Pathophysiological basis of CNS injury in cardiac surgical patients: detection and prevention

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The current understanding of adverse central nervous system (CNS) events following cardiac surgery involves several identifiable, evidence-based mechanisms: atherosclerotic emboli, microgaseous and microparticulate emboli, and hypoperfusion. Secondary factors, including patient co-morbidities and inherent genetic susceptibilities, as well as systemic inflammatory processes and a suboptimal metabolic milieu may interact to potentiate the extent of injury. In this review a number of these factors and their potential interactions will be explored with a view towards developing a comprehensive management strategy to minimize CNS injury. Perfusion (2006) 21, 203–208.

Cerebrovascular disease

Intrinsic cerebrovascular disease, in addition to the procedural risks of embolic and hypotensive episodes attending cardiac surgery, may play a significant role in the genesis of perioperative CNS injury. In a prospective study of 151 consecutive Japanese patients (115 male and 36 female, age range: 41–82 years) scheduled for coronary artery bypass grafting (CABG), carotid and intracranial arteries were examined for occlusive lesions with magnetic resonance angiography. Cervical carotid artery stenoses of >50% narrowing were detected in 16.6% of the subjects, and intracranial artery stenoses of >50% narrowing were detected in 21.2% of the subjects. In a similar study of 201 Korean patients presenting for CABG surgery, >50% of patients had evidence of either extracranial or intracranial atherosclerotic disease (ECAD, ICAD), while 13% of patients had evidence of both conditions. In this series, 25.4% of patients had single or multiple postoperative CNS complications, and ICAD was found to have a strong independent association with the development of CNS complications. The presence of both ECAD and ICAD was even more strongly associated with adverse CNS outcomes than ICAD alone.

Cardiopulmonary bypass

More than two decades ago, clinical physiology studies were focused on understanding the relationship between cerebral blood flow (CBF) and cerebral oxygen metabolism (CMRO₂) during cardiopulmonary bypass (CPB). This resulted in the generation of hypotheses relating the delivery of cerebral emboli as being proportional to CBF, and emphasized the role of cerebral emboli in the genesis of CNS injury. Specifically, alpha-stat pH management was hypothesized to result in a lower incidence of CNS injury due to lowered cerebral embolic delivery. Subsequently, there have been several independent, prospective, randomized clinical trials demonstrating improved neurological and neuropsychological outcomes associated with alpha-stat pH management in adult patients undergoing moderately hypothermic CPB. Pulsatile perfusion has also been shown to improve overall
clinical outcomes, and remains a topic of interest.

**Cerebral atheroemboli**

Atheroembolic load and risk of stroke can be decreased using ultrasound-guided assessment of the ascending aorta (epiaortic scanning; EAS) prior to surgical instrumentation. Palpation of the aorta is relatively insensitive for the detection of non-calcific plaque in the ascending aorta, with between 23.5 and 62% of all significant aortic atheroma undetected. The use of EAS provides accurate images of the aortic wall and lumen and allows for optimization of cannulation and clamp sites. As shown in Figure 1, in a study of 102 patients in whom EAS was performed directly after conventional aortic assessment by surgical palpation, EAS was associated with a significantly lower incidence of cerebral emboli associated with cannulation and release of the aortic crossclamp and partial clamp.

**EAS and modifications of surgical technique**

In the same study of those patients in whom EAS was performed directly after conventional aortic assessment by surgical palpation, as shown in Figure 2, in 23.5% of these patients, aortic scanning resulted in a change in surgical management of aortic instrumentation by relocation of clamp or cannulation sites. In another study, EAS of the ascending aorta was performed in 500 of a consecutive series of 540 patients, 50 years of age or older (mean 68 years), who underwent a variety of cardiac surgical procedures. Sixty-eight patients (13.6% of the total) with a mean age of 72 years (range: years 55–85) had significant atheromatous disease in the ascending aorta and were considered to be at increased risk for embolization. Palpation identified atheromatous disease in only 26 (38%) of these patients and underestimated its severity. A total of 168 modifications to the standard techniques for cannulation and clamping of the aorta were implemented in the 68 patients (mean: 2.5/patient) and included alterations in the sites of aortic cannulation (50 patients), aortic clamping (54 patients), attachment of the vein grafts (35 patients), and cannulation for infusion of cardioplegic solution (29 patients). Ten patients with severe diffuse atheromatous disease, underwent graft replacement of the ascending aorta with hypothermic circulatory arrest without aortic clamping. Permanent neurologic deficits occurred in five (1.0%) patients in the entire group, but in none of the 68 patients with significant atheromatous disease in whom modifications in technique were used. Others have reported similarly on the utility of EAS and reviewed various other surgical strategies to manage the atherosclerotic aorta.

**Microemboli**

Intraoperative studies involving transcranial Doppler (TCD) for identification of cerebral microemboli, and retinal angiography to detect retinal emboli have facilitated the identification of CPB-related techniques effective in reducing embolic events. Retinal angiography has demonstrated that flat-sheet membrane oxygenation provides significantly better protection against microembolic retinal ische-
Cerebral ischemia, and, by extension, cerebral ischemia, than bubble oxygenation, facilitating the introduction of membrane oxygenators as standard of care. TCD monitoring can detect the occurrence of embolic events in real time and allows modification of surgical and perfusionist technique. It has been shown that the numbers of emboli generated by perfusionist interventions (eg, drug injection and blood return from non-deaired syringes) are significantly decreased by awareness of TCD-detected embolic events, while TCD detection of intraoperative emboli has similarly identified entrainment of air from atrial cannulae, allowing timely correction by application and/or tightening of venous purse string sutures.

Another source of emboli during CPB results from the return of unprocessed cardiotomy suction blood exposed to pericardial and mediastinal surfaces. Pericardial suction blood has been associated with postoperative neurological injury, in part attributed to increased levels of hemolysis and fat in the circulation of this scavenged blood. Reinfusion of cardiotomy suction blood has been identified as a source of cerebral lipid microemboli after CPB in a canine model. Filtering, as well as treating shed blood with a blood cell processor before return to the extracorporeal circuit, has been demonstrated to reduce reinfusion of fat emboli.

### Hypoperfusion

Recognition and treatment of cerebral venous hypertension, arising as a consequence of surgical dislocation of the heart during either beating heart surgery (BHS) or conventional CPB, can be important in decreasing cerebral ischemia, especially in patients with pre-existing cerebrovascular disease, as noted above. Cerebral hypoperfusion from unrecognized cerebral venous obstruction, inadequate mean arterial pressure, or from hypocapnic cerebral alkalosis can be identified by multi-modality neuro- monitoring using regional cerebral oxygen saturation (rSO₂), electroencephalograph (EEG) and TCD.

Use of cerebral oximetry identifies a number of otherwise unrecognized causes of cerebral hypoperfusion, during both conventional CPB and BHS. Recognition and treatment of cerebral venous hypertension, arising as a consequence of surgical dislocation of the heart during either BHS or conventional CPB, in addition to cerebral hypoperfusion resulting from persistent positioning with the head turned to the extreme left side, cannula-obstructed venous outflow from brain, hypoxemia, low perfusion pressure, and inadequate hemoglobin concentration, have all been identified and successfully treated after detection using rSO₂ monitoring.

Compromised cerebral perfusion can also occur relatively frequently during BHS. Using combined EEG and cerebral oximetry, episodes of cerebral ischemia were identified in 15% of a series of 550 BHS patients, requiring various treatments, including a combination of pharmacological improvement of cardiac output, increased perfusion pressure and cardiac repositioning. In an analysis of jugular oxygen saturations during coronary artery grafting, 48% of patients experienced poor global cerebral oxygenation (<50%) during BHS in comparison to 27% of patients managed with CPB. Thus, while patients undergoing BHS may be exposed to significantly fewer cerebral emboli, the risk of cerebral hypoperfusion appears to be much greater than during CPB. It has also been demonstrated that, in patients with peripheral vascular disease, ‘blind’ application of a partial occlusion clamp to the aorta can increase stroke risk during BHS, again emphasizing the need for EAS prior to aortic instrumentation, irrespective of use of CPB.

In an interim analysis of our own randomized, prospective, blinded study, we demonstrated a significant shortening of length of stay associated with intraoperative rSO₂ monitoring and directed interventions in patients undergoing CABG surgery. Results from the overall randomized, blinded study of 200 CABG patients demonstrated prospectively that rSO₂ monitoring is associated with a significant decrease in cumulative major morbidities, including stroke, death, myocardial infarction, prolonged ventilatory support and renal failure.

Consistent with this result, Goldman et al. have recently reported that, in a large non-randomized series of 1698 cardiac surgical patients, a significant reduction in perioperative stroke rate, from 2.01 to 0.97%, was observed in patients in whom rSO₂ cerebral oximetry was used to optimize and maintain intraoperative cerebral oxygenation, in comparison to an untreated comparator group of 2077 similar patients operated on in the immediately preceding 18-month interval. While they had already undertaken a series of steps to minimize perioperative stroke rate in cardiac surgical patients, including routine epiaortic scanning, aprotinin administration, and avoidance of unprocessed cardiotomy blood, patient-specific management based on preservation of cerebral oximetry was able to significantly decrease perioperative stroke rate.
Inflammatory and metabolic mediators

The extent of CNS injury following various embolic or hypotensive insults, as already outlined, may be significantly exacerbated, depending on the clinical management of secondary factors. There is both experimental and clinical evidence that hyperglycemia is associated with exacerbation of neurological injury as well as a variety of other adverse outcomes, including wound infection and mortality among critically ill patients. In a series of cardiac surgical patients, McAlister et al. correlated average blood glucose on the first postoperative day with a variety of adverse outcomes (stroke, myocardial infarction, septic complication or death). For each 1 mmol/L increase above 6.1 mmol/L (1 mmol = 18 mg/dL), risk of these outcomes increased by 17%. A prospective study of critically ill patients suggests that the control of blood glucose levels, rather than insulin levels per se, account for apparent benefits in mortality. Avoidance or limitation of some of the following may effectively limit hyperglycemia, with the expectation of enhanced neurological outcomes: (1) glucose-containing intravenous, cardioplegic and pump-priming solutions; (2) enhanced awareness and treatment of catecholamine-induced hyperglycemia; and (3) more aggressive insulin dosing strategies.

Previous research has reported an association between the inflammatory processes and exacerbation of ischemic brain injury by various mechanisms, including increased capillary permeability, complement activation, neutrophil activation and thrombin-mediated protease activated receptor (PAR) upregulation. There is an intriguing association of aprotinin with lowered stroke risk, which may well include anti-inflammatory effects and specific inhibition of thrombin-activated PAR receptors. Whether this represents a direct cerebroprotective mechanism of aprotinin, or a non-specific benefit of lowered requirement for blood products, particularly platelet transfusion, is currently undergoing investigation.

The avoidance of cerebral hyperthermia, both during intraoperative rewarming, as well as in the immediate postoperative period, may also be important in limiting CNS injury. Cerebral hyperthermia in the setting of stroke is associated with increased morbidity and mortality. Hajat et al., in a meta-analysis of the effects of hyperthermia in the setting of stroke, reported increased morbidity and mortality amongst febrile patients. Hyperthermia worsens cerebral ischemia through several mechanisms: (1) increased release of neurotransmitters; (2) increased free radical production; (3) breakdown of the blood–brain barrier; (4) increased ischemic depolarizations in the focal ischemic penumbra; (5) impaired recovery of energy metabolism and inhibition of protein kinases; and (6) worsening of cytoskeletal proteolysis. In the setting of CABG surgery, Grocott et al. similarly found postoperative hyperthermia associated with greater neuropsychological dysfunction. Careful attention to arterial inflow temperature during rewarming and aggressive treatment of febrile reactions in the early postoperative interval, along with strict maintenance of perioperative euglycemia and strategies to decrease systemic inflammatory processes, are all important secondary factors that may be expected to optimize CNS recovery.

Summary

As the mechanisms of perioperative CNS injury are increasingly understood, strategies to minimize cerebral embolization, avoid cerebral hypoperfusion, and minimize whole body inflammatory processes offer the best hope for decreasing the risk of adverse CNS events and associated costs in an increasingly elderly and high-risk surgical population. An evidence-based review of best practices for

<table>
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<th>Table 1</th>
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<tr>
<td>I</td>
<td>The clinical team should manage adult patients undergoing moderate hypothermic CPB with alpha-stat pH management. (Class I, Level A)</td>
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<td>II</td>
<td>Limiting arterial line temperature to 37°C may be useful for avoiding cerebral hyperthermia. (Class IIa, Level B)</td>
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<td>III</td>
<td>The clinical team should maintain perioperative blood glucose concentration within an institution’s normal clinical range in all patients, including non-diabetics. (Class I, Level B)</td>
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<td>IV</td>
<td>Direct reinfusion to the cardiopulmonary bypass circuit of unprocessed blood exposed to pericardial and mediastinal surfaces should be avoided. (Class I, Level B)</td>
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<td>V</td>
<td>In patients undergoing cardiopulmonary bypass at increased risk of adverse neurological events, strong consideration should be given to intraoperative TEE or epiaortic ultrasound scanning of the aorta: 1. To detect non-palpable plaque (Class I, Level A) 2. For reduction of cerebral emboli (Class IIa, Level B)</td>
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<td>VI</td>
<td>Arterial line filters should be incorporated in the CPB circuit to minimize the embolic load delivered to the patient. (Class I, Level A).</td>
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<td>VII</td>
<td>Efforts should be made to reduce hemodilution, including reduction of prime volume in order to avoid subsequent allogenic blood transfusion. (Class I, Level A)</td>
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<td>VIII</td>
<td>Reduction of circuit surface area and the use of biocompatible surface modified circuits may be useful/effective at attenuating the systemic inflammatory response to cardiopulmonary bypass, and improve outcomes. (Class IIa, Level B)</td>
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1From: Shann et al. (2006).
cardiac surgical patients has recently prepared a summary of the recommendations (Table 1). There are preliminary data that applied neuromonitoring, specifically cerebral near-infrared spectroscopy, facilitates detection and treatment of cerebral ischemia and is associated with a lower incidence of morbidity and shorter postoperative hospitalization. Understanding the mechanisms of perioperative cerebral injury facilitates the development of effective clinical management strategies designed to decrease risk in an ever-aging and progressively sicker surgical population.

References


47 Striggow F, Riek-Burchardt M, Kiesel A et al. Four different types of protease-activated receptors are widely expressed in the brain and are up-regulated in hippocampus by severe ischemia. Eur J Neurosci 2001; 14: 595–608.


