Historical Perspectives

Myocardial Protection

The Rebirth of Potassium-Based Cardioplegia

Mark S. Shiroishi

The introduction of open-heart surgery more than 4 decades ago signaled a new era in medicine. For the 1st time, previously untreatable cardiac anomalies became amenable to surgical therapy. The use of the heart-lung machine seemed to grant the surgeon unlimited time in which to operate inside the heart. Still frustrated by poor operating conditions and the threat of air embolism, Denis Melrose introduced elective cardiac arrest in 1955. His use of a potassium citrate solution seemed to offer a safe method to effect a quiet, bloodless field. However, a few years after its inception, numerous reports began to question the safety of this approach, and the Melrose technique was abandoned in the early 1960s. Nearly 15 years elapsed before potassium-based cardioplegia regained popularity. During this period, topical hypothermia, coronary perfusion with intermittent aortic occlusion, and normothermic ischemia were evaluated and discarded. A few European investigators like Hoelscher, Bretschneider, and Kirsch had maintained their interest in chemical cardioplegia, and it was through their efforts that future researchers like Hearse and Gay spearheaded the return to potassium-based cardioplegia, which today forms the core of the cardiac surgeon's myocardial protective armamentarium and has contributed towards lowering operative mortality rates. ***(Tex Heart Inst J 1999;26:71-86)***

> *A hospital is not only an instrument of relief to the distressed who are immediately helped there, but also a means of helping others, by furnishing such principles and practice as may improve the art of Surgery and thus render the benefit more general.*
>
> – Joseph Warner, 1717-1801
> Surgeon to Guy's Hospital

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From: *The UCLA School of Medicine, University of California, Los Angeles*

Mr. Shiroishi is now a 2nd-year student at the UCLA School of Medicine. This essay was 1st runner-up in the 1998 competition for the Texas Heart® Institute Award for Undergraduate Writing in the History of Cardiovascular Medicine and Surgery.

Address for reprints:
Mark S. Shiroishi,
11811 Venice Blvd., Apt. 305,
Los Angeles, CA 90066

Nearly 45 years have passed since the introduction of modern open-heart surgery. When this novel therapy appeared for the 1st time, considerable optimism was felt by physicians and patients alike, for it seemed to offer the best opportunity for definitive correction of cardiac defects. The advent of extracorporeal circulation seemed to allow the surgeon unlimited time in which to operate inside the heart.

Still frustrated by poor operating conditions and the threat of air embolism, Denis Melrose introduced potassium citrate cardioplegia in 1955.[1] In the conclusion of his landmark communication, Melrose stated that "this method may offer an opportunity for useful surgery on the motionless heart, without the danger of air embolism." It is interesting to note that Melrose did not emphasize the concept of myocardial protection in his report. In fact, crystalloid-cardioplegia pioneer Mark Braimbridge has stated, "our whole edifice of cardioplegic myocardial protection has been built on serendipity."[2]

The usual cause of postoperative low-cardiac-output syndrome is not inadequate anatomical repair, but inadequate myocardial protection. The development of cardioplegic techniques has undoubtedly helped to lower mortality rates in cardiovascular surgery.[3] Today, potassium cardioplegic arrest is used by an overwhelming majority of surgeons as their primary method of myocardial protection.[4] This present report focuses on the origins of potassium-based cardioplegia and provides details on its initial rejection by the medical community in the 1960s and its eventual rebirth in the 1970s.

Physiologic Foundations of Cardioplegia

The principles that form the basis of cardioplegia date back to the work of English physician and pharmacologist Sydney Ringer (Fig. 1). While at University

Fig. 1 *Sydney Ringer*

(From: Bayliss WM. Principles of general physiology. London: Longmans, Green, 1915:206.)

College in London in 1883, Ringer[5] published a seminal paper in the *Journal of Physiology* that described the antagonistic effects of calcium and potassium ions on cardiac contraction. Ringer reported that if calcium was left unopposed by potassium salts, contractions strengthened until fusion of beats occurred and ventricular tetani ultimately resulted. Conversely, incremental increases of potassium resulted in weaker and weaker beats until cardiac asystole developed. Subsequent work by a multitude of physiologists in the late 19th and early 20th centuries extended Ringer's findings and provided the basis for the ionic theory of cardiac activity.

About 50 years after Ringer's report, D.R. Hooker applied potassium-induced elective cardiac arrest to rescue victims of electric shock. In 1929, Hooker[6] described the experimental use of potassium chloride to resuscitate dog hearts in ventricular fibrillation: upon coronary infusion of potassium chloride, the canine hearts stopped; and after washout of the potassium solution, a coordinated ventricular rhythm resumed. In the following year, Carl J. Wiggers[7] demonstrated that successive intraventricular injections of potassium and calcium salts halted fibrillation and restored a coordinated beat. It would be more than 2 decades before Henry Swan[8] would revisit this work in order to reverse ventricular fibrillation in hypothermic patients.

While it had been acknowledged for many years that sodium, calcium, and potassium ions were essential for cardiac activity, there existed considerable confusion over each ion's individual effects. In 1931, A.M. Baetjer and C.H. McDonald[9] provided a more detailed description of the cardiac function of these 3 ions. They found that sodium was chiefly responsible for the initiation and maintenance of spontaneous rhythmic contractions of the heart. Calcium was determined to be essential for the production of strong, mechanical contractions. And finally, potassium had antagonistic effects towards calcium and appeared to regulate the interaction between calcium and sodium.

In studying the effects of cold on frog and turtle hearts treated with modified Ringer's solution, George H. Zwikster and T.E. Boyd were prompted to expand the work of Baetjer and McDonald. In 1935, they reported findings that focused on the effects of excess potassium on cold-blooded hearts.[10] They discovered that ventricles ceased contractile activity when soaked for 1 to 2 hours in Ringer's solution modified to contain 0.2% to 0.4% potassium chloride. Appropriate contractions resumed once the preparations were exposed to standard Ringer's solution.

Because most of the investigators before 1940 had used ionic concentrations that differed drastically from those of standard Ringer's solution, C.R. Spealman[11] set out to determine the effects of varying the sodium, calcium, and potassium within "physiologically normal" concentrations. An increase in calcium-ion concentration augmented both the amplitude and the duration of the ventricular response. Increasing the potassium-ion concentration led to a decrease in both the atrioventricular (a-v) time interval and the duration of ventricular systole. No appreciable effects were seen when sodium-ion concentration was varied within the "normal" range.

Early Cardiac Surgery

The future of clinical cardiac surgery seemed bleak after the failed attempts at operative treatment of mitral stenosis in the 1920s.[12] However, the outlook began to improve when a number of congenital maladies began to yield to surgical therapy. In the 1930s and 1940s, surgeons such as Robert E. Gross,[13] Clarence Crafoord,[14] and Alfred Blalock[15] began developing operative techniques for the treatment of congenital anomalies, including patent ductus arteriosus, coarctation of the aorta, and tetralogy of Fallot. In the mid to late 1940s, the attention of surgeons such as Roy Cohn,[16] Gordon Murray,[17] and F.D. Dodrill[18] focused on the repair of atrial septal defects. Because their methods were all closed pro-

cedures, suboptimal results were all too common. The pump oxygenators available at the time were too cumbersome and unsafe to use clinically.[19] Open cardiac repairs that allowed unhurried, direct-vision corrections on an empty heart were necessary if clinical results were to improve.

Systemic Hypothermia

The use of hypothermia in cardiac surgery has been described as the single most important component of myocardial protection.[20-22] The University of Toronto's Wilfred Bigelow (Fig. 2) is generally credited with being the foremost contributor to this practice.[23] In the *Annals of Surgery* in 1950, Bigelow outlined his rationale.[24] He stated that in hypothermia

> . . . the oxygen requirements of tissues are reduced to a small fraction of normal. . . . Such a technic might permit surgeons to operate upon the "bloodless heart" without recourse to extra corporeal pumps, and perhaps allow transplantation of organs. . . . Intracardiac procedures upon human beings are heroic technics designed to open a stenosed mitral valve and close or produce a septal defect in an intact heart with little or no visual control. . . .intracardiac operations under direct vision are still not possible.[24]

Modern Open-Heart Surgery

The era of modern clinical open-heart surgery can be traced to a 1953 article in *Surgery* by the University of Minnesota's F. John Lewis and Mansur Taufic.[25] This report described how its authors—drawing heavily upon Bigelow's fundamental work—closed, under hypothermic inflow occlusion, an atrial septal defect in a 5-year-old child.

Extension of this work became possible after John Gibbon's development of a workable heart-lung machine. Following nearly 2 decades of experimental work, Gibbon[26] (Fig. 3) became the 1st surgeon to successfully apply such an apparatus in the repair of an atrial septal defect; the procedure was carried out on 6 May 1953, in an 18-year-old girl. In 1954, the University of Minnesota's C. Walton Lillehei[27] ini-

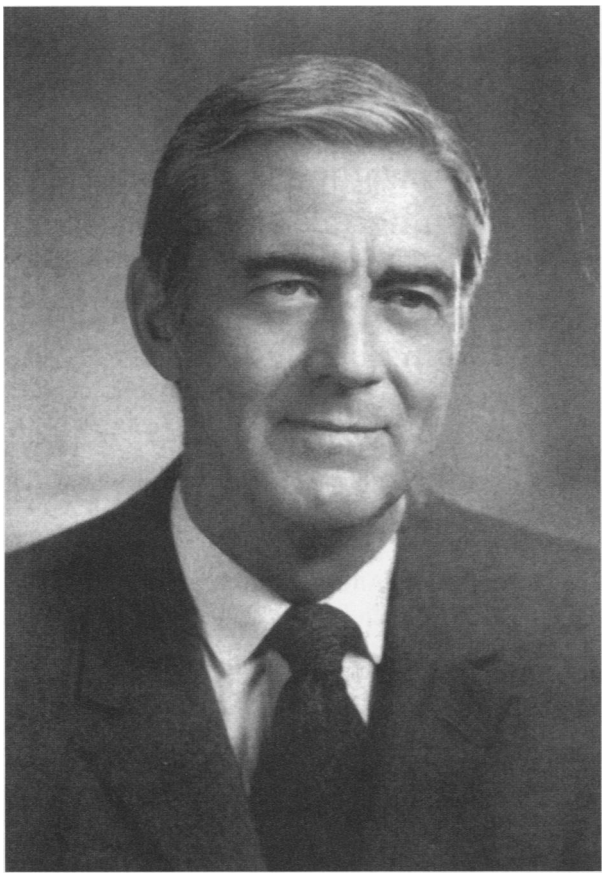

Fig. 2 *Wilfred G. Bigelow*

(From: Shumacker HB, Jr. The evolution of cardiac surgery. Bloomington: Indiana University Press, 1992:222. Reproduced by permission of the author.)

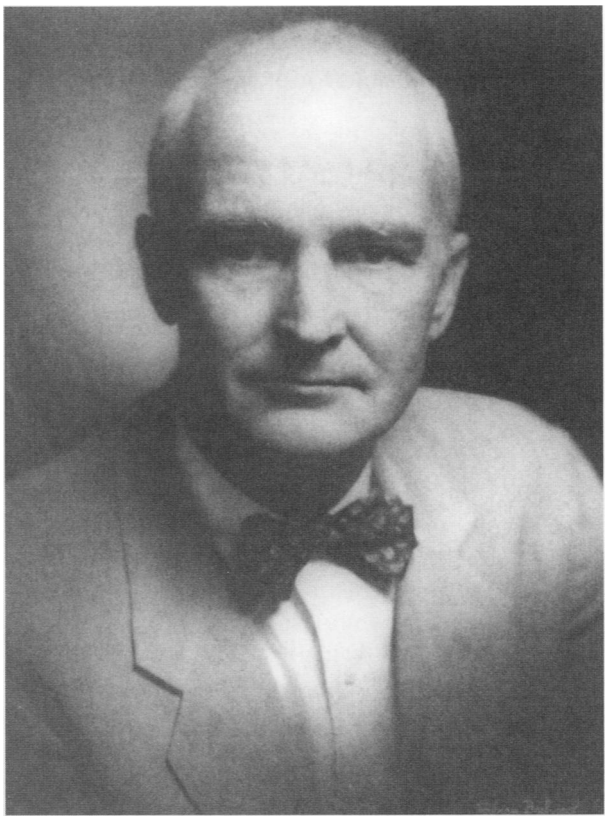

Fig. 3 *John H. Gibbon, Jr.*

(From: Shumacker HB, Jr. The evolution of cardiac surgery. Bloomington: Indiana University Press, 1992:[ii]. Reproduced by permission of the author.)

tiated the use of controlled cross-circulation and intermittent aortic occlusion to correct ventricular septal defects, atrioventricularis communis, isolated infundibular pulmonic stenosis, and tetralogy of Fallot. In 1955, John Kirklin[28] reported excellent results with the Mayo Clinic's modification of the Gibbon apparatus. Reliable extracorporeal circulation now enabled surgeons to operate inside the heart under direct vision.

Unforeseen Limitations

Although the introduction of extracorporeal circulation now permitted direct-vision intracardiac surgery, other problems soon became apparent.[29] First, there was the potential of lethal air embolism, once a beating heart was opened. Second, it was difficult to perform surgery on a contracting heart. And finally, antegrade flow from the coronary sinus and pulmonary veins, together with retrograde flow from the pulmonary artery, often obscured the operative field. If these obstacles were to be overcome, a quiet, bloodless heart would be necessary.

While it was recognized that reversible, elective cardiac arrest subjected the heart to ischemia, surgeons were more concerned with optimizing operating conditions and minimizing the risk of air embolism. This created a conflict between the surgeon's need for precise anatomical repair and the myocardium's demand for oxygen and substrate.

Denis Melrose

Frustrated by inadequate operating conditions during repairs of rheumatic mitral valves in the presence of aortic regurgitation, Denis Melrose (Fig. 4) and his colleagues at the Royal Postgraduate Medical School in London began experimentation with elective cardiac arrest.[2] In the 2 July 1955 issue of *The Lancet*, Melrose[1] published his famous study on experimental potassium citrate arrest. He began by saying

> The goal of cardiac surgeons must be the unhurried correction of cardiac abnormalities under direct vision. Toward this end are being developed many techniques for working within the bloodless heart and for excluding the possibility of air embolism after such interventions. . . . A most valuable contribution to this problem and indeed to the whole problem of intracardiac surgery would be made if the heart could be arrested and re-started at will, suffering no damage during periods of arrest and cessation of coronary blood flow.[1]

Citing the works of Ringer,[5] Hooker,[6] and A.V. Montgomery[8] as primary influences, Melrose described his initial experiments in 33 adult dogs that had been maintained with either the heart-lung machine or

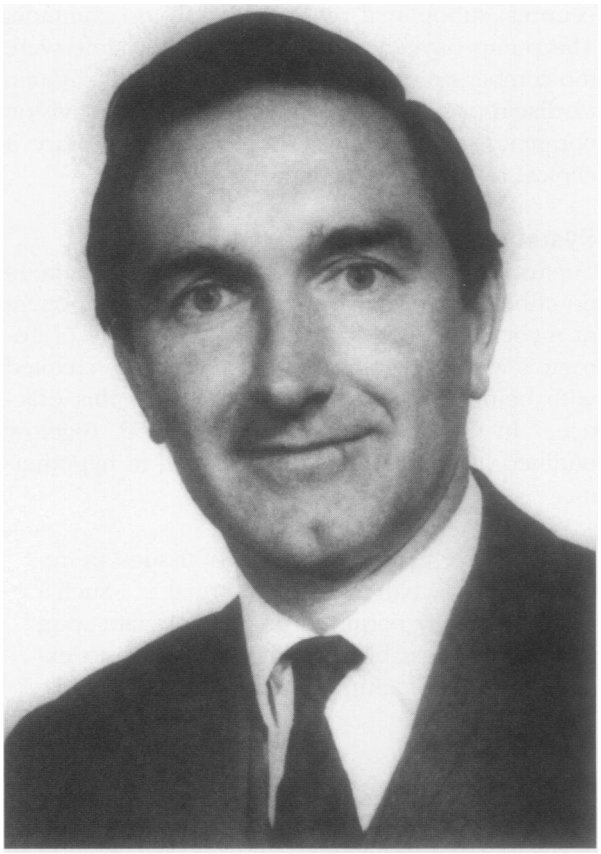

Fig. 4 *Denis G. Melrose*

(From: Engelman RM, Levitsky S, eds. A textbook of cardioplegia for difficult clinical problems. Mt. Kisco, NY: Futura Publishing Co., 1992:10. Reproduced with permission of Futura Publishing Co., Inc.)

systemic hypothermia. Ligation of the venae cavae, pulmonary artery, and aorta excluded blood from the heart. Diastolic arrest was accomplished and maintained for 15 minutes within 5 seconds of an injection of 25 to 100 mg/mL of potassium citrate into the aortic root. Throughout the period of arrest, the myocardium remained pink and serial coronary sinus samples revealed that little oxygen was being used by the heart. After a simulated intracardiac repair, easy manipulation of the flaccid heart obviated air embolism upon resuturing. Reperfusion with blood, in combination with cardiac massage, calcium chloride, adrenaline, and neostigmine, was necessary to restore a normal heart beat. In almost every instance, ventricular fibrillation resulted upon reperfusion. Electrical defibrillation was effective in only 70% of cases, and resumption of normal contraction was not reliable.

In order to improve their method, Melrose began experiments with isolated perfused hearts, using oxygenated Locke's solution. Hearts for this set of experiments were derived from 5 rabbits, a guinea pig, a kitten, and a puppy. With myocardial temperatures

ranging between 23 °C and 37 °C, diastolic arrest was accomplished within 10 to 20 seconds after injections of greater than 5 mg/mL of potassium citrate. This effect was maintained as long as the potassium citrate remained in the coronary circulation. No damage resulted after 15 minutes of zero coronary flow. Upon reperfusion with pure Locke's solution, a normal, spontaneous beat was consistently achieved.

Encouraged by his group's work with isolated perfused hearts, Melrose once again began experiments in intact animals. Here, 2 mL of a 25% potassium citrate mixture was diluted to 20 mL by blood. This solution was then injected into the aortic root of dogs. Normal cardiac activity resumed after 15 minutes of arrest and reperfusion.

Melrose concluded his *Lancet* paper by stating that

> The oxygen consumption of the quiescent heart is very low, and at normal body-temperature, cessation of the coronary circulation for over fifteen minutes does not endanger such a heart. Although a great deal of further work remains to be done, this method may offer an opportunity for useful surgery on the motionless heart, without the danger of air embolism.[1]

Two years after this pivotal report, several significant findings came to light. First, Melrose and his associates[30] demonstrated that the period of arrest could be extended to 30 minutes. Moreover, they theorized that even longer durations of arrest could be achieved if oxygenated blood were substituted for Locke's solution. Second, a separate study by H.H. Bentall and Melrose[31] found that lactic acid concentrations in the coronary effluent after potassium citrate arrest were about one-third as high as those that followed arrest without potassium citrate. It was clear that the arrested heart, although not performing any work, was still an ischemic organ with a significant metabolic rate.[32]

In 1958, Melrose and Frank Gerbode[32] published their successful collaborative work with potassium citrate arrest in 34 clinical cases of open-heart surgery at Stanford University Hospital. Their technique relied upon a 25% solution of potassium citrate diluted 1 part to 9 in oxygenated blood. When describing their method of induction, they stated, "The injection is terminated when the heartbeat ceases, no fixed quantity being given, and excess is avoided." In none of the cases did the heart fail to resume normal activity. However, in the discussion that followed, Melrose cautioned that "No patient has as yet lived for many years after elective arrest and we must wait on time for judgment as to its real merits." During these early years, the Melrose technique began to gain popularity and to show signs of promise.[33-35]

In 1958, Will Sealy and colleagues[36] at Duke University reported their modification of the Melrose method, which used a combination of potassium citrate, magnesium sulfate, and neostigmine to achieve ischemic periods as long as 52 minutes. It is interesting to note that Sealy's group coined the term "cardioplegia."[29]

While Melrose was conducting his work with potassium citrate in 1955, Conrad Lam and associates[37] from the Henry Ford Hospital in Detroit were investigating the application of potassium chloride to cardioplegia. Animal studies yielded good results, but Lam's clinical experience was complicated by the frequent occurrence of ventricular fibrillation. Although personal communications from Melrose to Lam suggested that his use of the chloride salt of potassium was responsible for this difficulty, Lam personally believed that the method of resuscitation, cardiac massage, was the culprit.[38] In the end, Lam's clinical difficulties stimulated a search for an alternative method of arrest.

Building on the work of Viking Björk,[39] Lam began experimentation in November 1955 with acetylcholine as a cardioplegic agent.[38] Lam's 1956 report[40] in *Surgical Forum* demonstrated excellent animal and clinical results. However, because the longest arrest period was only 35 minutes, this method of cardioplegia never gained popularity.

The Melrose Technique Abandoned

By the late 1950s and early 1960s, investigators were questioning the safety of potassium cardioplegia. In 1957, Peter Allen and C. Walton Lillehei[41] cautioned that potassium citrate arrest should be avoided, if possible, in patients who had extensive myocardial damage from any cause. Others reported the frequent occurrence of dysrhythmias after potassium citrate arrest.[42,43]

Following early accounts of unsatisfactory clinical results with the Melrose technique, a number of investigators returned to the laboratory to re-evaluate the method. In 1959, Daniel Nunn and colleagues[44] published a study in the dog, in which they compared aortic clamping with potassium citrate arrest. Five to 20 minutes of arrest by means of 2.5% potassium citrate resulted in ventricular fibrillation or ineffective cardiac action when the heart was restarted. On the other hand, no deleterious effects were noted after aortic occlusion of only 5 minutes' duration. Although these results were obtained from dogs, the authors concluded that temporary aortic occlusion seemed preferable to potassium citrate arrest in the clinical setting. In the same year, V.L. Willman and associates[45] published one of the 1st detailed works that examined myocardial function

after recovery from induced cardioplegia. Their studies in dogs found that cardiac arrest for 30 minutes by means of a 2.5% potassium citrate solution resulted in a profound, permanent decrease in cardiac output, cardiac stroke work, and total work. Arrest for 20 minutes resulted in similar, albeit less, cardiac deterioration. Also in 1959, James A. Helmsworth and coworkers[46] reported occurrence (in the dog) of unusual rigor of the left ventricle, irreversible ventricular fibrillation, and focal necrosis, after 30 minutes of arrest by the Melrose method.

John A. Waldhausen[47] and V.O. Björk[48] independently confirmed the findings of Willman and Helmsworth in 1960 and 1961, respectively. Björk stated, "The potassium method of Melrose seems to be a rather dangerous and doubtful one."[48] Waldhausen and colleagues[47] wrote

> The majority of patients operated upon for heart disease have an increased myocardial work load and although a successful correction of the anatomic lesion may substantially reduce this, the trauma of the operative procedure may offset this beneficial effect in the early postoperative period. . . .Thus the additional depression of ventricular function caused by cardiac arrest may be sufficient to result in fatal heart failure.

Furthermore, each investigator went on to advocate alternative methods for inducing cardiac arrest. Waldhausen's group supported the use of intermittent aortic occlusion, while Björk felt that hypothermic arrest was preferable.

Virtual abandonment of the Melrose technique was secured in 1960, in the wake of a report in the *Journal of Thoracic and Cardiovascular Surgery* by the National Heart Institute's James McFarland and colleagues.[49] As a consequence of the deaths of 2 patients who had undergone potassium citrate arrest and were subsequently shown to have histopathologic evidence of unusual necrosis, McFarland and coworkers re-evaluated the hearts of all patients who had died after open-heart procedures at their institution. They reported distinct clinical and pathological evidence of myocardial damage in 79% of their patients subjected to potassium citrate arrest. The lesions were typically seen as multiple, sharply defined microscopic areas of necrosis occurring in the central portion of the ventricular myocardium. This led to the National Heart Institute's abandonment of the Melrose technique and adoption of intermittent aortic occlusion or direct coronary perfusion.

Alternatives to the Melrose Technique

Nearly 15 years elapsed before chemical arrest of the heart regained popularity.[3] During this time, open-heart surgery was performed with either direct coronary perfusion/intermittent aortic occlusion, topical hypothermia, or normothermic ischemia.

Direct Coronary Perfusion. Largely on the basis of the theory that artificial perfusion was better than no perfusion at all, direct coronary perfusion with intermittent aortic occlusion became the preferred method of myocardial protection during the 1960s and early 1970s.[50] The early experimental and clinical studies of E.B. Kay,[51] J.B. Littlefield,[52] H.T. Bahnson,[53] and others[54] demonstrated that oxygenation of the myocardium could be maintained during aortotomy by direct cannulation and selective perfusion of the coronary arteries with oxygenated blood. As a result, operative results seemed to improve, and deaths declined.

However, this method was far from being technically and biologically perfect.[55-59] Coronary perfusion often flooded the operative field with blood. Placement of the coronary cannulae could be difficult and, once in place, the cannulae could obscure the surgeon's vision. Air and corpuscular elements could make their way into the coronary circulation. In addition, as G.E. Green and associates[60] pointed out, anatomical variations between coronary arteries could significantly influence the degree of myocardial perfusion. Others reported that cannulation or perfusion could irreparably damage the coronary arteries.[61-64] In 1972, Gerald Buckberg[65] from the University of California, Los Angeles found that nonphysiologic coronary perfusion could result in subendocardial ischemia and necrosis even when coronary arteries were widely patent.

Because a beating heart created less-than-ideal operative conditions, many surgeons began to induce fibrillation electrically. However, this technique was widely abandoned when Buckberg,[66] Hassan Najafi,[67,68] and their colleagues presented evidence that this method also promoted subendocardial necrosis.

Topical Hypothermia. Concurrent with the introduction of selective coronary perfusion, Norman Shumway and associates[69] introduced selective hypothermia in anoxic cardiac arrest in 1959. Their work was stimulated by that of F.S. Cross and associates,[70] who had perfused the coronary arteries with cold blood after induction of potassium asystole, to safely extend the arrest period. Shumway's group produced local hypothermia of the heart by simple perfusion of the suspended pericardial sac with a 4 °C solution of isotonic saline. Anoxic periods of up to 1 hour were well tolerated in their dogs during cardiopulmonary bypass with normothermic blood. Selective hypothermia was deemed desirable because it seemed to enable better control of myocardial temperature and avoided some of the problems encountered with potassium arrest and direct coro-

nary perfusion. During the following 2 years, several studies[71-73] pointed out the superiority of local hypothermic arrest over chemical arrest in regard to both oxygen uptake and post-arrest cardiac function.

Research into a modern surgical method for cardiac transplantation in the early 1960s enabled the experimental limits of selective hypothermia to be tested.[74] In 1962, Richard Lower, Shumway, and colleagues[75] presented evidence that it was possible to effectively preserve an arrested dog heart extracorporeally for more than 7 hours in 2 °C to 4 °C saline solution. Two years later, Shumway's group reported 4 deaths among 120 patients who underwent cardioplegia with local cardiac cooling.[76] There were no instances in which the myocardium failed to respond to periods of anoxic arrest that varied between 30 and 40 minutes in length. None of the deaths was attributable to the authors' method of myocardial protection.

Disenchanted with both continuous coronary perfusion and total body hypothermia, Paul W. Sanger and associates[77] demonstrated, in 1966, the superiority of topical hypothermia over coronary perfusion in open-heart operations for acquired heart disease. In 1973, Shumway and colleagues[21] reported excellent results with their technique for both coronary artery bypass and valve replacement surgery. They surmised that profound local hypothermia should provide up to 90 minutes of safe anoxic arrest.

The greatest limitation of topical cardiac hypothermia was the short duration of "safe" ischemic arrest. Several authors felt that 70 minutes was the upper limit of safety.[78,79] In addition to the limited arrest time, the flooded operative field and nonuniform cooling were other significant disadvantages.[20] As a consequence, this technique never gained wide application, and coronary perfusion remained the preferred mode of myocardial protection during this period.

Normothermic Ischemia. While it had been shown that more than 20 minutes of normothermic cardiac anoxia was deleterious to the dog heart, it was believed that the human heart would be more tolerant of this type of ischemic stress.[80] As a result, the technical difficulties posed by coronary artery perfusion stimulated some centers to adopt simple normothermic cross-clamping of the ascending aorta in the mid to late 1960s. In 1964, the Texas Heart Institute's Denton A. Cooley became the 1st surgeon to abandon coronary perfusion and adopt normothermic arrest in all cases.[81,82] For a period of about 7 years, normothermic anoxic arrest gained widespread acceptance and seemed to offer myocardial protection in excess of 45 minutes of ischemia.[83]

However, in 1971 and 1972 respectively, N.D. Colapinto[84] and S.R. Iyengar[85] and their colleagues reported the association of subendocardial necrosis with normothermic arrest. Similarly, G. Frank Tyers and coworkers[86] revealed systemic acidosis, persistent electrocardiographic changes, and other suboptimal results after normothermic arrest.

The term "stone heart" came into being in 1972 when Cooley and associates[82] described the small, spastic heart that was frozen in systole in a small number of patients following normothermic arrest. These patients died after unsuccessful attempts to wean them from cardiopulmonary bypass. Work by Arnold Katz,[87] David MacGregor,[88] and David Hearse[89] proposed that the depletion of myocardial adenosine triphosphate (ATP)—which was associated with prolonged normothermic ischemia—led to this catastrophic condition.

As in the case of topical hypothermia, time limitations led to the rejection of normothermic arrest. Less than 45 minutes of safe ischemic time and the spectre of the "stone heart" prevented this technique of myocardial protection from gaining popularity.[80,90]

The Rethinking of Potassium-Based Cardioplegia in Europe

Although chemical cardioplegia had been abandoned and the above methods of myocardial protection were being explored, several European investigators maintained active research programs into chemical cardioplegia throughout the 1960s. It can be maintained that the resurrection of potassium-based cardioplegia in the mid 1970s can be attributed to the work of these innovators.

In the early 1960s, B. Hoelscher from the Free University School of Medicine in Berlin published a series of German-language articles that sought to determine if the contemporary opposition to potassium citrate arrest was warranted. From this body of work, Hoelscher concluded that the damaging effects of the Melrose solution were due not to the potassium ion, but to the calcium- and magnesium-chelating action of the citrate ion.[91] This dual action of citrate was believed to lead to both intra- and extracellular edema.

In an attempt to develop a safer cardioplegic method, Hoelscher initiated experimentation with magnesium chloride and procaine amide, compounds known to have both membrane-stabilizing and cardiac-arresting effects.[91] In 1967, Hoelscher published a study[91] in the *Journal of Cardiovascular Surgery* that compared magnesium-chloride/procaine-amide arrest with potassium-citrate arrest. Potassium-citrate arrest led to histologic and functional defects upon reperfusion, but magnesium-chloride/procaine-amide arrest led to both rapid cardioplegia and uneventful recovery.

In addition to Hoelscher, another German pioneer was Hans J. Bretschneider (Fig. 5) from the University of Göttingen's Institute of Physiology. In 1975,

Fig. 5 *Hans J. Bretschneider*

(From: Engelman RM, Levitsky S, eds. A textbook of cardioplegia for difficult clinical problems. Mt. Kisco, NY: Futura Publishing Co., 1992:12. Reproduced with permission of Futura Publishing Co., Inc.)

TABLE I. Bretschneider's Solution No. 3 Used by Søndergaard

Sodium chloride	0.70 gram
Potassium chloride	0.75 gram
Magnesium chloride	0.20 gram
Procaine chloride	2.00 gram
Mannitol	43.50 gram
Aqua sterilisata ad	1000 mL

(From: Søndergaard T, Berg E, Staffeldt I, Szczepanski K. Cardioplegic cardiac arrest in aortic surgery. J Cardiovasc Surg [Torino] 1975;16:288-90. Reproduced by permission of Edizioni Minerva Medica.)

Bretschneider[92] described the logic behind each component of his "intracellular" cardioplegic solution. The sodium concentration of the "Bretschneider" solutions, as they came to be known, was the same as the intracellular concentration of sodium. This would prevent the excitation potential and thus prevent myocardial contraction. A calcium-free environment would also prevent contraction. Procaine was added to the solution to provide membrane stabilization, and mannitol maintained ideal osmolarity.

T. Søndergaard and colleagues from the University of Aarhus in Denmark were the 1st to begin clinical application of modified Bretschneider solutions. In 1975, his group published results of cardioplegic arrest in 100 consecutive patients who had undergone aortic valve replacement using Bretschneider's solution No. 3 (Table I).[90] Søndergaard's technique consisted of perfusing the aortic root with blood and glucose at a pressure of approximately 100 cm H_2O. Concomitantly, the heart was cooled by introduction of a 4 °C glucose solution into the pericardial cavity. Subsequently, the aortic infusion was changed to Bretschneider's solution No. 3 until asystole was achieved. Arrest times generally ranged between 70 and 100 minutes. The 6 deaths that occurred in Søndergaard's series of 100 patients were not attributed to cardioplegic methods. The group concluded by asserting the superiority of its method over the then-current technique of coronary perfusion.

It has been said that much of Bretschneider's work during this period went largely unnoticed due to 2 factors.[93] The 1st was the general shift away from chemical arrest during the 1960s and the 2nd was the fact that much of his work was published in the German literature.

Finally, another important contributor was U. Kirsch from Hamburg. In 1972, on the basis of the theory that magnesium-aspartate and procaine hydrochloride slow the decay of organic phosphates in myocardium, Kirsch published data reporting safe normothermic arrest for up to 80 minutes.[94] His cardioplegic solution contained 2.5% magnesium-aspartate and 0.3% procaine hydrochloride.

David Hearse and St. Thomas's Hospital Solution

In 1976, David Hearse (Fig. 6) from St. Thomas's Hospital in London published in *Circulation*[95] a landmark study on the isolated rat heart. In fact, according to Hearse's colleague Mark Braimbridge, "many surgeons have said to me since that it was this article which first persuaded them that cardioplegia was the way to go."[2]

In his report, Hearse outlined the basic components of the dominant form of crystalloid cardioplegic solution in use today. The stimulus for this work can be traced to the efforts of Braimbridge.[2] Braimbridge recalled that listening to presentations by Bretschneider and Søndergaard in Oslo in 1974—

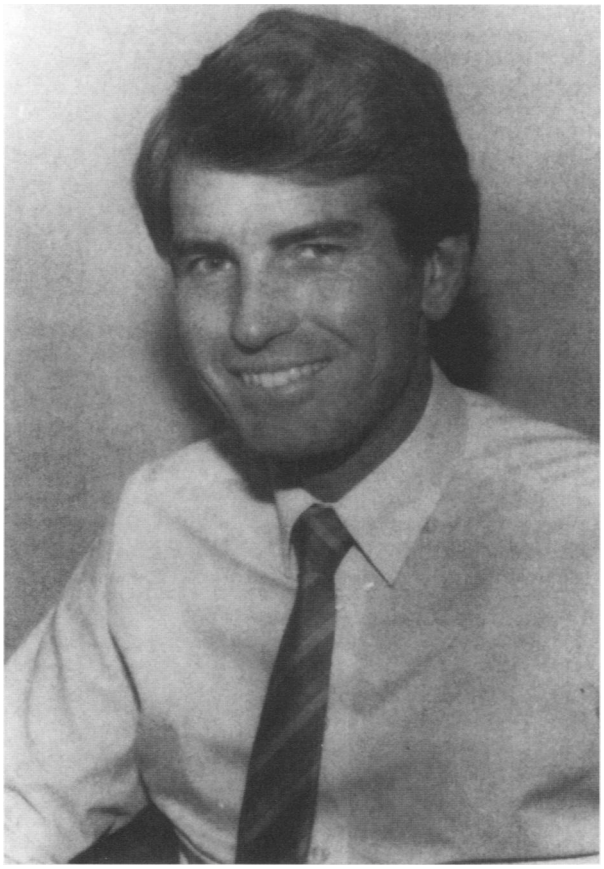

Fig. 6 *David J. Hearse*

(From: Engelman RM, Levitsky S, eds. A textbook of cardioplegia for difficult clinical problems. Mt. Kisco, NY: Futura Publishing Co., 1992:13. Reproduced with permission of Futura Publishing Co., Inc.)

and to a presentation of Kirsch's work in Hamburg in 1975—provided direction for his own studies on myocardial protection. After recruiting Hearse from Imperial College to St. Thomas's Hospital, Braimbridge suggested to him that studies on the effects of potassium, magnesium, and procaine should be initiated. Rather than the "intracellular" solutions of Bretschneider and Kirsch, Hearse proposed an "extracellular" cardioplegic solution that comprised Krebs Henseleit bicarbonate buffer at pH 7.4, 12 mM potassium, 16 mM magnesium, 10 mM ATP, 10 mM creatine phosphate, and 1 mM procaine.[95] Application of this solution to the isolated perfused rat heart demonstrated an improvement of aortic flow from 0% to 82% after 30 minutes of normothermic ischemia. Hearse went on to postulate that the topical hypothermia often used in clinical surgery might extend the protective capabilities of his solution.

On the basis of Hearse's work, Braimbridge instituted cold cardioplegia with St. Thomas's Hospital Solution No. 1 in 1975 (Table II).[96] This solution comprised 1L of 4 °C Ringer's solution, with the addition of 16 mM potassium chloride, 16 mM magnesium chloride, and 1 mM procaine hydrochloride. When the aortic root was perfused with this solution for 2 minutes, myocardial temperature was reduced to between 8 °C and 16 °C. After 90 minutes of aortic occlusion, St. Thomas's Hospital Solution No. 1 provided a degree of protection similar to that of coronary perfusion. After 120 minutes of aortic clamping, a 2nd infusion of cardioplegic solution was required to provide the same protection as coronary perfusion.

An improvement of St. Thomas's Hospital Solution No. 1 came about after studies were undertaken using detailed dose-response curves to determine the composition of an optimal cardioplegic solution.[95,97-101] In 1981, this work resulted in the introduction of St. Thomas's Hospital Solution No. 2, known commercially as "Plegisol" (Table III).[102] Essentially, the new formulation reduced the sodium, potassium, and calcium content, eliminated procaine, added bicarbonate, adjusted the pH to 7.8, and reduced the osmolarity. In 1987, Hearse and Braimbridge[102] published a comparative study that demonstrated the superiority of Solution No. 2 over No. 1. Although many differences existed between the two, they attributed this result to the lower calcium content of No. 2 (1.2 versus 2.4 mM).

TABLE II. Composition of St. Thomas' Hospital Solution No. 1

Composition of Ringer's Solution	**Concentration**
Calcium chloride	147 mM/L
Potassium chloride	4 mM/L
Sodium chloride	147 mM/L
Distilled water	1 L
Additives	
Magnesium chloride	16 mM/L
Potassium chloride	16 mM/L
Procaine hydrochloride	1 mM/L
Distilled water	20 mL
FINAL CONCENTRATION	
Calcium chloride	2 mM/L
Potassium chloride	16 mM/L
Sodium chloride	147 mM/L
Magnesium chloride	16 mM/L
Procaine hydrochloride	1 mM/L

(From: Braimbridge MV, Chayen J, Bitensky L, Hearse DJ, Jynge P, Čanković-Darracott S. Cold cardioplegia or continuous coronary perfusion? Report on preliminary clinical experience as assessed cytochemically. J Thorac Cardiovasc Surg 1977;74:900-6. Reproduced by permission of Mosby, Inc.)

TABLE III. Composition of St. Thomas' Hospital Cardioplegic Solutions

	No. 1 (MacCarthy)	No. 2 (Plegisol)
Sodium chloride	144 mmol/L	110 mmol/L
Potassium chloride	20 mmol/L	16 mmol/L
Magnesium chloride	16 mmol/L	16 mmol/L
Calcium chloride	2.4 mmol/L	1.2 mmol/L
Sodium bicarbonate	—	10 mmol/L
Procaine hydrochloride	1 mmol/L	—
pH	5.5-7.0	7.8
Osmolarity (mOsm/kg H_2O)	300-320	285-300

(From: Ledingham SJM, Braimbridge MV, Hearse DJ. The St. Thomas' Hospital cardioplegic solution. A comparison of the efficacy of two formulations. J Thorac Cardiovasc Surg 1987;93:240-6. Reproduced by permission of Mosby, Inc.)

Chemical Cardioplegia in America

The rediscovery of potassium cardioplegia in the United States was influenced primarily by the work of William A. Gay, Jr. (Fig. 7) and Paul A. Ebert (Fig. 8). During the late 1960s, Gay was still a surgical resident and his interest in myocardial protection was sparked by the early attempts at cardiac transplantation.[3] Encouraged by his mentors Will Sealy, David C. Sabiston, Jr., and Ebert, Gay began a series of experimental studies to devise a method of protecting the excised heart. Early studies with a variety of perfusates and perfusion devices were plagued by technical difficulties. Gay postponed his experiments while finishing his clinical residency, but resumed his work upon joining the Cornell faculty.

Stimulated by Kirsch's[94] successful use of a magnesium-based cardioplegic solution for up to 80 minutes of normothermic ischemia, Gay and Ebert published their famous 1973 study[103] of potassium-induced cardioplegia. Published in *Surgery* and titled "Functional, metabolic, and morphologic effects of potassium-induced cardioplegia," their study used an isolated, supported heart model that was arrested by injection of an osmotically balanced solution of 25 mEq/L potassium chloride in a 200 mEq/L sodium solution, with the addition of glucose and bicarbonate (Table IV). Chemically arrested hearts showed a 4-fold decrease in oxygen consumption in comparison with the beating, nonworking heart, the paced heart, and the fibrillating heart; this finding confirmed the work of McKeever and associates.[104] Hearts that underwent potassium arrest for 60 minutes displayed only mild reduction of ventricular function upon resuscitation, while those that experienced 60 minutes of normothermic ischemia could not be resuscitated. Gay and Ebert's improvement over the Melrose method was attributed to the isotonic nature of their solution (cf. Tables IV and V).

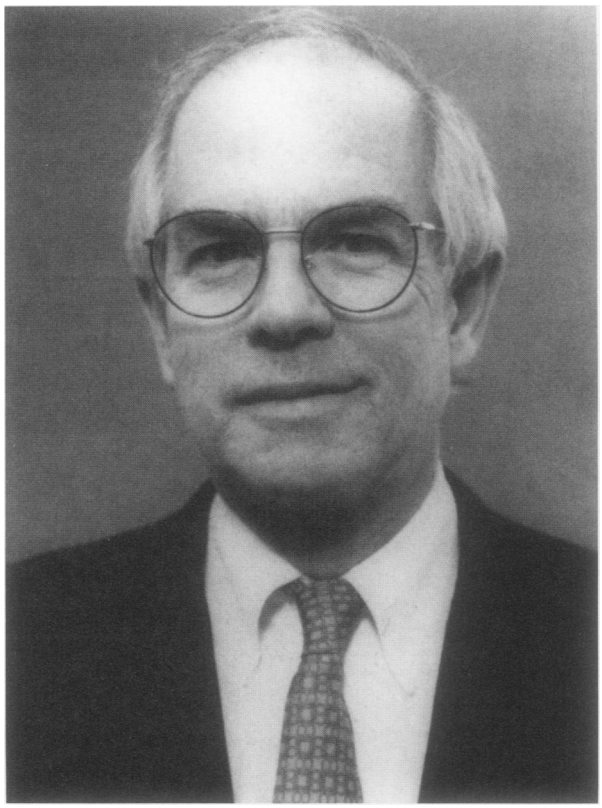

Fig. 7 *William A. Gay, Jr.*

(From: William A. Gay, Jr. Reproduced by permission.)

Two years after the Gay and Ebert publication, Tyers and G.F. Todd[105,106] reported their detailed studies on the deleterious effects of hyperkalemia associated with Melrose's and Lam's cardioplegic solutions. When they examined the potassium citrate concentrations used by Melrose, they calculated that they had ranged anywhere from 245 mEq/L to 980 mEq/L. When they studied Lam's solution, they found the potassium chloride concentration to be as high as 666 mEq/L. Regardless of whether the citrate or chloride salt of potassium was used, Tyers and Todd determined that potassium concentrations held around or below 26 mEq/L would limit ischemic damage reliably. In addition, they held that avoidance of hyperosmolarity greater than 400 mOsm/L would preserve the protective effect of potassium-induced arrest.

On the basis of Gay and Ebert's 1973 publication[103] and Bruce A. Reitz's 1974 study[107] (which demonstrated the viability of anoxic dog hearts arrested with hypothermic, hyperkalemic cardioplegic solution for 24 hours), Benson Roe initiated clinical myocardial protection with hypothermic potassium cardioplegic solution at the University of California,

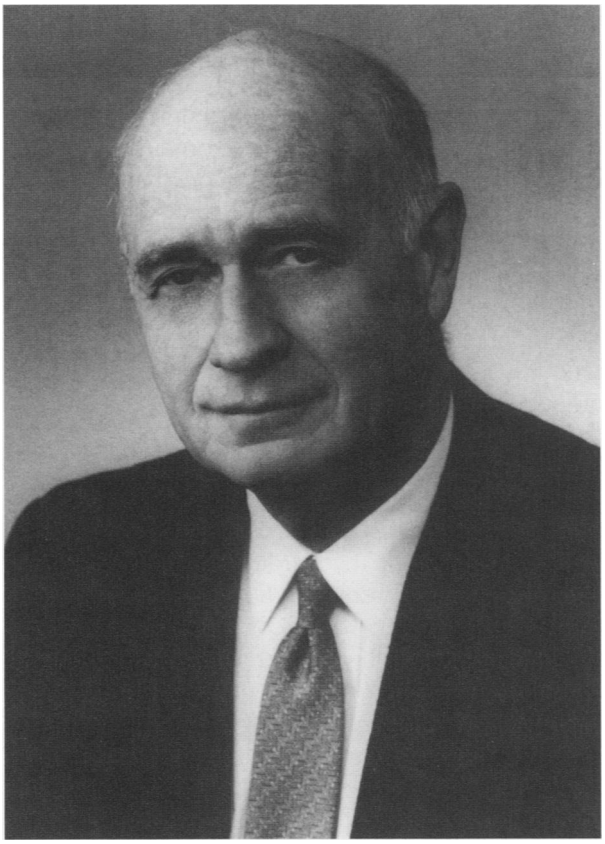

Fig. 8 *Paul A. Ebert*

(From: American College of Surgeons. Reproduced by permission.)

TABLE IV. Composition of High-Potassium Solutions Used by Gay and Ebert

Ingredient	**Amount** (g/1,000 mL)
Sodium chloride	4.0 (200 mEq/L)
Potassium chloride	2.5 (25 mEq/L)
Glucose	2.0
Sodium bicarbonate	1.0

pH = 7.5; osmolarity = 275 +/– 5 mOsm/L

(From: Gay WA Jr, Ebert PA. Functional, metabolic, and morphologic effects of potassium-induced cardioplegia. Surgery 1973;74:284-90. Reproduced by permission of Mosby, Inc.)

TABLE V. Composition of Melrose's Solution

Melrose's solution—$K_2(C_6H_3O_7) \cdot H_2O$ 250 g/L

Sodium	= 0 mEq/L
Potassium	= 25 mEq/L
pH	= 6.8
Osmol	= >500 mOsm/L

(From: Gay WA Jr, Ebert PA. Functional, metabolic, and morphologic effects of potassium-induced cardioplegia. Surgery 1973;74:284-90. Reproduced by permission of Mosby, Inc.)

San Francisco in 1973. In 1977, he reported excellent results in 204 patients using a cardioplegic solution with 20 mEq/L of potassium.[108] Arrest periods as long as 208 minutes were well tolerated, with only 2 of the 11 hospital deaths related to myocardial function.

Gerald Buckberg and Recent Cardioplegic Trends

By the very late 1970s, coronary perfusion had been abandoned and randomized clinical studies, such as that by Kirklin's group at the University of Alabama, Birmingham,[109] had established cold potassium cardioplegia as the dominant form of myocardial protection.

Gerald Buckberg (Fig. 9) of the University of California, Los Angeles can be credited with stimulating the major shift to the myocardial protective techniques used today. One important transition took place in 1977 when he and his colleagues determined that blood was the best cardioplegic vehicle.[110] Blood delivery of cardioplegic solution offered a number of advantages to the surgeon. These included augmented oxygen delivery, effective buffering by carbonic anhydrase, free-radical scavenging by red blood cells and plasma constituents, ideal oncotic pressure, and limitation or reversal of ischemic or reperfusion injury.[111] Furthermore, in a personal communication with this author, Buckberg stated that blood also provides the surgeon with many advantages "that cannot be measured."*

In addition to popularizing blood cardioplegia, Buckberg and colleagues[112] demonstrated, in 1976, the importance of intermittent reinfusion of cardioplegic solution because of washout from noncoronary collateral perfusion.

Today, cold-blood cardioplegia has emerged as "the preferred cardioprotective strategy in the United States."[113] A 1995 survey by Robinson of 1,413 American cardiac surgeons reported that more than 70% of respondents used blood cardioplegic solution, primarily of Buckberg's formulation.[4] The remaining respondents used crystalloid cardioplegic solution, primarily the St. Thomas's Hospital solution (Plegisol).

Retrograde Cardioplegia

The development of retrograde cardioplegic delivery grew out of the concern that myocardial protective

* Buckberg GD. Personal communication, 2 September 1998.

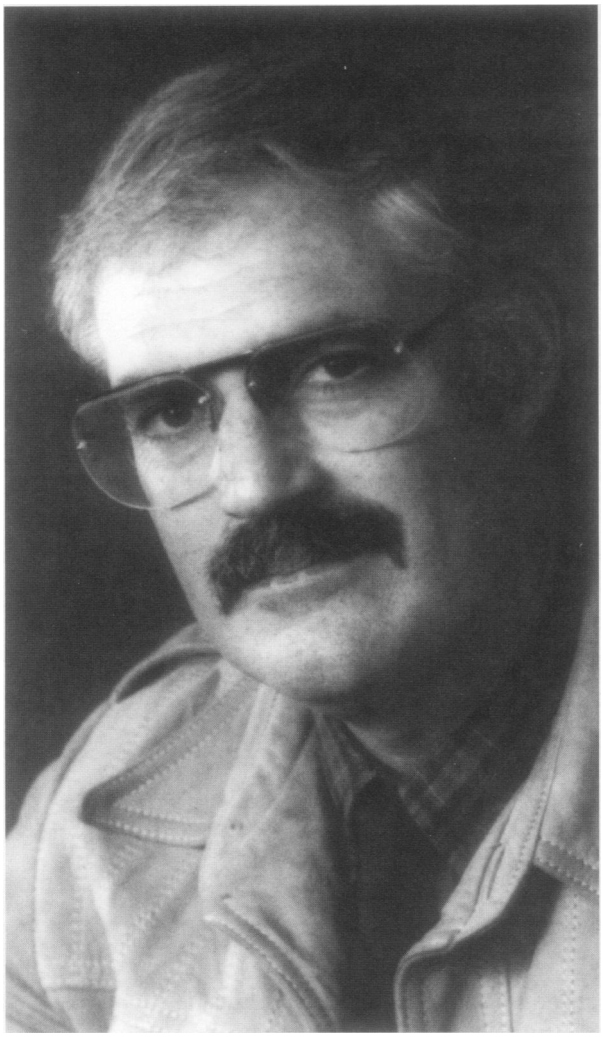

Fig. 9 *Gerald D. Buckberg*

(From: Cordell AR. Milestones in the development of cardioplegia. Ann Thorac Surg 1995;60:795. Reprinted with permission from the Society of Thoracic Surgeons.)

techniques might not be effective unless cardioplegic solutions perfused the entire heart.[114] The earliest report of retrograde cardioplegic administration dates back to 1956, when Lillehei cannulated the coronary sinus for delivery of crystalloid cardioplegic solution in patients with calcified aortic stenoses.[115] In 1967, Davies and colleagues[116] published a study showing that retrograde coronary sinus cardioplegia provided some myocardial protection in dogs. However, it was not until 1978 that Solorzano and colleagues[117] reintroduced clinical retrograde cardioplegia. Beginning in the early 1980s, authors such as Philippe Menasché[114] in Paris began accumulating a large experience with this technique. Robinson's survey[4] revealed that 60% of respondents used a combination of antegrade and retrograde cardioplegia in their practice, while 36% used only antegrade, and 4% used only retrograde approaches.

Hypothermic Cardioplegia

The temperature of cardioplegic solutions preferred by surgeons has remained relatively stable for nearly the last 20 years. A survey conducted in 1980 found that more than 95% of surgeons favored cardioplegic temperatures less than 12 °C and more than 80% preferred the temperature to be 4 °C to 6 °C.[118] A study from 1991 found that "most" preferred their solutions to be less than 10 °C and "more than half" favored the temperature to be less than 4 °C.[119] Robinson's 1995 report[4] found that more than 92% favored temperatures less than 12 °C and nearly 60% preferred temperatures less than 6 °C.

Continuous Warm-Blood Cardioplegia

Hypothermia, first introduced into clinical surgery by Bigelow in 1950,[24] is regarded as critical to effective protection of the myocardium, but several drawbacks are evident. Among them are activation of leukocytes, platelets, and complement, derangements of pH, instability of membranes, and promotion of edema.[120-122] These concerns prompted surgeons at the University of Toronto (where Bigelow introduced hypothermia) to examine continuous warm-blood cardioplegia, during the late 1980s and early 1990s.[23] Several subsequent studies with this technique showed no discernible advantage over standard intermittent hypothermic cardioplegia.[123-125] Uncertainties about such matters as appropriate flow rates, ideal composition of the cardioplegic solution, threat of neurologic complications, and problems with visualization have prompted reservations about the use of this technique.[113]

Conclusions

Cardiac surgery was the last of the major surgical specialties to develop. This was due in large part to the early attitude that operations upon the heart would be impossible. In 1896, the English surgeon Stephen Paget said, "Surgery of the heart has probably reached the limits set by Nature to all Surgery; no new method, no new discovery, can overcome the natural difficulties that attend a wound of the heart."[126] Despite this self-imposed limitation, a few courageous individuals persisted in their efforts to make cardiac surgery the highly effective therapy it is today. Much the same can be said about potassium-based cardioplegia. Following its virtual abandonment in the 1960s, its rebirth can be attributed to the creative and open-minded work of visionaries willing to break with convention.

Today, cardiac surgery has become a much safer endeavor, thanks in large part to the efforts of those engaged in cardioplegic development.

The surgeon pays attention to the detail described in his findings. This information must be appropriated by the physiologist. The physiologist does not believe the surgeon can think, while the surgeon thinks the physiologist cannot be practical. The surgeon-physiologist team is needed and this may occur in the same person. If so, the surgeon must possess basic physiologic knowledge and bring this to the practical area—the Operating Room. Solid surgical physiology must be converted to practical findings that are easily used clinically.*

Today, advances in myocardial protection—including the treatment of reperfusion injury, cardiopulmonary bypass, ischemic preconditioning, hyperpolarized arrest, and off-pump heart surgery—all serve to remind us of the need to constantly re-evaluate accepted methods.

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References

1. Melrose DG, Dreyer B, Bentall HH, Baker JBE. Elective cardiac arrest. Lancet 1955;2:21-2.
2. Braimbridge MV. European origins of cardioplegia. In: Engelman RM, Levitsky S, editors. A textbook of cardioplegia for difficult clinical problems. Mount Kisco: Futura, 1992:9-16.
3. Gay WA Jr. Potassium-induced cardioplegia: evolution and present status. Ann Thorac Surg 1989;48:441-3.
4. Robinson LA, Schwarz GD, Goddard DB, Fleming WH, Galbraith TA. Myocardial protection for acquired heart disease surgery: results of a national survey. Ann Thorac Surg 1995; 59:361-72.
5. Ringer S. A further contribution regarding the influence of the different constituents of the blood on the contraction of the heart. J Physiol 1883;4:29-42.
6. Hooker DR. On the recovery of the heart in electric shock. Am J Physiol 1929-30;91:305-28.
7. Wiggers CJ. Studies on ventricular fibrillation produced by electric shock. III. The action of antagonistic salts. Am J Physiol 1930;93:197-212.
8. Montgomery AV, Prevedel AE, Swan H. Prostigmine inhibition of ventricular fibrillation in the hypothermic dog. Circulation 1954;10:721-7.
9. Baetjer AM, McDonald CH. The relation of the sodium, potassium, and calcium ions to the heart rhythmicity. Am J Physiol 1931-32;99:666-80.
10. Zwikster GH, Boyd TE. Reversible loss of the all or none response in cold blooded hearts treated with excess potassium. Am J Physiol 1935;113:560-7.
11. Spealman CR. The action of ions on the frog heart. Am J Physiol 1940;130:729-38.
12. Shumacker HB Jr. The evolution of cardiac surgery. Bloomington: Indiana University Press, 1992:41-9.
13. Gross RE, Hubbard JP. Surgical ligation of a patent ductus arteriosus. Report of first successful case. JAMA 1939;112: 729-31.
14. Crafoord C, Nylin G. Congenital coarctation of the aorta and its surgical treatment. J Thorac Surg 1945;14:347-61.
15. Blalock A, Taussig HB. The surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia. JAMA 1945;128:189-202.
16. Cohn R. An experimental method for the closure of interauricular septal defects in dogs. Am Heart J 1947;33:453-7.
17. Murray G. Closure of defects in cardiac septa. Ann Surg 1948; 128:843-53.
18. Dodrill FD. A method for exposure of the cardiac septa. J Thorac Surg 1949;18:652-60.
19. Gibbon JH Jr. The maintenance of life during experimental occlusion of the pulmonary artery followed by survival. Surg Gynecol Obst 1939;69:602-14.
20. Roe BB. A history of clinical cardioplegia. In: Engelman RM, Levitsky S, editors. A textbook of clinical cardioplegia. Mount Kisco: Futura, 1982;1-7.
21. Griepp RB, Stinson EB, Shumway NE. Profound local hypothermia for myocardial protection during open-heart surgery. J Thorac Cardiovasc Surg 1973;66:731-41.
22. Roberts AJ. Preface. In. Roberts AJ, editor. Myocardial protection in cardiac surgery. New York: Marcel Dekker, 1987; v-viii.
23. Lichtenstein SV, Ashe KA, el Dalati H, Cusimano RJ, Panos A, Slutsky AS. Warm heart surgery. J Thorac Cardiovasc Surg 1991;101:269-74.
24. Bigelow WG, Lindsay WK, Greenwood WF. Hypothermia. Its possible role in cardiac surgery: an investigation of factors governing survival in dogs at low body temperatures. Ann Surg 1950;132:849-66.
25. Lewis FJ, Taufic M. Closure of atrial septal defects with the aid of hypothermia: experimental accomplishments and the report of one successful case. Surgery 1953;33:52-9.
26. Gibbon JH Jr. Application of a mechanical heart and lung apparatus to cardiac surgery. Minnesota Med 1954;37:171-80.
27. Lillehei CW, Cohen M, Warden HE, Varco RL. The direct-vision intracardiac correction of congenital anomalies by controlled cross circulation. Surgery 1955;38:11-29.
28. Kirklin JW, Donald DE, Harshbarger HG, Hetzel PS, Patrick RT, Swan HJC, et al. Studies in extracorporeal circulation. I. Applicability of Gibbon-type pump-oxygenator to human intracardiac surgery: 40 cases. Ann Surg 1956;144:2-8.
29. Cordell AR. Milestones in the development of cardioplegia. Ann Thorac Surg 1995;60:793-6.
30. Baker JBE, Bentall HH, Dreyer B, Melrose DG. Arrest of isolated heart with potassium citrate. Lancet 1957;2:555-9.
31. Bentall HH, Melrose DG. Elective cardiac arrest: lactic acid production in the arrested heart. J Physiol 1957;135:38P-39P.
32. Gerbode F, Melrose D. The use of potassium arrest in open cardiac surgery. Am J Surg 1958;96:221-7.
33. Sones FM Jr. Results of open heart surgery with elective cardiac arrest by potassium citrate in patients with congenital and acquired heart disease. Dis Chest 1958;34:299-316.
34. Kolff WJ, Effler DB, Groves LK, Peereboom G, Aoyama S, Sones FM Jr. Elective cardiac arrest by the Melrose technic. Potassium asystole for experimental cardiac surgery. Cleveland Clin Q 1956;23:98-104.

* Buckberg GD. Unpublished manuscript. Development of blood cardioplegia and retrograde techniques, the experimenter/observer complex.

35. Effler DB, Groves LK, Sones FM Jr, Kolff WJ. Elective cardiac arrest in open-heart surgery. Report of three cases. Cleveland Clin Q 1956;23:105-14.
36. Sealy WC, Young WG Jr, Brown IW Jr, Lesage A, Callaway HA Jr, Harris JS, et al. Potassium, magnesium, and neostigmine for controlled cardioplegia. Studies on the dog using extracorporeal circulation and hypothermia. Arch Surg 1958; 77:33-8.
37. Lam CR, Geoghegan T, Lepore A. Induced cardiac arrest for intracardiac surgical procedures. An experimental study. J Thorac Surg 1955;30:620-5.
38. Lam CR, Geoghegan T, Sergeant C, Green E. Clinical experiences with induced cardiac arrest during intracardiac surgical procedures. Ann Surg 1957;146:439-49.
39. Björk VO. Brain perfusions in dogs with artificially oxygenated blood. Acta Chir Scandinav 1948;96(Suppl 137):1-122.
40. Sergeant CK, Geoghegan T, Lam CR. Further studies in induced cardiac arrest using the agent acetylcholine. Surg Forum 1956;7:254-7.
41. Allen P, Lillehei CW. Use of induced cardiac arrest in open heart surgery. Results in seventy patients. Minnesota Med 1957;40:672-6.
42. Schramel RJ, Ross E, Morton RD, Creech O Jr. Observations on controlled cardiac asystole in intact dogs. Surg Forum 1957;8:348-51.
43. Young WG Jr, Sealy WC, Brown IW Jr, Hewitt WC Jr, Callaway HA Jr, Merritt DH, et al. A method for controlled cardiac arrest as an adjunct to open heart surgery. J Thorac Surg 1956;32:604-11.
44. Nunn DD, Belisle CA, Lee WH Jr, Parker EF. A comparative study of aortic occlusion alone and of potassium citrate arrest during cardiopulmonary bypass. Surgery 1959;45:848-51.
45. Willman VL, Cooper T, Zafiracopoulos P, Hanlon CR. Depression of ventricular function following elective cardiac arrest with potassium citrate. Surgery 1959;46:792-6.
46. Helmsworth JA, Kaplan S, Clark LC Jr, McAdams AJ, Matthews EC, Edwards FK. Myocardial injury associated with asystole induced potassium citrate. Ann Surg 1959;149:200-6.
47. Waldhausen JA, Braunwald NS, Bloodwell RD, Cornell WP, Morrow AG. Left ventricular function following elective cardiac arrest. J Thorac Cardiovasc Surg 1960;39:799-807.
48. Björk VO, Fors B. Induced cardiac arrest. J Thorac Cardiovasc Surg 1961;41:387-94.
49. McFarland JA, Thomas LB, Gilbert JW, Morrow AG. Myocardial necrosis following elective cardiac arrest induced with potassium citrate. J Thorac Cardiovasc Surg 1960;40:200-8.
50. Effler DB. Editorial: the mystique of myocardial preservation. J Thorac Cardiovasc Surg 1976;72:468-70.
51. Kay EB, Head LR, Nogueira C. Direct coronary artery perfusion for aortic valve surgery. Report of technique. JAMA 1953;168:1767-8.
52. Littlefield JB, Lowicki EM, Muller WH Jr. Experimental left coronary artery perfusion through an aortotomy during cardiopulmonary bypass. J Thorac Cardiovasc Surg 1960;40: 685-91.
53. Bahnson HT, Spencer FC, Busse EFG, Davis FW Jr. Cusp replacement and coronary artery perfusion in open operations on the aortic valve. Ann Surg 1960;152:494-505.
54. McGoon DC, Pestana C, Moffitt EA. Decreased risk of aortic valve surgery. Arch Surg 1965;91:779-86.
55. Bloomer WE, Anderson RM. Improved coronary perfusion cannulas and flowmeter as aids to coronary artery perfusion in open-heart surgery. Surgery 1962;52:430-2.
56. Bosher LH Jr, Edwards JF Jr, Pois AJ. An automatic coronary perfusion system for clinical application. J Thorac Cardiovasc Surg 1964;47;254-60.
57. Goldfarb D, Bahnson HT. Early and late effects on the heart of small amounts of air in the coronary circulation. J Thorac Cardiovasc Surg 1963;46:368-78.
58. Heilbrunn A, Zimmermann JM. Coronary artery dissection: a complication of cannulation. J Thorac Cardiovasc Surg 1965;49:767-71.
59. Morales AR, Fine G, Taber RE. Cardiac surgery and myocardial necrosis. Arch Pathol 1967;83:71-9.
60. Green GE, Bernstein S, Reppert EH. The length of the left main coronary artery. Surgery 1967;62:1021-4.
61. Fishman NH, Youker JE, Roe BB. Mechanical injury to the coronary arteries during operative cannulation. Am Heart J 1968;75:26-33.
62. Reed GE, Spencer FC, Boyd AD, Engelman RM, Glassman E. Late complications of intraoperative coronary artery perfusion. Circulation 1973;48(1 Suppl):III80-4.
63. Ramsey HW, De la Torre A, Linhart JW, Wheat MW Jr. Complications of coronary artery perfusion. J Thorac Cardiovasc Surg 1967;54:714-8.
64. Silver MD, Wigle ED, Trimble AS, Bigelow WG. Iatrogenic coronary ostial stenosis. Arch Pathol 1969;88:73-7.
65. Buckberg GD, Towers B, Paglia DE, Mulder DG, Maloney JV. Subendocardial ischemia after cardiopulmonary bypass. J Thorac Cardiovasc Surg 1972;64:669-84.
66. Buckberg GD, Hottenrott CE. Ventricular fibrillation. Its effect on myocardial flow, distribution, and performance. Ann Thorac Surg 1975;20:76-85.
67. Najafi H, Henson D, Dye WS, Javid H, Hunter JA, Callaghan R, et al. Left ventricular hemorrhagic necrosis. Ann Thorac Surg 1969;7:550-61.
68. Najafi H, Lal R, Khalili M, Serry C, Rogers A, Haklin M. Left ventricular hemorrhagic necrosis. Experimental production and pathogenesis. Ann Thorac Surg 1971;12:400-10.
69. Shumway NE, Lower RR, Stofer RC. Selective hypothermia of the heart in anoxic cardiac arrest. Surg Gynecol Obstet 1959;109:750-4.
70. Cross FS, Jones RD, Berne RM. Localized cardiac hypothermia as an adjunct to elective cardiac arrest. Surg Forum 1957; 8:355-9.
71. Gott VL, Bartlett M, Johnson JA, Long DM, Lillehei CW. High energy phosphate levels in the human heart during potassium citrate arrest and selective hypothermic arrest. Surg Forum 1959;10:544-7.
72. Greenberg JJ, Edmunds LH Jr, Brown RB. Myocardial metabolism and postarrest function in the cold and chemically arrested heart. Surgery 1960;48:31-42.
73. Bhonslay SB, Deterling RA Jr, Wallace HW, Rheinlander HF. Elective cardiac arrest. Experimental studies and a review of the literature. J Cardiovasc Surg 1961;2:168-75.
74. Lower RR, Stofer RC, Shumway NE. Homovital transplantation of the heart.1961;41:196-204.
75. Lower RR, Stofer RC, Hurley EJ, Dong E Jr, Cohn RB, Shumway NE. Successful homotransplantation of the canine heart after anoxic preservation for seven hours. Am J Surg 1962; 104:302-6.
76. Hurley EJ, Lower RR, Dong E Jr, Pillsbury RC, Shumway NE. Clinical experience with local hypothermia in elective cardiac arrest. J Thorac Cardiovasc Surg 1964;47:50-65.
77. Sanger PW, Robicsek F, Daugherty HK, Gallucci V, Lesage MA. Topical cardiac hypothermia in lieu of coronary perfusion. J Thorac Cardiovasc Surg 1966;52:533-41.
78. Brody WR, Reitz BA. Topical hypothermic protection of the myocardium. Ann Thorac Surg 1975;20:66-71.
79. Cohn LH, Collins JJ Jr. Local cardiac hypothermia for myocardial protection. Ann Thorac Surg 1974;17:135-40.
80. Goldman BS, Trimble AS, Sheverini MA, Teasdale SJ, Silver MD, Elliot GE. Functional and metabolic effects of anoxic cardiac arrest. Ann Thorac Surg 1971;11:122-32.

81. Messmer BJ, Hallman GL, Liotta D, Martin C, Cooley DA. Aortic valve replacement: new techniques, hydrodynamics, and clinical results. Surgery 1970;68:1026-37.
82. Cooley DA, Reul GJ, Wukasch DC. Ischemic contracture of the heart: "stone heart". Am J Cardiol 1972;29:575-7.
83. MacGregor DC, Mehta VS, Metni FN, Krajicek M, Kryspin J, Botz CC, et al. Normothermic anoxic arrest of the heart. Is there a means of estimating the safe period? J Thorac Cardiovasc Surg 1972;64:833-9.
84. Colapinto ND, Silver MD. Prosthetic heart valve replacement. Causes of early postoperative death. J Thorac Cardiovasc Surg 1971;61:938-44.
85. Iyengar SR, Ramchand S, Charrette EJ, Lynn RB. An experimental study of subendocardial hemorrhagic necrosis after anoxic cardiac arrest. Ann Thorac Surg 1972;13:214-24.
86. Tyers GF, Hughes HC Jr, Todd GJ, Williams DR, Andrews EJ, Prophet GA, et al. Protection from ischemic cardiac arrest by coronary perfusion with cold Ringer's lactate solution. J Thorac Cardiovasc Surg 1974;67:411-8.
87. Katz AM, Tada M. The "stone heart": a challenge to the biochemist. Am J Cardiol 1972;29:578-80.
88. MacGregor DC, Wilson GJ, Tanaka S, Holness DE, Lixfeld W, Silver MD, et al. Ischemic contracture of the left ventricle. Production and prevention. J Thorac Cardiovasc Surg 1975; 70:945-54.
89. Hearse DJ, Garlick PB, Humphrey SM. Ischemic contracture of the myocardium: mechanisms and prevention. Am J Cardiol 1977;39:986-93.
90. Søndergaard T, Berg E, Staffeldt I, Szczepanski K. Cardioplegic cardiac arrest in aortic surgery. J Cardiovasc Surg (Torino) 1975;16:288-90.
91. Hoelscher B. Studies by electron microscopy on the effects of magnesium chloride-procaine amide or potassium citrate on the myocardium in induced cardiac arrest. J Cardiovasc Surg (Torino) 1967;8:163-6.
92. Bretschneider HJ, Hübner G, Knoll D, Lohr B, Nordbeck H, Spieckermann PG. Myocardial resistance and tolerance to ischemia: physiological and biochemical basis. J Cardiovasc Surg (Torino) 1975;16:241-60.
93. Jynge P. Cardioplegia—basic principles and calcium control. In: Refsum H, Jynge P, Mjös OD, editors. Myocardial ischaemia and protection. New York: Churchill Livingstone, 1983:220-46.
94. Kirsch U, Rodewald G, Kalmár P. Induced ischemic arrest. Clinical experience with cardioplegia in open-heart surgery. J Thorac Cardiovasc Surg 1972;63:121-30.
95. Hearse DJ, Stewart DA, Braimbridge MV. Cellular protection during myocardial ischemia: the development and characterization of a procedure for the induction of reversible ischemic arrest. Circulation 1976;54:193-202.
96. Braimbridge MV, Chayen J, Bitensky L, Hearse DJ, Jynge P, Cankovic-Darracott S. Cold cardioplegia or continuous coronary perfusion? Report on preliminary clinical experience as assessed cytochemically. J Thorac Cardiovasc Surg 1977; 74:900-6.
97. Hearse DJ, Stewart DA, Braimbridge MV. Myocardial protection during bypass and arrest. A possible hazard with lactate-containing infusates. J Thorac Cardiovasc Surg 1976;72: 880-4.
98. Jynge P, Hearse DJ, Braimbridge MV. Myocardial protection during ischemic cardiac arrest. A possible hazard with calcium-free cardioplegic infusates. J Thorac Cardiovasc Surg 1977;73:848-55.
99. Hearse DJ, Stewart DA, Braimbridge MV. Myocardial protection during ischemic cardiac arrest. The importance of magnesium in cardioplegic infusates. J Thorac Cardiovasc Surg 1978;75:877-85.
100. Hearse DJ, Stewart DA, Braimbridge MV. Myocardial protection during ischemic cardiac arrest. Possible deleterious effects of glucose and mannitol in coronary infusates. J Thorac Cardiovasc Surg 1978;76:16-23.
101. Jynge P, Hearse DJ, Braimbridge MV. Protection of the ischemic myocardium. Volume-duration relationships and the efficacy of myocardial infusates. J Thorac Cardiovasc Surg 1978;76:698-705.
102. Ledingham SJM, Braimbridge MV, Hearse DJ. The St. Thomas' Hospital cardioplegic solution. A comparison of the efficacy of two formulations. J Thorac Cardiovasc Surg 1987;93:240-6.
103. Gay WA Jr, Ebert PA. Functional, metabolic, and morphologic effects of potassium-induced cardioplegia. Surgery 1973;74:284-90.
104. McKeever WP, Gregg DE, Canney PC. Oxygen uptake of the nonworking left ventricle. Circ Res 1958;6:612-23.
105. Tyers GF, Todd GJ, Niebauer IM, Manley NJ, Waldhausen JA. The mechanism of myocardial damage following potassium citrate (Melrose) cardioplegia. Surgery 1975;78:45-53.
106. Todd GJ, Tyers GF. Potassium-induced arrest of the heart: effect of low potassium concentration. Surg Forum 1975;26: 255-6.
107. Reitz BA, Brody WR, Hickey PR, Michaelis LL. Protection of the heart for 24 hr with intracellular (high K+) solution and hypothermia. Surg Forum 1974;25:149-51.
108. Roe BB, Hutchinson JC, Fishman NH, Ullyot DJ, Smith DL. Myocardial protection with cold, ischemic, potassium-induced cardioplegia. J Thorac Cardiovasc Surg 1977;73:366-74.
109. Conti VR, Bertranou EG, Blackstone EH, Kirklin JW, Digerness SB. Cold cardioplegia versus hypothermia for myocardial protection. Randomized clinical study. J Thorac Cardiovasc Surg 1978;76:577-89.
110. Follette DM, Mulder DG, Maloney JV, Buckberg GD. Advantages of blood cardioplegia over continuous coronary perfusion or intermittent ischemia. Experimental and clinical study. J Thorac Cardiovasc Surg 1978;76:604-19.
111. Barner HB. Blood cardioplegia: a review and comparison with crystalloid cardioplegia. Ann Thorac Surg 1991;52: 1354-67.
112. Nelson RL, Fey KH, Follette DM, Livesay JJ, DeLand EC, Maloney JV Jr, et al. Intermittent infusion of cardioplegic solution during aortic cross-clamping. Surg Forum 1976; 2741-3.
113. Buckberg GD. Update on current techniques of myocardial protection. Ann Thorac Surg 1995;60:805-14.
114. Menasché P, Kural S, Fauchet M, Lavergne A, Commin P, Bercot M, et al. Retrograde coronary sinus perfusion: a safe alternative for ensuring cardioplegic delivery in aortic valve surgery. Ann Thorac Surg 1982;34:647-58.
115. Lillehei CW, DeWall RA, Gott VL, Varco RL. The direct vision correction of calcific aortic stenosis by means of a pump-oxygenator and retrograde coronary sinus perfusion. Dis Chest 1956;30:123-32.
116. Davies AL, Hammond GL, Austen WG. Direct left coronary artery surgery employing retrograde perfusion of the coronary sinus. J Thorac Cardiovasc Surg 1967;54:848-55.
117. Solorzano J, Taitelbaum G, Chiu RC. Retrograde coronary sinus perfusion for myocardial protection during cardiopulmonary bypass. Ann Thorac Surg 1978;25:201-8.
118. Miller DW Jr, Ivey TD, Bailey WW, Johnson DD, Hessel EA. The practice of coronary artery bypass surgery in 1980. J Thorac Cardiovasc Surg 1981;81:423-7.
119. Hoffman D, Martella A, Frater RWM. Myocardial protection in US training [abstract]. Chest 1992;102(Suppl):75S.

120. 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 [B] 1973;44:1017-26.
121. Rahn H, Reeves RB, Howell BJ. Hydrogen ion regulation, temperature, and evolution. Am Rev Respir Dis 1975;112: 165-72.
122. Salerno TA, Houck JP, Barrozo CA, Panos A, Christakis GT, Abel JG, et al. Retrograde continuous warm blood cardioplegia: a new concept in myocardial protection. Ann Thorac Surg 1991;51:245-7.
123. Engelman RM, Rousou JA, Flack JE III, Deaton DW, Liu X, Das D. A prospective randomized analysis of cold crystalloid, cold blood and warm blood cardioplegia for coronary revascularization. In: Engelman RM, Levitsky S, editors. A textbook of cardioplegia for difficult clinical problems. Mount Kisco: Futura, 1992:159-71.
124. Lajos TZ, Espersen CC, Lajos PS, Fiedler RC, Bergsland J, Joyce LT. Comparison of cold versus warm cardioplegia. Crystalloid antegrade or retrograde blood? Circulation 1993; 88(5 Pt 2):II344-9.
125. Martin TD, Craver JM, Gott JP, Weintraub WS, Ramsay J, Mora CT, et al. Prospective, randomized trial of retrograde warm blood cardioplegia: myocardial benefit and neurologic threat. Ann Thorac Surg 1994;57:298-304.
126. Paget S. The surgery of the chest. London: John Wright, 1896:121-382.