# Myocardial Protection During Surgical Coronary Reperfusion

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Reperfusion injury in the surgical setting is defined as those metabolic, functional and structural consequences of restoring coronary flow (that is, aortic unclamping and revascularization) that can be avoided or reversed by modification of the conditions of reperfusion by the operating surgeon. The potential for reperfusion damage exists during cardiac surgery because temporary myocardial ischemia (that is, aortic clamping) is needed to produce a quiet, bloodless surgical field. Cold cardioplegic techniques have decreased the risks of ischemic myocardial damage during aortic clamping, but reperfusion damage can still occur when there is poor cardioplegic distribution (that is, coronary artery disease) or in hearts that have suffered ischemic damage before extracorporeal circulation is started (such as extending myocardial infarction, cardiogenic shock and the like).

The surgical setting affords the ideal opportunity for reperfusate modification because the components and conditions of the reperfusate are in the surgeon's control. This study reviews present understanding of the nature of reperfusion damage in the surgical setting and summarizes studies over the past 6 years which suggest that much of reperfusion damage can be avoided or reversed by adjusting the temperature, pressure and composition of reperfusate blood.

We define reperfusion injury in the surgical setting as those metabolic, functional and structural consequences of restoring coronary flow (that is, aortic unclamping and revascularization) that can be avoided or reversed by modification of the conditions of reperfusion by the operating surgeon. This damage occurs only when there has been inadequate myocardial protection during the preceding ischemic period. The development of cold cardioplegic techniques has decreased ischemic damage during aortic clamping provided that an appropriately designed cardioplegic solution is delivered in adequate amounts to all myocardial segments and replenished periodically (1). Significant ischemic events before aortic clamping will, however, deplete the heart of its energy reserves and thereby limit the effectiveness of cardioplegic protection.

The potential for reperfusion damage is always present during cardiac surgery (elective or emergency, with and without coronary artery disease) because temporary aortic clamping is needed to produce the quiet bloodless field necessary for ideal operating conditions. Our studies over the past 6 years (2–16) suggest that much of reperfusion damage may be *avoided* or *reversed* by adjusting the tem-

perature, pressure and composition of reperfusate blood. These early observations (17–19) of the benefits of surgical reperfusate modification led to the subsequent development of our current technique of blood cardioplegia to *prevent* ischemic damage.

This report will 1) summarize our current understanding of the nature of reperfusion damage in the surgical setting and define the types of patients and operative conditions most vulnerable to such damage; 2) list the principles evolving from our reperfusion research that we use clinically to modify this damage; and 3) review our data showing how such damage can be avoided and reversed.

## Nature of Surgical Ischemic and Reperfusion Injury

### Ischemic Injury

Myocardial ischemia (with or without hypothermia) results in the heart's reversion from aerobic oxidation of substrate (glucose, free fatty acids and lactate) by the Krebs cycle and oxidative phosphorylation (yielding 36 mol adenosine triphosphate [ATP]/mol glucose) to anaerobic glycolysis (yielding only 2 mol ATP/mol glucose) for energy production. Myocardial oxygen reserves are rapidly depleted in the absence of coronary flow, and energy demands cannot be met with anaerobic glycolysis alone (20). The accumulation of the end products of anaerobic glycolysis

(dihydronicotinamide adenine dinucleotide [NADH], hydrogen ion [H$^+$] and lactate) results in cellular acidosis that inhibits further anaerobic glycolysis (21–23). Simultaneously, cardiac amino acid metabolism is altered so that tissue levels of important amino acid (such as glutamate and aspartate) precursors of Krebs cycle intermediates are decreased. Loss of these amino acids deprives the heart of an alternate source of ATP production during ischemia and may limit resumption of oxidative metabolism during reperfusion (24–35).

*Limitation of anaerobic ATP production* leads to inhibition of cellular processes regulating cell volume (sodium-potassium ATPase pump) and increases cell membrane permeability to extracellular calcium, causing intracellular calcium content to increase. Impairment of ATP-dependent calcium pumping into the sarcoplasmic reticulum reduces calcium ion (Ca$^{2+}$) sequestration and results in subcellular organelle injury (because of deposition of calcium in mitochondrial crista spaces) and ultimate myofibrillar contracture (36,37).

*The cascade of injury progresses as the duration of ischemia and energy depletion increases.* Disagreement exists as to the exact point where irreversibility occurs. Jennings and Ganote (36,37) suggest that the working heart with regional ischemia is damaged irreversibly after 40 minutes; massive structural changes occur after reperfusion with unmodified blood. Ischemic damage of a working heart with coronary ligation is probably more extensive than in the surgical setting of global ischemia of a bypassed heart with hypothermia and cardioplegia. However, many ultrastructural changes after unmodified reperfusion (such as release of coronary ligature and thrombolysis) were not present during coronary flow interruption (37). This observation implies that modification of the conditions of reperfusion, as is possible during cardiac surgery, may avoid the changes we describe later.

## Reperfusion Injury

Aortic unclamping without reperfusate modification is followed by depression of left ventricular metabolic and mechanical function even after short ischemic intervals (9,38,39). It is unsettled whether this represents an unmasking of irreversible ischemically induced damage (36,37) or an active process of continued reperfusion injury.

*Metabolically,* reperfusion damage is characterized by the inability of the heart to take up and utilize oxygen normally. Kane (40) and Wood (41) and their co-workers found that mitochondrial oxygen uptake remains reduced after reperfusion, and identified a defect in electron transport in the respiratory chain. These abnormalities may be due to structural changes after reperfusion or functional alterations of the pathways of oxidative metabolism. Abnormalities in mitochondrial oxygen metabolism may also cause genera-

tion of cytotoxic oxygen metabolites which produce further profound changes in membrane lipids which alter morphology and function (42,43).

Previously, the metabolic defects caused by ischemia and reperfusion have been characterized by the degree of ATP depression (44). We believe these reduced ATP levels reflect both a loss of adenine nucleotide precursors (45–47) and, more importantly, an abnormality in the rate of ATP production due to a defect in mitochondrial oxidative metabolism (40).

*Controversy exists over the specific cause of mitochondrial dysfunction.* Jennings (37), Naylor (48) and Peng (49) and their co-workers reported abnormal mitochondrial calcium metabolism after reperfusion; the rapid calcium influx with inadequate sequestration results in dense mitochondrial calcium deposits seen by electron microscopy. This lowers ATP stores and production at a time when the heart needs to replenish energy deficits, repair damage incurred during ischemia and produce energy for ongoing circulatory function. Damage to the ATP-dependent cell volume regulatory apparatus results in edema formation and further deterioration of subcellular anatomy. Such edema may change intracellular ionic gradients causing arrhythmias, impair blood flow during reperfusion and decrease postischemic compliance.

## Vulnerability to Reperfusion Damage

The potential for intraoperative reperfusion damage is decreased substantially by cold cardioplegic techniques that lower myocardial energy demands and retard energy depletion during aortic clamping (17,50–52). The tolerance to a standard ischemic insult is decreased when energy levels are low before aortic clamping (53). Left ventricular subendocardial muscle ATP levels may be decreased in patients with cardiac hypertrophy (54,55) as well as in those with extensive coronary artery disease (56). Similar depletion of energy levels before aortic clamping may occur in patients with advanced heart disease (New York Heart Association, class IV) or those who sustain major supply-demand discrepancies, cardiogenic shock or cardiac arrest before cardioplegia can be initiated (57,58). In addition, unsatisfactory myocardial protection during aortic clamping, such as poor distribution of cardioplegic solution or inadequate replenishment, will deplete myocardial reserves.

## Interventions to Avoid or Reverse Reperfusion Damage

The remainder of this review will summarize our studies on reperfusate modification in hearts subjected to intentional ischemia before undergoing reperfusate modification.

## Avoidance of Reperfusion Damage

To study reperfusion injury, we used a model of the standard ischemic insult produced by 1 hour of topical hypothermic ischemic arrest, because this technique has been used clinically (59) and has been shown experimentally to produce acute (60) and chronic (61) myocardial damage. We tested the hypothesis that the metabolic and functional consequences of such an insult could be avoided almost completely by modifying the temperature, pressure and ionic composition of reperfusate blood during the early phases of reoxygenation (that is, the first 5 minutes).

The principles addressed in this aspect of our study (Table 1) include: 1) reducing ionic calcium available to enter the cell by chelation with citrate-phosphate-dextrose (CPD) (2,13), 2) making reperfusate pH alkalotic to counteract tissue acidosis and optimize enzymatic and metabolic function during recovery (62,63), 3) lowering energy demands by maintaining temporary cardioplegia during reperfusion to allow the limited oxygen utilization ability to be channeled toward reparative processes (4,13), 4) inducing hyperosmolarity and decreasing perfusion pressure (50 mm Hg) to reverse and minimize reperfusion edema (64–66), and 5) warming the reperfusate to optimize the rate of metabolic recovery (10).

When measured 30 minutes later (at a time when bypass would be discontinued in the clinical setting), each intervention improved, but did not restore postischemic metabolism and function to normal. A combination of these interventions, however, resulted in a level of cardiac metabolism, compliance and performance that was indistinguishable from control values (Fig. 1).

**Hypocalcemia.** Calcium deposition in mitochondria and myofibrillar contraction bands are consistent features of reperfusion injury (37,67). We chelated reperfusate ionic calcium with CPD to decrease cellular calcium influx, hoping the $Ca^{2+}$ metabolism would improve with reoxygenation. Our bioassay data suggested the best initial reperfusate $Ca^{2+}$ to be 1.0 mEq/liter, because this level of temporary hypocalcemia restored 82% contractility ( + dP/dt) and allowed 90% recovery of negative first derivative of left ventricular pressure ( − dP/dt) (a barometer of calcium sequestration
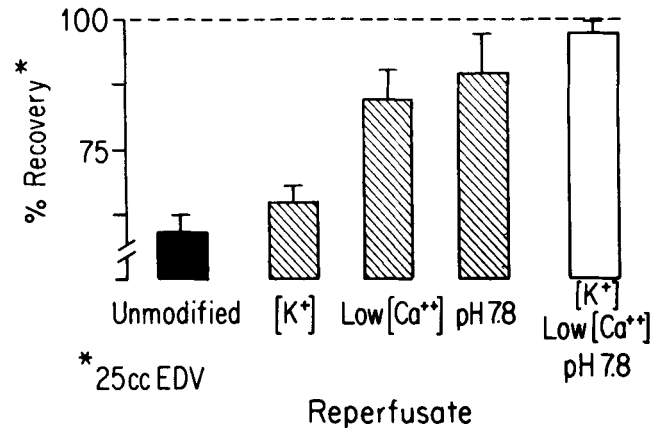


**Figure 1.** Recovery of left ventricular performance after 60 minutes of topical hypothermic ischemic arrest. Values are expressed as percent recovery of first derivative of left ventricular pressure ( + dP/dt). Note: 1) poorest recovery with unmodified reperfusion; 2) better, but incomplete, recovery with modification of reperfusate potassium ($K^+$), calcium ($Ca^{++}$) and pH; and 3) complete recovery with hypocalcemic, alkalotic blood cardioplegic reperfusion. EDV = left ventricular end-diastolic volume.

and myocardial relaxation) (13). Similar prevention of calcium influx can be accomplished pharmacologically with nifedipine (48,68), verapamil (48,69) and diltiazem (70). These drugs do, however, have a prolonged half life so that persistent myocardial depression caused by continued drug action after bypass may limit their usefulness. The proper antidote for these calcium antagonists, once developed, will likely lead to their replacing citrate-phosphate-dextrose which has a very transient effect.

**Alkalosis.** We reasoned that modifying reperfusate pH would be beneficial because metabolic processes are pH-dependent and would function best if pH was appropriate for temperature and the intracellular acidosis of ischemia was reversed immediately (71,72). Additionally, persistent acidosis would impair calcium ionic flux (73,74). Our bioassay data showed that pH 7.8 provided 90% recovery of left ventricular contractility (3,13). We selected tromethamine (THAM) buffer because it enters the cell readily, functions both intracellularly and extracellularly and may be more effective than ionic buffers (such as sodium bicarbonate) in ischemic tissue (75–77). Other buffers (78) may be equally useful, but we did not test them. THAM probably did not improve postischemic performance by direct inotropic and alkalotic effects because pH was 7.4 when function and metabolism were assessed, our dose was less than that reported to increase contractility (79) and no inotropic effect occurred in pilot studies where pH 7.4 THAM-containing blood perfusion was carried out (13).

**Hypocalcemia and alkalosis.** We anticipated that combining hypocalcemia and alkalotic reperfusion would have additional benefits because each decreased reperfusion damage markedly. Hearts reperfused with alkalotic hypocal-

**Table 1.** Principles of Reperfusate Modification

| Principle | Method |
|---|---|
| Provide oxygen | Blood (Hct 20 to 30%) |
| Lower energy demands | Cardioplegia (KCl) |
| Optimize metabolic rate | Normothermia (37°C) |
| Reduce calcium influx | Chelation (CPD) |
| Reverse acidosis | Buffer (THAM) |
| Avoid edema | Hyperosmolarity (360 mOsm) |
|  | Low pressure (50 mm Hg) |
| Replenish substrates | Glutamate (26 mM) |

CPD = citrate-phosphate-dextrose; Hct = hematocrit; KCl = potassium chloride.

cemic blood restarted more rapidly, fibrillated more vig-
orously and consumed more oxygen during the 5 minute
reperfusion interval than did hearts receiving either unmod-
ified, hypocalcemic or alkalotic reperfusate alone. However,
in contrast to our expectations, they functioned as poorly
as those receiving unmodified reperfusate (Fig. 2). We sus-
pect the improved metabolic milieu of alkalotic pH allowed
ventricular fibrillation to be more active despite hypocal-
cemia. Such fibrillation probably impeded subendocardial
blood supply when the reperfusion pressure was low (80).

**Cardioplegia.** Our use of a blood cardioplegic reper-
fusate was based on our observation that the ischemically
damaged heart has a limited capacity to utilize oxygen dur-
ing reperfusion (7,8,40,41). This led to the hypothesis that
maintaining arrest during initial reperfusion would provide
conditions whereby a greater portion of the oxygen delivered
on restoration of blood flow could be directed toward re-
parative processes instead of needless electromechanical
work (such as fibrillation). All reperfused hearts (except
those receiving blood cardioplegia) fibrillated and took up
only slightly more oxygen than needed to meet the basal
requirements of ventricular fibrillation (Fig. 3). Conversely,
hearts kept arrested during reperfusion took up the same
total amount of oxygen, but consumed 500% more oxygen
than needed to meet the low metabolic requirements of
arrest. We suspect this increased oxygen was used in part
to reestablish sodium-potassium ATPase pumps as hearts
receiving cardioplegic reperfusion developed less post-
ischemic edema than those that fibrillated. The excess ox-
ygen uptake was also likely used for the other forms of
reparative work that contributed to the improved postisch-
emic complicance (81% recovery) in contractility (77% re-
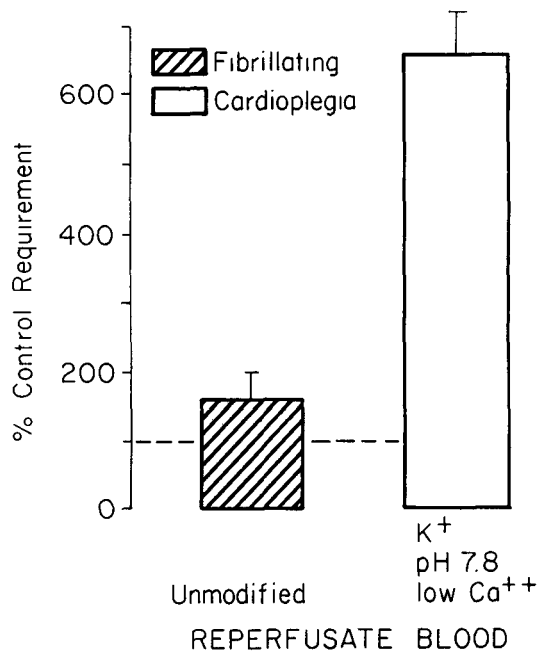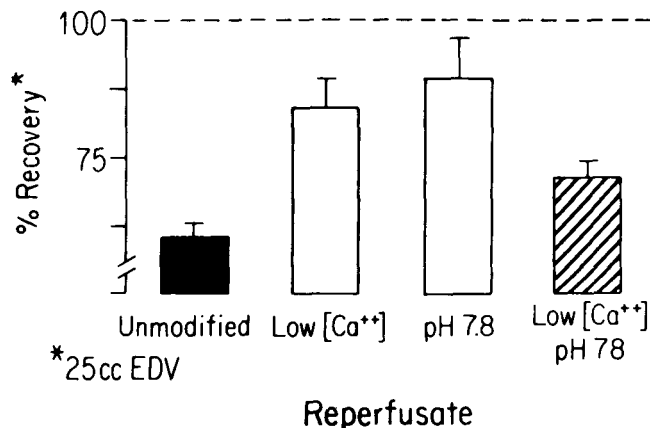covery) (13).



**Figure 3.** Average myocardial oxygen uptake during reperfusion
after 60 minutes' topical hypothermic ischemic arrest, expressed
as percent of control requirements. Note: 1) slight augmentation
of oxygen uptake in fibrillating hearts receiving unmodified re-
perfusate (**left**); and 2) marked augmentation of postischemic ox-
ygen uptake during warm cardioplegic reperfusion (**right**).

**Hyperosmolarity.** Myocardial edema can worsen re-
perfusion injury by increasing coronary vascular resistance
and oxygen diffusion distance, altering mitochondrial func-
tion and decreasing ventricular compliance (37,81–83). The
reperfusate was delivered at 40 to 50 mm Hg to avoid the
edema produced by high perfusion pressure (66). We made
the reperfusate hyperosmotic (360 mOsm) with hyperka-
lemia alone, as well as performing separate studies with
mannitol to distinguish the effects of cardioplegia from those
of hyperosmolarity. Both forms of hyperosmolarity produced
similar dehydration during reperfusion, as well as compa-
rable recovery of postischemic performance when measured
30 minutes later (80 versus 76% + dP/dt) (65). The effec-
tiveness of mannitol may have been decreased by fibrillation
during reperfusion which limited its distribution of mannitol
to regional myocardial segments (80) and caused needless
expenditure of oxygen for electromechanical activity.

**Hypocalcemia, alkalosis, cardioplegia and hyperos-
molarity.** In recognizing the limitations of modifying only
one or two aspects of the reperfusate, we reasoned that
combining all of them should provide maximal benefit. The
data recorded 30 minutes after reinstituting reperfusion sup-
port this hypothesis; postischemic left ventricular blood flow
and distribution were increased, left ventricular flow and
oxygen consumption augmented normally to meet increas-
ing metabolic demands, postischemic water accumulation

**Figure 2.** Postischemic left ventricular performance assessed by
isovolumetric function curves and expressed as percent control at
25 cc left ventricular end-diastolic volume (EDV). Note: 1) marked
depression in hearts receiving an unmodified reperfusate; 2) better
recovery in hearts receiving either a low calcium or pH 7.8 re-
perfusate; and 3) moderate depression of performance when pH
7.8 and hypocalcemia were combined.

was minimal, compliance better and myocardial performance was restored to preischemic levels (13).

**Clinical implications.** We concluded from these early studies that the deleterious changes in myocardial metabolism, water content, compliance and performance after temporary ischemia are caused in a large part by reperfusion injury that can be avoided by appropriate reperfusate modification. If true, this conclusion has significant clinical implications, because the composition and pressure of reperfusate blood are under the control of the cardiac surgeon and its possible manipulation may allow avoidance of the damage that may occur if cardiac protection during aortic clamping is less than ideal or if ischemic events precede aortic clamping. On the basis of these studies, we use a warm, low potassium (10 mEq/liter) blood cardioplegic reperfusate routinely in clinical practice; cardiac activity resumes regularly within 1 to 2 minutes after removing the aortic clamp.

After completing these experiments, it became obvious that the principles (such as cardioplegia, hypocalcemia, alkalosis and hyperosmolarity) underlying the composition of the warm blood cardioplegic reperfusate used to *avoid* reperfusion damage were precisely those we had applied in the past to *prevent* ischemic injury with asanguineous cardioplegia (18), differing only in the use of blood as the vehicle for delivering oxygenated cardioplegia solution and in solution temperature. These studies of reperfusion injury therefore preceded and subsequently led to our experimental and clinical use of cold blood cardioplegia as a method of preventing myocardial damage (17). We have shown that up to 4 hours of safe aortic clamping is possible with cold blood cardioplegia (14) (Fig. 4) and we and others use this method of myocardial protection to prevent ischemic damage during aortic clamping in all operations for acquired and congenital heart disease (17,50–52,85).

### Reversal of Reperfusion Damage

Ischemic and reperfusion injury become apparent during cardiac surgery only after extracorporeal circulation is discontinued. When severe myocardial damage prevents early discontinuation of cardiopulmonary bypass, the therapeutic options include either discontinuing bypass with pharmacologic (inotropic drugs) or mechanical support, or temporary resumption of extracorporeal circulation to "rest" the heart and improve the supply-demand balance. Most surgeons have observed temporary resumption of extracorporeal circulation to result in some hemodynamic improvement but rarely to allow complete recovery.

Experimentally, we simulated severe ischemic and reperfusion damage by subjecting dog hearts to 45 minutes of normothermic aortic clamping and unmodified reperfusion. Postischemic myocardial depression 15 minutes after unclamping was so profound that no heart could generate
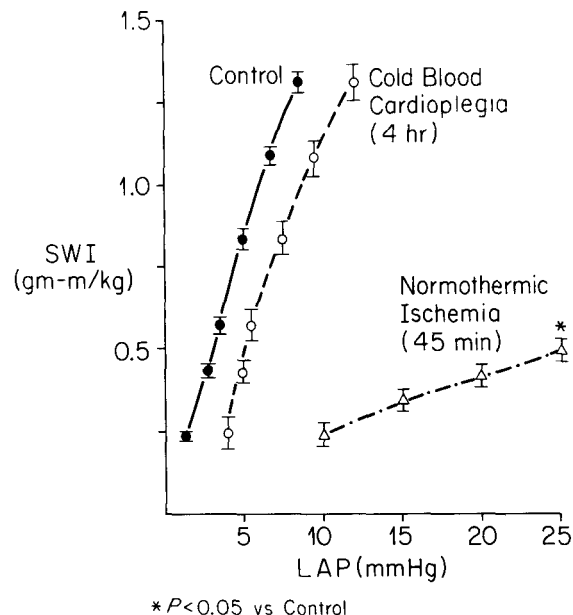


**Figure 4.** Postischemic myocardial performance during inscription of left ventricular function curves 30 minutes after unclamping the aorta. Note: 1) marked depression in function following 45 minutes of normothermic ischemia; and 2) normal function after 4 hours of multidose cold blood cardioplegia. LAP = left atrial pressure; SWI = stroke work index.

sufficient aortic pressure or cardiac output to support the systemic circulation. We then 1) contrasted the consequences of the early use of intropic drugs to allow discontinuation of bypass with those of temporary (30 minutes) prolongation of extracorporeal circulation (7); 2) compared the role of lowering oxygen demands with hypothermia (10) during temporary bypass prolongation with that of a brief continuous warm cardioplegic infusion to further decrease oxygen demands (secondary cardioplegia) (8); and 3) evaluated the possible benefits of amino acid substrate replenishment during reperfusion circulatory support (9,11).

**Early inotropic support versus prolonging bypass temporarily.** Dopamine infusion (10 to 30 μg/kg per min) increased the cardiac output of failing hearts to normal levels (Fig. 5) and allowed discontinuation of bypass with high filling pressures. This pharmacologically induced increase in contractility raised oxygen demands at a time when these damaged hearts demonstrated a marked inability to utilize delivered oxygen (only 17% oxygen extraction). Subendocardial flow did not increase to meet the demands of increased cardiac work and the lactate production that characterized these failing hearts before dopamine infusion became accentuated (Fig. 6). Persistent and severe myocardial damage was evident when final measurements were made 30 minutes later (no dopamine); myocardial edema was pronounced (3.3% water gain), left ventricular compliance was depressed (only 18% recovery, Fig. 7) and myocardial
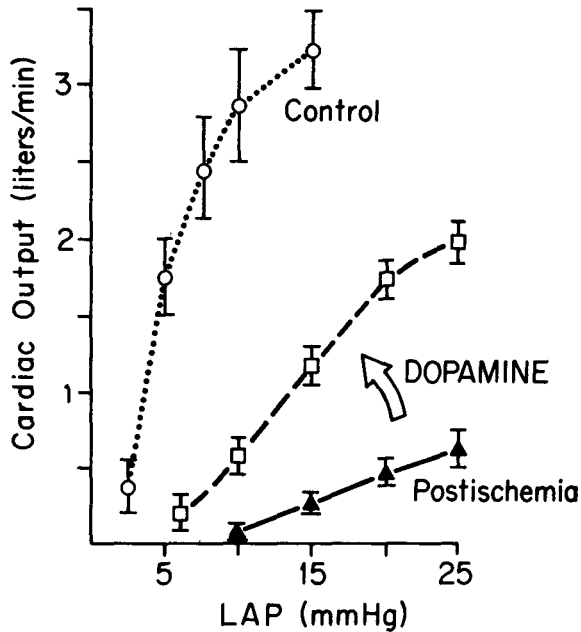
**Figure 5.** Myocardial performance 15 minutes after aortic unclamping following 45 minutes of normothermic arrest. Note: 1) cardiac output is profoundly depressed in all dogs after 45 mintues of normothermic ischemic arrest (postischemia); and 2) cardiac output is augmented with dopamine infusions, although higher left atrial pressure (LAP) is needed and significant depression from control is still present.

performance was inadequate to support the circulation without reinstitution of dopamine (Fig. 8).

In contrast, hearts treated with temporary prolongation of bypass showed progressive metabolic and hemodynamic



**Figure 6.** Myocardial lactate metabolism after ischemia. Note: 1) postischemic working hearts produce lactate; and 2) lactate production is accentuated during dopamine infusion.
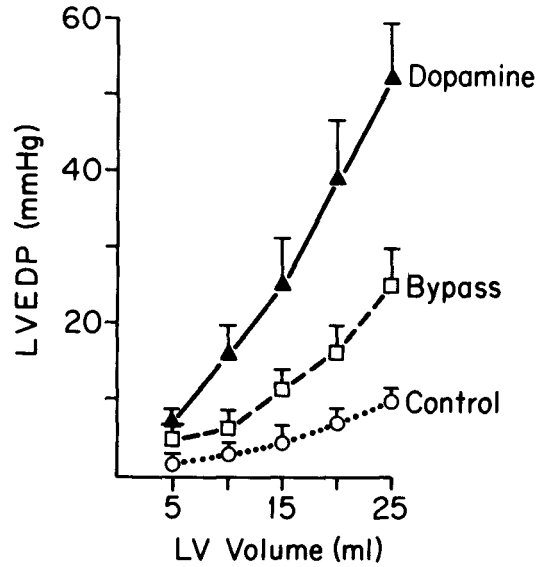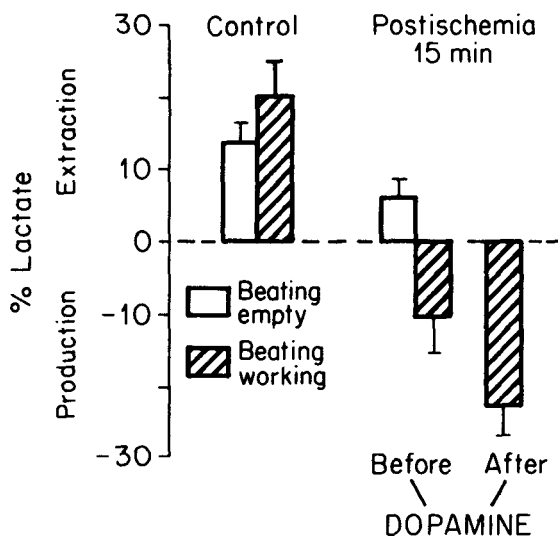


**Figure 7.** Left ventricular (LV) compliance 45 mintues after ischemia (45 minutes of normothermic arrest). Note: 1) marked loss of compliance in hearts treated with dopamine; and 2) a greater recovery of compliance in hearts treated with prolonged bypass. LVEDP = left ventricular end-diastolic pressure.

improvement after oxygen demands were lowered by venting and ensuring myocardial perfusion pressure with extracorporeal circulation. Myocardial edema was mobilized, left ventricular compliance improved, oxygen utilization increased and bypass could be discontinued without inotropic support (Fig. 8).

**Figure 8.** Left ventricular performance following 45 minutes of normothermic ischemic arrest when 1) dopamine was infused temporarily (15 minutes), 2) bypass was prolonged for 30 mintues; 3) secondary cardioplegia was administered for 5 minutes during prolonged bypass; and 4) glutamate was added to the secondary cardioplegic solution. Note also the near normal recovery occurred with substrate enhancement of secondary cardioplegic solution with glutamate. Abbreviations as in Figure 4.
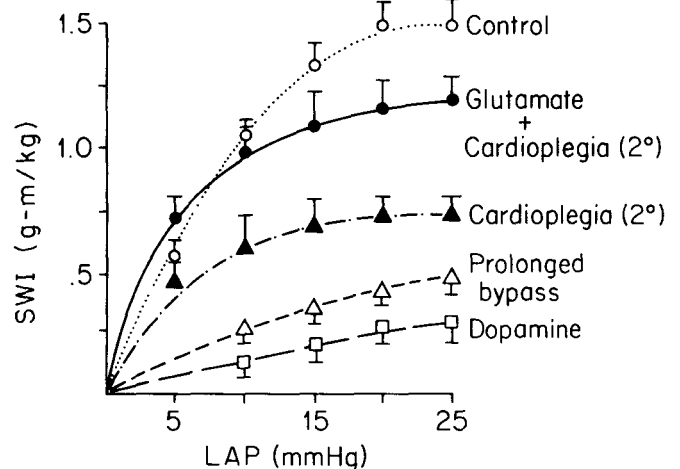
*The detrimental effects of increasing energy demands with inotropic drugs in ischemically damaged hearts are well recognized (86–88).* Our findings do not impugn the usefulness of inotropic drugs postoperatively, but suggest they should be used after the benefits of temporary prolongation of bypass are expended. This study did not, however, simulate the clinical conditions in which cardioplegia is used and incomplete washout of the cardioplegic solution can cause myocardial depression that is reversible by a single calcium injection (500 mg calcium chloride intravenously). Persistent myocardial depression after calcium injection, however, suggests ischemic and reperfusion damage is present and should be treated by briefly prolonging extracorporeal circulation.

*Myocardial recovery remained incomplete (only 35% of control values) despite the beneficial effects of prolonging bypass.* Our consistent findings of high coronary blood flow, narrow coronary arteriovenous oxygen difference, postischemic oxygen uptake that barely approaches the basal needs of the beating state (instead of the postischemic augmentation of oxygen uptake seen after reversible ischemia) (8,89) and failure to increase oxygen uptake during cardiac work led us to test the effects of lowering oxygen demands further with either hypothermia or a brief warm cardioplegic reperfusion during temporary prolonged bypass.

**Reperfusion hypothermia versus secondary cardioplegia.** Hypothermia is used routinely during ischemia to minimize damage through delay of ATP depletion and slowing of metabolic rate. During reperfusion, however, it is our hypothesis that 1) the temperature-dependent processes responsible for repair should be optimized by normothermia rather than retarded by hypothermia (10); 2) any electromechanical work of the bypassed heart is unneccessary and may needlessly expend the limited oxygen utilization capacity during reperfusion (4); and 3) a warm brief continuous cardioplegic infusion would allow this limited oxygen utilization capacity to be used to repair cellular processes (8).

*The decision to prolong bypass temporarily for 15 to 30 minutes in clinical practice* provides the cardiac surgeon with an obligatory and seemingly interminable interval of inactivity. We simulated the condition of severe ischemic and reperfusion damage (45 minutes' normothermic arrest plus 15 minutes' unmodified reperfusion) in which the surgeon decided to prolong bypass for 30 minutes. We then either reduced oxygen demands with an 18°C (pH 7.8) blood infusion for 10 minutes or clamped the aorta and rearrested the heart by delivering a 5 minute continuous infusion of 37°C blood cardioplegic solution (secondary cardioplegia) (8).

Hypothermia decreased demands by lowering heart rate, but was associated with a parallel reduction in myocardial oxygen uptake ($M\dot{V}O_2$) so that oxygen uptake remained below the basal requirements of the beating empty state at 18°C. Conversely, myocardial oxygen uptake during 37°C

blood cardioplegic infusion markedly exceeded basal demands of normothermic arrest (Fig. 9). Postischemic hearts allowed to beat during hypothermic coronary perfusion showed no more improvement of functional recovery than that achieved with prolonging normothermic bypass (35 versus 37%) (8,10). These hearts maintained a persistent inability to augment oxygen uptake when cardiac work was increased. In contrast, maintaining normothermia while lowering oxygen demands with cardioplegia resulted in a better ability to increase oxygen uptake (85 versus 40%) to meet the increased demands of the working state and the generation of 50% greater stroke work than either hypothermia or normothermic prolonged bypass (Fig. 8) (8).

*These findings suggest that reducing postischemic oxygen demands with hypothermia fails to improve recovery* because it slows the rate of metabolic processes responsible for repair. In contrast, reperfusion with secondary cardioplegia appears to be an effective method to channel the limited capacity for oxygen utilization of damaged myocardium toward reparative processes rather than obligating it to be expended needlessly for electromechanical work. The reversal of reperfusion damage was not complete, however, as oxygen extraction remained limited and left ventricular function recovered to only 47% of control. Prolongation of the interval of secondary cardioplegia to 10 minutes provided no additional benefit (8). These observations directed us to study the possibility that substrate replenishment of the cardioplegic solution might reverse the defective oxidative metabolic processes that we felt were important for recovery from ischemic and reperfusion injury.

**Reperfusion amino acid substrate replenishment.** We selected L-glutamate as the test amino acid for substrate replenishment of our blood cardioplegic reperfusate solution because it can be converted to α-keto glutarate, a Krebs cycle intermediate. Furthermore, it is lost from the myo-

**Figure 9.** Myocardial oxygen uptake during reperfusion after ischemia (45 minutes' normothermic arrest), expressed as percent of total requirements. Note: 1) hearts allowed to beat with and without hypothermia did *not* show postischemic augmentation of oxygen uptake; and 2) hearts given warm (37°C) cardioplegia showed expected augmentation of postischemic oxygen uptake.
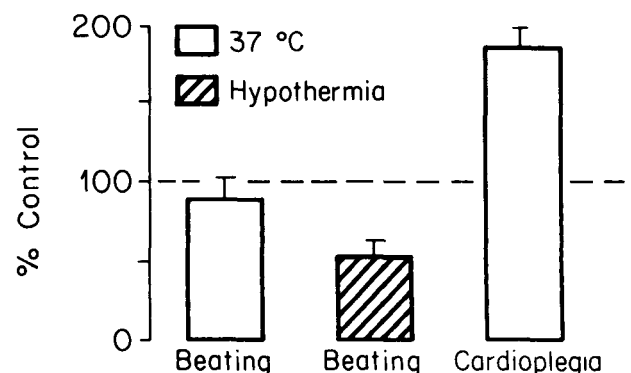
cardium during ischemia (25,26) and is taken up more in patients with ischemic heart disease than in patients with normal coronary arteries (24). Monosodium glutamate is a natural food substance that is used routinely during clinical hyperalimentation in amounts far less than the 26 mM dose used in our studies. It is, however, only one of several amino acids (such as aspartate, arginine and ornithine) that can be transformed to Krebs cycle intermediates involved in substrate-level phosphorylation during oxidative metabolism (27,29,33).

Our pilot observations showing glutamate alone to result in near complete return of oxidative metabolism and mechanical function after mild ischemic injury (9) (15 minutes' normothermic ischemia) prompted us to test it with the more severe ischemic insult of 45 minutes of global ischemia followed by unmodified reperfusion. We added L-glutamate to the secondary cardioplegic solution rather than testing it separately because we believe that reversal of severe ischemic and reperfusion damage requires simultaneous attention to several aspects of the supply-demand balance. Glutamate acts principally by enhancing substrate supply, but we suspect that its action may be limited unless the acidosis of ischemia is corrected (3,62,90), myocardial temperature is optimal for continued metabolism, calcium influx limited and energy demands reduced by cardioplegia (13).

*The salutary effects of reperfusion with glutamate cardioplegia were apparent metabolically* from the enhanced oxygen uptake and ATP repletion occurring during its infusion (Fig. 10). These benefits persisted 30 minutes later when extracorporeal circulation was discontinued and myocardial oxygen uptake increased more normally to meet
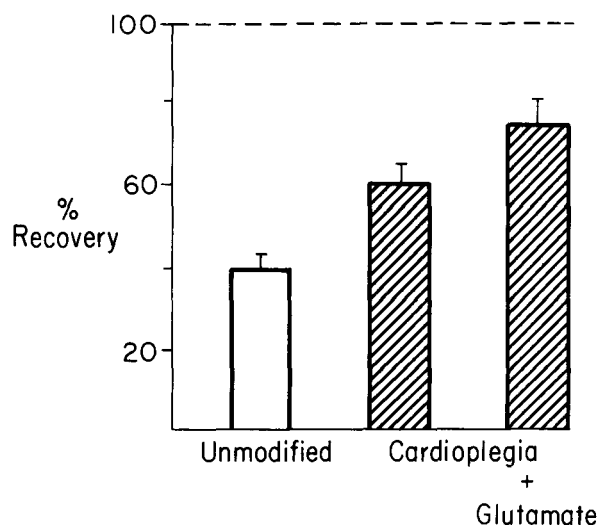
metabolic needs while cardiac performance returned to 80% of control values (Fig. 8) (11).

*We interpret these findings* to mean that reversal of reperfusion damage is possible by replenishment of a precursor of a Krebs cycle intermediate lost during ischemia. We reasoned, therefore, that glutamate inclusion in our standard blood cardioplegia may prevent this loss and allow a longer safe interval of aortic clamping. Our recent studies show that blood cardioplegia with and without glutamate permitted up to 4 hours of safe aortic clamping in normal hearts that were not subjected to preceding intervals of ischemia or reperfusion (14). These studies were carried out, however, under the ideal circumstances of normal hearts with good energy reserves and where optimal distribution of cardioplegic solution was ensured by patent coronary arteries. Such ideal conditions are clinically uncommon where there is coronary disease or left ventricular hypertrophy and where both factors may limit the effective distribution of cardioplegic solution and decrease the tolerance to standard ischemic insults (53,91,92).

## Combining Avoidance of Reperfusion Damage With Prevention of Ischemic Damage

**Warm blood cardioplegic induction.** Our improved understanding of the role of warm blood cardioplegia in avoiding and reversing reperfusion damage and that of cold blood cardioplegia in preventing ischemic injury allowed us to design a study to focus on a subset of patients whose hearts are less tolerant to the prolonged periods of aortic clamping needed for surgical repair because of preischemic ATP depletion (54–56,58). Cold cardioplegia is used routinely in such patients (New York Heart Association class IV, cardiogenic shock) but a significant risk of operative damage still exists (93,94). Cardioplegic induction is, in reality, the first phase of reperfusion when blood is the cardioplegic vehicle. We reasoned that blood cardioplegia is the ideal protective agent for these hearts because it has the potential of serving the dual purpose of avoiding reperfusion damage when given warm and preventing further energy depletion when given cold. We tested the hypothesis that warm induction of blood cardioplegia would optimize the rate of repair in energy-depleted hearts and improve their tolerance to a subsequent prolonged period (2 hours) of aortic clamping.

Our model for severe preischemic energy depletion was 45 minutes of normothermic global ischemia. This ischemic insult reduced subendocardial ATP by 80%, a level previously thought to be incompatible with functional recovery (44). These hearts were then either subjected to 2 additional hours of aortic clamping with multidose cold blood cardioplegia (to simulate the time needed for complex surgical repair) or given unmodified reperfusate without an added ischemic period (79). With the cardioplegic delivery system we use clinically (Fig. 11) (19), we compared the effects
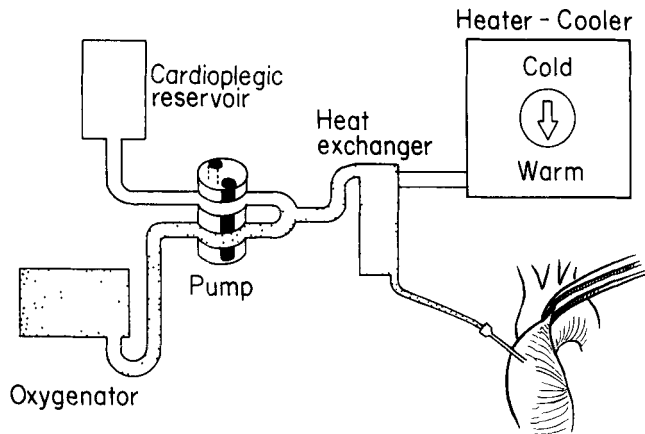
**Figure 10.** Transmural left ventricular adenosine triphosphate (ATP) content 15 minutes after ischemia (45 minutes of normothermic arrest). Note that L-glutamate-treated hearts showed the greatest ATP recovery.

**Figure 11.** Cardioplegia delivery system in current clinical use. Using a blood to cardioplegic tubing ratio of 4 to 1, blood from the oxygenator is mixed with cardioplegic solution, passed through a disposable heat exchanger (Shiley, USA) and infused into the aortic root. The temperature of the heat exchanger is regulated by the heater-cooler.



\* $P < 0.05$ vs 45 min Ischemia
\*\* $P < 0.05$ vs Cold Induction

**Figure 12.** Oxygen uptake in excess of basal requirements after ischemia. Net $O_2$ refers to oxygen consumed minus oxygen requirements for metabolic state. Note: 1) oxygen consumption below requirements in hearts allowed to beat on reperfusion; 2) oxygen consumption in excess of requirements during cardioplegic reperfusion; and 3) highest oxygen uptake with warm induction.

of a 5 minute period of 37°C cardioplegic induction followed by standard multidose cold blood cardioplegia to cold cardioplegic induction with a similar cardioplegic regimen for the following 2 hours of aortic clamping.

Hearts given unmodified reperfusate after 45 minutes of ischemia (simulating resuscitation after cardiac arrest without a subsequent ischemic period for cardiac repair) required multiple defibrillations, showed the characteristic depression in postischemic oxygen utilization (Fig. 12) and had markedly depressed ventricular performance (Fig. 13). In contrast, all hearts given blood cardioplegia as the initial reperfusate resumed beating spontaneously and consumed oxygen in excess of basal requirement during the infusion; the highest levels occurring with warm cardioplegic induction (13 versus 7 cc/100 g per min). Energy depleted hearts treated with cold induction recovered 63% of left ventricular performance after 2 hours of aortic clamping compared with 95% recovery after 4 hours of aortic clamping when cold blood cardioplegia was used in hearts with normal preischemic energy levels (14,16). This "limitation" of multidose cold blood cardioplegia in energy-depleted hearts was overcome by preceding it with a 5 minute period of warm cardioplegia; 85% recovery of left ventricular performance occurred (Fig. 13) (16).

**Glutamate enrichment of blood cardioplegic solution.** We have recently continued our studies of glutamate enrichment of blood cardioplegic solution by using both warm and cold L-glutamate blood cardioplegic induction in energy-depleted hearts subjected to an additional 2 hours of multidose cold blood cardioplegic aortic clamping. Glutamate enrichment of the cold blood cardioplegic solution did not increase oxygen utilization during cardioplegic induction, but allowed recovery comparable with that seen with
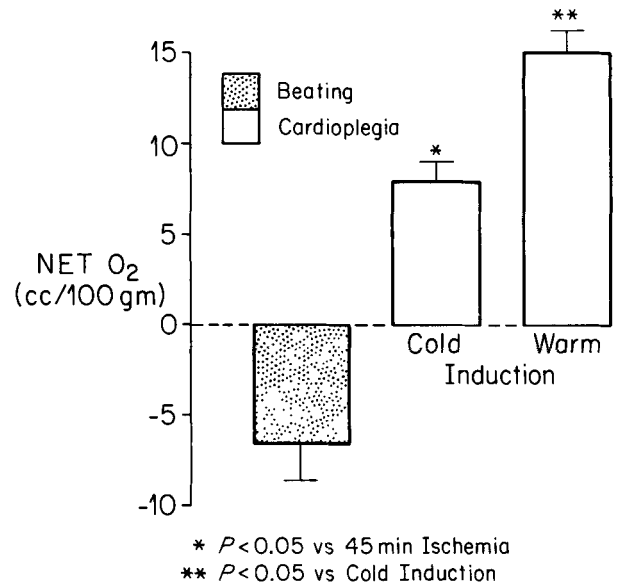
warm cardioplegic induction without glutamate (87% versus 85%) (96). Glutamate enrichment of the warm blood cardioplegic solution produced the greatest oxygen uptake during the period of cardioplegic induction and resulted in the highest functional recovery (94%) of all hearts tested.

*We think L-glutamate may play an important role in anaerobic substrate level phosphorylation during aortic clamping,* as well as replenishing the Krebs cycle intermediates lost during ischemia. Such replenishment allows better aerobic metabolism when oxygen is restored during reperfusion. We believe further study of glutamate and other amino acid cardioplegic supplements is required and suggest that amino acid supplementation of cardioplegic solutions will become a vital component of future efforts at intraoperative myocardial protection.

**Clinical application.** In clinical practice, we use this method of warm cardioplegic induction in high risk patients by varying the temperature of the heat exchanger as in these experiments (Fig. 11) (79). We find that prompt arrest can be induced with a warm cardioplegic solution by keeping potassium concentration at 25 mEq/liter during the 5 minute infusion and reducing the concentration to 10 mEq/liter during the subsequent 5 minutes of cold cardioplegic infusion and during replenishment at 20 minute intervals. This relatively long period of cardioplegic induction is not detrimental: 1) the heart is perfused continually with oxygenated blood while in a state of decreased metabolic demands; 2) the longer period of cold cardioplegia allows for better
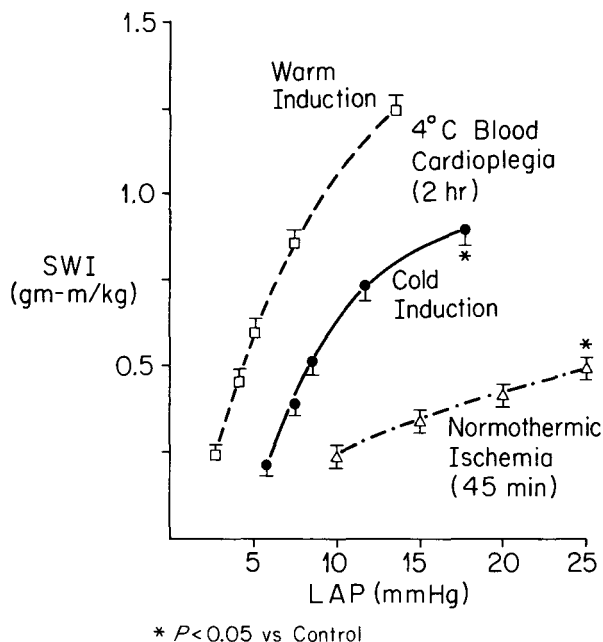
**Figure 13.** Left ventricular performance 30 minutes after blood reperfusion. Note: 1) normal postischemic performance with warm (37°C) cardioplegic induction; 2) moderate depression with cold (4°C) cardioplegic induction; and 3) severe depression after normothermic ischemia with unmodified reperfusion. LAP = left atrial pressure; SWI = stroke work index.

myocardial cooling, especially beyond coronary stenoses (15,91,92); 3) proximal or distal grafts or aortic valve removal can be carried out while the cardioplegic solution is being given; and 4) metabolic recovery is occurring during this period of induction (16). Our experimental findings were confirmed in a recent clinical report by Cunningham (96) showing as much as 35% augmentation of subendocardial ATP during warm blood cardioplegic induction in patients with advanced valvular disease undergoing extensive surgical repair with prolonged aortic clamping. Hopefully, further application of this technique will permit safer, prolonged aortic clamping in patients who are still considered to be in the high risk category.

## Conclusions

We conclude from these studies of myocardial protection during surgical reperfusion that the surgeon can play an active role in preventing, avoiding and reversing reperfusion damage because he is in control of the temperature and composition of reperfusate blood. The safety and simplicity of current cardioplegic techniques suggest they will find increasing usefulness during surgical revascularization of patients with acute and extending myocardial infarctions. The salutary effects of reperfusate modification provided by our studies also suggest that control of reperfusate com-

position during medical revascularization (such as with streptokinase) may allow for better functional recovery than that currently achieved with unmodified reperfusion.

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