Cerebral Protection During Cardiac Surgery

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Despite many advances in perioperative care, cerebral injury from cardiac surgery remains an important source of patient morbidity and mortality. This injury has a range of clinical manifestations, including stroke and encephalopathy, which occur in 1–3% and 10–15% of patients, respectively. Postoperative cognitive dysfunction (POCD) is more common, affecting 15–40% of patients 1 month after surgery. This form of cerebral injury involves alterations in attention, concentration, and executive cognitive tasks that are detected only with detailed psychometric testing. Debate is on going regarding whether POCD increases the risk for long-term cognitive decline and dementia, particularly in the elderly. Newman et al reported an association between POCD after CABG surgery and cognitive impairment 5 years later. In a longitudinal study, Selnes et al compared cognitive function in patients recovering from CABG surgery with that of a control group receiving medical management for coronary artery disease. Surgery and control groups showed decrements in cognition over time, but no differences in testing results were observed between the CABG surgery and the control groups 6 years after the initial evaluation. Van Dijk et al compared cognitive outcomes in patients 5 years after CABG surgery (performed with or without cardiopulmonary bypass, CPB) with a group of subjects without cardiac disease. After adjusting for differences in age, education, and co-morbidities, there was no difference in cognitive performance between CABG surgery patients and controls. Evered et al performed neuropsychological evaluations in patients undergoing total hip replacement surgery (THJR), patients undergoing CABG surgery, patients undergoing cardiac catheterization (CA), and non-procedural controls. Although the incidence of POCD at day 7 was higher in CABG surgery patients than in other patients, at 3 months the incidence of POCD was similar between groups: 21% for CA under sedation, 16% for THJR surgery, and 16% for CABG surgery (p=0.13). Accumulating data suggest that the impact of cardiac surgery on cognitive function is short lived, with recovery by 3 to 6 months after surgery in most patients. Further cognitive decline more likely results from the progression of coexisting cerebrovascular disease.

Etiology
Cerebral injury from cardiac surgery is believed to result primarily from cerebral embolism and cerebral hypoperfusion. It is hypothesized that the clinical manifestations depend on the size and location of the injury (e.g., motor areas vs. areas involved with cognition). Embolism and hypoperfusion can contribute to injury in the same or different areas in a given patient. Although, primary cerebral hemorrhage is believed to be a rare cause of cerebral injury, sensitive magnetic resonance imaging (MRI) methods suggest that punctuate hemorrhages can occur after surgery in some patients, such as those with endocarditis. Inflammatory processes resulting from CPB and organ ischemia/reperfusion and genetic susceptibility may further contribute to injury.

Insight into the mechanism(s) of perioperative cerebral injury have resulted from studies involving brain MRI or CT imaging. These studies suggest that 30–50% of strokes after cardiac surgery result from cerebral macroembolism, mostly arising from atherosclerosis of the ascending aorta. Cerebral microemboli (<200 µm) have multiple sources and can be gaseous or composed of particulate material. Atherosclerotic burden of the aorta has been found to be associated with the number of transcranial Doppler (TCD)-detected cerebral microembolic signals during CABG surgery. Lipogenous emboli lodged in small arterioles of the brain are found at autopsy in humans after cardiac surgery. Canine experiments suggest that fat arising from the cardiomyotomy suction aspirate is the major source of these lipid emboli. Current CPB filters are inefficient at removing fatty material. Some small studies have implicated cerebral microemboli as a cause of POCD by correlating the number of TCD-detected cerebral embolic signals with cognitive decline after CABG surgery. These results were not confirmed in subsequent studies of patients undergoing open-chamber valvular surgery, where more emboli are present. It is likely that the composition and not the number of microemboli is more important for the manifestations of cerebral injury.

Clinical evidence suggests that cerebral injury from hypoperfusion may be more common in contemporary practice due to the growing number of patients with preexisting, and typically clinically asymptomatic, cerebrovascular
Atherosclerosis of the ascending aorta is a known source of cerebral emboli that may cause stroke and possibly POCD.\textsuperscript{5} In patients presenting with stroke, aortic atherosclerosis is associated with blood hypercoagulability, which increases the risk for recurrent stroke and death.\textsuperscript{22} Two fundamental clinical issues related to atherosclerosis of the aorta are its detection and its surgical management. Epi-aortic ultrasound is more sensitive than direct palpation or TEE for detecting atherosclerosis of the ascending aorta.\textsuperscript{33,34} This method allows the surgeon to identify and avoid atheroma during aortic cannulation and cross-clamping. Approaches to surgical management of patients found to have an atherosclerotic aorta include: a) converting to off-pump surgery; b) using alternative sites for CPB cannulation; c) using the single cross-clamp technique to avoid partial aortic occlusion clamping for proximal

\textbf{Approaches to Cerebral Protection}

Cerebral ischemic injury can be global or focal, as well as temporary (e.g., period of circulatory arrest) or permanent (e.g., distal to embolus). Brain energy stores are rapidly depleted during ischemia, leading to depolarization and release of excitatory neurotransmitters. Cerebral ischemia triggers activation of multiple pathways (“ischemic cascade”) over a period of hours to days that determine the ultimate extent of injury and functional outcome.\textsuperscript{25} Other injury pathways activated lead to altered calcium homeostasis, free radical production, activation of proteases, and initiation of apoptosis. Vulnerability to injury varies between cell subtypes, with particular susceptibility occurring in neurons located in the hippocampus, cortex, cerebellum, corpus striatum, and thalamus.\textsuperscript{26} The central area of ischemic injury is surrounded by viable tissue that is vulnerable to infarction (“the ischemic penumbra”) from the secondary events that follow the initial injury. Cerebral protection during cardiac surgery, thus, can be broadly categorized into several basic strategies: 1) prevent injury from cerebral emboli; 2) ensure cerebral O\textsubscript{2} delivery/demand balance; and 3) prevent secondary brain injury to the ischemic penumbra.

\textbf{Reducing Cerebral Emboli}

Reducing cerebral embolism is the basis of various strategies for cerebral protection during cardiac surgery. Due to CPB’s purported role in increasing cerebral embolism (and increasing potentially injurious inflammatory processes), avoiding CPB by performing CABG surgery “off-pump” has been advocated as a means for reducing cerebral injury from surgery.\textsuperscript{27} Most data supporting this approach have been anecdotal and retrospective. Several prospectively randomized trials of off- versus on-pump CABG surgery have failed to demonstrate that avoiding CPB provides a clear reduction in stroke rate.\textsuperscript{28} In a prospectively randomized study of low-risk patients undergoing CABG surgery, there were no differences in the frequency of cognitive dysfunction 3 months or 5 years after surgery for patients randomized to on- versus off-pump surgery.\textsuperscript{29} In the VA Randomized On/Off Bypass Study, there was no difference between surgery groups in the rate of the composite outcome of death or complications (reoperation, new mechanical support, cardiac arrest, coma, stroke, or renal failure) within 30 days of surgery.\textsuperscript{30} The rate of graft patency at 1 year based on angiography was lower in the off-pump group (82.6% vs. 87.8%, p<0.01). In a review of 6665 patients followed for an average of 4.5 years, off-pump CABG was associated with an increased risk of repeat revascularization and major vascular events (cardiac death, repeat revascularization, MI, or stroke) compared with on-pump surgery.\textsuperscript{31} It has been argued that high-risk patients are a group that may benefit the most from CPB avoidance. More recently, however, in a randomized study of 341 high-risk CABG surgery patients (Euroscore \textgeq 5), avoiding CPB did not affect the frequency of stroke (4.0% vs. 3.7%; RR, 1.08; 95% CI, 0.37-3.14; p=1.0).\textsuperscript{28} The decision to carry out CABG surgery off-pump must be individualized, but the current data do not indicate that this surgical approach substantially improves neurological outcomes.

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bypass graft anastomosis; d) using fibrillatory arrest rather than cardioplegic arrest to avoid cross-clamping; e) avoiding proximal anastomosis by using arterial grafts; and f) replacing the ascending aorta under circulatory arrest. Improved neurological outcomes have been reported with epiaortic ultrasound-guided surgery and with practices that minimize the risk for embolization. A meta-analysis of 7 studies found that the rate of stroke was 0.31% for patients undergoing off-pump CABG with minimal aortic manipulations versus 1.35% for patients undergoing off-pump CABG with a side-clamp or proximal graft anastomosis device \( p=0.003 \).

Other interventions intended to reduce cerebral emboli during CPB include the use of in-line leukocyte-depleting filters and modified aortic CPB cannulae, but data to support the benefit of either for reducing cerebral injury are lacking. Mediastinal insufflation of CO\(_2\) (to increase the rate of absorption of intravascular emboli by substituting the more soluble CO\(_2\) for air in the surgical wound) may reduce the number of arterial emboli. In a study of 80 patients undergoing open chamber cardiac surgery, flooding of the surgical field with CO\(_2\) resulted in preserved P300 auditory evoked potentials (believed to be a sensitive marker for subtle cognitive changes) compared with patients not receiving this intervention. However, neurocognitive outcomes did not differ between the CO\(_2\) insufflation and control groups. Cardiomyopathy suction aspirate is high in lipid content and is a source of cerebral lipid microemboli in experimental canine CPB. Based on animal data and inferential data from humans, many centers adopted a practice of either discarding or processing cardiomyopathy suction aspirate before returning the blood to the CPB circuit. As platelets and coagulation factors are lost with either approach, this practice might increase the frequency of blood transfusions when the suction volume is high. This possibility is an important consideration, as transfusion of allogeneic packed red blood cells and platelets is associated with increased risk for stroke after cardiac surgery. Rubens et al reported no difference in the frequency of POCD 1 week or 3 months after CABG and/or aortic valve surgery between patients whose cardiomyopathy blood was processed with a cell saver compared with those who had direct return to the CPB circuit. Djaiani et al., however, found that processing cardiomyopathy blood with a continuous-flow cell saver led to a significantly lower rate of POCD 6 weeks after CABG surgery. These benefits were not sustained after 1 year of follow-up. Neither study showed a difference in the number of TCD embolic signals between cell-saver and control groups. In both studies, patients in the cell-saver group had higher rates of transfusion than controls. Of note, the median volume of aspirated cardiomyopathy blood in the Djaiani et al study (800 ml; range, 175 to 3840 ml) was higher than that in the study by Rubens et al (636 ml; 95% CI, 566 to 706 ml). Thus, the data are conflicting on whether the routine processing of cardiomyopathy suction aspirate with a cell saver improves neurological outcomes. Any benefits might depend on the volume of aspirated blood and/or the type of device used. Therefore, when large blood loss is not expected, avoiding the return of unprocessed cardiomyopathy suction aspirate to the CPB circuit is reasonable.

Improving Cerebral Oxygen Balance

**Blood Pressure Management:** Mean arterial pressure (MAP) is often kept at low levels (50 to 60 mmHg) during CPB based on data showing that cerebral blood flow (CBF) autoregulation is intact when \(\alpha\)-stat pH management is used. Whether this practice is appropriate for the rising proportion of patients with cerebrovascular disease is not clear. Gottesman et al., for example, found a relationship between a decrease in MAP by \(\geq 10\) mmHg from baseline during CPB and a risk for watershed stroke detected by MRI. More recent data suggest that maintaining MAP between 80 and 90 mmHg during CPB is associated with less delirium and less early cognitive dysfunction. Our group has reported in animal and clinical studies that real-time continuous monitoring of CBF autoregulation using transcranial Doppler or NIRS may provide a novel approach for individualizing MAP targets during CPB. That is, this method allows for MAP to be optimized within an individual’s autoregulatory range, thus reducing the potential of cerebral hyperperfusion. In a cohort of 232 patients, we found that the average MAP at the lower limit of CBF autoregulation was 66 mmHg (95% CI, 65-58 mmHg). The range of pressures, though, at the autoregulation threshold was 40 to 90 mmHg. Women tended to have a lower autoregulatory threshold than men, but predicting the appropriate MAP for CPB was not accurate based on demographic data, including preoperative MAP. These data suggest that monitoring CBF autoregulation in real-time might be necessary to identify the optimal MAP for CPB.
Red Cell Transfusion: Preoperative and intraoperative anemia has been linked in retrospective analysis with adverse outcomes, including stroke, particularly when Hct is <21% during CPB. In a prospectively randomized study, hemodilution to a Hct of 15–18% during CPB was found to be associated with increased neurocognitive impairment in elderly patients compared with a Hct ≥27%. Whether treatment of anemia with transfusion of packed red blood cells (PRBC) improves patient outcome was evaluated in a prospectively randomized clinical trial of 502 patients undergoing cardiac surgery with CPB, the TRACS study. Patients were randomly assigned to a liberal or restrictive transfusion group (Hct ≥30% or ≥24%, respectively). The hemoglobin level in the liberal transfusion group (10.5 g/dL; 95% CI, 10.4-10.6) was higher than that in the restrictive group (9.1 g/dL; 95% CI, 9.0-9.2; p<0.001). The frequency of the primary composite end-point of 30-day all-cause mortality or severe morbidity (cardiogenic shock, ARDS, or acute renal injury requiring dialysis or hemofiltration) was similar between groups [10% liberal vs. 11% restrictive; between-group difference, 1% (95% CI, −6% to 4%); p=0.85]. Non-leukocyte-depleted blood was used in this study, but the PRBC units were stored for a median of 3 days before transfusion. These variables have been associated with reduced risk from PRBC transfusion. Further, cell salvage was not used in the study patients. Independent of transfusion strategy, the number of transfused PRBC units was an independent risk factor for clinical complications or death at 30 days [hazard ratio for each additional unit transfused, 1.2 (95% CI, 1.1-1.4); p=0.002]. Transfusion of ≥5 units of PRBC was associated with mortality. The authors concluded that for patients undergoing cardiac surgery, outcomes do not differ with use of a liberal transfusion strategy or a restrictive strategy. The Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists clinical practice guidelines opine that “For patients on CPB with risk for critical end-organ ischemia/injury, it is not unreasonable to keep hemoglobin level at 7 g/dL or more.”

Temperature Management: Hypothermia is the most widespread cerebral protection strategy during cardiac surgery, a practice supported by a plethora of laboratory data. Clinically, hypothermia has been demonstrated to improve neurologic recovery in comatose survivors of cardiac arrest. Despite its widespread use, there is little clinical evidence that hypothermia is neuroprotective during cardiac surgery. The ineffectiveness of hypothermia might be explained by the absence of hypothermia during all periods of cerebral risk or inadvertent hyperthermia with re-warming. The latter might result from the proximity of the aortic cannula (returning warm blood) to cerebral vessels and/or inaccurate patient temperature monitoring that underestimates brain temperature. Rapid re-warming and postoperative hyperthermia are associated with risk for neurological complications. Re-warming to 34°C rather than to 37°C resulted in improved neurocognitive outcome after CABG surgery. However, at 3 months after CABG surgery, the rates of POCD were no different whether temperature was maintained at 37°C (with a circulating warming blanket) or at 34°C during CPB without re-warming. Our group has demonstrated that CPB re-warming is associated with impaired CBF autoregulation in a high proportion of patients. These results indicate that CBF is pressure-passive in some patients during re-warming at a time when systemic vascular resistance is typically low and cerebral metabolic rate increased. These conditions might lead to a CBF that is inadequate for metabolic demand. In that study, there was an association between impaired CBF autoregulation and stroke.

Neuromonitoring: NIRS provides an estimate of the adequacy of regional cerebral O2 supply. Cerebral O2 desaturations detected with NIRS are associated with postoperative cognitive decline and stroke. In a randomized study of 200 CABG surgical patients, NIRS-guided interventions were associated with less major organ injury (death, MI, stroke) and shorter ICU length of stay versus standard care. Algorithms have been proposed for treating cerebral O2 desaturation. Interventions include ensuring adequate CPB flow or cardiac output when not on CPB, increasing MAP, avoiding hypocarbia (decreasing gas-inflow), deepening anesthesia, increasing the FIO2, instituting pulsatile CPB flow, considering transfusion if indicated, administering anti-convulsant drugs when indicated, and considering hypothermia.
Protecting the Ischemic Penumbra

The ischemic penumbra is vulnerable to infarction because multiple injury pathways that comprise the ischemic cascade referenced earlier are activated. Microcirculatory changes resulting from brain injury, particularly inflammatory and hemostatic activation, can contribute to cerebral hypoperfusion due to the “no reflow” phenomenon. Thus, measures aimed at neuroprotective hemodynamic management may be critical to protection from secondary brain injury. Other measures for protecting the ischemic penumbra are mostly pharmacologic, including avoidance of hyperglycemia.

**Blood Glucose Control:** Hyperglycemia worsens experimental cerebral injury and is associated with poor neurological outcome after stroke in humans.\(^65\) Hyperglycemia worsens ischemic damage by multiple mechanisms. The relationship between serum glucose and stroke severity appears to be “U” shaped. Experimentally, the nadir glucose level associated with best neurological outcome appears to be in the 120 mg/dL range.\(^66\) Initial studies showing that intensive insulin treatment improves outcomes of critically ill patients were rapidly extrapolated to patients undergoing cardiac surgery.\(^67\) More recent data (the NICE-SUGAR study) demonstrated in a multicenter, randomized trial that a glucose target of 81 to 108 mg/dL was associated with higher mortality compared with a target of ≤180 mg/dL in adult critically ill patients. Importantly, these prior trials were conducted in the ICU.\(^68\) Data in cardiac surgery patients have not supported intensive insulin therapy for improving patient neurological outcomes. In a randomized trial of 400 patients undergoing cardiac surgery, the frequency of the composite outcome of death, cardiac morbidity, stroke, or renal failure was higher for patients given an insulin infusion to maintain intraoperative glucose between 80 and 100 mg/dL than for patients who received conventional treatment [insulin given when glucose was >200 mg/dL (\(p=0.02\))].\(^69\) A prospectively randomized trial found no difference in the frequency of neurological complications 6 weeks or 6 months after CABG surgery between patients who received intraoperative insulin when glucose was >100 mg/dL and those who received insulin when glucose was >200 mg/dL.\(^70\) In nonsurgical patients with stroke, maintenance of euglycemia with a glucose-insulin-potassium infusion conferred no benefits on 90-day mortality or functional outcome compared with controls.\(^71\) Administration of insulin when glucose is >140 mg/dL is recommended for nonsurgical patients with stroke.\(^72\)

**Drugs For Cerebral Protection:** A great deal of investigative energy has been invested testing multiple drugs for neuroprotection during cardiac surgery. For the most part, clinical trial results have been disappointing. Agents that showed promising effects in vitro via multiple mechanisms but failed to provide clinical protection against ischemic cerebral injury include barbiturates, propofol, Ca\(^{2+}\) channel blockers, NMDA receptor antagonists, anti-inflammatory agents, anti-oxidants, GABA receptor blockers, 17β-estradiol, piracetam, and others.\(^5,73-76\) Volatile anesthetics and xenon have laboratory-proven cerebral protective effects. A systematic literature review, nonetheless, concluded that evidence was insufficient to choose one anesthetic over another for the purposes of cerebral protection.\(^77\) Magnesium was investigated as a cerebral protectant in a randomized, blinded, placebo-controlled trial in 350 patients undergoing cardiac surgery.\(^78\) At a dose that increased serum levels to 1½ to 2 times normal, Mg\(^{2+}\) use was associated with improved cognitive performance 24 to 96 hours after surgery compared with placebo, but these benefits were not present 3 months after cardiac surgery. Experimentally, ketamine protects against ischemic neuronal injury by blocking NMDA receptors and by attenuating inflammation.\(^79\) In a small randomized pilot study \((n=52)\), the frequency of POCD 1 week after cardiac surgery was lower in patients who received ketamine than in those who received placebo (33% vs. 81%, \(p=0.001\)).\(^75\) Likewise, the frequency of delirium was lower for patients given ketamine during surgery than for those given placebo.\(^80\) Other promising early data have been reported with erythropoietin (EPO). Thirty-two patients undergoing CABG surgery were randomized to receive one of two doses of EPO or placebo starting the day before surgery.\(^81\) Two months after surgery, there was a trend toward a lower frequency of POCD in patients who received EPO \((p=0.085)\). In contrast, EPO failed to provide cerebral protective benefits and was associated with higher mortality and thromboembolic events compared with placebo in a large trial of patients with acute ischemic stroke.\(^82\) Early ongoing investigations of novel compounds that act on molecular, genomic, and proteomic targets have had exciting results.\(^83\) In a placebo-controlled, double-blinded trial of 242 patients undergoing cardiac surgery with CPB, investigators found no difference in the frequency of POCD between patients prospectively randomized to receive lidocaine and those who
received placebo (45.5% vs. 45.7%, respectively, \( p=0.97 \)). Diabetic patients who received lidocaine had a higher frequency of POCD than those who received placebo (\( p=0.004 \)). Hyperbaric \( O_2 \) was evaluated as a potential neuroprotective strategy in a study of 64 patients undergoing surgery with CPB. This therapy reduces inflammation and ischemic infarct volume in animals. Patients who received hyperbaric \( O_2 \) in three sessions 24, 12, and 4 hours before CPB had lower levels of inflammatory marker and a lower frequency of POCD 4 months after surgery compared with controls who received pressurized atmospheric air. Another exciting approach for cerebral protection in the preliminary phase of clinical investigations is remote limb transient ischemia. In a study of 33 patients with subarachnoid hemorrhage, limb preconditioning consisting of three 5-minute inflations of a blood pressure cuff every 24 to 48 hours for 14 days was found to be safe and well tolerated.

Table 1. Evidence-based strategies for cerebral protection during cardiac surgery.

<table>
<thead>
<tr>
<th>Strategies Supported by Clinical Investigations</th>
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<tr>
<td>Epiaortic ultrasound for detection of atherosclerosis of the ascending aorta</td>
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<td>Avoidance of hyperthermia during CPB re-warming</td>
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<tr>
<th>Strategies With Reasonable Level of Clinical Evidence</th>
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<tr>
<td>The use of a membrane oxygenator and an arterial line filter (( \leq 40 \mu m )) during CPB</td>
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<tr>
<td>( \alpha )-stat pH management during CPB</td>
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<tr>
<td>Single cross-clamp technique for proximal CABG anastomosis patients at risk for atheroembolism</td>
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<tr>
<td>NIRS monitoring especially in high-risk patients</td>
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<td>Arterial blood pressure kept &gt;70 mmHg during CPB in high-risk patients</td>
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<tr>
<th>Strategies That Are Acceptable and Considered Reasonable Treatment by Most Experts</th>
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<tr>
<td>Serum glucose should be kept (&lt;140 \text{ mg/dL} ) with an infusion of insulin</td>
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<tr>
<td>Consider processing cardiotomy suction aspirate with a cell-saver device</td>
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<tr>
<td>Transfusion of packed red blood cells should be considered in high-risk patients when hemoglobin is ( \leq 7 \text{ g/dL} ) or higher depending on other patient-specific considerations.</td>
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The existing data on pharmacologic neuroprotection during cardiac surgery must be considered in the context of several limitations, including the investigation of drugs with marginally positive preclinical data, the reliance on laboratory models that might not replicate clinical injury, often small study size, and limiting neurological assessments to only one aspect of cerebral injury (e.g., POCD). It is unclear what metrics would be required from the FDA for approval of a drug for the indication of cerebral protection during cardiac surgery (i.e., stroke vs. POCD). Certainly confirmation of a drug’s safety and efficacy in separate, adequately powered, multicenter, prospectively randomized, placebo controlled, double-blinded studies would be a prerequisite.

Conclusions

A comprehensive approach to cerebral protection that includes interventions to reduce cerebral embolism and ensure cerebral \( O_2 \) supply/demand balance may result in improved neurological outcomes. Strategies for improving neurological outcomes from cardiac surgery are summarized in the Table.

References

Disclosure

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