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Emboli Formation Rather Than Inflammatory Mediators Are Responsible for Increased Cerebral Water Content After Conventional and Assisted Beating-Heart Myocardial Revascularization in a Porcine Model

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Background and Purpose—Emboli and proinflammatory mediators are suspected of generating cerebral edema after coronary surgery. In contrast to cardiopulmonary bypass (CPB), off-pump coronary artery bypass surgery (OPCAB) reduces microemboli count and proinflammatory mediator release but carries the risk of hemodynamic instability. A microaxial blood pump can augment cardiac output.

Methods—Coronary bypasses were constructed in pigs with CPB and cardioplegia (n = 9), OPCAB (n = 9), or blood-pump support CAB (n = 9). Nine animals underwent sham operation. Embolus count was monitored and regional cerebral blood flow was assessed with microspheres in 21 brain specimens per animal (n = 189 per group). Interleukins 6 and 8 and tumor necrosis factor-α concentrations were determined. These variables were studied before, during, and for 4 hours after surgery. Finally, cerebral water content was determined.

Results—During CPB and blood-pump CAB, a significant number of emboli were counted in contrast to OPCAB and controls (P < 0.05). During CPB, regional cerebral blood flow was affected (32 of 189) and showed reactive hyperemia except in 10 specimens after aortic cross-clamp release. This impairment persisted in 20 specimens. During and after OPCAB, regional cerebral blood flow remained nearly unchanged but showed low flow during (58 of 189) and after (35 of 189) the blood-pump run. A significant increase in proinflammatory mediators was observed only in the CPB group. CPB and blood-pump CAB significantly increased cerebral water content (P < 0.05). A strong correlation between embolic load and cerebral water content was observed in all groups. No correlation between proinflammatory mediator release and cerebral water content was detected.

Conclusions—Emboli formation rather than inflammatory mediators are responsible for increased cerebral water content after conventional and assisted beating-heart myocardial revascularization. (Stroke. 2008;39:213-219.)

Key Words: brain edema ■ bypass surgery ■ cerebral blood flow ■ embolism

Many potential mechanisms contributing to postoperative neurologic morbidity after cardiac surgery have been discussed, but 2 major etiologic factors, hypoperfusion and embolus formation from various sources, are the most probable culprits. Patients experiencing neurologic deficits after cardiopulmonary bypass (CPB) have, on average, twice as many microemboli as those with no deficits, and cerebral complications occur more frequently in patients with more emboli. Hemodynamic impairment resulting in cerebral hypoperfusion during and after coronary bypass grafting performed with CPB or off-pump surgery (OPCAB) is well documented. In some cases, conversion from an off- to an on-pump procedure is necessary owing to the unfeasibility of reaching the target vessels or hemodynamic instability, leading to increased morbidity and mortality.

Hemodynamic stabilization during beating-heart myocardial revascularization by an intracardiac implanted blood pump can be achieved in experimental and clinical settings. The Impella Eject 100 blood pump (Impella Cardiovascular Systems, Aachen, Germany) has been developed to avoid hemodynamic instabilities while retracting the heart for exposure.

Furthermore, inflammatory mediators are suspected of causing damage to the blood-brain barrier in association with CPB, leading to cerebral edema. In OPCAB, reduced
inflammatory mediator levels compared with those during CPB have been detected.

We hypothesized that the embolus count on one hand and the release of proinflammatory mediators on the other could account for cerebral edema formation after surgery. Therefore, we sought a correlation between these 2 harmful factors and cerebral water content (CWC).

Materials and Methods
The study protocol was approved by the ethics committee for laboratory animals, Rhineland-Palatinate. All animals in this study received humane care in compliance with the Principles of Laboratory Animals formulated by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animal Resource published by the National Institutes of Health, Bethesda, Md.

Experimental Groups
In 36 adult German Landrace pigs of both sexes age 6 to 7 months and weighing 68 to 91 kg, an internal mammary artery–to–left anterior descending coronary artery bypass was performed. Group I received 60 minutes of normothermic extracorporeal circulation (ECC) with 40 minutes of cardioplegic arrest (n = 9); group II underwent a 60-minute off-pump procedure (n = 9); and group III underwent a 60-minute beating-heart procedure assisted by the Impella Elect 100 blood pump (n = 9). A fourth group without bypass surgery (sham operation, n = 9) served as a control.

Surgical Preparation
Animals were premedicated with 15 mg/kg ketamine, 3 mg/kg azaperone, and 2 mg atropine. General anesthesia was induced with 2 to 3 mg/kg sodium thiopental and 15 mg pmirrPramide. After oral intubation, the animals were pressure-controlled ventilated with a Servo 900b (Siemens Elema-Schönander AB, Solna, Sweden). Anesthesia was maintained intravenously with 3 to 6 mg/kg/h sodium thiopental and 7.5 mg/h pmirrPramide. During the 1-hour intervention, 45 mg midazolam was infused continuously. Arterial blood gases were maintained within physiologic ranges (ABL-System 615, Radiometer, Copenhagen, Denmark). An isotonic, iso-osmotic crystallloid solution (5 to 10 mL/kg; Braun, Melsungen, Germany) was administered.

Both femoral arteries were cannulated. A Swan-Ganz catheter (Edwards-Lifesciences, Unterschleissheim, Germany) was placed in the pulmonary artery via the femoral vein for cardiac output (CO) monitoring. After sternotomy, the internal mammary artery was dissected. A catheter was inserted into the left atrium for application of microspheres.

Experimental Protocol
After baseline measurements were taken, the animals were randomized to 1 of 4 groups. All animals received 500 U/kg heparin before the procedure and an equivalent dose of protamine afterward. Normothermia was maintained in all groups throughout the experiment. The surgical intervention lasted 60 minutes, followed by 4 hours of observation.

Surgical Set-Up
In group I, CAB was accomplished during 40 minutes of aortic cross clamping and cardioplegic arrest with 4°C to 8°C St. Thomas solution via the aortic root in a total of 60 minutes of CPB. The arterial cannula (Jostra, Hirrlingen, Germany) was inserted into the ascending aorta. A venous catheter (Jostra, Hirrlingen, Germany) was placed in the right atrium. A roller pump (Stöckert, Munich, Germany), a membrane oxygenator (Quadrox, Jostra, Hirrlingen, Germany), and a sterile tubing set containing a 40-μm arterial filter were used. The pump speed was adjusted to maintain a mean arterial pressure (MAP) between 55 and 80 mm Hg and to avoid the use of vasopressor medication during CPB.11 In group II, the internal mammary artery–to–left anterior descending coronary artery bypass was performed on the beating-heart with the use of a stabilizer (Octopus Medtronic), with a clamp occluding the completed bypass until the 40th minute.11

In group III, the blood pump was inserted into the left ventricle via the ascending aorta through a pursestring suture. Hydroxyethylstarch (6% solution; Braun, Melsungen, Germany) was infused immediately before pump insertion. The correct position was checked by measuring the difference between aortic and left ventricular diastolic pressures. Rotational speed was adjusted so that maximum ventricular unloading could be achieved. Pump flow ranged from 1.9 to 3.5 L/min. The Impella pump was operated for 60 minutes. The surgical procedure was identical to that in group II.

Cerebral Water Content
At the end of the experiment, the skull was opened and 20 mmol KCl was injected into the left atrium. Immediately thereafter, the brain was removed and a coronal slab of the frontal lobe (10 mm thick) was harvested. The right and left hemispheres were divided, and a slice of the medial aspect of each hemisphere (200 to 250 mg) was stored in preweighed separate glass containers. After it was dried in an oven at 110°C for 24 hours, each container was reweighed on the same scale. The difference between the initial and final weights was assumed to be the wet weight.16 CWC was calculated as (wet weight–dry weight)/wet weight×100.

Cerebral Perfusion Measurement
Regional cerebral blood flow (rCBF) was examined at baseline, twice during the surgical procedure (at 40 and 60 minutes), and 1 (120 minutes) and 4 (300 minutes) hours after bypass by fluorescence-labeled microspheres (Molecular Probes, Leiden, Netherlands).17 Two million microspheres per color were injected into the left atrium over 30 seconds. During CPB, the microspheres were injected into the arterial canula. A 10-mL reference blood sample was withdrawn from the abdominal aorta with a syringe pump (model 540210, TSE, Bad Homburg, Germany) over a 3-minute period starting 30 seconds before microsphere injection. After the samples for CWC measurement had been saved, the brain was removed, rinsed with saline, and placed in 4% paraformaldehyde. After 7 to 10 days of immersion in paraformaldehyde, 21 specimens per animal weighing 500 to 1500 mg were dissected from the fixed brain for digestion and dye extraction. We used a previously published protocol.18 CBF was assumed to be critically reduced when it was <23 mL/min×100 g, according to previously published data.19

Embolic Event Counting
Unilateral Doppler monitoring was performed over the right common carotid with a 2-MHz hand-held probe of a pulsed Doppler apparatus (Multi Dop X4, DWL, Sipplingen, Germany) and multirange embolus detection software (TCD-8, version 8.1; DWL, Sipplingen, Germany). The measurements were performed during the complete bypass grafting procedure for 60 minutes and during a 6-minute period before and after bypass. One examiner, who was present throughout the whole study, monitored the embolus count and evaluated the results. Criteria for the detection of microemboli were those of the International Consensus Group.20

Inflammatory Mediators and Free Serum Hemoglobin
Interleukins (IL) 6 and 8, tumor necrosis factor-α (TNF-α), and free serum hemoglobin concentrations were determined in serum samples obtained at baseline and at 70, 120, 180, and 300 minutes with use of porcine-specific ELISAs (R&D Systems, Wiesbaden-Nordenstadt, Germany). Free serum hemoglobin samples were analyzed spectrophotometrically with a Sigma Diagnostics serum hemoglobin kit.21 Whole blood was withdrawn from the femoral artery and centrifuged at 1000g after being allowed to clot for 2 hours. The resulting serum was stored at ~80°C until measurement.
Hemodynamic Parameters
ECG, left and right atrial pressures, MAP, and pulmonary arterial pressure were recorded at different time points. CO was determined continuously.

Statistics
Data are presented as mean±SEM. Statistical analysis was performed with SigmaStat 3.1 (Jandel Scientific Corp, San Rafael, Calif). The statistical significance of changes from baseline values within each group was tested with ANOVA for repeated measures. Differences between groups were analyzed by 1-way ANOVA comparing several groups. When values did not show a normal distribution, ANOVA for nonparametric values (Kruskal-Wallis test) was used with the multiple comparison method (Dunn’s method). A linear-regression calculation was performed to test the correlation between cerebral emboli count and CWC and between IL-6, IL-8, and TNF-α peak concentrations and CWC. Correlation coefficients (r) ≥0.7 and ≤−0.7 were assumed to indicate a correlation between these variables. Statistical significance was accepted at P≤0.05 after pairwise testing.

Results
All animals survived the surgery and the following 4 hours. All constructed anastomoses were open throughout the whole observation period, as confirmed by ultrasonic flow measurements.

Emboli Generation
Baseline values in the groups were not significantly different and ranged from 18±13 to 21±8 emboli. During CPB, 24±4.5 events occurred, and particularly during Impella assistance, a significant number (1391±337 events) of emboli was registered (P<0.05). In the CPB group, most of the emboli were counted after initiation of CPB and aortic cross-clamp release. During the Impella pump run, no identifiable events created the enormous amounts of emboli. In contrast to these 2 groups, only a few cerebral emboli were counted during OPCAB (21±7) and in control animals (42±33).

Regional Cerebral Blood Flow
Specimens were taken from the right and left cerebellum, medulla oblongata, pons, mesencephalon, right and left thalamus, right and left hypothalamus, and right and left hippocampus. Furthermore, specimens were dissected from both hemispheres of the cerebral cortex supplied by the anterior, middle, and posterior cerebral arteries, as well as from the border zones of the anterior/middle and middle/posterior cerebral arteries. Baseline values (189 specimens per group) in all specimens from all groups revealed normal CBF without significant differences between the groups (range, 25.4 to 159.6 mL/min×100 g in individual animals). At baseline, CBF was lowest in the hypothalamus (ECC, 31.4±1.2; OPCAB, 35.8±6.1; Impella, 34.4±2.2; and sham, 32.5±2.8 mL/min×100 g) and highest in the cortex (ECC, 59.2±7.8; OPCAB, 76.2±15.7; Impella, 87.4±7.5; and sham, 87.5±9.8 mL/min×100 g) in all groups. In control animals, cerebral perfusion was affected in 9 specimens in 2 animals (11 to 21.7 mL/min×100 g) during midazolam infusion. Four hours after cessation of midazolam infusion, no specimen revealed critical CBF (Figure 2).

Figure 1. rCBF in pigs before (pre), during 60 minutes of surgery, and 1 and 4 hours after surgery with (A) CPB (ECC group), (B) OPCAB, (C) Impella-supported beating-heart surgery (Impella), and (D) sham operation (sham). Values are mean±SEM. n is the number of animals per group. A. cer. ant/med r. indicates the border zone between the anterior cerebral artery and medial right hemisphere; A. cer. ant/med l., the border zone between the anterior cerebral artery and medial left hemisphere; A. cer. med/post r., the border zone between the middle cerebral artery and posterior right hemisphere; and A. cer. med/post l., the border zone between the middle cerebral artery and posterior left hemisphere. CBF was measured in the cortex. *P<0.05 vs pre-surgery rCBF.

During CPB with aortic cross clamping and cardioplegic arrest, rCBF was affected in 34 specimens (1.2 to 21.3 mL/min×100 g) from 6 animals. However, after aortic clamp release, rCBF showed reactive hyperemia (2- to 3.2-fold increase, Figure 1A) except for 10 specimens from 3 animals wherein an impaired rCBF was maintained (Figure 2). After separation from CPB, rCBF remained above baseline values (Figure 1A). In 9 and 20 specimens (1 and 4 hours, respectively, after separation from CPB in the same animals as during CPB), a critically reduced rCBF ranging from 1.4 to 19.8 mL/min×100 g was still maintained (Figure 2).

During OPCAB, rCBF showed only minor changes. In 13 and 28 specimens, critically reduced values (9.9 to 21.6 mL/min×100 g) were measured during bypass surgery in 4 animals (at 40 and 60 minutes of surgery, respectively). One hour after surgery, 8 specimens showed critically reduced rCBF values in 2 animals. At the end of the experiment, impaired cerebral perfusion was not observed in any of the specimens (Figure 2).

Impella blood-pump use reduced rCBF even more during and after surgery. In 58 and 57 specimens (3.7 to 22.1 mL/min×100 g) from 9 animals, critically impaired rCBF was detected after 40 and 60 minutes of surgery, respectively. One and 4 hours after Impella assistance, 38 and 35 specimens (4.3 to 21.9 mL/min×100 g) still showed impaired rCBF (Figure 2). The pattern of change of CBF during the
experiment was similar within the individual groups among the different brain areas. The depicted regions in Figure 1 are representative with respect to the pattern of change in CBF but not in terms of the absolute amounts of CBF.

Cerebral Water Content

CWC in the frontal lobe was significantly increased 4 hours after CPB (81.7±0.6%; range, 77.9% to 83.1%) and Impella assistance (81.9±0.4%; range, 81.1% to 82.6%). In contrast, there was no difference 4 hours after OPCAB surgery (79.7±0.6%; range, 77.9% to 81.4%) compared with sham-operated animals (79.9±0.6%; range, 78% to 81.6%). The correlation between cerebral emboli count and CWC was strong in every group (Figure 3, A–D; ECC: r=0.85, P<0.001; OBCAB: r=0.96, P<0.001; Impella: r=0.92, P<0.001; and sham: r=0.77, P=0.009).

Hemodynamic Parameters and Blood Gas Measurements

MAP at baseline was not significantly different among the groups (ECC, 91±3; OPCAB, 92±5; Impella, 91±3; and sham, 88±4 mm Hg) but was significantly decreased during revascularization in all treated groups (ECC, 67±4; OPCAB, 79±4; Impella, 84±3; and sham, 91±3 mm Hg), staying below preoperative values thereafter, most markedly in the ECC group. Only in this group was it necessary to administer norepinephrine to maintain adequate perfusion pressure after surgery. The maximum dose was 0.31 μg/kg×min.

CO at baseline was not significantly different among the groups (ECC, 4.5±0.2; OPCAB, 4.8±0.3; Impella, 4.7±0.4; and sham, 4.9±0.2 L/min). During surgery, CPB flow was adjusted to keep MAP >55 mm Hg, so a pump flow of 4.5±0.2 L/min resulted. Only in the OPCAB group was the decline in CO statistically significant during the procedure (3.4±0.2 L/min) and early thereafter (3.9±0.3 L/min). The Impella blood pump augmented CO (4.0±0.2 L/min) compared with the off-pump procedure.

The inspired O₂ fraction before revascularization was comparable among the groups (ECC, 34±1%; OPCAB, 33±0.6%; Impella, 36±0.8%; and sham, 33±0.7%). Normal
arterial blood gases and sodium concentrations were measured throughout the whole experiment in all groups. Except during CPB, the oxygen fraction was raised to 100%, so a significantly increased arterial oxygen tension resulted. Thereafter, the O₂ fraction could rapidly be reduced to preoperative values. Arterial pH values stayed in the normal range throughout the whole experiment in all groups, without significant differences among groups.

At baseline, hemoglobin concentration and hematocrit values were within physiologic range and were not significantly different among the groups (ECC: 9.0±0.2 mg/dL, 27.9±0.6%; OPCAB: 9.1±0.3 mg/dL, 28.2±0.9%; Impella: 9.5±0.2 mg/dL, 29.3±0.7%; and sham: 8.5±0.2 mg/dL, 26.4±0.5%). During surgery in the ECC group only, a significant decline in hemoglobin concentration and hematocrit value occurred (ECC: 7.1±0.2 mg/dL, 22.3±0.6%; OPCAB: 9.5±0.2 mg/dL, 29.3±0.6%; Impella: 9.5±0.2 mg/dL; 29.5±0.7%; and sham: 8.8±0.1 mg/dL, 27.3±0.3%), staying markedly below preoperative values throughout the whole postoperative period.

**Inflammatory Mediators and Free Plasma Hemoglobin**

A significant increase in concentration of the proinflammatory mediators IL-6 and IL-8 was observed 2 hours after surgery in the ECC group only, with a decline thereafter (Figures 4A–4C). TNF-α concentrations were elevated immediately after termination of CPB but also peaked 2 hours after surgery and declined thereafter. In the other groups, no significant increase in any proinflammatory mediator was observed. Free plasma hemoglobin concentrations revealed no significant increase throughout the experiment in any group (range, 67±9 to 81±6 mg/dL). In addition, there was no statistically significant difference among the groups at any time point.

Correlation analysis between IL-6, IL-8, and TNF-α peak concentrations and CWC revealed no evidence of a statistically significant pairwise relation between these parameters in any group (for IL-6, ECC: r=0.08, P=0.86; OBCAB: r=0.2, P<0.71; Impella: r=0.32, P<0.44; and sham: r=0.5, P=0.17; for IL-8, ECC: r=0.05, P<0.91; OBCAB: r=0.18, P<0.74; Impella: r=0.5, P<0.17; and sham: r=0.34, P=0.41, and for TNF-α, ECC: r=0.33, P<0.42; OBCAB: r=0.5, P<0.24; Impella: r=0.39, P<0.35; and sham: r=0.5, P=0.11).

**Discussion**

The major finding of this study is the strong correlation between the number of cerebral emboli and CWC 4 hours after surgery in all groups. Our data showed increased brain water content occurring in animals with a high embolic load during surgery. Even more important, in these animals the highest number of critically perfused areas was counted. Impaired neurologic outcome has been observed especially in patients after exposure to a large number of cerebral microemboli.1–3,5,22,23 This underlines the important effect of cerebral microembolism on neurologic outcome after cardiac surgery.

During surgery with CPB and cardioplegic arrest, adequate systemic flow was achieved, although immediately after initiation of CPB and infusion of cardioplegia, MAP signif-
icantly decreased. This hemodynamic impairment in conjunction with the infusion of crystalloidal priming and cardioplegic solution, resulting in a reduced oxygen-carrying capacity, leads to further impairment of the cerebral oxygen supply and reduced systemic vascular resistance. Hypoperfusion in conjunction with an impaired oxygen-carrying capacity occurs and may result in cerebral edema via ischemia caused by impaired local oxygen supply.

In a feline model, air embolism of the brain was attained by injecting blood foam into the innominate artery. Air embolism caused transient brain ischemia. During this period, tissue perfusion was inhomogeneous, with reduced flow rates in some areas and reactive hyperemia in most of the observed specimens. Reactive hyperemia was accompanied by brain swelling and an increase in intracranial pressure. These observations are in accordance with our findings. After aortic cross-clamp release, a microemboli shower occurred and resulted in inhomogeneous perfusion, with hyperaemic areas on one hand and impaired blood flow on the other. Fritz and Hossman explained reactive hyperemia by a reduced cortical pH, which caused dilation of the pial arteries. In contrast to our findings, air embolism in their model had little effect on CWC, but their experiments were terminated after 120 minutes and cerebral edema is known to peak 24 hours after transient middle cerebral artery ischemia.

Furthermore, inflammatory mediators are suspected of causing damage to the blood-brain barrier in association with CPB. Dewanjee et al reported brain edema on the basis of descriptive magnetic resonance imaging without a semiquantitative analysis. TNF-α concentrations were determined during CPB and 90 minutes thereafter, which peaked 30 minutes after termination of CPB. No statistical method was applied to correlate the observed brain edema with TNF-α concentrations.

In our experiments, the levels of proinflammatory mediators were not correlated with CWC measured 4 hours after 60 minutes of CPB. In addition, our data clearly exclude any association between proinflammatory mediators and cerebral edema formation in the Impella group. Cerebral vasoconstriction triggered by free serum hemoglobin as a further cause of cerebral hypoperfusion can also be excluded in our model. In clinical routine, this factor may play an important role because bypass times often exceed 1 hour and patient temperatures are lowered to <30°C. This generates hemolysis with a subsequent increase in free hemoglobin.

In summary, there are many factors contributing to postoperative brain edema: hemodynamic impairment, hemodilution, inflammatory mediator release, and microembolism. In addition, pulsatile CPB may affect the blood-brain barrier and result in brain edema. Surgery without CPB leads to a significantly impaired but not a critical hemodynamic status. Although MAP and CO were significantly reduced during surgery, rCBF was well preserved. Four hours after surgery, none of the observed specimens showed critically reduced rCBF. The lack of brain edema after an off-pump procedure with an on-pump procedure has previously been observed.

We conclude that in our model in the OBCAB group, the small number of microembolic events and preserved rCBF provided by a sufficient cerebral perfusion pressure resulted in unaltered CWC. Important to note is that although MAP and CO during surgery were significantly reduced, no MAP values under the cerebral autoregulatory limit were registered. The use of the microaxial blood pump augmented MAP and CO. However, it generated a massive number of emboli. The source of emboli in this group may be gaseous bubbles that are formed by cavitation. Significant inflammatory mediator release was not observed in our experiment in accord with recent publications.

We conclude that in the Impella group, the increased CWC was due to hypoperfusion triggered by microembolism alone. The massive numbers of emboli resulted in diffuse cerebral hypoperfusion, as indicated by the high numbers of critically perfused specimens during the pump run. Furthermore, there is evidence that injection of air results in immediate breakdown of the blood-brain barrier. In our model, embolization of atherosclerotic material could be excluded. None of the animals showed signs of atherosclerosis at organ removal. The aorta and the carotid arteries were free of atherosclerotic plaques in all animals.

Summary
We conclude that an off-pump procedure best preserves the cerebral circulation in the case of a hemodynamic status in which MAP lies within the cerebral autoregulative limit and CO is high enough to sustain this perfusion pressure. Furthermore, we demonstrated that a strong correlation between cerebral embolic load and the amount of resulting cerebral edema after coronary artery bypass grafting exists. IL-6, IL-8, and TNF-α peak concentrations were not correlated with CWC postoperatively in our model.

Limitations
These observations were made in previously healthy animals with normal organs without any evidence of atherosclerosis. Thus, our results should be carefully interpreted, and direct extrapolation to the clinical setting is not warranted.

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Disclosures
None.

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