Preconditioning during warm blood cardioplegia

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Received 8 July 1996; received in revised form 20 January 1997; accepted 11 February 1997

Abstract

Objective: Preconditioning describes the cardioprotective effects of multiple brief episodes of warm ischemia. The purpose of the study was to determine whether warm ischemia, during the intermittent delivery of warm blood cardioplegia, would induce preconditioning during cardioplegia arrest.

Methods: Dogs, 15, were randomized to a preconditioning protocol or to serve as controls. The control group received 60 min of continuous warm blood cardioplegia (WBC) followed by 30 min of warm arrested ischemia. The preconditioned group were arrested with WBC and then underwent three consecutive cycles consisting of 10 min of warm ischemia followed by 10 min of reperfusion. Reperfusion was provided by a continuous infusion of WBC. The preconditioning protocol was followed by 30 min of warm arrested ischemia. Myocardial functional recovery was assessed before cardiopulmonary bypass and cardioplegia arrest and again 30, 60 and 90 min after the arrest. Pressure-volume loops were used to measure the maximum elastance of the left ventricle ($E_{\text{max}}$), diastolic compliance, and used to calculate preload recruitable stroke work area.

Results: Myocardial functional recovery was better preserved after 30 min of warm arrested ischemia in those animals that had been preconditioned.

Conclusion: Preconditioning may be induced when warm blood cardioplegia is delivered intermittently during cardioplegia arrest. © 1997 Elsevier Science B.V.

Keywords: Arrest; Blood; Cardioplegia; Preconditioning

1. Introduction

Continuous warm blood cardioplegia maintains cardiac arrest and provides the myocardium with sufficient oxygen for aerobic metabolism [1]. Although the concept is attractive, the infusion of cardioplegia into the coronary circulation frequently obscures the operative field. This technical problem is often managed by temporarily interrupting the cardioplegia which subjects the myocardium to brief periods of warm ischemia [2,3]. Cardioplegia may be interrupted for as long as 15 min with the cumulative ischemia representing as much as 88% of the total cross-clamp time [3].

The cardioprotective effects of multiple brief episodes of warm ischemia have been reported in many earlier publications [4–8]. Although preconditioning is known to limit the size of myocardial infarction, more recent reports have shown that preconditioning may reduce myocardial stunning in models of reversible global ischemia [9–13]. In our experimental laboratory [14] we have examined the effects of multidose warm blood cardioplegia on myocardial metabolic and functional recovery. Adult mongrel dogs were randomized to receive intermittent warm or cold heart protection every 15 min during a 90 min arrest. Multiple pressure-volume loops were used to assess left ventricular function. Myocardial recovery was well preserved after multidose warm blood cardioplegia despite the fact that the myocardium had been subjected to warm ischemia [15]. These observations suggest that warm ischemia during cardioplegia arrest may induce myocardial preconditioning. To test this hypothesis, we preconditioned the myocardium during warm blood cardioplegia in an experimental animal model.
2. Methods

Adult mongrel dogs, 15, weighing between 20 and 25 kg were randomized to a preconditioning protocol or to serve as controls. The animals were cared for using the guidelines set forth by the Canadian Council on Animal Care.

2.1. Anaesthesia preparation

Anaesthesia was induced and maintained with sodium pentobarbital. After intubation, the animals were ventilated with a volume-regulated ventilator. Blood pressure was continuously monitored with an 8F USCI catheter (C.R. Bard, Bellerica, MA) positioned in the right femoral artery. Heparin sodium was administered in a dose of 4 mg/kg after performing a median sternotomy. An additional 30 mg of Heparin was added to the pump prime. The left femoral artery was cannulated with a 16F USCI cannula in preparation for cardiopulmonary bypass. A 5F Millar microtransducer-tipped catheter (Millar Instruments, Houston, TX) and a specially designed 7F conductance catheter were passed through the apex of the left ventricle. Two # 34 USCI cannulas, positioned in the superior and inferior vena cava, provided venous return during cardiopulmonary bypass. Extracorporeal circulation was established with a Medtronic Impeller Pump (Model 1835; Medtronic, Cardiovascular Systems Division, Roseville, MA) that would deliver non-pulsatile flow at a rate of 2.5 l/min per m². The core temperature was maintained at 37°C. The cava were snared and both ventricles were vented in order to ensure that the ventricles remained empty during cardioplegia arrest.

2.2. Myocardial preservation and preconditioning protocols

Cardiac arrest was initiated and maintained with warm antegrade blood cardioplegia. Ringers Lactate, 1 L, containing 80 mmol of K/l (High-Potassium Cardioplegia) or 20 mmol of K/L (Low-Potassium Blood cardioplegia) was delivered in a ratio of 1 part crystalloid to 4 parts blood. The cardioplegia was infused with a Shiley-Buckberg blood cardioplegia administration set (Shiley, 17600 Gillette Ave., Irvine, CA). The control group was arrested with warm high-potassium blood cardioplegia. After establishing an arrest, low-potassium warm blood cardioplegia was infused continuously into the ascending aorta at a rate of 150 cc/min, for a period of 60 min. The cardioplegia was then discontinued and the heart was subjected to 30 min of warm arrested ischemia. The preconditioned group were arrested with high-potassium warm blood cardioplegia. The myocardium was then preconditioned with three cycles of warm ischemia alternating with reperfusion. Each cycle consisted of 10 min of ischemia followed by 10 min of reperfusion (total of 60 min). The heart was reperfused during each 10 min period of reperfusion with continuous low potassium warm blood cardioplegia delivered at a rate of 150 cc/min. The preconditioned animals were then subjected to 30 min of warm arrested ischemia. The aortic cross-clamp was removed in both groups after 30 min of warm arrested ischemia. Cardiopulmonary bypass was discontinued 30 min later.

2.3. Myocardial hemodynamic function

Systolic and diastolic function of the left ventricle was determined from the simultaneous measurements of left ventricular pressure and volume [16,17]. Pressure was measured with a 5F Millar microtransducer tipped catheter (frequency response, 0–24 kHz). Volume was measured with a specially constructed 7F conductance catheter. The catheter contained eight electrodes. The proximal and distal electrodes served as the transmitting electrodes and were excited from a 24-V, 20 kHz source, which delivered a current of 100 μA. The other six electrodes served as the sensing electrodes. Simultaneous pressure and volume measurements were processed with a PC 486 computer which generated pressure-volume loops for each set of measurements. A new pressure-volume loop could be generated, processed, and stored every 2 s. Specially designed software was used to calculate the maximum elastance of the left ventricle ($E_{\text{max}}$), end-diastolic compliance, and recruitable stroke work (RSW). RSW was indexed to heart weight.

Hemodynamic measurements were made during rapid volume loading through the femoral artery cannula. Measurements were made before bypass and at 30, 60 and 90 min after the arrest. Blood gases were analyzed before each hemodynamic measurement and acidosis, when present, was corrected with sodium bicarbonate.

Left ventricular stroke work was calculated for each pressure-volume loop at each measured end-diastolic volume. Linear regression analysis of recruitable stroke work plotted against end-diastolic volume was used to determine the preload recruitable stroke work end-diastolic volume relationship. Preload recruitable stroke work area was defined as the area under the regression curve extrapolated to an end-diastolic volume of 50 ml [18]. The calculations were made using the following formula:

$$\text{PRSWA} = \frac{1}{2} M_{sw}(50 - V_{sw})^2$$

Where, PRSWA is the preload recruitable stroke work area, $M_{sw}$ is the slope of the regression curve, $V_{sw}$ represents the intercept and 50 is the extrapolation of the data to an end-diastolic volume of 50 ml.
3. Results

S.E of the mean. Analysis of variance (ANOVA) was used to analyze the data. The remaining animals in both groups went into spontaneous ventricular fibrillation, after unclamping the aorta, which was easily defibrillated.

Eight animals served as the controls. Seven animals were randomized to a control group or a preconditioning group. Inotropes were not used in any of the animals. Two animals in each group resumed sinus rhythm after removal of the aortic cross-clamp. The remaining animals in both groups went into spontaneous ventricular fibrillation, after unclamping the aorta, which was easily defibrillated.

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Diastolic compliance, reflecting the end diastolic pressure-volume relationship, was not significantly different between the two groups after bypass (Table 3). Comparison of diastolic compliance before and after cardioplegia arrest in each group also failed to demonstrate any significant change in diastolic function.

3.2. Discussion

As experience has been gained with the use of warm heart protection, an increasing number of centers have begun using intermittent warm blood cardioplegia because of the technical difficulties encountered with continuous blood cardioplegia. Pelletier and colleagues [21] randomized 200 patients, undergoing coronary artery bypass, to receive either intermittent antegrade warm blood cardioplegia or multidose cold blood cardioplegia. The core temperature was allowed to drift to 33–34°C. Cardioplegia was reinfused after each distal anastomosis; the duration of warm ischemia being minimized to less than 15 min. The mortality, the incidence of myocardial infarction, and the use of inotropic support was similar in both groups. Calafiore [3] used intermittent antegrade warm blood cardioplegia in 250 consecutive patients undergoing myocardial revascularization. These patients were compared with a cohort of patients who had multidose cold blood cardioplegia. Moderate systemic hypothermia was employed.

This method of analysis was chosen because both Krukenkamp [19] and Glower [20] have emphasized that the recruitable stroke work end-diastolic volume relationship best describes the overall systolic function of the left ventricle. This relationship is linear and is independent of preload and heart rate in contrast to the curvilinear relationship between stroke work and filling pressures.

2.4. Statistical methods

Results have been reported as the arithmetic mean ± S.E of the mean. Analysis of variance (ANOVA) was used for statistical comparisons.

3. Results

Mongrel dogs, 15, weighing 25 ± 0.8 kg were randomized to a control group or a preconditioning group. Eight animals served as the controls. Seven animals underwent a preconditioning protocol. All but one animal in the control group completed the study. In this animal a complete set of measurements could not be obtained at 90 min due to progressive deterioration in left ventricular function. Inotropes were not used in any of the animals. Two animals in each group resumed sinus rhythm after removal of the aortic cross-clamp. The remaining animals in both groups went into spontaneous ventricular fibrillation, after unclamping the aorta, which was easily defibrillated.

3.1. Measurements of left ventricular function

Preload recruitable stroke work area (PRSWA) was similar in both groups before cardioplegia arrest (Table 1). Comparison of PRSWA between groups at 30 min after cardioplegia arrest demonstrated significantly better systolic function in the preconditioned animals (P < 0.02). PRSWA was higher in the preconditioned group at 60 min but the difference was not significant (P < 0.13). However, PRSWA 90 min after the arrest was significantly higher in the preconditioned animals P < 0.02). Comparison of PRSWA before and after cardioplegia arrest within each group demonstrated that PRSWA was significantly lower in the control group at 30 min (Table 1). PRSWA returned to normal in the preconditioned animals at 90 min but remained depressed in the control group.

The maximum elastance of the left ventricle is illustrated in Table 2. There was no significant differences in Emax between the two groups after bypass. However, comparison of Emax before and after cardioplegia arrest in each group indicated that Emax was significantly lower in both groups at 30 min (Table 2). Systolic function remained significantly depressed in the control group at 60 and 90 min but returned to normal in the preconditioned animals 60 min after cardioplegia arrest.

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| Table 1 |
| Myocardial functional recovery before cardiopulmonary bypass and again 30, 60 and 90 min after the arrest |
| PRE-B | R² | Time (min) after cardioplegia arrest |
|       |     | 30 min | R² | P value | 60 min | R² | P value | 90 min | R² | P value |
| Control | 24 073 ± 1920 | 88 | 12 604 ± 2713 | 91 | <0.003 | 19 208 ± 3703 | 86 | <0.08 | 19 375 ± 3128 | 91 | <0.14 |
| Pre-C  | 32 000 ± 4997 | 95 | 22 271 ± 2408 | <0.2 | <0.22 | 26 923 ± 2825 | 87 | <0.22 | 31 893 ± 3425 | 95 | <0.36 |

Values are expressed as mean ± S.E. of the preload recruitable stroke work area (J/beat per 100×10⁻⁴ g).

PRE-C refers to those animals randomized to the preconditioning protocol. PRE-B represents the measurements made before cardiopulmonary bypass.Measurements after cardioplegia arrest were compared with pre-bypass measurements.

P values represent ANOVA comparisons within each group. Statistical comparisons between groups are found in the text.

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Cardioplegia was infused after each distal anastomosis with the duration of warm ischemia not exceeding 15 min. Interestingly, Calafiore reported that mortality, the incidence of low cardiac output syndrome, and peak CPK-MB was actually lower in those patients who had received intermittent warm blood cardioplegia. Mezzetti [22] randomized 30 patients, undergoing mitral valve operations, to receive antegrade multidose warm or cold blood cardioplegia. The core temperature was maintained at 37°C in the warm group and 27°C in those patients receiving cold heart protection. Cardioplegia was administered at least every 15 min. Myocardial metabolic and functional recovery was better in those patients protected with warm blood cardioplegia. Landymore and Associates [23] randomized 40 patients, undergoing coronary artery bypass, to receive multidose warm or cold antegrade blood cardioplegia. Unlike the three proceeding studies, the blood cardioplegia was delivered precisely every 15 min and both groups were maintained at 37°C during cardiopulmonary bypass. The only difference between the two groups, therefore, was the temperature of the cardioplegia. The mortality, the incidence of myocardial infarction, and myocardial metabolic and function recovery were similar in both groups. These studies report uncomplicated recoveries after multidose warm blood cardioplegia despite the fact that the heart has been subjected to multiple brief periods of warm ischemia.

Cardioplegia arrest reduces the energy requirements of the non-working heart from 6–8 ml O2/min per 100 g myocardium to 1–1.5 cc O2/min per 100 g of myocardium [15,24]. Although hypothermia contributes to myocardial preservation by lowering energy requirements, 85–90% of the protection derived from cardioplegia is related to the cessation of electromechanical activity. It was this reasoning that led Lichtenstein [1] to develop the concept of continuous warm blood cardioplegia for myocardial protection. Although described as a continuous cardioplegia technique, the cardioplegia is almost never delivered continuously and is frequently temporarily interrupted for periods of 10–15 min. Realizing that the intermittent delivery of warm blood cardioplegia must subject the myocardium to warm ischemia, we measured oxygen consumption and lactate production during intermittent warm blood cardioplegia [15]. Lactate production increased in a linear fashion for the duration of the ischemia and oxygen debt occurred in less than 5 min after interrupting the delivery of cardioplegia. Since multiple brief periods of warm ischemia appear to be well tolerated, as evidenced by preserved myocardial functional recovery after intermittent warm blood cardioplegia, it is plausible that the tolerance of the myocardium to warm ischemia might be secondary to ischemic preconditioning.

The preconditioned animals in this study received three 10 min periods of warm ischemia in order to simulate the ischemia that would occur when cardioplegia is temporarily interrupted during the completion of a distal coronary anastomosis. The myocardium was reperfused after each period of ischemia in order to follow a traditional preconditioning protocol. The control group received continuous warm blood during the same time frame, at a rate that would not subject the heart to warm ischemia, so that the control group would have an identical duration of cardiopulmonary bypass. Both groups were then subjected to 30 min of warm arrested ischemia. Although 30 min of ischemia during cardioplegia arrest is not analogous to the clinical situation, a period of prolonged ischemia is necessary in order to prove or disprove the hypothesis that warm ischemia during warm blood cardioplegia precondition the myocardium.

Our data have demonstrated that brief periods of warm global ischemia during cardioplegia arrest, proceeding a period of prolonged ischemia, reduces myocardial stunning. Systolic function, assessed from measurements of PRSWA and $E_{\text{max}}$, was better preserved in preconditioned animals. Not only were PRSWA and $E_{\text{max}}$ higher after cardioplegia arrest in the preconditioned animals but both these indices of systolic function had normalized at 90 min after the arrest. In contrast, PRSWA and $E_{\text{max}}$ never returned to baseline values in the control group.

Our data explain why the will tolerate multiple, brief periods of ischemia during cardioplegia arrest. Our observations, however, should not be inter-
Asimakis G, Inners-McBride K, Medellin G, Conti V. Ischaemic
sis.
off temporarily in order to complete a distal anastomo-
cognoscente of the fact the heart is being subjected to
originally described by Lichtenstein while being
blood cardioplegia in an almost continuous fashion as
interpreted to suggest that it is recommended to continually
subject the myocardium to warm ischemia. On the
contrary, every effort should be made to use warm
blood cardioplegia in an almost continuous fashion as
originally described by Lichtenstein while being
warm ischemia when the cardioplegia must be turned
off temporarily in order to complete a distal anastomosis.

References


Table 3

Diastolic compliance (mmHg/cc)

<table>
<thead>
<tr>
<th></th>
<th>R²</th>
<th>30 min</th>
<th>R²</th>
<th>60 min</th>
<th>R²</th>
<th>90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.2 ± 0.5</td>
<td>99</td>
<td>7.4 ± 0.7</td>
<td>99</td>
<td>NS</td>
<td>7.1 ± 0.6</td>
</tr>
<tr>
<td>PRE-C</td>
<td>6.8 ± 0.2</td>
<td>98</td>
<td>6.1 ± 0.7</td>
<td>70</td>
<td>NS</td>
<td>6.1 ± 0.3</td>
</tr>
</tbody>
</table>

PRE-C refers to those animals in the preconditioned group. Pre-B represents those measurements made before bypass. P values represent ANOVA comparisons within groups before and after bypass. Statistical comparisons between groups are found in the text.