Coronary artery bypass grafting supported with intracardiac microaxial pumps versus normothermic cardiopulmonary bypass: a prospective randomized trial

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Abstract

Objective: To analyze the difference in coronary artery bypass grafting (CABG) performed with normothermic cardiopulmonary bypass (CPB) and CABG supported with the intracardiac microaxial pump (ICP, Impella, Aachen, Germany). Methods: A prospective randomized study was conducted in seven centers. The study population consists of 199 patients undergoing isolated primary CABG (CPB group 94 patients, ICP group 105 patients). Both groups are equal in demographic variables, number of bypasses performed, and Euroscore predicted mortality. We analyzed clinical outcome, myocardial enzymes and blood parameters of hemolysis, organ function and inflammatory response. Results: Seventeen patients (16%), randomized in the ICP group, were switched to the CPB group. This was due to the inability to position the right side catheter adequately (n = 8), to a pump failure (n = 1) or to the perioperative decision that beating heart surgery is technically not possible (n = 8). There was no significant difference between the two study arms regarding the pump assistance time (CPB 67.1 ± 22.9 min; ICP 67.7 ± 30.3 min; P = 0.88861), the number of grafts (CPB 2.4 ± 0.7; ICP 2.3 ± 0.8) and the number of grafts to the back wall (CFX; both groups n = 37). There is no significant difference in clinical outcome, evolution of myocardial enzymes, indices of organ function and hemolysis. There is a reduced inflammatory response in the ICP group as indicated in the postoperative release of granulocyte elastase (CPB 259 ± 195; ICP 150 ± 126 µg/l; P < 0.00001) and complement C3 (CPB 0.73 ± 0.2; ICP 0.65 ± 0.2 g/l; P = 0.008). Conclusion: The intracardiac pump for the right heart is difficult to introduce. As a consequence the right side pump underwent design modifications. There were no differences in clinical outcome between both groups. The inflammatory response is significantly reduced in the ICP group. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Coronary artery bypass grafting; Microaxial blood pumps; Cardiopulmonary bypass; Myocardial support

1. Introduction

Cardiopulmonary bypass (CPB) is reported to evoke inflammatory reactions and is associated with postoperative complications as fluid retention, organ dysfunction and bleeding [1–5]. Several centers now perform beating heart surgery avoiding the CPB-mediated inflammatory response [6–8]. A third option in revascularization techniques is to perform supported beating heart surgery. Experimental studies have shown that mechanical support during short periods of ischemia leads to reduced myocardial oxygen consumption and improved myocardial contractility [9–11].

The primary objective of this study was to investigate and compare the safety and efficacy aspects in coronary artery bypass grafting (CABG) performed with normothermic
CPB and CABG supported with the intracardiac microaxial pump (ICP, Impella, Aachen, Germany).

The secondary objectives are to demonstrate the ability to provide sufficient hemodynamic support and to analyze the inflammatory response.

2. Materials and methods

2.1. Inclusion, exclusion and demographics

Between 22nd November 1999 and 19th December 2000, 199 patients were included in the study in seven centers in Germany and Belgium (RWTH Aachen, Charité Berlin, Herzzentrum Dresden, MH Hannover, University of Kiel, Herzzentrum Leipzig and University of Leuven). The local ethics committees had approved the study protocol. After informed consent, patients were randomized to undergo either revascularization with normothermic CPB (n = 94) or with support of the ICP (Impella, Aachen, Germany) (n = 105). Patients were included regardless of the degree of ischemic heart disease (single, double, triple vessel disease) but were only randomized if the surgeon judged that the supported beating heart procedure was technically possible. Major exclusion criteria were: patients younger than 18 years, ejection fraction \(<30\%\), cardiac index \(<2\ l/min\ m^2\), acute myocardial infarction within the last 24 h, pulmonary hypertension, body mass index (BMI) \(>37\ kg/m^2\), atrial fibrillation, serum creatinine \(>2.0\ mg/dl\) or severe pulmonary artery obstructive disease.

Table 1 shows the demographic data of the patient groups. Both groups are comparable in demographic variables, number of bypasses performed, and Euroscore predicted mortality.

2.2. The ICPs

The ICPs (Impella Cardiotechnik, Aachen, Germany) consist of a left ventricular and a right ventricular support pump (Fig. 1). The driving electromotor is miniaturized and incorporated in the pumps. The catheter contains the electrical supply. The left ventricular pump aspirates the blood from the ventricular cavity and expels it in the ascending aorta. In clinical conditions the pump provides \(4.2 \pm 0.5\ l/min\) at its maximal rotational speed of 32,500 rotations/min. The exact position of the pump is indicated by the differential pressure sensor displaying the pressure difference between left ventricular cavity and aorta. The inflatable ring balloon on the tip stabilizes the pump. The left side pump is positioned across the aortic valve and aspirates the blood from the left ventricle and pumps it in the ascending aorta.

2.3. Surgical procedure

In all patients surgical access was gained through a median sternotomy. After harvesting the arterial and/or venous bypass grafts, the patients received heparin with a target ACT of at least 400 s, which was antagonized with protamine sulfate after operation. The technique of normothermic CPB and treatment in the intensive care unit (ICU) was defined by individual institutional standards of each center.

The left side support pump was inserted via an introducer.
on the ascending aorta. The pump was then advanced across the aortic valve on guidance of the differential pressure sensor. Transesophageal echocardiography was used to confirm the position. The right side pump was introduced through a purse-string on the right atrium. The pressure channel at the tip of the cannula allows to confirm the presence of the cannula in the pulmonary artery. In the ICP group, regional ischemia was applied by snaring the target vessel.

2.4. Protocol

Technical ease of introduction and use of the ICP was assessed. Evolution of mean arterial pressure and mixed venous oxygen saturation were assessed during the procedure. Hemolysis (by means of plasma free hemoglobin), liver metabolism (defined by total bilirubin), renal function (defined by serum creatinine), myocardial ischemia (defined by creatine kinase, troponin I), cellular counts and inflammatory response (defined by lymphocyte counts, complement C3 and granulocyte elastase) were assessed preoperatively, perioperatively, on postoperative days 1–3, at discharge and at 3 months follow-up. A creatine kinase release exceeding three times the upper level of the normal value, with a 10% myocardial fraction, was considered to indicate a perioperative myocardial infarction.

2.5. Statistical analysis

All continuous data are shown with their mean value and standard deviation. The statistical analysis and statistical processing were performed using SAS statistical software (SAS Institute Inc., Cary, NC, USA). Differences between the two groups were analyzed with the Fisher exact test for nominal data and the Wilcoxon test for continuous data. A P-value <0.05 was considered statistically significant.

3. Results

3.1. Hemodynamic efficiency

Seventeen patients (16%) randomized in the ICP group were switched to the CPB group. This was due to the inability to position the right side catheter adequately (n = 8), to a pump failure (n = 1) or to the perioperative decision that beating heart surgery is technically not possible (n = 8).

There was no significant difference between the two study arms regarding the pump assistance time (CPB 67.1 ± 22.9 min; ICP 67.7 ± 30.3 min; P = 0.88861), the number of grafts (CPB 2.4 ± 0.7; ICP 2.3 ± 0.8) and the number of grafts to the back wall (CFX; both groups n = 37). The mean arterial pressure (Fig. 2) during pump assistance is significantly different between the groups (CPB 61.0 ± 7.4 mmHg; ICP 69.9 ± 7.5 mmHg; P = 0.0001).

Flow rates obtained by the ICP depend on the pressure head for the pump and the rotational pump speed (Fig. 3). The flow rates achieved during surgery at the highest rotational speed is 4.1 ± 0.6 l/min.

3.2. Patient outcome

Patient outcome (30-day mortality), perioperative myocardial infarction, reoperation rate and occurrence of CVA are shown in Table 2. There is no difference in patient outcome. There is no difference in postoperative release of troponin I or creatine kinase in both groups. All myocardial infarctions, except two, occurred in the same institution (as well in the ICP as in the CPB group).

There is no difference in ICU time or hospital stay. There is no difference in hemolysis as measured by free plasma hemoglobin (Fig. 4). However, four patients from the ICP group had a peak value of free plasma hemoglobin
for patients having CPB.

In Table 2, there is no difference in peri and postoperative evolution of granulocytes, leucocytes, monocytes or thrombocytes. The postoperative serum levels of D-dimers and antithrombin III were continuously higher for the CPB group but the differences are not significant. There is a significant difference in granulocyte elastase ($P < 0.00001$) and complement C3 ($P = 0.008$) release in relation to pump support. Both sensitive parameters of inflammatory response were significantly higher in the CPB group as compared to the ICP group.

### 4. Discussion

More and more CABG procedures are performed on the beating heart and evidence is growing that beating heart CABG reduces the morbidity of coronary surgery. Still it is obvious that beating heart surgery remains technically demanding and that the highest care is required to perform coronary anastomoses with the same quality as done on the cardioplegic arrested heart [12]. The success of beating heart CABG is based on the development of improved stabilizers and techniques to manipulate the heart. The hemodynamic challenge and the application of warm regional ischemia have given rise to the question of optimizing the technique with protective measures. The clinical benefit of additional strategies such as adenosine, beta-blockers, ischemic preconditioning or mechanical unloading are still to be elucidated.

Unloading of the left heart during coronary occlusions has been shown to be beneficial in animal studies as well as in clinical experience [9–11,13,14]. It results in reduced myocardial oxygen consumption during the procedure and leads to improved myocardial perfusion and superior myocardial function after the procedure [9–11]. The need for a right heart support system originates from the initial observation that lifting the heart leads to a kink of the right ventricle [15]. Several surgeons have overcome this

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**Table 2**

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>ICP</th>
<th>CPB</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>104</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Euroscore predicted mortality</td>
<td>3.2 ± 2.1</td>
<td>3.0 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality (30-day) %</td>
<td>2.9</td>
<td>2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Grafts performed</td>
<td>2.3 ± 0.8</td>
<td>2.4 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Grafts performed to RCA/LAD/CX (%)</td>
<td>47/87/37</td>
<td>44/92/39</td>
<td>NS</td>
</tr>
<tr>
<td>Q-wave AMI (%)</td>
<td>0</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Subendocardial AMI (%)</td>
<td>6.9</td>
<td>5.4</td>
<td>NS</td>
</tr>
<tr>
<td>Reoperation for bleeding (%)</td>
<td>5.7</td>
<td>2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>1.9</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Mean stay intensive care (h)</td>
<td>54 ± 62</td>
<td>42 ± 55</td>
<td>NS</td>
</tr>
<tr>
<td>Mean hospital stay (days)</td>
<td>10.6 ± 4.2</td>
<td>9.6 ± 3.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

*a* Acute myocardial infarction (AMI) is defined as a creatine kinase level exceeding three times the upper limit of the normal value with a 10% myocardial fraction. All infarctions but two occurred in the same center.

**Table 3**

<table>
<thead>
<tr>
<th>Cellular counts and plasma levels of inflammatory parameters at 2 h after the procedure</th>
<th>ICP</th>
<th>CPB</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucocytes (10×9/l)</td>
<td>12.3 ± 4.4</td>
<td>11.3 ± 4.4</td>
<td>NS</td>
</tr>
<tr>
<td>Granulocytes (%)</td>
<td>78 ± 8.1</td>
<td>78 ± 6.1</td>
<td>NS</td>
</tr>
<tr>
<td>Eosinophilic leucocytes (%)</td>
<td>1.48 ± 0.98</td>
<td>1.26 ± 0.97</td>
<td>NS</td>
</tr>
<tr>
<td>Basophilic leucocytes (%)</td>
<td>0.65 ± 0.41</td>
<td>0.65 ± 0.41</td>
<td>NS</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>5.31 ± 2.56</td>
<td>5.1 ± 2.72</td>
<td>NS</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>14 ± 7.5</td>
<td>13 ± 6.8</td>
<td>NS</td>
</tr>
<tr>
<td>Platelets (10×9/l)</td>
<td>144 ± 54</td>
<td>163 ± 50</td>
<td>NS</td>
</tr>
<tr>
<td>Antithrombin III (%)</td>
<td>60 ± 15</td>
<td>68 ± 15</td>
<td>0.00074</td>
</tr>
<tr>
<td>D-dimers (µg/dl)</td>
<td>0.75 ± 0.65</td>
<td>1.06 ± 2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Granulocyte elastase (µg/l)</td>
<td>150 ± 126</td>
<td>259 ± 195</td>
<td>0.000001</td>
</tr>
<tr>
<td>Complement C3 (g/l)</td>
<td>0.65 ± 0.2</td>
<td>0.73 ± 0.2</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*a* ICP, intracardiac pump; CPB, cardiopulmonary bypass.

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**Fig. 4.** Plasma free hemoglobin levels for the ICP supported group (solid line) and the CPB group (dotted line).
problem by manipulation measures such as Trendelenburg position, pericardial suspension stitches and opening of the right pleural cavity. In this study the introduction of the right side pump proved to be the most difficult part. The procedure was inadequate in 12 patients leading to further design changes of the right side catheter; the current right ventricular support system bypass the blood from the right atrium directly into the pulmonary artery avoiding the difficult guidance of the outflow cannula through the right heart. It is placed via standard cannulation of the right atrial appendage and the pulmonary artery and initiated by a quick connection.

Clinical outcome did not differ in both groups. However, the primary endpoint of this study was to evaluate the safety of a new revascularization technique with intravascular blood pumps. The focus of the study was feasibility, hemodynamic performance and hemolysis. Therefore, the study design and the limited number of patients (n = 200) allow no clear estimate of the advantages and disadvantages of this technique on clinical outcome. In addition, the inclusion of seven different centers attributes to the variety of the data and emphasizes the learning curve of such a new technology. The only relevant difference in this study is the reduced level of granulocyte elastase and complement C3 release in the ICP group indicating a reduced inflammatory response very similar to the findings in off-pump surgery. This reduction in inflammatory parameters did not result in any clinical effect. A reduced inflammatory response can be explained by the reduction of foreign material contact area. The patient’s own lungs are used for oxygenation and no cardiomyotomy suction or venting catheter is used. The finding that hemodilution is less pronounced in the ICP group might as well be of clinical interest.

The occasional occurrence of organ dysfunction and multiple organ failure associated with the use of CPB is evoked by the CPB-related inflammatory response [16]. Revascularization with mechanical support is not only similar to beating heart surgery in the reduction of inflammatory response, it is also technically very much alike. Therefore, it requires the same technical demands and entangles the same dangers as off-pump surgery. Having shown that the procedure is feasible and that inflammatory response is reduced does not delineate the correct indications for this technology. It is obvious that a great number of patients can undergo off-pump surgery without the need of any support. The unloading capacities of the intracardiac blood pumps can, however, play a crucial role in patients where hemodynamic support is preferred and especially in patients with reduced ventricular function.

Acknowledgements

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References


Appendix A. Conference discussion

Dr B. Messmer (Aachen, Germany): I am a little bit surprised that the bleeding is higher in the impaired group than it is in the regular ECC group because one would expect that in the ECC group the bleeding is a bigger problem. Do you have an explanation for that?

Dr Meyns: No. I must be very honest, I have the same surprise as you have. I expect that this bleeding should be less of a problem, but it turned out that there were more revisions for bleeding; although the difference was not significant, there were more revisions for bleeding, yes.

Dr A. Mazzucco (Verona, Italy): Referring to your final statement, are you actually telling us that use of this means of circulatory assistance is no longer to be your recommendation? I mean, are you going to stop using this machine?

Dr Meyns: Well, as a matter of fact we are doing more than 90% of our cases completely off-pump surgery. So the question is, where do you have the place of support of beating heart surgery? I personally believe that the unloading of the left ventricle might be critical in patients who have a bad ventricular function, but in the routine cases with a normal ventricular function, I think that off-pump surgery is the first choice.

Dr M. Irarrazaval (Santiago, Chile): You are planning to use this as support for off-pump cases?, because you are requiring a substantial manipulation of the aorta by introducing the pump through the aorta and the aortic valve, and you still have to do the proximals. So it will only be in a very selective group of patients where supposedly “off-pump plus” is more beneficial. Those that have probably a stronger need for a decreasing inflammatory response will be likely candidates. Is that your idea?

Dr Meyns: Well, as I just said, I think that the first choice in the non-emergent CABG patients should be complete off-pump surgery without any support, however, in patients where you have got problems with a bad ventricle or ongoing ischemia, I think that these pumps can help. But I agree completely, you still have the manipulation of the aorta, and in terms of the advantages of off-pump for stroke, this procedure will not give you any advantage.