



**T e c h n o l o g y  
A s s e s s m e n t  
P r o g r a m**

**Office of Patient Care Services**

**OPTIMAL TEMPERATURE FOR CARDIOPLEGIA  
DURING CORONARY ARTERY BYPASS GRAFTING:**

**A Systematic Review of Published Randomized Controlled Trials  
For Myocardial Protection**

Author: Karen Flynn, MS, DDS  
Manager, Technology Assessment Program

Contributors: Elizabeth Adams, RRT, MPH  
Research Analyst

Elaine Alligood, MLS  
Information Specialist

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**A SUMMARY FOR HTA REPORTS**  
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*This summary form is intended as an aid for those who want to record the extent to which a HTA report meets the 17 questions presented in the checklist. It is NOT intended as a scorecard to rate the standard of HTA reports – reports may be valid and useful without meeting all of the criteria that have been listed.*

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**For Myocardial Protection**  
**(September 2003)**

Item	Yes	Partly	No
Preliminary			
<b>1. Appropriate contact details for further information?</b>	√		
<b>2. Authors identified?</b>	√		
<b>3. Statement regarding conflict of interest?</b>			√
<b>4. Statement on whether report externally reviewed?</b>	√		
<b>5. Short summary in non-technical language?</b>	√		
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<b>7. Scope of the assessment specified?</b>	√		
<b>8. Description of the health technology?</b>	√		
How?			
<b>9. Details on sources of information?</b>	√		
<b>10. Information on selection of material for assessment?</b>	√		
<b>11. Information on basis for interpretation of selected data?</b>	√		
What?			
<b>12. Results of assessment clearly presented?</b>	√		
<b>13. Interpretation of the assessment results included?</b>	√		
What Then?			
<b>14. Findings of the assessment discussed?</b>	√		
<b>15. Medico-legal implications considered?</b>			√
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Valerie A. Lawrence, MD  
Physician Advisor, VA Technology Assessment Program  
Audie L. Murphy VA Medical Center  
Associate Professor, Department of Medicine  
University of Texas Health Science Center at San Antonio  
San Antonio, Texas

Edward Y. Sako, MD  
Cardiologist  
University of Texas Health Sciences Center at San Antonio  
San Antonio, Texas

Ralph G. DePalma, MD  
National Director of Surgery  
Veterans Health Administration  
Washington, D.C.

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## EXECUTIVE SUMMARY

**Note:** The appendix to this report contains a glossary with background to basic concepts.

- Ischemic heart disease is a leading cause of death in the developed world and a comparable burden of disease to VA and its patients. Indications for surgical intervention [coronary artery bypass grafting (CABG)] include specific anatomic lesions and evidence of significant ischemia despite optimal medical management.
- CABG involves arresting the heart's motion (cardioplegia) by chemical or electrical means, and emptying it of blood. During surgery, oxygenated blood flow to the rest of the body is maintained by cardiopulmonary bypass (CPB). However, the heart muscle itself lacks an oxygenated blood supply during CPB; it is therefore at risk for irreversible damage due to oxygen deprivation.
- Variation in methods for myocardial protection during CPB among thoracic surgeons in general and among VA cardiac surgery programs indicates a lack of consensus on optimal methods for protecting the myocardium from irreversible damage ("myocardial protection") during this temporary stoppage of blood supply. To that end, a systematic review of the literature could be useful. This review confirms that more recently published trial results do not materially change the conclusions of the most current national professional association statement (issued jointly by the American College of Cardiologists and American Heart Association in 1999).
- This qualitative systematic review addresses the manipulation of temperature in cardioplegic solutions as a means to protect the heart from damage due to lack of oxygen during CABG and CPB. The review was requested by the Veterans Integrated Service Network (VISN) 12 Quality Improvement Officer as support for quality assurance activities at VISN cardiac surgery programs.
- Seventeen published randomized controlled trials (one yielding two separate publications) met inclusion criteria for this review and are abstracted in Table 1. However, most of these trials were too small to produce statistically significant results. Many of the published trials also failed to include, or to report, critical indicators of methodologic quality such as convincing descriptions of randomization methods and blinding of patients to group assignments (Table 1A).
- The VA Technology Assessment Program (VATAP) searches also identified three published analyses of large databases (Table 2) relevant to cardioplegia temperature, two of which used data from randomized controlled trials. These analyses add little information to that already available from trial results, although they do contribute further support to the overall impression from the literature that is embodied in the ACC/AHA guidelines cited below, and with which this review concurs.

- Interpretation of the evidence provided by the published randomized controlled trials and database analyses is complicated by inconsistencies in cardioplegic techniques across randomized controlled trials, and by varying definitions of temperature categories. Inconsistencies among trials and methods make unreliable attempts to define independent effects of cardioplegia temperature or of other individual procedural variables in the group of complex procedures comprising CABG.
- The ACC/AHA guidelines for CABG (1999) found that “*no strong argument can currently be made for warm versus cold and crystalloid versus blood cardioplegia*” in patients with normal left ventricular function. The guidelines go on to report: “*...certain techniques may offer a wider margin of safety for special patient subsets.*” However, the evidence for such a wider margin of safety is documented only as: “*Several studies have suggested that blood cardioplegia (compared to crystalloid) may offer a greater margin of safety during CABG performed on patients with acute coronary occlusion, failed angioplasty, urgent re-vascularization for unstable angina, and/or chronically impaired left ventricular function.*”
- The present review, with searches last updated in September 2003, discovered no published clinical research that substantially changes the conclusions of the ACC/AHA guidelines.

**OPTIMAL TEMPERATURE FOR CARDIOPLEGIA DURING CORONARY ARTERY  
BYPASS GRAFTING:  
A Systematic Review Of Published Randomized Controlled Trials  
For Myocardial Protection**

**I. INTRODUCTION**

Quotations from the cardiac surgical literature summarize controversies and associated areas of variation in practice regarding methods for protecting the heart from damage while its motion is arrested and its oxygen supply temporarily suspended during coronary artery bypass graft (CABG) surgery:

*“Cardioplegia administration is either monitored by myocardial septal temperature, or is not monitored and is determined by a well-defined protocol. The optimal myocardial temperature or volume of cardioplegia that would achieve adequate myocardial protection remain elusive...there was no correlation between myocardial tissue pH and volume of cardioplegia administered. Temperature is a poor indicator of the metabolic state of the myocardium.”* (Dearani, 2001)

*“The objectives of every cardiac operation must be a technically perfect anatomic result, and avoidance or limitation of intra-operative damage in pursuit of this goal. Two prerequisites to accomplish these objectives are adequate visualization of the operative field to allow for surgical precision, and use of cardioprotective techniques that exclude intra-operative damage that can nullify the immediate and long-term benefits of surgical correction. Cardiac damage from inadequate myocardial protection leading to low output syndrome can prolong hospital stay and cost, and may result in delayed (i.e., not completely avoided) myocardial fibrosis (scarring after damage due to oxygen deprivation). Efforts to avoid this problem have led to the development of numerous methods of intra-operative myocardial management.”* (Buckberg, 1995)

*“Advances in science account for most surgical milestones. In cardiac surgery, improving myocardial protection is necessary to support the evolution of surgical techniques used for degenerative cardiac disease. A motionless, dry field is a prerequisite for any cardiac operation and is achieved almost universally by arresting the heart pharmacologically to prevent ischemia. Have these advances in myocardial protection changed outcomes?”* (Loop, 1992)

*“Should one perfuse with cold crystalloid cardioplegia (a high-potassium solution not based on blood; the term is used to differentiate the method from blood cardioplegia, in which the potassium is dissolved in blood) relying on myocardial cooling to reduce oxygen demand, or perfuse with oxygen-carrying blood albeit at warmer temperatures, such that oxidative phosphorylation and regeneration of high energy phosphates can continue?...Damage occurs not only during the period of anaerobic metabolism but during the re-perfusion period...From induction of cardiac arrest with warm blood cardioplegia and terminal “hot shot”...perhaps a natural evolution would have been to continue warm blood*

*cardioplegia through the period of aortic cross-clamping in an effort to sustain the myocardium.” (Curtis, 1996)*

*“For the busy clinical surgeon, keeping current on the medical literature in this changing field of myocardial protection is not an easy task. Since 1966, more than 4,500 articles and numerous books have been published in the world’s literature directly concerning this critical aspect of cardiac surgery; more than one-third of these publications have appeared in the past five years...However, what is the impact of this vast quantity of published studies on the current clinical practice and techniques of myocardial protection?” (Robinson, 1995)*

## A. Purpose

In the context of the needs and controversies outlined above, the Veterans Integrated Service Network (VISN) 12 Quality Improvement Officer requested a review of the published research evidence on the optimal temperature for cardiopulmonary bypass (CPB) and cardioplegia (see glossary, Appendix) during cardiovascular surgery, specifically for myocardial protection during coronary artery bypass grafting (CABG). The review would be used to help support quality assurance activities at VISN cardiac surgery programs.

When first presented to the VA Technology Assessment Program (VATAP) in December 1999, the request was attached to an urgent, two-day delivery schedule. To provide useful information within that schedule, VATAP planned a two-stage response, first identifying relevant randomized controlled trials (RCTs) and presenting their results in abstracted tabular form to the VISN 12 Quality Improvement Officer within his requested time frame.

This report represents the second step in the VATAP response process: a more fully developed, updated, externally (to the Program) reviewed, comprehensive overview and qualitative synthesis of RCT results.

For this report, VATAP conducted electronic literature database searches (the final search was performed in September 2003) to identify existing assessments and reports of RCTs. The RCT results were then qualitatively combined into this systematic review.

## B. Background

### **Disease Definition and Pathophysiology: Ischemic Heart Disease**

Ischemic heart disease is also known as coronary heart disease, coronary artery disease (CAD), or atherosclerosis. Ischemia refers to a diminished blood supply; with a reduced blood supply, oxygen and other substances essential to normal function are also diminished and tissue damage can result. Ischemic heart disease comprises acute myocardial infarction (AMI) and angina (variably present chest pain), both of which result from an imbalance between the oxygen demand of the heart muscle (normally met by the coronary arterial circulation under a wide range of workloads) and the blood

supply available to it. Blood flow through the coronary arteries most frequently is compromised by narrowing of the arteries due to atherosclerosis (accumulations within the coronary arteries of lipid covered by a cap of fibers with smooth muscle and inflammatory cells). The atherosclerotic lesion is frequently compounded by thrombus (clot) formation, leading to total vessel occlusion.

### **Burden of Ischemic Heart Disease**

Rates of ischemic heart disease, which causes over 476,000 deaths annually in the United States (or more than one in five US deaths), can be decreased by reducing modifiable risk factors such as high blood pressure, elevated blood cholesterol, tobacco use, insufficient physical activity, and poor nutrition.

Heart disease as an overall category was the leading cause of death in the US in 1998, while deaths specific to atherosclerosis were ranked at 14 (Kirschstein, 2000). In 1999, the costs (in billions) attributable to atherosclerosis were calculated as: \$6.2 total costs; \$5.5 direct costs; and \$0.7 indirect costs (Kirschstein, 2000).

Ischemic heart disease is equally prevalent and important in VA. In 1997, more than 150,000 VA hospital admissions were attributable to it. Mean costs in VA for that year were \$34,491 for patients with stable angina who had CABG (MDRC, 2000).

### **Medical Treatment**

Treatment of ischemic heart disease includes medical therapy to reduce myocardial oxygen consumption, improve coronary artery blood flow, and prevent disease progression. Commonly used pharmacological agents are beta-adrenergic blockers, nitrates, and calcium channel blockers.

Surgery is indicated for specific types or locations of atherosclerotic lesion, or for patients in whom drug therapy is unsuccessful in reducing symptoms. CABG is a mainstay of cardiac surgical practice for ischemic heart disease, and is the most frequently performed cardiac surgical procedure in VA (Tobler, 1995).

### **Coronary Artery Bypass Grafting (CABG)**

CABG involves stopping the heart and emptying it of blood. Narrowed or blocked sections of the coronary arteries are bypassed by suturing an end of one of the patient's own healthy vessels (often the saphenous vein, harvested from the patient's thigh) into the aorta, while the other end is inserted into the coronary artery beyond the obstructed segment. In an alternate procedure, the internal mammary artery may be freed from its usual position on the anterior thoracic wall and its distal end connected to the coronary artery beyond the site of obstruction. This constructs new pathways between the aorta, coronary arteries or other major arteries, provides bypasses around narrowed or blocked areas, and brings blood to areas of the heart for which the supply had previously been restricted.

### **CABG Outcomes**

Large data set analyses have identified a core set of patient-related variables that predict outcome probabilities during CABG hospitalization (ACC/AHA, 1999). Probabilities for death, stroke, and deep sternal wound infection range from 0.4% to 28%, 0.3% to 7%, and 0.4 to 7%, respectively. These rates depend on patient characteristics such as age, sex, urgency of surgery, and other diseases, and the general level of heart function. A similar set of predictive (for in-hospital mortality) patient characteristics was identified from data on 12,712 VA patients who had received CABG: general patient and heart function; priority (urgency) of surgery; number and anatomic location of narrowed coronary arteries; need for intra-aortic balloon pump prior to surgery; intravenous nitroglycerin use; recent myocardial infarction; and certain characteristics of the electrocardiogram and lung examination (Grover, 1993).

### **Cardiopulmonary Bypass**

While the heart is stopped during CABG, blood flow is maintained to the remainder of the body by cardiopulmonary bypass (CPB) using a pump oxygenator. CPB maintains blood flow to most of the body, but flow through the coronary arteries is suspended for the duration of the procedure, depriving the heart muscle, or myocardium, of its blood and oxygen supplies. These supplies are re-established when the procedure is completed, the clamp on the aorta is removed, CPB is stopped, and the heart resumes beating, thus restoring an anatomically and physiologically normal flow of blood through the heart and the rest of the body.

***Defining the optimal method for protecting the myocardium from irreversible damage (“myocardial protection”) during this temporary stoppage of blood supply is the central objective of the research represented by the literature reviewed here.***

### **Changes Over Time in Risk Characteristics of Patients Receiving CABG**

Mangano (1997) reports the rapidly escalating number of patients (to more than 800,000 annually, worldwide) who have received CABG during the last 2 decades. According to Mangano, in 1997 mortality associated with CABG ranged from 1% to more than 8%, with morbidity from 1% to 28%. These rates were predicted to increase as the population continues to age and higher risk patients are selected to receive the procedure. The costs associated with adverse cardiovascular outcomes can be predicted to increase correspondingly from the \$4 billion annually estimated at the time of Mangano’s publication (1997). Accordingly, therapeutic options to reduce adverse outcomes of CABG, including the manipulation of temperature during cardiopulmonary bypass, have been suggested and investigated.

Chitwood (1995) summarizes: *“The modern cardiac surgeon routinely has patients of advanced age with concurrent valve and coronary artery disease, major left ventricular hypertrophy, and impaired left ventricular function. Although these conditions were once relative contraindications to performing bypass procedures, advances in myocardial protection strategies now provide the means necessary to perform complex cardiovascular procedures safely. Whereas systemic, topical, and infusion hypothermia*

*combined with cardioplegia were the mainstays of myocardial protection in the past, recently a myriad of solutions have been tried in attempts to maintain cardiac electromechanical quiescence during surgical correction. Retrograde coronary sinus infusions of both warm and cold cardioplegic solutions have been shown to be both safe and effective.”*

### **Undesirable Effects of Cardiopulmonary Bypass**

A number of undesirable side effects occur to a greater or lesser degree with CPB itself. As Taylor (1998) notes, CPB is “non-physiologic”. Murkin (1993) further details the “profound physiologic disturbances” associated with CPB: acute hemodilution; aortic instrumentation; moderate or profound hypothermia; nonpulsatile perfusion; circulatory arrest; exclusion of the pulmonary circulation; and activation of various cascades of endocrine and humoral biochemical events. The ACC/AHA guidelines for CABG (1999) report on the variety of measures that have been tested as means of reducing the systemic adverse consequences of CPB (“a diffuse inflammatory response that may cause transient or prolonged multi-system organ dysfunction”). Utley (1996) notes that the continuing challenge of research and efforts to reduce costs and improve outcomes in patients receiving CPB has been to separate the morbidity associated with CPB from that caused by the patient’s disease and the cardiac surgical procedure itself.

### **Protecting the Heart and Brain From Damage During CABG**

The CPB-associated disturbances enumerated above can lead to blood coagulation abnormalities and gaseous or particulate emboli, which can damage the heart or brain. Neurologic changes after cardiac surgery are of particular concern (Taylor, 1998), and range from subtle cognitive deficits to stroke or coma so disastrous that it may be seen as canceling the benefits of an otherwise completely successful operation.

Buckberg (1995) cautions that inadequate protection of the heart during CPB can likewise nullify the immediate and long-term benefits of the procedure, even if surgery produces an anatomically perfect result. A heart damaged during CPB could experience low output syndrome, itself resulting in a prolonged hospital stay, increased costs, and eventual myocardial fibrosis with long-term compromise of heart function.

Cerebral and myocardial protection during CPB have not always received equivalent research emphasis. Newman (1996) reports that for the expanding elderly population that receives cardiac surgery, a lack of progress in brain protection, relative to the attention received by myocardial protection, has resulted in an increased incidence of stroke and cognitive impairment after cardiac surgery compared with cardiac complications.

The single published systematic review (Christakis, 1995) of the effect of CPB temperature on cardiac surgery outcome identified for the present review focused on neurologic dysfunction. Christakis (1995) found neurologic outcome to be independent of temperature of CPB. Other authors (e.g., Utley, 1996) report colder temperatures are more protective of neurologic function. Christakis concluded: “*Since stroke is both too rare and too variable in magnitude by chance alone, no studies to date have adequately*

assessed stroke severity in relation to systemic perfusion temperature or mode and route of cardioplegia delivery.” Birdi (1997) also notes a lack of equilibrium between attention paid to myocardial and cerebral protection: “The advantages of employing normothermic perfusion in regard to factors such as improved hemodynamic performance and reduced blood loss postoperatively need to be balanced against concerns regarding the inadequacy of cerebral protection offered by this method.”

However, Newman (1996), in a narrative review, summarizes: “While it remains immensely logical that reducing cerebral metabolic rate during times of ischemia would play a major role in reducing the extent of cerebral injury associated with both focal and global ischemia, research has not supported cerebral metabolic rate reduction as a primary mechanism in preventing cerebral injury.”

Robinson (1995) and Tobler (1995) found substantial variation in methods for myocardial protection during CPB among thoracic surgeons and VA cardiac surgery programs. Such variations in practice indicate a lack of consensus on optimal methods and further warrant the present systematic review effort.

### **Manipulation of Temperature During CPB**

Mauney (1995) provides a concise and readily accessible statement of current controversies regarding methods for stopping the heart (cardioplegia): “Advances in myocardial protection have been instrumental in making cardiac surgery safer. Debate exists over the optimal medium and the optimal temperature for cardioplegia. Currently blood cardioplegia is preferred over crystalloid; the optimal temperature, however, remains controversial.”

Mauney (1995) continues: “Both warm and cold cardioplegia use potassium-induced electromechanical arrest, thereby reducing oxygen consumption by 90% (over that) in the working heart. Hypothermic blood cardioplegia given every 15 to 30 minutes provides a bloodless operative field and reduces oxygen consumption by an additional 5% to 20%. Continuous warm cardioplegia avoids the deleterious effects of hypothermic ischemia and minimizes reperfusion injury. Perfusion is often interrupted for 5 to 10 minutes to allow adequate visualization of the operative site. Both warm and cold cardioplegia can be given either antegrade or retrograde.”

Buckberg (1995) summarizes the then-current controversies regarding cardiac protection during CPB: “The spectrum of cardioprotective strategies available for intra-operative management has led to the artificial creation of adversarial positions in regard to use of warm versus cold blood cardioplegia, antegrade versus retrograde delivery, and intermittent versus continuous perfusion.”

Utley (1996) reports that varying degrees of hypothermia (28 to 35°C) have been used by the majority of cardiac surgeons, although some prefer more profound hypothermia (22 to 27°C). Also according to these authors, a common practice is to allow the patient’s temperature to drift downward from room temperature during bypass without specifically using a heat exchanger for cooling.

McLean (1996) provides additional historical perspective on and a concise summary of the issues underlying the present VATAP report: these authors note that the “Golden Age of heart surgery” began in the 1950s. The provision of an empty heart to allow surgical access necessitated (at that time) total circulatory arrest. These authors further note that clinical reports using total inflow tract occlusion initially appeared in the 1950s, although it had been used in the laboratory considerably earlier. However, total inflow tract occlusion at normal body temperature can be reliably tolerated for only 90-second periods, after which the mortality rate increases. Systemic hypothermia was introduced as an adjunct to cold cardioplegic myocardial protection, minimizing the re-warming effects of *noncoronary collateral* circulation. In addition, the well-documented (according to McLean and Wong) neuro-protective effects of hypothermia were believed to be important in preserving cerebral function.

According to Birdi (1997), systemic hypothermia during CPB has been regarded as essential since the inception of cardiac surgery. The rationale for hypothermia has been to offer cerebral protection and a safety margin in case of technical difficulties with CPB. In the 1990s, it was suggested that some of the deleterious effects of CPB were initiated or exaggerated by hypothermia, leading to the hypothesis that normothermic CPB could offer advantages, such as reduced bleeding, shorter intubation (anesthesia) times, and improved post-operative hemodynamics. Birdi (1997) reports that the evidence available at that time was flawed by inconsistencies in cardioplegic techniques, and by inadequate definition of normothermic systemic perfusion. These flaws made definition of the independent effects of warm blood cardioplegia and normothermic CPB uncertain.

Cook (1999) provides a comprehensive overview of changing temperature for cardiopulmonary bypass. Cook notes: *“there have been a variety of changes in the cardiac surgical operating theater over the last several years...from the standpoint of patient physiology and management, perhaps the most substantial change has been the move to higher CPB temperatures.”* Cook goes on to detail the physiologic rationale for this change, the research that supported it, and subsequent changes in bypass technique.

The authors of the ACC/AHA guidelines for CABG (1999) found that *“no strong argument can currently be made for warm versus cold and crystalloid versus blood cardioplegia”* in patients with normal left ventricular function.

## II. METHODS FOR SYSTEMATIC REVIEW

### A. Scope of review

As the question that initiated this review related only to the optimal temperature of cardioplegia for myocardial (rather than brain function) preservation, this review will be confined to the research literature that may clarify that issue.

### B. Search strategy

VATAP searched MEDLINE®, HealthStar®, and EMBASE® on November 1999, June 2000, January 2001, and September 2003 using the terms “cardioplegia,” “cardiopulmonary bypass,” and “outcomes.” In searches after the first, all references containing cardioplegia and human were retrieved and examined.

Reference lists of initially obtained articles were examined to identify additional randomized controlled trials (RCTs). Finally, the databases of the Cochrane Collaboration and the International Network of Agencies for Health Technology Assessment (INAHTA) were searched to identify existing assessments.

One reviewer (KF) applied article selection criteria (below) and conducted the review, which was then critiqued by VA reviewers noted under “Acknowledgements”.

### C. Selection criteria

#### **Rationale for article selection criteria**

Evidence grading schemes routinely assign the highest grade to systematic reviews of RCTs (Cook, 1992). Therefore, any such review identified in the searches that directly addressed the assessment question would provide the core evidence for this report. Since the next highest grade of evidence is assigned to RCTs themselves, this report preferentially selects for RCTs.

While RCTs remain the research design of choice for testing hypotheses regarding a causal relationship between an intervention and particular outcomes, analyses of large databases or registries can make contributions to technology assessment (Antczak-Boukoms, 1991), including the evaluation of surgical procedures (Davis, 1991), and of particular technological processes within those procedures (Burdick, 1991). Therefore, analyses of large data sets were also included in the review.

#### **Article Selection Criteria, RCTs:**

- RCTs comparing CPB at different temperatures during CABG in humans and reporting cardiovascular outcomes;
- Articles in English (or with English abstracts in sufficient detail to provide required information) published after 1990 (since research clarifying changes in the routinely used temperature of CPB has been published since that date).

**Article Selection Criteria, Large Data Sets:**

- Greater than 500 patients who received CABG;
- Cardiovascular outcomes of CABG recorded and reported;
- Cardioplegia temperature at more than one level;
- Multivariate or logistic regression analyses conducted, with cardioplegia temperature and cardiovascular outcomes entered as variables into the model.

**D. Critical appraisal**

Clear descriptions of randomization methods, patient and/or investigator blinding, and of sample size or power calculations are important indicators of RCT quality (Deeks, 2003). Accordingly, VATAP used these characteristics as quality indicators (Table 1A) in its critical appraisal of clinical trials otherwise meeting inclusion criteria.

**III. RESULTS****A. Number of RCTs Meeting Inclusion Criteria**

VATAP search methods, as detailed above, led to the identification of 17 RCT reports meeting inclusion criteria (Table 1); one of these trials (Warm Heart Investigators, 1994) yielded more than one publication (Warm Heart Investigators, 1994; Fremes, 2000). The RCTs are abstracted in Table 1 and their results summarized in Table 1A. Two of the 17 RCTs compared not only different levels of cardioplegia temperature, but also blood and crystalloid cardioplegia. The remainder of the RCTs compared blood cardioplegia at different temperatures. Ten of the RCTs (59%) reported primary or direct measures of clinical cardiovascular outcomes, while the remaining trials relied on surrogate or indirect measures, such as biochemical markers of myocardial damage or of myocardial metabolism.

**B. Critical Appraisal: Indicators of RCT Quality**

Four of the RCTs in Table 1 mentioned randomization methods while only one (Warm Heart Investigators, 1994) reported sample size calculations (Table 1A). No RCTs reported blinding of patients to group assignment, although the Warm Heart Investigators (1994) did note that their trial was intentionally unblinded.

The published trials range in size from 30 (Tönz, 1995) to 1732 (Warm Heart Investigators, 1994) subjects enrolled. Six trials included fewer than 100 subjects, while only two clinical trials (Warm Heart Investigators and Martin, both 1994) enrolled more than 1000 subjects.

### C. RCT Results

Only one published RCT (Martin, 1994) found statistically significant and clinically important differences between cardioplegia temperature groups; the difference was in rates of post-CABG neurologic damage, and is not directly relevant to this review.

### D. Large Data Set Analyses

Two large data set analyses met inclusion criteria for this review (Table 2). One of these (Abramov, 2000) found surgical variables associated with different time intervals were associated with protective effects on morbidity and mortality. However, the analyses were not specific to cardioplegia temperature, nor did they clarify independent effects of particular surgical practices.

## IV. CONCLUSIONS AND DISCUSSION

Birdi (1997) states that reports available were flawed by inconsistencies in cardioplegic techniques and inadequate definition of normothermic systemic perfusion. These flaws made definition of the independent effects of warm blood cardioplegia and normothermic CPB uncertain. The ACC/AHA guidelines for CABG (1999) found *“no strong argument can currently be made for warm versus cold and crystalloid versus blood cardioplegia”* in patients with normal left ventricular function. The guidelines go on to report *“certain techniques may offer a wider margin of safety for special patient subsets.”* However, the evidence for such a wider margin of safety is documented only as: *“Several studies have suggested that blood cardioplegia (compared to crystalloid) may offer a greater margin of safety during CABG performed on patients with acute coronary occlusion, failed angioplasty, urgent re-vascularization for unstable angina, and/or chronically impaired left ventricular function.”*

The present review discovered no published research that changed those conclusions. This review reports 17 RCTs met inclusion criteria, including two reporting the same clinical trial (Warm Heart Investigators, 1994; Fremes, 2000). These reports were published since 1990. However, most of these clinical trials were quite small, including too few subjects for statistical significance or for subset analyses. The RCT also failed to report critical quality indicators such as randomization methods or prospective statistical power calculations. Further, attempts to blind patients or investigators to group assignment were either not made or not reported.

The methodological shortcomings of the published reviews would lead even a minimally skeptical reviewer to question the validity of the titles of the published articles. The current reviewer is forced to conclude that, as a group, the published studies purporting to be “randomized” offer little convincing evidence to assist in deciding the important issue of optimal temperature for myocardial protection during CPB for CABG.

Table 1. Abstracted details of RCTs (warm versus cold cardioplegia)

Reference	Subjects/methods	Statistically Significant Results/Conclusions
<b>Blood versus crystalloid cardioplegia and blood at different temperatures</b>		
Elwatidy, 1999	<p><b>Total subjects: 128</b> undergoing isolated CABG:</p> <ul style="list-style-type: none"> <li>• Group I (n = 47) – antegrade/retrograde tepid blood cardioplegia</li> <li>• Group II (n = 40) – antegrade/retrograde cold blood cardioplegia with topical cooling</li> <li>• Group III (n = 41) – antegrade crystalloid cardioplegia with topical cooling B</li> </ul>	<p><b>Spontaneous defibrillation:</b> Incidence higher in Group I</p> <p><b>Low cardiac output:</b> No differences among groups</p> <p><b>Hemodynamic recovery:</b> No differences among groups</p> <p><b>CK-MB levels:</b> Lower in Group I</p> <p><b>Acid release and oxygen extraction:</b> Higher in Group I than in II during cardioplegia and reperfusion</p> <p><b>Lactate release:</b> Lower in Group I at release of aortic cross-clamp and reperfusion</p> <p><b>ICU stay, ventilation time, hospital complications:</b> No differences among groups</p> <p><b>Conclusions:</b></p> <ul style="list-style-type: none"> <li>• <i>Tepid blood cardioplegia provides superior metabolic and functional recovery</i></li> <li>• <i>Crystalloid cardioplegia is associated with highest incidence of post-op arrhythmias</i></li> <li>• <i>No differences among groups in hospital morbidity or mortality</i></li> </ul>
Jacquet, 1999	<p><b>Total subjects: 200</b> consecutive patients randomized to:</p> <ul style="list-style-type: none"> <li>• Group I (n = 92) - Cold crystalloid cardioplegia with moderate systemic hypothermia</li> <li>• Group II (n = 108) - intermittent antegrade warm blood cardioplegia with systemic normothermia</li> </ul>	<p><b>Intra-operative:</b></p> <ul style="list-style-type: none"> <li>• Same median number of distal anastomoses, but total ischemic arrest and CPB shorter in group II</li> <li>• Mean blood pressure lower in group II</li> <li>• More patients in group II required vasopressors</li> <li>• Ventricular fibrillation after aortic cross-clamp release more frequent in group I</li> </ul> <p><b>General outcome variables:</b> Number of new Q-wave MI, duration of ICU stay, number of deaths, incidence of stroke not different between groups</p> <p><b>Hemodynamic data:</b> Intra-aortic balloon pump use, same in both groups except for higher right atrial pressure in cold group at 4 and 8 hours after operation</p> <p><b>Conclusions:</b></p> <ul style="list-style-type: none"> <li>• <i>Intermittent antegrade warm blood cardioplegia results in less myocardial cell damage than cold crystalloid cardioplegia, as assessed by the release of cardiac-specific markers</i></li> <li>• <i>The beneficial effect of warm cardioplegia has only marginal clinical significance</i></li> </ul>

Reference	Subjects/methods	Statistically Significant Results/Conclusions
<b>Blood at different temperatures</b>		
Franke, 2003	<p><b>Total subjects: 200</b> consecutive elective CABG patients randomized to</p> <ul style="list-style-type: none"> <li>• Intermittent antegrade cold (4°C) blood cardioplegia</li> <li>• Intermittent antegrade warm (33-34°C) blood cardioplegia</li> <li>• Randomization at time of anesthesia by drawing lots</li> </ul>	<ul style="list-style-type: none"> <li>• Preoperative and demographic data comparable between groups</li> <li>• Time on CPB and cross clamp time significantly shorter in warm group</li> <li>• Necessity for defibrillation after cardiac arrest significantly less frequent and of lower intensity in warm group;</li> <li>• No differences in hemodynamic stability or need for catecholamines between groups;</li> <li>• No differences in mortality, perioperative myocardial infarctions (MI), or need for intra-aortic balloon pump;</li> <li>• Cold group required significantly more frequent re-thoracotomy due to bleeding within early post-operative course;</li> <li>• Post-operative ischemia markers significantly lower in warm group.</li> </ul> <p><b>Conclusions:</b></p> <ul style="list-style-type: none"> <li>• <b>Intermittent antegrade warm blood cardioplegia is a safe and cost-effective method in elective on-pump CABG.</b></li> <li>• <b>Significantly lower incidence of ventricular arrhythmias and lower ischemic markers suggest improved myocardial protection compared to cold blood cardioplegia in these patients.</b></li> </ul>
Bical, 2001	<p><b>Total subjects: 30:</b> first-time isolated CABG:</p> <ul style="list-style-type: none"> <li>• Warm (37°C) intermittent antegrade blood cardioplegia</li> <li>• Cold (4°C)</li> <li>• Intermittent antegrade delivery for both groups</li> <li>• Intramyocardial pH continuously monitored</li> <li>• Myocardial metabolism assessed before cross-clamping, one minute after clamp removal, and 15 minutes after reperfusion</li> </ul>	<ul style="list-style-type: none"> <li>• Clinical outcomes and hemodynamic parameters identical for both groups: no deaths or perioperative MI;</li> <li>• Group differences: Metabolism at 1 minute post clamp removal: higher coronary sinus release of lactate in warm group, also lower intra-myocardial pH; and at day 1: lower release of troponin I in arm group;</li> <li>• No differences between groups in creatine kinase after reperfusion or during post-operative period;</li> </ul> <p><b>Conclusion:</b></p> <p><b>Warm intermittent antegrade blood cardioplegia provides equally effective post-ischemic functional recovery and better metabolic recovery than does cold intermittent antegrade blood cardioplegia.</b></p>
Chocron, 2000	<p><b>Total subjects: 135:</b> first elective CABG:</p> <ul style="list-style-type: none"> <li>• Cold (8°C)</li> <li>• Lukewarm (20°C)</li> <li>• Warm (37°C)</li> <li>• Antegrade intermittent cardioplegia delivery for all groups</li> <li>• Cardiac troponin I in serial venous blood samples used to compare ischemia among groups</li> </ul> <p><b>Exclusions</b></p> <ul style="list-style-type: none"> <li>• Aortic incompetence</li> <li>• Only one distal anastomosis required</li> <li>• Ejection fraction &lt; .30%</li> <li>• Reoperation</li> <li>• Concomitant valve disease or unstable angina</li> </ul> <p>Randomization list prepared in advance, assignment by sealed envelope on patients' arrival in operating room</p>	<p>Randomization produced equivalent groups for age, sex, ejection fraction, body surface area, number of distal anastomoses per patient, cross-clamp time, CPB duration</p> <p>2 patients (1.5%) died within 30 days, both from lukewarm group:</p> <ul style="list-style-type: none"> <li>• perioperative MI at hour 4</li> <li>• postoperative stroke on day 28</li> </ul> <p>Cardiac troponin I concentrations:</p> <ul style="list-style-type: none"> <li>• Higher in cold group than in intermediate or warm groups at hours 6,9, 12</li> <li>• Higher in lukewarm group at hour 6 than in warm group</li> <li>• Total release higher in cold group than in intermediate or warm groups</li> </ul> <p><b>Conclusions:</b></p> <ul style="list-style-type: none"> <li>• <b>Intermediate antegrade lukewarm blood cardioplegia is appropriate and clinically safe</b></li> <li>• <b>Cardiac troponin I release suggests that lukewarm cardioplegia is better than cold cardioplegia but less effective than warm cardioplegia in low risk patients, leading authors to recommend warm cardioplegia in low risk patients</b></li> </ul>

Stensrud, 1999	<p><b>Total subjects: 79</b></p> <ul style="list-style-type: none"> <li>• Normothermic (37°C)</li> <li>• Hypothermic (25°C)</li> </ul> <p><b>Exclusions:</b></p> <ul style="list-style-type: none"> <li>• Any fibrinolytic activity</li> <li>• Weight &lt; 45 kg</li> <li>• Platelet count &lt; 100x10<sup>3</sup>per mm<sup>3</sup></li> </ul>	<p>No differences in CPB or cross-clamp duration, heparin sodium, protamine, prothrombin time, thromboelastogram results, or transfusion requirements</p> <p><b>Conclusion:</b>  <i>When there is no difference in duration of CPB, normothermic and hypothermic groups demonstrated similar blood loss and transfusion requirements</i></p>
Fiore, 1998	<p><b>Total subjects: 52</b>, elective CABG:</p> <ul style="list-style-type: none"> <li>• Cold group (4°C) intermittent antegrade blood (n = 27)</li> <li>• Tepid group (29°C) intermittent antegrade blood (n = 25)</li> </ul>	<ul style="list-style-type: none"> <li>• Groups similar in all pre- and intra-operative variables</li> <li>• Mean septal temperature higher in tepid group</li> <li>• After reperfusion, tepid showed significantly greater lactate and acid release despite similar levels of oxygen extraction</li> <li>• Hearts protected with tepid cardioplegia showed significantly increased ejection fraction with volume loading and improvement in left ventricular function at 12 hours; also decreased need for postoperative inotropic support and frequency of ventricular fibrillation after cross-clamp removal</li> <li>• No hospital deaths</li> <li>• Similar post-operative courses in both groups</li> </ul> <p><b>Conclusions:</b></p> <ul style="list-style-type: none"> <li>• <i>Intermittent antegrade blood cardioplegia is a safe and efficacious method of myocardial protection and</i></li> <li>• <i>Demonstrates advantages when compared with cold blood cardioplegia in elective myocardial revascularization.</i></li> </ul>
Curtis, 1996	<p><b>Total subjects: 78</b>, isolated CABG</p> <ul style="list-style-type: none"> <li>• Moderate systemic hypothermia (n= 38) with antegrade dilute blood/cold potassium</li> <li>• Systemic normothermia (n = 40) with antegrade high potassium and warm blood cardioplegia</li> </ul>	<ul style="list-style-type: none"> <li>• Groups similar pre-operatively</li> <li>• Post-op need for inotropes, cardiac pacing, incidence of ventricular dysrhythmias, chest tube drainage, length of stay (LOS) not different between groups</li> <li>• No difference in mortality between groups</li> <li>• Peri-operative MI not significantly different between groups</li> </ul> <p><b>Warm group:</b></p> <ul style="list-style-type: none"> <li>• All patients developed spontaneous rhythm</li> <li>• Warm group required significantly less intra-operative defibrillation</li> <li>• Cross-clamp time/graft significantly greater</li> </ul> <p><b>Conclusions:</b></p> <ul style="list-style-type: none"> <li>• <i>CABG can be performed with continuous warm blood cardioplegia with low morbidity and mortality</i></li> <li>• <i>Continuous warm blood cardioplegia demonstrated no clear advantage over standard techniques that allow the technical ease of a bloodless field</i></li> <li>• <i>Metabolic and physiologic significance of spontaneous resumption of sinus rhythm upon aortic declamping remains to be defined</i></li> </ul>

Engelman, 1996	<p><b>Total subjects: 130</b></p> <ul style="list-style-type: none"> <li>• Cold (20°C) (n = 37)</li> <li>• Tepid (32°C) (n = 50)</li> <li>• Warm (37°C) (n = 43)</li> </ul> <p>All received antegrade/retrograde blood cardioplegia with 4:1 blood:crystalloid solution, interrupted as needed for visualization, but never interrupted for more than 10 minutes at any one time</p>	<ul style="list-style-type: none"> <li>• Groups were comparable pre- and intra-operatively</li> <li>• Smallest volume of cardioplegic solution administered in cold group (significant difference cold vs tepid, NS, cold vs warm)</li> <li>• No peri-operative or late mortality in any group</li> </ul> <p><b>Cold group:</b></p> <ul style="list-style-type: none"> <li>• Longer duration of intubation, significantly higher peak post-operative creatine kinase-MB level than warm group</li> <li>• Included highest mean weight gain, longest mean duration of intubation, and longest mean post-operative LOS (reflecting longer ICU stays necessitated by hypothermia)</li> <li>• Mean blood loss least, but NS</li> <li>• No patient required re-operation due to bleeding</li> <li>• Significantly higher prevalence of abnormal neurologic examinations prompting CT scanning</li> </ul> <p><b>Warm group:</b></p> <ul style="list-style-type: none"> <li>• Least CK-MB generation</li> <li>• Lowest inotrope use, but differences among groups NS</li> <li>• Use of intra-aortic balloon at any time highest</li> </ul> <p><b>Conclusions:</b></p> <ul style="list-style-type: none"> <li>• <b><i>Any profound difference of temperature on myocardial preservation was not apparent</i></b></li> <li>• <b><i>Myocardial and cardioplegic solution temperatures had no dramatic effect on prevalence of arrhythmias (atrial or ventricular), and do not deserve to dictate a specific perfusion temperature</i></b></li> <li>• <b><i>Short period in ICU can be most easily accomplished if significant hypothermia is avoided</i></b></li> <li>• <b><i>Reduced intubation time is temperature dependent and significantly longer post-operative LOS is associated with hypothermic perfusion</i></b></li> </ul>
Kaukoranta, 1995	<p><b>Total subjects: 101</b> elective CABG for severe disease:</p> <ul style="list-style-type: none"> <li>• Retrograde warm (37°C)</li> <li>• Retrograde mild hypothermic (28-29°C)</li> <li>• Short intermissions to cardioplegia during construction of distal anastomoses allowed</li> </ul>	<p><b>Similar between groups:</b></p> <ul style="list-style-type: none"> <li>• Clinical characteristics</li> <li>• Cardioplegia delivery rates</li> <li>• Aortic cross-clamp and CPB times</li> <li>• Number of distal anastomoses</li> </ul> <p><b>Mild hypothermia group:</b></p> <ul style="list-style-type: none"> <li>• Lower myocardial oxygen consumption at 30 minutes of cross-clamping</li> <li>• Smaller transcardiac pH difference</li> </ul> <p><b>Normothermic group:</b></p> <ul style="list-style-type: none"> <li>• Higher postoperative creatine kinase-MB levels</li> <li>• Higher heart rate</li> <li>• Smaller left ventricular stroke work index</li> <li>• Otherwise no major differences between groups including postoperative complications</li> </ul> <p><b>Conclusions:</b></p> <ul style="list-style-type: none"> <li>• <b><i>Mild hypothermia provided somewhat better myocardial protection under the conditions of this study</i></b></li> <li>• <b><i>Effects of different cardioplegia temperatures should be tested in patients with recent MI, unstable angina, severely depressed left ventricular function</i></b></li> </ul>

<p>Tönz, 1995</p>	<p><b>Total subjects: 30</b>, scheduled for first procedure of the day:</p> <ul style="list-style-type: none"> <li>• Warm (36°C)</li> <li>• Cold (28°C)</li> <li>• All either antegrade or retrograde</li> </ul> <p><b>Exclusions:</b></p> <ul style="list-style-type: none"> <li>• Ejection fraction &lt; 0.35</li> <li>• Age &gt; 65 years</li> <li>• Previous cardiac procedure</li> <li>• Impaired lung, liver, renal function</li> </ul>	<p><b>During CPB:</b> No differences between groups in need for vasopressors, urinary output, or fluid balance</p> <p><b>Early post-operative period:</b></p> <ul style="list-style-type: none"> <li>• Normothermic group had lower systemic vascular resistance and higher cardiac index without differences in vasoactive drugs</li> </ul> <p><b>Hypothermic group:</b></p> <ul style="list-style-type: none"> <li>• Higher blood loss with greater need for transfusions of erythrocytes and fresh frozen plasma</li> </ul> <p><b>Conclusions:</b></p> <ul style="list-style-type: none"> <li>• <b>Significant influence of CPB temperature on post-operative hemodynamics and blood loss</b></li> </ul>
<p>Hayashida, 1994</p>	<p><b>Total subjects: 72</b></p> <ul style="list-style-type: none"> <li>• Cold (8°C) (n = 12)</li> <li>• Tepid (29°C) (n = 12)</li> <li>• Warm (37°C) (n = 12)</li> </ul>	<ul style="list-style-type: none"> <li>• Myocardial oxygen consumption and anaerobic lactate release greatest during warm, intermediate during tepid, least during cold cardioplegia</li> <li>• Warm and tepid retrograde resulted in greater lactate and acid wash-out during reperfusion</li> <li>• Left ventricular stroke work indices greatest after warm antegrade cardioplegia</li> <li>• Warm antegrade cardioplegia increased aerobic metabolism and preserved left and right ventricular function</li> <li>• Tepid antegrade cardioplegia reduced anaerobic lactate and acid release during arrest and preserved cardiac function</li> </ul>
<p>Warm Heart investigators, 1994</p>	<p>Total subjects: 1732</p> <ul style="list-style-type: none"> <li>• Sample size adequate to test for 50% reduction in combined end point of death or Q-wave MI</li> </ul> <p>Stratified by surgeon and by urgent or elective and then randomized to:</p> <ul style="list-style-type: none"> <li>• Warm (33-37 °C) systemic temperatures allowed to drift, or active rewarming used (n = 860)</li> <li>• Cold (25-30 °C) by active cooling (n = 872)</li> <li>• Cardioplegia initially antegrade through aortic root or completed vein grafts (1659 patients) or retrograde via coronary sinus (73 patients)</li> <li>• After cross-over 6.3% received at least some retrograde cardioplegia</li> </ul>	<p><b>Patients:</b></p> <ul style="list-style-type: none"> <li>• 2 patients who had been randomized did not receive cardioplegia due to extensive aortic atherosclerosis</li> <li>• 66 patients who crossed from warm to cold (due to difficulty in obtaining or maintaining cardiac arrest or due to cardiac flooding) were counted in the warm group</li> <li>• No crossovers from cold to warm</li> </ul> <p><b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>• No differences between strata</li> <li>• Higher case-fatality rate in cold group (both cardiac and non-cardiac causes), but significance not reported</li> <li>• No significant interaction between cardioplegia assignment and surgical priority for any primary or secondary outcomes</li> </ul> <p><b>Reduced in warm group:</b></p> <ul style="list-style-type: none"> <li>• Low output syndrome</li> <li>• Non-fatal MI by enzyme criteria for patients with 5 or 6 samples</li> <li>• Mean area under CK-MB time-activity curve in warm patients with 5 or more samples</li> <li>• Electrical defibrillation after cross-clamp release</li> </ul> <p><b>Surgeons</b></p> <ul style="list-style-type: none"> <li>• Several participated briefly or intermittently</li> <li>• 7 who each contributed &gt; 100 patients were responsible for 88% of total</li> </ul> <p><b>Conclusions:</b></p> <ul style="list-style-type: none"> <li>• <b>re: warm versus cold effects unchanged whether or not low-volume surgeons were excluded</b></li> </ul>

<p>Fremes, 2000 <i>(late results of "warm heart trial")</i></p>	<p><b>Total subjects: 762</b> recruited from one warm heart trial center were followed for late events:</p> <ul style="list-style-type: none"> <li>• Warm and cold groups compared for demographic, angiographic, operative, and outcome variables (late death including perioperative deaths in this study)</li> </ul>	<p><b>Baseline variables:</b></p> <ul style="list-style-type: none"> <li>• Similar between warm and cold cardioplegia groups, except for excess of preoperative hypertension in warm group</li> </ul> <p><b>Operative variables:</b></p> <ul style="list-style-type: none"> <li>• Excess of re-operation in cold group</li> </ul> <p><b>Actuarial survival:</b></p> <ul style="list-style-type: none"> <li>• Significantly increased in warm group at 6 years after surgery when redo patients excluded from analysis</li> <li>• Increased risk of late death associated with: redo CABG; diabetes mellitus; renal insufficiency; increased age</li> <li>• Protective against late death: use of left internal thoracic artery; female sex</li> <li>• Use of warm cardioplegia did not significantly influence late survival in multivariate analysis when adjusted for other covariates</li> <li>• Late survival significantly reduced after ECG-defined MI and LOS</li> <li>• Nonfatal enzymatic MI does not significantly influence late survival</li> </ul>
<p>Rashid, 1994</p>	<p><b>Total subjects: 281:</b></p> <ul style="list-style-type: none"> <li>• <b>Intermittent cold blood cardioplegia: n = 144</b> antegrade delivery (28°C)</li> <li>• <b>Continuous warm blood cardioplegia: n = 137</b> (37°C) initially antegrade then switched to retrograde</li> </ul>	<p>No significant differences between groups in mortality, peri-operative MI, blood loss, post-operative neurologic deficit, need for care, non-fatal post-op complications, or hospital stay</p> <p><b>Warm group:</b></p> <ul style="list-style-type: none"> <li>• Sinus rhythm returned spontaneously with significantly greater frequency</li> </ul> <p><b>Cold group:</b></p> <ul style="list-style-type: none"> <li>• Greater transmyocardial oxidative stress</li> <li>• Serum CK-MB isoenzyme significantly higher at 2 hours post-operative (but difference disappeared by next day)</li> </ul> <p><b>Conclusions:</b></p> <ul style="list-style-type: none"> <li>• <b>Continuous warm blood cardioplegia provides comparable protection to that achieved with standard hypothermic techniques</b></li> </ul>
<p>Yau, 1993</p>	<p><b>Total subjects: 53</b> elective CABG by a single surgeon:</p> <ul style="list-style-type: none"> <li>• <b>Warm blood (37°C)</b> continuous cardioplegia infusion, systemic temperature allowed to drift to 30-32°C</li> <li>• <b>Cold blood (5°C)</b> intermittent cardioplegia with terminal "hot shot" and systemic cooling to 25-28°C</li> </ul> <p>Randomization by computer-generated table</p>	<ul style="list-style-type: none"> <li>• No significant differences between groups in pre- and intra-operative variables</li> <li>• Warm cardioplegia delivered for 60% of cross-clamp period, cold for 28% (significant difference, p =0.009)</li> <li>• One patient in cold group had deep sternal infection and died on postoperative day 22</li> <li>• One patient in warm group and two in cold group had perioperative MI (NS)</li> <li>• 3 patients in cold group had low output syndrome (p =0.07)</li> <li>• Systemic temperatures still higher in warm group at 3 hours after operation</li> <li>• No clinically or statistically significant differences in adenine nucleotides or degradation products</li> </ul> <p><b>Warm group</b></p> <ul style="list-style-type: none"> <li>• Greater volumes of cardioplegic solution and higher peak serum potassium concentration</li> <li>• Greater myocardial lactate production</li> <li>• Improved recovery of oxygen consumption during reperfusion</li> <li>• Total adenosine nucleotides fell further</li> <li>• Creatine kinase MB isoenzyme release reduced</li> <li>• 3 hours after operation, end-systolic elastance, pre-load recruitable stroke work index, and early</li> </ul>

		<p>diastolic relaxation increased</p> <ul style="list-style-type: none"> <li>• Greater active diastolic relaxation after warm cardioplegia</li> <li>• Oxygen consumption after 20 minutes of reperfusion was higher</li> </ul> <p><b>Conclusions:</b></p> <ul style="list-style-type: none"> <li>• <b>Increased systolic function after warm cardioplegia may have been related to improved myocardial protection, elevated arterial lactate concentrations, or increased circulating catecholamines</b></li> </ul>
<p>Gozal, 1996</p>	<p><b>Total subjects: 42</b> elective CABG:</p> <ul style="list-style-type: none"> <li>• Hypothermia (10°C)</li> <li>• Normothermia (33.5°C)</li> </ul> <p><b>Exclusions:</b></p> <ul style="list-style-type: none"> <li>• Poor left ventricular function (ejection fraction &lt; 40%)</li> <li>• Concomitant valvular disease</li> <li>• Anti-dysrhythmic medications</li> <li>• Left bundle branch block</li> <li>• Re-exploration for bleeding</li> </ul> <p>Two cardioplegia solutions (antegrade and retrograde intermittent delivery) used in all patients:</p> <ul style="list-style-type: none"> <li>• High potassium</li> <li>• Low potassium</li> </ul> <p>Both experimental groups received warm blood perfusion without cardioplegia before aortic declamping</p>	<p>6 patients were excluded from analyses (3 due to return to operating room for persistent bleeding, 3 due to uninterpretable Holter recording):</p> <ul style="list-style-type: none"> <li>• 75% of active cooling patients (hypothermic group) transitioned through ventricular fibrillation on initiation of CPB</li> <li>• 65% of normothermic group experienced atrial fibrillation</li> </ul> <p>On myocardial reperfusion:</p> <ul style="list-style-type: none"> <li>• 95% of normothermic group resumed sinus rhythm spontaneously</li> <li>• 25% of hypothermic group returned to sinus rhythm spontaneously</li> <li>• Similar incidence of intraventricular block and ST segment changes</li> </ul> <p><b>Conclusions:</b></p> <ul style="list-style-type: none"> <li>• <b>Hypothermic myocardial protection is associated with increased susceptibility for ventricular fibrillation and dysrhythmia, and with delayed recovery of conduction system</b></li> <li>• <b>Both methods provide adequate myocardial protection, but normothermia may accelerate recovery of the heart after CPB</b></li> <li>• <b>Myocardial and cardioplegic temperatures had no dramatic effect on prevalence of arrhythmias or other outcomes</b></li> </ul>

**Table 1A. Summary/Overview of outcomes and design or reporting weaknesses of the 17 RCTs**

Characteristic	Citation(s)	Results in favor of...	Comments
<b>Trials reporting primary or direct outcomes</b>			
<b>11/17 trials</b>	Franke, 2003	Warm blood cardioplegia ("safe and cost effective in on-pump elective CABG")	Antegrade/retracardiac delivery, systemic temperature not consistent between or among studies
	Bical, 2001	Warm blood cardioplegia ("equally effective functional recovery and better metabolic recovery")	
	Chocron, 2000	Lukewarm blood cardioplegia ("appropriate and clinically safe")	
	Elwatidy, 1999	Tepid blood cardioplegia (but no differences in hospital morbidity or mortality).	
	Jacquet, 1999	Warm blood cardioplegia (but only marginal clinical significance)	
	Fiore, 1998	Tepid blood cardioplegia ("demonstrates advantages when compared to cold blood cardioplegia in elective myocardial revascularization")	
	Curtis, 1996	Warm blood cardioplegia demonstrated "no clear advantage over standard techniques"	
	Engelman, 1996	"Temperature had no dramatic effect..."	
	Kaukoranta, 1995	Mild hypothermia "provided somewhat better myocardial protection under the conditions of the study"	
	Warm Heart Investigators, 1994	"Warm heart surgery is a safe and effective alternative to conventional hypothermic techniques"	
	Martin, 1994	"Retrograde warm blood cardioplegia provides excellent myocardial protection that compares favorably with cold oxygenated crystalloid techniques", but is associated with a significantly increased rate of neurologic damage.	
<b>Design/reporting weaknesses</b>			
Randomization method specified: <b>5/17 trials</b>	Franke, 2003	Drawing lots at time of anaesthesia	
	Chocron, 2000	Randomization list transferred to cards in sealed envelopes	
	Warm Heart Investigators, 1994	Stratified by surgeon and by urgent vs. elective; randomization by sealed envelope after patient's arrival in OR	
	Martin, 1994	Computer-generated random number assignment	
	Yau, 1993	Computer-generated randomization table	
Sample size calculation	Warm Heart Investigators, 1994		

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(statistical power) reported: <b>1/17 trials</b>			
Blinding of patients reported <b>0/17 trials</b>			

**Table 2. Abstracted details of large database analyses (plus relevant serendipitous or *post hoc* analyses of cardioplegia temperature)**

Reference	Subjects/Methods	Results
Mallidi, 2003	<p><b>6064 patients in Warm Heart Trial database:</b></p> <ul style="list-style-type: none"> <li>• 4532 warm or tepid cardioplegia</li> <li>• 1532 cold cardioplegia</li> <li>• 762 enrolled in Warm- Heart Trial (Table 1) were allocated to cardioplegia temperature randomly; remainder by surgeon preference.</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Cold blood cardioplegia:</b> peri-operative death, myocardial infarction, and death or myocardial infarction more common;</li> <li>• <b>Actuarial survival at 60 months:</b> 91.1%±1.4% warm group, 89.9%±1.3% cold group p = .09);</li> <li>• <b>Freedom from death or myocardial infarction:</b> 84.7%±1.8% in warm group, 83.2% ±1.6% in cold group (p = .16);</li> <li>• <b>Multivariate models:</b> cold blood cardioplegia was associated with poorer survival (risk ratio 1.3, 95% confidence interval 0.96-1.75, p = .09); and freedom from any death or late myocardial infarction (risk ratio 1.93, 95% confidence interval 1.56-2.39, p = .0001).</li> </ul> <p><b>Conclusions:</b></p> <ul style="list-style-type: none"> <li>• <b><i>In 6064 patients undergoing isolated CABG, warm or tepid blood cardioplegia may be associated with better early and late event-free survival than is cold cardioplegia.</i></b></li> </ul>
Flack, 2000	<p><b>885 patient randomized CABG Patch Trial data set</b> (including type and temperature of cardioplegia and surgical outcomes) 78% of patients received blood cardioplegia:</p> <ul style="list-style-type: none"> <li>• Cold blood at 3°C - 25°C</li> <li>• Cold blood with terminal “hot shot” (warm reperfusion)</li> <li>• Normothermic blood</li> </ul> <p>High risk patients (ejection fractions &lt; 36%) who had CABG with random assignment of cardioverter defibrillator implantation during the procedure</p>	<p><b>3 blood temperature groups compared:</b></p> <ul style="list-style-type: none"> <li>• No significant differences in baseline characteristics among groups</li> <li>• Normothermic group had longer CPB and cross clamp times, lower incidence of post-operative right ventricular dysfunction (95% of these patients had cardioplegia administered by combined antegrade retrograde route, which the RCT demonstrated to be associated with superior right ventricular protection; combined delivery routes may have confounded results)</li> <li>• Early mortality: cold blood, 3.5%; warm reperfusion, 2.4%, warm blood, 6% (NS)</li> <li>• Late mortality: cold blood, 22%, warm reperfusion, 19%, warm blood, 16% (NS)</li> <li>• Significantly lower incidence of conduction deficits with warm reperfusion</li> </ul> <p><b>Conclusions:</b></p> <ul style="list-style-type: none"> <li>• <b><i>No clear benefit for any cardioplegia blood temperature subgroup was found, although this could reflect the wide range of temperatures used for cold cardioplegia</i></b></li> </ul>
Abramov, 2000	<p>Data on <b>4839</b> CABG procedures were divided into 3 time cohorts for multivariate analyses:</p> <ul style="list-style-type: none"> <li>• 1990-92</li> </ul>	<p>Over time, there was a trend toward CABG in older patients with more comorbidities. Hospital mortality has remained stable but risk-adjusted mortality has declined constantly.</p> <p>Overall:</p> <ul style="list-style-type: none"> <li>• Mortality was 2.0%</li> </ul>

	<ul style="list-style-type: none"> <li>• 1993-95</li> <li>• 1996-98</li> </ul> <p>Clinical, operative, outcome data (hospital mortality or perioperative complications, MI, low output syndrome, intraaortic balloon pump insertion, cerebrovascular accident) were recorded</p>	<ul style="list-style-type: none"> <li>• Mortality + morbidity was 15.6%</li> </ul> <p>Use of warm cardioplegia increased significantly over time.</p> <p><b>Surgical variables</b> (warm cardioplegia, left internal mammary artery use, multiple arterial grafts) were protective in logistic regression for mortality and mortality + morbidity. When entered into the regression model, surgical variables largely eliminated independent protective effects of later time cohorts.</p> <p><b>Conclusions:</b></p> <ul style="list-style-type: none"> <li>• <b><i>Surgical practice is constantly changing. Advances in technology, anesthesia, intensive care, medical management, and myocardial protection have all contributed to reductions in risk-adjusted mortality, and morbidity, during the last decade.</i></b></li> </ul>
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## V. REFERENCES

Abramov D, Tamariz MG, Fremes SE, Guru V, Borger MA, Christakis GT, et al. Trends in coronary artery bypass surgery results: A recent, 9-year study. *Annals of Thoracic Surgery*, 2000; 70: 84-90.

American College of Cardiology/American Heart Association Task Force on Practice Guidelines: Guidelines for Coronary Artery Bypass Graft Surgery: Executive Summary and Recommendations. *Circulation*, 1999; 100: 1464-1480.

Antczak-Bouckoms A, Burdick E, Klawansky S, Mosteller F. Using medical registries and data sets for technology assessment. *International Journal of Technology Assessment in Health Care*, 1991; 7: 123-128.

Bical OM, Fromes Y, Paumier D, Gaillard D, Foiret JC, Trivin F. Does warm antegrade intermittent blood cardioplegia really protect the heart during coronary surgery? *Cardiovascular Surgery*, 2001; 9: 188-193.

Birdi I, Regragui I, Izzat MB, Bryan AJ, Angelini GD. Influence of normothermic systemic perfusion during coronary artery bypass operations: a randomized prospective study. *Journal of Thoracic and Cardiovascular Surgery*, 1997; 114: 475-481.

Buckberg GD. Update on current techniques of myocardial protection. *Annals of Thoracic Surgery*, 1995; 60: 805-814.

Burdick E, Falotico-Taylor J, Young JM. Technology assessment in the Coronary Artery Surgery Study. *International Journal of Technology Assessment in Health Care*, 1991; 7: 171-181.

Chitwood WR, Jr., Wixon CL, Norton TO, Lust RM. Complex valve operations: antegrade versus retrograde cardioplegia? *Annals of Thoracic Surgery*, 1995; 60: 815-818.

Chocron S, Kaili D, Yan Y, Toubin G, Latini L, Clement F, et al. Intermediate lukewarm 20 degree C antegrade intermittent blood cardioplegia compared with cold and warm blood cardioplegia. *Journal of Thoracic and Cardiovascular Surgery*, 2000; 119: 610-616.

Christakis GT, Abel JG, Lichtenstein SV. Neurological outcomes and cardiopulmonary temperature: a clinical review. *Journal of Cardiovascular Surgery*, 1995; 10: 475-480.

Cook DJ. Changing temperature management for cardiopulmonary bypass. *Anesthesia and Analgesia*, 1999; 88: 1254-1271.

- Cook DJ, Guyatt GH, Laupacis A, Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest*, 1992; 102: 305S-311S.
- Curtis JJ, Nawarawong W, Walls JT, Schmaltz RA. Continuous warm blood cardioplegia: a randomized prospective clinical comparison. *International Journal of Angiology*, 1996; 5: 212-218.
- Davis K. Use of data registries to evaluate medical procedures: coronary artery surgery study and the balloon valvuloplasty registry. *International Journal of Technology Assessment of Health Care.*, 1991; 7: 203-210.
- Dearani JA, Axford TC, Patel MA, Healey NA, Lavin PT, Khuri SF. Role of myocardial temperature measurement in monitoring the adequacy of myocardial protection during cardiac surgery. *Annals of Thoracic Surgery*, 2001; 72: S2235-2243; discussion S2243-2234, S2267-2270.
- Deeks J, Higgins J, Altman D, editors. Accessed: January, 2004. Analysing and presenting results; Section 8. Available: December, 2003.  
<http://www.cochrane.org/resources/handbook/hbook.htm>.
- Eagle KA, Guyton RA, Davidoff R, Ewy GA, Fonger J, Gardner TJ, et al. ACC/AHA guidelines for coronary artery bypass graft surgery: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1991 guidelines for coronary artery bypass graft surgery). *Circulation*, 1999; 100: 1464-1480.
- Elwatidy AM, Fadalah MA, Bukhari EA, Aljubair KA, Syed A, Ashmeg AK, et al. Antegrade crystalloid cardioplegia vs antegrade/retrograde cold and tepid blood cardioplegia in CABG. *Annals of thoracic surgery*, 1999; 68: 447-453.
- Engelman RM, Pleet AB, Rousou JA, Flack JE, 3rd, Deaton DW, Gregory CA, et al. What is the best perfusion temperature for coronary revascularization? *Journal of Thoracic and Cardiovascular Surgery*, 1996; 112: 1622-1632; discussion 1632-1623.
- Fiore AC, Swartz MT, Nevett R, Vieth PJ, Magrath RA, Sherrick A, et al. Intermittent antegrade tepid versus cold blood cardioplegia in elective myocardial revascularization. *Annals of Thoracic Surgery*, 1998; 65: 1559-1564; discussion 1564-1555.
- Flack JE, Cook JR, May SJ, Lemeshow S, Engelman RM, Rousou JA, et al. Does cardioplegia type affect outcome and survival in patients with advanced left ventricular dysfunction? Results from the CABG Patch trial. *Circulation*, 2000; 102: 84-89.
- Franke Ulrich FW, Korsch S, Wittwer T, Albes Johannes M, Wippermann J, Kaluza M, et al. Intermittent antegrade warm myocardial protection compared to intermittent cold blood cardioplegia in elective coronary surgery--do we have to change? *European*

*journal of cardio-thoracic surgery - official journal of the European Association for Cardio-thoracic Surgery*, 2003; 23: 341-346.

Fremes SE, Tamariz MG, Abramov D, Christakis GT, Sever JY, Sykora K, et al. Late results of the Warm Heart Trial: the influence of nonfatal cardiac events on late survival. *Circulation*, 2000; 102: 339-345.

Gates RN, Laks H. Retrograde cardioplegia. *Advances in Cardiac Surgery*, 1998; 10: 115-139.

Gozal Y, Glantz L, Luria MH, Milgalter E, Shimon D, Drenger B. Normothermic continuous blood cardioplegia improves electrophysiologic recovery after open heart surgery. *Anesthesiology*, 1996; 84: 1298-1306.

Grover F, Johnson R, Marshall G, Hammermeister K. Factors predictive of operative mortality among coronary artery bypass subsets. *Annals of Thoracic Surgery*, 1993; 56: 1296-1307.

Guyton RA, Gott JP, Brown WM, Craver JM. Cold and warm myocardial protection techniques. *Advances in Cardiac Surgery*, 1996; 7: 1-29.

Hayashida N, Ikonomidis JS, Weisel RD, Shirai T, Ivanov J, Carson SM, et al. The optimal cardioplegic temperature. *Annals of Thoracic Surgery*, 1994; 58: 961-971.

Investigators TWH. Randomised trial of normothermic versus hypothermic coronary bypass surgery. *Lancet*, 1994; 343: 559-563.

Jacquet LM, Noirhomme PH, Van Dyck MJ, El Khoury GA, Matta AJ, Goenen MJ, et al. Randomized trial of intermittent antegrade warm blood versus cold crystalloid cardioplegia. *Annals of Thoracic Surgery*, 1999; 67: 471-477.

Jegaden O, Eker A, Montagna P, Ossette J, Vial C, Guidollet J, et al. Antegrade/retrograde cardioplegia in arterial bypass grafting: metabolic randomized clinical trial. *Annals of Thoracic Surgery*, 1995; 59: 456-461.

Kaukoranta P, Lepojarvi M, Nissinen J, Raatikainen P, Peuhkurinen KJ. Normothermic versus mild hypothermic retrograde blood cardioplegia: a prospective, randomized study. *Annals of Thoracic Surgery*, 1995; 60: 1087-1093.

Kirklin JK, Kirklin JW. Cardiopulmonary bypass for cardiac surgery. In: Sabiston DC, Spencer FC, Eds. *Surgery of the Chest*. London: WB Saunders Company, 1990: 1107-1125.

Kirschstein R. 2003. Disease-specific estimates of direct and indirect estimates of illness and NIH support. Fiscal year 2000 update. [Web Site]. Available: June, 2000. <http://osp.od.nih.gov/ecostudies/COIreportweb.htm>.

Loop FD, Higgins TL, Panda R, Pearce G, Estafanous FG. Myocardial protection during cardiac operations. Decreased morbidity and lower cost with blood cardioplegia and coronary sinus perfusion. *Journal of Thoracic and Cardiovascular Surgery*, 1992; 104: 608-618.

Mallidi HR, Sever J, Tamariz M, Singh S, Hanayama N, Christakis GT, et al. The short-term and long-term effects of warm or tepid cardioplegia. *Journal of Thoracic and Cardiovascular Surgery*, 2003; 125: 711-720.

Mangano DT, The Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Effects of acadesine on myocardial infarction, stroke, and death following surgery: a meta-analysis of the 5 international randomized trials. *JAMA*, 1997; 277: 325-332.

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. *Annals of Thoracic Surgery*, 1994; 57: 298-302; discussion 302-304.

Mauney MC, Kron IL. The physiologic basis of warm cardioplegia. *Annals of Thoracic Surgery*, 1995; 60: 819-823.

McLean RF, Wong BI. Normothermic versus hypothermic cardiopulmonary bypass: central nervous system outcomes. *Journal of Cardiothoracic Vascular Anesthesia*, 1996; 10: 45-52; quiz 52-43.

MDRC. Accessed: September, 2003. The number one cause of death: heart disease. [Web Site]. Available: June, 2000. [http://www1.va.gov/resdev/prt/brief\\_15\\_v4.pdf](http://www1.va.gov/resdev/prt/brief_15_v4.pdf).

Menasche P. New strategies in myocardial preservation. *Current Opinion in Cardiology*, 1997; 12: 504-514.

Murkin JM. Anesthesia, the brain, and cardiopulmonary bypass. *Annals of Thoracic Surgery*, 1993; 56: 1461-1463.

Newman MF, Croughwell N.D. Blumenthal J.A., White W.D. Reves J.G. Cardiopulmonary bypass and the central nervous system: potential for cerebral protection. *Clinical Anesthesia*, 1996; 8: 535-605.

Planning. NOoSPa. Disease-specific estimates of direct and indirect costs of illness and NIH support. <http://www1.od.nih.gov/osp/ospp/ecostudies/COIreportweb.htm>.

Rashid A, Fabri BM, Jackson M, Desmond MJ, Grech ED, Battistessa SA, et al. A prospective randomised study of continuous warm versus intermittent cold blood cardioplegia for coronary artery surgery: preliminary report. *European Journal of Cardiothoracic Surgery*, 1994; 8: 265-269.

Robinson LA, Schwarz GD, Goddard DB, Fleming WH, Galbraith TA. Myocardial protection for acquired heart disease surgery: results of a national survey. *Annals of Thoracic Surgery*, 1995; 59: 361-372.

Stensrud PE, Nuttall GA, de Castro MA, Abel MD, Ereth MH, Oliver WC, Jr., et al. A prospective, randomized study of cardiopulmonary bypass temperature and blood transfusion. *Annals of Thoracic Surgery*, 1999; 67: 711-715.

Taylor KM. Brain damage during cardiopulmonary bypass. *Annals of Thoracic Surgery*, 1998; 65: S20-26; discussion S27-28.

Tobler HG, Sethi GK, Grover FL, Shroyer AL, Moritz TE, Henderson WG, et al. Variations in processes and structures of cardiac surgery practice. *Medical Care*, 1995; 33: Os43-58.

Tonz M, Mihaljevic T, von Segesser LK, Schmid ER, Joller-Jemelka HI, Pei P, et al. Normothermia versus hypothermia during cardiopulmonary bypass: a randomized, controlled trial. *Annals of Thoracic Surgery*, 1995; 59: 137-143.

Utlej JR, Gravlee GP. Special considerations in cardiopulmonary bypass. *Advances in Cardiac Surgery*, 1996; 7: 87-100.

Yau TM, Ikonomidis JS, Weisel RD, Mickle DA, Ivanov J, Mohabeer MK, et al. Ventricular function after normothermic versus hypothermic cardioplegia. *Journal of Thoracic and Cardiovascular Surgery*, 1993; 105: 833-843; discussion 843-834.

## VI. APPENDIX: GLOSSARY AND BASIC CONCEPTS

**Cardiopulmonary bypass (CPB)** - “a technique by which the pumping action of the heart and the gas exchange functions of the lung are replaced temporarily by a mechanical device, the pump oxygenator, attached to a patient’s vascular system” (Kirklin, 1990); “Cardiac and pulmonary bypass of entire circulation by venous drainage, mechanical gas exchange, and reperfusion of oxygenated blood into the arterial system.” (Tobler, 1995). During cardiac surgery CPB is accompanied by cardioplegia.

**Cardioplegia** - “the cessation of electromechanical activity in the heart” (McLean and Wong, 1996). Stopping the heart facilitates surgery but deprives critical tissues such as the myocardium and central nervous system of oxygen and nutrients critical to continued (or recovered after surgery) normal function. Accordingly, methods for protecting these tissues have been developed in parallel with cardiac surgery. An additional and related benefit of cardioplegia is that the non-working heart has substantially fewer metabolic demands and is subject to less injury from oxygen and nutrient deprivation.

**Cold cardioplegia** – Information for this and the next section, unless otherwise referenced, was obtained from Guyton (1996), Menasche (1997) and Curtis (1996).

Each 10°C reduction in temperature is accompanied by an approximately 50% reduction in metabolic rate. During cold cardioplegia, the heart may be cooled by infusion of cold solutions into the coronary arteries (perfusion hypothermia), by systemic cooling on CPB, or by local cooling with iced saline slush or cooling pads around the heart.

Cold protection essentially “freezes” biochemical pathways, nutrient stores, and critical chemical compounds in a functional state. As the heart is re-warmed, that functional state is restored to a greater or lesser degree. Since actual freezing (to 0°C or less), while producing near-complete preservation of the biochemical state at the time of freezing, would also produce cellular and sub-cellular damage, clinical cold myocardial protection involves somewhat higher temperatures (10 to 18°C). At these higher temperatures, metabolic processes continue, requiring the development of cardioplegia techniques that supply nutrients to the heart during the period of relative metabolic quiescence. These techniques include cold blood cardioplegia and oxygenated cold crystalloid (high potassium) cardioplegia.

While initial introduction of cold cardioplegia was accompanied by controversy about the necessity of mechanical arrest in addition to hypothermia, animal studies indicated that cold high potassium solutions provided additional benefit over myocardial protection solely by means of temperature control. Myocardial metabolism is reduced but not arrested with myocardial cooling.

**Warm cardioplegia** - “Warm heart surgery”, introduced at the University of Toronto in 1987 maintains normothermic perfusion of the heart while decreasing oxygen consumption by chemically induced electromechanical cardiac arrest. The physiological rationale is that the normothermic blood eliminates reperfusion injury and also allows the non-working heart to replenish high- energy phosphate stores. The rationale for continuous or nearly continuous warm blood cardioplegia is that it provides a nearly complete supply of nutrients with the heart metabolically quiescent warm. Chemical agents, rather than temperature, *per se*, arrest the heart and decrease its metabolic needs, which are supplied by the continuous infusion of blood at near normal temperature. Flack (2000) reports that potassium cardioplegia originated in 1955, when potassium citrate was used. Since the early method was associated with a high rate of myocardial necrosis, it was abandoned until the 1970s, when “crystalloid” formulations made use of lower potassium concentrations at isotonicity. Crystalloid cardioplegia was widely used until the 1980s, when blood-based potassium solutions were advocated for their ability to further improve myocardial protection.

Warm cardioplegia often involves the delivery of tepid, minimally diluted blood as a vehicle for arresting agents. Delivery may be via antegrade (aortic root, coronary ostia, saphenous vein graft) or retrograde (coronary sinus) routes. Choice of delivery route is based on the predicted distribution of cardioplegic solution, itself a function of anatomic pattern of coronary artery disease and collateral circulation, although the optimal route for routine use continues to be debated (Buckberg, 1995) and RCTs of antegrade versus retrograde delivery are still published (Jegaden, 1995). Gates (1998) reports widespread use of the retrograde route began in the late 1980s, facilitated by the development of a new cannula to access the coronary sinus. Retrograde and warm cardioplegia were often coupled. Jacquet (1999) reports that continuous warm blood cardioplegia has been routinely used by a growing number of surgeons. These authors believe it is superior over cold blood cardioplegia with respect to myocardial metabolic and functional recovery has been demonstrated.

The relative merits of continuous versus intermittent cardioplegia have been debated or investigated in RCTs (Fiore, 1998), although the potential for myocardial ischemia argues against the latter (Panos, 1993). Flooding of continuously infused cardioplegia in the operative field could hinder the surgeon’s visual access to the field and necessitate interruption of the infusion for technical reasons. Deliberately intermittent antegrade warm blood cardioplegia has been proposed as a solution to these technical problems and is therefore the primary independent variable in the randomized trial reported by Jacquet (1999). Additional independent variables manipulated by these authors were systemic temperature during bypass and cardioplegia temperature (Table1).



VA Technology Assessment Program  
Office of Patient Care Services (11T)  
VA Boston Healthcare System  
150 South Huntington Avenue  
Boston, MA 02130

Tel: 617.278.4469 Fax: 617.264.6587  
[vatap@med.va.gov](mailto:vatap@med.va.gov)  
<http://www.va.gov/vatap> <http://vaww.va.gov/vatap>

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