Ischemic preconditioning prior to myocardial protection with cold blood cardioplegia in coronary surgery

J. Cremer a,*, G. Steinhoff a, M. Karck a, T. Ahnssel a, M. Brandt a, O.E. Teebken a, D. Hollander b, A. Haverich a

a Department of Cardiovascular Surgery, Christian-Albrechts-University, Arnold-Heller-Strasse 7, D-24105 Kiel, Germany
b Department of Anesthesiology, Christian-Albrechts-University, Arnold-Heller-Strasse 7, D-24105 Kiel, Germany

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Abstract

Objective: Encouraging results on myocardial preconditioning in experimental models of infarction, stunning or prolonged ischemia raise the question whether preconditioning techniques may enhance conventional cardioplegic protection used for routine coronary surgery. Methods: A prospective clinical trial was conducted to investigate the effect of additional ischemic normothermic preconditioning prior to cardioplegic arrest applying cold blood cardioplegia in patients scheduled for routine coronary surgery (3 vessel disease, left ventricular ejection fraction < 50%). Two cross clamp periods of 5 min with the hearts beating in sinus rhythm were applied followed by 10 min of reperfusion, each (n = 7, group I). Inducing moderate hypothermia cold blood cardioplegia was delivered antegradely. In control groups, cold intermittent blood cardioplegia (n = 7, group II) was used alone. Coronary sinus effluents were analyzed for release of creatine kinase (CK), CK-MB, lactate, and troponin T at 1, 3, 6, 9, and 12 h. In addition, postoperative catecholamine requirements were monitored. Results: The procedure was tolerated well, and no perioperative myocardial infarction in any of the groups studied occurred. Concentrations of lactate tended to be higher in group I, but this difference was not significant. In addition, no significant differences for concentrations of CK, CK-MB, and troponin T were found. Following ischemic preconditioning an increased dosage of dopamine was required within the first 12 h postoperatively (group I: 2.63 ± 1.44 μg/kg/min, group II: 0.89 ± 1.06 μg/kg/min). Conclusions: Combining ischemic preconditioning and cardioplegic protection with cold blood cardioplegia does not appear to ameliorate myocardial protection when compared to cardioplegic protection applying cold blood cardioplegia alone. Inversely, contractile function seemed to be impaired when applying this protocol of ischemic preconditioning. © 1997 Elsevier Science B.V.

Keywords: Myocardial protection; Ischemic preconditioning; Cardiac Surgery; Troponin T

1. Introduction

Ischemic preconditioning is defined as a brief period of ischemia and reperfusion increasing the myocardial tolerance to a subsequent longer but sublethal period of ischemia by Murry [16]. Following the initial description this endogenous protective phenomenon has been widely investigated under experimental conditions. It is known today that preconditioning exerts its beneficial effects in reducing infarct size, improving functional recovery, reducing malignant arrhythmias, and diminishing ATP depletion. In addition to ischemia per se, a variety of basically different approaches were disclosed to be effective in inducing myocardial preconditioning. Among these, periods of hypoxia [8], induction of stress and heat shock proteins [14], and pharmacological preconditioning by use of, e.g. adenosine, epinephrine, or amphetamine are currently discussed [13,15,18].
In previous experimental settings, different in vivo and ex vivo models involving various species were used to assess potentially protective effects of preconditioning or to elaborate the underlying cellular or molecular mechanisms. In addition, non-uniform models of either global or regional myocardial ischemia were studied. As a consequence, only a minority of experimental studies may possess direct clinical implications addressing techniques of preconditioning applicable for open heart surgery, especially coronary surgery [4,8]. Few studies on ischemic preconditioning have been performed in patients undergoing routine coronary surgery. Results would suggest reduced ATP-depletion but fail to show evidence for improved functional recovery or reduced ischemic reperfusion injury [2,20]. Moreover, these studies combined ischemic preconditioning and intermittent aortic cross-clamping. The approach contrasts the most widely used cardioplegic arrest techniques for intraoperative myocardial protection. Addressing the question of combining routine cardioplegic protection with myocardial preconditioning, we conducted a prospective clinical trial comparing ischemic preconditioning and preservation with cold blood cardioplegia to arrest techniques with blood cardioplegia alone.

2. Materials and methods

2.1. Patient selection

A total of 14 patients (13 male, 1 female) underwent elective coronary surgery (between 5.95 and 9.95) and participated in this prospective clinical study after having been allocated to one of the groups randomly. All patients suffered from 3 vessel disease, revealed stable angina pectoris upon admission and were scheduled for primary procedures. Significant left main stem stenosis or reduced left ventricular function (ejection fraction ≤ 50%) were exclusion criteria as well as insulin dependent diabetes mellitus, treatment with sulfonylureas, or renal and hepatic dysfunction (Table 1).

<table>
<thead>
<tr>
<th>Myocardial protection</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preconditioning + intermittent cold, blood cardioplegia</td>
<td>Intermittent cold, blood cardioplegia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>n (m/f)</th>
<th>7 (6/1)</th>
<th>7 (7/0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.1 ± 4.6</td>
<td>58.1 ± 4.6</td>
</tr>
<tr>
<td>LV-EF (%)</td>
<td>64.8 ± 11.0</td>
<td>66.8 ± 11.2</td>
</tr>
<tr>
<td>3 vessel disease</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

m, male; f, female; LV-EV, left ventricular ejection fraction.

2.2. Surgical procedures and patient groups

Following induction of anesthesia (fentanyl, etomidate, pancuronium) the chest was opened via a median sternotomy while simultaneously harvesting adequate segments of saphenous vein. Subsequent to the preparation of IMA-grafts heparin (300 U/kg) was administered to obtain activated clotting times ≥ 700 s and cardiopulmonary bypass was instituted applying non-heparin coated tubing sets (Jostra, Hechingen, Germany) and oxygenators (Monovaly, Sorin, Munich, Germany).

Patients selected for ischemic preconditioning (group I, n = 7) were initially kept normothermic while the ascending aorta was cross-clamped with the heart being vented and beating empty in sinus rhythm. Two cross-clamp periods of 5 min were followed by 10 min of reperfusion each before moderate hypothermia (30°C) was induced (Table 2). In case of bradycardia (n = 2) the heart rate was kept at a rate of ≥ 80/min using atrial or ventricular pacing. The hearts stayed in sinus or ventricular rhythm without occurrence of episodes of ventricular fibrillation or tachycardia. Reversible ST-segment changes during ischemia were observed in every case but not quantified. Internal thoracic artery grafts were prepared during preconditioning and all distal anastomoses were subsequently performed under cardioplegic arrest achieved by intermittent antegrade delivery of cold blood cardioplegia (Köhler, Alsbach/Bergstrasse, Germany) according to the Buckberg protocol [6]. While constructing the proximal anastomoses in side clamping patients were rewarmed (35°C) and a multiperforated flexible catheter (2F, Baxter, Unterschleissheim, Germany) was inserted into the coronary sinus via the right atrium. Following termination of cardiopulmonary bypass (CPB) the heparin effect was antagonized by protamine chloride before closing the chest. All patients received antifibrinolytic treatment by use of aprotinin (1 million KIU loading dose + 1 million KIU CPB priming).

In the case of control patients, myocardial protection consisted of intermittent cold blood cardioplegia (group II, n = 7) delivered antegrade and under conditions of moderate hypothermia without prior preconditioning. Within cross-clamp times of 45.5 ± 8.1 min (group II) and 58.0 ± 8.0 min (group I, including periods of preconditioning) between 3.3 ± 0.7 and 3.8 ± 0.8 (group I) distal anastomoses were performed. Bypass times ranged between 91.2 ± 26.7 (group II) and 128 ± 12.2 min (group I) (n.s.).

Coronary sinus blood samples were analyzed for troponin T, CK, CK-MB and lactate release at 1, 3, 6, 9, and 12 h after termination of bypass. In addition, the average dosage of dopamine required for hemodynamic stabilization within the first 12 h postoperatively was calculated. Twelve lead electrocardiograms (ECG) were...
Table 2
Protocol of myocardial protection and reperfusion

<table>
<thead>
<tr>
<th></th>
<th>ischemic preconditioning</th>
<th>mode of cardioplegic arrest</th>
<th>reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>normothermic</td>
<td>moderate hypothermia (30°C)</td>
<td>normothermic</td>
<td></td>
</tr>
<tr>
<td>group I</td>
<td>IP  RP  IP  RP</td>
<td>intermittent cold blood cardioplegia</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>5'  10'  5'  10'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>group II</td>
<td></td>
<td>intermittent cold blood cardioplegia</td>
<td>+</td>
</tr>
</tbody>
</table>

recorded after 4 and 12 h as well as after 5 days. For assessment of the correct position of the coronary sinus catheter a radiological visualization applying contrast medium was used.

Troponin T was measured quantitatively in heparinized plasma samples using an ELISA in vitro-test (Boehringer, Mannheim, Germany).

The study protocol was approved by the local ethic committee and informed consent was obtained by each patient preoperatively. The physicians in charge of the postoperative patient management were blinded regarding the group allocation of the patients.

2.3. Statistical analysis

Except for dopamine requirement, which was given as mean and standard deviation (S.D.), all other study parameters are expressed as median values and confidence limits. Non-parametric methods were used for data evaluation. Comparison of groups was carried out by the Friedman test for intragroup differences within each group. A further analysis of both groups was performed by the Mann–Whitney test [12]. Statistical significance was regarded at \( P < 0.05 \). When differences between single values were not significant, the areas below the curves were compared by use of the Mann–Whitney test.

3. Results

All patients tolerated the procedure well and could be weaned from ventilation within 48 h. Serial ECG showed no evidence of new myocardial infarction in any case, nor were cerebrovascular accidents observed. No complications due to insertion of the coronary sinus catheter were observed. None of the patients developed high grade ventricular arrhythmias within the first 24 h under continuous ECG monitoring.

3.1. Creatine kinase isoenzyme M B

Within the postoperative 12-h period, plasma concentrations of CK-M B varied between 9.2 and 20.8 U/l. There were no significant inter- or intragroup differences (Table 3).

3.2. Creatine kinase

Highest CK-concentrations were found at 6 h in group I (289 U/l) and at 12 h in group II (296 U/l). The overall range varied between 204 and 296 U/l. There were no significant intergroup differences.

3.3. Troponin T

Release of troponin T was uniform within and between groups. Coronary sinus effluent concentrations between 0.35 and 0.70 ng/ml were found without a definite peak formation in both groups. Referring to individual levels we found 5 (group I), respectively, 4 (group II) out of 35 samples evaluated beyond 1.0 ng/ml troponin T.

3.4. Lactate

The highest lactate levels were obtained in group I at 3 h amounting to 1.42 mmol/l. Beyond 1 h all lactate concentrations remained lower in group II with a maximal concentration at 3 h (1.16 mmol/l), without statistical significance, though.
Table 3
Metabolic and ischemic serum parameters in coronary sinus effluents after 1, 3, 6, 9, 12 h

<table>
<thead>
<tr>
<th>Group</th>
<th>1 h Cl</th>
<th>3 h Cl</th>
<th>6 h Cl</th>
<th>9 h Cl</th>
<th>12 h Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK (U/l) I</td>
<td>217</td>
<td>107; 332</td>
<td>262</td>
<td>142; 328</td>
<td>289</td>
</tr>
<tr>
<td>II</td>
<td>217</td>
<td>205; 238</td>
<td>245</td>
<td>227; 274</td>
<td>226</td>
</tr>
<tr>
<td>CK-MB (U/l) I</td>
<td>15.5</td>
<td>7.3; 20.8</td>
<td>13</td>
<td>5.4; 22.9</td>
<td>11.9</td>
</tr>
<tr>
<td>II</td>
<td>20.8</td>
<td>8.5; 24.8</td>
<td>11.5</td>
<td>8.0; 22.0</td>
<td>12.8</td>
</tr>
<tr>
<td>Troponin T (ng/ml) I</td>
<td>0.67</td>
<td>0.40; 0.84</td>
<td>0.50</td>
<td>0.28; 0.66</td>
<td>0.50</td>
</tr>
<tr>
<td>II</td>
<td>0.50</td>
<td>0.22; 0.63</td>
<td>0.70</td>
<td>0.30; 0.89</td>
<td>0.52</td>
</tr>
<tr>
<td>Lactate (mmol/l) I</td>
<td>1.02</td>
<td>0.16; 1.54</td>
<td>1.42</td>
<td>0.58; 3.33</td>
<td>1.23</td>
</tr>
<tr>
<td>II</td>
<td>1.09</td>
<td>0.22; 1.57</td>
<td>1.16</td>
<td>0.67; 1.5</td>
<td>0.98</td>
</tr>
</tbody>
</table>

CK-MB, creatine kinase isoenzyme MB; CK, creatine kinase; CI, confidence interval; all data given as median and 90% confidence intervals.

3.5. Requirements for dopamine

The highest average dopamine requirement of $2.63 \pm 1.06 \mu g/kg/min$ was found in patients following preconditioning, as compared to $0.89 \pm 1.44 \mu g/kg/min$ (group II, n.s.) (Fig. 1). This appeared to be in agreement with the surgeon’s impression of a reduced contractility in preconditioned hearts (group I).

4. Discussion

The majority of experimental studies dealing with ischemic preconditioning could assess a striking benefit of myocardial protection as evidenced by ATP preservation and myocardial function or reduced release of ischemic markers and infarct size. It was our aim to introduce this endogenous protective mechanism into protocols of myocardial protection currently applied for routine cardiac surgery. But in contrast to experimental studies, we were unable to elaborate any beneficial effect of ischemic normothermic preconditioning combined with cold blood cardioplegic arrest in terms of the chosen metabolic and ischemic parameters.

Various reasons may be responsible for the lack of success of additional preconditioning in our study. The applied preconditioning protocol may not be effective under the selected conditions regarding ischemic and reperfusion intervals. However, comparable protocols of normothermic ischemic preconditioning in mammalian hearts using one or repeated periods of ischemia between 2 and 5 min followed by reperfusion periods of 3-10 min have already been successfully applied [1,7,11]. And in the setting of clinical cardiac surgery extensive experience exists with intermittent cross-clamping for routine coronary procedures supporting the safety of the chosen preconditioning protocol [3,5]. Furthermore, the few available data on ischemic preconditioning in routine coronary surgery have been filed using similar protocols of preconditioning but performing subsequent surgery in intermittent cross-clamping or during ventricular fibrillation [2,20]. Nevertheless, the results reported therein indicated a beneficial protective effect of preconditioning. In contrast, the combination of normothermic ischemic preconditioning and cardioplegic arrest using intermittent cold blood cardioplegia as provided by our protocol may exert detrimental or at least no salutary effects. This appeared to be in agreement with the surgeon’s impression of a reduced contractility in preconditioned hearts, when coming off bypass. But this obviously has to be substantiated with adequate functional data. However, in a protocol of normothermic ischemic preconditioning and crystalloid cardioplegic arrest definitively intending to mimic clinical procedures Bolling [4] has already been unable to document superior preservation of myocardial function following preconditioning in rabbit hearts. Similarly, Perrault and co-workers [17] also already doubted potential beneficial effects of clinical ischemic preconditioning combined with continuous retrograde warm blood cardioplegia. They found an increased intraoperative CK-MB release in the coronary sinus blood and a prolonged myocardial lactate production following preconditioning.
Another reason for missing a potential benefit of preconditioning in our study may be seen in selecting ischemic and metabolic parameters, even though obtained from coronary sinus effluents rather than reflecting myocardial function, coronary flow or myocardial energetics. But in several studies on myocardial protection such metabolic or ischemic markers could conclusively differentiate ischemic injury in relation to the applied protection protocols [3,10]. The most important factor that our results cannot significantly assess the superiority of one of both treatment modalities is probably related to the small sample size. Along with the clinical experience with intraoperative preconditioning we could not exclude that preconditioning under these circumstances might be harmful for myocardial function. Therefore, the study was limited to a small number of patients, although the study protocol has been accepted for larger groups.

However, the salutary effects reported for ischemic preconditioning under experimental conditions also may not be transferable to routine cardiac surgery. Thus, the majority of experimental investigations on preconditioning applied regional or global infarct models [7], prolonged periods of ischemia with the intention for stunning [4,9], or prolonged cold storage [8] prior to functional testing in isolated heart preparations. In addition, a few experimental studies [1,4,19,20] already do indicate that preconditioning might be associated with impairment of ventricular function, likewise myocardial stunning necessarily being part of the intended protective effect. As the primary effect of experimental preconditioning results in a reduction of infarct size, beneficial effects in a clinical setting may just be obtained in case of subsequent myocardial infarction. Thereby improved cardiac function could be only related to a smaller infarct size and not to a better tissue preservation. In consequence general applicability of ischemic preconditioning in routine coronary surgery must be questioned. Conversely, the situation in minimally invasive coronary surgery may be completely different, as a definite period of regional warm ischemia is regularly created when constructing the anastomoses avoiding CPB techniques.

From our present study we conclude that normothermic ischemic preconditioning combined with cardioplegic arrest does not effect superior myocardial protection when compared to conventional cardioplegic arrest techniques with cold blood cardioplegia alone. In addition, a negative effect comparable to myocardial stunning may occur even when applying ischemic intervals as short as 5 min each. Functional investigations under these conditions are required to substantiate such an assumption. Furthermore, experimental donor heart protection by use of additional preconditioning prior to harvesting should rather be transferable into clinical use as the applied experimental designs closely reflect clinical heart transplantation.

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References

