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Randomized trial comparing intermittent antegrade warm blood cardioplegia with multidose cold blood cardioplegia for coronary artery bypass

Abstract
Forty patients were randomized to receive antegrade multidose warm (WBC) or cold blood cardioplegia (CBC) during coronary artery bypass. Cardioplegia was infused at a predetermined dose every 10 min during cardioplegia arrest and core temperature was maintained at 37 °C in both groups during extracorporeal circulation. Patient profiles were similar in the two groups. Cardiac index, left ventricular stroke work index, and myocardial oxygen consumption were measured before bypass and during the first 7 h of reperfusion. There was no significant difference in myocardial metabolic and function recovery, the incidence of myocardial infarction, low cardiac output or death. Our data suggests that similar protection is provided with the two techniques of myocardial protection. [Eur J Cardio-thorac Surg (1996) 10:179–184]

Key words
Myocardial revascularization • Blood cardioplegia • Randomized clinical trial

Introduction

Warm heart surgery, as described by Lichtenstein and colleagues [11], relies upon a continuous infusion of normothermic blood for myocardial preservation, thus differing radically from more contemporary techniques of myocardial protection, which have employed cold cardioplegia delivered in a multidose fashion. The continuous infusion of hyperkalemic blood is intended not only to maintain cardiac arrest but to provide the myocardium with sufficient oxygen to support aerobic metabolism.

Our institution gradually adopted warm heart protection as the preferred method of myocardial preservation 3 years ago. Although warm blood cardioplegia (WBC) was originally described as a continuous cardioplegia technique, in reality the delivery of WBC is often interrupted because the continuous infusion often obscures the operative field. As our experience with WBC increased, we observed that temporary interruption of the cardioplegia during coronary artery surgery did not appear to increase morbidity, as evidenced by the infrequent need for inotropic support and the uncomplicated clinical outcomes after warm heart protection. As more reports appeared in the literature describing the use of WBC, it became evident that other centers also frequently delivered WBC in a multidose fashion [13, 28]. Lichtenstein and colleagues [13] reported that the infusion of cardioplegia is often temporarily interrupted, on occasion for up to 15 min, in order to provide the surgeon with a bloodless operating field. Yau and associates [28] have also used WBC in a multidose fashion. Yau randomized 74 patients to receive continuous warm antegrade, continuous warm retrograde, or multidose cold antegrade blood cardioplegia during coronary bypass. Cardioplegia was interrupted for 39% of the total cross-clamp time during antegrade WBC and for 25% of the cross-clamp time during retrograde WBC. Recovery did not appear to be adversely affected by the intermittent delivery of WBC. Similarly we have shown, in our experimental laboratory, that systolic and diastolic function are preserved when WBC is temporarily interrupted for periods not in excess of 10 min [8].

Despite the fact that WBC is often delivered in a multidose fashion, there have been almost no investigations focusing specifically on the use of intermittent warm heart protection. We, therefore, designed this prospective ran-
domized clinical trial to examine the effects of multidose WBC on myocardial metabolic and functional recovery.

Patients and methods

Forty patients, after having given informed consent, were randomized to receive antegrade warm or cold WBC blood cardioplegia (CBC) during elective aortocoronary bypass. Patients were included if they had three-vessel coronary artery disease and had a left ventricular ejection fraction greater than 25% determined by biplane angiography. Patients were excluded if they required concomitant surgery of had undergone prior cardiac operations.

Anesthetic protocol

Cardiac medications were continued until the time of operation. Chloral hydrate in a dose of 1 g was administered the night before surgery. Oral diazepam, 0.1-0.2 mg/kg, and intramuscular morphine, 0.1-0.2 mg/kg combined with 25 mg of promethazine, were administered on the morning of the operation. Induction was accomplished with an infusion of propofol, 2 mg/kg, and anesthetic maintained until bypass with sufentanil, 0.03 µg/kg per min. This was combined with a variable infusion of propofol that was delivered in the range of 50 µg/kg per min and titrated in response to surgical stimulation.

During the induction phase an arterial line was placed in the radial artery and a thermodilution Swan-Ganz catheter was floated into the pulmonary artery. A coronary sinus catheter (Baim coronary sinus flow catheter, model 75-2337) was positioned in the distal coronary sinus with the aid of fluoroscopy and injection of radiopaque dye.

Cardiopulmonary bypass and cardioplegia protocols

Cardiopulmonary bypass was initiated with a Shiley bubble oxygenator. Arterial return was provided with a No. 24 argyle cannula and a single two-stage Sarns cannula was used for venous return. Normothermia was actively maintained during bypass, with the nasopharyngeal temperature at 37°C. Blood cardioplegia was administered with a Shiley-Buckberg cardioplegia administration set that delivered cardioplegia in a ratio of 4 parts blood: 1 part 0.9% normal saline. Potassium was the only additive to the cardioplegia. The concentration in the cardioplegia was 20 mEq K/L. Warm blood was administered at 37°C and the cold blood at 8°C. The heart was arrested when the heart was electromechanically arrested and at the beginning of cardioplegia reinfusion once a steady flow was maintained through the coronary sinus catheter.

Randomization and statistical analysis

Patients were randomized using a computer-generated series of random numbers. The patients were assigned to either WBC or CBC after the institution of cardiopulmonary bypass. The results were reported as the mean ± the standard error of the mean (SEM). Analysis of variance (ANOVA) was used to compare continuous variables. The Fisher exact test was used for comparisons of nominal data.

Results

A total of 40 patients were randomized to receive either WBC or CBC. The patient profiles of both groups are illustrated in Table 1. The age, number of grafts, mean arterial blood pressure during bypass, clamp time, and pump times were similar in the two groups. The ejection fraction measured 41 ± 1% in those patients randomized to CBC and 46 ± 3% in those patients assigned to WBC (P < 0.3). Of the 40 patients, there were only two patients with an ejection fraction of greater than 50%.

The core temperature during bypass was maintained actively at 37°C. Following bypass and during the first 7 h after cardioplegia arrest, the core temperature remained within the normothermic range in both groups. Cardioplegia arrest was induced by administering 822 ± 19 cc of blood cardioplegia to the CBC group and 910 ± 41 cc to the WBC group. Total cardioplegia administered during cold heart protection measured 2934 ± 180 cc and during warm heart surgery 3395 ± 201 cc (NS). Serum potassium, after cardioplegia arrest, measured 5 ± 0.1 mmol/l after CBC and 4.9 ± 0.1 mmol/l following warm heart protection. Spontaneous electromechanical activity occurred between reinfusion of cardioplegia in six patients receiving WBC and eight patients receiving CBC. The length of time required to complete each distal anastomosis varied from 4-21 min (mean 7.0 min) during warm heart surgery and from 4-16 min (mean 7.2 min) during CBC. After removal

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient profiles (CBC cold blood cardioplegia; WBC warm blood cardioplegia; BP mean blood pressure in mmHg)</th>
</tr>
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<tbody>
<tr>
<td><strong>CBC</strong></td>
<td><strong>WBC</strong></td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 ± 2*</td>
</tr>
<tr>
<td>Number of grafts</td>
<td>2.9 ± 0.2</td>
</tr>
<tr>
<td>Mean BP (Bypass)</td>
<td>54 ± 5</td>
</tr>
<tr>
<td>Clamp time (min)</td>
<td>45 ± 4</td>
</tr>
<tr>
<td>Bypass time (min)</td>
<td>85 ± 7</td>
</tr>
</tbody>
</table>

* ±SEM
of the aortic cross-clamp, spontaneous sinus rhythm resumed in 19 patients who had received WBC and 15 patients who had received cold heart protection.

Coronary sinus saturations during cardioplegia arrest

Samples were obtained from the coronary sinus catheter just before terminating the infusion of cardioplegia when cardiac arrest had been achieved. The coronary sinus was also sampled at the beginning of each reinfusion of cardioplegia. The saturation of the blood drawn from the coronary sinus varied from 97 to 100% towards the end of the initial infusion of WBC, after establishing a cardiac arrest, and from 95 to 100% during the initial infusion of CBC. After the cardioplegia had been interrupted for 10 min, the coronary sinus saturation had fallen to 78±3% during warm heart protection with the lowest recorded saturation measuring value 70%. In those patients receiving CBC, the saturations measured 84±2% after 10 min of ischemia with a saturation of 61% representing the lowest saturation (NS).

Myocardial metabolic and functional recovery

Cardiac index and left ventricular stroke work index were similar in the two groups before bypass (see Table 2). Post-bypass systolic function was preserved and not significantly different between the groups during the first 7 h of reperfusion. Myocardial oxygen consumption was also similar before cardioplegia arrest and was maintained during early recovery (see Table 3).

Morbidity and mortality after cardioplegia arrest

Inotropic support was required in four patients after WBC and in two following CBC. There was one myocardial infarction in each group, diagnosed by enzyme and electrocardiogram (ECG) criteria. The patient who suffered a myocardial infarction during WBC required insertion of an intra-aortic balloon (IABP) in addition to inotropic support. The rise in CPK-MB after surgery, excluding those two patients who had myocardial infarctions diagnosed by ECG and enzyme criteria, measured 40.5±18 U/l after CBC and 35.0±9 U/l following WBC (NS).

There was one death. One patient, who had been randomized to warm heart surgery, died within the first 24 h after operation. The patient was a 58-year-old male with an ejection fraction of 28%. Angiography demonstrated marked hypokinesis of the anterior wall of the left ventricle with critical disease involving the right coronary artery and occlusion of the left anterior descending coronary artery (LAD). Bilateral internal thoracic arteries were used to revascularize the LAD and right coronary arteries. He required inotropic support and the IABP to wean him from bypass. Twelve hours after operation he developed a profound low cardiac output state and expired 24 h after surgery. Autopsy demonstrated patent grafts. Unexpectedly, the autopsy demonstrated critical disease involving the circumflex coronary artery and infarction in this distribution. The angiogram had only demonstrated wall irregularities 7 months before. The remaining 39 patients were discharged without major complications. These were no strokes in either group.

Discussion

Warm heart protection evolved from an awareness that myocardial oxygen requirements may be reduced by as much as 90% by electromechanical arrest [4], that hypothermia may impair aerobic metabolism and mitochondrial function [15, 22], and from reports that indicated that secondary WBC and terminal WBC (“Hot Shot”) improve myocardial recovery [10, 25]. Since the original report by Lichtenstein and colleagues [11] 4 years ago, there have been numerous reports from European and North Ameri-

### Table 2 Myocardial function recovery after coronary bypass (Pre-CPB pre-bypass; Post-CPB immediately post-bypass, LVSWI left ventricular stroke work index; H1–H7 hours of reperfusion ± SEM throughout)

<table>
<thead>
<tr>
<th></th>
<th>Cardiac index (l/min per m²)</th>
<th>Cardiac index (l/min per m²)</th>
<th>LVSWI (gm-m/m² per beat)</th>
<th>LVSWI (gm-m/m² per beat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-CPB</td>
<td>2.2 ± 0.12</td>
<td>2.2 ± 0.15</td>
<td>32 ± 2.3</td>
<td>28 ± 1.9</td>
</tr>
<tr>
<td>Post-CPB</td>
<td>2.4 ± 0.12</td>
<td>2.8 ± 0.13</td>
<td>23 ± 1.8</td>
<td>27 ± 1.8</td>
</tr>
<tr>
<td>H1</td>
<td>2.4 ± 0.12</td>
<td>2.6 ± 0.13</td>
<td>27 ± 1.8</td>
<td>29 ± 2.1</td>
</tr>
<tr>
<td>H3</td>
<td>2.6 ± 0.13</td>
<td>2.5 ± 0.17</td>
<td>26 ± 1.7</td>
<td>20 ± 1.7</td>
</tr>
<tr>
<td>H5</td>
<td>2.5 ± 0.13</td>
<td>2.7 ± 0.14</td>
<td>23 ± 1.6</td>
<td>26 ± 1.2</td>
</tr>
<tr>
<td>H7</td>
<td>2.7 ± 0.14</td>
<td>2.7 ± 0.11</td>
<td>23 ± 1.5</td>
<td>25 ± 1.2</td>
</tr>
</tbody>
</table>

### Table 3 Myocardial metabolic recovery after coronary bypass (Pre-CPB pre-bypass; Post-CPB immediately post-bypass; MVO₂ myocardial oxygen consumption; H1–H7 hours of reperfusion ± SEM throughout)

<table>
<thead>
<tr>
<th></th>
<th>MVO₂ (warm) (ml/min)</th>
<th>MVO₂ (cold) (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-CPB</td>
<td>8.7 ± 0.8</td>
<td>8.9 ± 1.5</td>
</tr>
<tr>
<td>Post-CPB</td>
<td>8.9 ± 0.9</td>
<td>8.2 ± 1.3</td>
</tr>
<tr>
<td>H1</td>
<td>11 ± 1.5</td>
<td>9.8 ± 1.4</td>
</tr>
<tr>
<td>H3</td>
<td>14 ± 1.9</td>
<td>16 ± 2.2</td>
</tr>
<tr>
<td>H5</td>
<td>14 ± 1.6</td>
<td>13 ± 2.2</td>
</tr>
<tr>
<td>H7</td>
<td>15 ± 1.8</td>
<td>20 ± 5.5</td>
</tr>
</tbody>
</table>

There was no significant difference between the two groups before or after bypass.
can centers describing their experience with warm heart protection [12, 20, 21, 26]. However, these reports either lacked controls or used historical cohorts for comparison. More recently, however, there have been two large randomized clinical trials comparing warm heart protection with CBC [17, 27]. The Warm Heart Investigators [27] randomized 1732 patients to continuous WBC and normothermic bypass or multidose CBC and systemic hypothermia (25–30°C). They reported no significant differences in postoperative mortality or ECG evidence of myocardial infarction. However, serum CKP-MB and the incidence of low cardiac output was higher after CBC. Mellitt [17] has also recently reported a large series of patients randomized to warm or cold heart protection. A total of 1001 patients received either WBC or cold oxygenated crystalloid cardioplegia. There was no significant difference in mortality, the incidence of myocardial infarction, use of inotropic support or the use of the intra-aortic balloon. Although these two clinical studies represent the first randomized trials designed to compare WBC with cold heart protection, the patients were not truly comparable because the core temperature during bypass varied between the patient groups.

Patients randomized to WBC in both these trials [17, 27] were not actively cooled during bypass whereas core temperature was lowered to 25–28°C in those patients receiving cold heart protection. The differences in the core temperature during bypass may have adversely influenced the outcome of patients randomized to CBC owing to the known effects of systemic hypothermia on postoperative core temperature. Marelli and associates [16] reported that systemic hypothermia during bypass often leads to residual hypothermia during the first few hours after operation. Patients with core temperatures below 35.5°C after return to the Intensive Care Unit were more unstable than those patients with core temperatures above 35.5°C and had impaired functional recovery, as indicated by lower cardiac indices. Residual hypothermia after operation not only adversely influences myocardial recovery but has been recognized to precipitate myocardial ischemia [3]. More recently, Landymore [6] demonstrated the effects of systemic hypothermia on early recovery after WBC. Animals were randomized to normothermic bypass or systemic hypothermia (28°C). Cardiac arrest was maintained for 60 min with a continuous infusion of WBC. Systolic and diastolic function, assessed by pressure-volume analysis, although normal immediately after the termination of bypass and re-warming, gradually deteriorated in those animals randomized to systemic hypothermia as the core temperature drifted downwards during early recovery. In contrast, core temperature and myocardial recovery were well maintained following normothermic bypass. Thus, the patients randomized to cold heart protection in both these large clinical trials [17, 27] might have actually fared better than those patients receiving warm heart protection if the core temperature during bypass had not been a variable.

**Limitations**

Myocardial metabolic and functional recovery were well preserved in our patients after both techniques of myocardial protection. There was no difference in mortality or morbidity, the incidence of myocardial infarction, or low cardiac output syndrome. It is possible, however, that the sample size may not have been large enough to detect a difference, although the results from two recent, large, randomized trials [17, 27] have also failed to demonstrate any distinct advantage of warm heart surgery over contemporary techniques of myocardial preservation. The strength of this randomized study is related to the design, which not only controlled for core temperature but also for the dosage of cardioplegia. The core temperature was actively maintained at 37°C to avoid the effects of residual hypothermia on early myocardial recovery and cardioplegia was delivered in a prescheduled dosage and at a timed interval of 10 min throughout cardioplegia arrest. The only other article that refers directly to the use of intermittent warm blood was a paper that was recently published by Doyle and colleagues [2]. These authors compared 66 consecutive patients that had received WBC with two historical cohorts that had received cold crystalloid cardioplegia (68 patients) or CBC (41 patients). Unlike in our study, the patients were systemically cooled to 30°C. Doyle found that there was no significant difference in the incidence of myocardial infarction, the operative mortality, or other clinically significant parameters between the three groups.

**Tolerance of the myocardium to warm ischemia**

The arrested myocardium utilizes 1.5 cc O₂/100 g of myocardium per minute at 37°C which represents a decrease of 85–90% [4]. However, the oxygen consumption of the normothermic-arrested myocardium is actually 60% greater than the oxygen consumed by the arrested myocardium at 10°C, which translates into a reduction in the length of warm ischemia that may be tolerated by arrested myocardium. Landymore [5] measured coronary sinus lactate production and myocardial oxygen consumption during antegrade WBC. The infusion of cardioplegia was interrupted for periods that ranged from 1 to 10 min. Coronary sinus lactate concentration increased linearly with the duration of ischemia, while an oxygen debt occurred after 4–5 min of warm ischemia. In a subsequent experiment [7], animals were subjected to 5, 10, and 15 min of warm ischemia during antegrade WBC. Systolic and diastolic function were preserved until the duration of ischemia reached 15 min. Surprisingly, however, recovery was not adversely affected when antegrade WBC was administered in a multidose fashion every 15 min during a 90-min arrest, despite the fact that the myocardium had been subjected to multiple episodes of warm ischemia [7]. Similarly, excellent clinical outcomes have been associated
with the use of intermittent WBC although this has been temporarily interrupted for up to 15 min [13, 28]. The tolerance of the myocardium to warm ischemia during WBC may be explained in part by a phenomenon known as preconditioning.

Ischemic preconditioning

Ischemic preconditioning is a term that has been coined to describe the cardioprotective effects of brief, repetitive episodes of warm ischemia. Lange [9] has shown that repetitive ischemia in anesthetized dogs, surprisingly, was not associated with cumulative deterioration in myocardial function. The LAD was occluded for 5 or 15 min on three consecutive occasions. Each interval of ischemia was separated by 30 min of reperfusion. Regional wall motion deteriorated after the first episode of ischemia but was not influenced by subsequent ischemia. Swain [24] occluded the LAD for three 12-min intervals separated by 10 min of reperfusion. High energy phosphates decreased after the initial ischemia but were not unduly influenced by subsequent exposures to ischemia. Murray [19] compared the size of the myocardial infarction after coronary ligation in preconditioned and non-preconditioned dogs. Preconditioning was accomplished by four 10-min coronary occlusions separated by 5 min of reperfusion. Preconditioning reduced the size of the infarction by 25%. Although the mechanism of preconditioning is not fully understood, Liu [14] has shown that preconditioning activates the A1 adenosine receptors. Adenosine is known to exert a cardioprotective effect when administered during ischemia [1, 23].

Although warm ischemia during WBC does not fit the classical definition of preconditioning, it is plausible that these mechanisms may play a role during warm heart surgery. Recent experiments in our laboratory, employing WBC for myocardial protection, support this contention. In these experiments, animals were randomized to preconditioning or controls. The preconditioned animals were arrested with antegrade WBC. After the arrest, the hearts of the preconditioned group were subjected to three consecutive episodes of 10 min of warm ischemia followed by 10 min of reperfusion with WBC. These hearts were then subjected to 30 min of normothermic ischemia. The control animals were arrested with antegrade WBC and then were continuously perfused for 60 min with WBC followed by 30 min of warm ischemia. Myocardial functional recovery was better preserved in the group that had been preconditioned. These observations support the concept that multiple short episodes of warm ischemia may protect the myocardium from injury when antegrade WBC is interrupted during cardioplegia arrest.

Clinical implications

Cardioplegia was initially designed to provide the surgeon with a quiet, bloodless operating field. Antegrade WBC, although having some theoretical advantages over cold antegrade heart protection, does not provide the surgeon with a bloodless operating field, and often subjects the myocardium to warm ischemia. Thus, until warm heart protection has been shown to demonstrate clear superiority over CBC, a modified approach to myocardial preservation should be considered, which includes the use of frequent infusions of CBC while maintaining the core temperature in the range of 32–33 °C. Multidose CBC provides the surgeon with a dry operating field and avoids the pitfalls of normothermic ischemia. Modified core cooling protects the brain during periods of low flow or hypotension and reduces the incidence of residual hypothermia of 25–28 °C during cardiopulmonary bypass.

References


