Reduction of Infarct Size Following Coronary Occlusion

By Eugene Braunwald, Peter R. Maroko, and Peter Libby

ABSTRACT

Several pharmacological and hemodynamic interventions were found to alter acute ischemic injury of the myocardium and subsequent necrosis following coronary occlusion. Reduction in myocardial damage occurred when myocardial oxygen needs were reduced (beta-blocking agents, intra-aortic balloon counterpulsation, and digoxin in the failing heart), when coronary perfusion was improved (reperfusion, elevation of coronary perfusion pressure), when the provision of energy by means of anaerobic glycolysis was augmented (glucose-insulin-potassium, hyperkemic glucose), when the diffusion of oxygen and of substrates to the ischemic cells was improved (hyaluronidase), when the autolytic and heterolytic processes in the myocardium following coronary occlusion were stabilized (hydrocortisone). On the other hand, interventions which increased myocardial oxygen consumption (such as tachycardia, isoproterenol, digoxin, glucagon, and bretylium in the nonfailing heart) and which decreased coronary perfusion, increased myocardial ischemic damage. This concept of reduction in infarct size is being applied to patients in pilot studies, and initial results with hyaluronidase are promising.

KEY WORDS myocardial oxygen consumption reperfusion isoproterenol balloon counterpulsation hyaluronidase myocardial infarction epicardial S-T-segment electrocardiograms

In patients hospitalized with acute myocardial infarction, the principal causes of death have been arrhythmias and pump failure. Whereas the mortality rate due to arrhythmias has been reduced by modern monitoring techniques and more vigorous prophylaxis and treatment of arrhythmias during the past decade, the death rate following mechanical failure manifested by cardiogenic shock and/or pulmonary edema remains prohibitive. It is now appreciated that the size of the necrotic zone in patients with acute myocardial infarction associated with pump failure is generally larger than that exhibited by patients without pump failure who succumb to myocardial infarction. Accordingly, any intervention that could decrease the extent of tissue death and by this mechanism reduce the frequency of intractable cardiogenic shock and pulmonary edema could be extremely useful, not only by reducing immediate mortality, but, perhaps more importantly, by leaving the patient who has suffered a coronary occlusion a greater quantity of viable myocardium. Such a patient might well be less likely to develop chronic heart failure, and would in any case have a greater reserve of functioning myocardium should another coronary occlusion occur at a later time.

The recognition that myocardial infarction can occur without total coronary obstruction, coupled with a more complete understanding of factors determining myocardial oxygen requirements, have led to the hypothesis that the extent of an infarct, or even its occurrence, can result simply from an imbalance between oxygen supply and demand. The importance of decreased availability of oxygen in disturbing the balance between myocardial oxygen supply and demand is evident in patients with coronary artery disease, in whom arterial hypotension and acute anemia may cause infarction in the absence of coronary occlusion. There are also local factors that could limit oxygen supply, namely, an increase in ventricular systolic compression of the coronary vessels, a shortened diastolic interval, and coronary vasoconstriction of neurogenic, humoral, or pharmacological origin. Thus, when coronary occlusion occurs, the survival of the tissue normally perfused by the obstructed vessel depends on the balance between the oxygen available to that segment of the myocardium and its oxygen requirements. Hence, the relationship between myocardial oxygen supply and demand is potentially of great importance, since it might influence the total quantity of myocardium which remains viable following coronary occlusion.

The factors which influence myocardial oxygen consumption are primarily myocardial wall tension, the inotropic state, heart rate, and myocardial shortening against a load (Fenn effect); these have been reviewed elsewhere.
A vicious cycle can be established in the presence of coronary atherosclerosis and myocardial ischemia. Thus, any process which increases myocardial oxygen demands and intensifies ischemia may reduce the overall contractility of the left ventricle. This depression of left ventricular function may be compensated for by dilatation of the ventricle; in accord with Laplace’s law, this results in an augmentation of tension development at any level of ventricular pressure. An elevation of tension, in turn, leads to even higher levels of oxygen consumption, which exacerbates ischemia, hence further depressing myocardial function and thus initiating this vicious cycle.

Prediction of Myocardial Ischemic Injury by Epicardial S-T-Segment Electrocardiograms

To test the hypothesis that the extent of myocardial ischemic injury can be modified by hemodynamic or pharmacological interventions, a method was developed in which myocardial ischemic injury in dogs was estimated by determining electrocardiographic S-T-segment elevations in multiple epicardial leads during repetitive 20-minute coronary occlusions* (Fig. 1). This technique overcomes several difficulties inherent in other methods of studying this problem. Since observations are carried out in the same heart and at the same epicardial sites, the influence of variations of coronary artery distribution among different animals is eliminated, as each dog serves as its own control. When a drug is given during one of the occlusions, the alteration in the extent and magnitude of S-T-segment elevation is taken as an index of changes in myocardial ischemic injury (Fig. 2).

To establish the value of this technique in the prediction of myocardial necrosis, the correlation between acute epicardial S-T-segment elevation and the ultimate fate of the ischemic myocardial tissue was investigated. In hearts studied 24 hours after coronary occlusion, sites with normal epicardial S-T segments (0 to 2 mv of elevation 15 minutes after occlusion) showed normal myocardial creatine phosphokinase (CPK) activities 24 hours later, whereas sites showing S-T-segment elevations exceeding 2 mv showed myocardial CPK depression 24 hours later (Fig. 3). There was an inverse correlation between the S-T-segment elevation at 15 minutes following occlusion and the CPK activity 24 hours later at the same site (Fig. 4). Thus, S-T-segment elevation at each epicardial site predicts the integrity of the myocardium beneath the electrode 24 hours later, as reflected in CPK activity.\textsuperscript{8, 12-18} It was also shown that epicardial S-T-segment elevation 15 minutes after occlusion predicted the development of myocardial necrosis both 24 hours\textsuperscript{12-18} and 7 days later,\textsuperscript{19} as judged by histological appearance (hematoxylin and eosin staining, staining for glycogen and for fat droplets). Moreover, electron microscopic studies

\begin{figure}[h]
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\caption{Right panel: Schematic representation of the anterior surface of the heart. The coronary arteries and branches and sites of the epicardial electrocardiograms are marked. L.A. = left anterior descending coronary artery; L.A. = left atrial appendage; L.C. = left circumflex coronary artery; Con = control, Ocll = occlusion. From Maroko et al.\textsuperscript{8}}
\end{figure}

\textsuperscript{8} Supplement III to Circulation Research, Vols. 34 and 35, September 1974
were in complete agreement with the histological observations.12, 17

There is considerable additional evidence that epicardial S-T-segment elevation recorded in this manner directly reflects myocardial cellular injury. Thus, a correlation exists between the magnitude of ischemic alteration of the myocardial cellular membrane potential and the height of the epicardial S-T segment.18 There is also a good correlation between S-T-segment elevation and intramyocardial PO2 5 minutes after coronary occlusion,19 as well as between S-T-segment elevation and the development of anaerobic metabolism when coronary blood flow is reduced.20 Furthermore, it has been demonstrated that during myocardial ischemia, epicardial sites exhibiting S-T-segment elevations are sites of pronounced subendocardial and epicardial ischemia, reflected in adenosine triphosphate (ATP) depletion, and of anaerobic metabolism, reflected in local lactate accumulation.21

Effect of Myocardial Oxygen Consumption on Myocardial Ischemic Injury and Infarct Size

The hypothesis that the extent of an infarct can result from an imbalance between oxygen supply and demand was tested by applying physiological and pharmacological interventions which increase myocardial oxygen consumption in the nonfailing heart. 6, 22 These included isoproterenol, digitalis, glucagon, bretylium, and pacing-induced atrial tachycardia. All were found to increase the severity and extent of myocardial injury following acute coronary occlusion (Fig. 2). If the increase in ischemic injury resulted from an augmentation of myocardial oxygen consumption, then the opposite effect should be achieved with interventions which reduce myocardial oxygen consumption. Accordingly, the influences of the administration of propranolol and practolol were studied. 6, 22 Both drugs were found to reduce myocardial ischemic
injury following coronary artery occlusion. Moreover, the effect of digoxin on the extent of the ischemic injury was also studied in failing heart, in which it decreases myocardial oxygen consumption, and it was found that the extent and severity of myocardial ischemic injury were also reduced under these circumstances. All the aforementioned experiments taken together supported the conclusion that myocardial oxygen demand is an important factor in the determination of infarct size following coronary artery occlusion.

In order to study the importance of the oxygen supply to the ischemic myocardium, either hemorrhagic hypotension or arterial hypertension was induced following coronary occlusion. The former increased, and the latter reduced, the extent of myocardial ischemic injury. The relationship between aortic pressure and myocardial oxygen consumption is a complex one, however. When the heart is dilated and as a consequence of the operation of Laplace's law the myocardial tension and, therefore, oxygen consumption are elevated, a reduction of arterial pressure (through its effect on ventricular afterload) could favorably alter the balance between myocardial oxygen supply and demand, thereby reducing ischemic injury following coronary occlusion. Intra-aortic balloon counterpulsation is a treatment modality which combines a reduction in myocardial oxygen needs with an increase of coronary flow. It, too, was found to reduce the extent and magnitude of myocardial ischemic injury substantially.

**Effect of Metabolic and Other Interventions on Infarct Size**

Next, the analysis of the relationship between myocardial energy requirements and supply was extended to anaerobic myocardial metabolism. Normally, the heart derives essentially all of its energy through aerobic metabolism. However, the myocardium possesses the capacity to derive energy from anaerobic glycolysis in the absence of oxygen. Considering also that by increasing glucose concentration and through the addition of insulin the quantity of glucose that penetrates the cells can be augmented, it was reasoned that the size of a myocardial infarct might also be dependent on the balance between the availability and the demand.
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Another promising approach to reducing infarct size is the administration of pharmacological doses of hydrocortisone. When given either 30 minutes or 6 hours after coronary occlusion, it was shown to reduce myocardial ischemic injury and subsequent necrosis. This action is evident through its effect on epicardial S-T-segment elevation, on myocardial CK activity (Fig. 4), and on histological appearance (Fig. 5). While the precise mechanism of action of this intervention is also not known, several possibilities can be considered: first, stabilization of lysosomes; second, stabilization of cell membranes; and third, reduction in heterolytic activity of the inflammatory cells. While the effect of corticosteroids in patients with acute myocardial infarction is controversial, the aforementioned findings might help to explain the reported reduction in mortality in patients with acute myocardial infarction treated with hydrocortisone.

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Since hyaluronidase increases diffusion through the extracellular space, and may thereby facilitate delivery of nutrients to ischemic cells, its influence on the size of experimentally produced infarcts was also analyzed. Hyaluronidase was found to decrease myocardial ischemic injury, and ultimately myocardial necrosis, substantially. It was effective either as pretreatment or when administered one-half hour following coronary occlusion. There was a dramatic decrease in S-T-segment elevation, a sparing effect of myocardial CK activity (Fig. 4), and 45% of biopsies which were expected to progress to necrosis were normal 24 hours after occlusion as a consequence of the administration of hyaluronidase (Fig. 5).

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Effect of Delayed Interventions

From an analysis of the results presented above, it is apparent that several interventions can decrease infarct size when applied prior to or shortly after coronary occlusion. But if this concept of protection of ischemic myocardium were to be broadly applicable clinically it would be necessary to determine whether infarct size would be reduced several hours after coronary occlusion. It was found that even when applied up to 6 hours after occlusion, the actions of isoproterenol, propranolol, methoxamine, norepinephrine, hydrocortisone, hemorrhagic hypotension, intra-aortic balloon counterpulsation, and the combination of glucose-insulin-potassium with propranolol are directionally the same as when the intervention is carried out prior to or just following coronary obstruction (Fig. 6).

The principal conclusion resulting from these studies is that the myocardial tissue perfused by a vessel which becomes occluded is not necessarily destined to become irreversibly damaged. Rather, following coronary occlusion substantial portions of the myocardium remain for a number of hours in what might be considered to be a "twilight zone." This tissue bordering the infarct evidently receives some nourishment from the neighboring vessels. The reduction of myocardial oxygen needs (beta-adrenergic blocking agents, intra-aortic balloon counterpulsation), the improvement of coronary perfusion (elevation of coronary perfusion pressure, intra-aortic balloon counterpulsation), the provision of energy by means of anaerobic glycolysis (glucose-insulin-potassium, hypertonic glucose), the improvement of the opportunity for diffusion of oxygen and/or substrates to ischemic cells (hydrocortisone), and possibly the stabilization of autolytic and heterolytic processes in the myocardium following coronary occlusion (hydrocortisone) all appear to be capable of favorably altering the state of the myocardial tissue in the border zone, thus favoring its ultimate survival. Conversely, of equal importance is the increase in infarct size following coronary occlusion, which might occur as a consequence of deleterious effects on the border zone in a number of hemodynamic conditions which frequently occur clinically. These include tachycardia, arterial hypotension, and the actions of agents which improve contractility, such as isoproterenol, digitalis, glucagon, and bretylium in the absence of marked cardiac dilatation.18

Clinical Observations

Using a 35-lead serial precordial electrocardiographic technique, observations in patients indicated that a predictable reduction in the magnitude of S-T-segment elevation occurs as a simple function of time in patients with uncomplicated infarcts, and that factors which affect the magnitude of ischemic injury observed in the dog with acute coronary occlusion are also operative in patients.22 It was observed in individual patients that an increase in S-T-segment elevations occurred as a consequence of arterial hypotension, after development of ischemic pain, and after ventricular fibrillation, and that a reduction occurred after propranolol administration22 and following the intravenous administration of practolol.23 More recently, the influence of hyaluronidase administration was studied.24 While the reduction in the sum of precordial S-T-segment elevation in the nontreated group was approximately 20% of the initial value after 2 and 6 hours of observation, in the hyaluronidase-treated group the reduction exceeded 50%. Also, while some patients in the control group showed extension of

Comparison between S-T-segment elevation 15 minutes after occlusion (on the abscissa) and log CKP (creatine phosphokinase) activity 24 hours later in the same myocardial sites. Lower line: Control group; log CKP = -0.061 S-T + 1.26 (14 dogs; no. of specimens = 102; r = -0.78). Middle line: Administration of glucose-insulin-potassium and of propranolol starting 3 hours after occlusion; log CKP = -0.034 S-T + 1.26 (6 dogs; no. of specimens = 48; r = 0.72). Upper line: Reperfusion of coronary arteries 3 hours after occlusion; log CKP = -0.011 S-T + 1.31 (6 dogs; no. of specimens = 48; r = -0.66). The slope of the lower line is statistically different from the slope of other lines, showing lower CKP depression due to glucose-insulin-potassium and propranolol administration or to reperfusion done 3 hours after occlusion.

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their infarctions, reflected by an increase in the sum of S.T-segment elevations, all patients who received hyaluronidase showed a reduction in this parameter. It is therefore apparent that precardial electrocardiographic mapping exhibits changes parallel to those measured by the epicardial technique and may provide a useful clinical tool for determining changes in the extent of ischemic injury.

Serial creatine phosphokinase disappearance curves and noninvasive methods for recording myocardial wall motion may provide other approaches for examining the efficacy of various interventions.

The potential importance of the aforementioned observations derives from the fact that the magnitude of infarcted myocardium is a major determinant of the deterioration of ventricular performance, and that once a critical quantity of myocardial tissue has become necrotic, pump failure will ensue. Therefore, the reduction of myocardial necrosis following acute coronary occlusion might offer the patient a larger reserve of contractile myocardium, which results in better cardiac function and could possibly protect the patient from the development of pump failure in the course of a subsequent coronary occlusion. It must, however, be emphasized that relatively few clinical observations have been made up to this time and that exhaustive investigations will still have to be conducted in patients before it is suggested that these concepts should be widely applied clinically.

References


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Discussion

Dr. E. I. Chazov, Moscow, U.S.S.R.: I think the results you have described mark the beginning of a new era in our ideas regarding possible treatment for patients with acute myocardial infarction. As I understand it, two preparations which have been utilized are hyaluronidase and a mixture of glucose, insulin, and potassium. Since these drugs have effects on cell permeability and the microcirculation, it would be interesting to know if electron microscopy has revealed changes in cell swelling or congestion, as described by Dr. Jennings. Do you plan to study the membranes of the myocardial cells in the ischemic zone to elucidate fully the mechanisms of action of these agents? Third, in your experiments, have you observed formation of thrombi, or are these simply occlusions without thrombosis?

My final question, which probably also troubles you to a considerable degree, is about the problem of pathogenesis of cardiogenic shock. Would it be possible to "speculate," as they say in English, or "fantasize," as they say in Russian, regarding the possibility that in the pathogenesis of cardiogenic shock the perinecrotic zone, or perhaps the myocardial condition as a whole, is of primary importance?

Dr. Braunwald: In reply to the first question, we have carried out some detailed electron microscopic studies, and we do find cell swelling, which is reduced by the glucose, insulin, and potassium mixture. We have not carried out any detailed analysis of the microcirculation. It is something we think is very important, but we believe the studies should be carried out by people who have more experience and talents in this area.

As far as the pathogenesis of cardiogenic shock is concerned, I think we have a great deal to learn from examination of the hearts obtained at post-mortem. Dr. Jennings, I'm sure, has more light that he can shed on this than I. But I have not seen the heart of a patient who died in cardiogenic shock which did not have massive myocardial necrosis. If one looks at the light microscopic picture, one is impressed that infarction is a dynamic process. There are islands of apparently viable myocardium interspersed with areas of myocardium which clearly show varying degrees of injury.

To put it in the simplest terms, I visualize the pathogenesis of some instances of cardiogenic shock in the following way. First, there is sufficient insult to reduce coronary perfusion markedly. This reduction of coronary perfusion then converts the "twilight zone" to night, as it were; that is, the marginally perfused perinecrotic zone loses its viability. As the process advances, we are often forced to treat the patient with agents that augment myocardial oxygen needs. Although these drugs may maintain the blood pressure, they may actually increase the amount of myocardial necrosis. A vicious cycle could thus be established, resulting in the death of the patient. Perhaps the only way this cycle could be broken, short of cardiac transplantation or a totally implanted mechanical heart, would be to maintain the circulation in some manner so that the intermediate zones remain viable and the necrosis does not spread.

I agree with you that it may often be the spread of the peri-infarction zone that is responsible for a patient's demise from cardiogenic shock. In some patients, however, there is so much infarcted tissue initially that the spread of necrosis is not a signi-
cant cause of mortality. Other patients with borderline cardiac function might be saved by containment of the necrosis.

Dr. Chazov: Do you use anticoagulant drugs in these patients?

Dr. Braunwald: I use anticoagulant drugs routinely in the treatment of patients with myocardial infarction, unless specific contraindications exist.

Dr. Chazov: It seems to be an appropriate time to study not only the necrotic, but also the perinecrotic zones of the myocardium. Laboratory and clinical investigators, who are both represented in this symposium, could contribute to improved understanding of the metabolism of perinecrotic zones. Dr. Braunwald’s report demonstrates the great possibilities of this approach.

In our research we have been studying the role of thrombosis formation in myocardial infarction. We believe that following a primary coronary occlusion, a secondary thrombus may form in the peri-infarction area. The increasing frequency of discovery of thrombosis with time following occlusion supports this hypothesis. It is possible that the zone of secondary ischemia caused by this progressive thrombosis could be returned to normal with the early use of anticoagulants and fibrinolytic therapy.

Dr. A. M. Chernukh, Moscow, U.S.S.R.: As a pathophysiologist, I cannot refrain from congratulating you for an extremely elegant experiment, Dr. Braunwald. Clinicians and basic scientists have found it difficult to study the changes in permeability of cells and the microcirculation prior to an infarction and the response of a heart which has already been compromised by a previous infarction. It seems to me that your method to some extent removes the experimental difficulties which exist during a permanent occlusion, when only the final stage of the process can be studied.

In our country, just as in the United States, people were quite enthusiastic in the past about hyaluronidase. There have been numerous studies of its anti-inflammatory and anticoagulative properties. Dr. Mieglewetzki in our country studied hyaluronidase extensively, but at that time it was not possible to study the permeability of the microcirculation. Neither electron microscopy nor fluorescent microscopy was available.

It is of great interest to me to observe the further development of your research. I am particularly interested in the study of the walls of microvessels—the precapillaries, capillaries, and postcapillary venules. Such studies might not only clarify the mechanism of action of hyaluronidase, but also shed light on the role of the microcirculation in delivery of oxygen to the myocardium. I want to congratulate you once again on your research, which has produced such interesting results.

Dr. Robert M. Berne, Charlottesville, Virginia: I should like to know whether you have made any direct determinations of oxygen tension or interstitial pressure in the ischemic areas of the hearts in your animal experiments? Perhaps hyaluronidase works not by facilitating diffusion, but by decreasing tissue pressure and relieving compression of the thin-walled blood vessels.

I should also like to know whether you have made any measurements of xenon clearance from areas bordering the ischemic tissue as an indicator of collateral flow? Such measurements could lead to an understanding of the mechanisms of some of the interventions you have described.

Dr. Braunwald: No, we haven’t.

Dr. Robert B. Jennings, Chicago, Illinois: First, it think it is worth re-emphasizing the dynamic nature of events in the myocardium following coronary occlusion. Medical students are first shown the static nature of the final result of a myocardial infarction in pathology, and this concept stays with them throughout their time as clinicians. I don’t think the state of the myocardium following occlusion is static until the infarct is completely healed.

Second, I think there’s a difference between large and small areas of ischemic injury and their response to these various interventions. I noted that you emphasized that you were dealing with a relatively small area of ischemia. Most investigators seem to think that all infarcts are the same. You have emphasized that they are not.

Finally, I think that at this conference we are seeing two different approaches to the problem of preventing ischemic cell death. I should much prefer to learn the cause of cell death from the basic point of view. I would like to know what kills myocardial cells—what causes them to enter a state of irreversible injury? Having this knowledge, we should be able to design a rational intervention to prevent irreversible changes from occurring. I think you have shown very clearly that the problem can be successfully approached indirectly, namely, by manipulating factors which expand or diminish areas of ischemia. Through favorable modifications in the relationship between myocardial oxygen supply and demand, it is possible to intervene in an area of acute myocardial ischemic injury and
reduce the amount of cell death. If you are too successful with the indirect approach, we may never solve the problem.

Dr. G. A. Langer, Los Angeles, California: The action of hyaluronidase is indeed interesting. We have just completed a quantitative stereometric and ultrastructural study of the interstitial space. "Interstitial space" is a misnomer; only 5% of the interstitial area is free space, and that is probably an artifact. If we exclude blood vessels and examine the interstitium per se, 60% is filled with a ground substance in which there is a very high concentration of negatively charged material which is almost certainly mucopolysaccharide.

Preston and Snowden studied incorporation of glycoprotein material in an interface between two freely diffusible chambers. It is interesting that the incorporation of this material does not affect the free diffusion rate of neutral substances. The glycoprotein greatly inhibits the free diffusion of negatively charged substances and, interestingly enough, through a Donnan mechanism greatly augments free diffusion permeability of positively charged substances. It would be very interesting to look at the effects of hyaluronidase in such a model.

Finally, is beta-blockade more effective in limiting infarct size when applied soon after coronary occlusion rather than later?

Dr. Braunwald: All the interventions are more effective the earlier they are applied.

Dr. Langer: The large potassium efflux following occlusion stimulates myocardial sympathetic nerve endings, resulting in a large local catecholamine release. Early beta-blockade may be effective against these intrinsic, as well as extrinsically derived, catecholamines.
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