Specialty Conference

Cardiac Ischemia. Part II—Reperfusion and Treatment

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GLENN A. LANGER, MD: In the previous issue we reviewed the physiologic and metabolic responses to cardiac ischemia. It was noted that there were immediate (within seconds to minutes) alterations in potassium flux and loss of contractile function after the onset of ischemia. These responses are implicated in the electrical dysfunction that results in sudden death and in the mechanical dysfunction that produces early pump failure. Following this acute phase there is a period of one to six hours during which metabolic dysfunction develops, which can be accurately monitored with the use of positron emission tomography (PET). These studies indicate the possibility of a major dissociation of blood supply and metabolic activity in the ischemic zone. The preservation of metabolic activity, as defined by PET, can be used as an objective indication in the determination of benefits to be expected by reperfusion.

In this issue the focus is on treatment with emphasis on surgical reperfusion (Dr Gerald Buckberg) and thrombolytic therapy and percutaneous transluminal angioplasty (PTCA) (Dr Jan Tillisch).

Myocardial Response to Reperfusion

GERALD D. BUCKBERG, MD:* The immediate recovery of regional contractility does not follow normal blood reperfusion after a duration of coronary occlusion as short as 15 minutes,[1] and segmental shortening may not return for as long as a month after two hours of temporary ischemia, if the working heart is reperfused with unmodified blood.[2,3] Coronary occlusion of six hours' duration is thought to produce such extensive transmural necrosis[4,5] that clinical muscle salvage cannot be expected even a year after reperfusion. Consequently, there is limited enthusiasm for either medical (streptokinase or angioplasty or both) or surgical—that is, coronary artery grafting—revascularization in patients who have had acute occlusion for six hours.

Our experimental studies have extended the period of regional ischemia to this six-hour interval. Our results, first, show the remarkable structural and functional integrity of transmural myocardial tissue after six hours of ischemia; second, document the extensive "reperfusion injury" produced by normal blood reperfusion with the heart in a beating working state after only four hours of ischemia, and third, show that modification of reperfusion damage, muscle salvage and immediate functional recovery is possible after six hours of ischemia by careful *control of the conditions and composition of reperfusion.*[6]

These experimental studies form the basis for our current clinical approach to treating acute myocardial infarction surgically. We shall present our preliminary surgical results and propose a new potential strategy whereby regional blood cardioplegic reperfusion on total bypass without thoracotomy—that is, in the catheterization laboratory—can be accomplished.

Experimental Studies in Animals

In experimental studies on anesthetized dogs whose chests have been opened, the proximal left anterior descending coronary artery was occluded with the heart in a working state to produce an area of risk of about 30%, and regional contractility was assessed by ultrasonic crystals.[6] All dogs underwent cannulation of the femoral artery and right atrium by way of the femoral vein; left ventricular venting was accomplished by the transaortic route (Figure 1) to allow reperfusion on total vented bypass in dogs undergoing controlled reperfusion. These cannulae were connected to a pump oxygenator circuit, and a catheter was placed into the distal left anterior descending coronary artery for regional cardioplegic reperfusion only in those dogs who received blood cardioplegic reperfusion.

Experimental groups differed in duration of ischemia and method of reperfusion:

- *Ischemia without reperfusion.* Seven dogs underwent six hours of acute coronary artery occlusion without reperfusion and transmural biopsy specimens were taken for ultra-

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ABBREVIATIONS USED IN TEXT

ATP = adenosine triphosphate
CoQ_{10} = coenzyme Q_{10}
IV = intravenously
PET = positron emission tomography
PTCA = percutaneous transluminal coronary angioplasty
TPA = tissue plasminogen activator
TTC = triphenyltetrazolium chloride

structural and mitochondrial functional analyses after prolonged ischemia.

• *Normal blood reperfusion in working hearts.* Nine dogs underwent two hours of acute coronary artery occlusion and seven dogs underwent four hours of acute occlusion followed by reperfusion with normal blood at systemic pressure (removal of occluding clamp) in working hearts to simulate angioplasty in a catheterization laboratory without the use of bypass.

• *Blood cardioplegic reperfusion during total vented bypass.* In 20 dogs, the left anterior descending coronary artery was occluded for two hours (5 dogs), four hours (8 dogs) and six hours (7 dogs), respectively. All hearts received regional blood cardioplegic reperfusion on total vented bypass. The conditions of reperfusion and composition of the reperfusion were controlled in the following manner: The conditions of reperfusion, which was modified, included (1) total heart decompression by vented bypass to prevent wall tension from developing in the damaged heart during reperfusion, thereby increasing its oxygen demands[7]; (2) gentle reperfusion pressure—that is, 50 mm of mercury—to limit postischemic edema produced by sudden reperfusion[8]; (3) regional cardioplegia to keep energy demands as low as possible during temporarily controlled reperfusion[8]; (4) normothermia to optimize the rate of cellular repair,[9] and (5) prolonged reperfusion duration—that is, 20 minutes—to maximize excess oxygen uptake relative to demands and avoid premature imposition of high-energy demands.[10] Total bypass was continued for 30 minutes after regional reperfusion and then stopped to allow observation for one additional hour with the heart in the working state.

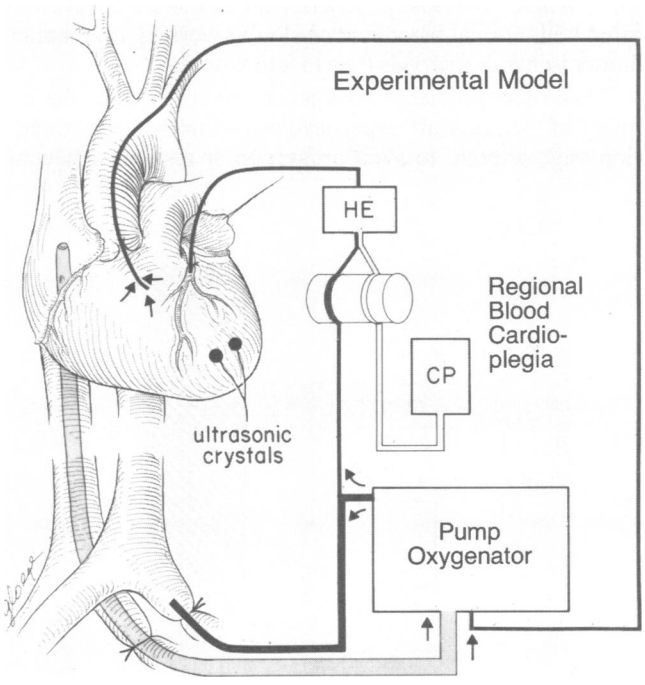

Figure 1.—Experimental model showing peripheral cannulation technique used to achieve total vented bypass without requiring direct right atrial, aortic or left ventricular penetration. Regional contractility was determined by ultrasonic crystals, and regional cardioplegic reperfusion delivered into the coronary artery directly (this can be achieved by a coronary balloon passed fluoroscopically; see text for description). CP = cardioplegic delivery system, HE = heat exchange

TABLE 1.—*Cardioplegic Solution*

Principle	*Constituent*	*Final Concentration*
Provide oxygen	Blood	Hematocrit 20% to 30%
Maintain arrest	Potassium chloride	12 to 16 mEq/liter
Buffer acidosis	Tromethamine	pH 7.5 to 7.6
Avoid edema	Glucose	>400 to 450 mosm
Restore substrate	Glucose	>400 mg per dl
	Aspartate	13 mmol/liter
	Glutamate	13 mmol/liter
Scavenger O_2 radical	Coenzyme Q_{10}	80 μg/ml
Limit calcium entry	Cardioplegic delivery	150 to 250 μmol Ca^{++}
	Diltiazem	300 μg/kg body weight

The reperfusion composition was modified to permit (1) oxygenation with blood, providing substrate (O_2) to generate energy to repair cellular processes[11]; (2) cardioplegia (hyperkalemia) to keep the heart from resuming electromechanical activity and raising O_2 demand[9]; (3) replenishment of amino acid precursors or Krebs' cycle intermediates (that is, glutamate, aspartate) needed to ensure more effective oxidative metabolism to produce energy for cell repair and subsequent mechanical function[12]; (4) limiting calcium influx by reperfusate hypocalcemia (150 to 250 μmol) with citrate-phosphate-dextrose to reduce calcium load, and adding a calcium channel blocking drug (that is, diltiazem) (which could continue to retard calcium cell entry after normocalcemic reperfusion is started)[13]; (5) reversal of acidosis with a buffer to provide an optimal intracellular milieu for effective resumption of metabolic function[14]; (6) hyperosmolarity—that is, using glucose—to minimize postischemic edema and permit cell volume regulation to occur more gradually when normothermic blood flow is restored[15]; (7) membrane stabilization with the use of coenzyme Q_{10} (CoQ_{10}) to avoid damage to the phospholipid bilayer[16,17] and glucocorticoids to limit lysozymal disruption[18]; (8) counteracting oxygen free radicals with oxygen free-radical scavenger—that is, CoQ_{10}—to limit the cytotoxic effects of these compounds, and (9) hyperglycemia to enhance the osmotic effects and perhaps initiate compartmental anaerobic energy production at the onset of reperfusion.[19] These reperfusate principles were accomplished with the agents shown in Table 1—which defines the regional reperfusate used in these studies—but may also be accomplished by other, untested agents (that is, different buffers, oxygen radical scavengers, calcium channel blocking and cardioplegic drugs) that produce these desired effects.

Ischemia for six hours without reperfusion produced only mild structural alterations. Myofibrils were intact, mitochondria showed integrity of the inner and outer membranes and only mild clarification of the matrix. At least 200 mitochondria were examined in each muscle layer in each heart by the low protein denaturation technique,[20] and the average mitochondrial grades ranged from 1.2 in epicardial muscle to 1.9 in endocardial muscle (grade 6 is complete disruption) (Figure 2). This ultrastructural integrity was accompanied by

substantial retention of mitochondrial respiratory function; the adenosine triphosphate (ATP) production rate (stage 3 respiration × adenosine diphosphate/0) was maintained at 64% of control levels (589 versus 925 nmol ATP per grams protein per minute) after six hours of regional ischemia.

Dyskinesia (systolic bulging) persisted throughout the ischemic interval in all experiments. Reperfusion with normal blood with the heart in the beating, working state failed to restore regional systolic shortening after two or four hours of ischemia ($-35\% \pm 6\%$ and $-13\% \pm 4\%$ systolic shortening) measured after the first hour of observation after revascularization. In contrast, immediate recovery of systolic shortening occurred in each of 13 hearts reperfused with substrate-enriched blood cardioplegia on total vented bypass after two and four hours of ischemia ($52 \pm 2\%$ and $40 \pm 7\%$) and in six of seven hearts ($21 \pm 6\%$ systolic shortening) undergoing control reperfusion after six hours of coronary artery occlusion (Figure 3).

Acute coronary artery occlusion produced profound transmural ischemia, reducing flow (radioactive microspheres) to less than 5% of control levels. Reperfusion with normal blood with the heart in the beating, working state after only two hours of ischemia restored transmural flow to only 47% of control levels. In contrast, all hearts reperfused after six hours of ischemia with blood cardioplegia on total vented bypass had pronounced transmural hyperemia (Figure 4).

Histochemical muscle damage (triphenyltetrazolium chloride [TTC] nonstaining) was least severe (12% area of nonstaining versus area at risk) after two hours of ischemia followed by controlled conditions and composition of reperfusate and most severe (73% area of nonstaining versus area at risk, $P < .05$) following normal blood reperfusion after four hours of regional ischemia. More extensive nonstaining followed controlled reperfusion in nonbypassed hearts after four hours of ischemia than after controlled reperfusion following six hours of regional ischemia (73% versus 55%, $P < .05$).

Uncontrolled reperfusion (normal blood in working hearts) after four hours of ischemia produced moderately severe transmural architectural disruption, with the most severe damage (grades 3.7 and 3.4) in endocardial and midmyocardial muscle; there was breakdown of mitochondrial cristae, with filling of the mitochondrial space with amorphous vesicles and intensely stained material. In contrast, the average grade for mitochondrial change after blood cardioplegia reperfusion on total vented bypass was comparable to that occurring with ischemia alone (1.2 and 1.9) where inner and outer mitochondrial membranes were intact and myofibrils were unaltered.

These experimental studies show that immediate partial recovery of regional contractile function is possible after as long as six hours of acute coronary artery occlusion, provided that the conditions of reperfusion and composition of reperfusate are controlled carefully. Such control results in higher postischemic flows and in superior ultrastructure when compared with normal blood reperfusion of working hearts after shorter ischemic intervals (two to four hours).

These data provide experimental confirmation of the inability of "successful" reperfusion with streptokinase or angioplasty, or both, to avoid infarction or restore early con-

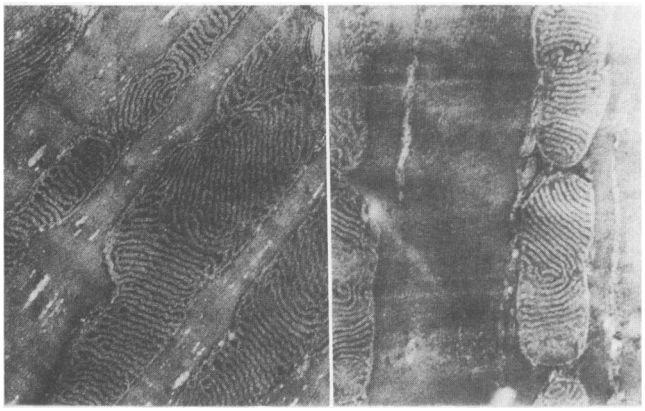

Figure 2.—The mitochondrial ultrastructure, prepared by the low denaturation embedding technique, shows a relatively normal appearance of mitochondria after 6 hours of ischemia (right panel) compared with control (left panel).

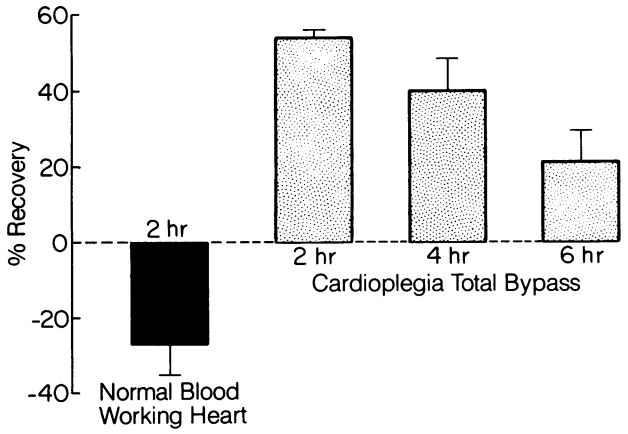

Figure 3.—Segmental shortening after reperfusion, expressed as percentage of recovery of systolic shortening, is compared with control after normal blood reperfusion in working heart (solid bar) and substrate-enriched blood cardioplegic reperfusion on total vented bypass (stippled bars). Note failure to recover systolic shortening after uncontrolled reperfusion at 2 hours (solid bar) and immediate recovery of systolic shortening after 2, 4 and 6 hours of ischemia after controlled reperfusion.

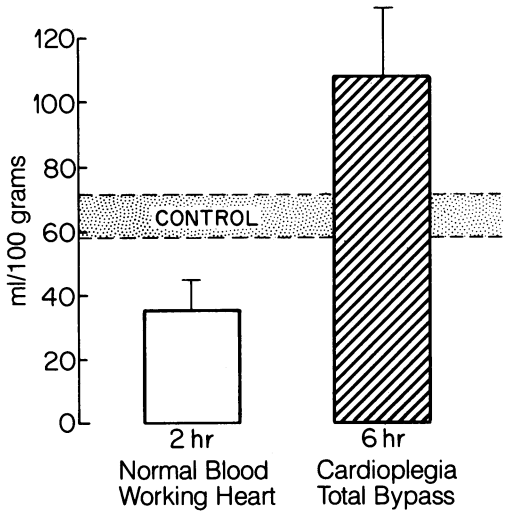

Figure 4.—Left ventricular transmural blood flow (microspheres) is shown after reperfusion with normal blood in working heart (open bar) and substrate-enriched blood cardioplegic solution on total bypass (hatched bar). Control values are shown in stippled bar. Note the low reflow with uncontrolled reperfusion after 2 hours of ischemia and hyperemic flows after 6 hours of ischemia and controlled reperfusion. Units given represent the mean ± standard error.

TABLE 2.—*Global and Regional Contractility*

Cardiac Indices	*Medical Treatment*	*Surgical Treatment*
Global ejection fraction, %	41±2*	47±2*
Regional recovery		
Wall-motion score†	2.5±0.5*	1.3±0.2*‡
Points <2.0	2 of 21 (10%)	12 of 12 (100%)

*Values are mean ± standard error.
†Wall-motion grade: grade 0=normal, grade 1=mild to moderate hypokinesis, grade 2=severe hypokinesis, grade 3=akinesis, grade 4=dyskinesis.
‡$P < .05$.

TABLE 3.—*Control During Reperfusion*

Approach	*Surgical Treatment*	*Medical Treatment*
Arterial inflow	Aorta	Femoral artery
Venous return	Right atrium	Right atrium (via femoral vein)
Ventricular vent	Left ventricle (direct)	Left ventricle (transaortic)
Regional reperfusion	Coronary artery bypass grafting	Coronary catheter

tractile function to regional segments revascularized in the catheterization laboratory.[21-23]

Preliminary Clinical Studies

The principles of reperfusion control emerging from these experimental studies were applied by us in a preliminary series of patients with acute evolving myocardial infarction. We compared the results after surgical control of the conditions of reperfusion and composition of the reperfusate with those achieved by "successful" streptokinase or angioplasty or both, where no attempt was made to exert reperfusate control except to restore blood flow per se to the ischemic segment.

A total of 33 consecutive patients with acute coronary artery occlusion underwent either medical or surgical revascularization. Medical reperfusion was with normal blood in 21 patients in the catheterization laboratory (that is, streptokinase therapy, N = 11; angioplasty, N = 10) after 4.4 ± 0.5 hours of acute coronary artery occlusion. Surgical reperfusion was with substrate-enriched (glutamate plus aspartate) blood cardioplegia during coronary artery grafting after naturally occurring occlusion in 12 patients revascularized 8.8 ± 6 hours (range 7.4 to 13.5 hours) after occlusion.[21]

Medical revascularization produced cardiogenic shock (stroke work index <20 grams • m per m^2, pulmonary artery wedge pressure >20 mm of mercury) in 7 of 21 previously hemodynamically stable patients—5 with single-vessel disease—whereas surgical revascularization reversed cardiogenic shock in 6 of 12 patients with preoperative hemodynamic instability due to coronary occlusion. Surgical results were superior in incidence of infarction as recorded by electrocardiogram (57% versus 100%, $P < .05$), severe ventricular tachyarrhythmias (0% versus 43%, $P < .05$), recovery of global ejection fraction (47% versus 41%), recovery of significant regional contractility (100% versus 9%, $P < .05$) and duration of hospital stay (8.8 versus 11 days, $P < .05$), despite a delay of surgical treatment for as long as 12 hours. No patient died (Table 2).

These preliminary clinical results are directly comparable with those achieved experimentally and may lead to the conclusion that selected patients with acute coronary artery occlusion should be treated surgically. Control of the conditions and composition of reperfusion may, however, be achieved medically without thoracotomy (Table 3). The right atrium can be decompressed by way of the femoral vein, arterial influx can be delivered through the femoral artery and left ventricular decompression can be achieved by using a catheter passed transaortically from a peripheral artery, while the regional cardioplegic reperfusate can be administered through a reperfusion catheter advanced through the clot and stenosis as occurs with angioplasty done emergently.

This proposed future approach to patients with acute coronary artery occlusion is shown in Figures 5 and 6. The process of infarction can be arrested by placing a patient on total

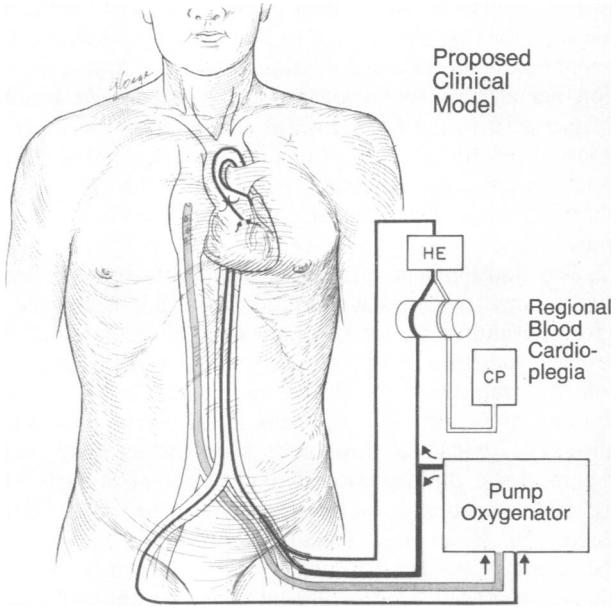

Figure 5.—Proposed experimental model of total vented bypass and regional cardioplegic reperfusion without thoracotomy. Note that the venous return catheter is advanced from the femoral vein to the right atrium, that arterial inflow is through the femoral artery, that left ventricular decompression is achieved by means of a transaortic catheter from the femoral artery and that the reperfusate catheter is passed into the coronary artery by way of the coronary ostia from the femoral artery. CP = cardioplegic delivery system, HE = heat exchanger

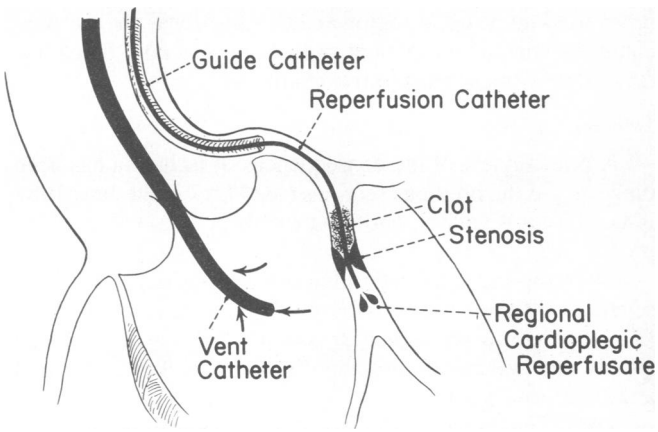

Figure 6.—A close-up version is shown of a proposed technique to decompress the left ventricle via a ventricular vent catheter passed across the aortic valve and a regional cardioplegic catheter passed through a coronary guide catheter, through clot and across the stenotic region into a distal coronary vascular bed (see text for description).

vented bypass in the catheterization laboratory so that an angiogram can be safely carried out and the decision made whether to do controlled regional reperfusion followed by angioplasty (single-vessel disease) or to transport the patient to the operating room on total vented bypass for surgical revascularization (multivessel disease or occluded arteries, or both, that cannot be penetrated by a guidewire).

We interpret the findings of these experimental and clinical studies to indicate that muscle salvage and restoration of early contractile function is possible in myocardium that is ischemic for six or more hours, if there is rigid control of the reperfusate conditions and composition.

Current Approaches in the Treatment of Ischemia

JAN H. TILLISCH, MD:* After many decades of therapeutic focus on the consequences of ischemic injury—arrhythmias, pump failure or mechanical lesions, such as mitral regurgitation, aneurysm or septal defects—in the past decade there has been a shift in the focus toward ameliorating the ischemic injury itself, first by attempting to reduce myocardial oxygen demands and, more recently, by pharmacologically or mechanically restoring perfusion during the evolution of an ischemic injury.

The development of clinical techniques of reperfusion during acute myocardial infarction has made necessary the careful examination of the complex interplay of factors that result in ischemic injury. The duration of ischemia is not the sole determinant of the degree of myocardial injury. The severity of the ischemia (as determined by the presence or absence of collateral flow or by spontaneous early partial reperfusion), the myocardial oxygen demands during the ischemic period and, more important, at the time of reperfusion, the preocclusive metabolic state of the myocardium, the nature of the reperfusate and the hydrodynamics of the actual reperfusion process all may have a significant determinative effect on the degree of myocardial salvage achieved by reperfusion.

We have witnessed during the past five years a flood of clinical and experimental studies showing the technical ability to achieve reperfusion in patients with acute infarction with safety and with a success rate varying between 30% and 100%, depending on the techniques chosen and the patient population studied. The metabolic and functional state of the reperfused myocardial region and the functional and survival characteristics of the patient population are now being addressed in various investigative studies.

Ischemic Injury

A brief review of the consequences of ischemia has been presented in the previous sections (see Part I in the June 1987 issue of THE WESTERN JOURNAL OF MEDICINE, volume 146, pp 713-723).

The temporal sequence of these processes depends on the severity of the ischemia and the metabolic state of the myocardium, as determined largely by the relation between oxygen supply and demand before and during the ischemic interval and at the time of reperfusion.

The optimal current and future therapy for acute ischemic injury must be considered in light of these events. Three general approaches to acute ischemic injury may be considered: first, the more "traditional" approach of attempted pharmacologic reduction in myocardial oxygen demands and enhancement of supply, coupled with aggressive treatment of secondary complications of myocardial infarction (arrhythmia, pump failure) but without attempts at reperfusion; second, attempted reperfusion using thrombolytic agents, particularly streptokinase or tissue plasminogen activator, and third, "mechanical" reperfusion using percutaneous transluminal angioplasty or coronary artery bypass grafting.

Therapy Without Reperfusion

The first mode of therapy is clearly not a static one. Recent studies have suggested that the aggressive use of nitroglycerin given intravenously (IV) in the early stages of acute myocardial infarction reduces postinfarction morbidity.[24] Controversy remains about the initial use of β-blockade in patients with evolving myocardial infarction.[25] Metabolic enhancement with glucose-insulin-potassium infusions seems to be beneficial.[26] The impact, however, of newer pharmacologic means of manipulating myocardial metabolic demands has been difficult to discern, hampered to some extent by the lack of sensitivity of the diagnostic methods used to judge that impact.

Thrombolytic Therapy

Thrombolytic reperfusion has been achieved by the intracoronary administration of streptokinase in about 60% to 80%[22,27] of patients with occluded infarct-related arteries. In these two large randomized studies, the mortality results were discrepant; in the study reported by Rentrop and associates,[22] no significant difference in mortality rates was observed, while in the western Washington trial, a slightly improved survival was noted in the treatment group at one year, but only after statistical adjustment for nonmatching variables in the two groups.[27] As with previous uncontrolled trials, those patients in whom reperfusion was achieved had improved mortality rates, not surprisingly showing that thrombolysis had apparent benefit but that the overall success in a large patient group was limited by the actual success in achieving reperfusion. Because of the need for cardiac catheterization to use this form of therapy, with the attendant delay in application and the logistic difficulties of having catheterization facilities on demand, intracoronary thrombolysis seems to have only a limited application, given the marginal effects observed on mortality results and the lack of effect on ventricular function.[23,27]

Intravenous administration of thrombolytic agents has the obvious appeal of greater speed and ease of administration, with the concomitant drawback, particularly in the case of streptokinase, of an increased systemic thrombolytic state with consequent increased risk of bleeding complications. The reports of nonrandomized trials have suggested again that successful thrombolysis was associated with an improvement in survival both of myocardium at risk and of patients. Documented successful reperfusion, however, was achieved in only 35%[28] in one randomized trial, although higher rates of successful thrombolysis have been reported.[29]

Despite the rather low success rate of the use of IV streptokinase, several studies have shown a lower mortality rate with its use as compared with conventional therapy.[30,31] Factors that may influence those results will be discussed subsequently. Nonetheless, a more consistently effective thrombolytic agent has been sought, and initial trials with tissue plasminogen activator (TPA), derived from recombinant

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DNA technology, are promising. TPA does not induce a systemic thrombolytic state, a theoretic advantage in terms of hemorrhagic complication. The risk of hemorrhage, however, appears to be due to subsequent heparin therapy in most instances, rather than the dose or type of thrombolytic agent. A study comparing IV streptokinase with IV TPA found that 60% achieved reperfusion with TPA as against 35% with streptokinase. Despite this large difference in successful thrombolysis, the hospital mortality rate was not significantly different. The previously shown benefits of successful thrombolysis (as against the benefits accruing to the applied therapy as a whole) suggest that an improved incidence of successful reperfusion is associated with improved myocardial salvage and therefore mortality in the treatment group. The correlation, however, of improved myocardial salvage and improved patient mortality figures has not as yet been conclusively shown with intravenous thrombolytic agents.

Several factors influence the success of thrombolytic reperfusion in myocardial salvage; other factors may influence the effect on patient mortality rates.

The time to reperfusion is obviously a critical factor. Attempted reperfusion after more than 1½ to 2 hours of chest pain in patients with evolving "transmural" infarctions has been associated with little or no effect on regional myocardial function judged by wall-motion studies within one to two weeks of therapy.[32,33] This was found despite comparable success in reperfusion in "early" and "late" treatment groups. Indeed, no study has suggested that reperfusion success itself is influenced by the time of treatment relative to the onset of symptoms. It is the degree of myocardial salvage that seems influenced. Nonetheless, one cannot definitively state from present data that beneficial effects of thrombolytic reperfusion accrue only to those treated early. Subgroup analysis of the reported studies has not been done in such a way as to determine whether enhancing global myocardial blood flow by reperfusion may affect long-term morbidity without necessarily affecting myocardial salvage in the region of the infarction. Findings of the western Washington intracoronary streptokinase trial, where mortality was marginally improved in the treated group without a discernible effect on ventricular function, may be interpreted as supporting the hypothesis of improved survival without "salvage" of infarcting tissue.[23,27] Moreover, analysis of ventricular function in this trial was done at a mean of eight weeks after acute infarction, a sufficient time period to permit return of function of "stunned" but viable myocardium. Determination of regional or global ventricular function at shorter intervals (3 to 14 days in most published thrombolytic trials) may fail to show recovery of function of reperfused myocardium, which at a later date will show improvement in contractile performance, particularly in those patients treated beyond one to two hours of ischemia.

The intensity of ischemia may be an even more important influence on ventricular function and ultimate patient survival than the duration. Three components of this factor may be operative. First, the degree of residual flow through a partially occluded artery, or the degree of spontaneous early reperfusion—that is, before treatment—has been seen only in studies where coronary angiography was done before administration of the thrombolytic agent. The presence of an incompletely occluded artery before therapy (or in control groups) is associated with greater short-term improvement in ventricular function.[22,34] The second component affecting the intensity of ischemia is the presence of collateral flow at the time of pretreatment angiography. Several studies have shown that the improvement in ventricular function after successful reperfusion occurs largely in patients who had angiographically demonstrable collateral flow to the infarct vessel distribution.[35,36] The presence of collateral, residual or early spontaneous reperfused flow seems to have a major effect on the degree of ventricular salvage achieved by thrombolysis, despite being insufficient to avoid infarction altogether. A third component of the ischemic state is the degree of residual coronary luminal narrowing after thrombolysis. Several studies indicate more successful return of contractility in the region of infarct when the residual stenosis was modest[37] or when percutaneous transluminal coronary angioplasty (PTCA) was done early after successful thrombolysis.[38] In addition to the possible beneficial effects of increased blood flow through a minimally obstructed artery on myocardial recovery, the incidence of postthrombolytic reocclusion was lower in those patients with less residual stenosis.[37]

Another factor that may influence the extent of myocardial salvage consequent to reperfusion is the mechanical loading condition of the ventricle at the time of reperfusion. Although often difficult to assess clinically, experimental studies by Buckberg (see previous section) and by Laschinger and associates[39] show the importance of reduced myocardial oxygen requirements through reduction of mechanical work during reperfusion. Whether pharmacologic manipulation of hemodynamics using aggressive coronary and systemic vasodilatation, calcium channel blocking agents or β-blockade have particularly beneficial effects at the time of reperfusion is as yet unexplored but theoretically attractive.

Percutaneous Transluminal Angioplasty

Percutaneous transluminal coronary angioplasty as a mode of primary reperfusion during the evolution of acute infarction has advantages over thrombolytic therapy but clearly counterweighing disadvantages, principally related to the delay in initiating therapy.

The published success rate for reperfusion with PTCA is comparable to the intracoronary administration of thrombolytic agents.[40] The concern noted earlier about the deleterious effects of the residual stenosis is of course obviated by PTCA. Evidence from several studies suggests enhanced recovery of ventricular function with PTCA compared with that with thrombolysis alone.[41,42] The delay inherent in angioplasty, however, although of only modest statistical significance in a large study, may be of major individual significance in a patient with a large but partially collateralized anterior infarction. Again, one must weigh the risk of delay with PTCA as against the risk of failure to reperfuse with IV streptokinase or TPA.

The combination of PTCA with the intracoronary administration of streptokinase or TPA does not seem to enhance successful reperfusion, nor does it diminish the delay in therapy associated with the use of an angiographic technique. The initial use of IV thrombolytic agents (after placing an intraarterial sheath) and then the subsequent use of PTCA seem to offer several advantages: therapy is begun early, ineffective reperfusion may be addressed at cardiac catherization with either additional intracoronary thrombolysis or with PTCA and residual stenosis can be directly dealt with at the time. The disadvantages are that the safety of urgent coronary artery bypass grafting should PTCA result in vascular trauma or reocclusion is compromised by the thrombolytic state; the

logistic concerns regarding the necessity for 24-hour availability of catheterization laboratory remain, and a post-thrombolytic, late-catheterization procedure to determine the degree of vessel patency means a patient would require two coronary angiograms, with the additional expense and risk. If these objections are met with evidence of improved long-term survival, morbidity and ventricular function, then this form of therapy may be an appropriate choice.

Coronary Artery Bypass Grafting

DeWood and colleagues have repeatedly shown that there is a low mortality rate when coronary artery bypass grafting is done within the first six hours of infarction.[43] Although uncontrolled, these studies are compelling if not totally convincing. The delay in reperfusion with immediate coronary artery bypass grafting is substantially greater than with other forms of reperfusion. Logistic and as-yet-undetermined cost considerations aside, the ability to achieve adequate and complete revascularization must be weighed against the loss of possibly salvageable myocardium with this delay. Data discussed previously by Dr Buckberg, however, show that the experimental treatment of ischemic injury is best done when "the conditions and composition" of the reperfusate can be controlled. The period of time during which substantial myocardial salvage can be expected is prolonged substantially by confining initial metabolic efforts after reperfusion to the cellular tasks of membrane maintenance, calcium sequestration, volume regulation and replenishment of metabolic intermediates, high-energy phosphate precursors and stores before requiring contractile work to be done.

The clinical dilemma is determining when the time is past for unmodified and uncontrolled reperfusion. When, in an ischemic injury, does the benefit of a rapidly administered but only partially successful reperfusion technique become less than that provided by modified controlled reperfusion with the attendant delay in application? Moreover, will the logistic concerns and associated co-morbidity of immediate coronary artery bypass grafting be small enough to permit the widespread application of this technique? These critical questions remain to be answered.

Combining PTCA with modification of reperfusion as previously presented has exciting potential for shortening the delay and lessening the morbidity of surgical intervention implicit in selecting immediate coronary artery bypass grafting as therapy, but retains some of the advantages of more effective myocardial salvage, as shown experimentally with coronary artery bypass grafting and controlled reperfusion. This form of therapy awaits further development and validation of its effectiveness.

Current Clinical Choices

At this time, hard clinical data sufficient to determine a clinical course in a patient with acute myocardial infarction are not yet available. Clinical experience, however, coupled with current understanding of the pathophysiology of ischemic injury, permits some guidelines to be developed, with the usual caveats that individual patients require individual approaches and that continued reevaluation of results is required in areas where proof does not yet exist.

Patients who present with acute myocardial infarction and symptoms of a duration of one to two hours or less are best treated with intravenous thrombolytic therapy. Exceptions would of course be those with major hemorrhagic risk or advanced age. The presence of prior myocardial infarction, severe hemodynamic compromise or extension of an acute infarction into other vascular distributions would be situations wherein myocardial salvage may not entirely depend on thrombolysis of a single vessel but rather on the cascade of increased demand on adjacent myocardium with a compromised blood supply. In such cases, the best approach seems to be immediate coronary artery bypass grafting with modified reperfusion of the infarcted vessel and revascularization of other arteries.

In patients who present with an apparent duration of ischemia of between two and four hours, the ability to preserve substantial myocardium seems to be limited largely to those with incomplete occlusion or a collateralized infarct region. The delay associated with demonstration of that state by angiography and proceeding to use either PTCA or thrombolysis with PTCA to follow may therefore have relatively little consequence in terms of myocardial salvage. The greater reperfusion success rate with PTCA, or the intracoronary use of thrombolytic agents, and the opportunity at catheterization to discover a need for multiple lesion revascularization by coronary artery bypass grafting or PTCA might lead one to select coronary angiography as the first step in managing a patient with ischemic injury of two to four hours' duration. If IV tissue plasminogen activator proves to be as successful as PTCA or intracoronary thrombolysis (about 70%), then this would seem to be the preferred initial choice, until such time that nonsurgical controlled reperfusion might become a reality.

It is in this group of patients with ischemia of sufficient duration to militate against myocardial salvage with any but modified reperfusion that there is the greatest confusion as to appropriate therapy. Clearly, diagnostic methods are needed to attempt to differentiate patients in whom sufficient residual flow in the infarct region persists to mandate an early attempt at noninvasive thrombolysis. A short delay in therapy attendant to applying some diagnostic method of differentiating the potentially salvageable from irreversibly injured myocardium would be a reasonable price to pay, if it permits more appropriate application of therapy.

Patients who present with evidence of ischemia for longer than four to six hours will, in general, derive no benefit from immediate thrombolytic techniques. The maximum interval with modified direct reperfusion is as yet unknown. Clearly some patients with chest pain of more than four to six hours will still have substantial myocardium at risk but salvageable. The absence of electrocardiographic Q waves, the continued presence of substantial ST-segment elevation and the presence of hypokinesis or dyskinesis as against akinesis on echocardiography may be "soft" indicators of continued viability. Again, diagnostic methods of determining tissue viability need to be validated.

With any of these techniques, concurrent therapy with IV nitroglycerin, aggressive treatment of congestive heart failure, rigorous control of hypertension and treatment of tachycardia are supplemental and important. Continued investigation into the benefits of pharmacologic agents that may enhance anaerobic metabolism, diminish transmembrane calcium flux, prevent generation of oxygen-free radicals and diminish myocardial membrane injury must be particularly tested in the reperfusion model and subsequently in that clinical setting.

What was once conceived of as an irreversible insult—the

cessation of flow to contracting myocardium—has been shown after short intervals to be partially and potentially reversible. The temporal limits of reversibility in cases of acute ischemic injury have not as yet been clearly defined.

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