The goals of myocardial protection during cardiac surgery are not only to facilitate the operation by providing a quiet bloodless field, thereby facilitating the precision of the operation, but also to avoid iatrogenic injury induced by cardiopulmonary bypass itself or by surgically imposed ischemia. In addition, myocardial protective strategies are geared to preventing reperfusion injury upon resolution of the coronary occlusion and the ultimate release of the aortic cross clamp. Cardioplegia plays a very important role in myocardial protection strategies. Acting as a selective perfusion agent, cardioplegia solutions can alter or inhibit ischemic injury by virtue of hypothermia and asystole. In addition, cardioplegia can be used to avoid reperfusion injury by altering the conditions of its delivery and the composition of the solution using various adjunctive agents and pharmacologic therapies for which cardioplegia solutions serve as a vector. Future strategies, particularly for off-pump surgical procedures, may incorporate systemic delivery of therapeutic agents to the heart directly either in conjunction with or without cardioplegia.

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INTRODUCTION

Myocardial ischemia, whether imposed by hypotension or shock, occlusive coronary artery disease, or aortic cross clamping during cardiopulmonary bypass, has the potential to impose severe damage to the myocardium and the coronary vascular endothelium. Periods of normothermic global ischemia as brief as 45 minutes will cause severe contractile dysfunction of the myocardium and as little as 15 minutes of regional ischemia will produce dysfunction in the absence of infarction ("stunning") (1, 2). If global or regional ischemia is severe and prolonged enough, frank necrosis of the myocardium will result. Interestingly, the damage imposed on the heart from ischemia is compounded after restoration of blood flow (reperfusion injury). Consequently, myocardial protective strategies should target amelioration of both ischemic and reperfusion injuries.

The goals of myocardial protection during cardiac surgery are not only to facilitate the operation by providing a quiet bloodless field, but also to avoid iatrogenic injury that occurs as a result of extracorporeal circulation, cross clamping the aorta, revascularizing an ischemic segment of myocardium, and then subsequently releasing the cross clamp. Other goals are to terminate clinical ischemia that is secondary to coronary occlusion or severe hypotension, and ultimately to prevent reperfusion injury upon resolution of the coronary occlusion and the ultimate release of the aortic cross clamp.

VICTIMS AND TIMING OF SURGICAL ISCHEMIC-REPERFUSION INJURY

There are numerous victims of ischemic-reperfusion injury. The myocyte is an extremely important casualty in the injury process, because it is the metabolic and functional center of the heart; it requires the greatest oxidative metabolism and ATP turnover rate to support its relentless energy demand. Although the myocyte has been most commonly recognized as the primary casualty of surgical ischemic-reperfusion injury, new victims of injury have recently been identified, most notably the coronary vascular endothelium. The coronary endothelium is not merely an inert cellophane layer or boundary at the vascular interface. It is, rather, an extremely active and important tissue or organ, because it releases a number of vasoactive factors that regulate organ blood flow and systemic blood pressure. It is also the immediate interface between the blood and the underlying myocardium and myocytes, a location that implies a gatekeeper function. The endothelium contributes either to the etiology of a number of disease states (i.e., thrombosis, hypertension) or is the target of various disease states (i.e., atherosclerosis, ischemic-reperfusion injury), as shown in Figure 1a. The endothelium plays a dual role; not only is it a source of deleterious activators (including platelet activating factor (PAF), endothelin-1 (ET-1), superoxide anion, histamine) that may injure coronary vascular endothelium, but the endothelium is also a source of nitric oxide (NO), adenosine, and prostacyclin (3) (Figure 1b), which protect against endothelial cell injury. Interestingly, NO can play a dual role of protector and injury mediator depending upon the amount released and presence of degradation metabolites (4–6). The larger epicardial macrovessels are less sensitive to injury, whereas, the smaller intramyocardial microvessels—arterioles and capillaries—are extremely sensitive to injury because of their close proximity to the ischemic myocardium. The high sensitivity of the vascular endothelium to the detrimental inflammatory effects of ischemia and reperfusion (7) after myocardial revascularization is amplified in patients with such diseases as hypertension, hypercholesterolemia, and diabetes mellitus (8, 9).

The heart of the patient undergoing cardiac surgery using cardiopulmonary bypass is vulnerable to myocardial injury at
several time points during the operation; categorized briefly as (1) antecedent to bypass; (2) during cardiopulmonary bypass initiation—the so-called “prebypass window” during which hypotension, arrhythmias (i.e., ventricular fibrillation) or acute occlusive coronary occlusion compromise the adequacy of blood flow before institution of cardiopulmonary bypass. Reperfusion injury can be sustained during this time window in patients with resolving vasospasm and a return to normotensive conditions following resuscitative efforts after ventricular fibrillation. Ischemic and reperfusion injuries can be encountered during the period of aortic cross clamp and the institution of cardioplegia using chemical arresting solutions. Ischemia during this time occurs with unresolved coronary artery stenosis, which impairs the distribution of cardioplegia to the myocardium distal to the occlusion. Ischemia is also encountered with obstructions within the vascular graft, whether related to mechanical impediments to flow (graft kinks, tight anastomosis) or emboli (air or particulate matter), and during inadequate cardioplegia delivery pressures. Reperfusion injury during this time can be sustained with each infusion of cardioplegia solution. The etiology of injury at this time is complex, and may be related to the composition of the cardioplegia solution, the delivery pressure and volume of cardioplegia (10).

Ischemia can also occur when the aorta is unclamped, and reperfusion is initiated. The potential causes of ischemia at this time include: (1) hypotension immediately after cross clamp removal or more likely during the weaning process; (2) thrombosis or mechanical obstruction of the vascular graft(s); (3) ventricular fibrillation leading to hypotension and maldistribution of blood flow to the subendocardium; or (4) vasospasm of the grafted vessel (i.e., left internal mammary artery). Reperfusion injury, on the other hand, may occur with resuscitative efforts after ventricular fibrillation or other severe arrhythmias, resolved hypotension or during delivery of secondary cardioplegia.

PATHOPHYSIOLOGY OF ISCHEMIA AND REPERFUSION

Figure 2 shows the purported mechanisms (and hence therapeutic targets) of injury during ischemia and reperfusion. Ischemic injury to a large extent is dependent upon the duration of the ischemic event, whether global or regional in nature. With ischemia being defined as the mismatch between oxygen supply (coronary blood flow and oxygen extraction) and oxygen demand (determined by the work load, wall stress, and inotropic state of the heart), the severity of ischemia is an important factor determining subsequent injury. The severity of ischemia may be offset by increased collateral blood flow. There is a linear relationship between collateral blood flow and infarct size; whereas, a similar clear-cut relationship has not been established between blood flow and contractile dysfunction. Although collateral blood flow may be considerable (2–50%) in regional ischemia, it is limited to non-coronary bronchial flow during global ischemia, which may be 1–3% of normal myocardial blood flow. The severity of ischemia may also be partially offset by the ambient level of glycolytic metabolism supplying energy in the form of ATP to maintain the intracellular and extracellular ions in an appropriate distribution. However, the myocardium has little glycolytic reserve and few biochemical adaptations to anaerobiosis to make this an efficient source of ATP. Two moles of ATP can be generated from each mole of glucose by glycolysis, while 36 moles of ATP can be generated by aerobic metabolism of one mole of glucose. The influx of calcium from a higher extracellular concentration to a lower intracellular concentration may occur during ischemia, and other ion shifts also occur, most notably accumulation of sodium and loss of potassium from the cell cytosol.

Reperfusion injury is, in large part, related to the preceding duration and severity of ischemia, because ischemia sets the stage for subsequent reperfusion injury. For example, oxygen radicals are thought to be generated primarily during the early moments of reperfusion, with a smaller but persistent generation during later phases of reperfusion, at which time continuous oxygen is being delivered to the myocardium. Hence, the environment for oxygen radical generation has been set up by the ischemic event, but adequate oxygen (and the presence of key generators such as neutrophils) for radical production are not available until reperfusion.

Neutrophils are a major player in reperfusion injury, because it is during the early moments of reperfusion that these inflammatory cells become activated, adhere to vascular endothelial cells, and propagate injury. In addition, neutrophils are carried to the previously ischemic tissue by blood flow made available only after reperfusion. Neutrophils are a primary source of oxygen radicals, as well as cytokines and other noxious agents (Figure 3). The interaction between neutrophils and vascular endothelium is an obligatory step to further neutrophil-
mediated damage, which forms a predominant component of reperfusion injury.

The ionic shifts that occurred during ischemia are further exaggerated during reperfusion, as water moves from the vascular compartment to the interstitial compartment leading to interstitial edema following ionic influx. Interstitial water follows the intracellular accumulation of chloride, leading to cellular water gain, edema, and swelling. Interstitial and intracellular swelling, as well as neutrophil accumulation in the vascular compartment leads to increased microvascular resistance and impairment to blood flow ("no reflow"), and possibly to a secondary ischemia attributable to microvascular collapse. Calcium is another contributor to reperfusion injury; (11–15) calcium may accumulate in the myocardium and particularly in the mitochondria. Calcium accumulation in mitochondria effectively poisons the ATP-generating capacity of the mitochondria, and the cell eventually dies.

**ROLE OF CARDIOPLEGIA IN REDUCING SURGICAL ISCHEMIC-REPERFUSION INJURY**

Cardioplegia offers a selective perfusion to the heart and the administration of agents to the heart in higher concentrations than may not otherwise be well tolerated when delivered systematically because of complications (i.e., hypotension). When these drugs are delivered selectively to the heart at cardioactive concentrations, dilution with systemic circulation may render the drugs benign to other organs. This is certainly the case with the most basic component of cardioplegia—potassium—which is often administered at five times the normal blood concentration.

It is important to understand that cardioplegia exerts cardioprotection during both ischemia and reperfusion because of the intimate link between ischemic injury (which sets the stage for later injury) and reperfusion injury. Cardioprotection by cardioplegia is exerted by modifying both the conditions of reperfusion and the composition of the reperfusate. In its simplest formulations, cardioplegia avoids ischemic injury primarily by substantially (>90% compared to the working heart) reducing oxygen demands by rapidly initiating hypothermia and cardiac asystole (16). Cardioplegia also avoids reperfusion injury by specifically targeting the pathophysiological mechanisms and mediators involved. Beneficial modifications of the conditions of cardioplegia infusion include infusion pressure, duration of infusion, volume of infusion of cardioplegia solution, and temperature of the solution. The methods by which cardioplegia reduces ischemic injury and reperfusion injury are discussed below. Finally, cardioplegia can be viewed as a vector for pharmacologic therapies to the heart using agents that target a specific aspect of either ischemic injury or reperfusion injury.

The inclusion of any pharmacologic agent in a cardioplegic solution should be based on scientific principles tested in the laboratory and supported by scientific literature. There should be a target toward which the agent or additive is aimed. This target could be the trigger of injury, the mechanism that perpetuates injury, or the victim of injury. Timing of pharmaceutical delivery is also very important; (17) a pharmacological agent that is given either before or after its intended target is involved in the injury process may not provide optimal cardioprotection. For example, if the therapy is designed to exert actions on mechanisms operative during ischemia, administration at reperfusion may be ineffective. Accordingly, agents that activate KATP channels on the myocyte may be ineffective when given during reperfusion (18, 19). This missed opportunity may also occur if adenosine, a potent cardioprotective autacoid, is given only during pretreatment and ischemia, and not during reperfusion, which limits adenosine’s actions to only several of many possible windows of opportunity (17, 20). Although adenosine has been shown to exert a portion of its effects before and during ischemia, it also has significant cardioprotective effects exerted during reperfusion. To target a specific mechanism, the appropriate time for action must be understood and the agent added at that point in time. In addition to the appropriate timing of administration, the appropriate physiological environment, such as hypothermia versus normothermia, or blood versus crystalloid cardioplegia solutions, must also exist. Although hypothermia has numerous advantages, as discussed below, it also reduces membrane fluidity and ligand–receptor interactions upon which many drugs depend for their effect. Therefore, hypothermia may attenuate the effectiveness of certain drugs. Furthermore, adequate delivery is extremely important, because the cardioplegic formulation cannot exert the effect for which it is designed if it is not adequately delivered to the target area; that is, by maldistribution of cardioplegia so-
olution, shunting, or reduced exposure due to abbreviated infusion periods.

**REDUCING ISCHEMIC INJURY**

### Immediate Arrest:
Table 1 presents potential cardioprotective strategies that can be used during cardiopulmonary bypass and cardiac arrest; that is, to reduce injury related to ischemia specifically. The first strategy in avoiding or reducing ischemic injury is to avoid the ischemia altogether. This principle forms the basis for continuous perfusion strategies, such as fibrillatory arrest or continuous cardioplegia delivery. Another strategy is to reduce the severity of ischemia by initiating immediate asystole (thereby avoiding the initial depletion of high-energy phosphates that occurs with “agonal” cardiac contractions). Asystole can be achieved either by membrane depolarization with potassium, or alternatively, by using drugs that activate (open) ATP-sensitive potassium (K<sub>ATP</sub>) channels (i.e., aprikalim or adenosine), thereby initiating hyperpolarizing arrest (21–25). Besides achieving cardiac arrest, which is cardioprotective in itself, activation of the K<sub>ATP</sub> channels may further protect the heart by limiting calcium accumulation, thereby limiting calcium-mediated injury.

### Hypothermia:
Another cornerstone of myocardial protection is hypothermia, which is most frequently initiated simultaneously with infusion of cardioplegic solutions. Hypothermia reduces the metabolic rate and, hence, energy depletion during ischemia. Profound levels of myocardial hypothermia can be achieved by delivering 4°C cardioplegia; the level of hypothermia can then be further controlled with topical ice and pericardial lavage. However, hypothermia has the potential for producing deleterious effects, including myocardial edema (through inhibiting ion pump activity), reduced membrane fluidity, and impaired function of membrane receptors upon which some pharmacologic therapy (i.e., adenosine, adrenergic agonists/antagonists) depends.

Reducing oxygen demand by hypothermia is important, particularly with the use of blood cardioplegia. Figure 4 depicts the oxygen consumption (representing oxygen demand) of a normally beating heart (working), a vented heart on cardiopulmonary bypass, and a chemically arrested (and perfused) heart over a range of various temperatures. Oxygen consumption is substantially reduced by venting the left ventricle (i.e., decompression) compared to a beating heart working to support the systemic circulation. This reduction in oxygen demands is achieved by reducing the pressure and volume work of the heart. However, the greatest decrease in oxygen demand takes place when the heart is chemically arrested, thus reducing oxygen requirements by an additional 50% relative to the beating empty heart. This decrease in oxygen demand is made more profound by inducing hypothermia. Little further reduction of oxygen demand per unit time is gained below 22°C myocardial temperature. However, oxygen debt may accumulate over time, which is an important consideration between infusions of

<table>
<thead>
<tr>
<th>Principle</th>
<th>Mechanism</th>
<th>Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce O&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Hypothermia</td>
<td>Blood, crystalloid, ice slush, aspartate</td>
</tr>
<tr>
<td>demand</td>
<td>Perfusion</td>
<td>lavage</td>
</tr>
<tr>
<td></td>
<td>Topical/lavage</td>
<td>Asystole, KCl, adenosine (?), hyperpolarizing agents</td>
</tr>
<tr>
<td>Substrate supply and</td>
<td>Oxygen</td>
<td>Blood, perfluorocarbons, crystalloid (?)</td>
</tr>
<tr>
<td>utilization</td>
<td></td>
<td>Glucose, citrate-phosphate-dextrose</td>
</tr>
<tr>
<td>Amino acids</td>
<td></td>
<td>Glutamate, aspartate</td>
</tr>
<tr>
<td>Buffer acidosis</td>
<td></td>
<td>Hypothermia (Rosenthal factor), intermittent infusions</td>
</tr>
<tr>
<td>Buffers</td>
<td></td>
<td>Blood, tromethamine, bicarbonate, phosphate</td>
</tr>
<tr>
<td>Optimize metabolism</td>
<td></td>
<td>Warm induction (37°C), warm reperfusion</td>
</tr>
<tr>
<td>Reduce CA&lt;sup&gt;2+&lt;/sup&gt;</td>
<td>Hypocalcemia</td>
<td>Citrate, Ca&lt;sup&gt;2+&lt;/sup&gt;-channel blockers, K-channel openers (?)</td>
</tr>
<tr>
<td>overload</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduce edema</td>
<td>Hyperosmolarity</td>
<td>Glucose, KCl, mannitol</td>
</tr>
<tr>
<td>Moderate infusion</td>
<td></td>
<td>50 mmHg</td>
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<tr>
<td>pressure</td>
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intermittent cardioplegia when a small oxygen debt accumulates over the intermittent periods (i.e., 20 min), and hence this O2 debt may become significant after 20 minutes of “protected” ischemia before the next infusion of cardioplegia.

The importance of hypothermia was first introduced by Bigelow and colleagues (26, 27) and Shumway and Lower (28) by using systemic or topical hypothermia. The benefits of hypothermia have been emphasized by early studies from Dr. Hearse’s laboratory in London that show increased percent recovery of contractile function in hearts that were made ischemic for sixty minutes as myocardial temperature decreased from 36 to 4°C (Figure 5) (29, 30). As the myocardial temperature during ischemia is decreased, the extent of posts ischemic functional recovery increases substantially. Subsequent studies have also demonstrated that cardiac arrest is additive to the cardioprotection of hypothermia (31).

Although hypothermia reduces oxygen demands and clearly protects the heart by reducing the severity of ischemia, it also holds disadvantages as previously discussed. Although these deleterious components of hypothermia can be largely overcome by normalizing cardioplegia temperature to 37°C, normothermic cardioplegia may fail to reduce ischemic injury when delivery is discontinuous, as demonstrated by Hearse et al. (29, 30). Therefore, hypothermia and normothermia each embrace certain advantages as well as disadvantages. Can the best of both thermal worlds be combined to capitalize on the advantages of hypothermia and minimize the negative effects in a conceptually simple delivery strategy applicable to the operating room? A warm/cold induction strategy applying both normothermic and hypothermic modalities was introduced by Rosenkranz et al., (32) in which the initial phase of cardioplegia was delivered at 37°C to optimize oxidative metabolic rate and drug–receptor interactions, and the second phase of cardioplegia was hypothermic to reduce oxygen demand between intermittent infusion periods. With a cold induction modality, less oxygen is taken up during the initial moments, implying incomplete repayment of the oxygen debt accrued during normothermic ischemia. In contrast, there is much greater oxygen consumption during warm induction, implying a more adequate repayment of the oxygen debt. This dual temperature strategy of warm/cold induction has been associated with greater post-cardioplegia functional recovery in ischemically injured hearts as compared to a hypothermic induction strategy (32).

**Oxygenation:** Oxygenation of the ischemic myocardium during cross clamp is important to maintain oxidative metabolism and an optimal level of ATP production. The oxygen demand under hypothermic temperatures in normal hearts is low enough that either oxygenated crystalloid solutions or blood-based solutions may fully meet the demands. Tissue oxygenation can be facilitated by delivering intermittent infusions of the cardioplegia solution, which reduces the oxygen debt incurred since the last infusion, and which also washes out key metabolites accumulated between infusions. However, the adequacy in satisfying the oxygen debt is important in determining the degree of myocardial protection. In normal hearts, the oxygen debt may be relatively small and repaid easily. However, the oxygen demand in hearts subjected to antecedent normothermic ischemia, or a period of “protected” ischemia between intermittent infusions of cardioplegia may be increased and may exceed the capacity of crystalloid solutions to reimburse this debt fully. Although hypothermia shifts the oxyhemoglobin dissociation curve to the left, which impairs unloading of oxygen to the myocardium being infused with blood cardioplegia, acidosis of the myocardium achieved during ischemia, as well as other forces created in the ischemic myocardium may shift the curve partially back to the right, resulting in a facilitation of oxygen unloading, even at profound hypothermia. The desaturated appearance of effluent (coronary venous) blood cardioplegia during the early phase of infusion and intermittent infusions may substantiate this unloading of oxygen from hemoglobin to the myocardium. Oxygen extraction has been observed to occur at 4°C cardioplegia temperatures and may be critical to myocardial protection with blood cardioplegia (33). In a study by Vinten-Johansen et al. (33) postischemic left ventricular function in a heart subjected to antecedent nor-

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**Figure 5:** Recovery of aortic flow in Langendorff-perfused hearts subjected to 60 minutes of global chemically induced (hyperkalemic, single dose) cardioplegia at various temperatures, followed by reperfusion.

**Note:** The greatest recovery of this manifestation of function occurred at temperatures below 24°C. (Taken from Hearse DJ. The protection of the ischemic myocardium: Surgical progress vs. clinical failure? Prog Cardiovasc Dis. 1988;30:381–402).
mothermic ischemia was improved when blood cardioplegia was fully oxygenated as compared to groups in which it was only partially saturated or nearly desaturated. In addition to endogenous adaptations of the heart during ischemia, which increase the unloading of oxygen from hemoglobin, there are some agents under development which allosterically alter the affinity of hemoglobin for oxygen and effectively enhance unloading of oxygen at hypothermic temperatures. In addition, blood cardioplegia may be supplemented with perfluorochemicals, which increase the oxygen in the plasma or crystalloid compartments available for delivery.

Substrate Enhancement: Another way of reducing ischemic injury would be to supply metabolic substrates, which enhance anaerobic metabolism between infusions of cardioplegia solutions. One such adjunct is glucose, which increases the availability of glucose (in the presence of insulin and potassium) for glycolysis during ischemia. Another strategy is to supplement the cardioplegic solution with glutamate (34, 35) and aspartate (36) to enhance metabolism during ischemia and maintain the appropriate balance of reducing equivalents in the cell by enhancing the malate–aspartate shuttle. This adjustment of the intracellular reducing equivalents enhances ATP generation not only during intermittent infusions of oxygenated cardioplegia, but also after reperfusion when oxygen is in plentiful supply. In addition, glutamate and aspartate ostensibly restore Krebs cycle intermediates that may have been lost during ischemia. Enhancement of cardioplegia with glutamate and aspartate results in improved cardioplegic oxidative metabolism and function. The benefits of glutamate and aspartate supplementation may be realized in the previously ischemic heart more than in the normal heart (34–36), because Krebs cycle intermediates are not lost in the latter.

Buffering of Tissue Acidosis: Buffering of acidosis may conceptually be an important strategy. The ischemic myocardium suffers from significant accumulation of hydrogen ions that reduces tissue pH. This tissue acidosis impairs enzyme kinetics and, hence, myocardial metabolism. Buffering this acidosis with histidine, THAM, bicarbonate, or endogenous buffering agents is directed toward either normalizing tissue pH, or providing a relatively alkalotic pH, adjusting for temperature for better enzyme action and better metabolism. However, pH adjustment strategies have recently been challenged by studies showing that acidosis protects the heart, partially by inhibiting calcium accumulation by attenuating the sodium–hydrogen exchange system (40, 41).

Prevention of Calcium Accumulation. Calcium accumulation also can occur during the period of myocardial ischemia, but the predominant tissue accumulation of calcium seems to occur during reperfusion. This accumulation can be prevented by chelating the calcium directly with citrate in the form of citrate-phosphate-dextrose (CPD), which can be added to blood cardioplegic solutions. In crystalloid solutions, calcium can be adjusted simply by appropriately reducing the amount of calcium. In both blood cardioplegia and crystalloid cardioplegia formulations, calcium entry into the cell can alternatively be reduced by including magnesium in the solution, which acts as a calcium channel blocker. Pharmacologic calcium channel antagonists that block the calcium (L-type) channels have not been found to be affective in attenuating calcium accumulation.

PREVENTION OF REPERFUSION INJURY

There are a number of aspects of reperfusion injury that are targeted by strategic use of cardioplegia, as summarized in Table 2.

Calcium Accumulation. By incorporating either direct calcium chelators (i.e., citrate) or the calcium channel blocker or magnesium, cardioplegia prevents calcium accumulation during reperfusion. Citrate, in the form of CPD, is also useful during reperfusion. The use of Na⁺–H⁺ exchange inhibitors may also attenuate Ca²⁺ accumulation via the Na⁺–Ca²⁺ exchanger.

Edema: Edema, which manifests itself during the reperfusion period when water and solutes can escape from “leaky” capillaries, can be counteracted by: (1) such hyperosmotic agents such as glucose, mannitol, and albumin; and (2) by observing low or “gentle” (re)perfusion pressures (42–44). This strategy of low delivery pressures prevents the pressure component of the vascular Starling forces governing transcapillary fluid movement from favoring excess water transfer from the intravascular compartment to the interstitium (45).

Neutrophils as Targets of Therapy: As discussed previously, neutrophils are key players in reperfusion injury. Cardioplegic additives and supplements are available to target the neutrophil at a number of critical points in the process effectively (46–48). Under normal conditions, the neutrophil does not interact with and adhere to the vascular endothelium to any significant extent. Although ischemia may set up for the recruitment of neutrophils by activating the endothelium by cytokines, oxygen radicals, and complement, the neutrophils are not present in the ischemic myocardium until reperfusion (49). Upon reperfusion, the neutrophils may become activated either directly or by interaction with the coronary vascular endothelium, leading to adherence to the endothelium, release of superoxide radicals and other noxious agents that induce further injury to the endothelium (vascular leak, edema, dysregulation of blood flow) (7, 50, 51). The initial interaction between activated neutrophils and activated endothelium (Figure 6) is a prerequisite step for the explosive participation of neutrophils in reperfusion injury. The interaction between neutrophils and vascular endothelium is exquisitely choreographed, involving “rolling” of the neutrophils across the endothelium, a loose attachment that progresses to a firm adherence, which then is followed by emigration of neutrophils across the endothelium into the proximity of the myocyte, where they may induce further damage (necrosis). Therefore, both the vascular endothelial cells and myocytes are victims of “reperfusion injury” (5, 52–55). The consequences of injury to the endothelium
include increased permeability and edema, impaired vasodilation and regulation of blood flow (i.e., “no-reflow” or “low-reflow” thrombosis), and amplification of neutrophil recruitment (5, 52–55). The surgically relevant consequences of neutrophil-mediated injury to myocytes include contractile dysfunction (“stunning”), necrosis, and apoptosis.

This neutrophil-mediated injury to coronary vascular endothelium and myocytes can be addressed by using several strategies. The simplest of these is by removing neutrophils from the systemic circulation or selectively in the delivered cardioplegia by use of leukocyte filters or other leukodepletion strategies (56). Alternatively, therapies can directly target the activation of the neutrophil itself by use of adenosine, nitric oxide, various inhibitors of complement activation reactions, and the use of antibodies against complement fragments to remove them from “active duty.” Alternative to inhibiting neutrophils directly, the initial adherence of the neutrophils to the vascular endothelium can be attenuated by adenosine (17, 26, 57, 58) or nitric oxide, (59–62) which inhibit a number of mechanisms involved in neutrophil adherence. There are also various antibodies to adhesion molecules on the neutrophil or the endothelium specifically involved in forming cell–cell bonds that can be included in cardioplegic solutions (48).

Oxygen radicals are important mediators of reperfusion injury (49, 63–67). Superoxide radicals and other reactive oxygen species are produced from the neutrophil when it is activated. In addition, radicals are also generated from the endothelium by the xanthine oxidase system, possibly from NAD(P)H oxidase in the endothelium and from the mitochondria. When considering the use of antioxidants as adjuncts to cardioplegic solutions, access to the various compartments represented by these sources of reactive oxygen species is necessary for therapeutics to exert their maximum effect. For ex-

Table 2: Strategies for the reduction of reperfusion injury with cardioplegia

<table>
<thead>
<tr>
<th>Principle</th>
<th>Method</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent Ca(^{2+}) accumulation</td>
<td>Citrate (CPD)</td>
<td>Direct Ca(^{2+}) chelation</td>
</tr>
<tr>
<td></td>
<td>Ca(^{2+}) channel blockers</td>
<td>Antagonism of L-type channels</td>
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<tr>
<td></td>
<td>Magnesium</td>
<td>Physical blockade of influx</td>
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<tr>
<td></td>
<td>Low Na(^{+})</td>
<td>Decrease Na/Ca(^{2+}) exchange antiport</td>
</tr>
<tr>
<td>Avoid edema</td>
<td>Hyperosmolarity</td>
<td>Counteract solute transmigration into parenchyma</td>
</tr>
<tr>
<td></td>
<td>Glucose, K(^{+}), Mannitol</td>
<td></td>
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<tr>
<td></td>
<td>Albumin</td>
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<tr>
<td></td>
<td>Low delivery pressure</td>
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<tr>
<td>Target-specific therapy</td>
<td>Filters</td>
<td>Reduce neutrophil population</td>
</tr>
<tr>
<td></td>
<td>Antibodies to:</td>
<td>Inhibit adherence to endothelium</td>
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<tr>
<td></td>
<td>Adhesion molecules</td>
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<tr>
<td></td>
<td>Carbohydrate Sialyl Le(^{X})</td>
<td></td>
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<tr>
<td></td>
<td>Complement inhibitors and receptor antagonists</td>
<td>Inhibits neutrophil activation and recruitment</td>
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<tr>
<td></td>
<td>Adenosine</td>
<td>Inhibits neutrophils and endothelial activation</td>
</tr>
<tr>
<td></td>
<td>Nitric oxide</td>
<td>Inhibits necrosis</td>
</tr>
<tr>
<td>Oxygen radicals</td>
<td>Allopurinol, nitric oxide, SOD/CAT</td>
<td>Scavenges, detoxifies, or inhibits production of oxygen radicals</td>
</tr>
</tbody>
</table>

SOD = superoxide dismutase; CAT = catalase.

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**Figure 6:** Schematic diagram of the initial interactions between vascular endothelium and activated neutrophils in response to endothelial stimulators such as superoxide anion (O\(_{2}\)), histamine (Hist), or thrombin (Thromb), or neutrophil activators such as C5a, platelet-activating factor (PAF) or FMLP. Note: Both neutrophils and endothelium are activated during ischemia-reperfusion, most likely by some of the activators shown. The interaction is characterized by a well-orchestrated interaction involving rolling of neutrophils on the endothelium, loose and firm adherence. These stages are mediated by the adhesion molecules indicated. EC = endothelial cells; SMC = smooth muscle cells; MYOC = myocytes.
ample, such large molecular weight agents as the enzymes superoxide dismutase and catalase, responsible for converting the superoxide anion to hydrogen peroxide and finally water (respectively) may not cross the cell membrane to scavenge intracellular sources of radicals. In addition, these enzymes will not easily insert themselves into the microenvironment created by neutrophils (predominant sources of superoxide anions) adhering to the vascular endothelium. The failure of oxygen radical scavengers to consistently inhibit injury may be related in large part to this inability to enter the appropriate compartment in which the radicals are generated, or to interruption of only a part of the oxygen radical cascade. Therefore, both the target molecule (oxygen radical) and the compartment (intracellular, interstitial, intermitochondrial) are very important considerations when using oxygen radical-related therapy. Failure to consider the compartment and source of oxygen radical species, as well as the species generated, may be reasons why oxygen radical therapy has presented such diverse and discrepant results in the literature (64–68).

SUMMARY

Cardioplegia plays a very important role in myocardial protection strategies. Acting as a selective perfusion agent, it can alter or inhibit ischemic injury by virtue of hypothermia and asystole and can be used to avoid reperfusion injury by altering the conditions of its delivery and its composition with various adjunctive agents and pharmacologic therapies for which cardioplegic solutions serve as a vector.

Recently, the need for cardioplegia has been challenged by reports of ischemic preconditioning (giving the myocardium a brief period of ischemia, which then releases certain cardioprotective mediators), which can marshall the endogenous protective mechanisms of the heart. Several studies showing that fibrillatory arrest and intermittent cross clamping as preconditioning trigger have had excellent outcomes, but are opposed to studies by Perrault et al. (69), in which global ischemic preconditioning actually increases posts ischemic damage in patients undergoing cardiac surgery. There is also concern about whether such complex constituents as buffers, amino acids, and calcium chelators are needed to avoid ischemic or reperfusion injury successfully with “all blood” cardioplegia formulations in the surgical setting. In addition, such technological changes as laser revascularization and minimally invasive surgery (keyhole or MIDCAB) in which cardiopulmonary bypass (and, hence, the technology that allows delivery of cardioplegia) is avoided have challenged the basic tenets of myocardial protection and the role played by cardioplegia. Future strategies of surgical myocardial protection may incorporate systemic infusion of therapeutic agents that are delivered to the heart by “homing” molecules either with or without cardioplegia. Agents will be developed in the future that will have a broad spectrum of effects with multiple windows, multiple targets in various organs, hence addressing multiple organ effects of ischemia as occurs with cardiopulmonary bypass and deep hypothermic circulatory arrest. Any future strategy must be simple so as not to distract the surgical team from the primary mission of providing an excellent surgical outcome.

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REFERENCES

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