Cerebrospinal Fluid Markers of Brain Injury, Inflammation, and Blood-Brain Barrier Dysfunction in Cardiac Surgery

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Background. **Neurocognitive dysfunction occurs frequently after open-heart surgery. Cerebral microembolization, inflammation, blood-brain barrier (BBB) dysfunction, and impaired cerebral oxygenation are considered among possible etiologies. The relationships between intraoperative microembolic signals and the release of cerebrospinal fluid (CSF) markers of inflammation, neuronal and glial cell injuries, and BBB function were evaluated after cardiac surgery with cardiopulmonary bypass.**

Methods. **Ten patients undergoing aortic valve replacement were included. The CSF was obtained the day before and 24 hours after surgery for assessment of neuronal damage (neuron-specific enolase, total tau, and neurofilament light chain protein), glial cell injury (S-100B, glial fibrillary acidic protein), BBB integrity (CSF to serum albumin ratio) and cytokines (interleukin-6, interleukin-8). Intraoperative extent of microemboli and their occurrence were described using the transcranial Doppler technique.**

Results. **Intraoperatively, 354 ± 79 microemboli were detected; 81% after release of the aortic cross clamp. The S-100B and glial fibrillary acidic protein increased by 35% ($p < 0.01$) and 25% ($p = 0.055$), respectively. Neuron-specific enolase, total tau, and neurofilament light chain protein, were not significantly affected by the surgery. The CSF albumin increased by 13% ($p < 0.05$) while serum albumin decreased by 27% ($p < 0.0001$). Thus, CSF to serum albumin ratio increased by 61% ($p = 0.011$). There was a 3.5- and 12-fold increase in interleukin-6 ($p < 0.001$) and interleukin-8 ($p < 0.05$), respectively. Microembolic signals did not correlate to changes in CSF glial injury markers, the CSF to serum albumin ratio, or CSF cytokines.**

Conclusions. **Cardiac surgery with cardiopulmonary bypass causes cerebral inflammation, glial cell injury, and BBB dysfunction without biochemical signs of neuronal damage. These changes are not associated with intraoperative microembolization.**

(Ann Thorac Surg 2012;94:549–55)

Neurologic dysfunction after open-heart surgery procedures is still a substantial cause of postoperative morbidity. The incidence of stroke after surgical aortic valve replacement is considered to be approximately 4% to 6% [1]. Postoperative neurologic dysfunction in its widest definition, including subtle cognitive dysfunction, is considered to have an incidence of 50% to 70% [2]. Cerebral microembolization, cerebral inflammation, blood-brain barrier (BBB) dysfunction, and cerebral oxygen supply or demand mismatch are considered among possible etiologies of post-cardiac surgery cognitive dysfunction [3].

Serum biochemical markers of glial and neuronal cell injury, as for example S-100B and neuron-specific enolase (NSE), respectively, have been suggested to be associated with cerebral damage and postoperative cognitive dysfunction after cardiac surgery [4–6]. Studies measuring NSE or S-100B may, however, be flawed as NSE measurements are sensitive to hemolysis (red blood cell enolase) [7] and that extracerebral sources may partly explain the increases in serum S-100B after cardiopulmonary bypass (CPB) [8]. This could also explain why there is a poor relationship between the number of intraoperative cerebral microemboli and the release of S-100B in serum after cardiac surgery. This is in contrast to a recent report on patients undergoing transcatheter aortic valve implantation, where a close correlation between the number of cerebral emboli and postprocedural release of S-100B was described [9].

Investigators have proposed that cognitive dysfunction after cardiac surgery may be related to a cerebral inflammatory phenomenon [3, 10]. Cardiac surgery is associated with a profound systemic inflammatory response due to the surgical trauma, the return of shed mediastinal blood, and the interaction between blood and the artificial surfaces of the CPB circuit [2]. Data on the cerebral inflammatory response to cardiac surgery are, however, scarce [2, 3].

Little information is present on the effects of cardiac surgery with CPB on the integrity of the BBB [3]. Previous studies have demonstrated the presence of brain edema

Accepted for publication April 12, 2012.

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Published by Elsevier Inc

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2012.04.044

Abbreviations and Acronyms

BBB = blood brain barrier
CPB = cardiopulmonary bypass
CSF = cerebrospinal fluid
GFAP = glial fibrillary acidic protein
IL-6/-8 = interleukin-6/-8
MAP = mean arterial pressure
MES = microembolic signals
NF-L = neurofilament light chain protein
NSE = neuron-specific enolase
RMCA = right medial cerebral artery
SAVR = surgical aortic valve replacement
TCD = transcranial Doppler
T-tau = total tau

early after cardiac surgery with CPB [11], which could to some degree be explained by a BBB dysfunction [3]. Post-cardiac surgery BBB dysfunction could tentatively be caused by a cerebral inflammatory response [12] or other initiating events such as brain ischemia because of cerebral embolization [3].

In the present prospective, descriptive study on patients undergoing surgical aortic valve replacement (SAVR), we circumvented the shortcomings of serum markers of glial and neuronal cell injury after cardiac surgery by the measurements of the release of cerebrospinal fluid (CSF) markers of neuronal (NSE, total tau [T-tau], and neurofilament light chain protein [NF-L]) and glial cell injury (S-100B, glial fibrillary acidic protein [GFAP]). Secondly, we wanted to evaluate whether cardiac surgery with CPB causes a cerebral inflammatory response or BBB dysfunction by the measurement of CSF cytokines and CSF to serum albumin ratio, respectively, before and after the procedure. We tested the hypothesis that there is an association between the intraoperative cerebral microembolic load, as measured by transcranial Doppler (TCD), and CSF markers of neuronal or glial cell injuries, as well as CSF markers of cerebral inflammation and BBB dysfunction.

Patients and Methods

This study complies with the Declaration of Helsinki. The Human Ethics Committee of the University of Gothenburg approved the study protocol and all patients signed an informed, written consent. The study was registered at www.clinicaltrials.gov; identifier: NCT01319799. Inclusion criteria were the following: (1) elective isolated open SAVR with a biological valve prosthesis, (2) normal preoperative coagulation tests (ie, partial thromboplastin time less than 45 seconds and prothrombin time [international normalized ratio] < 1.5 and a platelet count $>$ 80,000); (3) absence of recent (< 1 week) treatment with thrombolytic or potent antiplatelet drugs; and (4) preoperative left ventricular ejection fraction 0.50 or greater. Exclusion criteria were abnormal coagulation tests (see above) or abnormal thromboelastograms in the morning on the first postoperative day, and preexisting neurologic deficits.

Premedication consisted of flunitrazepam (0.015 mg/kg orally) in addition to morphine (0.15 mg/kg) and scopolamine (0.006 mg/kg) intramuscularly. Anesthesia was induced with fentanyl (10 μg/kg) followed by a bolus of propofol (0.5 mg/kg). Before and after CPB, anesthesia was maintained with sevoflurane 0.5% to 2.5% in a 50% O_2/air mixture. During CPB, anesthesia was maintained with propofol at a rate of 2 to 4 mg/kg per hour. Anesthetic depth was monitored by an auditory evoked potential monitor (AEP Monitor/2; Danmeter, Odense, Denmark) and adjusted to an evoked potential index of 15% to 25%. Norepinephrine was used to maintain a mean arterial pressure within the range 70 to 80 in the pre-CPB and post-CPB period, and a mean arterial pressure within the range of 60 to 80 mm Hg during CPB. A standard neurologic examination and assessment of focal neurologic impairment were performed the day before and the day after the operation by the same investigator.

The CPB perfusion system consisted of a hollow fiber membrane oxygenator, and a Sarns 9000 max pump (Sorin Group, Mirandola, Italy). A nonpulsatile perfusion of 2.4 L· minute $^{-1} \cdot$ m $^{-2}$ was maintained. The pump was primed with acetated Ringers solution and mannitol, with the hematocrit maintained between 25% and 35%. The $Paco_2$ (partial pressure of carbon dioxide, arterial), Pao_2 (partial pressure of oxygen, alveolar), and pH measurements were performed online. The $PaCO_2$ was maintained at 38 to 45 mm Hg and was uncorrected for body temperature. The PaO_2 was maintained at 180 to 195 mm Hg. During CPB, the body temperature was maintained at 36°C in all patients. A cell-saver device was not used for the processing of shed mediastinal blood.

Transcranial Doppler

The right medial cerebral artery was insonated by the transtemporal approach at a depth of approximately 50 mm using standard criteria [13]) immediately before anesthesia induction. We used a 2-MHz power M-mode TCD monitor (ST3; Spencer Technologies Seattle, WA), with the probe fixed in position using a head frame. The Doppler signals were continuously monitored and saved to the monitor hard drive. Two neurosonologists independently evaluated the TCD data files offline. They manually traced and rejected artifacts and identified true microembolic signals (MES), in consensus, using criteria for embolic signals on spectral and power motion-mode Doppler TCD [14].

The following intraprocedural events were defined with respect to the appearance of MES in the right medial cerebral artery: (1) Aortic cannulation before start of CPB; (2) CPB before aortic cross-clamp; (3) during aortic cross-clamp; (4) declamping of aorta to end of CPB; (5) end of CPB to aortic decannulation; and (6) aortic decannulation to sternum closure. The duration of each of these events was recorded in each patient.