Myocardium Utilizes More Oxygen and Glucose During Tepid Blood Cardioplegic Infusion in Arrested Heart

Muharrem I. BADAK,1 MD, Ugur GURCUN,1 MD, Berent DISCIGIL,1 MD, Mehmet BOGA,1 MD, Erdem A. OZKISACIK,1 MD, and Emin A. ALAYUNT,2 MD

SUMMARY

The aims of this study were to evaluate myocardial metabolic activity during tepid blood cardioplegic infusion in the arrested heart in comparison with cold blood cardioplegia and to assess the early clinical outcomes of these patients.

Thirty patients undergoing first elective coronary artery bypass grafting surgery were included and randomized to two groups (T for tepid and C for cold), 15 patients in each. Myocardial protection was similar in both groups except for the reinfusion of blood cardioplegia, which was 6°C in group C and 28°C in group T (same temperature as the body perfusion). The route of cardioplegic reinfusion was antegrade during the first reinfusion and retrograde during the second reinfusion. In order to assess myocardial metabolic activity, myocardial oxygen consumption (MVO₂), myocardial glucose uptake, and myocardial lactate and acid production were all calculated. Arterial and coronary venous blood samples were obtained from the aortic root cannula and coronary sinus.

During cardioplegic reinfusions in the ischemic period, the calculated values of myocardial oxygen extraction, oxygen consumption, and glucose uptake were higher in group T than in group C (P < 0.05). This difference was observed during both antegrade and retrograde delivery of cardioplegic solution. Myocardial lactate production was greater in group C than in group T during cardioplegic reinfusion, both antegrade and retrogradely (P < 0.05). In all patients, cardiopulmonary bypass was terminated in the first attempt. The clinical outcome was similar in both groups.

The results of this study indicate that globally ischemic myocardium is able to utilize more oxygen and glucose during cardioplegic reinfusions at a tepid temperature in comparison to cold. In addition, the data showed evidence of less myocardial injury and better left ventricular function throughout the critical period of recovery from global ischemia for the heart protected by tepid cardioplegia. (Int Heart J 2005; 46: 219-229)

Key words: Tepid blood cardioplegia, Myocardial metabolism

It has been a challenge to develop optimal cardioplegic solutions and methods for delivery to improve the protective effect of the cardioplegic solution in open-
heart surgery. Blood cardioplegia was introduced in the 1970s and provides superior myocardial protection over crystalloid cardioplegia. Currently, a variety of methods are in use and subject to investigations in terms of delivery, pressure, time, and temperature of the cardioplegic solutions. Enrichment of the solution with metabolically active ingredients has also been shown to improve myocardial protection. Different temperatures of cardioplegic solution during induction were shown to have a significant impact on the metabolic activity of the heart. In the beginning, reducing the metabolic activity of the heart was considered to play a key role in protecting the myocardium from ischemia. Hypothermic cardioplegia was first introduced in the 1960s. Several studies then appeared suggesting that hypothermic cardioplegia may damage the myocardium and vascular endothelium. As a result of this, continuous normothermic blood cardioplegia was introduced. Since normothermic blood cardioplegia has often been used with normothermic body perfusion, this modality may expose the patients to a higher risk of the neurologic complications of open-heart surgery. Tepid (lukewarm) blood cardioplegia, which uses the same temperature throughout the entire body allowing moderate body hypothermia, was introduced to overcome this higher risk of neurologic complications of normothermia while providing more physiologic myocardial metabolic activity.

The aims of this study were to evaluate myocardial metabolic activity during tepid blood cardioplegic infusion in the arrested heart in comparison with cold blood cardioplegia and to assess the early clinical outcomes of these patients.

**METHODS**

Thirty patients undergoing their first elective coronary artery bypass graft operation were included in this prospective, randomized study comparing tepid and cold blood cardioplegia. Patients were asked to volunteer for the study and informed consent was obtained.

The patients were randomized into two groups (T for tepid and C for cold), 15 patients in each group. Exclusion criteria were the presence of concomitant heart valve disease, left ventricular aneurysm, unstable angina, or impaired left ventricular function. There were no significant differences between the two groups in terms of mean age, male-female ratio, extent of coronary lesions, left ventricular ejection fraction, functional status, or risk scoring of the patients (Table I).
Surgical technique: A Swan-Ganz catheter was placed through the internal jugular vein following endotracheal intubation. A median sternotomy was made, heparin given (3 mg/kg), aortic and two-stage venous cannulae were inserted, and a standard cardiopulmonary bypass carried out using moderate systemic hypothermia (28°C). In all patients, the left internal mammary artery was used for the left anterior descending coronary artery and a saphenous vein for the other coronaries. All distal anastomoses were performed under aortic cross-clamping while proximal anastomoses were made with a site-biting clamp on the ascending aorta.

Preparation and delivery of cardioplegic solution: In all patients, specially designed cardioplegic delivery cannulas (CalMed, Irvine, CA, USA) were inserted into both the aortic root and coronary sinus. Blood cardioplegia was prepared by mixing the pump blood with a high potassium crystalloid solution (20 mEq/L K+ in saline) in a 4:1 ratio and delivered using a cardioplegia system (Dideco, Mirandola, Italy). Immediately after cross-clamping of the ascending aorta, cardioplegia was given antegrade at a dose of 10 mL/kg with an aortic root pressure of 70 mmHg via an aortic root cannula proximal to the aortic clamp and cardiac arrest was achieved. The temperature of the cardioplegic solution was 37°C (warm induction) in both groups. Following each distal coronary anastomose, reinfusions of 200 mL of blood cardioplegia containing 10 mEq/L of potassium were given at a temperature of 6°C in group C and 28°C in group T (same temperature as the body perfusion). Reinfusion of cardioplegic solution was required twice during the cross-clamping period in all patients and the time interval of each cardioplegia infusion was 20 minutes. The route of cardioplegic
reinfusion was antegrade during the first reinfusion and retrograde during the second reinfusion. When given antegradely, aortic root pressure was maintained at 50 mmHg; when given retrogradely, coronary sinus pressure was maintained at 40 mmHg. Before the Cross clamp was removed, blood cardioplegia with the addition of a 20% mannitol solution (80 mL/L) was administered antegradely at a dose of 10 mL/kg at a temperature of 37°C (hot shot) for group C and 28°C (tepid shot) for group T. CPB was terminated when rectal temperature reached 36°C. Cardioplegic delivery pressures were measured via side ports attached to cardioplegia cannulas and coronary vascular resistance was calculated by dividing the pressure by the flow rate. Myocardial temperature was monitored throughout the aortic cross clamping period by inserting a temperature probe into the septum. Topical cooling was not used.

**Oxygen, lactate, and pH assays:** Metabolic activity, myocardial oxygen consumption (MVO₂), myocardial glucose uptake, and myocardial lactate and acid production were all calculated and comparisons were made in order to assess myocardial metabolic activity.

Arterial and coronary venous blood samples were obtained from the aortic root cannula and coronary sinus cannula just before the aortic Cross clamp was applied, then during reinfusions of blood cardioplegia during aortic Cross clamping, and finally immediately after the aortic Cross clamp was removed. During reinfusions, sampling was conducted when half of the calculated cardioplegia volume was given. Coronary venous blood was withdrawn at the time of antegrade delivery of cardioplegia while aortic root blood was sampled when cardioplegia was infused retrogradely.

Each blood sample was assayed for hemoglobin (Hb), partial pressure of oxygen (pO₂), carbon dioxide (pCO₂), pH, oxygen saturation (O₂ sat) (Roche, Omni C, Germany), and lactate and glucose levels.

Oxygen content was calculated as follows: oxygen content = 1.39 hemoglobin x oxygen saturation + 0.0031 oxygen tension. Myocardial oxygen extraction (O₂ Ext) was calculated as oxygen content of the arterial or cardioplegic blood minus the oxygen content of the coronary venous effluent (or aortic root blood proximal to the Cross clamp during retrograde delivery of cardioplegia). Myocardial oxygen consumption was then calculated by simply multiplying the oxygen extraction value by the flow rate of blood cardioplegia (MVO₂ = O₂ Ext × flow). Measurements were made at 37°C and corrected to the myocardial temperature that was recorded simultaneously with the blood sampling.

Myocardial glucose uptake was calculated in the same manner as oxygen extraction.

For lactate concentration, blood samples were mixed with a measured volume of 6% perchloric acid. Lactate concentration was measured in the protein-
free supernatant by an enzymatic method (Rapid Lactate Stat Pack kit; Calbiochem-Behring, La Jolla, CA). Myocardial lactate production was calculated as the lactate concentration of the coronary venous effluent (or aortic root effluent for retrograde delivery) minus the lactate concentration of the arterial blood or cardioplegic solution.

In order to calculate myocardial acid production, the hydrogen concentration ([H⁺]) of the blood sample was determined as [H⁺]=antilog (-pH). Myocardial acid production was then calculated in the same manner as lactate production.6)

Hemodynamic measurements: Heart rate (HR), mean arterial blood pressure (mABP), pulmonary artery pressure (PAP), right atrial pressure (RAP), and pulmonary capillary wedge pressure (PCWP) were measured and cardiac output (CO) was calculated using a thermodilution technique. All measurements were obtained immediately before and after the CPB period, and at 4, 12, and 24 hours postoperatively. Left ventricular stroke work index (LVSWI), right ventricular stroke work index (RVSWI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), and stroke volume index (SVI) were calculated for each sampling time using the monitor's computing system.

Creatine kinase measurement: Creatine kinase (CK) and its isoenzyme CKMB were measured in venous blood samples obtained immediately after and 6, 12, 24, 48, and 72 hours following removal of the aortic Cross clamp.

Clinical outcome: In the postoperative period, all patients were monitored for arrhythmia and ischemia on ECG. The need for inotropic support, use of intraaortic balloon pumping and in-hospital mortality in the two groups were compared.

Statistical analysis: All data were entered in the SPSS (10.0) statistical analysis program for Windows. The unpaired Student’s t-test was used to compare continuous variables. All parameters and the variances were homogeneous according to the Levene test. Comparisons of clinical parameters were evaluated by the chi-square analysis. Data are expressed as the mean ± standard deviation of the mean. Statistical significance was assumed at a probability level of less than 0.05.

RESULTS

The patient characteristics and intraoperative data were similar in the two groups, except for the septal myocardial temperature during cardioplegic arrest, which was higher in the tepid group (Table I).

Cardioplegic infusion rates, aortic root pressure, and coronary sinus pressure were similar in both groups (data not shown). Coronary vascular resistance was lower in group T during all cardioplegic infusions, however, it reached statistical significance only at the time of hot shot and tepid shot infusions prior
Cross clamp removal; 0.54 ± 0.11 versus 0.37 ± 0.09 mmHg/mL/min, in group C versus group T, respectively \( (P < 0.05) \).

**Myocardial metabolism during ischemia and reperfusion:** The two groups were similar in terms of preischemic (before Cross-clamp on) and postischemic (after Cross-clamp off) myocardial oxygen extraction, lactate production, and acid production. In the preischemic period, myocardial oxygen extraction was 5.2 ± 0.9 mL/dL versus 5.4 ± 1.1 mL/dL; lactate production was 4.6 ± 1.2 mmol/L versus 4.9 ± 1.5 mmol/L; acid production was 4.8 ± 0.8 mmol/L versus 5.5 ± 1.0 mmol/L in group T versus Group C, respectively \( (P > 0.05) \). In the postischemic period, myocardial oxygen extraction was 2.5 ± 0.6 mL/dL versus 2.4 ± 0.5 mL/dL; lactate production was 1.5 ± 0.4 mmol/L versus 1.8 ± 0.5 mmol/L; and acid production was 3.6 ± 1.0 mmol/L versus 4.5 ± 1.1 mmol/L in group T versus group C, respectively \( (P > 0.05) \).

During cardioplegic reinfusion in the ischemic period, the calculated values for myocardial oxygen extraction, oxygen consumption, and glucose uptake were higher in group T compared to group C (Table II, \( P < 0.05 \)). This difference was observed during both antegrade and retrograde delivery of cardioplegic solution (Table II).

In the ischemic period, myocardial lactate production was greater in group C than in group T during both antegrade and retrograde cardioplegic reinfusions, (Table II, \( P < 0.05 \)). However, there was no difference in acid production during cardioplegic reinfusions in the ischemic period (Table II).

**Hemodynamic measurements:** The hemodynamic measurements are summarized in Table III. There were no significant differences in heart rate or mean arterial pressure values between the two groups. Pulmonary capillary wedge pressure and cardiac index were also similar at all times measured. The only significant difference between the groups was noted in the early post cardiopulmonary bypass period, at which time hearts protected by tepid blood cardioplegia displayed a higher left ventricular stroke work index \( (P < 0.05) \).

Right atrial pressure (CVP) values were found to be higher in the tepid group at the 4\textsuperscript{th} and 12\textsuperscript{th} post-CPB, however, no other significant differences were observed in the hemodynamic measurements of right ventricular function (Table III).

**Postoperative release of creatine kinase:** In the tepid group, the release of CK-MB isoenzyme remained lower throughout the early postoperative course compared to the cold group. The difference reached statistical significance at 6, 12, and 24 hours postoperatively (Figure).
Clinical outcomes: In all patients, cardiopulmonary bypass was terminated in the first attempt. The number of patients who required defibrillation was significantly higher in the cold group (5 patients versus 1 patient; \( P < 0.05 \)). There were no hospital deaths, and no patient required intraaortic balloon pumping. One patient in the cold group needed inotropic drug administration postoperatively and one patient in the tepid group required reopening of the sternum because of bleeding. No patient had a perioperative myocardial infarction. No neurologic deficit, transient or permanent, was identified. Antiarrythmic drugs were needed in one patient in the cold group (for atrial fibrillation) and in two patients in the tepid group (for atrial fibrillation in one and frequent ventricular premature beats in the other).
Hypothermic cardioplegia has known protective effects on myocardium by its lowering of oxygen demand when the blood supply must be interrupted for technical advantages. However, its well-documented deleterious effects, including impairment of mitochondrial energy generation and substrate utilization, promoted the introduction of warm cardioplegia. Even though warm cardioplegia enhances myocardial aerobic metabolism, the necessity of continuous cardioplegia administration may interfere with the technical performance of the operation. Tepid cardioplegia was introduced recently since controversy exists on a safe duration of cardioplegia interruption under normothermic conditions. In addition to being as effective as the warm technique in promoting aerobic metabolism, tepid cardioplegia offered additional protection during cardioplegic interruptions.

Although there are many studies in the literature whose aims were to establish the optimum tepid temperature for minimal ischemic damage to the myocardium during cardioplegia, there is still no agreement. The temperatures of tepid cardioplegic solutions studied have ranged from 28 to 34°C. It has been reported that 34°C can be achieved by leaving the patient at the temperature of the operating room. The direction of the delivery of cardioplegia (antegrade/retrograde) and the frequency of the application (continuous/intermittent) were also different in the studies reported. With these variations in mind, we designed this study to compare the tepid temperature of 28°C (active cooling) with cold temperature for both directions (antegrade and retrograde) during intermittent application.
The results of the present study have demonstrated that a cardioplegic heart consumes more glucose and oxygen while producing less lactate during tepid blood cardioplegia infusions in comparison to cold cardioplegic solution (Table II). The direction of delivery of the cardioplegic solution, antegrade or retrograde, did not make any difference in terms of oxygen use and lactate production. Several studies have been published showing the status of myocardial metabolism during recovery from the cardioplegic arrested period. The present study provides additional information to the small number of published studies on myocardial metabolism at the time of cardioplegic infusion during Cross-clamping of the aorta.

Hayashida, et al reported that tepid cardioplegia produced a myocardial oxygen consumption similar to that of warm cardioplegia during cardioplegic arrest, suggesting the preservation of mitochondrial function. While myocardial oxygen consumption was greater with warm or tepid compared to cold, anaerobic lactate and acid washout was less with tepid or cold than warm blood cardioplegia. Lactate and acid washout were the lowest after tepid and the greatest after warm blood cardioplegia at the time of Cross-clamp release. It has been postulated that lactate production is a reflection of anaerobic metabolism, while glucose uptake and oxygen extraction reflect the aerobic metabolic state of myocardium.11)

Our report differs from Hayashida, et al in that tepid cardioplegia was given intermittently following each distal anastomosis and terminated with a tepid shot, while cold cardioplegia was given in the same fashion but terminated with a hot shot. Myocardial oxygen extraction, lactate production, and acid production did not differ between the tepid and cold cardioplegia groups in the postischemic period. This may be due to the warming effect of the terminal hot shot given in the cold cardioplegia group.

Postoperative hemodynamic stability, the course of cardiac enzymes, and clinical outcome are considered as the indicators used in assessing how well the myocardium is protected. However, myocardial metabolic measurements have been reported to be better indicators. The present study has clearly demonstrated how cardioplegic temperature can affect cardiac metabolism.12,13) The myocardium was able to use more oxygen and more glucose while producing less lactate compared to the cold group by increasing the temperature of the blood cardioplegic solution, such as in the tepid group. This more aerobic status of myocardial metabolism during cardioplegic reinfusions in the arrested heart might be the reason for the early recovery observed in the hearts protected by tepid blood cardioplegia. Since PCWP values were similar regardless of the cardioplegic solution used, the higher LVSWI values observed in the hearts protected by tepid
cardioplegia may be attributed to the increase in left ventricular diastolic compliance.

Tepid cardioplegia produced less myocardial injury as evidenced by the lower plasma levels of CK-MB throughout the first 24 hours following the cessation of cardiopulmonary bypass (Figure).

Higher Parsonnet scores indicate diffused proximal coronary artery diseases. In our study, since the Parsonnet scores of the patients were higher, we applied antegrade followed by retrograde cardioplegia to maximize its protective effect on myocardial metabolism. Electrical defibrillation was needed in only one patient in the tepid group, while it was required in five patients in the cold group after cross-clamp removal. It has been reported that returning to sinus rhythm spontaneously may be a sign of good protection of the myocardium during an ischemic period.14) The clinical outcomes of patients in both groups were similar. This may be due to the selection of study patients among the ones who did not have any other cardiac or systemic problems that may complicate the postoperative care.

In conclusion, the results of the present study demonstrate that globally ischemic myocardium was able to utilize more oxygen and glucose during cardioplegic reinfusions at a tepid temperature in comparison to a cold temperature. In addition, the data showed evidence of less myocardial injury and better left ventricular function throughout the critical period of recovery from global ischemia for the heart protected by tepid cardioplegia.

REFERENCES