Effect of closed minimized cardiopulmonary bypass on cerebral tissue oxygenation and microembolization

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Objective: Coronary artery bypass grafting with cardiopulmonary bypass carries a risk for neurologic complications because of cerebral hypoperfusion and microembolization. The basic goals of a novel closed minimized extracorporeal circulation are to prevent excessive hemodilution and to avoid blood-air interface. The aim of this prospective randomized study was to determine the effect of using the minimized extracorporeal circulation system compared with open conventional extracorporeal circulation on cerebral tissue oxygenation and microembolization.

Methods: Forty patients undergoing coronary artery bypass grafting (20 in each group) were continuously monitored for changes in cerebral oxygenated hemoglobin and tissue oxygenation index by using near-infrared spectroscopy. Total microembolic count and gaseous embolic count in both median cerebral arteries were monitored with multifrequency transcranial Doppler instrumentation.

Results: In the conventional extracorporeal circulation group there was a highly significant reduction in both cerebral oxygenated hemoglobin and tissue oxygenation index from the start to the end of cardiopulmonary bypass ($P < .01$). The rate of decrease in cerebral oxygenated hemoglobin after aortic cannulation was faster in the conventional extracorporeal circulation group (F test = 9.03, $P < .001$). No significant changes with respect to cerebral oxygenated hemoglobin or tissue oxygenation index occurred in the minimized extracorporeal circulation group, except at the beginning of rewarming ($P < .01$). Total embolic count, as well as gaseous embolic count, in the left and right median cerebral arteries was significantly lower in the minimized extracorporeal circulation group (all $P < .05$). Postoperative bleeding was greater ($P < .05$) and the transfusion rate was higher ($P < .05$) in the conventional extracorporeal circulation group.

Conclusions: Use of closed minimized cardiopulmonary bypass compared with conventional open cardiopulmonary bypass preserves cerebral tissue oxygenation and reduces cerebral microembolization.

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As operative mortality for coronary artery bypass grafting (CABG) has decreased, greater attention has focused on neurologic and neurobehavioral complications of cardiopulmonary bypass (CPB). Furthermore, the same processes that injure the brain also appear to cause dysfunction of other vital organs.

Abbreviations and Acronyms

- ANOVA = analysis of variance
- CABG = coronary artery bypass grafting
- CECC = conventional extracorporeal circulation
- CPB = cardiopulmonary bypass
- MECC = minimized extracorporeal circulation
- MO = membrane oxygenator
- NIRS = near-infrared spectroscopy
- O_2Hb = oxygenated hemoglobin
- Sao_2 = arterial oxygen saturation
- TCD = transcranial Doppler
- TOI = tissue oxygenation index

Therefore there are great clinical and economic incentives to improve brain protection during cardiac surgery.

Despite considerable research, the characteristics of optimal CPB perfusion remain to be defined. Profound hypotension combined with prolonged cerebral hypoperfusion is clearly injurious to the brain. A desire to reduce the use of homologous blood products has resulted in the tolerance of a lower hematocrit value during cardiac surgery. However, reduced oxygen carrying capacity might expose the brain to hypoxia, particularly during rewarming, in the presence of significant cerebrovascular disease, or both. Additionally, traditional CPB featuring an open reservoir and large blood-air interfaces puts the patient at risk for gaseous cerebral microemboli.

In the attempt to reduce CPB-inherent side effects, a minimized extracorporeal circulation system (MECC system) was developed and clinically evaluated.[1] This new concept is based on the idea of a closed low-prime-volume circuit consisting of a rotary blood pump and a membrane oxygenator (MO) as the only components. The venous blood returns through active drainage. There is no venous reservoir nor is there a cardiotomy suction device. The shed blood is separated from the systemic circulation. The components, including the tubing, are heparin coated.

To evaluate the beneficial effects of the MECC system because of its design features (low prime volume, no blood-air interface, and biocompatible surface) on cortical cerebral tissue oxygenation and occurrence of cerebral microemboli, we conducted a prospective randomized study comparing the MECC system with conventional CPB.

Patients and Methods

Patient Selection

Forty patients scheduled for urgent or elective CABG surgery for triple-vessel disease were enrolled between June and November 2004. Exclusion criteria were greater than 60% carotid artery stenosis, previous transient ischemic attack or cerebrovascular attack, previous psychiatric illness, history of severe cerebral trauma or neurosurgery, recent myocardial infarction (within 1 month), renal failure (chronic hemodialysis), left ventricular ejection fraction of less than 30%, emergency operation, reoperation, or combined valvular surgery. Patients were randomized into 2 groups (conventional extracorporeal circulation [CECC] and MECC groups) by using computer-generated random allocations. The study was approved by the institutional ethics committee, and all patients provided written informed consent.

Perfusion Technology

CECC group. A standard open bypass circuit was used, consisting of uncoated PVC tubing, a hard-shell venous reservoir, a microporous MO (Quadrox^D; Maquet Cardiopulmonary, Hirrlingen, Germany), and a roller pump (HL 20, Maquet Cardiopulmonary). The circuit contained a 40-μm arterial line blood filter (Pall Corp, East Hills, NY) and was primed with 1500 mL of a balanced crystalloid/colloid solution (1000 mL of Ringer's solution, 200 mL of mannitol 20%, and 300 mL of hydroxyethyl starach 6%).

MECC group. The MECC system (Maquet Cardiopulmonary) consisted of a preconnected closed CPB circuit containing a RotaFlow centrifugal pump and a Quadrox^D diffusion MO. A flowmeter and a bubble sensor were integrated in the drive unit of the centrifugal pump. The MO contained a heat exchanger. Furthermore, the system featured a tip-to-tip heparin coating (Bioline Coating, Maquet Cardiopulmonary). No arterial or venous line filters were included. Priming volume of the system was 500 mL (Ringer's solution). The extracorporeal flow rate for both systems was set at $2.4 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$.

Anesthesia

A standardized anesthetic protocol for all patients was used. Anesthesia was introduced with intravenous administration of 0.3 μg/kg sufentanil and 2 mg/kg etomidate, and neuromuscular blockade was achieved with 150 μg/kg cisatracurium. Anesthesia was maintained by infusion of $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ midazolam supplemented with bolus doses of sufentanil and cisatracurium. No volatile agents were used. In both groups aprotinin was administered before CPB in a dose of 2 million KIU. Patients were ventilated to achieve normocapnia with air and oxygen (fraction of inspired oxygen, 0.4-0.45).

Anticoagulation in the CECC group was attained by administration of 300 IU/kg heparin to achieve an activated clotting time of longer than 400 seconds. In the MECC group 150 IU/kg heparin were administered with a target activated clotting time level of 250 seconds. For both groups, alpha-stat blood gas management was applied.

Surgical Intervention and Cardioplegia

After median sternotomy, the left internal thoracic artery and other graft material was harvested. Heparinization was followed by standard venous and arterial cannulation: a 24F arterial cannula for the ascending aorta and a 32/37F 2-stage cannula for the right atrial appendage. Venting was accomplished by using a needle in the ascending aorta, which was connected through a drop chamber to the venous line (MECC group) or to the reservoir (CECC group). Cardioplegic solution (a mixture of 30 mL of KCl 14.9% and 6 mL of $MgSO_4$ 50 Vol%) was administered through the aortic root after aortic crossclamping. Surgical intervention was performed during mild hypothermia (esophageal temperature, 33°C-

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34°C). The coronary anastomoses were constructed by means of hand suturing. Cardioplegia boluses were given after each distal anastomosis. Proximal anastomoses were done on the side-clamped aorta during reperfusion. After rewarming, the patient was weaned off CPB, and heparin was neutralized.

Near-infrared Spectroscopy

Principles and techniques of near-infrared spectroscopy (NIRS) and spatially resolved NIRS have been described previously.[2-4] Changes in oxygenated hemoglobin (O_2Hb) and tissue oxygenation index (TOI) were recorded with the NIRO 300 near-infrared spectroscope (Hamamatsu Photonics KK, Hamamatsu City, Japan). After induction of anesthesia, a photoconductive detector containing a near-infrared light-transmitting optode and a light detector was placed in the right frontotemporal region below the hairline, avoiding the frontal sinus and temporal muscle.

Monitoring started 10 minutes before sternotomy and continued until skin closure. Data were recorded at 0.5-second intervals and averaged into 60-second epochs. After data extraction to a personal computer with NIRO 3000L software, analyses were done at 12 different time points: T0, 10 minutes before sternotomy (baseline); T1, sternotomy; T2, 10 minutes after sternotomy; T3, aortic cannulation; T4, CPB onset; T5, aortic crossclamp on; T6, 15 minutes after aortic crossclamping; T7, beginning of rewarming; T8, aortic crossclamp off; T9, CPB end; T10, 15 minutes after CPB end; and T11, skin closure.

Chromophore concentration changes (change in O_2Hb) were measured in micromoles per liter. Cerebral saturation, as expressed by the TOI, is the ratio of oxygenated to total tissue hemoglobin and was measured in percentages of oxygen saturation of hemoglobin.

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Transcranial Doppler Monitoring

During surgical intervention, both middle cerebral arteries were monitored for microemboli by using multifrequency transcranial Doppler (TCD) instrumentation (EmboDop; DWL, Singen, Germany). Cerebral microemboli were continuously identified and differentiated automatically (solid and gaseous emboli). The principles of detection and differentiation of cerebral microemboli with multifrequency (2.5 and 2.0 MHz) Doppler monitoring has been described previously.[5,6] The insonation and reference gate depths were 55 and 40 mm, the sample volume was 11 mm, the filter setting was 200 Hz, power was 188 mW, and scale was 150/120. The detection threshold for microemboli was a Doppler energy increase of 28 dB·ms or greater (ie, a ≥7-dB power increase that lasted ≥4 ms in both 2.0- and 2.5-MHz frequency channels). TCD monitoring was performed continuously from skin incision to skin closure. To eliminate the influence of anesthesia and aortic manipulation (mainly solid emboli) on total embolic count, a standardized window for embolus detection for all patients was defined: 2 minutes after aortic crossclamping through 1 minute before aortic crossclamp removal. During this period, total embolic count and gaseous embolic count were detected for both the right and left hemispheres.

Hemodynamic Monitoring

Blood pressure (systolic, diastolic, and mean), heart rate, central venous pressure, and arterial oxygen saturation (Sao_2) were monitored by using a patient monitoring system (Sirecust 1281; Siemens, Munich, Germany). Parameters were recorded at baseline, at onset of CPB, every 10 minutes during CPB, at the end of CPB, and at skin closure. During CPB, the values of mean arterial pressure, hematocrit, and Sao_2 were averaged.

Study Conditions and Recording of Clinical Parameters

Several study conditions have been predefined for standardization. Operations were performed by 2 experienced surgeons (AL and BW). The random allocation of the perfusion method was not communicated to the surgeon before the operation. During perfusion, hematocrit values were not allowed to decrease to less than 0.28; otherwise, packed red cells were transfused. When mean arterial pressure decreased to less than 50 mm Hg, a bolus of 0.01 mg of norepinephrine was administered. Units of packed red cells were transfused, and norepinephrine use and clinical events were recorded. The study parameters were entered into a computer database and processed in a blinded manner by a single investigator (AK).

Sample Size Calculation and Statistical Analysis

The primary outcome variable was the change in O_2Hb. A minimum sample size of 34 patients (17 per group) provided 80% power ($\alpha = .05$, $\beta = .2$) to detect an absolute difference in O_2Hb of 5% between the groups at any time point by using 2-way analysis of variance (ANOVA; version 5.0, nQuery Advisor; Statistical Solutions Ltd, Cork, Ireland). We randomized 40 patients to account for possible dropouts by using a 1:1 randomization (20 patients per group). Continuous data are expressed as means ± standard deviation. Changes in O_2Hb and TOI over time were analyzed by using repeated-measures ANOVA with the post-hoc Bonferroni correction to protect against type I errors (false-positive results). The Greenhouse-Geisser F test was used to detect group differences and changes over the time course.[7] Intergroup comparisons for preoperative, perioperative, and postoperative data were assessed by using the 2-sample Student *t* test for continuous variables and the Fisher exact test for proportions. Statistical analysis was performed with the SPSS software package (version 12.0; SPSS Inc, Chicago, Ill).

Results

All patients completed the study. Demographic data are shown in Table 1. There were no significant differences between groups regarding age, sex distribution, body mass index, ejection fraction, grafts per patient, CPB time, or aortic crossclamp time. There were no in-hospital deaths, myocardial infarctions, or major neurologic deficits. Two patients in the CECC group experienced transient psychomotor syndrome. All patients were discharged with no late neurologic complications.

Mean arterial pressure decreased from 80.2 ± 23.5 mm Hg at baseline to 64.1 ± 11.5 mm Hg during CPB in the CECC group ($P = .03$, paired *t* test), whereas it remained stable in the MECC group (75.5 ± 14.8 vs 73.4 ± 7.6 mm Hg; $P = .50$, paired *t* test). Fifteen (75%) of the 20 patients in the CECC group and 5 (25%) of 20 patients in the MECC

TABLE 1. Patient characteristics and preoperative data

Variable	CECC group (n = 20)	MECC group (n = 20)	*P* value
Age (y)	63 ± 8	67 ± 8	.16
Female sex (%)	20	30	.18
BMI (kg/m^2)	28.3 ± 1.7	28.5 ± 1.8	.70
Hypertension (%)	85	90	.64
Hyperlipidemia (%)	85	75	.44
Diabetes mellitus (%)	30	40	.28
EF (%)	61.8 ± 12.6	57.4 ± 14.7	.28
Grafts per patient	3.8 ± 0.9	3.7 ± 0.8	.89
CPB time (min)	89 ± 22	83 ± 16	.38
Crossclamp time (min)	51 ± 13	52 ± 12	.62

Data are presented as means ± standard deviation where shown. *CECC*, Conventional extracorporeal circulation; *MECC*, minimized extracorporeal circulation; *BMI*, body mass index; *EF*, ejection fraction; *CPB*, cardiopulmonary bypass.

group needed norepinephrine boluses (0.01 mg) to keep the mean arterial pressure at greater than 50 mm Hg ($P < .001$). The mean hematocrit value during CPB was 29.3 ± 2.8 in the CECC group and 34.5 ± 5.1 in the MECC group ($P = .003$). Blood transfusions were needed in 7 (35%) of 20 patients in the CECC group and 0 (0%) of 20 patients in the MECC group ($P < .001$). The mean Sao_2 during CPB was 98.8% ± 0.8% in the CECC group and 98.6% ± 1.1% in the MECC group ($P = .61$).

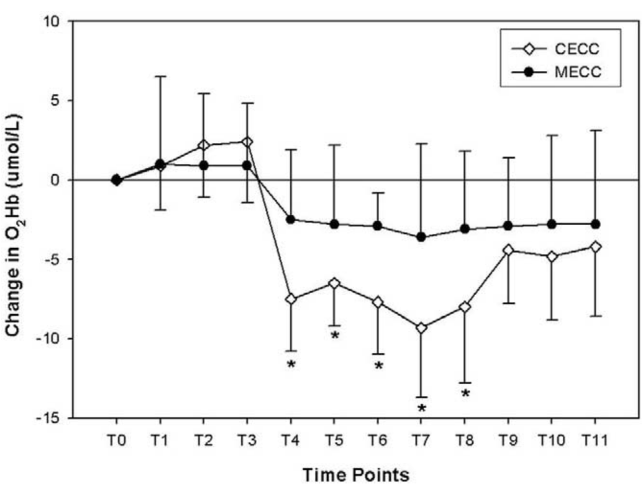

Figure 1. Cerebral oxygenated hemoglobin *(O_2Hb)* concentration changes during surgical intervention with conventional *(CECC)* or minimized *(MECC)* extracorporeal circulation. Depicted are the differences between the chromophore concentration at each time point and baseline. During cardiopulmonary bypass (T4-T9), there was a marked decrease in O_2Hb in the CECC group, whereas values in the MECC group remained relatively unimpaired (F test = 9.03 on 1 *df* for testing differences in the slopes, $P < .0001$). *Asterisks* denote statistically significant group differences ($P < .01$). Differences relative to baseline within each group are described in the text. Data are presented as means, and *error bars* represent the standard deviation.

Near-infrared Spectroscopy

Compared with baseline values, in the CECC group a significant reduction in O_2Hb concentration was recorded starting at the onset of CPB, with the greatest difference at the beginning of rewarming and persisting until skin closure (Figure 1). Repeated-measures ANOVA indicated a faster rate of O_2Hb reduction in the CECC group ($F = 9.03$, $P < .0001$).

Likewise, TOI significantly decreased from baseline values in both groups ($P < .0001$). Although the rate of this reduction in TOI was not significantly different between the 2 groups ($F = 1.92$, $P = .15$), mean TOI levels were less in the CECC group compared with those in the MECC group

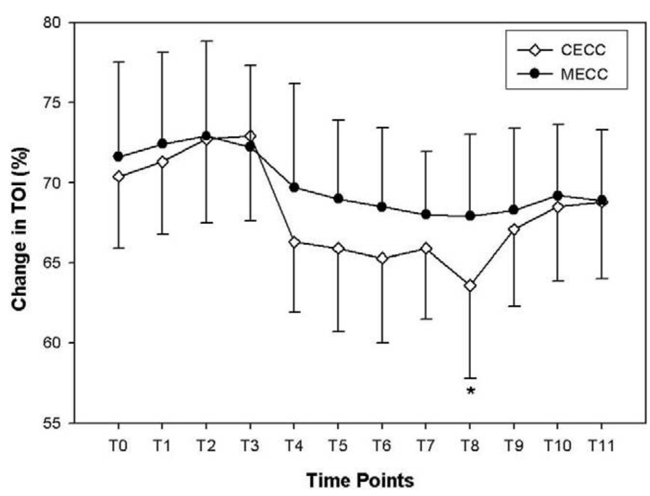

Figure 2. Time course of cerebral tissue oxygenation index *(TOI)*, the ratio of oxygenated to total tissue hemoglobin, expressed as a percentage. During cardiopulmonary bypass (T4-T9), there was a significant decrease in the conventional extracorporeal circulation *(CECC)* group ($F = 406.5$, $P < .0001$), whereas the decrease was less dramatic in the minimized extracorporeal circulation *(MECC)* group. The *asterisk* indicates a statistically significant difference between the 2 groups ($P < .01$). Within-group changes in TOI are described in the text.

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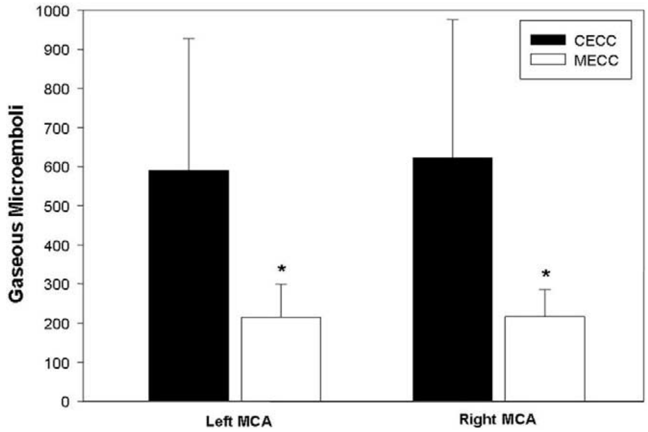

Figure 3. Gaseous microembolic count during aortic crossclamping detected by using multi-frequency transcranial Doppler scanning in the left and right median cerebral artery *(MCA)*. Error bars denote standard deviation. Gaseous embolic counts were significantly lower in the minimized extracorporeal circulation *(MECC)* group (*$P < .05$, Student *t* test). *CECC*, Conventional extracorporeal circulation.

at the beginning of rewarming (Figure 2). In the CECC group, compared with baseline values, repeated-measures ANOVA indicated that TOI levels were significantly lower at the start of CPB, continuing at all time points through the end of CPB (all $P < .01$). In the MECC group means levels of TOI were significantly lower than baseline values only at the beginning of rewarming and when the aortic crossclamp was off (both $P < .01$).

TCD Monitoring

TCD monitoring was not possible in 4 patients (2 in each group) because of an insufficient acoustic temporal bone window. In the remaining 36 (90%) patients, cerebral microemboli were detected during all operations, with a mean total embolic count of 1591 ± 555 in the CECC group and 733 ± 162 in the MECC group ($P = .02$). Of the microemboli, 76% in the CECC group and 77% in the MECC group were automatically identified as gaseous ($P = .85$). As shown in Figure 3, the gaseous embolic count detected in the left middle cerebral artery was 589 ± 338 in the CECC group and 215 ± 84 in the MECC group ($P = .02$). Similarly, the gaseous embolic count observed in the right middle cerebral artery was 623 ± 353 in the CECC group and 216 ± 69 in the MECC group ($P = .02$).

Discussion

This is the first study to provide data on simultaneous recording of cerebral oxygenation changes and occurrence of microemboli in 2 different CPB settings. There have been 2 main findings in our study, suggesting a superiority of the closed minimized CPB system. Individuals in the MECC group experienced a less severe decrease in cerebral tissue oxygenation and a reduced incidence of cerebral microemboli.

Cerebral perfusion during CPB is influenced by a number of factors, including hemodilution, hypotension, loss of pulsatile flow, impairment of the autoregulatory mechanisms of cerebral blood flow, and embolic events. Furthermore, it might be the result of inflammatory changes that lead to increased permeability across the blood-brain barrier, resulting in cerebral edema.[8,9] The findings observed in our study might be caused primarily by major technologic achievements of the MECC system: the absence of blood-to-air contact and the major reduction of hemodilution. In addition, the fully heparin-coated MECC system has been shown to produce less inflammatory activation compared with an uncoated, open CPB system.[10,11] Another factor that was potentially brain protective was the preserved perfusion pressure in the MECC group as a consequence of the closed system (volume-constant perfusion). Volume loss into the reservoir in open systems might lead to an inadvertent decrease in perfusion pressure necessitating vasoconstrictors. It was an important observation in our study that MECC circulation resulted in more or less the same blood pressure level as before and after bypass. However, patients in the CECC group showed a significant blood pressure decrease and required administration of vasoconstrictors more frequently. Finally, although not a goal of this study, we observed that there was no need for homologous blood transfusions in the MECC group. As in our routine CPB management, the lowest tolerable hematocrit value was defined to be 0.28. In a retrospective analysis on 5000 patients, Habib and coworkers[12] have recently shown that hemodilutional anemia during CPB can result in inadequate oxygen delivery and, consequently, ischemic organ injury. They found that neurologic complications, organ failure, and sepsis were significantly increased as the lowest hematocrit value decreased to less than 0.22. It is therefore vital to keep the hematocrit value in tolerable ranges. In this context a blood-saving CPB device like the MECC system should be of interest in view of an ageing, multimorbid patient population.

Near-infrared Spectroscopy

Near-infrared light in the wavelength range between 700 and 1000 nm penetrates biologic tissue and bone, which makes transcranial measurements feasible.[13] The technique of NIRS has been used to evaluate cerebral cortical oxygenation changes during carotid surgery,[14] CABG,[15-19] and off-pump cardiopulmonary bypass surgery.[20] The clinical application of intracranial NIRS in adults has been hampered by concerns over contamination by extracranial tissues. In a series of 60 patients who underwent carotid endarterectomy, Al-Rawi and associates[21] demonstrated the sensitivity of TOI to intracranial and extracranial changes (clamping of the internal or external carotid artery) of 87.5% and 0%, respectively, with a specificity of 100% and 0%, respectively. They concluded that in the absence of significant blood pressure changes or extracranial-to-intracranial anastomoses, the NIRO 300 reflects changes in cerebral tissue oxygenation with a high degree of sensitivity and specificity.

Cerebral oxygenation is autoregulated during cardiac surgery before and after CPB. During CPB, hemoglobin value, temperature, pH, and P_{CO_2} are the major determinants of the changes in cerebral oxygenation. The main causes of impaired cerebral oxygenation are the decrease in hemoglobin with hemodilution, vasoconstriction caused by hypocapnia, and the leftward shift of the hemoglobin binding curve caused by alkalosis and hypothermia.[16] Like others,[15-17,20] we have found in our CECC patients that the onset of CPB was associated with a reduction in cortical cerebral tissue oxygenation, in particular a decrease in O_2Hb. This decrease can easily be interpreted as a consequence of blood-free prime-induced hemodilution.

With the MECC setting, it was anticipated that prevention of excessive hemodilution should aim for a better cortical cerebral oxygenation. Consequently, we found a significant decrease of both TOI and O_2Hb primarily in the CECC group, whereas the changes in the MECC group did not reach significant levels, except at the beginning of rewarming. In contrast to Talpahewa and colleagues,[20] who observed a complete recovery of O_2Hb by the end of CPB in conventional CABG, values for our CECC patients remained decreased through the end of surgical intervention. This is remarkable because the patients in the study by Talpahewa and colleagues were normothermic, a condition that would generally tend to increase oxygen demand.[22] An explanation could be that their patients were largely transfused at the end of the operation. Unfortunately, no data on target hematocrit value were provided, which we believe is a drawback of the study. The persistence of low O_2Hb values (and, to a lesser extent, TOI) in our study suggests that after conventional CPB, the reestablishment of autoregulatory mechanisms of cerebral blood flow takes time and might not be accomplished when the patient leaves the operating room.

TCD Scanning

Cerebral microemboli, which can be detected in all patients subjected to CPB, has long been considered a predominant cause of neurologic injury during cardiac surgery.[23] Several investigations have revealed an association between neuropsychologic decrease and intraoperative cerebral microembolic load. It is widely accepted that particulate embolization originating from aortic manipulation adversely affects outcome in patients undergoing cardiac surgery.[24] We therefore focused on gaseous microembolization, which is mainly attributed to the design of CPB. Air might reach the systemic circulation from the bypass circuit and as an inevitable consequence of intracardiac procedures. Biologic particles arise from components of the circulation and the operative site. Nonbiologic particles arise from the extracorporeal circuit, the cardiotomy reservoir, and foreign material introduced into the operative site. Differentiation between solid and gaseous microemboli is possible by insonating an embolus simultaneously with 2 different ultrasound frequencies.[25] The reflected ultrasound power depends on the insonating ultrasound frequency, and this dependency differs for solid and gaseous elements. Solid microemboli reflect more ultrasound power at a higher compared with a lower frequency, whereas the opposite is the case for gaseous emboli.

Our data show that under standardized conditions, the use of a closed minimized bypass circuit is associated with a decreased incidence of cerebral microembolizations compared with that seen in a traditional open CPB system. Furthermore, we demonstrated that after excluding the effect of major vascular manipulation, gaseous microemboli contribute mostly ($>$70%) to the total embolic load independently of the method used. The total amount of gaseous microemboli, however, was significantly lower in the closed minimized system. Whether solid or gaseous emboli are more dangerous to the brain remains speculative. Solid microemboli of a certain size are more likely to occlude the microvasculature, whereas gaseous emboli might be expected to migrate through. However, it has been shown that larger volumes of intra-arterial air can disturb brain metabolism.[26]

The reduction of gaseous microemboli by using the MECC system might be primarily due to its closed design, with consequent omission of cardiotomy suction and a venous reservoir. The largest blood-air interface exists within the MO. The Quadrox^D diffusion-type MO, which was used in the MECC system, provides additional safety because of its tight hollow-fiber membrane. In contrast to conventional microporous MOs, in which gas passes through pores in the wall of the capillaries, the tight membrane in the Quadrox^D prevents crossing of microbubbles from the gaseous to the liquid layer. This feature, originally designed to prevent plasma leakage in the long-term run, has been shown to be feasible also in the clinical setting of CABG surgery.[27]

Other means of air entrapment have been described, even in cardiac catheter interventions. Lund and coworkers[28] performed TCD monitoring in 47 unselected patients undergoing left-sided heart catheterization. They found a median number of 754 cerebral microemboli, with 92% being gaseous. There was a correlation between the occurrence of emboli and the procedures performed, such as catheter flushings and contrast dye applications. Maneuvers during cardiac operations, such as intravenous drug applications, catheter flushings, and thermodilution boluses, might thus contribute to the microembolic load.

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Concerns have been raised against a potential air entrapment through the venous cannulation site caused by the negative venous line pressure in the MECC system. Although the present study was not primarily designed to evaluate the safety of the closed circulation, our findings suggest that there was no additional source of gaseous emboli when kinetic venous drainage was applied.

Study Limitations

The number of microemboli, in particular gas bubbles, was probably underestimated. When clusters of microemboli enter the Doppler sample volume at the same time, it is at present impossible for the Doppler instrumentation to count each single embolus. This is often the case during intravenous injections or catheter flushings. We therefore kept those maneuvers to a minimum during TCD recording. However, because the CECC patients required more norepinephrine boluses during perfusion, it is possible that more emboli entered the circulation in that group.

Despite significant differences both in cortical cerebral oxygenation changes and occurrence of cerebral microemboli, we did not observe differences in the occurrence of major neurologic events between the groups. Assessment of neurocognitive dysfunction with subtle neuropsychologic tests would have been inappropriate because of the limited number of patients. Whether the observed changes are clinically significant or merely represent signal variations requires further validation.

In conclusion, this prospective randomized study shows that the conceptional advantages of a closed minimized CPB system can translate into greater cerebral protection during CABG surgery. Additional studies are necessary to shed light on the clinical importance of these observations.

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Discussion

Dr Gabriel S. Aldea *(Seattle, Wash)*. I congratulate Drs Khosravi and Liebold and their colleagues for a very thoughtful presentation on a topic that has been of interest to our group for a long time but is gaining interest recently.

The authors reviewed their experience comparing in a randomized nonblinded fashion the differential effects of MECC, which consists of heparin-bonding circuits, a closed system, and minimal hemodilution, to CECC on cerebral tissue oxygenation and microembolism in patients undergoing primary CABG. The group concludes the use of this new system reduces gaseous cerebral emboli as measured by TCD analysis and preserved cerebral oxygenation as measured by NIRS.

Although I fully support the use of these systems and the general aspects of the findings, I have several comments and questions for the authors.

First, this technology is not particularly new. In fact, our group and many others have evolved these concepts over the course of the past decade. In addition to our group, the other champions of this technology include my previous colleagues in Boston, Dr O's group in Sweden, Dr V r in Switzerland, and most recently Dr B and D s from France. In fact, at this meeting several years ago we presented the stepwise incremental benefits of heparin-bonded circuits, closed systems, lower anticoagulation, and elimination of on markers of thrombin generation, inflammation and neuronal injury including S100 beta and NSC and near-complete blunting of many of the deleterious effects that previously were considered to be inevitable complications of coronary bypass. Most important, what we have shown is very different from what you have demonstrated in the study from the *New England Journal of Medicine,* which is preservation of neurologic and neuropsychologic function in patients when you observe these principles of closed systems and biocompatibility. The MECC system is a brand name for a specific configuration of these advances, which essentially eliminates both the venous reservoir and a cardiotomy suction and makes perhaps the application of these techniques and technology easier in certain circumstances. This past May in the *Annals of Thoracic Surgery* the group demonstrated that using this technology you can again decrease both complement activation and S100 beta in patients undergoing CABG.

The questions that I have for you are the following. First, you vary, by my account, five different systems when you compare the MECC system and the conventional system. You have made five different changes in the technology, and the question is which is contributing to the outcomes that you have shown? You compared an open versus a closed system. You compared a heparin-bonded circuit to a noncoated system, full versus lower anticoagulation, two different oxygenator designs, large versus full prime so 400 versus 1500 mL, centrifugal versus, and finally elimination of filters in the MECC group altogether. This design makes it very difficult to assign specific benefits to individual changes in a technique. By current practices, the use of open systems in and of itself requires using chemical and filters which in and of themselves were demonstrated by Dr David Stump and colleagues at Wake Forest to be associated with and particulate cerebral emboli. In addition, the prime volumes that you have shown alone, which you can achieve by other techniques such as retrograde arterial and venous priming with a closed collapsible venous reservoir and elimination of interface, and the beneficial effects of heparin-bonded circuits, would account perhaps for the decreasing need for transfusion and the hypotension, that may have caused and explained the differences in your tissue oxygen delivery. I'd like your comments on your experimental design.

Dr Khosravi. Thank you very much for your questions. You are right, the idea of minimizing the CPB, at least for coronary surgery, is not new. However, despite its conceptional advantages over standard CPB, the MECC system failed to gain wide acceptance among cardiac surgeons in both Europe and the US. The reasons for not using a minimized system might be multifactorial. Mainly, conservative surgeons fear air entrapment into the closed circulation leading to neurologic sequelae. The aim of the present study, therefore, was to test whether the MECC system was as safe as a conventional CPB system in terms of cerebral microemboli generation (or even safer). Moreover, we aimed to demonstrate a neuroprotective effect by showing its better cerebral oxygenation capacity. It was not our intention to investigate which of the technological changes caused the most beneficial effects in the patients.

Undoubtedly the absence of a venous reservoir and the avoidance of excessive hemodilution are two of the major factors responsible for the favorable outcome in our patients, but as I mentioned we wanted to study the advantages of this minimized system in general, not of its components in particular.

Dr Aldea. Since the study focuses on cerebral protection, why was the side-biting clamp used for construction of proximal anastomoses? Our group and the Brigham & Women's group have shown that over 60% of all emboli that are caused during CPB result from this maneuver alone. It seems to me that one can use cleaner techniques and eliminate this altogether.

Dr Khosravi. I'm sorry, I didn't understand exactly.

Dr Aldea. You used a partial occlusion clamp to construct a partial anastomosis and that's probably the most injurious maneuver in CPB in causing particulate emboli. As a general principle, I think that is something that we can eliminate altogether as a necessary maneuver when we perform CABG surgery.

I have several questions regarding your TCD analysis. One of them refers to your emphasis on looking only at gaseous emboli, not at particulate emboli. You describe it a bit in your manuscript, but I think most of us believe that particulate emboli are more serious and perhaps more commonly associated with permanent neurologic injury. You show a significant difference between the open system, which we all agree is unnecessary in most cases, and a closed system. However, the number of emboli that you show even in the closed system is tenfold higher than the number of gaseous emboli or particulate emboli that we have seen with similar technology. My concern is that when you are eliminating the venous reservoir altogether and you are venting the aortic root or have any leakage around the venous purse string, you might introduce some air and gaseous emboli into your system while eliminating any possibility of de-airing.

Dr Khosravi. I think the absolute number of emboli detected is

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strongly dependent on the method used. We focused on gaseous emboli since we believe that formation of gaseous emboli is indeed caused by factors inherent in extracorporeal circulation, whereas particulate emboli are mainly derived from manipulation of the heart and the aorta. By choosing a detection window without aortic manipulation, we were able to obtain more gaseous than particulate emboli counts. The number of gaseous counts differed significantly between the two methods, whereas the particulate counts did not. Coming back to your point that air may enter the circuit via the venous purse string, we always observed a distinct filling of the right heart and atrium, meaning that there is a greater chance to have blood leakage than air entrapment. In our opinion, an active air removal in this setting is completely unnecessary.

Dr Aldea. This is a very important development in general using these technologies, but since most of the procedures that we do now are open cardiac procedures, how would you translate some of these advances to intracardiac procedures?

Dr Khosravi. There is a study from Remadi's group in France which used the MECC for aortic valve replacement. Our own experience in open cases is rather limited and not so enthusiastic. First, you must ensure that there is no atrial septal defect or use a double venous cannulation. Second, you are facing quite a large amount of intracardiac suction blood and you must have a concept of intraoperative blood processing. Thus, you give up part of your MECC principles. Therefore, we now restrict the use of the MECC system to CABG cases.