heart is well visualized, localization of the region of the heart that is under-perfused is facilitated.

Thallium-201 scintigraphy has been employed recently to study patients with acute MI.(67-69) It is somewhat premature to judge the potential for ^{201}Tl scintigraphy in sizing infarcts since the work is at a relatively early state.(70) The major advantage of this technique is that it can be utilized to give almost immediate information within minutes of the patients admission to the hospital. The major disadvantages are that current resolution of the scans is not sufficient to yield an estimate of infarct size in absolute terms and that both old infarcts and transient ischemia as well as new infarct appear as perfusion defects. We have recently demonstrated that serial scintigraphy after a single dose of ^{201}Tl, the repeat scan being done 4-8 hours after the initial one, has the potential of reducing one of these limitations of ^{201}Tl scintigraphy.(69) The repeat scan was invariably smaller than the initial one in patients with uncomplicated MI and more nearly corresponded to the area of PYP deposition and presumably gave a more accurate estimate of the infarcted zone than did the initial scan. Since the reduced thallium defect on the repeat scan probably represents a region that was transiently ischemic, serial scintigraphy after a single dose also appears to have the additional advantage of giving an approximate representation of the amount of ischemic as well as infarcted muscle.

Dual imaging with <u>both</u> ^{201}Tl and PYP (68-69,71-73) is likely to yield a more accurate estimate of infarct size than either imaging technique alone.

Technological improvements in myocardial scintigraphy are in advanced phases of development and have promise for greater resolution of the infarcted area and for three-dimensional representation of the infarct. Among these techniques are <u>emission</u> computed tomography, which utilizes similar computer techniques to computer assisted tomography (CAT scanning) that is used with tissue absorption of x-rays (74-75), and computer processing of two-dimensional views to obtain a three-dimensional representation. (76)

In order to summarize the current status of infarct sizing, I have compared the major techniques currently in use to an ideal technique. (Table III). No single technique currently satisfies all the criteria suggested by Drs. Braunwald and Maroko for an ideal technique and substantial effort is being expended in refining old techniques and searching for new ones.

Table III

VALUE AND LIMITATIONS OF TECHNIQUES UTILIZED
TO ASSESS THE EXTENT OF MYOCARDIAL NECROSIS

FULFILLMENT OF CURRENT METHODS OF CRITERIA FOR AN IDEAL TECHNIQUE*

		Electrocardiographic			Scintigraphic	
Criteria for an Ideal Technique as recommended by Drs. E. Braunwald and P. Maroko	Hemodynamic Evaluation	ST-Segment Analysis	ST-Segment and QRS Analysis	Estimation of CK Depletion from Heart	"Hot Spot"	"Cold Spot"
1. Safe and Noninvasive	0	X	X	X	X	X
2. Simple, inexpensive, and easy to apply	0	X	X	0	X	X
3. Capable of predicting extent of necrosis to be expected if no interventions were employed	0	X	X	?	0	0-?
4. Capable of assessing the extent of necrosis that actually develops	0	0	X	X	X	X
5. Capable of providing data on potential and actual infarct size in absolute terms	0	0	0	X	0	0
6. Useful when applied immediately after the patient's admission	X	X	X	0-?	0	X
7. Applicable to all patients with MI	0	0	0	0	X	0

* X = Yes ? = Possibly 0 = No

LIMITING INFARCT SIZE BY PROTECTING ISCHEMIC MYOCARDIUM

With the foregoing background information in mind, I should like to devote the remainder of the discussion to a brief review of the status of the specific major interventions for limiting infarct size that have been investigated. These interventions can be outlined according to their rationale. (Table IV)

Table IV

Rationale Of Interventions Designed To Limit Infarct Size

Interventions designed to favorably alter the hemodynamic status of the patient.

Interventions designed to limit infarct size by favorably altering the relationship between myocardial oxygen demand and delivery.

Interventions designed to favorably alter the metabolism of ischemic myocardium.

Interventions designed to reduce autolytic (stablilize lysosomal membranes) or heterolytic (modify inflammatory response) processes or both.

Interventions Designed To Limit Infarct Size By Favorably Altering The Hemodynamic Status Of The Patient

Characterization of patients with acute MI with hemodynamic measurements has delineated several distinctive subsets.(34-35) This characterization has been particularly important for patients with hypotension after MI. Management of the patients in each of these subsets is designed to maintain optimal coronary artery perfusion and cardiac output with the least myocardial oxygen demand that is possible. It seems likely that this management may aid in interupting the viscious cycle of hypotension and increasing loss of jeopardized tissue in patients with cardiogenic shock syndromes. Several centers have carefully studied these patients and there seems to be general consensus that a general scheme of management can be recommended. (35,77) (Table V)

Table V

POTENTIALLY USEFUL THERAPEUTIC INTERVENTONS IN PATIENTS AFTER MI BASED ON HEMODYNAMIC CATEGORY

(MODIFIED FROM FORRESTER, ET AL*)

Hemodynamic Category	$\overline{PA}$ (mmHg)	$\overline{PCW}$ (mmHg)	CI ($l/min/m^2$)	Intervention	Comments
1. Normal	≤15	≤12	Normal:3.4±0.6	None	--------
2. Hypotension with normal $\overline{PCW}$ and/or CI	≤15	≤12	Wide Range: <1.5 to 2.5	Repletion of Vascular Volume	Many are volume depleted (e.g. diuretics) or have inappropriate peripheral vasodilation.
3. Left ventricular failure					
a. Mild	≥15	≥18	>2.0<2.5	Diuretics	Dyspnea, mild pulmonary vascular congestion.
b. Severe	≥15	>22	>1.5<2.0	Diuretics	Pulmonary Vascular Congestion and Pulmonary Edema.
				?Vasodilators± Dopamine	See section on Vasodilators.
				?Cardiac Glycosides	With CHF and dilated heart, the net effect of digitalis on $\dot{M}VO_2$ is usually a decrease.
4. Cardiogenic Shock	≥15	≥18	Usually very low, almost invariably <2.0	Dopamine, Norepinephrine ?Vasodilators ?Circulatory assistance and early revascularization	Maintain mean arterial pressure 70-80. Maintain $\overline{PCW}$ 15-18. See section on Vasodilators. See sections on circulatory assistance and early revascularization.

$\overline{PA}$ = mean pulmonary artery pressure

$\overline{PCW}$ = mean pulmonary capillary wedge pressure

CI = cardiac index

* Forrester JS, Chatterjee K, Jobin G: A new conceptual approach to the therapy of acute myocardial infarction. Adv. Cardiol. 15:111, 1975.

Interventions Designed Limit Infarct Size By Favorably Altering The Relationship Between Myocardial Oxygen Demand And Delivery.

Since an increased oxygen demand of the heart and a decreased myocardial perfusion and oxygen delivery appear to increase infarct size, it follows that decreasing the oxygen demand of the heart and improving myocardial perfusion and oxygen delivery might limit the eventual size of an infarction. Many of the interventions that have been investigated or are undergoing investigation or are planned are based on this rationale. Some of these possibilities are outlined in Table VI, and may be divided into interventions that reduce $M\dot{V}O_2$ or improve coronary arterial blood flow and/or oxygen delivery or both of these.

Table VI

INTERVENTIONS DESIGNED TO LIMIT INFARCT SIZE BY FAVORABLY ALTERING THE RELATIONSHIP BETWEEN MYOCARDIAL OXYGEN DEMAND AND DELIVERY

I. Interventions To Reduce $M\dot{V}O_2$

- A. Avoid agents that increase $M\dot{V}O_2$
  1. Isoproterenol and Epinephrine
  2. Digitalis (except in failing heart and with atrial tachyarrhythmias)
  3. Glucagon
  4. Bretylium tosylate (Bretylol^R)
- B. Reduce $M\dot{V}O_2$ - β-adrenergic blockade
- C. Reduce $M\dot{V}O_2$ - Vasodilator therapy to reduce afterload or preload or both
- D. Reduce intracellular free fatty acid levels

II. Interventions That May Improve Coronary Arterial Flow And/Or O_2 Delivery

- A. Directly
  1. Oxygen administration
  2. Improve microcirculation by decreasing cell swelling by increasing the osmolaity e.g. Mannitol, Hypertonic Glucose
  3. Thrombolytic agents
  4. Heparin (?)
  5. Early coronary artery bypass graft surgery
- B. Indirectly through improved flow through collateral vessels
  1. Increased arterial pressure
  2. Hyaluronidase

III. Interventions To Reduce $M\dot{V}O_2$ And Improve Coronary Arterial Flow - Circulatory Assistance

Avoid Agents That Increase $M\dot{V}O_2$

Agents that increase $M\dot{V}O_2$ have been found to have the potential for increasing infarct size. The major drugs that fall into this category include the β-adrenergic agonists, isoproterenol and epinephrine, glucagon, and the antiarrhythmic agent bretylium tosylate, which has recently been cleared for clinical use, and digitalis in the non-failing heart. (Reviewed in 6). Lest the point with digitalis be overemphasized, it must be mentioned that with an enlarged and/or failing heart, or in the presence of atrial tachyarrhythmias, the net effect of digitalis on myocardial oxygen demand is apt to be a decrease, since the increased $M\dot{V}O_2$ occasioned by an increased contractile state is countered by a drop in $M\dot{V}O_2$ due to smaller heart size (LaPlace relationship) or the decreased heart rate. Avoiding use of agents that increase $M\dot{V}O_2$ in the immediate post-MI period is now commonly accepted and presumably has already been of substantial practical value since isoproterenol, epinephrine, and glucagon were commonly used in the past for patients with left ventricular pump failure after MI and digitalis was sometimes used "prophylactically", in the absence of left ventricular failure or atrial tachyarrhythmias.

Reduction of $M\dot{V}O_2$ with β-Adrenergic Blockade

Treatment with β-adrenergic blocking agents appears to have promise in protecting ischemic heart and has received considerable recent investigation.(54,78-92)

These studies have generally, but not universally, (85) shown favorable results. Propranolol has also been reported to decrease the incidence of infarct extension.(93) An additional benefit is that propranolol has antiarrhythmic effects. Whether β-adrenergic blockade favorably or unfavorably influences blood flow to ischemic myocardium is still unclear. (Reviewed in 85).

However, the very mechanisms by which β-adrenergic blockade exerts its affects, slowing the heart rate and reducing myocardial contractility, necessitate that this treatment modality be employed in patients with acute MI with caution and with continual reassessment of the state of the patients' left ventricular function. It cannot be employed in the face of frank left ventricular failure. A national multi-center trial, which includes Parkland Hospital, has just begun testing the efficacy of propranolol in the acute MI period and should provide valuable information on the precise role of β-blockers post-MI. This trial (MILIS) is prospective and randomized and utilizes intravenous propranolol the first two days (0.15mg/kg in three divided doses) and then orally (beginning with averages doses of 160mg/day with gradually diminishing doses) for 10 days. Infarct size (judged by PYP scans, precordial ST and QRS maps, and estimation of CK depletion from heart), mortality, arrhythmias, and other clinical parameters will be assessed in these patients.

Reduction of $M\dot{V}O_2$ by Reducing Afterload or Preload or Both With Vasodilators

A familiar clinical saw is that nitroglycerin and related drugs are contraindicated in the first few days after acute MI. As with most such saws, this one is likely based on both substantial truth and inaccuracy. Indeed, hypotension, a decreased cardiac output, and a reflex

tachycardia or a profound bradycardia may accompany the use of sublingual nitroglycerin in the immediate post-MI period, especially in patients with normal or low filling pressures of the left ventricle. (94-96) However, protection of ischemic myocardium with nitroglycerin and other vasodilators is an attractive hypothesis that has recently and is currently undergoing considerable testing. (94-129) The hypothesis has been proposed in light of the century of experience with nitroglycerin in relieving angina pectoris (chiefly by reducing $M\dot{V}O_2$ by decreasing left ventricular preload) and in view of the large number of recent reports of salutory responses to left ventricular "unloading" in patients in chronic congestive heart failure. (Ventricular unloading was reviewed at these exercises June 30, 1977 by Dr. Jere H. Mitchell). There is some disagreement between the results of these studies which at first appears extremely confusing. These conflicting results may best be understood in the light of two major considerations: [1] different vasodilators may have different hemodynamic effects and effects on the distribution of coronary artery blood flow, and [2] the effect of a vasodilator may depend to a large extent on the patient's systemic blood pressure and the presence and severity of left-sided congestive heart failure.

The chief agents that have been investigated are nitroglycerin and isosorbide dinitrate with or without agents (methoxamine or phenylephrine) to prevent any accompanying hypotension and tachycardia, and intravenous nitroprusside, phentolamine, or trimethaphan. Table VII summarizes the hemodynamic effects of various vasodilator agents used in patients with left ventricular failure complicating acute myocardial infarction.

Table VII

Summary Of Hemodynamic Effects Of Various Vasodilator Drugs Used In Patients With Left Ventricular Failure Complicating Recent Myocardial Infarction

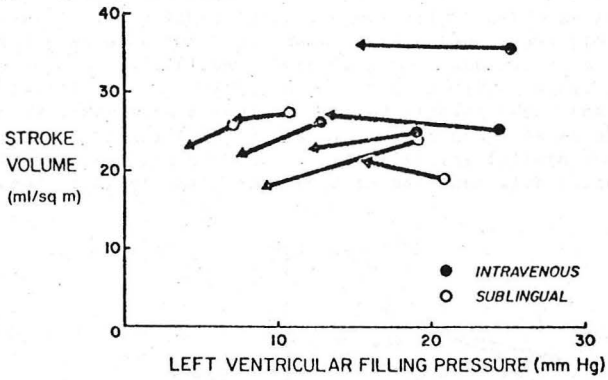
Vasodilator	Heart Rate	Blood Pressure	Cardiac Output	Systemic Vascular Resistance	Pulmonary Capillary Wedge Pressure
Nitroglycerin and Isosorbide dinitrate	No change	Decrease	Slight or no increase	Decrease or no change	Decrease
Nitroprusside	No change	Decrease	Increase	Decrease	Decrease
Phentolamine	Increase	Decrease	Increase	Decrease	Decrease
Trimethaphan	No change	Decrease	Slight or no increase	Decrease or no change	Decrease

Modified from Pamley and Chatterjee. (Ref. No. 97)

Nitroglycerin and Isosorbide Dinitrate

Nitroglycerin administered sublingually or intravenously and isosorbide dinitrate administered sublingually or orally have similar hemodynamic effects in patients post-MI and can be considered together. These agents increase venous capacitance causing a decreased circulating blood volume and hence a decreased left sided filling pressure. They have only a slight effect on arteriolar tone and usually decrease systemic blood pressure only slightly. The decreased preload tends to decrease stroke volume; the decreased afterload tends to raise stroke volume slightly. The net effect on stroke volume is consequently usually negligible. In patients with left ventricular failure there is usually no change or a slight increase in stroke volume; but in the absence of failure, there may be a slight decrease in stroke volume. (Figure 3) (97-98)

FIGURE 3



Effects of intravenous (n = 40) and sublingual (n = 33) nitroglycerin on hemodynamics in patients with acute myocardial infarction. As summarized from the literature, patients were divided as far as possible into those with an initial left ventricular (LV) filling pressure greater than 15 mm Hg and those with an initial LV filling pressure less than 15 mm Hg. Results of each study in those two categories are indicated by the individual lines. It is apparent that the predominant effect of nitroglycerin is to reduce LV filling pressure, and that a reduction in stroke volume tended to occur in patients whose initial LV filling pressure was low.

From Parmley and Chatterjee. (Ref. No. 97)

A reflex tachycardia may occur, especially if left-sided filling pressures are low and the cardiac output falls. Nitrates have no direct inotropic or chronotropic effects on the heart.

It can be predicted then that in patients with left-sided failure, nitrates will lead to a net decrease in myocardial oxygen demand and protection of ischemic myocardium and this has been demonstrated in several studies.(99-105) While some have suggested maintaining blood pressure and blocking reflex tachycardia during nitrate administration with methoxamine or phenylephrine is needed, (100-101, 106) others have reported no difference or a diminution in the beneficial effects of nitrates.(107-108) It seems likely that the differences reported have to do with the nature of the patients studied and that patients with left ventricular failure would benefit more from nitrates alone. (97,101) Nitrates have the additional benefit of protecting against ventricular fibrillation.(127-128)

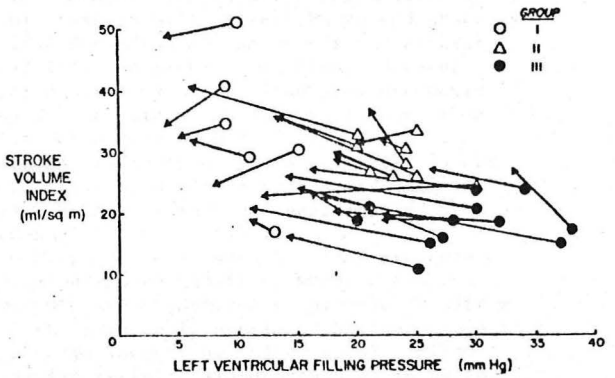
Nitroprusside

The hypotensive effects of nitroprusside have been known for 50 years. It, too, has recently been extensively studied as an agent for left ventricular unloading including patients with acute MI.(97-98,102, 109-113) Nitroprusside, infused intravenously, both increases venous capacitance and decreases arteriolar resistance but has no direct inotropic or chronatropic effect on the heart. Consequently in patients after MI with left ventricular failure there is generally a decrease in left-sided filling pressure, systemic vascular resistance, and blood pressure. Due to the decreased afterload, there is a moderate increase in stroke volume and cardiac output. (Figure 4) As with nitroglycerin, nitroprusside in patients with normal left-sided filling pressures may reduce stroke volume. A reflex tachycardia also often complicates the use of nitroprusside in patients without left ventricular failure, but usually does not occur or is of small magnitude in patients with failure.(112)

FIGURE 4

From

Parmley and Chatterjee (Ref. No. 97)



Effects of nitroprusside on a group of patients with acute myocardial infarction. Group I patients are those with an initial left ventricular (LV) filling pressure of less than 15 mm Hg. Group II patients had a LV filling pressure greater than 15 mm Hg and a stroke work index greater than 20 gm-m/sq m. Group III had a LV filling pressure greater than 15 mm Hg and an initial stroke work index less than 20 gm-m/sq m. All patients in group III had severe power failure and many had the classical signs of cardiogenic shock. Note that in group II and group III patients, the response to nitroprusside was usually an increase in stroke volume together with a reduction in LV filling pressure. In group I patients, however, there was a reduction in stroke volume in some patients, which accompanied the reduction in LV filling pressure.

Consequently, it could be also be expected that the net effect of nitroprusside on ischemic myocardium would also be a protective one due to a decrease in $M\dot{V}O_2$. However, the data with nitroprusside are more controversial than with nitroglycerin. Both good (110) and bad (102) responses on protecting jeopardized heart have been reported.

Part of these apparent differences may also relate to differences in the left-sided filling pressures in the two groups and the poor responses may be seen chiefly in patients without left ventricular failure.

Other explanations must also be considered. Among them is that nitrates and nitroprusside may affect the distribution of blood flow between normal and ischemic heart.(102,109,115-116,122-124,126) A "coronary steal syndrome" has been proposed.(114) The normal coronary arterial bed has substantial capacity for dilatation. The coronary arteries that supply an ischemic myocardial bed are often maximally dilated or nearly so. Consequently, drugs which are potent dilators of the coronary bed may paradoxically decrease flow to ischemic muscle under some conditions, since dilatation of arteries to normal heart reduces the perfusion pressure to the ischemic muscle, and since the arterioles supplying that muscle have little or no further capacity for dilatation. It has been suggested (102) that nitroprusside may decrease coronary blood flow to ischemic muscle and thus explain the deleterious effects seen in some patients. However, changes in regional myocardial metabolism, function, and perfusion due to nitroprusside infusion may also be related to the presence or absence of left-sided heart failure.(109,115-116) It is not possible to draw final conclusions at present on the effects of nitrates and nitroprusside on coronary blood flow to ischemic heart.

Another explanation for the differences that have been reported may relate to the greater hypotensive action of nitroprusside. The optimum pressure to preserve blood flow to ischemic heart after acute MI in man, yet without unduly raising $M\dot{V}O_2$, is not known and probably varies from patient to patient depending on the number and severity of coronary obstructions and left ventricular function. However, it is likely that a substantial drop in systemic blood pressure would lead to a drop in perfusion to ischemic heart that would more than offset the beneficial effects of a reduced $M\dot{V}O_2$.(117)

To resolve these questions, randomized, prospective trials are clearly necessary and are underway both with nitrates (104,118-119) and nitroprusside.(120-121) The latter is a national multi-center trial directed by Dr. Jay Cohn.

Patients with presumed MI who have a systolic blood pressure of 100 mm Hg or greater and mean pulmonary capillary wedge pressure greater than 12 mm Hg of mercury are randomized to placebo or nitroprusside within 48 hours of the pain of infarction. Nitroprusside is given until the wedge pressure is lowered by 40% or until a blood pressure of (76 + 0.2 x baseline systolic blood pressure) mm Hg is

reached (note that this would never be less than 96 mm Hg). Infarct size, mortality, infarct extension, new onset of shock, and the presence of arrhythmias are determined in a 3 month follow-up. They are about one-half the way to their target of 1000 patients. **The preliminary** results of that study to date were presented in part **recently in order** to demonstrate that the trial was safe - an issue called into question by some of the data mentioned earlier. At the date of that report there were no significant differences between treated and control patients with respect to enzyme release from the infarct.(120)

Phentolamine

The hemodynamic responses to intravenous phentolamine in patients with acute MI are very similar to those of nitroprusside. It has α-adrenergic blocking activity, and directly decreases arteriolar and venous tone. In patients with left ventricular failure, there is often a small rise in stroke volume and cardiac output. Unlike nitroprusside, phentolamine often leads to a tachycardia for reasons that are not clear. The tachycardia may be related to a phentolamine-mediated synthesis and release of cardiac norepinephrine.(126,130-131) These positive inotropic and chronotropic effects of phentolamine and its cost (several hundred to over a thousand dollars/day) limit its usefulness as an infarct-limiting agent.

Trimethaphan

Trimethaphan has been used to treat patients with hypertension and acute MI and reported to result in an eventual infarct size (by estimation of CK depletion) less than that initially predicted.(132) This agent led to a significant reduction in arterial pressure and a reduction of left-sided filling pressures in most patients, but cardiac output did not significantly change. Trimethaphan has the advantage of not leading to a reflex tachycardia since it is a ganglionic blocking agent. In most ways, then, the hemodynamic effects of trimethaphan were somewhat similar to those of nitrates in other patients. The efficacy of trimethaphan is limited by [1] a marked dependence on the patient's position (reflex responses to systemic venous pooling are blocked) and [2] the development of tachyphylaxis after several days.

The results of this study support the usual practice of fairly aggressive treatment of marked, sustained hypertension in the post-MI period. As an aside, there are currently no data available regarding treatment of mild hypertension in the post MI period. In dogs with experimental infarction, increasing the arterial blood pressure increases coronary flow which more than offsets the resulting increased $M\dot{V}O_2$. But in men with acute MI, it is unknown whether the result to ischemic muscle from the decreased flow and the decreased $M\dot{V}O_2$ resulting from treating mild elevations in blood pressure would be beneficial or detrimental. Experimentation in this setting would be very valuable.

Reduce Intracellular Free Fatty Acids

Since the increased levels of free fatty acids that occur in ischemic muscle increase $M\dot{V}O_2$ and may increase the incidence of serious arrhythmias (see above), various interventions have been employed to reduce myocardial extraction of fatty acids. Agents that inhibit peripheral lipolysis (133-135), infusions of albumin free of lipids (134), and infusions of glucose-insulin-potassium ("GIK Solution") (see below) have been utilized after MI to try to limit infarct size. The results appear promising, but are too limited to draw any conclusions at this point.

Interventions That May Improve Coronary Arterial Flow And/Or O_2 Delivery Directly

Oxygen Administration

Hardly anything is more ingrained as a clinical reflex than oxygen administration in the CCU. However, since oxygen can be deleterious in some circumstances, its use in the post-MI period has recently been investigated relative to preservation of ischemic heart. The question to be addressed is whether there are any costs to an increased oxygen delivery accomplished by an increased fraction of oxygen in the inspired air. (F_iO_2) The evidence is somewhat conflicting. An increased F_iO_2 was found to decrease measurements of myocardial injury in experimental animals (137) and patients.(138) However, in the absence of initial hypoxia, an increased F_iO_2 increases total systemic vascular resistance which increases $M\dot{V}O_2$ (139-140) and reduces coronary arterial flow in the normal heart. Beneficial effects of hyperbaric oxygen in protecting ischemic heart were found in one study (141) and not found in another.(142)

Improve Microcirculation By Decreasing Cell Swelling By Increasing The Osmolality

Myocardial cell swelling that accompanies infarction may reduce nutrient blood flow by compressing capillaries.(30) Prevention of this swelling by hyperosmotic agents such as mannitol, has been investigated by Dr. Willerson, by Drs. John Powell and Alexander Leaf and their associates. In experimental animals such treatment has been shown to not only increase flow to ischemic muscle but also to improve the function and reduce the oxygen consumption of the ischemic myocardium and to decrease cell necrosis.(143-150) The use of mannitol has been found to be effective before or after coronary occlusion. The mechanism of mannitol's action in this setting is not completely known, but probably is not solely due to decreased cell swelling.

However, in these studies the osmolality was raised about 30-40 mOsm above control values. With such greatly increased serum osmolality, substantial shifts of fluid to the intravascular space occur, consequently carrying some risk to the post-MI patient. At lower, less risky osmolality values, it may not be as effective.(4) Further, the protective effect, even at full doses, may be short-lived, lasting about 1 hour.(150a)

Thrombolytic Agents

Lysis of acute coronary thrombosis is also a somewhat attractive hypothesis, as it was as a means for the treatment of pulmonary embolization.(151) There is not much data available. The results of two clinical trials were negative (152-153), while four patients in a small clinical study may have benefited.(154)

Heparin

Anticoagulants were used for years in treating patients with MI and were effective chiefly in preventing pulmonary embolization due to traditional MI therapy—prolonged bedrest. Recently, use of anticoagulants post-MI has been largely restricted to patients with an unusually great potential for thromboembolic complications.(156) However, it has been proposed recently that heparin in doses that are fully anticoagulating doses or greater may protect ischemic myocardium, perhaps by preventing coagulation in the microvasculature and thereby imporoving flow to ischemic heart.(157-158) The results with very high doses in dogs (157) after experimental MI were more impressive than the results with anticoagulant doses after acute MI in men.(158)

The potential for hemorrhage with heparin is well known. As well, heparin raises circulating free fatty acids so that a role for heparin in limiting infarct size is still very speculative.

Emergency Coronary Artery Bypass Surgery

The ultimate in improving myocardial perfusion and oxygenation would seem to be emergency coronary artery bypass surgery. In experimental animals very early reperfusion (within 3 hours) following transient coronary occlusion was reported in several studies to protect ischemic myocardium. (159-162) When reperfusion was delayed until 5 hours after the first CK elevation, some animals appeared to have lessened necrosis, but in other animals it appeared to extend the infarct.(163) Later reperfusion has been demonstrated to lead to histologic evidence for accelerated necrosis and hemorrhage.(164) Reperfusion after more than 90-120 minutes of coronary artery occlusion in the dog may fail to return substantial flow to the infarcted zone, the so called "no reflow" phenomenon.(165)

Patients usually reach the hospital 4-6 hours after the apparent onset of MI and require another hour or two for the admission and evaluation process so that surgery could rarely be performed earlier than 6-8 hours after the onset of the infarct except for the rare case of infarct occurring in the catheterization lab or coronary care unit. In light of these data from the dog lab, it seems that in the patient with an uncomplicated MI, early bypass surgery is apt to do far more harm than good to the ischemic muscle. The mortality of bypass surgery in men after MI has been better than might have been predicted, but is still prohibitively high compared to the expected in-hospital mortality after MI treated in the usual way.(166-168) Consequently emergency revascularization has been restricted for the most part to certain carefully selected patients with cardiogenic shock and in patients with infarcts occurring under observation and under circumstances allowing almost immediate surgery.(169)

Interventions That May Improve Coronary Arterial Flow—Indirectly Through Improved Flow Through Collateral Vessels

Increased Arterial Pressure

As was pointed out earlier, the "ideal" blood pressure for patients after MI is unknown and likely varies from patient to patient (see section on Vasodilators). Because of the concern that an increased

arterial pressure would do more harm than good, due to a raised $M\dot{V}O_2$ incompletely compensated for by increased coronary arterial flow, it is not customary to raise the blood pressure post-MI in patients who are normotensive.

However, in patients with cardiogenic shock, it is important to maintain perfusion of vital organs and the mean arterial pressure should be maintained at about 70-80 mm Hg. Investigation alluded to earlier has made it clear that pressor agents with a marked β-adrenergic action on the heart should be avoided. The preferred agents are nor-epinephrine (170) and dopamine.(171-172)

Hyaluronidase

Hyaluronidase is an enzyme that catalyzes the hydrolysis of hyaluronic acid, a viscous polysaccharide which is found in the interstices of tissues. It is ordinarily used as an adjuvant to increase the absorption of subcutaneously injected materials. Administration of hyaluronidase intravenously to reduce infarct size was first proposed in 1959.(173a) It has recently undergone testing as a means of protecting ischemic heart. Its mechanism of action in this regard is unknown but has been presumed to be due to penetration of the infarcted and ischemic zones by the enzyme with subsequent depolymerization of mucopolysaccharides. This might then lead to increased nutrient flow to ischemic heart, increased removal of noxious substances, increased collateral blood flow, or direct protective effects on the microvasculature.(173b) Intravenously injected hyaluronidase has been found to reduce ischemic myocardial injury trials with experimental animals (54,173-178) and in two controlled trials with a total of 115 patients who had sustained an acute MI.(179-180)

Administration of hyaluronidase to limit MI has several major advantages: [1] its use is simple, [2] it does not depress left ventricular contractility, and [3] it has a very low toxicity (0.08% incidence of allergic reactions is the only known side effect and these can usually be avoided by performance of a skin test prior to intravenous administration).

A multi-clinic prospective randomized trial of hyaluronidase began August 1 of this year as part of the aforementioned MILIS trial which also includes a trial of propranolol. At entry patients who are candidates for β-adrenergic blockers will be randomized into propranolol, hyaluronidase and placebo groups. Those who are not candidates for propranolol will be a separate subset and will be randomized into hyoluronidase and placebo groups. Follow-up will be as outlined earlier for propranolol.

Interventions To Reduce $M\dot{V}O_2$ And Improve Coronary Arterial Flow - Circulatory Assistance

Circulatory assistance is, in theory, a particularly attractive intervention to limit infarct size since it has been shown in a number of studies in dogs and in patients to [1] reduce myocardial oxygen demand and [2] improve myocardial perfusion. (Reviewed in 169, 181-182).

With intra-aortic balloon pumping a balloon, positioned in the descending thoracic aorta through the femoral artery, is alternately rapidly deflated during systole and inflated during diastole thereby

lowering systolic blood pressure and $M\dot{V}O_2$ and raising diastolic pressure thereby increasing coronary arterial perfusion pressure. With external circulatory assistance, the trunk and extremities (usually just the lower extremities and lower trunk) are enclosed in a rigid box which has an inflatable bag inside it which inflates and deflates in synchrony with the cardiac cycle. While external assistance is less invasive than intra-aortic balloon pumping, it is less hemodynamically effective and is annoying to the patient, who is fairly vigorously rocked about. Furthermore, many patients find the systolic lower body negative pressure quite uncomfortable or intolerable. For these reasons, external circulatory assistance is not in widespread use currently, although data from a cooperative study of 126 patients suggested that this technique lowers the mortality of patients with MI complicated by mild heart failure.(183)

Intraaortic balloon pumping (IABP) is a very invasive procedure and its use has been largely restricted to patients with cardiogenic shock after MI, continued angina pectoris or malignant arrhythmias unrelieved by medication, and for transient support following open-heart surgery. The use of IABP alone in medical patients has been somewhat disappointing. Improvement has generally been only temporary.(184) Consequently, circulatory assistance after MI is currently used chiefly as a means of hemodynamic support until selected patients with cardiogenic shock can undergo coronary arteriography and bypass surgery.(169,181-183)

Interventions Designed To Limit Infarct Size By Favorably Altering The Metabolism Of Ischemic Myocardium

Glucose-Insulin-Potassium (GIK) Solution

Use of glucose-insulin-potassium (GIK) solution as a metabolic support for ischemic myocardium following MI was first proposed by Dr. Sodi-Pallares and his associates 16 years ago.(185-186) But in spite of the several hundred publications that have appeared regarding GIK and the heart (187) since then, the efficacy of this treatment and its mechanism remain controversial. Clinical trials until about 5 years ago lacked comparability and had substantial flaws in experimental design.(187-188) Consequently, it was hard to draw any firm conclusions regarding the efficacy of GIK on infarct size, mortality and arrhythmias in patients with MI.

If the disputable assumption that GIK can reach the necrotic and peri-infarction zones of heart after MI is accepted, there are a number of possible mechanisms that can be invoked for a beneficial effect on ischemic muscle. Among the major possibilities are:

1. Facilitation of glucose transport across ischemic myocardial cell membranes,
2. Lowering of serum concentration of free fatty acids,
3. Beneficial effects of a hyperosmolar solution on ischemic myocardium, and
4. Stabilization of resting cell membrane potentials in ischemic myocardium.

Investigation has provided some support for GIK-mediated facilitation of glucose transport in anoxic (189) and ischemic (190,191) heart, for lowering of serum free fatty acid levels below the threshold for myocardial

uptake (192), and for stabilization of resting cell membrane potentials during acute ischemia.(193) However, GIK as given by one group with reported success for patients with acute MI does not significantly increase serum osmolality.(192)

In the last few years, the potential role for GIK post-MI has been re-investigated in more comparable and better designed studies. GIK administered to dogs beginning 30 minutes after coronary occlusion reduced the eventual extent of necrosis (194) and ECG evidence for myocardial injury.(191) A comparison of 70 consecutive patients with acute MI treated with GIK had a lower mortality than 64 apparently comparable patients managed in the same CCU (Myocardial Infarction Research Unit of the University of Alabama Medical Center) during the previous year.(192) With these results, the same group have begun employing GIK in a prospective blinded, randomized fashion.(195) To date 50 patients have been randomized. GIK was begun within 12 hours of the pain of MI and continued for 48 hours. No differences were found in CK-estimated (155d) infarct size, but there were no deaths in the GIK group. The GIK group also had significantly less serious ventricular ectopic activity and significantly better left ventricular function. That study is being continued at that center.

In contrast, the group at the University of Auckland, New Zealand studied 36 patients within 12 hours of infarct and also found improved hemodynamic function but no difference in CK-estimated (155d) infarct size and more mortality in the GIK group. In view of this, they felt that they could not ethically justify continuation of their study.

There is a major difference between the two studies, however. Patients in New Zealand were given more glucose and had increased left-sided filling pressures, heart rate, cardiac index, and blood pressure. The resulting increase in $M\dot{V}O_2$ might have negated any protective metabolic effect of GIK. The Alabama group gave GIK in a manner such that $M\dot{V}O_2$ was not increased.

An infusion of GIK post-MI has relatively little risk. Hyperglycemia or hyperkalemis may occur, especially in patients with diabetes and/or renal disease.(192) Rare pulmonary consolidation of uncertain etiology (?chemical pneumonitis or GIK-induced in situ pulmonary thrombosis) has been reported.(197) A minor limitation is that ST segment analysis and thallium scintigraphy are of limited value in assessing the protective effect of GIK because of the membrane-altering effects of GIK.

A role for GIK in protecting ischemic heart seems possible, but substantial further work appears necessary before it can be recommended for general use.

Inhibition Of Myocardial Extraction Of Fatty Acids

(See Previous Sections)

Carnitine

Infusion of carnitine in order to maintain levels of free carnitine in ischemic heart, thereby reversing the inhibition of adenine nucleotide translocase by long chain acyl CoA esters and restoring mitochondrial function, has been tested in dogs with acute coronary artery ligation with encouraging results judged by ST-segment elevation and tissue concentration of high energy phosphates.(198)

Interventions Designed To Limit Infarct Size By Reducing Autolytic or Heterolytic Processes Or Both

Corticosteroids

Release of lysosomal proteases into the cystosol occurs in ischemic muscle (31,32) and might contribute to myocardial damage as might heterolytic processes occurring with the inflammatory response to MI. Corticosteroids may protect ischemic myocardium due to their well known stabilizing effect on lysosomal membranes (31,199-200), although this effect may be only to delay rather than to prevent lysosomal disruption.(201)

The first use of corticosteroids in experimental myocardial infarction was reported in 1951 by Johnson and his associates (and published in 1953, ref 202). Several other groups reported their findings almost simultaneously and from that beginning and ever since, the results have been conflicting and controversial. Large numbers of studies in experimental animals and in patients have been published with remarkably divergent results. Part of the problem no doubt lies in the considerable differences in study design, drug dose, and lack, until recently, of sensitive means to detect changes in myocardial injury. Another problem is that most animal studies were not continued beyond 24 hours after the infarct. However, recent results with patients continue to be confusing. Positive results on mortality (203) and infarct size (204) were reported in two relatively large, non-randomized controlled trials. But other recent trials have demonstrated no change in mortality or infarct size (205) and a deleterious effect on infarct size.(206) The latter study (206) also found more serious ventricular arrhythymias in the steroid group.

Since corticosteroids administered chronically delay the healing process after MI (207-208) and thereby enhance the risk of myocardial rupture or aneurysm formation (208), administration of these drugs after MI may carry significant risk. Vogel and Lucchesi recently editorialized that given the potential risk and lack of convincing evidence of efficacy, another large clinical trial with steroids and the size of infarcts was not warranted.(209) However, such a trial, supported by the Upjohn Co., is underway, but utilizes only two 30mg/kg doses of methylprednisolone, the first given within 12 hours of the onset of MI and the second 3 hours later. It is the hope of the designers of that study to avoid a delay in the healing phase by utilizing only acute steroid administration. The accession rate in that study has been slow and no results are currently available.(210)

Other Anti-inflammatory Interventions

Myocardial injury has also been decreased post-MI in experimental animal models with administration of other agents that modify the inflammatory process: [1] cobra venom factor (a protein that leads to depletion of C3 and C5, thereby preventing some of the chemotaxtic and leukotaxtic effects of the complement system)(211), [2] aprotinin (an inhibitor of the kallikrein system) (212), and [3] ibuprofen, a non-steroidal anti-inflammatory drug.(213)

CONCLUSIONS

Summary Of The Current Status Of The Major Interventions Which Have Been Proposed To Limit Infarct Size

Of the interventions which have been proposed to limit infarct size, eight have received enough animal and human investigation to allow an interim assessment of the efficacy, safety, ease of application, and applicability to patients with acute MI. My admittedly arbitrary assessments are listed in Table VIII.

None of these interventions are ready to be performed as a matter of routine in the coronary care unit. The results of the clinical trials that are underway should provide answers about the role of hyaluronidase, β-adrenergic blockers, and vasodilators and perhaps about GIK and corticosteroids in the next few years.

What Have We Learned That Should Be Brought To Bear In Routine Care For Patients With Acute MI?

These hundreds of investigations have demonstrated some facts that can be utilized now in the routine CCU care of patients in the first few days after MI. In many cases, the soundness of prior common sense clinical judgment has been confirmed, but some former practices have been found unsound.

In order to prevent undue increases in $M\dot{V}O_2$, patients should be treated with quietude, reassurance, and (when necessary) sedation. Pain should be promptly relieved by opiate analgesics. Prophylactic use of cardiac glycosides in the absence of heart failure or cardiac enlargement or atrial tachyarrhythmias should be avoided. However, in the presence of these complications, the net effect of cardiac glycosides is often a decrease in $M\dot{V}O_2$. Mild heart failure should be managed with diuretics alone unless the patient is already hypovolemic. Later in the course of the MI, when infarct size is fixed, utilization of cardiac glycosides is often necessary and appropriate. Isoproterenol, epinephrine, and glucagon should be avoided. When it is necessary to increase the blood pressure, dopamine or norepinephrine are the drugs of choice. The mean arterial pressure should be raised to about 70-80 mm Hg. Rapid arrhythmias should be promptly treated but bretylium tosylate should be avoided in the first few days after MI. Profound (diastolic > 120mm) and sustained (>2 hours after admission) hypertension should be treated. Care should be taken to avoid precipitous drops in blood pressure and a decrease in blood pressure > 25-30 mm from the patient's usual level should be avoided, however. If the blood pressure is to be treated emergently, trimethaphan is the drug of choice over nitroprusside.

If a patient who has been taking propranolol is admitted with an MI, propranolol should be continued unless there is evidence for congestive failure. If the failure is mild, propranolol should be tapered over a 2-3 day period. If the failure is more marked, propranolol should be discontinued immediately.

If the patient is hypoxemic, he should be given oxygen by nasal prongs or by mask to assure satisfactory arterial O_2 saturation. While it is customary to give normoxemic patients O_2 administration, I think we should

keep an open mind about that custom - it may not help and it may harm.

If a patient who has been taking nitrates is admitted with MI, nitrates should be used with caution or not at all for the first few days unless it is clear that left-sided filling pressure is elevated or unless monitoring of the left-sided filling pressure is to be carried out.

Table VIII

SUMMARY OF THE CURRENT STATUS OF THE EIGHT INTERVENTIONS THAT HAVE BEEN PROPOSED TO LIMIT INFARCT SIZE THAT HAVE RECEIVED SUBSTANTIAL ANIMAL AND HUMAN INVESTIGATION

Intervention	Evidence for Efficacy	Safety	Ease of Application	Applicable to all Patients?	Large Clinical Trial Planned or Ongoing?	Comments
Hyaluronidase	+++	+++	+++	Yes	Yes (MILIS)	----------
Propranolol	+++	++	+++	No	Yes (MILIS)	Contraindicated in patients with CHF. Requires constant watch for insidious CHF.
Vasodilator (Nitrates and Nitroprusside)	+++	++	++	No	Yes (VA Co-op, nitroprusside)	Only for patients with increased PCW. Requires Swan-Ganz catheter.
GIK	++	++	++	Yes	No	Requires central venous line and frequent serum $[K^+]$ and glucose determinations.
Glucocorticoid	++	+ - ++	+++	Yes	Yes (?)	Delayed infarct healing clouds its use. Slow accession rate in clinica trial.
Mannitol	++	++	+++	No	No	Must watch for intravascular fluid overload. Probably best used as temporary support while planning for other interventions.
IABP	++	+	+	No	No	Generally restricted to patients with cardiogenic shock in whom surgery is contemplated.
Emergency CABG Surgery	+	+	0	No	No	Only for selected patients with cardiogenic shock.

Legend
+++ Substantial
++ Moderate
+ Slight
0 None

GIK = Glucose-insulin-potassium
PCW = Mean Pulmonary capillary wedge pressure
CABG = Coronary artery bypass surgery
CHF = Congestive heart failure
IABP = Intra-Aortic Balloon Pump

REFERENCES

1. Harnarayan C, Bennett MA, Pentecost BL, Brewer DB: Quantitative study of infarcted myocardium in cardiogenic shock. Br Heart J 32:728-732, 1970.
2. Page DL, Caulfield JB, Kastor JA, Desanctis RW, Sanders CA: Myocardial changes associated with cardiogenic shock. N Engl Med J 285:133-137, 1971.
3. Cox JR Jr, Roberts R, Ambos HD, Oliver C, Sobel BE: Relations between enzymatically estimated myocardial infarct size and early ventricular dysrhythmia. Circulation 53(Suppl I):I-150-I-155, 1976.
4. Braunwald E: Protection of the ischemic myocardium. Introductory remarks. Circulation 53(Suppl I):I-1-I-2, 1976.
5. Tennant R, Wiggers CJ: The effect of coronary occlusion on myocardial contraction. Am J Physiol 112:351-361, 1935.
6. Hillis LD, Braunwald E: Myocardial ischemia. N Engl Med J 296:971-978, 1034-1041, 1093-1096, 1977.
7. Schlant RC: Metabolism of the heart, in The Heart (Hurst JW and Logue RB, eds.) Chap 9. Second edition. McGraw-Hill, New York. 1970.
8. Scheuer J, Penpargkul S: Myocardial Metabolism, in Clinical Cardiology (Willerson JT, Sanders CA, eds.) Grune and Stratton, New York, 1977.
9. Tennant R: Factors concerned in the arrest of contraction in an ischemic myocardial area. Am J Physiol 113:677-682, 1935.
10. Katz AM, Hecht HH: The early "pump" failure of the ischemic heart. Am J Med 47:497-502, 1969.
11. Poole-Wilson PA: Is the early decline of cardiac function in ischaemia due to carbon dioxide retention? Lancet 2:1285-1287, 1975.
12. Steenbergen C, Deleeuw WG, Rich T, Williamson JR: Effects of acidosis and ischemia on contractility and intracellular pH of rat heart. Circ Res 41:849-858, 1977.
13. Tsien RW: Possible effects of hydrogen ions in ischemic myocardium. Circulation 53(Suppl I):I-14-I-16, 1976.
14. Nakamura Y, Schwartz A: The influence of hydrogen ion concentration on calcium binding and release by skeletal muscle sarcoplasmic reticulum. J Gen Physiol 59:22-31, 1972.
15. Williamson JR, Safer B, Rich T, Schaffer S: Effects of acidosis on myocardial contractility and metabolism. In Experimental and Clinical Aspects On Preservation Of The Ischemic Myocardium (Hjalmarson A, Werko L, ed.) pp 35-42, Sweden, Molndal, 1976.
16. Fuchs F: Chemical properties of the calcium receptor site of troponin as determined from binding studies. In Calcium Binding Proteins (Drabikowski W, Strzelecka-Golaszewska H, Carafoli E, eds) pp 1-27. Elsevier, Amsterdam, 1974.
17. Stuhl JT, Buss JE: Calcium binding properties of beef cardiac troponin. J Biol Chem (in press).

18. Schädler MH: Proportionale Aktivierung Von ATPase - Aktivitat und Kontrakions - spannung durch Calciumionen in isolierten contractilen Strukturen verscheidener Muskelarten. **Pflügers** Arch ges Physiol 296:70-90, 1967.
19. Williams GJ, Collins S, Muir JR, Stephens MR: Observations on the interaction of calcium and hydrogen ions on ATP hydrolysis by the contractile elements of cardiac muscle. In Recent Advances in Studies on Cardiac Structure and Metabolism, Vol 5, pp 273-280. (Fleckenstein A, Dhalla NS, ed). University Park Press, Baltimore, 1975.
20. Kentish J, Nayler WG: Effect of pH on the Ca^{2+}-dependent ATPase of rabbit cardiac and white skeletal myofibrils. J Physiol 265: 18-19P, 1977.
21. Poole-Wilson PA: Measurement of myocardial intracellular pH in pathological states. J Mol Cell Cardiol 10:511-526, 1978.
22. Neely JR, Whitmer JT, Rovetto MJ: Effect of coronary blood flow on glycolytic flux and intracellular pH in isolated rat hearts. Circ Res 37:733-741, 1975.
23. Rovetto MJ, Lamberton WF, Neely JR: Mechanisms of glycolytic inhibition in ischemic rat hearts. Circ Res 37:742-751, 1975.
24. Wood JM, Sordahl LA, Lewis RM, Schwartz A: Effect of chronic myocardial ischemia on the activity of carnitine palmityl coenzyme A transferase of isolated canine heart mitochondria. Circ Res 32:340-347, 1973.
25. Mjøs OD, Kjekjus JR, Lekven J: Importance of free fatty acids as a determinant of myocardial oxygen consumption and myocardial ischemic injury during norepinephrine infusion in dogs. J Clin Invest 53:1290-1299, 1974.
26. Kjerjus JK, Mjøs OD: Effect of free fatty acids on myocardial function and metabolism in the ischemic dog heart. J Clin Invest 51:1767-1776, 1972.
27. Shrago E, Shug A, Elson C, Spennetta T, Crosby C: Regulation of metabolite transport in rat and guinea pig liver mitochondria by long chain fatty acyl coenzyme A esters. J Biol Chem 249:5269-5274, 1974.
28. McLean P, Gumaa KA, Greenbaum AL: Long chain acyl CoAs, adenine nucleotide translocase and the coordination of the redox states of the cytosolic and mitochondrial compartment. FEBS Lett 17:345-350, 1971.
29. Schwartz A, Wood JM, Allen JC, Bornet EP, Entman MK, Goldstein MA, Sordahl LA, Suzuki M, Lewis RM: Biochemical and morphologic correlates of cardiac ischemia. I.Membrane systems. Am J Cardiol 32:46-61, 1973.
30. Leaf A: Cell swelling: a factor in ischemic tissue injury. Circulation 48:455-458, 1973.
31. Hoffstein S, Weissman G, Fox AC: Lysosomes in myocardial infarction. Studies by means of cytochemistry and subcellular fractionation, with observations on the effects of methylprednisolone. Circulation 53(Suppl I):I-34-I-41, 1976.

32. Decker RS, Poole AR, Griffin EE, Dingle JT, Wildenthal K: Altered distribution of lysosomal cathepsin D in ischemic myocardium. J Clin Invest 59:911-921, 1977.
33. Braunwald E, Maroko PR: Limitation of infarct size. Current Problems In Cardiology 3:1-51, 1978.
34. Scheidt S, Ascheim R, Killip T: Shock after acute myocardial infarction. Am J Cardiol 26:556-564, 1970.
35. Swan HJC, Forrester JS, Diamond G, Chatterjee K, Parmley WW: Hemodynamic spectrum of myocardial infarction and cardiogenic shock: A conceptual model. Circulation 45:1097-1110, 1972.
36. Kostuk WJ, Ehsami A, Karliner JS, Ashburn WL, Peterson KL, Ross J Jr, Sobel BE: Left ventricular performance after myocardial infarction assessed by radioisotope angiography. Circulation 47:242-249, 1973.
37. Rigo P, Murray M, Strauss HW, Taylor D, Kelly D, Weisfeldt M, Pitt B: Left ventricular function in acute myocardial infarction evaluated by gated scintophotography. Circulation 50:678-684, 1974.
38. Schelbert HR, Henning H, Ashburn WL, Verba JW, Karliner JS, O'Rourke RA: Serial, non-invasive measurement of the left ventricular ejection fraction early and late after myocardial infarction. Am J Cardiol 38:407-415, 1976.
39. Pulido JI, Doss J, Twieg D, Blomqvist CG, Falkner D, Horn V, DeBates D, Tobey M, Parkey RW, Willerson JT: Submaximal exercise testing after acute myocardial infarction: myocardial scintigraphic and electrocardiographic observations. Am J Cardiol 42:19-28, 1978.
40. Corya BC, Rassmussen S, Knobel SB, Feigenbaum H: Echocardiography in acute myocardial infarction. Am J Cardiol 36:1-10, 1975.
41. Kerber RF, Abboud FM: Echocardiographic detection of regional myocardial infarction - an experimental study. Circulation 47: 997-1005, 1973.
42. Nixon JV, Blomqvist CG, Willerson JT: Serial echocardiography in patients with acute myocardial infarction: Its value and prognostic significance. European J Cardiol (in press).
43. Borer JS, Bachrach SL, Green MV, Kent KM, Epstein SE, Johnston GS: Real-time radionuclide cineangiography in the noninvasive evaluation of global and regional left ventricular function at rest and during exercise in patients with coronary-artery disease. N Engl J Med 296:839-844, 1977.
44. Pardee HEB: An electrocardiographic sign of coronary artery obstruction. Arch Intern Med 26:244-257, 1920.
45. Ross J Jr: Electrocardiographic ST segment analysis in the characterization of myocardial ischemia and infarction. Circulation 53(Suppl I):I-73-I-81, 1976.
46. Maroko PR, Kjekshus JK, Sobel BE, Watanabe T, Covell JW, Ross J Jr, Braunwald E: Factors influencing infarct size following coronary artery occlusions. Circulation 43:67-82, 1971.
47. Mueller JE, Maroko PR, Braunwald E: Precordial electrocardiographic mapping: A technique to assess the efficacy of interventions to limit infarct size. Circulation 57:1-18, 1978.

48. Braunwald E: ST segment mapping realistic and unrealistic expectations. Circulation 54:529-532, 1976.
49. Akiyama T, Hodges M, Biddle TL, Zawrotny B, Van Gellow C: Measurement of S-T segment elevation in acute myocardial infarction in man. Comparison of a precordial mapping technique and the Frank Vector System. Am J Cardiol 36: 155-162, 1975.
50. Fozzard HA, DasGupta DS: ST-segment potentials and mapping: theory and experiments. Circulation 54:523-537, 1976.
51. Madias JE, Hood WB: Value and limitations of precordial ST-segment mapping. Arch Int Med 138:529-530, 1978.
52. Holland RP, Brooks H: TQ-ST segment mapping: Critical review and analysis of current concepts. Am J Cardiol 40:110-129,1977.
53. Surawicz B: The disputed S-T segment mapping: Is the technique ready for wide application in practice? Am J Cardiol 40:137-140, 1977.
54. Hillis LD, Askenazi J, Braunwald E, Radvany P, Muller JE, Fishbein MC, Maroko PR: Use of changes in the epicardial QRS complex to assess interventions which modify the extent of myocardial necrosis following coronary artery occlusion. Circulation 54:591-598, 1976.
55. LaDue JS, Wroblewski F, Karmen A: Serum glutamic oxaloacetic transaminase activity in human acute myocardial infarction. Science 120:497-499, 1954.
56. Kjekshus JK, Sobel BE: Depressed myocardial creatine phosphokinase activity following experimental myocardial infarction in the rabbit. Circ Res 27:403-414, 1970.
57. Shell WE, Kjekshus JK, Sobel BE: Quantitative assessment of the extent of myocardial infarction in the conscious dog by means of analysis of serial changes in serum creatine phosphokinase activity. J Clin Invest 50:2614-2625, 1971.
58. Sobel BE, Bresnahan GF, Shell WE, Yoder RD: Estimation of infarct size in man and its relation to prognosis. Circulation 46:640-648, 1972.
59. Roe CR, Starmer CF: A sensitivity analysis of enzymatic estimation of infarct size. Circulation 52:1-5, 1975.
60. Shell WE, Lavell JF, Covell JW, Sobel BE: Early estimation of myocardial damage in conscious dogs and patients with evolving acute myocardial infarction. J Clin Invest 52:2579-2590,1973.
61. Roberts R, Henry PD, Sobel BE: An improved basis for enzymatic estimation of infarct size. Circulation 52:743-754, 1975.
62. Bonte FJ, Parkey RW, Graham KD, Moore J, Stokely EM: A new method for radionuclide imaging of myocardial infarcts. Radiology 110: 473-474, 1974.
63. Parkey RW, Bonte FJ, Meyer SL, Atkins JM, Curry GC, Willerson JT: A new method for radionuclide imaging of acute myocardial infarction in humans. Circulation 50:540-546, 1974.
64. Stokely EM, Buja LM, Lewis SE, Parkey RW, Bonte FJ, Harris RA Jr, Willerson JT: Measurement of acute myocardial infarcts in dogs with ^{99m}Tc-stannous pyrophosphate scintigrams. J Nucl Med 17: 1-5, 1976.

65. Botvinik EH, Shames D, Lappin H, Tyberg JV, Townsend R, Parmley WW: Noninvasive quantitation of myocardial infarction with technetium 99m pyrophosphate. Circulation 52:909-915, 1975.
66. Holman BL, Lesch M, Zweiman FG, Temte J, Lown B, Gorlin R: Detection and sizing of acute myocardial infarcts with ^{99m}Tc (Sn) tetracycline. N Engl J Med 291:159-163, 1974.
67. Wackers FJT, Sokole EB, Samson G, van der Schoot JB, Lie KI, Liem KL, Wellens HJJ: Value and limitations of thallium-201 scintigraphy in the acute phase of myocardial infarction. N Engl J Med 295:1-5, 1976.
68. Parkey RW, Bonte FJ, Stokely EM, Lewis SE, Graham KD, Buja LM, Willerson JT: Acute myocardial infarction imaged with technetium-99m stannous pyrophosphate and thallium-201: A clinical evaluation. J Nucl Med 17:771-779, 1976.
69. Smitherman TC, Osborn RC Jr, Narahara KA: Serial myocardial scintigraphy after a single dose of thallium-201 in men following acute myocardial infarction. Am J Cardiol 42:177-182, 1978.
70. Wackers FJT, Becker AE, Samison G, Sokole EB, van der Shoot JB, Vet A JTM, Lie KI, Durrer D, Wellens H: Location and size of acute transmural myocardial infarction estimated from thallium-201 scintiscans. Circulation 56:72-78, 1977.
71. Zaret BL, DiCola VC, Donabedian RK, Puri S, Wolfson S, Freedman GS, Cohen LS: Dual radionuclide study of myocardial infarction: Relationships between myocardial uptake of potassium-43, technetium-99m stannous pyrophosphate, regional myocardial blood flow and creatine phosphokinase depletion. Circulation 53:422-428, 1976.
72. Henning H, Shelbert HR, Righetti A, Ashburn W, O'Rourke R: Dual myocardial imaging with technetium-99m pyrophosphate and thallium-201 for detecting, localizing, and sizing myocardial infarction. Am J Cardiol 40:147-155, 1977.
73. Berger HJ, Gottschalk A, Zaret BL: Dual radionuclide study of acute myocardial infarction: Comparison of thallium-201 and technetium-99m stannous pyrophosphate imaging in man. Ann Intern Med 88:145-154, 1978.
74. Keyes JW Jr, Leonard PF, Brody SF, Svetkoff DJ, Rogers WL, Lucchesi BR: Myocardial infarct quantification in the dog by single photon emission computed tomography. Circulation 58: 227-232, 1978.
75. Weiss ES, Hoffman EJ, Phelps ME, Welch MJ, Ter-Pogossian MM, Sobel BE: External detection of altered metabolism of ^{11}C-labelled substrates in ischemic myocardium. Clin Res 23:383A, 1975. (abstr)
76. Lewis M, Buja LM, Saffer S, Mishelevich D, Stokely E, Lewis S, Parkey R, Bonte F, Willerson J: Experimental infarct sizing using computer processing and a three-dimensional model. Science 197:167-169, 1977.

77. Forrester JS, Chatterjee K, Jobin G: A new conceptual approach to the therapy of acute myocardial infarction. Adv Cardiol 15:111-123, 1975.
78. Maroko PR, Libby P, Covell JW, Sobel BE, Ross J Jr, Braunwald E: Precordial S-T segment elevation mapping: an atraumatic method for assessing alterations in the extent of myocardial ischemic injury. Am J Cardiol 29:223-230, 1972.
79. Pelides LJ, Reid DS, Thomas M, Shillingford JP: Inhibition by β-blockade of the ST segment elevation after acute myocardial infarction in man. Cardiovasc Res 6:295-301, 1972.
80. Reimer KA, Rassmussen MM, Jennings RB: Reduction by propranolol of myocardial necrosis following temporary coronary artery occlusion in dogs. Circ Res 33:353-363, 1973.
81. Libby P, Maroko PR, Covell JW, Malloch CI, Ross J Jr., Braunwald E: Effect of practolol on the extent of myocardial ischemic injury after experimental coronary occlusion and its effects on ventricular function in the normal and ischemic heart. Cardiovasc Res 7:167-173, 1973.
82. Mueller HS, Ayres SM, Religa A, Evans, RG: Propranolol in the treatment of acute myocardial infarction: effect on myocardial oxygenation and hemodynamics. Circulation 49:1078-1087, 1974.
83. Waagstein F, Hjalmarson AC: Double-blind study of the effect of cardioselective beta-blockade on chest pain in acute myocardial infarction. In Experimental and Clinical Aspects on Preservation of the Ischemic Myocardium. (Hjalmarson A, Werko L, ed) pp 201-202, Sweden, Molndal, 1976.
84. Gold HK, Leinbach RC, Maroko PR: Propranolol-induced reduction of signs of ischemic injury during acute myocardial infarction. Am J Cardiol 38:689-695, 1976.
85. Peter T, Norris RM, Heng MK, Singh BN, Clarke ED: Reduction of creatine kinase release after acute myocardial infarction by propranolol. Circulation 56(Suppl III):III-64, 1977 (abstr).
86. Rasmussen MM, Reimer KA, Kloner RA, Jennings RB: Infarct size reduction by propranolol before and after coronary ligation in dogs. Circulation 56:794-798, 1977.
87. Baroldi C, Silver MD, Lixfeld W, McGregor DC: Irreversible myocardial damage resembling catecholamine necrosis secondary to acute coronary occlusion in dogs: Its prevention by propranolol. J Mol Cell Cardiol 9:687-691, 1977.
88. Vatner S, Baig H, Manders WT, Ochs H, Pagani M: Effects of propranolol on regional myocardial function, electrograms, and blood flow in conscious dogs with myocardial ischemia. J Clin Invest 60:353-360, 1977.
89. Vatner SF, Baig H, Manders WT, Murray PA: Effects of a cardiac glycoside in combination with propranolol on the ischemic heart of conscious dogs. Circulation 57:568-575, 1978.
90. Kloner RA, Fishbein MC, Cotran RS, Braunwald E, Maroko PR: The effect of propranolol on microvascular injury in acute myocardial ischemia. Circulation 55:872-880, 1977.
91. Hillis D, Khuri S, Kloner R, Tow D, Barsamian E, Maroko P, Braunwald E: Direct evidence for the beneficial effect of propranolol on myocardial ischemia following coronary artery occlusion. Am J Cardiol 41:359, 1978 (Abstr).

92. Tomoike H, Ross J Jr, Franklin D, Crozatier B, McKown D, Kemper WS: Improvement by propranolol of regional myocardial dysfunction and abnormal coronary flow pattern in conscious dogs with coronary narrowing. Am J Cardiol 41:689-696, 1978.
93. Pitt B, Weiss JL, Schulze RA, Taylor DR, Kennedy HL, Caralis D: Reduction of myocardial infarct extension in man by propranolol. Circulation 54(Suppl II):II-29, 1976 (abstr).
94. Epstein SE, Borer JS, Kent KM, Redwood DR, Goldstein RE, Levitt B: Protection of ischemic myocardium by nitroglycerin: experimental and clinical results. Circulation 53(Suppl I):I-191-I-197, 1976.
95. Williams DO, Amsterdam EA, Mason DT: Hemodynamic effects of nitroglycerin in acute myocardial infarction. Circulation 51:421-427, 1975.
96. Come PC, Pitt B: Nitroglycerin-induced severe hypotension and bradycardia in patients with acute myocardial infarction. Circulation 54:624-628, 1976.
97. Parmley WW, Chatterjee K: Vasodilator therapy. Current Problems in Cardiology 2:8-75, 1978.
98. Chatterjee K, Parmley WW, Ganz W, Forrester J, Walinsky P, Crexells C, Swan HJC: Hemodynamic and metabolic responses to vasodilator therapy in acute myocardial infarction. Circulation 48:1183-1193, 1973.
99. Smith ER, Redwood DR, McCarron WE, Epstein SE: Coronary artery occlusion in the conscious dog: effects of alterations in arterial pressure produced by nitroglycerin, hemorrhage, and alpha-adrenergic agonists on the degree of myocardial ischemia. Circulation 47:51-57, 1973.
100. Myers RW, Scherer JL, Goldstein RA, Goldstein RE, Kent KM, Epstein SE: Effects of nitroglycerin and nitroglycerin-methoxamine during acute myocardial ischemia in dogs with pre-existing multivessel coronary occlusive disease. Circulation 51:632-640, 1975.
101. Borer JS, Redwood DR, Levitt B, Cagin N, Bianchi C, Vallin H, Epstein SE: Reduction in myocardial ischemia with nitroglycerin or nitroglycerin plus phenylephrine administered during acute myocardial infarction. N Engl J Med 293:1008-1012, 1975.
102. Chiariello M, Gold HK, Leinbach RC, Davis MA, Maroko PR: Comparison between the effects of nitroprusside and nitroglycerin on ischemic injury during acute myocardial infarction. Circulation 54:766-773, 1976.
103. Epstein SE, Kent KM, Goldstein RE, Borer JS, Redwood DR: Reduction of ischemic injury by nitroglycerin during acute myocardial infarction. N Engl J Med 292:29-35, 1975.
104. Derrida JP, Sal R, Chiche P: Nitroglycerin infusion in acute myocardial infarction. N Engl J Med 297:336, 1977.
105. Awan NA, Amsterdam EA, Zakanddin V, DeMaria AN, Miller RR, Mason DT: Reduction of ischemic injury by sublingual nitroglycerin in patients with acute myocardial infarction. Circulation 54:761-765, 1976.
106. Hirshfeld JW Jr, Borer JS, Goldstein RE, Barret MJ, Epstein SE: Reduction in severity and extent of myocardial infarction when nitroglycerin and methoxamine are administered during coronary occlusion. Circulation 49:291-297, 1974.
107. Flaherty JT, Reid PR, Kelly DT, Taylor DR, Weisfeldt ML, Pitt B: Intravenous nitroglycerin in acute myocardial infarction. Circulation 51:132-139, 1975.

108. Come PC, Flaherty JT, Baird MG, Rouleau JR, Weisfeldt ML, Greene HL, Becker L, Pitt B: Reversal by phenylephrine of the beneficial effects of intravenous nitroglycerin in patients with acute myocardial infarction. N Engl J Med 293:1003-1007, 1975.
109. da Luz PL, Forrester JS, Wyatt HL, Tyberg JV, Chagrasulis R, Parmley WW, Swan HJC: Hemodynamic and metabolic effects of sodium nitroprusside on the performance and metabolism of regional ischemic myocardium. Circulation 52:400-407, 1975.
110. Awan NA, Miller, Zakanddin V, DeMaria AN, Amsterdam EA, Mason DT: Reduction of ST segment elevation with infusion of nitroprusside in patients with acute myocardial infarction. Am J Cardiol 38: 435-439, 1976.
111. Ramanathan KB, Bodenheimer MM, Banka VS, Helfant RH: Contrasting effects of nitroprusside and phentolamine in experimental myocardial infarction. Am J Cardiol 39:994-999, 1977.
112. Franciosa JA, Guiha NH, Limas CJ, Rodriguera E, Cohn JN: Improved left ventricular function during nitroprusside infusion in acute myocardial infarction. Lancet 1:650-654,1972.
113. Armstrong PW, Walker DC, Burton JR, Parker JO: Vasodilator therapy in acute myocardial infarction. A comparison of sodium nitroprusside and nitroglycerin. Circulation 52:1118-1122, 1975.
114. Codini MA, Barfeld PA, Spindola FH: Paradoxical effect of nitroglycerin on left ventricular wall motion in coronary artery disease. Am J Cardiol 37:127, 1976 (abstr).
115. LaJemtal TH, Nelson RG, Sonnenblick EH, Kirk ES: Preload and afterload changes induced by nitroprusside: beneficial and detrimental effects on ischemia. Circulation 54(Suppl II):II-69, 1976 (abstr).
116. Kerber RE, Abboud FM: Effect of alterations of arterial blood pressure and heart rate on segmental dyskinesis during acute myocardial ischemia and following coronary reperfusion. Circ Res 36: 145-155, 1975.
117. Miller RR, Awan NA, DeMaria AN, Amsterdam EA, Mason DT: Importance of maintaining systemic blood pressure druing nitroglycerin administration for reducing ischemic injury in patients with coronary disease. Am J Cardiol 40:504-508, 1977.
118. Bussmann WD, Bartmann F, Berghof E, Wagner P, Kaltenbach M: Random study on effect of i.v. nitroglycerin on CK and CKMB infarct size. Circulation 56(Suppl III):III-65, 1977 (abstr).
119. Becker LC, Bulkley BH, Pitt B, Flaherty JT, Weiss JL, Gerstenblith G, et al: Enhanced reduction of thallium 201 defects in acute myocardial infarction by nitroglycerin treatment: initial results of a prospective randomized trial. Clin Res 26:219A, 1978 (abstr).
120. Steele BW, Cohn JN, Franciosa JA, Archibald D: Serial CK isoenzyme activity during nitroprusside infusion in a multihospital study of acute myocardial infarction. Circulation 56(Suppl III):III-65, 1977 (abstr).
121. Franciosa JA, Cohn JN, Archibald D: Course of arterial and pulmonary wedge pressures after acute myocardial infarction: effect of nitroprusside. Am J Cardiol 41:413, 1978 (abstr).

122. Bache RJ: Effect of nitroglycerin and arterial hypertension on myocardial blood flow following acute coronary artery occlusion in the dog. Circulation 57:557-562, 1978.
123. Cohn PF, Maddox D, Holman BL, Markis JE, Adama DF, See JR, Idoine J: Effect of sublingually administered nitroglycerin on regional myocardial blood flow in patients with coronary artery disease. Am J Cardiol 39:672-678, 1977.
124. Capurro NL, Kent KM, Smith HJ, Aamodt R, Epstein SE: Acute coronary occlusion: prolonged increase in collateral flow following brief administration of nitroglycerin and methoxamine. Am J Cardiol 39:679-683, 1977.
125. Martins J, Kerber R, Marcus M: Wall thinning, stress and perfusion of acute ischemic myocardium: comparative effects of nitroprusside and nitroglycerin. Am J Cardiol 41:360, 1978 (abstr).
126. Capurro NL, Kent KM, Epstein SE: Comparison of nitroglycerin-, nitroprusside-, and phentolamine-induced changed in coronary collateral function in dogs. J Clin Invest 60:295-301, 1977.
127. Kent KM, Smith ER, Redwood DR, Epstein SE: Beneficial electrophysiologic effects of nitroglycerin during acute myocardial infarction. Am J Cardiol 33:513-516, 1974.
128. Borer JS, Kent KM, Goldstein RE, Epstein SE: Nitroglycerin-induced reduction in the incidence of spontaneous ventricular fibrillation during coronary occlusion in dogs. Am J Cardiol 33:517-520, 1974.
129. Bussmann W, Lohner J, Kaltenbach M: Orally administered isosorbide dinitrate in patients with and without left ventricular failure due to acute myocardial infarction. Am J Cardiol 39:91-96, 1977.
130. Chatterjee K, Parmley WW: The role of vasodilator therapy in heart failure. Prog Cardiovasc Dis 19:301-325, 1977.
131. Walinsky P, Chatterjee K, Forrester J, Parmley WW, Swan HJC: Enhanced left ventricular performance with phentolamine in acute myocardial infarction. Am J Cardiol 33:37-41, 1974.
132. Shell WE, Sobel BE: Protection of jeopardized ischemic myocardium by reduction of ventricular afterload. N Engl J Med 291:481-486, 1974.
133. Oliver MF, Rowe MJ, Luxton MR, Miller NE, Neilson JM: Effect of reducing circulating free fatty acids on ventricular arrhythmias during myocardial infarction and on ST-segment depression during exercise-induced ischemia. Circulation 53(Suppl I):I-210-I-213, 1976.
134. Mjøs OD: Effect of reduction of myocardial free fatty acid metabolism relative to that of glucose on the ischemic injury during experimental coronary artery occlusion in dogs. Experimental and Clinical Aspects on Preservation of the Ischemic Myocardium. Edited by A Hjalmarson, L Werko. Sweden, Molndal, pp 29-34, 1976.
135. Kjekshus JK, Mjøs OD: Effect of inhibition of lipolysis on infarct size after experimental coronary artery occlusion. J Clin Invest 52:1770-1778, 1973.
136. Russell RO Jr, Rogers WJ, Mantle JA, et al: Glucose-insulin-potassium, free fatty acids, and acute myocardial infarction in man. Circulation 53:Suppl I:I-207-I-209, 1976.

137. Maroko PR, Radvany P, Braunwald E, Hale SL: Reduction of infarct size by oxygen inhalation following acute coronary occlusion. Circulation 52:360-368, 1975.
138. Madias JE, Madias NE, Hood WB Jr: Precordial ST-segment mapping. 2. Effects of oxygen inhalation on ischemic injury in patients with acute myocardial infarction. Circulation 53:411-417, 1976.
139. Sukumalchantra Y, Levy S, Danzig R, Rubins S, Alpern H, Swan HJC: Correcting arterial hypoxemia by oxygen therapy in patients with acute myocardial infarction. Effect on ventilation and hemodynamics. Am J Cardiol 24:838-852, 1969.
140. Ganz W, Donoso R, Marcus H, Swan HJC: Coronary hemodynamics and myocardial oxygen metabolism during oxygen breathing in patients with and without coronary artery disease. Circulation 45:763-768, 1972.
141. Kawamura M, Sakakibara K, Sakakibara B, Kodokoro H, Takahashi H, Kobayashi S, Konishi S, Uno Y: Protective effect of hyperbaric oxygen for the temporary ischaemic myocardium: Macroscopic and histologic data. Cardiovasc Res 10:599-604, 1976.
142. Ledingham IMcA, Marshall RJ, Parratt JR: The effects of hyperbaric oxygen (2ATA) on the haemodynamic, metabolic, and electrocardiographic consequences of acute myocardial ischaemin anaesthetized greyhounds. Jour of Phys 268:16P-17P, 1977.
143. Willerson JT, Powell WJ, Guiney TE, Stark JJ, Sanders CA, Leaf A: Improvement in myocardial function and coronary blood flow in ischemic myocardium after mannitol. J Clin Invest 51:2989-2998,1972.
144. Willerson JT, Watson JT, Hulton I, Fixler DE, Curry GC, Templeton GH: The influence of hypertonic mannitol on regional myocardial blood flow during acute and chronic myocardial ischemia in anesthetized and awake intact dogs. J C lin Invest 55:892-902, 1975.
145. Willerson JT, Curry GC, Atkins JM, Horwitz LD: Influence of hypertonic mannitol on ventricular performance and coronary blood flow in patients. Circulation 51:1095-1100, 1975.
146. Wildenthal K, Adcor RC, Crie JS, Templeton GH, Willerson JT: Negative inotropic influence of hyperosmotic solutions on cardiac muscle. Am J Physiol 229:1505-1509, 1975.
147. Powell WJ, DiBona DR, Flores J, Leaf A: The protective effect of hypertonic mannitol in myocardial ischemia and necrosis. Circulation 54:603-615, 1976.
148. Powell WJ, DiBona DR, Flores J, Frega N, Leaf A: Effects of hypertonic mannitol in reducing ischemic cell swelling and minimizing myocardial necrosis. Circulation 53(Suppl I):I-45-I-49, 1976.
149. Willerson JT, Weisfeldt ML, Sanders CA, Powell WJ Jr: Influence of hyperosmolar agents on hypoxic cat papillary muscle function. Cardiovasc Res 8:8-17, 1974.
150. Kloner R, Reimer K, Willerson JT, Jennings R: Reduction of experimental myocardial infarct size with hyperosmolar mannitol. Proc Soc Exp Biol Med 151:677-683, 1976.
150a. Fixler DE, Buja LE, Wheeler JM, Willerson JT: Influence of mannitol on maintaining coronary flows and salvaging myocardium during ventriculotomy and during prolonged coronary artery ligation. Circulation 56:340-346, 1977.

151. The urokinase pulmonary embolism trial: a national cooperative study. Circulation 47(Suppl II):II-1-II-108, 1973.
152. Brogden RN, Spreight TM, Avery GS: Streptokinase: a review of its clinical pharmacology, mechanism of action, and therapeutic uses. Drugs 5:357, 1973.
153. Burkhart F, Duckert F, Stanb PW, Frick PG, Schireizer W, Koller F: Die Fibrinolytische Therapie beim akuten Myokardinfarkt. Schweizerische Medizinische Wochenschrift 103:1814, 1973.
154. Witteveen SAG J, Hemker HC, Hollaar, Hermens W Th: Quantitation of infarct size in man by means of plasma enzyme levels. Br Heart J 37:795-803, 1975.
155a. Sobel BE, Roberts R, Larson KB: Estimation of infarct size from serum MB creatine phosphokinase activity: applications and limitations. Am J Cardiol 37:474-485, 1976.
155b. Sobel BE, Markham J, Karlsberg RP, Roberts R: The nature of disappearance of creatine kinase from the circulation and its influence on enzymatic estimation of infarct size. Circ Res 41:836-844, 1977.
155c. Roe CR, Cobb FR, Starmer CF: The relationship between enzymatic and histologic estimates of the extent of myocardial infarction in conscious dogs with permanent coronary occlusion. Circulation 55: 438-449, 1977.
155d. Norris RM, Whitlock RML, Barratt-Boyes C, Small CW: Clinical measurement of myocardial infarct size: modification of a method for the estimation of total creatine phosphokinase release after myocardial infarction. Circulation 51:614-620, 1975.
156. Seltzer A: Use of anticoagulant agents in acute myocardial infarction. Am J Cardiol 41:1315-1317, 1978.
157. Saliba MJ Jr: Effects of heparin in large doses on the extent of myocardial ischemia after acute coronary occlusion in the dog. Am J Cardiol 37:599-604, 1976.
158. Saliba MJ Jr, Kuzman WJ, Marsh DG, Lasry JE: Effect of heparin in anticoagulant doses on the electrocardiogram and cardiac enzymes in patients with acute myocardial infarction: A pilot study. Am J Cardiol 37:605-607, 1976.
159. Maroko PR, Libby P, Ginks WR, Bloor CM, Shell WE, Sobel BE, Ross J: Coronary artery reperfusion. I. Early effects on local myocardial function and the extent of myocardial necrosis. J Clin Invest 51:2710-2716, 1972.
160. Ginks WR, Sybers HD, Maroko PR, Covell JW, Sobel BE, Ross J: Coronary artery reperfusion. II Reduction of myocardial infarct size at one week after coronary occlusion. J Clin Invest 51:2717-2723, 1972.
161. Cox JL, Daniel TM, Boineau JP: The electrophysiologic time course of acute myocardial ischemia and the effects of early coronary artery reperfusion. Circulation 48:971-983, 1973.
162. O'Brien CM, Carroll M, O'Rouke PT, Rhodes EL, Gago O, Kirsh MM, Morris JD, Sloan HE: The reversibility of acute ischemic injury to the myocardium by restoration of coronary flow. J Thorac Cardiovasc Surg 64:840-846, 1972.

163. Bresnahan GF, Roberts R, Shell WE, Ross J, Sobel BE: Deleterious effects due to hemorrhage after myocardial reperfusion. Am J Cardiol 33:82-86, 1974.

164. Lang TW, Corday E, Gold H, Meerbaum S, Rubins S, Costantini C, Hirose S, Osher J, Rosen V: Consequences of reperfusion after coronary occlusion: Effects on hemodynamic and regional myocardial metabolic function. Am J Cardiol 33:69-81, 1974.

165. Kloner R, Ganote CE, Jennings RB: The "no reflow" phenomenon after temporary coronary occlusion in the dog. J Clin Invest 54:1496-1508, 1974.

166. Sustaita H, Chatterjee K, Matloff JM, Marty AT, Swan HJC, Fields J: Emergency bypass surgery in impending and complicated acute myocardial infarction. Arch Surg 105:30-35, 1972.

167. Cohn LH, Garlin R, Herman MV, Collins JJ, Barsamian EM: Aorto-coronary bypass for acute coronary occlusion. J Thorac Cardiovasc Surg 64:503-513, 1972.

168. Cheanzechai C, Effler DB, Loop FD, Groves LK, Sheldon WC, Razavi M, Sones FM: Emergency myocardial revascularization. Am J Cardiol 32:901-908, 1973.

169. Mundth ED: Mechanical and surgical interventions for the reduction of myocardial ischemia. Circulation 53(Suppl I):I-176-I-182, 1976.

170. Lesch M: Inotropic agents and infarct size: Theoretical and practical considerations. Am J Cardiol 37:508-513, 1976.

171. Crexells C, Bourassa MG, Biron P: Effects of dopamine on myocardial metabolism in patients with ischemic heart disease. Cardiovasc Res 7:438-445, 1973.

172. Holzer J, Karliner JS, O'Rourke RA, Pitt W, Ross J Jr: Effectiveness of dopamine in patients with cardiogenic shock. Am J Cardiol 32: 79-84, 1973.

173a. Martins de Oliveira J, Carballo R, Zimmerman HA: Intravenous injection of hyaluronidase in acute myocardial infarction; Preliminary report of clinical and experimental observations. Am Heart J 57:712-722, 1959.

173b. Askenazi J, Hillis LD, Diaz PE, Davis MA, Braunwald E, Maroko PR: Mechanism of reduction of myocardial injury by hyaluronidase. Am J Cardiol 37:118, 1976 (abstr).

174. Maclean D, Fishbein MC, Maroko PR, Braunwald E: Hyaluronidase-induced reductions in myocardial infarct size. Direct quantification of infarction following coronary artery occlusion in the rat. Science 194:199-200, 1976.

175. Kloner RA, Fishbein MC, Maclean D, Braunwald E, Maroko PR: Effect of hyaluronidase during the early phase of acute myocardial ischemia. An ultrastructural and morphometric analysis. Am J Cardiol 40:43-49, 1977.

176. Maroko PR, Libby P, Bloor CM, Sobel BE, Braunwald E: Reduction of hyaluronidase of myocardial necrosis following coronary artery occlusion. Circulation 46:430-437, 1972.

177. Braunwald E, Maroko PR: Effects of hyaluronidase and hydrocortisone on myocardial necrosis after coronary occlusion. Am J Cardiol 37:550-556, 1976.

178. Hillis LD, Fishbein MC, Braunwald E, Maroko PR: The influence of the time interval between coronary artery occlusion and the administration of hyaluronidase on salvage of ischemic myocardium in dogs. Circ Res 41:26-31, 1977.
179. Maroko PR, Davidson DM, Libby P, Hagan AD, Braunwald E: Effects of hyaluronidase administration on myocardial ischemic injury in acute infarction: a preliminary study in 24 patients. Ann Intern Med 82:516-520, 1975.
180. Maroko PR, Hillis LD, Muller JE, Tavazzi L, Heyndrickx CR, Ray M, Chiariello M, Distante A, Askenazi J, Salerno J, Carpentier J, Reshetnaya NI, Radvany P, Libby P, Raabe DS, Chazov EI, Bobba P, Braunwald E: Favorable effects of hyaluronidase on electrocardiographic evidence of necrosis in patients with acute myocardial infarction. N Engl J Med 296:898-903, 1977.
181. Willerson JT: Discussion of the influence of counterpulsation on experimental and clinical myocardial ischemia. Circulation 53 (Suppl I):I-183-I-185, 1976.
182. Scheidt SS: Preservation of ischemic myocardium with intraaortic balloon pumping: Modern therapeutic imperative or primum non nocere? Circulation 58:211-214, 1978.
183. Messer JV, Willerson JT, Loeb HS, Criley JM, Amsterdam EA, Banas JA, and Collaborating Investigators: Evaluation of external pressure circulatory assist in acute myocardial infarction. Clin Res 23: 197A, 1975 (abstr).
184. Willerson JT, Curry GC, Watson JT, Leshin SJ, Ecker RR, Mullins CB, Platt MR, Sugg WL: Intraaortic balloon counterpulsation in patients in cardiogenic shock, medically refractory left ventricular failure, and/or recurrent ventricular tachycardia. Am J Med 58:183-191, 1975.
185. Sodi-Pallares D, Testelli MR, Fishleder BL, Bisteni A, Medrano GA, Friedland C, DeMicheli A: Effects of an intravenous infusion of a potassium-glucose-insulin solution on the electrocardiographic signs of myocardial infarction. Am J Cardiol 9:166-181, 1962.
186. Sodi-Pallares D, Bisteni A, Medrano GA, Testelli MR, DeMicheli A: The polarizing treatment of acute myocardial infarction. Dis Chest 43:424-432, 1963.
187. Kones RJ: Glucose, insulin, potassium therapy for heart disease in Glucose, Insulin, Potassium and the Heart: Selected Aspects of Cardiac Energy Metabolism. pp 249-338. Futura Publishing Company. New York. 1975.
188. Brachfeld N: The glucose-insulin-potassium (GIK) regimen in the treatment of myocardial ischemia. Circulation 48:459-462, 1973.
189. Morgan HE, Henderson MJ, Regan DM, Park CR: Regulation of glucose uptake in muscle. I. The effects of insulin and anoxia on glucose transport and phosphorylation in the isolated, perfused heart of normal rats. J Biol Chem 236:253-261, 1961.
190. Opie LH, Bruyneel K, Owen P: Effects of glucose, insulin, and potassium infusion on tissue metabolic changes with first hour of myocardial infarction in the baboon. Circulation 52:49-57, 1975.

191. Opie LH, Owen P: Effect of glucose-insulin-potassium infusions on arteriovenous differences of glucose and of free fatty acids and on tissue metabolic changes in dogs with developing myocardial infarction. Am J Cardiol 38:310-321, 1976.
192. Rogers WJ, Stanley AW, Breinig JB, Prather JW, McDaniel HG, Maraski RE, Mantle JA, Russell RO Jr, Rackley CE: Reduction of hospital mortality rate of acute myocardial infarction with glucose-insulin-potassium infusion. Am Heart J 92:441-454, 1976.
193. Regan TJ, Harman MA, Lehan PH, Burke WM, Oldewartel HA: Ventricular arrhythmias and K^+ transfer during myocardial ischemia and intervention with procaine amide, insulin, or glucose solution. J Clin Invest 46:1657-1668, 1967.
194. Maroko PR, Libby P, Sobel BE, Bloor CM, Sybers HD, Shell WE, Covell JW, Braunwald E: Effect of glucose-insulin-potassium infusion on myocardial infarction following experimental coronary artery occlusion. Circulation 45:1160-1175, 1972.
195. McDaniel HG, et al: Personal communication regarding data submitted for publication to Circulation.
196. Heng MK, Norris RM, Singh BN, Barratt-Boyes C: Effects of glucose and glucose-insulin-potassium on halmodynamics and enzyme release after acute myocardial infarction. Br Heart J 39:748-757, 1977.
197. Dye LD, Shin MS, Witten D, Russel RO Jr, Rackley CE, Hogg DE: Pulmonary consolidation associated with infusion of a glucose-insulin-potassium solution in acute myocardial infarction. Chest 73:179-182, 1978.
198. Folts JD, Shug AL, Koke JR, Bittar N: Protection of the ischemic dog myocardium with carnitine. Am J Cardiol 41:1209-1214, 1978.
199. Spath JA Jr, Lane DL, Lefer AM: Protective action of methylprednisolone on the myocardium during experimental myocardial ischemia in the cat. Circ Res 35:44-51, 1974.
200. Hearse DJ, Humphrey SM: Enzyme release during myocardial anoxia: a study of metabolic protection. J Molec Cell Cardiol 7:463-482, 1975.
201. Decker RS, Poole AR, Dingle JT, Wildenthal K: Effects of methylprednisolone on lysosomal cathepsin D in ischemic myocardium. Clin Res 26:482A, 1978 (abstr).
202. Johnson AS, Scheinberg SR, Gerisch RA, Saltzstein HC: Effect of cortisone on the size of experimentally produced myocardial infarcts. Circulation 7:224-228, 1953.
203. Barzilae D, Plavnick J, Hazani A, Einath R, Kleinhaus N, Kanter Y: Use of hydrocortisone in the treatment of myocardial infarction. Chest 61:488-491, 1972.
204. Morrison J, Reduto L, Pizzarello R, Geller K, Maley T, Culotta S: Modification of myocardial injury in man by corticosteroid administration. Circulation 53(Suppl I):I-200-I-203, 1976.
205. Peters RW, Norman A, Parmley WW, Emilson BB, Scheinman MM, Cheitlin M: Effect of therapy with methylprednisolone on the size of myocardial infarcts in man. Chest 73:483-488, 1978.

206. Roberts R, DeMello V, Sobel BE: Deleterious effects of methylprednisolone in patients with myocardial infarction. Circulation 53(Suppl I):I-204-I-206, 1976.
207. Kloner RA, Fishbein MC, Lew H, Maroko PR, Braunwald E: Mummification of the infarcted myocardium by high dose corticosteroids. Circulation 57:56-63, 1978.
208. Bulkley BH, Roberts WC: Steroid therapy during acute myocardial infarction: A cause of delayed healing and of ventricular aneurysm. Am J Med 56:244-250, 1974.
209. Vogel WM, Lucchesi BR: Methylprednisolone and the size of myocardial infarcts. Chest 73:444-445, 1978.
210. Keelan JP: Medical Research Division of the Upjohn Co. Personal Communication.
211. Maroko PR, Carpenter CB, Chiariello M, Fishbein MC, Radvany P, Knostman JD, Hale SL: Reduction by cobra venom factor of myocardial necrosis after coronary artery occlusion. J Clin Invest 61:661-670, 1978.
212. Diaz PE, Maroko PR: The effects of aprotinin on myocardial ischemic injury following experimental coronary artery occlusion. Clin Res 23:108A, 1975 (abstr).
213. Maclean D, Fishbein MC, Blum RI, Braunwald E, Maroko PR: Long-term preservation of ischemic myocardium by ibuprofen after experimental coronary artery occlusion. Am J Cardiol 41:394, 1978 (abstr).