SYMPOSIUM ON THE PRESENT STATUS OF REPERFUSION OF THE ACUTELY ISCHEMIC MYOCARDIUM. PART I

ELIOT CORDAY, MD, FACC, *and* **SAMUEL MEERBAUM, PhD, FACC,** *Guest Editors*

Introduction

ELIOT CORDAY, MD, FACC, SAMUEL MEERBAUM, PhD, FACC

Los Angeles, California

Elucidation of reperfusion phenomena has taken on a new significance because of the recent clinical developments emphasizing prompt restoration of perfusion for the protection and salvage of jeopardized myocardium during acute myocardial ischemia or evolving infarction. Among the striking new reperfusion approaches are the emergency treatment of coronary occlusions by intracoronary or intravenous administration of thrombolytic agents, acute coronary bypass surgery, percutaneous transluminal coronary angioplasty, release of angiospasm by pharmacologic agents and coronary venous delivery of oxygenated blood by synchronized hypothermic retroperfusion.

The last decade of rapid transition and innovative development has seen a reexamination of established concepts of myocardial ischemia and reperfusion, along with consideration of newly recognized problems. Thus, prior emphasis on lowering of oxygen demands through ventricular unloading has given way to methods capable of effectively resupplying oxygen to the acutely ischemic myocardium. Mechanisms of partial or total coronary obstruction are being reexamined in relation to platelet deposition, spasm and coronary thrombosis in an effort to determine the dynamics of the processes that could lead to acute ischemia and infarction. Yet, even when promptly treated with drugs or reperfusion, mechanical, electrophysiologic or metabolic function of an ischemic zone may not be fully restored for weeks. Because of persisting derangements during the early reperfusion period, the latter should be considered potentially hazardous, requiring continued careful monitoring and extended conservative management. Some investigators have even questioned the benefits of an eventual partial or patchy myocardial salvage, which could be more apparent than real if it was associated with arrhythmogenicity, chronic ischemia, infarct expansion or extension (1,2). At present, there is no assurance that current understanding of reperfusion is adequate to resolve all questions, and further studies will surely be needed to test the newer concepts.

As part of this reexamination, the current symposium begins in this issue of *JACC* with surveys of selected basic pathophysiologic questions about reperfusion, and includes specific experimental contributions. The symposium will continue in next month's issue with clinical reviews and studies providing an update on recent reperfusion developments.

Consequences of Reperfusion

Evidence that sudden restoration of coronary blood flow may result in serious structural and functional derangements, even when instituted as early as 1 hour after an acute coronary occlusion in dogs, was already demonstrated in our 1975 symposium on reperfusion (3), and has been corroborated in numerous publications (4–7). Thus, restoration of epicardial coronary artery flow after 3 hour proximal occlusion in closed chest dogs failed to salvage the acutely ischemic myocardium in about one-third of the animals, even though there still was, on the average, a significant reduction in infarct size (8). Furthermore, such reperfusion of the jeopardized tissue was generally associated with a substantially delayed return of function (metabolic, contractile and electrophysiologic), although myocardial viability and eventual survival could be demonstrated (9).

The potentially serious ultrastructural and functional derangements could be attributed to a "no reflow" phenomenon characterized by cell swelling, tissue edema, cellular calcium influx and washout of accumulated metabolites and

From the Division of Cardiology, Cedars-Sinai Medical Center, and the Department of Medicine, University of California, Los Angeles School of Medicine, Los Angeles, California.

Address for reprints: Eliot Corday, MD, Cedars-Sinai Medical Center, Division of Cardiology, 8700 Beverly Boulevard, Halper 3, Los Angeles, California 90048.

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electrolytes. When accentuated, these reperfusion effects lead to structural changes and irreversible myocardial damage marked by explosive cell swelling and mitochondrial calcium phosphate accumulations (10,11).

Effects of the Ischemic Process on Reperfusion

It is important to note that evolving or intermittent myocardial ischemia and partial or full restoration of myocardial perfusion may be viewed as interdependent dynamic processes that occur in many settings of ischemic heart disease. Clearly, the severity of myocardial injury associated with an ischemic syndrome will depend most importantly on the grade and persistence of the perfusion defect and on demands imposed on the regionally ischemic myocardium by the prevailing physiologic state. Single or repeated reperfusion superimposed on an ischemic injury could exacerbate the progressive damage. Such a process may apply in severe stenosis of a major coronary artery or intermittent coronary obstructions by angiospasm, and could be a precursor of thrombotic coronary artery occlusion evolving into myocardial infarction (12).

Reversible versus irreversible ischemia. Reperfusion would be expected to follow a very different path when applied to potentially reversible versus irreversible ischemic injured myocardium. In severe but still reversible myocardial ischemia, such as has been described in the earliest stage after an acute coronary occlusion, the ultrastructural changes include a rapid loss of glycogen, the development of apparent intracellular edema and mitochondrial swelling and pyknosis (9,13). Contractile activity is rapidly lost within several beats and creatine phosphate as well as adenosine triphosphate and creatine phosphate reserves decrease as glycolysis and anaerobic metabolism develop in the absence of sufficient coronary collateral circulation. With total decline in glycogen, sharply diminished circulation and increasing cytoplasmic concentrations of protons, dihydronicotinamide adenine dinucleotide and lactate, the myocardium is unable to provide for basal cellular energy requirements and the limits of viability are reached.

The fully reversible ischemic period has been estimated in the dog's posterior papillary muscle or free wall subendocardium as 20 to 40 minutes after an acute coronary occlusion. Near transmural necrosis has been generally reported in dog myocardium anywhere from 4 to 6 hours postocclusion, after an endocardial to epicardial "necrotic wave propagation" (14). Therefore, to save cardiac tissue before it becomes irrevocably destined to die, reperfusion must be started before the onset of significant irreversible injury, or ischemia must be treated before reperfusion to prevent or delay the critical transition from reversible to irreversible states. Although one would wish to generalize in terms of a critical period of survival, no such universal criterion is possible in the presence of variable amounts of compensatory coronary collateral blood supply.

Delayed return of function after reperfusion. As previously mentioned, reperfusion of acutely ischemic but reversibly injured myocardium can be associated with a most significant and potentially dangerous delay in the return of function. This period of stunned or obtunded function after reperfusion may last for weeks when reperfusing after only 20 minutes to 1 hour of acute coronary occlusion, with the eventual outcome uncertain in view of a possible extension of damage (7). The effects of reperfusion are probably more complex when, as is often the case, one deals with combinations of regionally reversible and irreversible ischemic injury. Mixed or patchy salvage by reperfusion, or else through coronary collateral supply, would be reflected in varying improvements in regional ventricular function. The latter is also influenced by mechanical tethering of adjoining segments, changes in myocardial stiffness due to edema, derangement caused by arrhythmias and abnormal metabolism after reperfusion. Prolonged dysfunction of injured ischemic zones could, in the absence of effective treatment, lead to serious global consequences, such as hypotension or shock, and further ischemia and infarction (15–17). Collateral circulation may, of course, develop gradually over a period of hours or days whenever there are adequate anatomically preexisting coronary collateral channels.

It is necessary to evaluate the true effectiveness of reperfusion for as long as several weeks after its initiation to clearly establish resumption of normal myocardial perfusion and regional as well as global cardiac function (7,9). This suggests that early stress testing and intensive rehabilitation during the obtunded postreperfusion state could precipitate more damage and should be delayed until adequate and stable cardiac function is reestablished. Early reperfusion phenomena may also affect the outcome of coronary bypass surgery, during which apparently reversibly ischemic myocardium undergoes a perioperative infarction in about 5 to 10% of candidates, despite the fact that in 70% of those examined the bypass grafts remained patent (18). The incidence, cause and mechanisms of this damage are still being debated but they could be due to reperfusion derangements of ischemia that may be minimized by treatment such as gradual reperfusion (19) or retroperfusion of the coronary sinus (20).

Irreversible ischemic injury. Beyond the point when major irreversible ischemic injury has ensued, reperfusion might not be effective at all; in fact it may even cause a major extension of myocardial damage. However, it is often unclear to what degree the eventual outcome was inevitable in view of the extent and character of acute ischemic injury just before reperfusion. Thus, necrosis of myocardium after an acute coronary occlusion is followed in time by irreversible damage to its microvasculature, so that sudden reperfusion at normal rate and pressure may rupture intramural

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microvessel walls with consequent myocardial hemorrhages and augmented interstitial edema. Irreversible acute ischemic injury is also most often associated with substantial metabolite accumulations, which in themselves, are responsible for accelerated vicious cycles of ischemic damage and necrosis. The rapid and major washout of metabolites, enzymes and electrolytes during reflow has been recognized as a likely cause for some of the harmful consequences of reperfusion, such as the development of hazardous arrhythmias. Washout of adenonine, hypoxanthine and inosine apparently precludes rapid resynthesis of ATP, whereas a sudden cell reflow with calcium may be related to persisting contractile derangements. Moreover, until it is resorbed, edema could limit the extent of contractile recovery.

Severe postreperfusion edema, characterized through measurements of significantly increased tissue wall thickness (by two-dimensional echocardiography), has recently been correlated with the extent of eventual myocardial necrosis (21). Such early postreperfusion wall thickness measurements could be used clinically to predict myocardial viability or infarction. However, questions about reflow impedance through regional tissue swelling and its effect on eventual postreperfusion salvage or residual derangements are yet to be fully explored. Another effect involves significant temporary derangements of contractile and metabolic function in zones adjacent to, and even remote from, a regional irreversible acute ischemic injury. These remote derangements can add to global dysfunction and potentially limit recovery after reperfusion (22).

Current Developments in the Field of Reperfusion

Ultrastructural correlates of ischemic injury. In their contribution to this symposium, Schaper and Schaper (23) review ultrastructural correlates of ischemic injury after coronary occlusions of various durations, as well as the subsequent and consequent changes noted during reperfusion followed up to 48 hours. As anticipated, the cellular degradation depended on the duration and degree of ischemic injury before reperfusion, with eventual necrosis extending from the subendocardial layer for brief occlusion to the subepicardium for longer periods of coronary occlusion. Reperfusion produced only limited alterations in the presence of slight ischemia, in contrast to marked structural deterioration of irreversibly injured myocardium. In reversible ischemic injury, extended reperfusion appears to be characterized by lysozomal enzyme activity "scavenging" intracellular debris, and structural reorganization that contributes to recovery of injured myocytes. In contrast, irreversibly damaged myocyte lysozomes do not contribute to autophagocytosis. The investigators also examine the accuracy of postreperfusion measurements of myocardial necrosis using tetrazolium-type substances. Although they conclude that the histochemical methodology is generally adequate, they do not rule out that reperfusion may accelerate destruction of ischemic tissue that is already very close to the "point of no return."

Functional and biochemical improvement during reperfusion. Ellis et al. (24) followed up dogs for 2 weeks of reperfusion, after 2 hours coronary occlusion and compared measurements of cardiac function and adenosine triphosphate, as well as creatine phosphate with similar measurements in nonreperfused control dogs (with 2 weeks of maintained occlusion). In their model, 2 hours of occlusion with 4 hours of reperfusion led to a 24% largely subendocardial necrosis, compared with 89% essentially transmural necrosis after 6 hours of permanent occlusion. Two-dimensional echographic study revealed thinning in the acutely ischemic region and failure of the central portion of the ischemic zone to develop active wall thickening in the first 72 hours of reperfusion. Yet, a significant partial return to approximately 20% thickening was found 14 days after reperfusion (compared with 48% in preocclusion control), in contrast to persisting regional thinning in permanently occluded dogs. It required a period of 7 days for recovery of ATP levels in salvaged reperfused zones to near preocclusion levels. Both functional and biochemical recovery during reperfusion was achieved only after significant delay.

Incidence and treatment of reperfusion arrhythmias. Reperfusion-induced arrhythmias and ventricular fibrillation have been studied often, but their mechanisms and optimal treatment remain unclear. Thandroyan et al. (25) describe alpha- and beta-adrenoceptor antagonist effects on ischemic myocardial metabolism and incidence of ventricular fibrillation. Prazosin and phentolamine given before coronary artery occlusion protected against reperfusion ventricular fibrillation, whereas previous reserpinization failed. The $alpha_2$-antagonist, yohimbine, was found to have antiarrhythmic potential and dl-propranolol and metoprolol were also effective, but atenolol had no effect. The investigators noted that membrane-stabilizing activity rather than receptor antagonism explains the apparent prevention of postreperfusion fibrillation by beta-adrenoceptor antagonists. Ischemic tissue metabolism could not be clearly associated with reperfusion arrhythmias, in spite of indications from previous studies (26).

Coronary venous retroperfusion. To treat the acutely ischemic and essentially inaccessible myocardium beyond a coronary occlusion and thus prevent hazardous early reperfusion derangements, Haendchen et al. (20) applied moderately hypothermic coronary venous synchronized retroperfusion in closed chest dogs because it has been shown to extend viability and function of reversibly injured ischemic myocardium. Untreated 3 hour coronary occlusion followed by 7 days reperfusion was compared with retroperfusion treatment from 30 minutes to 3 hours occlusion followed by 7 days of reperfusion. Two-dimensional echo-

cardiography was employed to map ischemic and nonischemic segmental function, and the extent of myocardial necrosis was delineated by triphenyl-tetrazolium-chloride. The retroperfusion treatment decreased mortality and mean infarct size, significantly enhanced global as well as ischemic segmental function during the coronary occlusion and minimized early and later reperfusion derangements. Further study is needed to test the effectiveness of this form of treatment, with longer periods of coronary occlusion and more extended durations of retroperfusion.

Surgical revascularization in evolving myocardial infarction. This symposium will be continued in the next issue of *JACC,* with emphasis on the clinical aspects of reperfusion. DeWood et al. (27) will reevaluate comparative results of early (within a mean of 4.8 hours from symptom onset) versus late (mean 9.2 hours) surgical revascularization in evolving acute anterior transmural myocardial infarction. Two-dimensional echographic study of contraction demonstrated that the early revascularization was significantly more effective in recovery of segmental function after reperfusion. Quoting indications that such surgical reperfusion can be performed with low mortality (2 to 5%), the authors urge that the revascularization be performed as early as possible in the course of an evolving myocardial infarction, and point to a need for better markers of tissue salvage.

Myocardial preservation during bypass surgery. Rosenkranz and Buckberg (28) review newly modified myocardial protection and preservation during coronary bypass surgery for safety, simplicity and optimal effectiveness. In particular, myocardial cooling and control of reperfusate blood composition were optimized to almost completely avoid the metabolic and functional consequences of hypothermic cardioplegic ischemic cardiac arrest, specifically by modifying the temperature, pressure and ionic content of blood reperfusate during the first 5 minutes of reoxygenation. The authors describe a combined intervention that allows up to 4 hours of safe aortic clamping with cold blood cardioplegia and returns cardiac metabolism and ventricular compliance to control levels. This was achieved by: 1) chelation to decrease available ionic calcium; 2) the correcting alkalosis of reperfusate; 3) maintenance of temporary cardioplegia during reperfusion; 4) maintenance of hyperosmolarity and lower perfusion pressure to minimize edema; and 5) warming of the reperfusate.

Intracoronary thrombolysis during evolving infarction. Experience with intracoronary thrombolysis is reviewed by Ganz et al. (29), who provided some recent data on lytic treatment of an evolving myocardial infarction within its early stage (up to 3 hours). An important point is that such a nonsurgical reperfusion technique can be effective and relatively safe, but only if the treatment is instituted very early after the initial symptoms. Myocardial salvage was reported by the authors using a new intracoronary thallium imaging method, and functional improvements after the reperfusion were measured with two-dimensional echocardiography. The authors also review suggestive evidence of reduced mortality through early reperfusion, but these are not randomized studies. Coronary reocclusion phenomena are discussed and the importance of appropriate continuing anticoagulation emphasized.

Intravenous versus intracoronary thrombolytic reperfusion. Thrombolytic reperfusion is discussed by Schröder (30), who compared the newest intravenous administration versus intracoronary artery treatment. In 50 patients with up to 13 weeks follow-up, a high dose (500,000 to 1,050,000 IU) intravenous infusion carried out over a period of 30 to 60 minutes resulted in an 84% reperfusion success rate, verified by creatine kinase-MB enzyme analysis and coronary angiography in the fourth week. This compared with a 25% demonstrated spontaneous clot lysis within 8 weeks in an equivalent control group of 52 patients without streptokinase or heparin treatment. In a total of 69 patients, streptokinase infusion was begun in 36 within 3 hours after onset of symptoms, and none exhibited reocclusion. In contrast, reinfarction occurred in 6 of 33 patients with later streptokinase infusion. Schröder (30) considers ultimate clot lysis equally effective with intravenous and intracoronary routes. Even though the time to lysis may be considerably longer (60 to 120 minutes) than with intracoronary application, earlier intravenous administration in an emergency facility may well make up for this difference. The authors believe that the combination of intravenous and intracoronary streptokinase may increase the successful lysis rate to more than 90% and they quote a European Cooperative Group Trial of intravenous streptokinase that suggests significant lowering of 6 month mortality and improved left ventricular function in successfully recanalized patients.

Coronary venous retroinfusion of streptokinase. A variant of streptokinase thrombolysis was explored experimentally by Meerbaum et al. (31). In closed chest dogs with an induced proximal coronary artery thrombus, retrograde regional coronary venous infusion of streptokinase at a low rate of less than 2,000 IU/min resulted in lysis within a mean of 50 minutes. An equivalent dosage of streptokinase administered systemically also led to lysis but significantly later, in an average of 132 minutes. Although the significance and limitation of this new method remain to be assessed, it is interesting to note that this retrograde thrombolytic technique can be combined with synchronized coronary venous retroperfusion treatment to protect the jeopardized ischemic myocardium while awaiting effective reperfusion by lysing of the thrombus. The retroperfusion method was readily applied, promptly improved contractile function of ischemic cardiac regions in dogs and significantly extended viability of jeopardized myocardium.

Coronary angioplasty. Williams et al. (32) discuss percutaneous transluminal coronary angioplasty (PTCA), which may bear some relation to reperfusion, because its aim is a

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significant and prompt enhancement of myocardial perfusion. Severe coronary stenosis often depletes flow reserve capacity and coronary angioplasty clearly improved this capacity. Alpha-adrenergic tone withdrawal in normal patients is responsible for increased coronary flow under stress, whereas patients with coronary artery disease fail to show this response. After successful angioplasty coronary flow is again increased during stress, suggesting restoration of normal alpha tone. Williams et al. (32) report no arrhythmias because of the angioplasty-induced increased perfusion. Longer term studies are required to characterize the rate at which segmental myocardial function returns with angioplasty and to elucidate incidence and mechanisms of eventual angioplasty failures (31 of 95 in the reported study [32]).

Current Perspective on Reperfusion Issues

We now recapitulate what seems to us is the current state of the understanding of reperfusion. Reperfusion derangements should be viewed against the background of the mode, extent and severity of the myocardial ischemic injury before reperfusion. Certainly, as coronary stenosis differs from full coronary artery occlusion, effects of a temporary or intermittent ischemia from continuous ischemia, while vasospasm appears distinct from platelet deposition or intracoronary thrombosis. As discussed, the consequences of reperfusion will be more extensive and indeed permanent when applied after irreversible ischemic injury. Nonetheless, it is important to be aware of the potential effects of reperfusion and to expand our understanding beyond attempts to generalize it as a "3 to 4 hour critical period" of coronary occlusion beyond which reperfusion may not be beneficial. In fact, this period will differ from patient to patient and depends on many factors, including the size of the ischemic involvement, extraneous cardiac demands and compensatory coronary collateral supply to the jeopardized myocardium.

It would seem that we are still unable to fully explain the underlying causes and mechanisms of reperfusion arrhythmias, although they may well be related to rapid electrolyte washout and can be decreased through gradual reperfusion. Reperfusion-induced hemorrhages have been the focus of several recent studies (33,34), and some satisfaction was derived from the fact that the hemorrhages are generally included within the irreversibly damaged cardiac tissue. Yet, hemorrhage exacerbates tissue swelling which results in obtunded myocardium and functional derangements, which, in turn, are related to the size of the eventually developed infarction. The "lagging return of mechanical or metabolic function," even when reperfusion involves reversibly injured myocardium, has been highlighted and we may expect more clarification of mechanisms, implications and treatment. We believe that the ultrastructural and functional end points of reperfusion effectiveness deserve further study, because it is absolutely essential to ascertain weeks or months after the reperfusion if salvage is complete and permanent, or if the reperfused zones may be the seat of further chronic ischemia and arrhythmogenicity.

Equally important, throughout the early and subsequent period of reperfusion, it is necessary to have an accurate picture of alterations in myocardial contraction and perfusion. Repeated coronary angiography is, of course, quite valuable but must be limited from a practical standpoint. We find that the new computerized imaging techniques of contrast enhanced digital angiography, thallium and technetium methodologies and computerized myocardial contrast two-dimensional echocardiography will provide quantitative data on the extent of regional and global function and dysfunction. They will reveal, in particular, the spontaneous or treated course of contraction, chamber volume phasic wall thickness and thinning plus perfusion in both ischemic reperfused and normal zones of the heart (20,21). These measurements should prove to be valuable supplements of prevalent electrocardiographic and cardiac enzyme methods that have been of limited value in the quantitative assessment of reperfusion. It is important to provide prompt, long-term accurate monitoring to provide documented evidence of the therapeutic effectiveness of measures which protect jeopardized myocardium during the crucial acute stages of ischemia and reperfusion.

It is satisfying to note the substantial success of new techniques such as thrombolysis and percutaneous transluminal coronary angioplasty; however, caution is indicated until the longer term effects and results can be correctly assessed. We believe that problems such as the severe post-reperfusion derangements and perioperative infarction after acute coronary occlusions or revascularization indicate a need for further study of reperfusion mechanisms. Improved models are also needed to investigate incomplete or gradual rather than total and suddenly applied reperfusion, because the mode of reperfusion would influence the derangements caused by rapid washout, calcium overloading, myocardial edema, microvascular damage and hemorrhages (19). Finally and fundamentally, reperfusion must be applied as early as possible, while much of the myocardium is viable and injury is still reversible. Wherever possible, irreversible myocardial damage must be avoided and viability maintained through treatment promptly delivered to the most severely jeopardized region. This treatment should be started very early after the initial acute ischemic event and carried through the early and unstable reperfusion period until effective restoration of perfusion, contraction, metabolism and electrophysiologic function is achieved.

An optimal treatment cannot be specified as yet and would depend on many considerations, such as the nature and extent of ischemic injury. However, retrograde coronary venous delivery of arterial blood and hypothermia to the jeopardized region is promising and may provide the desired

support before and after coronary reperfusion (20). Caution should be exercised to minimize physical stress and myocardial demands during the critical period after reperfusion, which may extend up to several weeks and during which function may slowly recuperate. We believe that an excellent opportunity now exists for rational application of reperfusion, along with appropriate and essential monitoring utilizing modern cardiac imaging techniques.

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