Ischemic preconditioning improves preservation with cold blood cardioplegia in valve replacement patients

Guohu Li*, Shenxi Chen, Erxiong Lu, Yuanjian Li
Department of Cardiothoracic Surgery, Xiangya Hospital, Hunan Medical University, Changsha 410008, Hunan, PR China

Received 12 October 1998; received in revised form 26 January 1999; accepted 2 February 1999

Abstract

Objective: The purpose of this study was to test the hypothesis that ischemic preconditioning improves myocardial protection in valve replacement patients undergoing cold-blood cardioplegic arrest and to study the mechanisms of human myocardial ischemic preconditioning initially. Methods: Forty patients who required double valve replacement were studied. After the institution of cardiopulmonary bypass, 20 patients were preconditioned with two cycles of 3 min of aortic cross-clamping and 2 min of reperfusion before cardioplegic arrest (group IP). Twenty patients were not preconditioned as controls (group C). All hearts were arrested with 4°C cold-blood cardioplegic solution. During perioperation, the blood samples were collected from coronary sinus and radial artery, which were used to measure calcitonin gene-related peptide (CGRP) and creatine kinase-MB (CK-MB). The right atrial myocardial tissue was collected to measure superoxide dismutase/malondialdehyde (T-SOD/MDA) and to observe myocardial ultrastructure. Hemodynamic data were measured.

Results: After reperfusion for 30 min, myocardial MDA was significantly lower in group IP than in group C (2.6 ± 0.2 vs. 3.8 ± 0.3 nM/mg) and T-SOD was significantly higher in group IP than in group C (13.1 ± 12.1 vs. 9.2 ± 1.2 IU/mg). Ischemic preconditioning significantly increased the production of myocardial CGRP just after preconditioning (92.0 ± 4.1 vs. 52.3 ± 4.5 pg/ml) and the begin of reperfusion (95.3 ± 3.8 vs. 61.2 ± 4.9 pg/ml), and deduced the release of CK-MB at 12 h post-reperfusion (77.5 ± 9.2 vs. 136.5 ± 8.9 IU/l).

Conclusions: Ischemic preconditioning enhance cardioplegic protection in valve replacement patients. The possible protective mechanism was that ischemic preconditioning decreased the production of oxygen free radicals. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Ischemic preconditioning; Calcitonin gene-related peptide; Oxygen free radical; Cardiac surgery

1. Introduction

Modern myocardial preservative techniques have revolutionized cardiac surgery. Many myocardial preservative methods focus on the composition of the cardioplegic solution and temperature manipulation [1]. However, all of these studies are concerned with extraneous myocardial preservation. Ischemic preconditioning is an endogenous myocardial protective measure. In recent years, many studies have demonstrated that human myocardium can also be preconditioned [2–4]. Our recent research [5] and others [6,7] have found that ischemic preconditioning can improve myocardial preservation of patients undergoing cardiac operation.

The mechanism responsible for ischemic preconditioning has been studied in animals. There is an increasing amount of evidence that endogenous myocardial protective substance may play an important role in ischemic preconditioning. However, we have little research about the myocardial protective mechanism of human myocardial ischemic preconditioning. Our recent research suggests that ischemic or CGRP-induced preconditioning improves isolated rat myocardial preservation with cardioplegia [8]. CGRP may be an...
endogenous myocardial protective substance [9]. The present study was designed to evaluate the effects of ischemic preconditioning on myocardial preservation with cold-blood cardioplegic arrest in patients undergoing double valve replacement and to study the mechanisms of human myocardial ischemic preconditioning. How can ischemic preconditioning increase the production of human myocardial CGRP?

2. Materials and methods

The clinical trial was approved by both the university scientific association and the local ethics committee. Written informed consent was obtained from each patient before the operation.

2.1. Patients and operative details

From March 1997 to March 1998, 40 patients undergoing double valve replacement with mechanical prostheses were prospectively entered into this study. Anesthesia was uniform in all cases and consisted of a standardized combination of fentanyl citrate and pancuronium bromides. It was maintained with intravenously administered propofol and inhalation of isoflurane. After endotracheal intubation, the lungs were ventilated with a volume-cycle respirator (Ohmeda, Excel 210, USA). The left radial artery was catheterized to monitor arterial pressure. The right internal jugular vein was catheterized with pulmonary artery Swan Ganz catheter to monitor hemodynamic data. The electrocardiogram and body temperature were also monitored. Cardiopulmonary bypass (CPB) was established with a crystalloid-albumin-blood prime (Stockert III, Germany; Sarns membrane oxygenator, USA). All patients achieved crystalloid-albumin-blood prime (Stockert III, Germany; Sarns membrane oxygenator, USA). All patients achieved crystalloid-albumin-blood prime (Stockert III, Germany; Sarns membrane oxygenator, USA).

2.2. Collection of assay of blood samples

Blood samples were collected from the radial artery before ischemia and after reperfusion for 30 min and 12 h, which were used to measure the creatine kinase MB (CK-MB, Beijing Chongshong Company, China). Blood samples were collected from the coronary sinus (12 F pediatric cardiac sump catheter, model 12013, Medtronic-DLP, USA) before ischemia, after ischemic preconditioning or 10 min after CPB and at the beginning of reperfusion. Calcitonin gene-related peptide was measured (CGRP, RIA, Beijing East-Asia Immune Institute, China).

2.3. Hemodynamic measurement

Before CPB, at 30 min (CPB is completed) and 12 h after reperfusion hemodynamic data were recorded from pulmonary Swan Ganz catheter (Space lab, 90303B USA).

2.4. Electron microscopic observation of myocardium

Before ischemia and at 30 min after reperfusion, the right atrium myocardium samples in each group were collected to measure superoxide dismutase/malondialdehyde (T-SOD/MDA, Nanjing Jiangzheng Biological Engine Institute, China), and to observe myocardial ultrastructure (Hitachi 600, Japan). According to myocardial semiquantitative analysis methods of Schaper, et al. [9] we recorded the myocardial ultrastructural damage in a blind manner. The intercellular junctions, intracellular and extracellular edema, mitochondria, nuclei and myofibrils were analyzed separately in each biopsy specimen by a semi-quantitative method with scoring from 0 (unchanged) to 3 (severe alterations). A total score of all ultrastructure changes less than 5 were defined as slight damage, scores ranging from 5 to 10 were defined as moderate and scores exceeding 10 were defined as severe ultrastructure damage.

2.5. Statistical analysis

Results are presented as the mean ± SEM. Comparisons

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group C</th>
<th>Group IP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio (M/F)</td>
<td>12/8</td>
<td>13/7</td>
</tr>
<tr>
<td>Age (years)</td>
<td>34 ± 5</td>
<td>32 ± 4</td>
</tr>
<tr>
<td>Aortic cross-clamping (mm)</td>
<td>86.5 ± 10.4</td>
<td>88.2 ± 11.7</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>116.5 ± 11.2</td>
<td>119.3 ± 10.5</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.2 ± 0.1</td>
<td>3.3 ± 0.2</td>
</tr>
</tbody>
</table>

*There were no significant differences between the two groups. NYHA class, American Heart Association class.
of two groups were made by unpaired t-test. Differences were considered significant when the P-value was <0.05.

3. Results

The major preoperative and intraoperative variables were similar in the two groups (Table 1). One patient in group C was excluded for the problem of coronary catheter. There were no operative deaths (to 30 days postoperatively) in two groups. The cardiac index in group IP was significantly higher than that in group C after reperfusion for 30 min and 12 h (Table 2).

Ischemic preconditioning deduced the production of oxygen free radicals at 30 min after reperfusion. The content of myocardial MDA in group IP was significantly lower than that in group C, and the content of myocardial SOD in group IP was significantly higher than that in group C (Table 2). Ischemic preconditioning increased the production of myocardial CGRP. The contents of CGRP in group IP were significantly higher than that in group C at the time just after ischemic preconditioning and reperfusion (Table 3).

3.1. Electron microscopic observation

In group C, many mitochondria were swelling. The cristae of mitochondria were dissolved and disappeared. Parts of myofibrils were relaxed. In group IP, parts of mitochondria were dissolved and disappeared. Parts of myofibrils were relaxed. In group IP, parts of mitochondria were dissolved and disappeared. Parts of myofibrils were relaxed. In group IP, parts of mitochondria were dissolved and disappeared. Parts of myofibrils were relaxed.

Table 3

<table>
<thead>
<tr>
<th>Group</th>
<th>Before ischemia</th>
<th>CPB 10 min or after IP</th>
<th>Reperfusion 0.5 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>30.6 ± 5.4</td>
<td>52.3 ± 4.5</td>
<td>61.2 ± 4.9</td>
</tr>
<tr>
<td>IP</td>
<td>32.7 ± 40</td>
<td>91.0 ± 4.1*</td>
<td>95.3 ± 3.8*</td>
</tr>
</tbody>
</table>

CGRP, calcitonin gene-related peptide; CPB, cardiopulmonary bypass. *P < 0.05 versus control.

3.2. Early clinical observation

Ventricular arrhythmia and inotropic agent were less in group IP than in group C in the early postoperative period (Table 6).

4. Discussion

Ischemic preconditioning has been used to increase the myocardial protection in clinical cardiac surgery [5–7], and some authors [6] have reported the largest recorded-human surgical ischemic preconditioning series. But some authors have also found that ischemic preconditioning has not enhanced cardioplastic protection in cardiac surgery [10]. What caused the paradoxical results of ischemic preconditioning in conjunction with hypothermia or cardioplegia in surgical myocardial protection? Which needs to be studied in future? It was possible that many factors would effect the results, such as preconditioning protocols, operative details, anesthetization routine, myocardial protection and inotropic agent [11]. The most important effective factor was whether the preconditioning protocols could stimulate myocardium to produce endogenous self-preservation. In our study, ischemic preconditioning with two cycles of 3 min occlusion and 2 min reperfusion was also more likely to be applicable clinically and could significantly improve myocardial preservation in the setting of hypothermic arrest with cold-blood cardioplegia in valve replacement operations.

The mechanisms of the myoprotective properties of ischemic preconditioning are multiple and include activa-

Table 4

<table>
<thead>
<tr>
<th>Group</th>
<th>Edema (U/mL)</th>
<th>T-SOD (nM/mg)</th>
<th>MDA (lU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>1.6 ± 0.2</td>
<td>0.8 ± 0.1</td>
<td>0.2 ± 2.4</td>
</tr>
<tr>
<td>IP</td>
<td>1.1 ± 0.2*</td>
<td>0.6 ± 0.1*</td>
<td>0.1*</td>
</tr>
</tbody>
</table>

*P < 0.05 versus control.
tion of A1 adenosine receptors [12], activation of adenosine triphosphate-sensitive potassium channels [13], induction of heat-shock proteins [14], production of endogenous myocardial protective substance [15]. Although the mechanism of human myocardial ischemic preconditioning is still not completely understood, there is evidence that involvement of adenosine receptors and K-ATP channel activation can be operative in human [16,17]. Adenosine infusion prior to bypass surgery has been shown to improve hemodynamic function and reduce creatine kinase release in cardiac surgery [18].

Our results indicated that ischemic preconditioning reduced myocardial MDA formation and the consumption of myocardial SOD after reperfusion, and also showed that the contents of myocardial CGRP were significantly increased after ischemic preconditioning. CGRP may be an endogenous myocardial protective substance [9]. Some studies suggested that myocardial ischemic preconditioning could produce myocardial endogenous protective substance, which cause cardioprotection by activation of protein kinase C [19,20]. Whether human myocardial ischemic preconditioning could increase the production of myocardial CGRP, CGRP could increase the activation of protein kinase C and produce myocardial protective effect by inhibition of lipid peroxidation, which still needs to be proven with further research in future.

In summary, the present study suggests that ischemic preconditioning can improve myocardial preservation in valve replacement patients with cold-blood cardioplegic arrest. Ischemic preconditioning could probably improve myocardial protection by decreasing formation of oxygen free radicals.

Acknowledgements

This work was supported by a grant from the Scientific Commission of Hunan Province in China.

References


