Prospective Randomized Comparison of Coronary Bypass Grafting With Minimal Extracorporeal Circulation System (MECC) Versus Off-Pump Coronary Surgery

Valerio Mazzei, MD; Giuseppe Nasso, MD; Giovanni Salamone, MD; Filippo Castorino, MD; Antonello Tommasini, MD; Amedeo Anselmi, MD

Background—We aimed to evaluate the clinical results and biocompatibility of the minimal extracorporeal circulation system (MECC) compared with off-pump coronary revascularization (OPCABG).

Methods and Results—In a prospective randomized study, 150 patients underwent coronary surgery with the use of MECC and 150 underwent OPCABG. End points were (1) circulating markers of inflammation and organ injury, (2) operative results, and (3) outcome at 1-year follow-up. Operative mortality and morbidity were comparable between the groups. Release of inflammatory markers was similar between groups at all time points (peak interleukin-6 167.2 ± 13.5 pg/mL, P = 0.14, OPCABG versus MECC group, respectively). Peak creatine kinase was 419.3 ± 103.5 versus 326 ± 84.2 mg/dL (P = 0.28), and peak S-100 protein was 0.13 ± 0.08 versus 0.29 ± 0.1 pg/mL (P = 0.058, OPCABG versus MECC group, respectively). Length of hospital stay and use of blood products were similar between groups. Two cases of angina recurrence at 1 year in the MECC group were observed versus 5 cases observed in the OPCABG group (P = 0.44). A residual perfusion defect at myocardial nuclear scan was less frequent among patients in the MECC group (3 versus 9 cases, P = 0.14; odds ratio 0.32, 95% confidence interval 0.07 to 1.32). Six (OPCABG group) versus 3 (MECC group) coronary grafts were occluded or severely stenotic at 1 year (P = 0.33, odds ratio 0.47, 95% confidence interval 0.09 to 2.14).

Conclusions—Clinical results of coronary revascularization with MECC are optimal when this procedure is performed by experienced teams. Postoperative morbidity is comparable to that with OPCABG. MECC is associated with little pump-related systemic and organ injury. It may achieve the benefits of OPCABG (less morbidity in high-risk patients) while facilitating complete revascularization in the case of complex lesions unsuitable for OPCABG. (Circulation. 2007;116:1761-1767.)

Key Words: surgery • coronary disease • grafting • cardiopulmonary bypass • complications
institution a total of 300 individuals according to the following criteria: The patient was scheduled for elective isolated myocardial revascularization performed via full median sternotomy and had been judged technically suitable for both OPCABG and MECC. Indication for coronary surgery was established on the basis of current published guidelines.6 We excluded all patients with documented preoperative systemic proinflammatory status and/or steroid administration within 6 months before surgery, as well as patients who had single-vessel disease.

After inclusion, patients were randomized to receive either off-pump surgery (OPCABG group) or minimal extracorporeal circulation (MECC group) according to a computer-generated algorithm. The local ethics committee approved the protocol, and all patients provided written consent to enter the study.

Study End Points
Main study end points were release of circulating markers of organ injury and release of circulating markers of inflammation. Secondary study end points were in-hospital results (including mortality and complications) and clinical outcome at 1-year follow-up.

Preoperative Evaluation
Chest radiography, transthoracic echocardiography, and coronary angiography with cineventriculography were performed in all patients before surgery.

Surgical Strategy
Because the study subject (use of MECC) is very technical, we began this investigation only after we had achieved a satisfactory experience with and mastery of this technique. No major changes were introduced in our surgical and anesthesia protocols during the study period. A median sternotomy approach was performed in all patients. MECC (Jostra MECC system, Jostra Inc, Hirrlingen, Germany) is a fully heparinized, closed-loop circuit that minimizes blood-air contact (absence of cardiotomy reservoir). Blood is drained from the right atrium by a conventional cannula, passes through a centrifugal pump and a membrane oxygenator with integrated heat exchanger, and is pumped into the ascending aorta. A cardioplegia line is available, and the intrapericardial suction device line drains to the centrifugal pump. A filter is added in the arterial line to remove microbubbles and particles. The system can support flows ranging from 0.5 to 7 L/min and requires half-dose systemic heparinization (150 IU/kg, target activated clotting time between 250 and 300 seconds). Total length of the circuit is <1 m. Particular care must be taken to avoid air intake into the circuit, especially at the site of the right atrial pursestring suture and during connection of the venous cannula to the venous line. We used multidose normothermic blood cardioplegia delivered by the antegrade route. After institution of CPB through MECC and cardioplegic arrest, bypass grafting is performed in a standard fashion similar to that used for on-pump CABG. When the proximal anastomoses are performed and stable heart rhythm is obtained, the flow is gradually decreased, and after achievement of stable hemodynamic status, the patient is disconnected from the circuit. In patients operated on with OPCABG, an apical suction heart positioner and tissue stabilizer devices were used (Xpose II, Guidant Corp, Cupertino, Calif). During heart dissection, patients were placed in the Trendelenburg position.

The left internal thoracic artery was harvested skeletonized and was always used to graft the left anterior descending coronary artery only or the left anterior descending coronary artery and the diagonal branch (sequential grafting). The great saphenous vein was used to revascularize non–left anterior descending coronary artery targets. During operations, a traditional heart-lung machine was available in the operating room. Both the use of MECC and the performance of OPCABG are challenging techniques with long training curves; the operations included in the present study were performed by the same surgeon (VM) trained in both techniques.

Biochemical Methods
Blood samples were collected from a peripheral vein at the following time points: (1) the day before the operation; (2) immediately after weaning from extracorporeal circulation (MECC group) and immediately after performance of the last proximal anastomosis and release of tissue stabilizers (OPCABG group); (3) 6 hours postoperatively; and (4) 24 hours postoperatively. The samples were centrifuged at 5000 rpm for 10 minutes, and the supernatant was stored at −80°C. Content of interleukin-6 (IL-6) and of S-100 protein was determined in equal amounts of supernatant with an ELISA kit (Bender MedSystems Inc, Burlingame, Calif) according to the manufacturer’s instructions and expressed in picograms per milliliter. Creatine kinase (CK) content was determined by standard laboratory measurements.

Postoperative Monitoring and Follow-Up
During the intensive care unit stay, details of the course of each patient were collected prospectively. Adverse postoperative events included in the analysis were death, renal insufficiency, stroke, shock, sepsis, and myocardial infarction. Follow-up lasted 12 months after hospital discharge and was 99.3% complete; 2 patients were lost to follow-up. Surviving patients underwent clinical examination and instrumental follow-up (including surface ECG and transthoracic echocardiography) at 1, 6, and 12 months postoperatively; all of these patients also had a functional test by means of a myocardial stress perfusion nuclear scan within 12 months after surgery.

Statistical Analysis
All data were included prospectively in an electronic database and processed with SPSS (Statistical Package for Social Sciences) software release 11.0 for Windows (SPSS, Chicago, Ill). Data analysis was performed blindly with respect to the nature of surgery undergone by the patients. Continuous variables are expressed as mean±SD. Categorical variables are expressed as percentages. The 2-tailed Student t test for continuous variables and χ2 test for discrete variables were used for group comparisons. Yates correction was applied when appropriate. The α-level was 0.05. For survival analysis, Cutler-Edender actuarial survival curves were constructed. Sample size and power calculations were performed with PS software, version 2.1.30 for Windows.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
In-Hospital Results
One hundred fifty patients were assigned to the MECC group and 150 to the OPCABG group. Preoperative features of the study groups are summarized in Table 1 and conditions are defined in Table 2. In Table 3, operative details and in-hospital results are reported (end point 3). In 6 patients, emergency conversion to standard CPB occurred (4 because of hemodynamic instability and in 2 because of severe ventricular arrhythmias), and these patients were excluded from the present study. In the MECC group, we observed 5 cases of difficulty in weaning the patient from extracorporeal circulation; these patients required reinstitution of the MECC circuit and maximal inotropic support. Three of these patients were transferred to the intensive care unit after placement of an intra-aortic counterpulsator in the operating room, and they experienced low-output syndrome during the course of...
their stay in the intensive care unit. In the OPCABG group, 2 individuals required the use of an intra-aortic balloon pump under similar conditions. Overall, operative times were slightly higher in the MECC group (P=0.027); this is reasonable owing to time lost for the placement of the canula and for the institution of and weaning from extracorporeal circulation. No other statistically significant differences in intraoperative technical factors were evident between the groups. In-hospital mortality (defined as 30-day mortality) was 1.4% and 2% in the MECC and OPCABG groups, respectively (2 versus 3 patients; P=0.99). No statistically significant differences existed in length of intensive care unit and hospital stay, complications rate, or need for allogeneic transfusion. Causes of death were multiorgan failure in 3 cases, myocardial infarction in 1, and stroke in 1. Despite institution of an extracorporeal circuit, MECC patients were characterized by low hemodilution, with a mean drop in hematocrit comparable to that of OPCABG patients (7.8±1.2% versus 6.7±2.4%, P=0.18). This result is striking mainly if compared with the degree of hemodilution associated with CPB with a heart-lung machine as reported in the literature (mean 15% fall in hematocrit).

Biochemical Results

We adopted IL-6 as a marker of systemic inflammation and CK and S-100 protein as markers of myocardial and brain injury (end points 1 and 2). Figure 1 displays the mean release of biochemical indicators at the various study time points. IL-6 peaked at the 6th postoperative hour but dropped by nearly 50% at the 24th hour in both groups (peak IL-6 167.2±13.5 versus 181±6.5 pg/mL in the OPCABG versus MECC group, respectively; P=0.14). CK serum activity rose regularly over time; reasonably, the expected fall in CK activity occurred later than the 24-hour time point (peak CK 419.3±103.5 versus 326±84.2 mg/dL in the MECC versus OPCABG group, respectively; P=0.28). S-100 protein values displayed a peak at the end of surgery (0.13±0.08 versus 0.29±0.1 pg/mL in the OPCABG versus MECC group, respectively; P=0.058); this peak was more evident among patients who underwent surgery with use of MECC. The mean release of these markers at the other time points was not statistically different. Of note, all markers showed a similar temporal pattern in both groups, and although the mean values for MECC patients (dotted line in Figure 1)
were regularly above those of OPCABG patients, a statistically significant difference always was present between the curves. The calculation of statistical power for analysis of the intergroup difference with regard to the levels of IL-6, CK, and S-100 protein yielded values >0.90 in all 3 cases.

One-Year Results

The 1-year mortality rate was 2.7% and 3.4% in the MECC and OPCABG groups, respectively ($P=0.99$; Table 4). Figure 2 displays overall survival and angina-free survival. Both overall survival and angina-free survival rates were not statistically different between the study groups at any time point. Two and 5 patients in the MECC and OPCABG group, respectively, complained of recurrence of angina at 1 year. Each of these patients showed a residual perfusion defect on a control stress myocardial nuclear scan. Perfusion defects were less frequent among individuals in the MECC group (3 versus 9 cases), although the difference was not statistically significant ($P=0.14$, odds ratio 0.32, 95% confidence interval 0.07 to 1.32). These patients underwent control coronary angiography that revealed occlusion or severe stenosis of 9 coronary grafts (8 venous grafts and 1 internal mammary artery graft) in 9 patients (6 belonging to the OPCABG group, $P=0.33$, odds ratio 0.47, 95% confidence interval 0.09 to 2.14) and progression of disease of native coronary arteries in 3 patients.

Table 4. End-of–Follow-Up Results

<table>
<thead>
<tr>
<th></th>
<th>MECC Group</th>
<th>OPCABG Group</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-year mortality</td>
<td>4 (2.7)</td>
<td>5 (3.4)</td>
<td>0.99</td>
</tr>
<tr>
<td>Angina recurrence</td>
<td>2 (1.4)</td>
<td>5 (3.4)</td>
<td>0.44</td>
</tr>
<tr>
<td>Perfusion defect*</td>
<td>3 (2)</td>
<td>9 (6)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Values are number of patients (%).

*At control stress myocardial nuclear scan.
Discussion

Despite technological ameliorations and improvements in anesthesiological care, the morbidity related to traditional CPB cannot be abolished completely. The concept of MECC is based on previous research on the heparin-coated circuit, a reduced systemic heparin dose, and avoidance of cardiotomy suction. These have been associated with less activation of granulocytes and platelets, minimal blood transfusion, and rapid postoperative mobilization. The advantages of MECC for coronary surgery compared with conventional OPCABG have been documented with regard to less inflammatory activation, better global organ protection, and brain injury during extracorporeal circulation is mainly due to the release of inflammatory mediators with the potential to alter the brain-blood barrier. Previous findings in the literature support this concept. Taken together with the finding that the rate of cerebrovascular accidents was not significantly different between the study groups, this indicates that MECC achieves a degree of brain protection that is comparable to that attributed to off-pump procedures. Tailored investigations will be needed to address the neurocognitive outcome of individuals who undergo surgery with MECC. For this purpose, neuron-specific enolase and the tau protein may be more useful markers than the S-100 protein.

Some authors have noted no effect on 5-year cognitive and cardiac outcomes if CPB is avoided. However, complete revascularization may be not achievable off-pump in all individuals owing to the complex anatomy of coronary lesions and the possibility of hemodynamic instability while the beating heart is being manipulated. The present study suggests that MECC can achieve clinical results that are comparable to those of OPCABG. Although nonelective patients were excluded from the present study because we still do not use MECC for nonelective surgery, no further restrictions were imposed with regard to enrollment, and the study patients presented with a wide spectrum of comorbidities. Therefore, the present prospective randomized investigation compares OPCABG with coronary revascularization with MECC in a large institution-based cohort of routine cardiac surgical practice. These results should be considered provisional and worthy of further investigation, because the relatively small sample size of the present study is a potential drawback to our conclusions about 1-year mortality rates.

The major finding of the present investigation is that the degree of systemic inflammatory reaction and organ (cardiac and brain) damage after coronary revascularization with the heart arrested and with the use of MECC is comparable to that seen in patients who were operated on without any form of CPB. Contact between blood and the foreign surfaces of the extracorporeal circuit has long been believed to be the main trigger of blood cell activation and cytokine release. The present experience also confirms previously published findings that blood-air contact and total length of the circuit are the main determinants of such activation and subsequent tissue injury. MECC is a closed circuit and involves little or no blood-air contact. It also combines heparin coating with the small total length of the circuit. Heparin coating may decrease thrombin formation and even inflammatory reaction. The open blood reservoir for extracorporeal perfusion is independently associated with greater systemic activation than with a closed reservoir. MECC also requires a small priming volume (≈500 mL), which contributes to less hemodilution in the early postoperative period.

The S-100 protein previously has been suggested as a marker of brain injury during extracorporeal circulation. Its levels rise considerably during standard CPB compared with OPCABG. Previous studies suggested that a major portion of circulating S-100 protein may be of extracerebral origin, and this must be acknowledged as a potential limitation of the present findings. However, no cardiotomy suction was used in the study groups, and a cell-saving device was used exclusively to treat the shed blood; at the same time, differences between the study groups were few and nonsignificant. These factors might preserve the diagnostic value of S-100 protein in the present study. In the MECC group, serum levels of S-100 protein were not significantly higher than those found in the OPCABG group. This suggests that brain injury during extracorporeal circulation is mainly due to the release of inflammatory mediators with the potential to alter the brain-blood barrier. Previous findings in the literature support this concept. Taken together with the finding that the rate of cerebrovascular accidents was not significantly different between the study groups, this indicates that MECC achieves a degree of brain protection that is comparable to that attributed to off-pump procedures. Tailored investigations will be needed to address the neurocognitive outcome of individuals who undergo surgery with MECC. For this purpose, neuron-specific enolase and the tau protein may be more useful markers than the S-100 protein.

Inadequate myocardial protection and tissue inflammation are the main determinants of myocardial damage during cardioplegic arrest and hence of postoperative myocardial recovery. It is also known that a reduced inflammatory reaction is associated with less myocardial injury at a cellular/molecular level (less oxyradical stress and less disturbance of cellular calcium homeostasis). OPCABG and MECC were associated with similar degrees of mean IL-6 release, with a 14-pg/mL difference at peak. The difference was not statistically significant at any time point. Given this perspective, MECC may facilitate myocardial protection compared with conventional CPB. In support of this idea, serum CK activity showed no statistically significant differences between groups, and previous investigations evidenced a significantly lower release of troponin T after MECC than with standard CPB. Data indicate that the extent of myocardial damage is comparable between OPCABG and MECC with cardioplegic.
arrest and adequate myocardial protection. Varying degrees of cardiac manipulation during surgery raise questions about the reliability of CK in these settings and are acknowledged as a potential limitation to this conclusion. All investigated markers had comparable temporal courses in both groups (rising and dropping at the same time intervals). This suggests that common pathophysiological mechanisms are at the root of such variations. Hence, surgical trauma appears to play a predominant role over the extracorporeal circulation achieved by MECC in the triggering of systemic damage.

With regard to secondary outcomes, the present results also suggest that the rates of mortality and angina-free survival at 1-year follow-up may not be statistically different between patients who had coronary revascularization with MECC versus OPCABG. Larger sample sizes are needed, however, to provide a definitive answer on this topic. Graft patency rates are another major issue. Recently, a meta-analysis of randomized trials of OPCABG versus on-pump revascularization has underscored the fact that OPCABG is associated with a significant increase in the overall graft occlusion rate, particularly the venous graft occlusion rate, compared with on-pump surgery.22 In the present study, we found a non-statistically significant lower perfusion defect rate and graft occlusion rate in the MECC group. It is difficult to draw conclusions from this finding, because the patient population was too small, and therefore, the study had insufficient statistical power to reliably address these problems; a comparison of MECC versus on-pump CABG is needed to clarify this issue. Additionally, previously published data on mid-term follow-up of coronary revascularization with the use of MECC are very scarce. However, the present data indicate that MECC may be associated with a better outcome of coronary grafts; this might be explained by the achievement of a still and bloodless operating field as in traditional on-pump revascularization. Further investigation on this topic is warranted. A multicentric study would have the potential to enroll adequate patient populations and demonstrate the reproducibility of the results of MECC.

Taken together, the evidence suggests that OPCABG and coronary surgery with MECC and cardioplegic arrest should be considered equivalent tools with respect to reduction of postoperative morbidity. Although these conclusions are provisional and warrant further investigation, MECC may be used in high-risk patients when complex anatomy of coronary lesions renders off-pump surgery technically unreasonable. From a technical point of view, a less challenging procedure (or the possibility of achieving complete revascularization of coronary targets that are unsuitable for off-pump procedures) may be beneficial in such a setting. MECC dramatically lessens the CPB-related systemic inflammatory reaction, thus improving organ protection. The present data confirm previous findings that blood-air contact and total length of the circuit are the main determinants of blood cell activation.

Disclosures

None.

References

CLINICAL PERSPECTIVE

In the current era of worsening risk profile of the population referred for cardiac surgery, avoidance of the use of a pump and the subsequent adverse systemic reaction has been regarded as a strategy to manage the risk of perioperative mortality and morbidity in coronary revascularization. However, the applicability of off-pump coronary artery bypass grafting is limited by its demanding profile and by the possibility of incomplete revascularization in some cases with complex anatomy of the coronary lesions. The present investigation provides evidence that the degree of the systemic inflammatory reaction and the release of markers of end-organ damage are comparably modest whether coronary revascularization is performed off-pump or on-pump with the use of the minimal extracorporeal circulation system. This biochemical finding is reflected by the comparability of mortality, morbidity, and intensive care unit/hospital length of stay after the use of either strategy despite a similar preoperative risk profile of the study groups. This experience ultimately poses 3 questions: (1) Can the minimal extracorporeal circulation system and off-pump coronary artery bypass grafting be considered equivalent tools to obtain a lower rate of perioperative morbidity? (2) If yes, should we more liberally use the minimal extracorporeal circulation system to perform on-pump coronary surgery in elderly and high-risk candidates? And (3) will this facilitate complete revascularization and perhaps better graft patency rates than with off-pump coronary artery bypass grafting? Adequate answers to these questions cannot be obtained without rigorous continuing multicenter investigations.
Prospective Randomized Comparison of Coronary Bypass Grafting With Minimal Extracorporeal Circulation System (MECC) Versus Off-Pump Coronary Surgery
Valerio Mazzei, Giuseppe Nasso, Giovanni Salamone, Filippo Castorino, Antonello Tommasini and Amedeo Anselmi

_Circulation_. 2007;116:1761-1767; originally published online September 17, 2007;
doi: 10.1161/CIRCULATIONAHA.107.697482
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/116/16/1761

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/