Review

Warm Blood Cardioplegia for Myocardial Protection:

Concepts and Controversies

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Warm blood cardioplegia has been an established cardioplegic method since the 1990s, yet it remains controversial in regard to myocardial protection. This review will describe the physiologic and technical concepts behind warm blood cardioplegia, as well as outline the current basic and clinical research that evaluates its usefulness. Controversies regarding this technique will also be reviewed. A long history of experimental data indicates that warm blood cardioplegia is safe and effective and thus suitable myocardial protection during cardiopulmonary bypass surgeries. ***(Tex Heart Inst J 2020;47(2):108-16)***

Despite a long history and ample evidence in the medical literature, warm blood cardioplegia remains a complex and controversial topic. Many surgeons hesitate to adopt this technique because of their perceived ambiguity about its effectiveness in complex procedures or their uncertainty regarding technique. This review describes the physiologic basis for warm blood cardioplegia in adult cardiac surgery and outlines the current basic and clinical research that evaluates the usefulness of this technique when compared with cold blood and crystalloid cardioplegia.

Key words: *Cardioplegic solutions/administration & dosage/therapeutic use; heart/physiopathology; heart arrest, induced/methods; myocardial reperfusion/methods; myocardial reperfusion injury/prevention & control; randomized controlled trials as topic; temperature; treatment outcome; ventricular function*

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Historical Background

One of the most pressing concerns after open heart surgery is perioperative myocardial damage. Surgeons must balance their actions between maintaining a motionless, bloodless field to facilitate surgical precision and limiting intraoperative myocardial damage. The optimal temperature for myocardial protection is still debated. Hypothermia was used as the mainstay for myocardial preservation from its discovery in the 1950s until the early 1990s.[1] The concept of myocardial arrest was first introduced in 1955 by Melrose and colleagues[2] and was traditionally accomplished by using hypothermic potassium-enriched cardioplegic solution. In 1977, terminal warm blood cardioplegia was reported to limit reperfusion injury after hypothermic cardioplegia,[3] and subsequent study results showed accelerated recovery and reduced metabolic derangement with this method.[4,5] In 1983, warm induction followed by cold cardioplegia was suggested for myocardial protection on the premise that inducing cardioplegia in the ischemic and energy- and substrate-depleted heart is the first phase of reperfusion and that warm induction could actively resuscitate the heart.[6] Continuous warm cardioplegia was introduced by Lichtenstein and colleagues[7] in 1989 in a single case report. It was thought that the use of continuous warm cardioplegia would close the loop, providing continued oxygen delivery and continued metabolism of the heart, avoiding ischemia altogether. After its introduction, retrograde continuous delivery became a popular method for warm cardioplegia,[8] and this practice evolved into alternating antegrade and retrograde delivery.[9] On the basis of animal studies by Tian and associates,[10] which showed that warm blood cardioplegia could be safely interrupted for up to 10 min, Calafiore and Mezzetti[9] reported clinical success with intermittent warm blood cardioplegia, which continues to be used today.

Physiologic Basis of Warm Blood Cardioplegia

Blood cardioplegic solution releases only 50% of its total oxygen content when cooled to 20 °C, and only 37% to 38% when cooled to 10 °C, because of the leftward shift of the oxyhemoglobin dissociation curve with hypothermia.[11] In addition, normothermic cardioplegic arrest results in an oxygen requirement of 1.1 mL oxygen/100 g/min, greater than 90% reduction of baseline values.[12] If oxygenated blood can reach

the arrested myocardium, oxygen demand can be met via warm cardioplegia. Oxygen demand is reduced to less than 0.3 mL/100 g/min at 20 °C.[12] However, reduction in intracellular concentrations of metabolites and high-energy phosphates and suboptimal recovery of contractile function after intermittent hypothermic cardioplegia suggests that anaerobic metabolism does not completely meet the substantially reduced metabolic needs of the arrested hypothermic heart.[13] In fact, researchers have found that extremely low myocardial temperatures (<10 °C) may inhibit energy-generating processes, such as glycolysis, more than they inhibit energy consumption.[14] Finally, hypothermia has been shown to destabilize cell membranes, inhibit sodium-channel pumps, and cause calcium sequestration, thus resulting in edema, reperfusion injury, and impaired sarcoplasmic reticulum function.[14-16]

Technical Considerations

Optimal Temperature. Most investigators have reported using warm cardioplegia at 37 °C, and others, at temperatures above 35 °C. In contrast, cold cardioplegia temperatures range between 4 and 15 °C, most below 10 °C.

Delivery Route. To induce cardiac arrest, warm blood cardioplegia can be delivered in an antegrade or retrograde fashion. In antegrade cardioplegia, the aorta is clamped and warm blood cardioplegic solution is delivered through the aortic root at a rate of 300 mL/min, along with a high-potassium cardioplegic mixture (target concentration, 20–25 mmol/L). Once the heart is arrested, a low-potassium solution (concentration, 7–10 mmol/L) is used at flow rates of 100 to 150 mL/min to maintain cardiac arrest. Warm blood cardioplegic solution containing at least 4 to 5 g of hemoglobin per 100 mL carries greater than 10 mL oxygen per 100 mL—more than enough to adequately oxygenate the arrested myocardium. In cases where myocardial activity resumes, repeat arrest can be accomplished with use of a high-potassium cardioplegic solution or lidocaine (50–100 mg). If myocardial activity continues, cardioplegic solution may be cooled to tepid or cold temperatures until the heart stops. To avoid hyperkalemia, ultrafiltration is recommended, and when the potassium level exceeds 5 mEq/L, the potassium concentration in the cardioplegic solution should be decreased.

Protecting the Right Side of the Heart. Cardiac venous drainage comprises 2 systems: the greater system drains approximately 70% of blood into the right atrium, and the lesser system drains approximately 30% of blood directly into the cardiac chambers.[17] The lesser system is composed of the arteriosinusoidal and Thebesian vessels.

Retrograde cardioplegia delivery enables 70% of blood to perfuse the arrested myocardium through the coronary sinus and 30% to enter the ventricular chambers through the Thebesian and arteriosinusoidal vessels. Arrest is initiated in an antegrade fashion, followed by retrograde flow of approximately 100 to 150 mL/min. Coronary sinus pressure is usually maintained between 30 and 50 mmHg and monitored continuously. It has been argued that flow to the right ventricle (RV) may be deficient in the retrograde approach because retrograde flow to the RV has been estimated to be 20% that of antegrade flow.[18] However, during arrest, the RV oxygen demand is lower than the 1.1 mL needed by the left ventricle (LV). Thus, retrograde delivery is sufficient to meet the requirements of the arrested right side of the heart.[19] In addition, retrograde delivery may provide more uniform distribution of cardioplegic solution in advanced coronary artery disease because it is delivered through the venous system, thus bypassing any coronary artery stenosis.

Higher flow rates of 250 to 300 mL/min are advisable for operations involving valves or dilated and hypertrophic hearts, which have higher metabolic demands.[20,21] A left superior vena cava is not an absolute contraindication to this technique, but intermittent antegrade cardioplegia may be preferable, or cardioplegia can be delivered through completed vein grafts. As an alternative, the left superior vena cava can be cannulated. Continuous warm blood cardioplegia may mask the surgical field during crucial parts of any operation. However, continuous cardioplegia is not necessary; it can be interrupted for up to 10 min for adequate exposure.[22]

Table I summarizes the technical aspects of warm cardioplegia.

Outcomes of Warm versus Cold Cardioplegia

The Warm Heart Trial, published in 1994, was among the first randomized trials to compare the results of warm and cold cardioplegia.[23] It included 1,732 patients randomized to intermittent antegrade warm or intermittent antegrade cold cardioplegia for coronary artery bypass grafting (CABG). Investigators found that myocardial enzyme release (12.3% vs 17.3%; P <0.001) and postoperative low-output syndrome (6.1% vs 9.3%; P <0.01) were lower after cardiac surgery in the warm group. However, there was no difference in nonfatal Q-wave myocardial infarction (MI), in-hospital mortality rates, or 30-day mortality rates.[23] At 84 months, the survival rate was significantly reduced in patients who had nonfatal perioperative outcomes, such as low-output syndrome (P <0.0001).[24] The original trial data showed that these nonfatal perioperative outcomes were significantly more prevalent among the cold group. A substudy of this trial by Christakis and colleagues[25] stratified patients into high, medium, and low risk. It showed a significant reduction in morbidity and mortality rates overall as defined by death, low-output syndrome, or MI: 15.9% (warm) versus 25.2% (cold) (P <0.01). The risk reduction was similar in all 3 risk categories, indicating that warm cardioplegia has a similar effect on outcomes among high-, medium-, and

TABLE I. The Ten Commandments of Warm Blood Cardioplegia

1. Maintain coronary sinus pressure >30 mmHg.
2. Maintain flow >100–150 mL/min in most cases.
3. Maintain flow >250 mL/min in surgery involving valves, or dilated or hypertrophic hearts.
4. Do not interrupt cardioplegia for >10 min.
5. If the potassium level is >5 mEq/L, reduce potassium delivery or give warm blood only.
6. If myocardial activity begins, resume high-potassium solution.
7. If activity continues, add lidocaine 50–100 mg to the cardioplegic solution.
8. If there is still activity, cool the cardioplegic solution.
9. Use ultrafiltration to prevent hyperkalemia.
10. Maintain systemic blood temperature at 32 °C.

low-risk patients.[25] A statistically insignificant reduction of in-hospital death was shown in multiple randomized trials around the same time.[26-29] Figure 1 shows an overview of the effect of warm cardioplegia on in-hospital mortality rates.

Mallidi and associates[30] conducted a prospective cohort study of 6,064 patients from 1989 through 2000 to evaluate the short- and long-term clinical outcomes of cold versus warm or tepid cardioplegia during CABG. The large sample size of this study enabled evaluation of low-frequency events. Cold cardioplegia was found to be an independent risk factor for early death or MI (adjusted odds ratio [OR]=1.70; 95% CI, 1.30–2.21; P <0.0001). They also reported significantly higher risk of postoperative intra-aortic balloon pump (IABP) insertion (OR=1.77; 95% CI, 1.31–2.39; P=0.0002) and low-output syndrome in the cold group (OR=1.71; 95% CI, 1.42–2.05; P=0.0006), but no significant difference in stroke risk. Patients were monitored for 6 years after their initial operation. Cold cardioplegia was not a significant predictor of late death alone (P=0.09) but did predict the combined endpoint of late death or MI (P=0.0001). Similar results were reported by investigators in a retrospective cohort study, which showed significant decreases in overall and in-hospital death, need for inotropic support, peak creatine kinase-myocardial band isoenzyme (CK-MB) levels, and intensive care unit stay in the warm versus cold group.[31] Other study results have not shown such clear benefits. Pelletier and colleagues[32] found no significant difference in clinical outcomes between groups, yet results of a retrospective cohort study indicated a detrimental effect of warm cardioplegia when aortic cross-clamp time was 75 min or longer.[33] Cardiac-related death was more prevalent in the warm group (P=0.015); however, this is the only study in the literature documenting a significantly inferior outcome of warm cardioplegia in the context of mortality rates.

Yau and associates[34] evaluated the effects of cardioplegia temperature on ventricular function. The authors concluded that although warm cardioplegia resulted in greater lactate production, recovery of oxygen consumption improved during reperfusion. This finding correlated clinically with increased preload-recruitable stroke work index and increased early diastolic relaxation. Therefore, ventricular recovery was found to be superior in warm versus cold cardioplegia. Landymore and colleagues[35] did not find LV stroke work index to be significantly different between warm and cold cardioplegia and concluded that both methods are suitable. Investigators in multiple studies have shown improved electrophysiologic function with the use of normothermic cardioplegia, which correlates clinically to fewer new or permanent conduction disturbances, including ventricular arrhythmia.[31,36,37]

The effects of cardioplegic temperature on clinical outcomes in aortic valve replacement surgery remain equivocal. In a prospective randomized study by Ascione and associates[38] in 2002, cold cardioplegia was associated with decreased myocardial ischemia in comparison with warm cardioplegia in patients undergoing valve replacement surgery. They found increased levels of lactate and troponin I, as well as a higher alanine/glutamate ratio, in patients in the warm-blood group.[38] These results were mirrored by those of a recent study in which warm blood cardioplegia was found to be inferior to cold crystalloid cardioplegia in patients with severely hypertrophic LVs who underwent aortic valve surgery.[39] These differences in myocardial markers of ischemia, however, do not appear to translate into inferior clinical outcomes. Calafiore and co-authors[40] retrospectively compared patients who underwent intermittent antegrade warm or intermittent antegrade cold cardioplegia for valve surgery and found significantly lower cardiac-related mortality rates in the warm cardioplegia group (P <0.01). There was also significantly higher recovery of

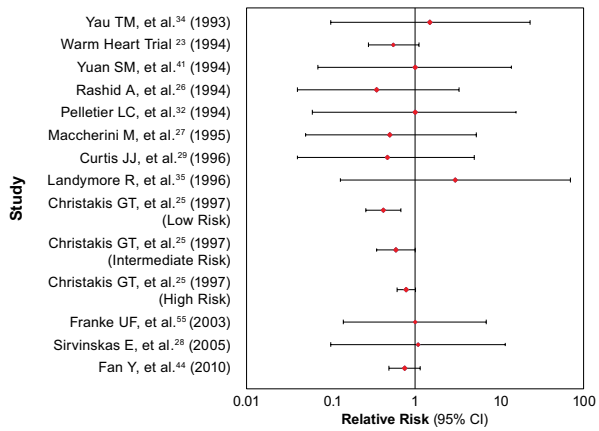

Fig. 1 *Forest plot shows the effect of warm cardioplegia on in-hospital mortality rates after cardiac surgery in 12 studies. The vertical line indicates a relative risk of 1.*

spontaneous rhythm (P <0.0001) and a lower incidence of low-output syndrome and ventricular dysrhythmia. These results have been corroborated by other investigators who have found higher rates of return of spontaneous rhythm, shorter postoperative ventilation times, and lower postoperative CK-MB levels in patients undergoing warm cardioplegia than in those undergoing cold blood or cold crystalloid cardioplegia.[41-43] The consensus is that warm cardioplegia is adequate, if not superior, in protecting hypertrophied LVs during valve procedures, provided that flow is adequate.

Caputo and colleagues[14] reviewed the history of and clinical evidence for intermittent warm cardioplegia. On the basis of results from several animal and human studies, they concluded that "intermittent warm cardioplegia is safe and effective." Fan and associates[44] conducted a meta-analysis of 41 randomized clinical trials that compared the outcomes of warm and cold cardioplegia after cardiac surgery. Collectively, the analysis included 5,879 patients—2,944 in the warm-blood group, 2,007 in the cold-blood group, and 928 in the cold crystalloid group. The study results showed no significant difference in all-cause death, MI, length of stay, postoperative atrial fibrillation, or IABP use, when comparing warm and cold cardioplegia. The authors, however, documented significant improvement in postoperative cardiac index (weighted mean difference [WMD]=0.28; 95% CI, 0.26–0.31; P <0.00001) with warm versus cold cardioplegia. The day 0 and peak cardiac troponin levels and peak CK-MB were all significantly lower in the warm cardioplegia group (WMD= –0.61; 95% CI, –1.04 to –0.17; P=0.006; WMD= –1.45; 95% CI, –2.47 to –0.42; P=0.006; and WMD= –8.03; 95% CI, –13.08 to –2.97; P=0.002, respectively). The authors concluded that both warm and cold cardioplegia were adequate for myocardial protection and that warm cardioplegia was associated with improved postoperative hemodynamic performance and less myocardial injury. The study, however, did not evaluate long-term outcomes.

Abah and associates[45] conducted a best-evidence review to answer whether warm or cold blood cardioplegia was superior for myocardial protection. They summarized the findings of 20 best-evidence studies, which included meta-analyses as well as prospective cohort, retrospective cohort, and randomized trials. The authors concluded that warm and cold cardioplegia have similar short-term mortality rates. They also found that warm cardioplegia reduces adverse postoperative events. A meta-analysis comparing blood and crystalloid cardioplegia included meta-regression analysis, which showed no relationship between the outcomes of death, MI, and low-output syndrome, delivery route, temperature, or timing of delivery.[46]

Most studies comparing warm and cold cardioplegia were done more than a decade ago. Many advances have been made in surgical equipment and cardiac care since that time, so updated studies are needed to provide a more accurate evaluation of clinical outcomes. In a more contemporary study, Candilio and colleagues[47] compared perioperative myocardial injury in patients who had antegrade cold-blood cardioplegia, cross-clamp fibrillation, or antegrade retrograde warm cardioplegia. They found a significantly lower level of perioperative high-sensitivity troponin T in the warm group than in the cold group (P=0.018) or the fibrillation group (P=0.044).[47] Results of a prospective observational study in 2015 showed no difference in perioperative MI or spontaneous return of rhythm between intermittent antegrade warm and cold cardioplegia, but IABP use and postoperative CK-MB levels were significantly lower in the warm group. Aortic cross-clamp time was not significantly different between the groups.[48] In contrast, intermittent warm cardioplegia had no statistically significant effect on clinical outcomes when compared with cold cardioplegia in a study by Kuhn and co-authors.[49] It did, however, result in greater endothelial injury quantified by levels of circulating endothelial cells, von Willebrand factor, and soluble thrombomodulin. Zeriouh and coworkers[50] analyzed perioperative outcomes and long-term survival after warm versus cold cardioplegia in emergency and elective CABG situations. They found no significant difference in perioperative results and similar long-term mortality rates between groups. The authors suggested that intermittent warm cardioplegia is more cost-effective than cold and should be used in both elective and emergency situations.[50]

Tables II and III summarize clinical study results.

Issues and Controversies

Delivery Route and Temperature

The ideal delivery technique and temperature for normothermic cardioplegia are still debated. Hayashida and colleagues[51] compared warm, tepid, and cold cardioplegia and antegrade versus retrograde delivery of each. They concluded that warm retrograde cardioplegia results in greater oxygen consumption and lactic acid release, as well as delayed ventricular recovery. Warm antegrade cardioplegia similarly increased oxygen consumption and lactic acid release, but it promoted the immediate restoration of ventricular function in high-risk patients. The LV stroke work index was significantly greater after warm antegrade and tepid antegrade cardioplegia than after cold antegrade cardioplegia (P <0.05) after 12 hours. Although cold cardioplegia reduced metabolic demand, functional delays in ventricular recovery limited its usefulness in resuscitation, according to the authors.[51] Tepid retrograde cardioplegia resulted in decreased oxygen consumption and metabolite release, yet ventricular recovery was slow. A tepid

TABLE II. Summary of Findings in Randomized Studies

Reference	Purpose	Findings
Yau TM, et al.[34] (1993)	Effects of cardioplegia temperature on ventricular function	Increased preload-recruitable stroke work index and increased early diastolic relaxation in warm group
Warm Heart Trial[23] (1994)	Risk of myocardial enzyme release, low-output syndrome, MI, death, and stroke in warm vs cold cardioplegia	No significant difference in mortality, stroke, or MI rates; reduction in myocardial enzyme release and low-output syndrome
Pelletier LC, et al.[32] (1994)	Comparison of warm and cold antegrade intermittent cardioplegia on clinical and biochemical outcomes	No significant difference in clinical outcomes (death, MI), but rates of increase of CK-MB and troponin T levels lower in warm group
Yuan SM, et al.[41] (1994)	Comparison of cold crystalloid and warm blood cardioplegia	Greater return of spontaneous rhythm in warm group; significantly shorter postoperative ventilatory support time in warm group
Rashid A, et al.[26] (1994)	Comparison of intermittent cold and continuous warm cardioplegia	Comparable myocardial protection in continuous warm and intermittent cold groups
Anderson WA, et al.[42] (1995)	Usefulness of retrograde warm cardioplegia for patients with LV hypertrophy undergoing AVR	No significant difference in myocardial ATP, CK-MB, or lactate production
Maccherini M, et al.[27] (1995)	Effect of warm vs cold cardioplegia on diaphragmatic paralysis	Warm cardioplegia eliminates diaphragmatic paralysis
Landymore R, et al.[35] (1996)	Evaluation of cardiac index, LV stroke work index, and myocardial oxygen consumption after warm or cold cardioplegia	No significant difference in any measure
Gozal Y, et al.[37] (1996)	Evaluation of electrophysiologic recovery after normothermic or hypothermic cardioplegia	Greater return of spontaneous rhythm in normothermic than in hypothermic patients
Curtis JJ, et al.[29] (1996)	Effect of warm vs cold cardioplegia on clinical outcomes	Longer cross-clamp time per graft with warm technique; no difference between groups in postoperative need for inotropic support, cardiac pacing, incidence of ventricular dysrhythmia, chest tube drainage, hospital stay, and death
Bouchart F, et al.[43] (1997)	Comparison of continuous warm blood, intermittent cold blood, and intermittent cold crystalloid technique to protect hypertrophied ventricles	All cardioplegia techniques safe for isolated aortic stenosis surgery, with continuous warm blood cardioplegia appearing to be best
Christakis GT, et al.[25] (1997)	Overall prevalence of morbidity and mortality in Warm Heart Trial, stratified by risk	Significant reduction in overall morbidity and mortality in warm group
Fremes SE, et al.[24] (2000)	Late survival and outcomes of Warm Heart Trial	Nonsignificantly higher 72-mo survival in warm group; 84-mo survival significantly reduced in those who had nonfatal perioperative outcomes
Ascione R, et al.[38] (2002)	Comparison of markers of myocardial ischemia in warm vs cold cardioplegia in patients undergoing AVR	Increased levels of lactate and troponin I and increased alanine/glutamate ratio in warm blood group
Kuhn EW, et al.[49] (2015)	Evaluation of endothelial injury after intermittent warm or intermittent cold cardioplegia	Warm cardioplegia associated with higher extent of endothelial injury than cold cardioplegia, without differences in clinical endpoints

ATP = adenosine triphosphate; AVR = aortic valve replacement; CK-MB = creatine kinase-myocardial band enzyme; LV = left ventricular; MI = myocardial infarction

antegrade technique was suggested to provide the best myocardial protection, not only in ensuring cardioplegic delivery but also in reducing metabolite demands.

Neurologic Complications

Engelman and associates[52] analyzed postoperative neurologic function and fibrinolytic potential among patients randomized to cold, tepid, and warm perfusate and cardioplegia during coronary revascularization surgery. The Mathew scale uniformly decreased postoperatively, but no significant distinction occurred between groups (P >0.5). The cold group had significantly more patients with clinically suspected stroke, but there was no significant difference in computed tomography–confirmed stroke incidence between groups (P=0.1). Another trial, by the Emory University group,[53] confirmed the similar effectiveness of normothermic and hypothermic cardioplegia for myocardial preservation but raised the possibility of an increased incidence of postoperative neurologic events. However,

TABLE III. Summary of Findings in Cohort and Observational Studies

Reference	Purpose	Findings
Flack JE 3rd, et al.[36] (1992)	Effect of cardioplegia temperature on postoperative conduction disturbances	Fewer conduction disturbances immediately postoperatively and at late follow-up in warm group
Calafiore AM, et al.[31] (1995)	Effect of cardioplegia temperature on death, recovery of spontaneous rhythm, low-output syndrome, and other clinical outcomes after AVR	No significant difference in all-cause death; lower cardiac-related death, low-output syndrome, and ventricular dysrhythmia; warm group had higher recovery of spontaneous rhythm, and shorter extubation time, intensive care unit stay, and hospital stay
Calafiore AM, et al.[40] (1996)	Clinical outcomes of patients undergoing AVR with use of intermittent antegrade warm vs intermittent antegrade cold cardioplegia	No significant difference in all-cause death, but warm group had significant decreases in cardiac-related death, incidence of low-output syndrome, dysrhythmia, awaking time, extubation time, bleeding, and intensive care unit stay
Mallidi HR, et al.[30] (2003)	Effect of warm vs cold cardioplegia on early death or MI, postoperative IABP, low-output syndrome, stroke, and survival at 60 mo	Increased incidence of early death or MI, IABP, and low-output syndrome in cold group; no significant difference in stroke or late mortality rates
Sirvinskas E, et al.[28] (2005)	Comparison of warm, tepid, and cold crystalloid cardioplegia	Lower postoperative troponin T, as well as shorter intubation time and length of hospital stay, in warm group
Liakopoulos OJ, et al.[33] (2010)	Comparison of death and major adverse cardiac events between warm and cold cardioplegia for aortic cross-clamp time >75 min	Increased all-cause and cardiac-related death and increased major adverse cardiac events in warm group
Candilio L, et al.[47] (2014)	Comparison of antegrade cold, antegrade retrograde warm, and cross-clamp fibrillation techniques	Significantly lower levels of high-sensitivity troponin T in warm group than in cold and fibrillation groups
Baig MA, et al.[48] (2015)	Comparison of intermittent antegrade warm blood cardioplegia and intermittent antegrade cold blood cardioplegia for myocardial protection	Better myocardial protection and less frequent use of IABP and lower peak CK-MB level in early postoperative period in warm group than in cold group
Zeriouh M, et al.[50] (2015)	Evaluation of warm and cold cardioplegia in emergency vs elective settings	Similar short- and long-term outcomes in cold and warm cardioplegia across elective and emergency settings
Nardi P, et al.[39] (2018)	Investigation of myocardial injury and short-term outcome in patients undergoing cold crystalloid or warm blood cardioplegia	Lower CK-MB, troponin I, and aspartate aminotransferase levels at time 0 in cold crystalloid group than in warm blood group; no significant difference in perioperative MI, postoperative major complications, or in-hospital mortality rates

AVR = aortic valve replacement; CK-MB = creatine kinase-myocardial band enzyme; IABP = intra-aortic balloon pump; MI = myocardial infarction

systemic normothermia is not necessary to administer warm blood cardioplegia. Moreover, the use of a partially occluding clamp technique for the construction of the proximal anastomoses and the use of hyperglycemic crystalloid solutions in the Emory trial may have exacerbated intraoperative neurologic injury. In a study where cardioplegic temperature was altered but cardiopulmonary bypass was performed at normothermia, there was no difference in stroke rates between cold, tepid, or warm cardioplegia groups.[54] Similarly, in studies where both warm and cold cardioplegia were performed with systemic hypothermia, stroke rates were low and did not differ significantly.[55] Thus, we recommend that, with warm cardioplegia, systemic perfusion be maintained at 32 to 33 °C to protect the brain.

Duration of Ischemic Intervals

Many surgeons opt not to use warm delivery because of their misconception that warm cardioplegia should not be interrupted. Initially, interrupting cardioplegic flow had been shown experimentally to be deleterious in porcine heart models.[56,57] However, many results of animal studies have since shown that warm cardioplegia may be safely interrupted for about 10 min without detrimental effects.[10,58,59] In one animal study, no detrimental effects were seen after ischemic periods of up to 15

min.[60] These findings correlated with those in human studies. Rousou and co-authors[22] studied the correlation between intermittent warm cardioplegia and negative clinical outcomes and found that repeatedly interrupting cardioplegic flow for up to 10 min per interruption and keeping the cumulative interruption time ≤45% of the arrest period has no adverse clinical or metabolic effects on the myocardium. Ali and Kinley[61] concluded that intermittent antegrade warm cardioplegia was safe when cross-clamp time was less than 90 min. Furthermore, Lichtenstein and associates[62] studied the effects of the longest single interruption as well as cumulative ischemic time during interrupted warm cardioplegia and found that the former has the largest effect on outcomes. They concluded that a reasonable margin of safety exists with intermittent antegrade warm blood cardioplegia, and that repeated interruptions of warm blood cardioplegia are unlikely to lead to adverse clinical results if single interruptions are shorter than 13 min.[62]

Right Ventricular Protection

Preserving the RV is a challenge during cardioplegic arrest, especially in patients who have an occluded right coronary artery that blocks antegrade flow. Retrograde flow provides a less robust distribution to the RV but may mitigate this problem. Honkonen and associates[63] found that recovery of RV function after coronary surgery is improved with warm continuous cardioplegia compared with intermittent cold cardioplegia. Kulshrestha and colleagues[19] studied RV ejection fraction (RVEF) pre- and postoperatively in patients undergoing retrograde warm cardioplegia and found no difference in postoperative RVEF but a significantly improved RV systolic work index (P <0.0001). Furthermore, results of a similar study showed improved RVEF in patients who had intermittent warm cardioplegia compared with those who had cold cardioplegia.[64] In the CABG Patch Trial, the rate of RV dysfunction after normothermic cardioplegia was lower than that after cold, suggesting that interrupted warm cardioplegia adequately protects the right side of the heart.[65]

Conclusion

A long history of experimental data indicates that warm blood cardioplegia during cardiac surgery is safe and effective. Care must be taken to maintain coronary sinus pressure between 30 and 50 mmHg, to maintain flow between 100 and 150 mL/min in CABG operations and higher than 250 mL/min in surgeries involving valves or dilated or hypertrophic hearts, and to ensure that cardioplegic delivery is not interrupted for longer than 10 min. Warm cardioplegia and cold cardioplegia result in similar short-term mortality rates, but warm cardioplegia may reduce adverse postoperative events and morbidity. In conclusion, warm cardioplegia protects the myocardium adequately during cardiopulmonary bypass operations, and its use should be continued.

References

1. 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(5):849-66.
2. Melrose DG, Dreyer B, Bentall HH, Baker JB. Elective cardiac arrest. Lancet 1955;269(6879):21-2.
3. Follette DM, Steed DL, Foglia RP, Fey KH, Buckberg GD. Reduction of postischemic myocardial damage by maintaining arrest during initial reperfusion. Surg Forum 1977;28:281-3.
4. Caputo M, Dihmis WC, Bryan AJ, Suleiman MS, Angelini GD. Warm blood hyperkalaemic reperfusion ('hot shot') prevents myocardial substrate derangement in patients undergoing coronary artery bypass surgery. Eur J Cardiothorac Surg 1998;13(5):559-64.
5. Teoh KH, Christakis GT, Weisel RD, Fremes SE, Mickle DA, Romaschin AD, et al. Accelerated myocardial metabolic recovery with terminal warm blood cardioplegia. J Thorac Cardiovasc Surg 1986;91(6):888-95.
6. Rosenkranz ER, Buckberg GD, Laks H, Mulder DG. Warm induction of cardioplegia with glutamate-enriched blood in coronary patients with cardiogenic shock who are dependent on inotropic drugs and intra-aortic balloon support. J Thorac Cardiovasc Surg 1983;86(4):507-18.
7. Lichtenstein SV, el Dalati H, Panos A, Slutsky AS. Long cross-clamp time with warm heart surgery. Lancet 1989;1(8652):1443.
8. Salerno TA, Houck JP, Barrozo CA, Panos A, Christakis GT, Abel JG, Lichtenstein SV. Retrograde continuous warm blood cardioplegia: a new concept in myocardial protection. Ann Thorac Surg 1991;51(2):245-7.
9. Calafiore AM, Mezzetti A. Intermittent antegrade normothermic blood cardioplegia. In: Salerno TA, editor. Warm heart surgery. Chicago: Mosby-Yearbook; 1996. p. 77-89.
10. Tian G, Xiang B, Butler KW, Calafiore AM, Mezzetti A, Salerno TA, Deslauriers R. A 31P-nuclear magnetic resonance study of intermittent warm blood cardioplegia. J Thorac Cardiovasc Surg 1995;109(6):1155-63.
11. Digerness SB, Vanini V, Wideman FE. In vitro comparison of oxygen availability from asanguinous and sanguinous cardioplegic media. Circulation 1981;64(2 Pt 2):II80-3.
12. Buckberg GD, Brazier JR, Nelson RL, Goldstein SM, McConnell DH, Cooper N. Studies of the effects of hypothermia on regional myocardial blood flow and metabolism during cardiopulmonary bypass. I. The adequately perfused beating, fibrillating, and arrested heart. J Thorac Cardiovasc Surg 1977;73(1):87-94.
13. Mauney MC, Kron IL. The physiologic basis of warm cardioplegia. Ann Thorac Surg 1995;60(3):819-23.
14. Caputo M, Ascione R, Angelini GD, Suleiman MS, Bryan AJ. The end of the cold era: from intermittent cold to intermittent warm blood cardioplegia. Eur J Cardiothorac Surg 1998;14(5):467-75.
15. Liu X, Engelman RM, Wei Z, Maulik N, Rousou JA, Flack JE 3rd, et al. Postischemic deterioration of sarcoplasmic reticulum: warm versus cold blood cardioplegia. Ann Thorac Surg 1993;56(5):1154-9.
16. Liu X, Engelman RM, Rousou JA, Flack JE 3rd, Deaton DW, Das DK. Normothermic cardioplegia prevents

intracellular calcium accumulation during cardioplegic arrest and reperfusion. Circulation 1994;90(5 Pt 2):II316-20.
17. Hochberg MS, Austen WG. Selective retrograde coronary venous perfusion. Ann Thorac Surg 1980;29(6):578-88.
18. Buckberg GD. Antegrade/retrograde blood cardioplegia to ensure cardioplegic distribution: operative techniques and objectives. J Card Surg 1989;4(3):216-38.
19. Kulshrestha P, Rousou JA, Engelman RM, Flack JE 3rd, Deaton DW, Wait RB, Hampf HM. Does warm blood retrograde cardioplegia preserve right ventricular function? Ann Thorac Surg 2001;72(5):1572-5.
20. Martella AT, Hoffman DM, Nakao T, Frater RW. Continuous normothermic retrograde cardioplegia for valve surgery. J Heart Valve Dis 1994;3(4):404-9.
21. Menasche P, Tronc F, Nguyen A, Veyssie L, Demirag M, Lariviere J, et al. Retrograde warm blood cardioplegia preserves hypertrophied myocardium: a clinical study. Ann Thorac Surg 1994;57(6):1429-35.
22. Rousou JA, Engelman RM, Flack JE 3rd, Deaton DW, Rifkin R, Elmansoury A. Does interruption of normothermic cardioplegia have adverse effects on myocardium? A retrospective and prospective clinical evaluation. Cardiovasc Surg 1995;3(6):587-93.
23. Randomised trial of normothermic versus hypothermic coronary bypass surgery. The Warm Heart Investigators. Lancet 1994;343(8897):559-63.
24. 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(19 Suppl 3):III339-45.
25. Christakis GT, Lichtenstein SV, Buth KJ, Fremes SE, Weisel RD, Naylor CD. The influence of risk on the results of warm heart surgery: a substudy of a randomized trial. Eur J Cardiothorac Surg 1997;11(3):515-20.
26. Rashid A, Fabri BM, Jackson M, Desmond MJ, Grech ED, Battistessa SA, Page RD. A prospective randomised study of continuous warm versus intermittent cold blood cardioplegia for coronary artery surgery: preliminary report. Eur J Cardiothorac Surg 1994;8(5):265-9.
27. Maccherini M, Davoli G, Sani G, Rossi P, Giani S, Lisi G, et al. Warm heart surgery eliminates diaphragmatic paralysis. J Card Surg 1995;10(3):257-61.
28. Sirvinskas E, Nasvytis L, Raliene L, Vaskelyte J, Toleikis A, Trumbeckaite S. Myocardial protective effect of warm blood, tepid blood, and cold crystalloid cardioplegia in coronary artery bypass grafting surgery. Croat Med J 2005;46(6):879-88.
29. Curtis JJ, Nawarawong W, Walls JT, Schmaltz RA. Continuous warm blood cardioplegia: a randomized prospective clinical comparison. Int J Angiol 1996;5(4):212-8.
30. 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. J Thorac Cardiovasc Surg 2003;125(3):711-20.
31. Calafiore AM, Teodori G, Mezzetti A, Bosco G, Verna AM, Di Giammarco G, Lapenna D. Intermittent antegrade warm blood cardioplegia. Ann Thorac Surg 1995;59(2):398-402.
32. Pelletier LC, Carrier M, Leclerc Y, Cartier R, Wesolowska E, Solymoss BC. Intermittent antegrade warm versus cold blood cardioplegia: a prospective, randomized study. Ann Thorac Surg 1994;58(1):41-9.
33. Liakopoulos OJ, Kuhn EW, Choi YH, Chang W, Wittwer T, Madershahian N, et al. Myocardial protection in cardiac surgery patients requiring prolonged aortic cross-clamp times: a single-center evaluation of clinical outcomes comparing two blood cardioplegic strategies. J Cardiovasc Surg (Torino) 2010;51(6):895-905.
34. Yau TM, Ikonomidis JS, Weisel RD, Mickle DA, Ivanov J, Mohabeer MK, et al. Ventricular function after normothermic versus hypothermic cardioplegia. J Thorac Cardiovasc Surg 1993;105(5):833-44.
35. Landymore R, Murphy JT, Hall R, Islam M. Randomized trial comparing intermittent antegrade warm blood cardioplegia with multidose cold blood cardioplegia for coronary artery bypass. Eur J Cardiothorac Surg 1996;10(3):179-84.
36. Flack JE 3rd, Hafer J, Engelman RM, Rousou JA, Deaton DW, Pekow P. Effect of normothermic blood cardioplegia on postoperative conduction abnormalities and supraventricular arrhythmias. Circulation 1992;86(5 Suppl):II385-92.
37. 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(6):1298-306.
38. Ascione R, Caputo M, Gomes WJ, Lotto AA, Bryan AJ, Angelini GD, Suleiman MS. Myocardial injury in hypertrophic hearts of patients undergoing aortic valve surgery using cold or warm blood cardioplegia. Eur J Cardiothorac Surg 2002;21(3):440-6.
39. Nardi P, Vacirca SR, Russo M, Colella DF, Bassano C, Scafuri A, et al. Cold crystalloid versus warm blood cardioplegia in patients undergoing aortic valve replacement. J Thorac Dis 2018;10(3):1490-9.
40. Calafiore AM, Teodori G, Bosco G, Di Giammarco G, Vitolla G, Fino C, Contini M. Intermittent antegrade warm blood cardioplegia in aortic valve replacement. J Card Surg 1996;11(5):348-54.
41. Yuan SM, Zhu LB, Li GS, Liu MH, Dong C, Yu YF, et al. Myocardial protection of cold crystalloid and warm blood cardioplegia. A comparative study. Chin Med J (Engl) 1994;107(7):515-20.
42. Anderson WA, Berrizbeitia LD, Ilkowski DA, Cha R, Gu J, Fernandez J, et al. Normothermic retrograde cardioplegia is effective in patients with left ventricular hypertrophy. A prospective and randomized study. J Cardiovasc Surg (Torino) 1995;36(1):17-24.
43. Bouchart F, Bessou JP, Tabley A, Hecketsweiller B, Mouton-Schleifer D, Redonnet M, et al. How to protect hypertrophied myocardium? A prospective clinical trial of three preservation techniques. Int J Artif Organs 1997;20(8):440-6.
44. Fan Y, Zhang AM, Xiao YB, Weng YG, Hetzer R. Warm versus cold cardioplegia for heart surgery: a meta-analysis. Eur J Cardiothorac Surg 2010;37(4):912-9.
45. Abah U, Garfield Roberts P, Ishaq M, De Silva R. Is cold or warm blood cardioplegia superior for myocardial protection? Interact Cardiovasc Thorac Surg 2012;14(6):848-55.
46. Sa MP, Rueda FG, Ferraz PE, Chalegre ST, Vasconcelos FP, Lima RC. Is there any difference between blood and crystalloid cardioplegia for myocardial protection during cardiac surgery? A meta-analysis of 5576 patients from 36 randomized trials. Perfusion 2012;27(6):535-46.
47. Candilio L, Malik A, Ariti C, Khan SA, Barnard M, Di Salvo C, et al. A retrospective analysis of myocardial preservation techniques during coronary artery bypass graft surgery: are we protecting the heart? J Cardiothorac Surg 2014;9:184.
48. Baig MA, Sher-I-Murtaza M, Iqbal A, Ahmad MZ, Farhan Ali Rizvi HM, Ahmed N, et al. Clinical outcomes of intermittent antegrade warm versus cold blood cardioplegia. J Pak Med Assoc 2015;65(6):593-6.

49. Kuhn EW, Choi YH, Pyun JM, Neef K, Liakopoulos OJ, Stamm C, et al. Endothelial injury associated with cold or warm blood cardioplegia during coronary artery bypass graft surgery. Biomed Res Int 2015;2015:256905.
50. Zeriouh M, Heider A, Rahmanian PB, Choi YH, Sabashnikov A, Scherner M, et al. Six-years survival and predictors of mortality after CABG using cold vs. warm blood cardioplegia in elective and emergent settings. J Cardiothorac Surg 2015;10:180.
51. Hayashida N, Ikonomidis JS, Weisel RD, Shirai T, Ivanov J, Carson SM, et al. The optimal cardioplegic temperature. Ann Thorac Surg 1994;58(4):961-71.
52. Engelman RM, Pleet AB, Rousou JA, Flack JE 3rd, Deaton DW, Gregory CA, Pekow PS. What is the best perfusion temperature for coronary revascularization? J Thorac Cardiovasc Surg 1996;112(6):1622-33.
53. Martin TD, Craver JM, Gott JP, Weintraub WS, Ramsay J, Mora CT, Guyton RA. Prospective, randomized trial of retrograde warm blood cardioplegia: myocardial benefit and neurologic threat. Ann Thorac Surg 1994;57(2):298-304.
54. Chocron S, Kaili D, Yan Y, Toubin G, Latini L, Clement F, et al. Intermediate lukewarm (20 degrees C) antegrade intermittent blood cardioplegia compared with cold and warm blood cardioplegia. J Thorac Cardiovasc Surg 2000;119(3):610-6.
55. Franke UF, Korsch S, Wittwer T, Albes JM, 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? Eur J Cardiothorac Surg 2003;23(3):341-6.
56. Matsuura H, Lazar HL, Yang XM, Rivers S, Treanor PR, Shemin RJ. Detrimental effects of interrupting warm blood cardioplegia during coronary revascularization. J Thorac Cardiovasc Surg 1993;106(2):357-61.
57. Ericsson AB, Kawakami T, Vaage J. Intermittent warm blood cardioplegia does not provide adequate myocardial resuscitation after global ischaemia. Eur J Cardiothorac Surg 1999;16(2):233-9.
58. Tonz M, Krogmann ON, Hess OM, Leskosek B, Mihaljevic T, von Segesser LK, Turina MI. Effect of intermittent warm blood cardioplegia on functional recovery after prolonged cardiac arrest. Ann Thorac Surg 1996;62(4):1146-51.
59. Kawasuji M, Yasuda T, Tomita S, Sakakibara N, Takemura H, Watanabe Y. Near-infrared monitoring of myocardial oxygenation during intermittent warm blood cardioplegia. Eur J Cardiothorac Surg 1997;12(2):236-41.
60. de Oliveira NC, Boeve TJ, Torchiana DF, Kantor HL, Titus JS, Schmidt CJ, et al. Ischemic intervals during warm blood cardioplegia in the canine heart evaluated by phosphorus 31-magnetic resonance spectroscopy. J Thorac Cardiovasc Surg 1997;114(6):1070-80.
61. Ali IM, Kinley CE. The safety of intermittent warm blood cardioplegia. Eur J Cardiothorac Surg 1994;8(10):554-6.
62. Lichtenstein SV, Naylor CD, Feindel CM, Sykora K, Abel JG, Slutsky AS, et al. Intermittent warm blood cardioplegia. Warm Heart Investigators. Circulation 1995;92(9 Suppl): II341-6.
63. Honkonen EL, Kaukinen L, Pehkonen EJ, Kaukinen S. Right ventricle is protected better by warm continuous than by cold intermittent retrograde blood cardioplegia in patients with obstructed right coronary artery. Thorac Cardiovasc Surg 1997;45(4):182-9.
64. Christakis GT, Buth KJ, Weisel RD, Rao V, Joy L, Fremes SE, Goldman BS. Randomized study of right ventricular function with intermittent warm or cold cardioplegia. Ann Thorac Surg 1996;61(1):128-34.
65. Flack JE 3rd, Cook JR, May SJ, Lemeshow S, Engelman RM, Rousou JA, Deaton DW. Does cardioplegia type affect outcome and survival in patients with advanced left ventricular dysfunction? Results from the CABG Patch Trial. Circulation 2000;102(19 Suppl 3):III84-9.