Myocardial injury in hypertrophic hearts of patients undergoing aortic valve surgery using cold or warm blood cardioplegia

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Abstract

Objectives: Myocardial protection techniques during cardiac surgery have been largely investigated in the clinical setting of coronary revascularisation. Few studies have been carried out on patients with left ventricular hypertrophy where the choice of delivery, and temperature of cardioplegia remain controversial. This study investigates metabolic changes and myocardial injury in hypertrophic hearts of patients undergoing aortic valve surgery using antegrade cold or warm blood cardioplegia. Methods: Thirty-five patients were prospectively randomised to intermittent antegrade cold or warm blood cardioplegia. Left ventricular biopsies were collected at 5 min following institution of cardiopulmonary bypass, 30 min after cross-clamping the aorta and 20 min after cross-clamp removal, and used to determine metabolic changes during surgery. Metabolites (adenine nucleotides, amino acids and lactate) were measured using high pressure liquid chromatography and enzymatic techniques. Postoperative myocardial troponin I release was used as a marker of myocardial injury. Results: Ischaemic arrest was associated with significant increase in lactate and alanine/glutamate ratio only in the warm blood group. During reperfusion, alanine/glutamate ratio was higher than preischaemic levels in both groups, but the extent of the increase was considerably greater in the warm blood group. Troponin I release was markedly (P < 0.05, Mean ± SD) lower at 1, 24 and 48 h postoperatively in the cold compared to the warm blood group (0.51 ± 0.37, 0.37 ± 0.22 and 0.27 ± 0.19 vs. 0.75 ± 0.42, 0.73 ± 0.51 and 0.54 ± 0.38 ng/ml for cold vs. warm group, respectively). Conclusions: Cold blood cardioplegia is associated with less ischaemic stress and myocardial injury compared to warm blood cardioplegia in patients with aortic stenosis undergoing valve replacement surgery. Both cardioplegic techniques, however, confer sub-optimal myocardial protection. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Ischaemia; Reperfusion; Valve (disease); Hypertrophy; Energy metabolism

1. Introduction

The heart muscle can adapt to environmental changes by altering the metabolic rates of specific proteins or, in the short term, by changing flux through metabolic pathways to maintain its state of equilibrium [1]. In hearts with aortic stenosis, left ventricular hypertrophy leads to increases in left ventricular end-diastolic volume and pressure, myocardial work and oxygen demand [2]. The metabolic state of severely hypertrophied myocardium is anaerobic [3]. This is likely to make the heart more vulnerable to ischaemia and reperfusion injury, a situation seen during open heart surgery.

Major advances have been made in the preservation of myocardial function during open heart surgery since the introduction of cardioplegic arrest. However, despite variation in the composition of cardioplegia, myocardial protection has been based primarily on hyperkalemic solutions [4]. This decreases electromechanical activity and therefore significantly reduces oxygen demand [5]. Hypothermia has also been used as it can further reduce oxygen demand by decreasing basal metabolic rate. However, hypothermia may have adverse effects like inhibiting the Na-pump to cause oedema and shifting of the oxygen–haemoglobin dissociation curve leftward [6]. It is not surprising therefore that the optimal temperature of cardioplegia remains controversial [5]. Continuous warm blood cardioplegia has been widely advocated as a more physiological approach, but perfusion is often interrupted to allow adequate visualisation of the operative site [5]. Intermittent delivery has been proposed as an equally effective and more practical technique [7].
where the choice of optimal cardioplegia remains controversial [7–10]. This is mainly due to the fact that techniques used to protect hearts with ischaemic disease are uncritically extended to hypertrophic hearts and because of our limited knowledge of metabolic changes in hypertrophic hearts during surgery. We have recently shown that the metabolic state of hypertrophic hearts is different from those with ischaemic disease [11]. Clearly a difference in metabolic state between the two pathologies requires different protective strategies as one stated aim of myocardial protection is to improve metabolic preservation. The present study was designed to examine the extent of metabolic derangement, myocardial injury and clinical outcome in patients with hypertrophic hearts undergoing aortic valve replacement surgery using intermittent antegrade cold or warm blood cardioplegia.

2. Materials and methods

Thirty-five patients were prospectively randomised to intermittent antegrade cold blood cardioplegia (n = 16) or intermittent antegrade warm blood cardioplegia (n = 19).

Exclusion criteria included: coronary artery disease, concomitant aortic regurgitation, left ventricular ejection fraction of less than 30%, history of congestive heart failure, diabetes mellitus and re-operation. Eligibility for surgery was based on the medical history, echocardiography and the most recent angiogram. The endpoints of the study were myocardial metabolic changes, myocardial injury and clinical outcome. The study was approved by the United Bristol Healthcare Trust Ethics Committee and all patients gave informed consent.

2.1. Operative procedures

Anaesthetic technique and surgical procedure have been previously reported [11].

Briefly, propofol infusion at 3 mg/kg/h was combined with remifentanyl infusion at 0.5–1 µg/kg/min. Neuromuscular blockade was achieved by 0.1–0.15 mg/kg pancuronium bromide or vecuronium and the lungs ventilated to normocapnia with air and oxygen (45–50%). Mean arterial pressure of 60 mmHg or above was maintained with increments greater than 3.1 mEq/l and a troponin I concentration of 20 mM K+ and 5 mM Mg2+. The cold blood cardioplegic solution was a mixture of the patients blood withdrawn from the CPB circuit and St. Thomas’ I cardioplegic solution (4 blood:1 St Thomas’ I) [6]. The warm blood cardioplegia was a modification of the method described by Calafiore et al. [7] with the patients blood taken from the CPB circuit with added K+ and Mg2+. Following cross-clamping and opening of the ascending aorta, the cardioplegic solution was administered directly into the coronary ostia (a routine practice in our unit), as a 1 l bolus (700 ml in the left followed by 300 ml in the right) at a pressure of 150 mmHg (total delivery time approximately 3 min). Infusions of 200 ml for each ostium were repeated at 15 min intervals.

2.2. Clinical data

Perioperative clinical outcome was prospectively inserted in the Patient Analysis and Tracking Systems (PATS; Dendrite Clinical Systems Ltd, London, UK). Heart rate and rhythm were continuously monitored and displayed on a monitor inclusive of an automated detector of arrhythmia during the first 72 h postoperatively (Solar 8000 Patient Monitor, Marquette Medic. Systems, Milwaukee, USA). Twelve-lead electrocardiographic recordings were performed preoperatively, 2 h postoperatively and then daily thereafter until discharge. Clinical diagnostic criteria for perioperative myocardial infarction (MI) were new Q waves of greater than 0.04 ms, and/or a reduction in R waves greater than 25% in at least two leads. Biochemical diagnostic criteria for perioperative MI were peak troponin I concentrations higher than 3.7 µg/l and a troponin I concentration greater than 3.1 µg/l 12 h postoperatively or greater than 2.5 µg/l at 24 h postoperatively [12,13].

2.3. Collection of ventricular biopsy specimens

In all 35 patients, two full wall thickness transmural biopsies of the left ventricular apical or antero-lateral free wall (4–12 mg wet weight) were taken using a ‘Trucut’ needle (Baxter Healthcare Corporation, Illinois 60015, USA). The first biopsy was taken 5 min after institution of CPB (control), the second after 20 min of reperfusion following removal of the aortic cross-clamp. In addition to the two biopsies, a third biopsy (ischaemic) was also collected from 20 patients (ten in each group), 30 min after cross-clamping the aorta. Each specimen was immediately frozen in liquid nitrogen until processing analysis of metabolites. The analyses was performed by a research technician blind to the operative technique used.
2.5. Troponin I assay

Recent years have witnessed an increased use of myocardial troponin I as marker of myocardial injury [15]. Blood concentration of troponin I was determined prior to surgery, and 1, 4, 12, 24 and 48 h postoperatively. The assay was performed using ACCESS™ Immunoassay System, Beckman Instruments, Inc. Chaska, MN, USA.

2.6. Statistical analysis

Data were expressed as mean ± standard deviation (SD) except in the figures where mean ± standard error is used.

Categorical variables were analysed using either the Fisher’s exact test or the χ² test where appropriate. Comparison between continuous variables was made using a non-parametric test (Wilcoxon’s signed rank test). All statistical analyses mentioned were performed with the aid of a computerised software package, Statview for Windows (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Clinical outcome

Preoperative characteristics are shown in Table 1. There were no differences between the two groups. Intra and postoperative data are shown in Table 2. There were no inhospital deaths, and one perioperative myocardial infarct in the warm blood group. The total incidence of postoperative arrhythmias including requirement for temporary pacing, permanent pacemaker and atrial fibrillation was higher in the warm blood group (P = 0.05 vs. cold blood). No differences were observed between groups with regard to postoperative incidence of renal, respiratory and neurological complications (data not shown).

3.2. Myocardial metabolic changes during ischaemia

Fig. 1 and Table 3 show the myocardial concentration of metabolites in biopsies collected from 20 patients (ten in each group) after 30 min ischaemia and compared to control biopsies. There were no significant changes in the myocardial concentration of adenine nucleotides (ATP + ADP), in either group during 30 min of ischaemia (Fig. 1). There was
an increase in lactate and alanine/glutamate ratio in the warm but not in the cold blood group (Fig. 1).

3.3. Myocardial metabolic changes upon reperfusion

Fig. 2 and Table 4 show the myocardial concentration of metabolites in biopsies collected from all patients 20 min after reperfusion and compared to their respective control biopsies. The myocardial concentration of adenine nucleotides in ventricular biopsies collected after reperfusion was lower than control in the warm group, but not in the cold blood group (Fig. 2). The alanine/glutamate ratio was markedly increased upon reperfusion for both groups, but the extent of the increase was marked in the warm blood group (Fig. 2). There were no significant differences

Table 3
Changes in myocardial metabolites during ischaemia

<table>
<thead>
<tr>
<th></th>
<th>Cold blood (n = 10)</th>
<th>Warm blood (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Ischaemia</td>
</tr>
<tr>
<td>ATP (nmol/mg protein)</td>
<td>33.0 ± 11.3</td>
<td>33.3 ± 9.8</td>
</tr>
<tr>
<td>ADP (nmol/mg protein)</td>
<td>8.3 ± 3.7</td>
<td>5.9 ± 2.9</td>
</tr>
<tr>
<td>Glutamate (nmol/mg protein)</td>
<td>88 ± 26</td>
<td>78 ± 22</td>
</tr>
<tr>
<td>Alanine (nmol/mg protein)</td>
<td>18.0 ± 8.3</td>
<td>21.3 ± 9.3</td>
</tr>
</tbody>
</table>

* The concentration of metabolites expressed as mean ± SD (nmol/mg protein) measured before ischaemia (control) and 30 min after cross-clamping the aorta (ischaemia). Number (n) of patients in each group is also shown. * Significantly different from corresponding control. ** Significantly different from corresponding control and from ischaemia biopsy in the cold blood group.
between the concentration of lactate in control and reperfusion biopsy, for both groups.

3.4. Myocardial injury

There was a considerable postoperative release of troponin I in both groups (Fig. 3). However, comparisons between groups showed a higher release of troponin I in the warm blood group at 1, 24 and 48 h postoperatively.

3.5. Myocardial injury and arrhythmias

In order to determine whether there is a relationship between postoperative arrhythmias and troponin I release, patients from both groups with arrhythmias (Table 2) were divided into those who needed pacing (early arrhythmias, \( n = 6 \)) and those who experienced atrial fibrillation (late arrhythmias, \( n = 5 \)). Patients requiring pacing showed a considerable increase in troponin I release at 1, 4 and 48 h postoperatively compared to patients who did not experience arrhythmias (Fig. 4A). Whether this is a consequence of the myocardial injury, pacing or both, is not readily apparent. Patients who experienced atrial fibrillation showed a higher increase in troponin I release at 24 and 48 h postoperatively, compared to patients without arrhythmias (Fig. 4B). Given that all episodes of atrial fibrillation occurred 48–72 h postoperatively, it is likely that the arrhythmias was a consequence and not the cause of the higher troponin I release.

4. Discussion

To the best of our knowledge, this is the first study that simultaneously investigates metabolic changes, myocardial injury and clinical outcome in patients with hypertrophic hearts secondary to aortic stenosis undergoing valve replacement surgery using cold or warm intermittent antegrade blood cardioplegia.

The accumulation of lactate during ischaemia in the warm

Table 4
Changes in myocardial metabolites upon reperfusion

<table>
<thead>
<tr>
<th></th>
<th>Cold blood (( n = 16 ))</th>
<th>Warm blood (( n = 19 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Reperfusion</td>
</tr>
<tr>
<td>ATP</td>
<td>34.9 ± 10.4</td>
<td>28.1 ± 12</td>
</tr>
<tr>
<td>ADP</td>
<td>13.9 ± 8.2</td>
<td>12.5 ± 7.5</td>
</tr>
<tr>
<td>Glutamate</td>
<td>89 ± 25</td>
<td>68 ± 31</td>
</tr>
<tr>
<td>Alanine</td>
<td>18.9 ± 7.5</td>
<td>23.9 ± 7.4*</td>
</tr>
</tbody>
</table>

\( *P < 0.05 \) vs. corresponding control and ischaemia biopsy in the cold blood group.

\( **P < 0.01 \) vs. corresponding control and ischaemia biopsy.

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Fig. 3. Myocardial injury. Myocardial troponin I release shown at different time points postoperatively. Warm (closed circles) and cold (open circles) blood cardioplegia. Data are presented as mean ± SE and expressed as ng/ml. *\( P < 0.05 \) vs. cold group.

Fig. 4. Myocardial injury and arrhythmias. Postoperative troponin I release in patients with or without postoperative arrhythmias. Patients (from both cold and warm groups) without arrhythmias (open triangles, \( n = 21 \)) were compared to patients with arrhythmias (closed triangles). The latter group was divided into (A) those requiring pacing (\( n = 6 \)) or (B) those suffering from atrial fibrillation (\( n = 5 \)). Data are presented as mean ± SD and expressed as ng/ml. *\( P < 0.05 \) vs. patients without arrhythmias.
blood group is consistent with significant anaerobic metabolism. This is also confirmed by the significantly higher alanine/glutamate ratio. This ratio is a marker of ischaemic stress as during anaerobic metabolism, glutamate concentration falls and alanine levels rise [1,14,16]. The warm ischaemic electromechanical arrest, however, did not influence the levels of adenine nucleotides, although a trend to fall in ATP concentration was evident. It is likely that the period of ischaemia (biopsies were collected after 30 min cross-clamp) interrupted by one reperfusion episode, may not be sufficient to offset the balance between ATP supply (glycolysis) and demand (basal metabolism). However, as time progresses there will be an increase in energy demand particularly as myocardial wall tension begins to increase and as energy supply decreases as acidosis associated with lactate accumulation slows down glycolysis [17].

The reduced myocardial metabolic stress observed with the cold blood cardioplegia might be in part, due to the effects of hypothermia itself, which might have reduced the O_2 demand of the hypertrophic heart. It has been shown that while the oxygen consumption of a normal normothermic, non-working vented heart (6–8 ml O_2/100 g/min) is reduced to 0.6–1.5 ml O_2/100 g/min by potassium cardioplegia, cardioplegia itself at normothermia is not effective in reducing the basal energy requirement of the myocyte [18,19]. However, hypothermia may contribute to decrease this basal energy requirement of the myocyte, as it has been shown that the potassium arrested heart has a myocardial consumption of 0.31 ml O_2/100 g/min at 22°C and of 0.135 ml O_2/100 g/min at 10–12°C [18].

Early after reperfusion, both groups had elevated alanine/glutamate ratio indicating metabolic stress. This was higher in the warm blood group suggesting that these hearts were less able to adjust to the energy demands associated with the resumption of electromechanical activity, compared to hearts arrested with cold blood cardioplegia. This was confirmed by the greater myocardial injury (release of troponin I) in the warm blood group compared to the cold blood group.

This work suggests that myocardial injury may be responsible for the occurrence of supraventricular arrhythmias, as patients who experienced atrial fibrillation (all between 48–72 h postoperatively) had already high troponin I levels at 24 h. However, whether the need for pacing is the cause or the consequence of the increase in troponin I release cannot be directly established. It seems unlikely for a short period of sequential atroventricular pacing early after surgery to be the cause of the rise in troponin I release 1 h postoperatively. Furthermore, pacing was never required beyond 24 h (except for one patient who needed permanent pacing) although troponin I levels were still significantly elevated 48 h postoperatively. However, these conclusions should be considered with caution as the number of patients suffering arrhythmias was relatively less.

The results of this study suggest that the myocardial protection of hypertrophic hearts with intermittent antegrade warm blood cardioplegia is not as effective as with hearts with ischaemic disease [11]. This might be explained by the fact that the two pathologies have different metabolic demands [11] and supports the view that techniques for protection of hearts with ischaemic disease cannot be applied uncritically to hypertrophied hearts. For example, as the underlying disease is aortic stenosis, the hypertrophy of the left ventricle leads to increases in both left ventricular end-diastolic volume and left ventricular end-diastolic pressure [2], which increase myocardial work and O_2 demand. In this situation, two of the primary determinants of myocardial O_2 demand (tension developed by the myocardium and duration of systole) are increased. At the same time, myocardial O_2 supply is impeded owing to an elevated end diastolic pressure, causing a decrease in coronary perfusion pressure. Finally, the Venturi effect of the jet of blood flowing through the aortic valve and past the coronary arteries may reduce pressure in the coronary ostia enough to reverse systolic coronary blood flow. These factors make the heart more susceptible to ischaemia, even in the absence of concurrent atherosclerotic coronary disease [2].

Although the results of this study show that the myocardial protection of hypertrophic hearts is superior when using cold cardioplegia, they also demonstrate a marked degree of myocardial injury associated with this method of cardioplegia. Potential improvements of this technique in patients with left ventricular hypertrophy might be achieved by a final dose of warm blood cardioplegia ‘hot shot’ prior to removal of the aortic cross-clamp. Continuous delivery of warm blood cardioplegic solutions, demonstrated to be beneficial in ischaemic hearts [20–22], might improve myocardial protection of hypertrophic heart and prevent the deleterious effects associated to the intermittent delivery [23–24]. Once an optimal technique of myocardial protection for hypertrophic hearts is identified, this technique can then be investigated in patients requiring both coronary revascularisation and aortic valve replacement at the same time.

In conclusion, evidence of metabolic derangement and reperfusion injury, indicating sub-optimal myocardial protection, was seen in both cold and warm blood cardioplegia. However, cold blood cardioplegia was associated with a relatively reduced metabolic derangement and myocardial reperfusion injury and improved clinical outcome.

Acknowledgements

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References


