Normothermic blood cardioplegia

Alternative or adjunct?

Normothermic blood cardioplegia was developed originally to be used during cardioplegic induction and reperfusion as an adjunct for enhancing metabolic reversal of biochemical alterations occurring before, during, and after total myocardial ischemia. This adjunct was introduced clinically after extensive experimental testing. By contrast, continuous normothermic blood cardioplegia without hypothermia was introduced clinically without a scientific infrastructure and has generated great interest because of its simplicity and encouraging early results, but has caused substantial confusion. This report is written to (1) clarify the role of normothermic blood cardioplegia as an adjunct to available hypothermic and antegrade and retrograde methods of myocardial protection, rather than as an alternative to them, (2) call attention to the misconception that continuous coronary perfusion avoids ischemia inasmuch as "unintentional ischemia" may occur despite continuous coronary perfusion, (3) identify theoretic and practical limitations of warm continuous retrograde blood cardioplegia exposed by testing after its clinical introduction, (4) enumerate the unanswered questions posed after clinical use of this method, and (5) focus on the self-imposed inflexibility created by adoption of adversarial positions in regard to cardioprotective strategies that impedes our ability to combine, rationally, the spectrum of approaches to myocardial protection that have evolved from the recognized limitations of individual methods. (J THORAC CARDIOVASC SURG 1994;107:860-7)

Gerald D. Buckberg, MD, *Los Angeles, Calif.*

The objective of every cardiac operation is a technically perfect anatomic correction resulting in postoperative cardiac function that comes as close to normal as possible. Two prerequisites to accomplish this goal are adequate visualization of the operative field for surgical precision and cardioprotective strategies that (1) reverse preexistent metabolic abnormalities and (2) exclude intraoperative damage that can nullify immediate and long-term benefits of repair. Deep cardiac hypothermia was the principal method of limiting ischemic damage before introduction of cardioplegic techniques. This led to the axioms that "all is well if the heart is kept as cold as

possible" and that "there is a constant battle against the clock during aortic clamping." Current data suggest that these concepts are no longer applicable.

Blood cardioplegia is responsible for this conceptual change because the heart is oxygenated when blood cardioplegia is given and aortic clamping time is no longer synonymous with ischemic time, especially when warm and cold blood cardioplegia techniques are combined. An added misconception is that ischemic damage is avoided if the heart is perfused continually during extracorporeal circulation. This understandable belief has led to a false sense of security that results in "unintentional ischemia" despite continuous coronary perfusion, as shown by extensive experimental studies. These studies form the scientific infrastructure for development of myocardial management techniques used currently. The clinical introduction of continuous warm blood cardioplegia without any experimental testing has generated great interest and caused substantial confusion. This analysis tries to clarify the role of normothermic blood cardioplegia in the spectrum of available methods of myocardial protection.

From the Division of Cardiothoracic Surgery, UCLA School of Medicine, Los Angeles, Calif.

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Address for reprints: Gerald D. Buckberg, MD, UCLA Medical Center, Department of Surgery, B2-375 CHS, 10833 LeConte Ave., Los Angeles, CA 90024-1741.

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Normothermic and hypothermic blood cardioplegia

The emergence of warm blood cardioplegia as a cardioprotective strategy stems from the recognition that (1) normothermic cardioplegic arrest results in myocardial oxygen consumption that is about 10% of that of the beating working heart, or about 1 ml/100 gm/min,^{2,3} (2) hypothermia adds only a small additional decrement,^{3,4} and (3) specific warm blood cardioplegic formulations during induction and reperfusion enhance metabolic reversal of biochemical alterations that occur before, during, and after aortic clamping, when applied with intermittent cold blood cardioplegia.⁵ The demonstrable advantages of normothermic blood cardioplegic modifications in routine elective operations are unestablished,⁶ whereas the salutary effects in high-risk patients and after prolonged aortic clamping are clear.^{7,8} The benefits of hypothermia include, in addition to a small decrement in myocardial oxygen consumption, retarding recurrence of electromechanical activity when the cardioplegic solution is washed away by noncoronary collateral blood flow and slowing the rate and force of the processes leading to myocardial damage⁴ when coronary flow must be interrupted to produce "intentional ischemia" to create the bloodless field needed for technical precision.⁹ Deep hypothermia may, however, cause adverse effects, including edema caused by inactivation of the sodium/potassium adenosine triphosphate exchange that regulates cell volume,¹⁰ alteration of platelets and leukocytes,¹¹ reduction of membrane stability,¹² and impairment of calcium flux.¹³ Preoccupation with reducing myocardial temperature below 15° C makes little physiologic sense because oxygen uptake in the arrested heart is negligible at less than 20° C (less than 0.3 ml/100 gm/min).⁴ These limitations of hypothermia notwithstanding, experimental study of 4° C blood cardioplegia shows that up to 4 hours of safe aortic clamping can be achieved in normal hearts with unobstructed arteries, provided sufficient doses are administered intermittently to counteract noncoronary collateral washout.¹⁴

Concern over the adverse consequences of systemic and cardiac hypothermia and intraoperative ischemia, coupled with experimental and clinically proven benefits of warm blood cardioplegic induction and reperfusion, led the surgical team at the University of Toronto (where hypothermia was introduced by Bigelow, Lindsay, and Greenwood¹⁵ in 1950) to suggest warm heart surgery without hypothermia but with cardioplegia: the patient and heart are kept at 37° C, and cardioplegic flow is delivered continuously when feasible.¹⁶ They reasoned that (1) electromechanical arrest lowered oxygen demands to sufficiently low levels that hypothermia was

superfluous and (2) use of continuous warm blood cardioplegia would "close the loop" and allow "perfect protection" by avoiding ischemia completely. This technique is attractive because of its simplicity and the implied suggestion that continuous perfusion avoids ischemia. Early clinical results with either antegrade¹⁶ or retrograde¹⁷ cardioplegia were encouraging, but were not superior to results using techniques with an extensive experimental basis, and subsequent data indicated unforeseen problems (for example, increased cerebral complications,¹⁸ right ventricular dysfunction, and ischemia caused by inadequate flow¹⁹).

Lichtenstein, Abel, and Salerno²⁰ suggested that warm cardioplegic flow could be interrupted intermittently, and precondition the heart, on the basis of studies of regional ischemia that showed brief intermittent normothermic ischemia reduces myocardial stunning and limits necrosis after subsequent prolonged regional ischemia.²¹ Conversely, brief prebypass ischemia before prolonged aortic clamping with cold cardioplegia worsens rather than improves recovery.²² *The objective of cardioprotective approaches during cardiac operations is complete avoidance of myocardial stunning and necrosis, and current data²³ support the use of hypothermia to lower metabolism during intervals of aortic clamping when normothermic perfusion is stopped.*

Myocardial stunning was described in 1982 as temporary functional depression without necrosis after brief (15 minute) normothermic regional ischemia.²⁴ The reversible low-output syndrome after inadequate myocardial protection is the cardiac surgical counterpart of this phenomenon and has been responsible for the extensive studies of methods of myocardial protection over the past 20 years. It seems ironic that the same normothermic ischemia that gave rise to the term *myocardial stunning* is used to justify stopping coronary flow because blood obscures the operative field and is responsible also for the development of cardiac hypothermia to limit ischemic damage.

Warm blood cardioplegia: starting points, end points, and median lethal dose (LD₅₀)

Cardioplegic research has not, in general, followed established procedures for drug testing. The LD₅₀ concept is used routinely in pharmacologic studies whereby the starting point is an intervention in a model that kills 50% of live organisms; its effectiveness or end point is compared with this starting point. Consequently, an intervention is (1) ineffective if it does not change the starting point, (2) toxic if less than 50% viability results, and (3) defined as effective by how much more than 50% viability it produces. The starting point of most studies of myo-

cardial protection is the normal heart so that the LD₅₀ approach has no relevance to them, inasmuch as any intervention that fails to maintain biochemical and mechanical integrity must be considered ineffective. Consequently, the normal heart model is useful only to test the safety of interventions such as multidose cold blood cardioplegia that allows normal biochemical and mechanical function to recover completely after 4 hours of aortic clamping¹⁴; the starting point is the same as the end point.

We cardiac surgeons rarely get the chance to operate on normal hearts, so our clinical starting point conforms more closely to the LD₅₀ model in pharmacologic studies. Experimental study of the energy- and substrate-depleted heart model has been useful to develop strategies intended to metabolically resuscitate the heart, because cold cardioplegia confers no metabolic benefit other than offsetting further damage.⁵ The concepts of warm induction and reperfusion of blood cardioplegia developed from such models, whereby extensive testing of various cardioplegic modifications resulted in a regimen that restored function to ischemically damaged hearts,^{5, 25-29} with the rationale for individual factors described previously.^{1, 30} *Normothermia is only one element in this regimen and is included to optimize the rate of metabolic recovery, which is retarded by hypothermia.*³¹

The objective of adding normothermic blood cardioplegia to cold intermittent blood cardioplegia is to use a cardioprotective strategy in the impaired myocardium that acts in concert with mechanical repair to restore near normal biochemical and mechanical function (that is, a normal starting point). Conversely, cold cardioplegic techniques alone can *only* prevent further damage so that total reliance is placed on the mechanical benefits of operative correction to improve cardiac performance. For example, the operative mortality rate for the surgical treatment of cardiogenic shock approximates 50% with conventional hypothermic cardioprotective techniques, because left ventricular power failure progresses unabatedly despite revascularization.^{32, 33} In contrast, use of warm blood cardioplegic induction and reperfusion with intermittent cold blood cardioplegia lessens the duration of postoperative circulatory support and improves mortality.³⁴

Continuous coronary perfusion and "unintentional ischemia"

Efforts to avoid intentional ischemia by continuous coronary perfusion are not new, but it has been impossible to provide homogeneous flow distribution by continuous perfusion techniques. Every prior attempt has been accompanied by the creation of "unintentional ischemia" because of the artificial conditions imposed to facilitate

technical repair (for example, beating empty heart, ventricular fibrillation, arrest).

"Unintentional ischemia" occurs when there is subendocardial underperfusion in the beating heart that is either hypertrophied or contains obstructed coronary arteries.^{35, 36} Sapsford, Blackstone, and Kirklin³⁷ reported that continuous perfusion of the hypertrophied beating empty heart during aortic valve replacement produced the same damage as hypothermic ischemia without cardioplegia. The "unintentional ischemia" produced by continuous coronary perfusion was most evident with ventricular fibrillation during aortic valve replacement. The classic observations of Taber, Norales, and Fine³⁸ and Najafi, Henson, and Dye³⁹ document subendocardial hemorrhagic necrosis, which was shown subsequently to be caused by an imbalance between energy supply and demand owing to redistribution of flow away from fibrillating subendocardial muscle where energy demands are high.^{2, 35} Myocardial contracture occurred sometimes after defibrillation, producing the same end point of "stone heart" that may follow normothermic ischemia,⁴⁰ in which the mechanism of injury is an imbalance between the absence of supply caused by "intentional ischemia" in an arrested heart with low oxygen demands. Prolonged normothermic ischemia⁴⁰ is no longer used because the advantages of ideal operating conditions are nullified by severe ischemic injury. Established methods of warm and cold cardioplegic myocardial management have essentially avoided the iatrogenic complication of massive hemorrhagic subendocardial necrosis, so that current generations of cardiac surgeons are spared the discouraging experience of this extreme example of inadequate myocardial protection.

These lessons of the past concerning "unintentional ischemia" have relevance today with the use of warm continuous retrograde blood cardioplegia. Coronary sinus retroperfusion results in systematic underperfusion of the right ventricle, which receives less than 20% of flow delivered to the left ventricle.⁴¹ Furthermore, inhomogeneous left ventricular perfusion is more pronounced with retrograde versus antegrade cardioplegia.⁴² The combined antegrade/retrograde methods are complementary in ensuring more homogeneous perfusion of both ventricles.⁴¹

Retrograde cardioplegic perfusion drains preferentially via thebesian veins so that it is readily understandable why (1) there is scant drainage from the coronary ostia during aortic valve replacement and (2) the right ventricle becomes cold despite limited nutritive flow,⁴¹ as venovenous connections in the right ventricular free wall and septum allow cooling by conductance. Cold intermittent retrograde cardioplegia reduces the supply/demand im-

balance during isolated coronary sinus retroperfusion and provides good, but inconsistent right ventricular recovery; this limitation is overcome by adding intermittent antegrade perfusion.¹⁹ The potential for impaired right ventricular performance may be accentuated with right ventricular hypertrophy or if coronary artery obstruction limits antegrade perfusion; right ventricular hypothermia is a valuable adjunct under these conditions. The nonhomogeneous distribution of nutritive (that is, capillary) left ventricular retrograde flow⁴² makes inhomogeneous perfusion more likely in hypertrophied hearts, in which optimum flow rates are not yet established. Consequently, inadequate continuous warm blood cardioplegic perfusion might cause the same "unintentional ischemia" or "stone heart" as occurred with ventricular fibrillation or ischemia without cardioplegia. Postoperative univentricular or biventricular failure or death after continuous warm retrograde blood cardioplegia reflects a problem that hypothermia and antegrade cardioplegia might avoid, and which is caused directly by an inflexible approach based on the misconception that "all is well if the heart is perfused continually."

Normothermic continuous blood cardioplegia: theory, facts, and questions

The inhomogeneity of warm retrograde cardioplegic distribution to the left and right ventricles contradicts the theory that warm cardioplegia resuscitates the heart continuously.⁴³ Furthermore, the process of resuscitation requires more than normothermia to optimize metabolic rate, and prolonged perfusion of specialized solutions intended for limited application during induction and reperfusion may have adverse systemic effects (for example, hypocalcemia, alkalosis, hypotension caused by vasodilation) that must be defined and counteracted.

Despite the satisfying early clinical findings,^{16, 44} subsequent experimental data have exposed some other limitations of warm continuous cardioplegia as compared with cold continuous or intermittent cold antegrade/retrograde blood cardioplegic delivery in jeopardized myocardium.^{45, 46} Ischemic damage in jeopardized muscle is minimized by continuous cold versus warm retrograde blood cardioplegic perfusion, probably because insufficient retrograde capillary perfusion is compensated by hypothermic lowering of oxygen demands.⁴⁶ Both clinical and experimental studies document that arterial and coronary sinus perfusion are delivered to different vascular beds.^{42, 47} Furthermore, intermittent cold antegrade/retrograde blood cardioplegia provides superior results to those of continuous antegrade or retrograde warm cardioplegia under experimental conditions when warm cardioplegic flow is interrupted intermittently, as must be

done clinically to optimize visualization during construction of distal anastomoses.²³ The cumbersome operating conditions caused by blood obscuring the operative field can be solved partially by techniques that improve visualization, but it is not established whether continuous perfusion is necessary. These observations emphasize that both warm and cold cardioplegic techniques, as well as antegrade and retrograde methods of delivering cardioplegia, may be useful and complementary adjuncts that should be integrated into the cardiac surgeon's armamentarium.

Additional questions raised by missing data concerning warm heart surgical techniques include (1) What cardioplegic flow rates are needed to ensure all areas receive sufficient flow to meet metabolic needs, especially in patients with right and/or left ventricular hypertrophy? (2) How long can flow be interrupted before ischemic damage occurs in normal or jeopardized muscle, and how can these changes be overcome with restoration of flow? (3) Is the ideal composition of the cardioplegic solution different from that used for cold cardioplegia? (4) What is the optimal blood/cardioplegic ratio for minimizing hemodilution, yet maintaining the benefits of warm reperfusion when flow must be interrupted? (5) Will production of hyperkalemia and hyperglycemia with continuous cardioplegia require specialized techniques and expensive devices such as hemoconcentrators or dialysis machines to restore a normal electrolyte and metabolic profile? (6) Does normothermic whole body perfusion lead to increased bleeding as a result of higher systemic flow rates?⁴⁸ (7) Is the recently reported increased prevalence of cerebral complications¹⁸ an acceptable occurrence, in view of the unproven benefits of warm techniques over those used when mild to moderate systemic hypothermia is used? (8) Are these cerebral complications related to decreased perfusion pressure that can be overcome by pulsatile perfusion or vasoconstrictor administration, or are they caused by early and late hypercoagulability? (9) Will more fatal perfusion accidents occur because of the limited time available for the perfusionist to stop cardiopulmonary bypass and correct problems before irreversible ischemic cerebral damage occurs?

Continuity, comparisons, and confusion

The "ideal" cardioplegic method is one that can be integrated into the operation so that (1) work can begin as soon as the aorta is clamped and the heart quieted, (2) the work can proceed without interruption, and (3) cardiopulmonary bypass can be discontinued promptly after unclamping with near normal myocardial function. Disruption of the *continuity* of the operation to give cardioplegia or use field-clearing devices (suckers, blowers,

vessel occluders, traction tapes, irrigation, and so on.) and to add extra personnel has been, until now, essential to limit intraoperative damage. Continuous coronary perfusion requires such field-clearing maneuvers, and they are "needed" (1) under the misconception that continuous coronary perfusion ensures adequate blood cardioplegic delivery and (2) because *comparisons* in experimental studies with inherent design limitations suggest some superiority of continuous warm blood cardioplegia over intermittent blood cardioplegic methods.⁴⁹ The outcome of these studies is determined, of course, by their experimental design and the *confusion* created by different outcomes can be clarified only by analysis of the responsible pathophysiologic principles.

The basic objectives of warm blood cardioplegia are that (1) normothermia optimizes aerobic metabolism and (2) resuscitation occurs over time, so that duration of infusion is more important than dose. Understanding the concept of delivery over time versus dose will avoid *confusion* over interpreting results of studies that compare warm and cold cardioplegic methods. For example, delivery of initial and/or terminal warm blood cardioplegia by dose (for example, 10 ml/kg) at a fixed pressure may provide only a 1- to 2-minute infusion to an ischemic heart with maximally dilated coronary arteries and deprive the myocardium of its full benefits. Consequently, continuous warm blood cardioplegia may prove more beneficial than subsequent interspersed cold infusions, despite the disadvantage of a bloody operative field requiring field-clearing devices. Similarly, restricting delivery of a specific formulation of a normothermic cardioplegic reperfusion to 5 minutes after regional ischemia (for example, percutaneous transluminal coronary angioplasty closure) when the superiority of its prolonged infusion (for example, 20 minutes) is established⁵⁰ will limit its effectiveness. Under these conditions, continuous infusion of formulations previously untested in damaged hearts⁵¹ may be beneficial because time-related benefits of metabolic repair were allowed to become evident, and results are related less to blood cardioplegic composition.

Confusion over the issue of dose versus duration was compounded unintentionally by our study of "overdose" reperfusion normothermic blood cardioplegia⁵² in which application of concepts developed in regional ischemic studies (that is, 20 minutes of segmental perfusion at 50 mm Hg pressure) to the global ischemic model caused myocardial stunning, because a 3500 ml dose was given to 25 kg dogs. Global depression by overdose cardioplegia offset the metabolic benefits of warm reperfusion, and this shortcoming was overcome by limiting the total dose and duration.⁵² Conversely, delay in regional recovery did not alter global myocardial performance in regional

studies,⁵⁰ inasmuch as this segment was nonfunctional before treatment and any functional recovery was beneficial. These experimental findings form the basis of our clinical use of brief warm induction and reperfusion in high-risk patients and prolonged regional reperfusion after acute coronary occlusion^{34, 50, 53} or after postoperative intractable ventricular fibrillation.^{54, 55}

Unfortunately, precise monitoring of "how much is enough" is unavailable, so that we have applied the experimentally determined end point of the return of myocardial oxygen consumption to basal levels (that is, 1 ml/100 gm/min) in the arrested decompressed heart.⁵⁶ The clinical indicator is when the coronary effluent turns red, signifying minimal oxygen uptake, but this may be misleading because it reflects only the drainage of the region perfused by that delivery route. Reversal of flow (that is, from antegrade to retrograde) results often in increased oxygen and glucose uptake and lactate washout and indicates that different vascular beds are perfused by delivering cardioplegic solution in either direction.⁴⁷ It is hoped that clinical monitoring methods will be developed for precise determination of the dose and duration of normothermic blood cardioplegia to optimize its benefits so that intermittent cold ischemia can be used to maximum advantage for surgical precision.

Cardioprotective adversarial positions: an imaginary dividing line

Cardiac surgeons have assumed, for uncertain reasons, adversarial positions in regard to cardioprotective strategies: ventricular fibrillation versus ischemia; crystalloid versus blood cardioplegia; warm versus cold cardioplegia; antegrade versus retrograde delivery; continuous versus intermittent cardioplegia. This has led to the creation of an imaginary dividing line that places them in the awkward position of (1) aligning themselves on one side of the line or another to avoid the appearance of indecision and incomplete allegiance and (2) becoming prisoners of self-imposed inflexibility that may limit clinical adoption of more comprehensive and effective cardioprotective strategies.

The introduction of warm heart surgery has been a valuable contribution because it renews focus on the important issues of normothermic blood cardioplegia and continuous coronary perfusion as cardioprotective *adjuncts* rather than *alternatives* to the methods that have been tested extensively. Recognition that aerobic metabolism can be supported by blood cardioplegic perfusion allays anxiety that there is a "battle against the clock when the aortic clamp is in place" and clarifies that "ischemic time and crossclamp time are not synonymous," provided homogeneous cardioplegic distribution

is ensured either by combining the benefits of antegrade and retrograde delivery or by adding hypothermia when regional distribution is inadequate to meet energy demands. The major technical limitation of continuous blood cardioplegia is to limit visualization and potentially compromise surgical precision, but this shortcoming can be overcome by intermittent cold ischemia to slow the rate and force of cell damage that is accelerated by normothermia.

Retrograde delivery permits continuous coronary perfusion when visualization is not essential (for example, constructing proximal anastomoses with the aorta vented, placing sutures from valve anulus to valve ring or prosthesis, closure of atrium or aorta). Subsequent strategies will probably include current and future cardioprotective methods, and their acceptance will, I hope, be unimpeded by the rigidity of thinking that underlies the current confusion and retards progress in this evolving field. Incorporation of warm cardioplegia and continuous coronary perfusion into any strategy will likely expedite evolution toward an integrated approach that allows cardiac operations to be done more safely in the increasing number of high-risk patients who require surgical repair of congenital and acquired lesions.

REFERENCES

1. Buckberg GD. Myocardial protection: an overview. *Semin Thorac Cardiovasc Surg* 1993;5:98-106.
2. Buckberg GD, Brazier JR, Nelson RL, Goldstein SM, McConnell DH, Cooper N. Studies of the effects of hypothermia on regional myocardial blood flow and metabolism during cardiopulmonary bypass. I. the adequately perfused beating, fibrillating and arrested heart. *J THORAC CARDIOVASC SURG* 1977;78:87-94.
3. Bretschneider HJ, Hubner G, Knoll D. Myocardial resistance and tolerance to ischemia: physiological and biochemical basis. *J Cardiovasc Surg* 1975;16:241-60.
4. Buckberg GD. Myocardial temperature management during aortic clamping for cardiac surgery. *J THORAC CARDIOVASC SURG* 1991;102:895-903.
5. Rosenkranz ER, Okamoto F, Buckberg GD, Robertson JM, Vinten-Johansen J, Bugyi H. Safety of prolonged aortic clamping with blood cardioplegia. III. aspartate enrichment of glutamate-blood cardioplegia in energy-depleted hearts after ischemic and reperfusion injury. *J THORAC CARDIOVASC SURG* 1986;91:428-35.
6. Fontan F, Madonna F, Naftel DC, Kirklin JW, Blackstone EH, Digerness S. Modifying myocardial management in cardiac surgery: a randomized trial. *Eur J Cardiothorac Surg* 1992;6:127-36.
7. Rosenkranz ER, Buckberg GD, Mulder DG, Laks H. Warm induction of cardioplegia with glutamate-enriched blood in coronary patients with cardiogenic shock who are dependent on inotropic drugs and intraaortic balloon support: initial experience and operative strategy. *J THORAC CARDIOVASC SURG* 1983;86:507-18.
8. Kirklin JW. The science of cardiac surgery. *Eur J Cardiothorac Surg* 1990;4:63-71.
9. Kirklin JW. Technical and scientific advances in cardiac surgery over the past 25 years. *Ann Thorac Surg* 1990;49:26-31.
10. Kaijser L, Jansson E, Schmidt W, Bomfim V. Myocardial energy depletion during profound hypothermic cardioplegia for cardiac operations. *J THORAC CARDIOVASC SURG* 1985;90:896-900.
11. Teoh KH, Christakis GT, Weisel RD. Dipyridamole reduces myocardial platelet and leukocyte deposition following ischemia and cardioplegia. *J Surg Res* 1987;42:36-44.
12. McMurchie EJ, Raison JK, Cairncross KD. Temperature-induced phase changes in membranes of heart: a contrast between the thermal response of poikilotherms and homeotherms. *Comp Biochem Physiol* 1973;44:1017-26.
13. Bridge JHB. Relationships between the sarcoplasmic reticulum and sarcolemmal calcium transport revealed by rapidly cooling rabbit ventricular muscle. *J Gen Physiol* 1986;88:437-73.
14. Robertson JM, Vinten-Johansen J, Buckberg GD, Rosenkranz ER, Maloney JV Jr. Safety of prolonged aortic clamping with blood cardioplegia. I. Glutamate enrichment in normal hearts. *J THORAC CARDIOVASC SURG* 1984;88:395-401.
15. Bigelow WG, Lindsay WK, Greenwood WF. Hypothermia: its possible role in cardiac surgery. *Ann Thorac Surg* 1950;132:849-66.
16. Lichtenstein SV, Ashe KA, el Dalati H, Cusimano RJ, Panos A, Slutsky AS. Warm heart surgery. *J THORAC CARDIOVASC SURG* 1991;101:269-74.
17. Salerno TA, Christakis GT, Abel J, et al. Technique and pitfalls of retrograde continuous warm blood cardioplegia. *Ann Thorac Surg* 1991;51:1023-5.
18. Martin TD, Craver JM, Gott JP, et al. A prospective randomized trial of retrograde warm blood cardioplegia: myocardial benefit and neurologic threat. *Ann Thorac Surg* [In press].
19. Partington MT, Acar C, Buckberg GD, Julia PL. Studies of retrograde cardioplegia. II. Advantages of antegrade/retrograde cardioplegia to optimize distribution in jeopardized myocardium. *J THORAC CARDIOVASC SURG* 1989;97:613-22.
20. Lichtenstein SV, Abel JG, Salerno TA. Warm heart surgery and results of operation for recent myocardial infarction. *Ann Thorac Surg* 1991;52:455-60.
21. Cohen MV, Liu GS, Downey JM. Preconditioning by a brief coronary occlusion preserves wall motion in ischemia/reperfusion. *Circulation* 1990;82(Suppl):III271.
22. Bolling SF, Olzanski DC, Childs KF, Gallagher KP. Does cardiac "preconditioning" result in enhanced postischemic functional recovery. *Surg Forum* 1991;42:239-42.
23. Matsuura H, Lazar HL, Yang XM, Rivers S, Treanor PR,

- Shemin RJ. Detrimental effects of interrupting warm blood cardioplegia during coronary revascularization. *J THORAC CARDIOVASC SURG* 1993;106:357-61.
24. Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. *Circulation* 1982;66:1146-9.
25. Rosenkranz ER, Vinten-Johansen J, Buckberg GD, Okamoto F, Edwards H, Bugyi H. Benefits of normothermic induction of cardioplegia in energy-depleted hearts, with maintenance of arrest by multidose cold blood cardioplegic infusions. *J THORAC CARDIOVASC SURG* 1982;84:667-76.
26. Okamoto F, Allen BS, Buckberg GD, Bugyi HI, Leaf J. Studies of controlled reperfusion after ischemia. XIV. reperfusate conditions: Importance of ensuring gentle versus sudden reperfusion during relief of coronary occlusion. *J THORAC CARDIOVASC SURG* 1986;92:613-20.
27. Follette D, Fey K, Livesay J, Maloney JV Jr, Buckberg GD. Studies on myocardial reperfusion injury. I. Favorable modification by adjusting reperfusate pH. *Surgery* 1977;82:149-55.
28. Follette DM, Fey K, Buckberg GD, et al. Reducing postischemic damage by temporary modification of reperfusate calcium, potassium, pH, and osmolality. *J THORAC CARDIOVASC SURG* 1981;82:221-38.
29. Okamoto F, Allen BS, Buckberg GD, Young HH, Bugyi HI, Leaf J. Studies of controlled reperfusion after ischemia: XI. reperfusate composition: interaction of marked hyperglycemia and marked hyperosmolality in allowing immediate contractile recovery after four hours of regional ischemia. *J THORAC CARDIOVASC SURG* 1986;92:583-93.
30. Buckberg GD. Strategies and logic of cardioplegic delivery to prevent, avoid, and reverse ischemic and reperfusion damage. *J THORAC CARDIOVASC SURG* 1987;93:127-39.
31. Lazar HL, Buckberg GD, Manganaro A, Becker H, Mulder DG, Maloney JV Jr. Limitations imposed by hypothermia during recovery from ischemia. *Surg Forum* 1980;31:312-5.
32. DeWood MA, Spores J, Notske RN, et al. Medical and surgical management of myocardial infarction. *Am J Cardiol* 1979;44:1356-64.
33. Berg RJ Jr, Selinger SI, Leonard JL, Grunwald RP, O'Grady WP. Immediate coronary artery bypass for acute evolving myocardial infarction. *J THORAC CARDIOVASC SURG* 1981;81:493-7.
34. Allen BS, Rosenkranz ER, Buckberg GD, et al. Studies on prolonged acute regional ischemia. VI. Myocardial infarction with left ventricular power failure: a medical/surgical emergency requiring urgent revascularization with maximal protection of remote muscle. *J THORAC CARDIOVASC SURG* 1989;98:691-703.
35. Hottenrott CE, Towers B, Kurkji HJ, Maloney JV Jr, Buckberg GD. The hazard of ventricular fibrillation in hypertrophied ventricles during cardiopulmonary bypass. *J THORAC CARDIOVASC SURG* 1973;66:742-53.
36. Becker H, Vinten-Johansen J, Buckberg GD. Critical importance of ensuring cardioplegic delivery with coronary stenoses. *J THORAC CARDIOVASC SURG* 1981;81:507-15.
37. Sapsford RN, Blackstone EH, Kirklin JW. Coronary perfusion versus cold ischemic arrest during aortic valve surgery. *Circulation* 1974;49:1190-9.
38. Taber RE, Morales AR, Fine G. Myocardial necrosis and the postoperative low cardiac output syndrome. *Ann Thorac Surg* 1967;4:12.
39. Najafi H, Henson D, Dye WS. Left ventricular hemorrhagic necrosis. *Ann Thorac Surg* 1969;7:550.
40. Cooley DA, Reul GJ, Wukasch DC. Ischemic contracture of the heart: "stone heart." *Am J Cardiol* 1972;29:575-7.
41. Partington MT, Acar C, Buckberg GD, Julia P, Kofsky ER, Bugyi HI. Studies of retrograde cardioplegia. I. Capillary blood flow distribution to myocardium supplied by open and occluded arteries. *J THORAC CARDIOVASC SURG* 1989;97:605-12.
42. Aldea GS, Hou D, Fonger JD, Shemin RJ. Inhomogeneous and complementary antegrade and retrograde delivery cardioplegic solution in the absence of coronary artery obstruction. *J THORAC CARDIOVASC SURG* [In press].
43. Ali IS, Al-Nowaiser O, Deslauriers R, et al. Continuous normothermic blood cardioplegia. *Semin Thorac Cardiovasc Surg* 1993;5:141-50.
44. Salerno TA, Houck JP, Barrozo CAM, et al. Retrograde continuous warm blood cardioplegia: a new concept in myocardial protection. *Ann Thorac Surg* 1991;51:245-7.
45. Matsuura H, Lazar HL, Yang X, et al. Warm vs. cold blood cardioplegia: Is there a difference? *Surg Forum* 1991;42:231-2.
46. Diehl JT, Pontoriero M, Connolly R, Schwartz S, Cleveland RJ. Alternative methods of retrograde cardioplegia delivery: effects on preservation of the ischemic left ventricle after acute coronary artery occlusion and reperfusion [Abstract]. American Association for Thoracic Surgery program booklet, 1992:60-1.
47. Buckberg GD, Beyersdorf F, Kato NS. Technical considerations and logic of antegrade and retrograde blood cardioplegic delivery. *Semin Thorac Cardiovasc Surg* 1993;5:125-33.
48. Rousou JA, Engelman RM, Flack JE III, Deaton DW, Liu X, Das DK. Comparison of normothermic vs. hypothermic cardioplegia in patients undergoing coronary artery bypass grafting. *Surg Forum* 1991;42:237-9.
49. Liu X, Engelman RM, Wei Z, et al. Postischemic deterioration of sarcoplasmic reticulum: warm vs. cold blood cardioplegia. *Ann Thorac Surg* 1993;56:1154-9.
50. Allen BS, Okamoto F, Buckberg GD, et al. Studies of controlled reperfusion after ischemia. XV. immediate functional recovery after 6 hours of regional ischemia by careful control of conditions of reperfusion and composition of reperfusate. *J THORAC CARDIOVASC SURG* 1986;92:621-35.
51. Brown WM, Jay JL, Gott JP, et al. Warm blood cardioplegia: superior protection after acute myocardial ischemia. *Ann Thorac Surg* 1993;55:32-41.

52. Kofsky ER, Julia PL, Buckberg GD, Quillen JE, Acar C. Overdose reperfusion blood cardioplegia: a preventable cause of postischemic myocardial depression. *J THORAC CARDIOVASC SURG* 1991;101:275-83.
53. Allen BS, Buckberg GD, Fontan FM, et al. Superiority of controlled surgical reperfusion versus percutaneous transluminal coronary angioplasty in acute coronary occlusion. *J THORAC CARDIOVASC SURG* 1993;105:864-84.
54. Beyersdorf F, Acar C, Buckberg GD, et al. Studies on prolonged acute regional ischemia. IV. Aggressive surgical treatment for intractable ventricular fibrillation after acute myocardial infarction. *J THORAC CARDIOVASC SURG* 1989;98:557-66.
55. Beyersdorf F, Kirsh MM, Buckberg GD, Allen BS. Warm glutamate/aspartate-enriched blood cardioplegic solution for perioperative sudden death. *J THORAC CARDIOVASC SURG* 1992;104:954-60.
56. Allen BS, Okamoto F, Buckberg GD, Leaf J, Bugyi H. XII. Considerations of reperfusate "duration" vs "dose" on regional functional, biochemical, and histochemical recovery. Studies of controlled reperfusion after ischemia: Reperfusate conditions. *J THORAC CARDIOVASC SURG* 1986;92:594-604.