Regional Ischemic Preconditioning Enhances Myocardial Performance in Off-Pump Coronary Artery Bypass Grafting*

Jari Laurikka, MD; Zhong-Kai Wu, MD; Pekka Iisalo, MD; Liisa Kaukinen, MD; Eva L. Honkonen, MD; Seppo Kaukinen, MD; and Matti R. Tarkka, MD

Objectives: We intended to investigate whether ischemic preconditioning (IP) enhances myocardial performance in patients who undergo off-pump coronary artery bypass grafting (CABG).

Design: A controlled, randomized, prospective study.

Setting: A university hospital.

Patients: Thirty-two patients with left anterior descending coronary artery (LAD) or two-vessel heart disease (including LAD) who were to undergo off-pump CABG were randomized into an IP group and a control group.

Interventions: IP was induced by occluding the LAD twice for a 2-min period followed by 3-min LAD reperfusion before bypass grafting of the first coronary vessel.

Measurements and results: Registration included hemodynamic data from the peripheral artery and the pulmonary artery, and the measurement of cardiac troponin I (CTnI) and creatine kinase isoenzyme MB (CK-MB) values. IP resulted in a complete recovery of the mean stroke volume index (SVI) after the operation. In the control subjects, the mean SVI showed a significant reduction postoperatively (p = 0.039). On the first postoperative day, the increase in the mean heart rate (HR) was also significantly lower in the IP patients. The CTnI level was statistically significantly lower in the IP group (p = 0.043), and IP patients tended to have a smaller CK-MB release after surgery (not significant). The duration of mechanical ventilation, the length of stay in the ICU, and the use of inotropic medication did not increase after the IP protocol.

Conclusions: Two cycles of regional 2-min IP in the LAD, followed by 3 min of reperfusion, proved to be applicable and safe in patients undergoing off-pump myocardial revascularization, it tended to decrease the immediate myocardial enzyme release, it prohibited the postoperative increase in HR, and it enhanced the recovery of SVI. (CHEST 2002; 121:1183–1189)

Key words: coronary artery bypass grafting; ischemic preconditioning; off-pump; myocardial protection

Cardiopulmonary bypass (CPB) and cardioplegic cardiac arrest with aortic cross-clamping are used mainly to achieve adequate exposure to target vessels, but they carry a risk for local myocardial injury and systemically detrimental inflammatory effects.1,2 These harmful effects may be mediated by the generation of free radicals during reperfusion.3,4 Conventional CPB surgery also predisposes the patient to postoperative neurologic impairments that range from cognitive deficits to strokes.5,6 This may be associated with the occurrence of cerebral microembolisms that are generated by CPB and cross-clamping, especially from the diseased ascending aorta.5,6

*From the Department of Surgery (Drs. Laurikka, Wu, Iisalo, and Tarkka), and the Department of Anesthesiology and Intensive Care (Drs. L. Kaukinen, Honkonen, and S. Kaukinen), Division of Cardiothoracic Surgery, Tampere University Hospital, Tampere, Finland.

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Correspondence to: Matti Tarkka, MD, Department of Surgery, Division of Cardiothoracic Surgery, Tampere University Hospital, 33521 Tampere, Finland; e-mail: matti.tarkka@tays.fi
Myocardial revascularization on the beating heart without CPB has gained increasing popularity because it may avoid the damage induced by CPB with hypothermia, aortic cannulation, and cross-clamping. Surgical procedures on the beating heart require less blood to be transfused and afford shorter hospital stays, lower rates of organ dysfunction (including cerebrovascular complications), fewer hemorrhagic complications, and lower mortality rates in high-risk patients. Thus, surgical procedures on the beating heart reduce the cost of surgery. However, a less optimal operative field and limited access may result in incomplete procedures. The ischemic period during grafting may cause contractile dysfunction and vascular endothelial injury, and involves a risk of myocardial necrosis.

Ischemic preconditioning (IP) is created by a brief period of myocardial ischemia followed by reperfusion, and it increases myocardial tolerance to subsequent long-term ischemic insult. IP has been widely studied and has proved to be one of the most potent endogenous myocardial mechanisms protecting against ischemia/reperfusion injury in experimental models as well as in humans. IP delays myocardial damage, preserves high-energy phosphates, suppresses arrhythmias, and improves postischemic functional recovery. IP also results in the depletion of myocardial glycogen, which, during the ischemia, finally results in reduced lactate production, and it potentially also protects endothelium in the coronary vessel.

The procedure of off-pump myocardial revascularization requires a period of coronary artery occlusion, which results in regional ischemia. IP and intracoronary shunts have been used to limit ischemic injury, but the use of the shunt in a vulnerable coronary artery may damage the endothelium. IP has been considered to be a promising method for achieving myocardial protection, although controversial results concerning the effectiveness of IP also have been shown. Reports on IP in patients undergoing off-pump CPB surgery are still few in number, and not all of those studies are even randomized. Therefore, we aimed at investigating the IP effects in patients undergoing off-pump coronary artery bypass grafting (CABG) in a randomized controlled study.

Materials and Methods

The study design was accepted by the Ethical Committee of Tampere University Hospital, Finland, and informed consent was obtained from all patients.

Patients

Thirty-two CABG patients with single-vessel or two-vessel coronary artery disease involving the left anterior descending coronary artery (LAD) alone or in combination with the right coronary artery (BCA), or the diagonal branch (ie, left diagonal artery) were randomized into an IP group (n = 16) and a control group (n = 16). The randomization was carried out in the operating room by opening a sealed, nontransparent protocol envelope. The IP group received the IP treatment before the first graft anastomosis, while routine operative methods were used in the control subjects.

The preoperative characteristics of the patients in the respective groups were similar. There were no statistically significant differences between the two groups in terms of patient age, sex, New York Heart Association class, the location of the diseased vessel, the vessels that were bypassed, risk factors, type of incision, and time of vessel occlusion (Table 1). The groups did not differ significantly in medical history, and the number of patients receiving medication blocking the β-adrenergic receptors was equal in both groups.

Preconditioning Protocol

The IP protocol was achieved by occluding the LAD with silicon tape. After identifying the LAD, two pieces of silicon tape were used proximal to and distal to the site of the anastomosis. The LAD was occluded for 2 min and then was released for 3 min. The procedure was repeated once. Other vessels were not used for IP.

Table 1—Preoperative Data*

<table>
<thead>
<tr>
<th>Variable</th>
<th>IP Group (n = 16)</th>
<th>Control Group (n = 16)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>68.6 ± 7.9</td>
<td>55.3 ± 10.6</td>
<td>0.32</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>4</td>
<td>0.33</td>
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<tr>
<td>Male</td>
<td>15</td>
<td>12</td>
<td></td>
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<tr>
<td>NYHA class</td>
<td>2.9 ± 0.7</td>
<td>2.8 ± 0.7</td>
<td>0.83</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>61.1 ± 9.3</td>
<td>66.8 ± 6.5</td>
<td>0.05</td>
</tr>
<tr>
<td>LAD stenosis, %</td>
<td>85.3 ± 14.4</td>
<td>90.3 ± 12.7</td>
<td>0.69</td>
</tr>
<tr>
<td>Cleveland risk score†</td>
<td>11/3/2</td>
<td>10/5/1</td>
<td>0.64</td>
</tr>
<tr>
<td>Single LAD</td>
<td>12</td>
<td>11</td>
<td>0.99</td>
</tr>
<tr>
<td>LD/LOM/RCA</td>
<td>2/0/2</td>
<td>4/1/0</td>
<td>0.78</td>
</tr>
<tr>
<td>LAST/sternotomy</td>
<td>8/8</td>
<td>8/8</td>
<td>1.0</td>
</tr>
<tr>
<td>Total occlusion time, min</td>
<td>31.3 ± 15.6</td>
<td>33.3 ± 15.9</td>
<td>0.71</td>
</tr>
<tr>
<td>LAD occlusion time, min</td>
<td>23.6 ± 6.7</td>
<td>24.7 ± 10.8</td>
<td>0.74</td>
</tr>
<tr>
<td>Other vessel occlusion</td>
<td>26.0 ± 7.7</td>
<td>27.6 ± 9.8</td>
<td>0.79</td>
</tr>
<tr>
<td>time, min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoflurane before grafting</td>
<td>2</td>
<td>3</td>
<td>0.99</td>
</tr>
<tr>
<td>Norepinephrine (bolus)</td>
<td>3</td>
<td>3</td>
<td>0.65</td>
</tr>
<tr>
<td>before grafting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocking medication</td>
<td>15</td>
<td>15</td>
<td>0.47</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>3</td>
<td>4</td>
<td>1.0</td>
</tr>
<tr>
<td>medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-acting nitrate</td>
<td>13</td>
<td>13</td>
<td>0.65</td>
</tr>
<tr>
<td>medication</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values given as mean ± SD or No. of patients, unless otherwise indicated. NYHA = New York Heart Association; LD = left diagonal artery; LOM = left obtuse marginal artery; LAST = left anterior small thoracotomy.
†Values given as total No. of patients with scores of 0/1/2.
Anesthesia and Surgical Technique

A standardized anesthetic technique was used with sufentanil (7.8 µg/kg), midazolam (0.10 to 0.125 mg/kg for induction and 0.20 mg/kg for maintenance), and pancuronium (0.22 mg/kg). Anesthetic depth was monitored by heart rate (HR) and systemic BP. In the event of sudden increase in HR, the depth of anesthesia was increased with isoflurane for a short period. Other inhalation anesthetics agents were not used, the temperature of the patient was monitored, so that excessive temperature shifts did not occur. Episodes of hypotension were treated with a bolus injection of norepinephrine.

After a patient underwent a median sternotomy or left anterior small thoracotomy, 1 mg/kg heparin was administered on the completion of left internal mammary artery harvesting. Two milliliters papaverine (10 mg/mL) was injected into the distal left internal mammary artery to prevent arterial spasm. The LAD was identified and exposed for a distance of 2 to 3 cm, and two silicon snares were applied proximally and distally to the selected site of the anastomosis. A stabilizer (Origin; Menlo Park, CA) was used at the anastomosis site to provide a relatively still operative field. A CO₂ blower (Ernst Biegler; Mauerbach, Austria) was used to achieve a bloodless anastomosis site. The same procedure also was adopted for anastomosis in other vessels. If multiple grafts were considered, the first anastomosis after the IP protocol was always in the non-LAD vessel by means of a venous or radial artery graft. Intracoronary shunts were not used.

Hemodynamic Measurements and Treatment

HR, central venous pressure (CVP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), cardiac output, and right ventricular ejection fraction (RVEF) were monitored. Derived cardiovascular variables, namely, cardiac index, stroke volume index (SVI), systemic vascular resistance index (SVRI), pulmonary vascular resistance index (PVRI), and right ventricular end-diastolic volume index (RVEDVI), were calculated using standard formulas. Right ventricular (RV) function was measured using a fast-response volumetric thermistor-tipped pulmonary artery catheter (93A-434 h, 7.5F; Baxter Health Care Corp; Irvine, CA) and a microprocessor (Explorer; Baxter Health Care Corp), which allowed the measurement of the diastolic washout plateaus of a thermodilution cardiac output curve using exponential curve analysis. All measurements based on the thermodilution technique were made at end expiration in triplicate using ice-cold saline solution. The mean value of three consecutive measurements was registered for analysis. Before each measurement of the RVEF, the correct position of the catheter and the right atrial delivery site were confirmed by analysis of the transduced pressure waveform. Hemodynamic data were collected at the following four time points: (1) baseline (ie, before the induction of anesthesia); (2) 1 h after revascularization; (3) 6 h after revascularization; and (4) first postoperative day (POD).

Perioperatively, volume infusion was designed to maintain filling pressures at least at the preoperative level and at an optimal level heart performance. Therapy with inotropes (dopexamine, < 1.5 µg/kg/min) or epinephrine (< 0.1 µg/kg/min) was administered to maintain the cardiac index at > 2.0 L/min/m². Amrinone (< 10 µg/kg/min) or norepinephrine (< 0.2 µg/kg/min) was used when dopexamine or epinephrine was insufficient to maintain cardiac output. These infusions, when needed, were continued for at least 6 h. Inotropic therapy was not discontinued at the time points when the hemodynamic parameters were measured. Perioperative infarction was diagnosed if any new Q wave appeared (ie, ranging to one third of the QRS height and lasting for > 0.04 s) or when the level of creatine kinase isoenzyme MB (CK-MB) was > 100 µg/L. The team in the ICU was blinded from the study.

Biochemical Markers

Blood samples were collected from peripheral vessels in the following manner: (1) before IP or vessel occlusion; (2) after the IP protocol in the IP group; (3) 5 min after revascularization; (4) 10 min after revascularization; (5) 6 h after revascularization; (6) during the first POD; and (7) during the second POD. Samples were collected in heparin-coated plastic tubes and underwent centrifugation. Serum samples were measured with an analyzer (Chiron ACS180 Plus; Chiron Diagnostics Corporation; East Walpole, MA) using a direct chemiluminescence method.

Statistical Analysis

Statistical analyses were performed using a statistical software package (SPSS, version 9.0; SPSS Inc; Chicago, IL). An unpaired Student t test (two-tailed) was used for continuous data, and a χ² test or Fisher’s Exact Test was used for categoric data when comparing variables between the groups. In the tests of hemodynamic and biochemical data, an analysis of variance was performed in the repeated-measures design with Bonferroni correction. Data are presented as the mean ± SD. Significance was assumed when p < 0.05.

Results

All but one patient fulfilled the terms of the study protocol. The treatment of this patient (from the IP group) had to be converted to the traditional CPB operation because of technical problems with the LAD anastomosis, and he was excluded from the study due to incomplete data collection. Consequently, one additional patient was recruited for randomization. None of the patients experienced perioperative myocardial infarctions based on our ECG and CK-MB level criteria. None of the patients required an intra-aortic balloon pump, and none presented with cerebral complications.

Hemodynamic Data

The mean HR increased in both groups, but the elevation was more significant among the control subjects, especially on the first POD (p = 0.035 [analysis of variance with repeated-measures design]). There were no significant differences between the groups in terms of mean arterial pressure, CVP, MPAP, PCWP, RVEDVI, SVRI, and PVRI (Table 2).

The baseline of the cardiac index was 2.96 ± 0.74 L/min/m² in the control group and 2.64 ± 0.45 L/min/m² in the IP group (p = 0.175 [t test]). The cardiac index decreased slightly 1 h after reperfusion in the control group (2.54 ± 0.85 L/min/m²) and subsequently recovered (6 h after reperfusion,
3.62 ± 0.90 L/min/m²; first POD, 3.34 ± 0.78 L/min/m²). In the IP group, on the other hand, the cardiac index increased at all three time points after the operation (1 h after reperfusion, 2.74 ± 0.45 L/min/m² [p = 0.666]; 6 h after reperfusion, 3.70 ± 1.41 L/min/m² [p = 0.010]; and first POD, 3.69 ± 0.93 L/min/m² [p = 0.001, t test]). A comparison between the two groups revealed no statistically significant differences in cardiac index after the operation (p = 0.262 [analysis of variance for repeated measures]) [Fig. 1].

The baseline of the SVI was 49.4 ± 6.1 mL per beat per m² in the IP group and 50.8 ± 8.1 mL per beat per m² in the control group (p = 0.598 [t test]). The SVI decreased after the operation in the control group (1 h after vessel reperfusion, 38.3 ± 9.3 mL per beat per m² [p = 0.001]; 6 h after vessel reperfusion, 41.4 ± 9.5 mL per beat per m² [p = 0.008]; and first POD, 39.4 ± 8.9 mL per beat per m² [p = 0.001, t test]). In the IP group, on the other hand, the SVI was slightly decreased at first and then recovered (1 h after vessel reperfusion, 43.8 ± 14.5 mL/beat/m² [p = 0.174]; 6 h after vessel reperfusion, 46.2 ± 15.9 mL/beat/m² [p = 0.465]; and first POD, 50.5 ± 11.8 mL/beat/m² [p = 0.759, t test]). In a comparison between the two groups, the SVI was statistically significantly better in the IP group (p = 0.039 [analysis of variance for repeated measures]) [Fig. 2].

RVEF was measured in 13 IP patients and in 10 control subjects without RCA stenosis. There were no statistically significant differences in RVEF before (43.4 ± 7.5% vs 41.4 ± 5.8%, respectively; p = 0.499 [t test]) or after the operation (1 h after declamping, 45.1 ± 7.9% vs 40.8 ± 9.4%; 6 h after declamping, 44.1 ± 10.3% vs 46.3 ± 8.7%; and first POD, 41.0 ± 6.7 vs 37.6 ± 7.5% [p = 0.652, analysis of variance for repeated measures]) [Fig. 3].
Biochemical Markers

Between the IP patients and control subjects, there was no difference in the baseline level of cardiac troponin I (CTnI) (0.1 ± 0.1 vs 0.1 ± 0.1 μg/L, respectively; p = 0.461 [t test]) or of CK-MB (0.5 ± 0.3 vs 0.7 ± 0.7 μg/L, respectively; p = 0.196 [t test]). CTnI and CK-MB levels increased significantly after the operation, reaching peak values on the first POD (CTnI: IP patients, 1.8 ± 4.2 μg/L; control subjects, 4.6 ± 9.6 μg/L; CK-MB: IP patients, 7.8 ± 11.8 μg/L; control subjects, 11.0 ± 14.6 μg/L). IP resulted in lower values for CTnI release after the operation (p = 0.045 [analysis of variance for repeated measures]) [Fig. 4]. IP patients also had a lower CK-MB release after the operation but without a statistically significant difference (p = 0.100 [analysis of variance for repeated measures]) [Fig. 5]. General linear model analysis showed that the levels of both CTnI and CK-MB after the operation were significantly associated with the total coronary artery occlusion time (p = 0.025 and p = 0.031, respectively).

Postoperative Care

Two patients in the control group experienced ventricular fibrillation after releasing a coronary artery occlusion. There were no statistically significant differences between the groups in the duration of mechanical ventilation and the length of stay in the ICU. Likewise, the use of inotropic or nitroglycerine infusions was similar in the two groups (Table 3).

DISCUSSION

Minimally invasive surgical techniques for CABG often lead to a beating, normothermic, but regionally ischemic heart. Ischemic injury is manifested as contractile dysfunction and vascular endothelial injury. Because of the limited tolerance of the working heart to ischemia under normothermia, the risk of irreversible myocardial damage becomes consid-
end-diastolic pressure. In the present study, the RV, as shown by decreased RVEF and increased RV function, has been reported to be decreased in patients after they underwent an off-pump bypass procedure, even when remote areas of the myocardium from subsequent sustained coronary artery occlusion. Adequate regional ischemia in a beating heart, results in myocardial ischemia/reperfusion injury, as also indicated in our patients by the significant release of CTnI and CK-MB after the operation and by temporary contractile dysfunction (stunning) as demonstrated by a higher HR and a reduced SVI. These findings, which reflect potential injury in cellular viability, were also closely associated with the target vessel occlusion times.

The RV myocardium has been recognized as being the most vulnerable during an on-pump CABG operation. The combined delivery of cardioplegia is insufficient to ensure myocardial protection to the posterior ventricular septum and the RV free wall. Even in addition, experiments with induced anteroseptal myocardial infarction in pigs have shown systolic and diastolic dysfunction in the RV, as shown by decreased RVEF and increased RV end-diastolic pressure. In the present study, the change in RV function in patients after they have undergone an off-pump bypass procedure was not substantial, reflecting the presence of intact biventricular (and septal) myocardial function. Acute anterior/septal infarctions did not occur in either of the groups, despite the fact that the main target vessel was, most frequently, the LAD. All the patients in whom RVEF measurements were made had obstructed RCAs, which favors better postoperative contractility in the RV and may also explain why patients in the IP group did not demonstrate changes in RVEF.

Despite abundant evidence showing that a short period of LAD occlusion protects the heart against subsequent sustained ischemia, there are reports indicating that IP does not improve short-term myocardial function in animals and in simulated conditions resembling those of off-pump surgery. These reports, however, suggest that IP may provide longer term benefits such as improved endothelium-dependent relaxation, endothelial viability, improved β-adrenergic regulation, better postischemic myocardial blood flow, and reduced neutrophil accumulation. When judging these results, it should be noted that they were performed on relatively healthy animal hearts, and the conclusions as such may not be applied to the human hearts undergoing off-pump surgery with obstructed coronary arteries and the potential for collateral circulation.

Table 3—Postoperative Care

<table>
<thead>
<tr>
<th>Variable</th>
<th>IP Group (n = 16)</th>
<th>Control Group (n = 16)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VF after anastomosis</td>
<td>0</td>
<td>2</td>
<td>0.48</td>
</tr>
<tr>
<td>Mechanical ventilation, h</td>
<td>7.8 ± 3.4</td>
<td>8.8 ± 4.2</td>
<td>0.47</td>
</tr>
<tr>
<td>Stay in intensive care, h</td>
<td>21.7 ± 1.7</td>
<td>22.4 ± 1.8</td>
<td>0.27</td>
</tr>
<tr>
<td>Duration of inotropes, h</td>
<td>12</td>
<td>11</td>
<td>0.99</td>
</tr>
<tr>
<td>Dopaexamine or epinephrine</td>
<td>2.1 ± 4.2</td>
<td>3.4 ± 6.8</td>
<td>0.52</td>
</tr>
<tr>
<td>Amrinone/norepinephrine</td>
<td>3</td>
<td>2</td>
<td>0.99</td>
</tr>
<tr>
<td>Free of nitroglycerine</td>
<td>8</td>
<td>8</td>
<td>0.99</td>
</tr>
<tr>
<td>Duration of nitroglycerine, h</td>
<td>8.8 ± 10.0</td>
<td>8.7 ± 10.1</td>
<td>0.97</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD or No. of patients, unless otherwise indicated. VF = ventricular fibrillation.

Local IP in patients undergoing off-pump surgery favored myocardial functional recovery, but its effect was not as evident as in our on-pump patients who had undergone global IP. Obviously, aortic cross-clamping to generate global ischemia for IP renders more IP stimulus from the myocardium than does the local occlusion of the LAD (which only affects the septal and anterior left ventricle). On the other hand, the safety of our patients prevented us from endangering more of the myocardium. LAD occlusion also might have produced less of an IP effect due to the effects of potential collateral circulation in the distal LAD area. The detailed evaluation of the effects of existing collateral circulation is difficult. Since our patients had high-grade coronary artery stenoses, collateral circulation may have reduced the maximal myocardial area that was able to generate the IP effect. Collateral circulation may also directly prevent contractile dysfunction by reducing the size of the ischemic zone. On the other hand, the use of anesthetic agents and inotropic medications in the control group may produce effects resembling IP, thus diluting the studied effect.

In the present study, 2 min of ischemia was chosen for IP because the results of studies of patients...
undergoing coronary angioplasty have shown that IP effects are induced when the vessel is occluded for > 90 s. The use of IP with repeated cycles of ischemic stimuli has been proposed to ensure the protective effects. The ideal IP protocol should have a minimal permanent ischemic effect, and vessel occlusion should not be repeated many times to prevent inconvenience to the main bypass procedure, but should, on the other hand, induce the maximal myocardial protective effects. In conclusion, we have shown that two periods of 2 min of ischemia in the LAD area followed by 3 min of reperfusion has cardioprotective effects in patients undergoing off-pump CABG, as demonstrated by a smaller amount of specific enzyme release and a slightly better hemodynamic recovery.

REFERENCES

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