



Neuroprotection in cardiac surgery

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One of the most important innovations in cardiac surgery over the last 50 years has been the development of cardiopulmonary bypass (CPB). CPB unquestionably has saved lives by allowing complex surgery on the heart while keeping mortality rates low. CPB may also be the cause of significant morbidity, however, particularly in the central nervous system (CNS), where complications ranging from overt stroke to encephalopathy (delirium) to subtle cognitive dysfunction continue to occur. Indeed, this problem is becoming worse as improvements in technique allow cardiac surgery to be performed in increasingly older and sicker patients. As a result, new developments are needed to protect the brain during cardiac surgery. This article reviews past and present neuroprotective efforts and outlines a framework for the future development of techniques for neuroprotection during cardiac surgery.

Pharmacologic neuroprotection

There are currently no pharmacologic therapies approved by the United States Food and Drug Administration (FDA) (or other foreign regulatory agencies) for the prevention or treatment of cardiac surgery-associated cerebral injury despite numerous previous investigations of specific pharmacologic agents in this setting (Table 1). The problem is being investigated in several ongoing clinical trials, however.

Thiopental

One of the first agents investigated for its neuroprotective ability in cardiac surgery was thiopental. In a landmark study in the early 1980s, Nussmeier et al

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Table 1

Pharmacologic neuroprotective agents studied in cardiac surgery

Thiopental
Propofol
Acadesine
Aprotinin
Nimodipine
GM1 ganglioside
Dextromethorphan
Remacemide
Lidocaine
Beta-blockers
SOD mimetics (pergogotein)
Complement inhibitors (h5G1/1-scFv; pexelizumab)
Platelet-activating factor antagonists (lexiphanth)
Clomethiazole

administered enough thiopental to maintain isoelectricity on the electroencephalogram (EEG) from before cannulation to CPB termination [1]. By postoperative day 10, neurologic complications were reduced significantly in thiopental recipients but not in control subjects. These encouraging results, though not universally accepted, soon led to the routine use of high-dose thiopental during valvular and other open ventricular procedures. This quick translation into clinical practice was not surprising given the understanding at that time of barbiturates and their potential ability to suppress cerebral oxygen metabolism [2]. The initial optimism about thiopental use soon was tempered, however, by later studies showing no beneficial effect of thiopental on neurologic outcome after coronary artery bypass grafting (CABG) surgery [3,4] and by the knowledge that the sedation produced by barbiturates was often long lasting. As a result, thiopental now is used much less frequently in the setting of cardiac surgery.

In retrospect, the beneficial effects of thiopental seen by Nussmeier et al initially but not on long-term follow-up may not have been related to any direct neuroprotective effect. Instead they may have been related to an indirect reductive effect on emboli containing cerebral blood flow (CBF). The well known cerebral vasoconstrictive effects of thiopental that include matching CBF with a barbiturate-induced reduction in cerebral oxygen metabolism rate (CMO_2) may have reduced the embolic load to the brain during CPB and, as a result, beneficially affected neurologic outcome. Furthermore, it has been shown since that isoelectricity itself is not necessary to incur a neuroprotective benefit from barbiturates [5]. The effect of subisoelectric doses of barbiturates has not been studied in patients, however.

Propofol

Propofol affects $CMRO_2$ and CBF in much the same way as thiopental does. Propofol also has been shown to have some antioxidant and calcium-channel

antagonist properties. Its neuroprotective abilities have been evaluated in an experimental model of cerebral ischemia [6] and in a prospective randomized clinical trial to determine whether propofol-induced burst suppression of the EEG would reduce the incidence or severity of cerebral injury during valvular surgery [7]. In the clinical trial, patients were randomized to receive either burst-suppressive doses of propofol or none at all. At 2 months, neuropsychologic outcomes were the same in both groups. The authors concluded that burst-suppressive doses of propofol provide no neuroprotection during valvular cardiac surgery.

Acadesine

In the early 1990s, the adenosine-regulating agent acadesine was studied for its ability to improve myocardial outcome; its ability to prevent stroke was examined as a secondary outcome [8]. Compared with placebo, both high- and low-dose infusion of acadesine lowered the stroke rate ($P=0.016$). As neurologic outcome was not the primary endpoint of the study, however, no further attempt was made to confirm these findings. In several preclinical studies in experimental settings, other adenosine-like agents have provided neuroprotection. Although their neuroprotective benefit remains unproven, adenosine-regulating agents are a potentially beneficial class of drugs whose application in cardiac surgery is understudied.

Aprotinin

An agent that has received much attention is the nonspecific serine protease inhibitor aprotinin. First developed in the 1950s for the treatment of pancreatitis, in the past 20 years it has found new uses, including the prevention of blood loss and transfusion during cardiac surgery. In a large, multicenter, placebo-controlled trial of aprotinin's blood loss reducing effects during primary or redo coronary artery bypass graft (CABG) and valvular surgery, high-dose aprotinin lowered the stroke rate ($P=0.032$) [9,10]. Aprotinin's mechanism of action remains unclear, however. Initially it was believed that aprotinin's antiinflammatory effects may prevent some of the adverse inflammatory sequelae of cerebral ischemia. Studies in animal models in the setting of cerebral ischemia, however, failed to show any beneficial effect on either functional or neurohistologic outcome [11]. As with thiopental, the initial enthusiasm for aprotinin has been tempered over time by the realization that its beneficial effects may not be caused by any direct neuroprotective effect but instead to an indirect effect on cerebral emboli. Brooker et al have identified cardiotomy suction as a major source of cerebral emboli during CPB [12]. From this finding, one could infer that if a drug reduces the amount of particulate-containing blood returning from the operative field to the cardiotomy reservoir (by decreasing overall blood loss), then cerebral emboli (and the resulting neurologic consequences) also might be reduced. No published studies have assessed the primary effects of aprotinin on neuropsychologic or neurologic outcome after CABG.

Nimodipine

Calcium and its inhibition play key roles in the ischemic cascade leading to irreversible damage. Calcium propagates cerebral ischemic injury; the calcium channel blocker nimodipine exerts beneficial effects on subarachnoid hemorrhage and experimental cerebral ischemia. In a randomized, double-blind, placebo-controlled, single-center trial, the effects of nimodipine on neurologic, neuroophthalmologic, and neuropsychologic outcomes after valvular surgery were studied [13–15]. An external review board later suspended the study because of safety concerns (ie, increased rates of bleeding and death in the nimodipine group) after the study investigators already had enrolled 150 of a planned 400 patients. Although this sparked some controversy and much debate, an interim review at the time the study was stopped revealed no differences in neuropsychologic outcomes between the study groups.

GM1 ganglioside

Because it exerts beneficial effects on spinal cord injuries, the monosialo-ganglioside GM1 ganglioside has been studied for its neuroprotective abilities during cardiac surgery [16]. Its potential beneficial effects include preservation of neuronal membranes and reduction of excitatory amino acid signal transmission. In a preliminary (but underpowered) trial, Greico et al observed no such beneficial effects in patients undergoing cardiac surgery [16]. The authors were able to use this pilot trial as a testing ground for statistical methodology useful for measuring differences in neurocognitive outcome, however, thereby establishing a template for later trials.

Dextromethorphan

Dextromethorphan (an agent also known for its antitussive activity) exerts nonspecific antagonistic effects on *N*-methyl-D-aspartate (NMDA), whose receptor plays a major role in cerebral ischemic injury and has been proposed to play a role in CPB-associated cerebral injury. Two studies have examined specifically the neuroprotective ability of NMDA receptor antagonism in the setting of cardiac surgery. One of those studies focused on remacemide, which is discussed later. The other study focused on dextromethorphan in the setting of pediatric cardiac surgery, using EEG and MRI to gauge neuroprotection [17]. Because of the study's small size, no differences were seen. There have been no other studies of NMDA receptor antagonists in the setting of pediatric cardiac surgery.

Remacemide

NMDA receptor-modulated excitotoxicity has received much attention in the field of neuroprotection. Although limited by distressing psychomimetic side effects, trials in human stroke victims, supported by a wealth of experimental data, have portrayed NMDA receptor antagonists as robust neuroprotective agents. In

this context, the antiepileptic drug remacemide, a noncompetitive NMDA antagonist, was evaluated for its neuroprotective ability in the setting of CABG surgery [18]. In brief, remacemide was given orally for 4 days before surgery. A battery of 12 neurocognitive tests was performed 1 week before and 8 weeks after surgery. A deficit was defined as a decrease of one standard deviation in two or more of the tests within the neurocognitive battery. In addition, the patients were evaluated for learning ability by subtracting the postoperative neurocognitive score from the preoperative score to arrive at a *Z* score (a continuous measure of learning ability). Although remacemide did not seem to improve neurocognitive deficits ($P=0.60$), it did seem to have a beneficial effect on *Z* scores ($P=0.028$). For the first time an adequately powered study of a neuroprotective agent in the setting of cardiac surgery thus showed a beneficial effect in cognitive tests. Unfortunately, because it took so long to perform the trial and to analyze and publish its data, remacemide currently is not being developed for this indication. Nevertheless, the findings underscore the potential of NMDA receptor antagonists for neuroprotection during cardiac surgery.

Lidocaine

Intravenous lidocaine, a sodium channel-blocking and potentially antiinflammatory agent, recently has been investigated for its neuroprotective abilities. In a study of 55 patients undergoing valvular surgery, lidocaine was infused continuously (in an antiarrhythmic dose of 1 mg/min) from before anesthetic induction to 48 hours after surgery [19]. Neurocognitive tests were performed before and up to 6 months after surgery. Neurocognitive outcomes at postoperative day 8 were significantly better in the lidocaine group ($P=0.025$). Though relatively small, this study demonstrates lidocaine's potential for neuroprotection in cardiac surgery. Larger and longer-term studies are currently underway to prove its efficacy.

Beta-blockers

Beta-blocker therapy is used widely in patients with cardiac disease, especially to prevent adverse myocardial events. A recent retrospective single-center study of more than 2500 patients in the setting of cardiac surgery suggests that beta-blockers can also improve postoperative neurologic outcomes (ie, stroke, TIA, or encephalopathy) [20]. Beta-blocker recipients had a significantly lower incidence of neurologic deficit than did non-beta-blocker recipients. Although the reasons for the benefit are not clear, it has been suggested that it involves cerebrovascular tone and CPB-related inflammatory events. The beta-blocker carvedilol, which is known to exert mixed adrenergic-antagonist effects, to act as an antioxidant, and to inhibit apoptosis, also has shown neuroprotective ability [21].

Pegorgotein

Antioxidant therapies may have a role to play in neuroprotection during cardiac surgery. Reactive oxygen species (ROS) are involved intimately in

ischemic reperfusion injury; they also are generated by the whole-body inflammatory response associated with CPB. Drugs that mimic the protective ability of superoxide dismutase (SOD), an endogenous enzyme involved in the catabolism of free radicals, have been used in the setting of experimental ischemia and reperfusion with promising results. Pegorgotein, a monomethoxypolyethylene-glycol covalently linked to SOD, has been shown to protect against reperfusion-mediated cardiac and neuronal injury in animal studies. A recent study evaluated the ability of pegorgotein to reduce neurocognitive deficits in 67 patients undergoing primary elective CABG surgery [22]. The patients were randomized to receive placebo, 2000 IU/kg pegorgotein, or 5000 IU/kg pegorgotein. Although the study was halted prematurely by the drug manufacturer for reasons that are not clear, the interim review revealed no difference in neurocognitive outcome among groups.

C5 complement inhibitor (pexelizumab)

The inhibition of complement pathways is being studied now as a means of preventing cerebral injury after cardiac surgery [23]. In a small study of cognitive function in 18 patients, an inhibitor of C5 called pexelizumab (h5G1.1-scFv) reduced the number of visuospatial deficits seen at hospital discharge. Large scale (phase III) investigations of pexelizumab revealed that it exerts a weak but positive neuroprotective effect [24]. Further studies are pending.

Lexiphanth

The ability of platelet activating factor (PAF) antagonists to exert neuroprotective effects in experimental models of cerebral ischemia [25] has led to their study in several clinical settings. PAF is believed to modulate postischemic injury by way of the release of cerebral cellular lipids and free fatty acids that may in turn cause cellular injury and cerebral edema [26]. In a recent study of 150 patients who received either placebo or one of two different doses of the PAF antagonist lexiphanth, however, the drug showed no protective effects on neuropsychologic performance 3 months after cardiac surgery [27]. Again, this study was significantly underpowered, a recurring and troublesome feature of many investigations in the field of neuroprotection during cardiac surgery [27].

Clomethiazole

Recently, the γ -aminobutyric acid (GABA) receptor antagonist clomethiazole has been evaluated for its neuroprotective effects during CABG surgery. GABA has been shown repeatedly to be an important neuroprotective target in focal and global models of experimental ischemia. In one recent well designed and conducted study, however, clomethiazole failed to decrease adverse neurocognitive outcome after cardiac surgery [28].

Future pharmacologic neuroprotection

The obstacles to finding a pharmacologic solution to the problem of neuroprotection during cardiac surgery, especially in a steadily aging population, are numerous. The apparent lack of efficacy seen in larger nonsurgery-related stroke trials clearly is impeding progress in the field. Repeated failures have led to reluctance by some drug developers to pursue the relatively small (when compared with the stroke-afflicted population in general) market of patients undergoing cardiac surgery. Others, however, have seen an opportunity to aim at a relevant model (patients with cardiac surgery-related brain injury) whose therapeutic window (preinjury drug administration) is defined more easily.

Although the etiology of cardiac surgery-related cerebral injury is not completely clear, it is convenient to use the ischemic cascade to understand the problem. This is not to say that this cascade is the only pathway by which injury may occur; inflammation alone or in combination with ischemia also may play a role. Still, in light of irrefutable data documenting cerebral emboli during cardiac surgery, it is clear that cerebral ischemia at the microfocal level likely occurs in many patients undergoing cardiac surgery.

The complexity of the ischemic cascade, which continues to influence future drug development, makes it difficult to decide on which drug to study. The unique problems posed by CPB and its inflammatory pathways suggest one worthy avenue of research. In addition, preliminary investigations by others and us into the expression of genes involved in inflammatory [29] and apoptotic pathways [30] suggest other potential avenues of research. Indeed, there are more than 450 different potential targets (eg, ion channels, receptors) for which modifying drugs can be developed. If one multiplies this number by the number of compounds that can be directed at each target, then the choice of which drug to study becomes a problem that is unlikely to be overcome without using a strategy that involves mechanistic information.

With so many potential drug targets, the need for a systematic method of screening potential neuroprotective compounds is clear. At the very least, such screening needs to move as smoothly and quickly as possible from the *in vitro* setting into clinically relevant animal models in which their efficacy can be demonstrated [31]. Then and only then should such compounds proceed to clinical trials. Until recently [32], this approach to drug discovery had not been used.

Temperature

Deliberate hypothermia is still the only reliable method of neuroprotection against injuries related to cerebral ischemia from any cause [33–40]. As such, it is clearly desirable. Even after ischemic injury and reperfusion, delayed hypothermia reduces cell damage in animal models [41–45]. Hypothermia can lead to undesirable effects, however, such as shivering and increased oxygen consumption if uncontrolled and may contribute postoperatively to wound infections and

longer hospital stays [46–48]. Cardiac surgeons and anesthesiologists therefore often urge perfusionists to warm aggressively in an attempt to avoid the usual decrease in temperature that occurs after CPB.

At the other end of the spectrum, hyperthermia is also clearly undesirable. Even small increases in brain temperature (1° – 2° C) exacerbate a recent brain injury. Evidence for this comes from laboratory and clinical studies. Dietrich and associates noted that the histopathologic consequences of temporary forebrain ischemia were significantly worse in rats maintained at 39° C compared with those maintained at 37° C [36]. Others have noted that postischemic cerebral hyperthermia (40° C) in piglet models was associated with persistent deterioration of neurobehavioral outcome after global ischemia [49]. Several laboratory studies have demonstrated that even small differences in intraschemic brain temperature determine the extent of focal ischemic neuronal injury [33–36,38,50–52]. The mechanism behind hyperthermia's deleterious consequences relates not only to increases in excitotoxic neurotransmitter release [53,54], oxygen free radical production [55], intracellular acidosis [56], and blood–brain barrier permeability [57], but also because it modulates protein kinase [58] and destabilizes the cytoskeleton [59]. Consequently, neuronal injury in susceptible regions can be converted to frank infarction, leading to accelerated neuronal death and increased mortality [33–36,38,50–52].

The clinical data are equally convincing. Some researchers have noted an association between body temperature and stroke severity in patients who have suffered acute stroke. Kammersgaard et al reported an association between low body temperature at hospital admission and decreased mortality and morbidity in stroke patients, noting that even small differences in temperature predicted marked differences in these outcomes [60]. Such findings suggest that measures should be taken to decrease brain temperature in the setting of acute cerebral injury. A large randomized clinical trial now underway is testing the benefit of inducing modest hypothermia in unselected patients with stroke [60]. Conversely, other findings suggest that hyperthermia in stroke patients may increase pathologic damage and mortality [36,61]. In two studies of patients with acute strokes, fever worsened prognosis with respect to stroke severity, infarct size, mortality, and overall outcome in survivors [62,63].

Similarly, brain temperature during cardiac surgery involving CPB may influence the extent or severity of neurologic injury [64–66]. Unfortunately, cerebral hyperthermia probably occurs frequently during rewarming, although it may not be reflected in the nasopharyngeal temperature [67–73]. In one's zeal to cool the patient and protect vital organs—particularly the brain—the rewarming phase therefore must not be neglected. It seems that slow rewarming may be beneficial [74] in part because it avoids the spike in temperature that occurs with too rapid warming, thereby avoiding damaging cerebral hyperthermia. The location of temperature monitors during the rewarming phase also may affect outcome. The jugular venous blood temperature is somewhat higher than the nasopharyngeal or esophageal temperature [67–73] and dramatically higher than either the bladder or rectal temperature; in fact, the temperature gradient between

the bladder and the jugular bulb can vary by as much as 5°C [67]. This phenomenon is clinically relevant because of the relationship of jugular venous blood temperature to brain temperature. Although the jugular venous blood temperature does not measure cerebral cortical temperature precisely, it is measured in venous blood and so cannot be greater than brain temperature; this was confirmed in a previous study by direct measurement of cerebral temperature in patients with head injuries [75]. The best reflection of jugular venous blood temperature is pump outflow temperature [76].

A related area of controversy and current research concerns whether hypothermia is better than normothermia during CPB [64–66,77–83]. Certainly the brain is better protected if it is hypothermic at the time of an ischemic insult. The timing of hypothermia induction during cardiac surgery, however, may leave the brain unprotected at critical times. During routine CPB, hypothermia always is initiated after aortic cannulation and CPB onset, and patients always are rewarmed before CPB termination. The risk for brain macroembolism during the hypothermic period is low because the heart is excluded from the circulation by the aortic cross-clamp. Conversely, the risk for micro- and macroembolism is highest during aortic cannulation, cross-clamping and unclamping, CPB onset, and weaning from CPB. During these periods, the brain is normothermic and vulnerable. Because induction of hypothermia commits the surgeon to a later phase of rewarming, care must be taken to avoid rapid rewarming and excessive peak temperatures [74,84–86].

At least one study has shown that hypothermia affords more neuroprotection during CPB than does normothermia. In that study, the stroke rate in normothermic patients was much greater than in hypothermic patients [66]. On closer examination, however, it seems that the putative protective benefit was relative. As it turns out, patients in the normothermic group were warmed actively to maintain normothermia; thus, the relative benefit was probably less because of the “protective” effect of hypothermia than because of the “harmful” effect of the cerebral hyperthermia in the normothermic group. In addition, there were significant differences in serum glucose that may have confounded the results [87,88].

Although shedding light on a complex issue, the results of this and other recent clinical cardiac surgery trials continue to cause confusion. Hypothermia has been shown to protect against overt stroke [66] but not against cognitive dysfunction [66,79,83]. One reason for this is the distinct difference between the two outcomes. For instance, it is well documented that even mild hypothermia (33°–35°C) confers a protective effect on neurologic function, and some investigators believe that this holds true even when mild hypothermia is induced after an ischemic event. Some clinicians therefore wean high-risk patients from CPB at slightly lower temperatures (approximately 35°–36°C) [89,90]. Though this practice must be weighed against the potential risks for hemodynamic instability and bleeding, it is certainly prudent to avoid a nasopharyngeal or tympanic membrane temperature of 38°–39°C. To achieve this goal, however, rewarming needs to be started early enough to allow gradual attainment of the desired nasopharyngeal or tympanic temperature while ignoring the bladder and

rectal temperatures. Although an “afterdrop” in temperature always occurs after CPB, one should not risk causing cerebral hyperthermia in an effort to avoid such a drop. Because perioperative strokes are not predictable, efforts should be made to control temperature in all patients undergoing cardiac surgery, even if the effect on cognitive outcome is less clear.

Meanwhile, a few studies have looked at postoperative temperature management and cerebral injury in cardiac surgery patients [68,91,92]. Recently, Bissonnette et al examined the jugular venous blood temperature in infants and children during the first 6 hours after cardiac surgery and found the mean to be $39.4 \pm 0.7^\circ\text{C}$ [68]. This was $1^\circ\text{--}2^\circ\text{C}$ higher than the tympanic, rectal, or esophageal temperatures measured simultaneously. Others studied the body temperatures in 300 adult patients during the first 48 hours after hypothermic CPB and found that at least 38% became hyperthermic ($\geq 38.5^\circ\text{C}$) [91]. In that study, the jugular venous blood temperature during the first 5 hours of rewarming in the intensive care unit exceeded the bladder temperature by almost 0.5°C . Grocott and associates also demonstrated recently that hyperthermia commonly occurs during the first 24 hours after CABG and that there is a direct relationship between postoperative fever and cognitive loss at 6 weeks after surgery [92]. Because many of the overt strokes that follow cardiac surgery occur after operation [93,94], the presence of cerebral hyperthermia can only exacerbate the tissue injury that ensues. Postoperative intervention with a potentially beneficial (though as yet unknown) strategy to prevent post-CABG fever therefore is warranted.

Emboli reduction

There is convincing evidence that cardiac surgery exposes the patient to hundreds, if not thousands, of cerebral emboli, and that a strong relationship exists between this embolic shower and changes in cognitive function [95,96]. The sources of particulate and gaseous emboli during cardiac surgery are many. Consequently, numerous strategies have been proposed to reduce this harmful embolic load and thereby confer neuroprotection.

The CPB circuit itself contributes to the embolic load. It generates particulate emboli in the form of platelet-fibrin aggregates and other debris. Gaseous emboli can be created or augmented in the circuit through turbulence-related cavitation and vacuum-assisted venous drainage [97]. The intrinsic ability of the circuit to allow the passage of air entrained from the venous return cannula through the oxygenator itself varies considerably between manufacturers but remains a significant source of gaseous emboli in the circuit.

Recently, the impact of perfusionist interventions on cerebral embolic load has been examined. Borger et al found that the injection of various drugs and blood into the venous reservoir can allow gaseous emboli direct passage into the arterial flow, but that reducing these perfusionist interventions not only decreases embolization but also may reduce neuropsychologic impairment [98]. In addition,

as significant quantities of air can be entrained into the heart from the surgical field, flooding the surgical field with CO₂ has been touted as an effective way to lessen the embolic load [99]. It remains unclear, however, whether this technique specifically reduces cerebral injury. Although the conventional oxygenator/venous reservoir design allows for the purging of considerable amounts of entrained air before it can reach the inflow cannula, the arterial line filter handles a great deal of whatever is left. Because the capacity of the filter is limited and finite, however, significant amounts of gaseous and particulate emboli still pass into the aortic root. Few other emboli-reducing strategies have been studied sufficiently to determine their effect on cognitive function after cardiac surgery.

The type and placement of the aortic cannula may help minimize cerebral emboli. Newer types of aortic cannulas have been designed to reduce the emanation of sandblasting-type jets, incorporate endoaortic baffles, or allow regional brain hypothermia while diverting emboli away from the cerebral vessels [100–103]. One new design undergoing widespread evaluation incorporates a net-like extension that can be inserted during times of cross-clamp removal [104,105]. The placement of cannulas may have a harmful or beneficial effect. Placing a cannula into an area laden with atheromatous debris may cause the direct embolization of atherosclerotic material in the aorta. On the other hand, placing an aortic cannulae distal to the cerebral vessels may reduce embolic load [106].

Embolization by intraoperatively shed mediastinal blood has received attention recently. Such blood, when brought from the surgical field by cardiomy suction, may contribute to the particulate load in the CPB circuit and may increase significantly the cerebral embolic load [12]. Particulate or lipid-laden material that originates from the sternotomy site may enter the circuit and so become available for embolization. Most of this material is small enough or deformable enough to pass through standard arterial line filters. The amounts of such material may be lessened by using blood salvage devices (ie, cell savers) to process the blood before it returns to the venous reservoir. The ability of the cell saver to decrease the amount of particulate matter entering the circuit, however, must be balanced against its washing away of platelet and coagulation factors. The right balance likely lies in using the cell saver to process blood up to certain (though as yet undefined) volume, then returning to the use of cardiomy suction. Studies of cognitive outcome in this setting are underway.

As mentioned, the liberation of atheromatous material from the aortic wall is a significant source of cerebral embolization. Unlike the evidence linking stroke to atheroma [107–110], the evidence linking atheroma to cognitive decline after cardiac surgery is not as clear [111]. Yet, regardless of whether or not atheromatous material causes cognitive dysfunction, its importance in the etiology of cardiac surgery-associated stroke warrants the development of strategies for managing it. Several techniques are being used to minimize the threat of embolization by atheromatous material, but the most effective method is to avoid disrupting the atheromatous aorta in the first place by identifying and avoiding it. The widespread use of transesophageal echocardiography and epi-aortic scanning is useful in this regard and has improved tremendously our understanding of the

risks involved in the patient with a severely atheromatous aorta. In a recent study, epi-aortic scanning allowed for “knowledgeable avoidance” [112] of the atheromatous ascending aorta during cannulation, clamping, and anastomosis placement in patients undergoing cardiac surgery [113]. As a result, the incidence of cognitive decline was lower in those patients who underwent epi-aortic scanning than in those patients who did not. Though limited by its small study population ($n=47$), this study and its results were intriguing nonetheless. Meanwhile, newer technologies such as proximal and distal coronary artery anastomotic devices are being evaluated for their ability to minimize manipulation of the ascending aorta during cardiac surgery [114]. None of these devices has been tested yet in large prospective randomized trials, however.

Clearly, the approaches being taken to minimize the risk for cerebral embolization during cardiac surgery vary widely. In many cases, the approach involves altering a standard of practice to allow the use of a new device. It is always important to consider, however, what additional risk might be inherent in doing so. Modified techniques and equipment thus need to be evaluated thoroughly before they enter widespread use in the clinic.

Off-pump cardiac surgery

Technologic advances, particularly in myocardial stabilizing devices, have led to a relative explosion in the use of the off-pump coronary artery bypass (OPCAB) technique. Although OPCAB has not been shown yet in long-term prospective randomized controlled studies to be an optimal treatment for coronary disease (ie, graft patency), it is clear that it and similar operations are here to stay. Consequently, the question arises whether OPCAB (and similar techniques) will lead to a reduction in the neurologic complications of cardiac surgery. There is evidence to suggest it will, but it is unlikely to be a panacea.

Studies so far suggest that OPCAB reduces but does not eliminate cognitive decline completely [115]. The reasons are unclear but likely reflect the complex pathophysiology involved. For example, if inflammatory processes do indeed play a role in either initiating or propagating cerebral injury, then those components of the OPCAB procedure that contribute to stress and inflammatory responses (eg, sternotomy, heparin administration, and wide hemodynamic swings) [116] may explain in part why cognitive dysfunction still occurs. In addition, traditional embolic theories of cerebral injury remain relevant because manipulation of the ascending aorta (eg, the use of partial occluding or “side-biting” clamps during the creation of proximal anastomoses) is performed still during many OPCAB operations. As already discussed, such manipulation entails the risk for particulate embolization.

As in most other areas of research, only large prospective controlled studies definitively reveal whether OPCAB procedures can indeed reduce neurologic complications and, if so, which patients would be optimal targets. One such study evaluated cognitive dysfunction in 281 patients undergoing OPCAB and found

that even though there was a reduction in cognitive decline in the early months after surgery there was no difference between groups at 1-year follow-up [115]. Though this trial is the largest to date, its failure to detect a difference at 1 year was related partly to an inadequate sample size and a lack of statistical power [117].

Deciding which patients to consider for OPCAB must take into account multiple factors. For example, is OPCAB the best choice for the high-risk neurologic patient, because complete and adequate revascularization may be compromised to reduce the possibility of a debilitating stroke? Conversely, is OPCAB the best choice for the younger patient with a lower risk for neurologic complications but a greater potential gain from the long-lasting patency that can probably be achieved just as well by conventional CABG?

Off-pump surgical techniques are entering a period of rapid development. Robotic techniques are burgeoning and interventional cardiologists are making their own significant advances that may preclude the need for many CABG procedures in decades to come [118–121]. It is not clear now which of these technologies will survive and which will not. What is clear, however, is that cardiac surgery 10 years from now will be performed very differently from the way it is today.

Delayed/postoperative stroke

Despite the many strategies, proven or not, for protecting the brain during cardiac surgery, the postoperative period remains a period of high risk for the development of delayed stroke. It has long been recognized that not all strokes that occur after cardiac surgery occur before recovery from anesthesia [122]. Only in the last decade has this phenomenon of delayed stroke been documented more clearly. Indeed, an estimated 25%–66% of perioperative strokes occur after postoperative day 2 [93,94,122–124].

Several potential risk factors and mechanisms responsible for these delayed strokes have been proposed. Carotid stenosis, atrial fibrillation, and prolonged postoperative hypotension may be involved. Studies have implicated asymptomatic carotid stenosis [125] and prolonged postoperative anemia [122] but have not provided much supporting data. Recently, Hogue et al [93] noted a strong, previously unreported interaction between postoperative atrial fibrillation and low cardiac output syndrome. Congestive heart failure is another potential risk factor, because small ventricular clots might embolize to the brain postoperatively [123]. Embolization from aortic atheromatous plaque is a distinct possibility, just as it is in the intraoperative period. In addition, because the postoperative period is an intense period of hypercoagulability, there may be an increased risk for thrombosis in nearly occluded cerebral vessels or embolization of an intracardiac or other intravascular thrombus.

Until recently, the therapeutic options for dealing with a new-onset stroke in the postoperative period were limited. Although thrombolytic therapy might be considered for new-onset strokes occurring outside the setting of surgery,

generally this is contraindicated after cardiac surgery in light of the recent major trauma. The limited use of direct intraarterial tissue plasminogen activator (tPA) in such cases, however, has been evaluated recently. In a small case series, 13 patients who suffered a new-onset stroke after cardiac surgery were taken to the neuroradiology suite for cerebral angiography and intraarterial tPA administration in an attempt to dissolve the offending thrombus [126]. In addition, the clot was manipulated mechanically with the angiographic catheter to aid in its dissolution. Although mortality in this study was significantly high, death was almost always attributable to cerebral causes (brain herniation caused by edema) and not to any excessive hemorrhaging. This treatment option clearly deserves more evaluation and at least should be carefully considered for use in patients with a new-onset postoperative stroke.

A great deal of valuable clinical information about ventricular function and atheromatous burden, possibly even carotid stenosis, is gathered in the intraoperative period. Unfortunately, this information is often lost in the shuffle of postoperative care for these patients. The intraoperative period therefore offers an opportunity, often underused, for the anesthesiology team to influence the subsequent perioperative course for these patients. For example, gathering information about atheromatous burden is important, because the presence of significant aortic plaque is an established risk factor for primary and recurrent stroke [106–108]. That said, it is not clear what should be done during the postoperative follow-up of patients who have severe atheroma. Therapies such as statins, antiplatelet agents, and other anticoagulants might be evaluated for their ability to provide long-term protection against stroke in this population once discharged from the hospital.

Magnetic resonance imaging

Until recently, neuroimaging has added little to the understanding of the pathogenesis of post-CABG neurologic dysfunction [127]. Conventional magnetic resonance imaging (MRI) techniques have demonstrated new ischemic lesions, but this has not been seen consistently in all studies [128–134]. More recently, diffusion-weighted MRI (DW-MRI) has allowed differentiation of acute from chronic ischemia [135]. In addition to distinguishing changes indicating old and new ischemic lesions, DW-MRI has demonstrated an increase in brain water content within 1 hour after CABG [136,137]. This cerebral edema subsequently reverted to normal by 1 week after CABG.

The correlation of MRI changes with cognitive dysfunction, however, is not clear, as few studies have combined MRI with cognitive interrogation. One recent study in 35 patients undergoing CABG with CPB included DW-MRI and magnetic resonance spectroscopy (MRS), together with neurocognitive testing, all performed before and serially after surgery [138]. As summarized by Wityk in the accompanying editorial [127], there were several important observations in this study. As with previous studies, there was the suggestion of increased brain edema

after surgery, but none of the patients had an overt new focal neurologic deficit or encephalopathy after surgery. There were new lesions on the postoperative DW-MRI scans in 26% of the patients, however, which progressed to infarction on scans performed 10–14 days later [138]. There was no correlation between the presence of lesions on DW-MRI scans and cognitive dysfunction. Notably, however, the presence of transient changes in cerebral N-acetylaspartate (NAA) was observed on early postoperative MRS studies (performed on postoperative days 3–5). The extent of the decline in the NAA/creatinine ratio was related closely to deterioration in neurocognitive function and correlated with increased patient age and longer CPB duration. Normalization of the NAA/Cr ratio accompanied the recovery of neurocognitive performance 10–14 days later [138].

Another intriguing pilot study in a small number of patients ($n=27$) undergoing CABG with CPB demonstrated that almost a third of patients suffered an otherwise silent postoperative brain infarct 3–12 months *after* surgery [139]. These findings suggest that new brain infarcts continue to occur beyond the immediate perioperative period and that late cognitive decline after CABG may not necessarily be attributable solely to perioperative events [140].

MRI has been suggested as a useful measure of outcome in studies of pharmacologic amelioration of acute stroke [141]. In the setting of cardiac surgery, the assessment of potential interventions such as pharmacologic neuroprotective agents or changes in surgical technique require large-scale trials and potentially long periods of follow-up [126]. A surrogate marker for brain injury other than overt changes would be useful, but additional studies are needed to determine whether postoperative MRI and MRS studies correlate with more persistent impairment in this setting.

Future of neuroprotection

The future of neuroprotection in the setting of cardiac surgery will be faced with several continuing problems. First and foremost is the problem of standardizing studies in patients, surgical procedures, other surgical parameters affecting outcome, and neurologic tests (ie, endpoints to be measured and the timing of those endpoints). A more daunting problem is the sheer size of the trials that are required to render meaningful outcomes that might lead to improved pharmaceutical and interventional strategies. This particular problem is being addressed now by larger multicenter consortiums. Another problem is the definition of what constitutes neurologic and neurocognitive outcomes. Determining the incidence of adverse events largely depends on how one defines the adverse events. Yet another problem is that of funding. Assuming that a well designed study to examine neurocognitive outcome requires at least approximately 400 enrolled patients (200 in each group), it quickly becomes apparent that considerable resources, financial and otherwise, are needed to complete these types of studies. This is magnified by a factor of 10 if overt stroke, which has a much lower incidence than cognitive dysfunction, is the principal endpoint. If one were to

study all potential compounds and techniques adequately, it would take billions of dollars and decades to determine which are most efficacious. Finally, although great strides have been made in recent decades, one of the largest problems is that the etiology of neurologic injury after cardiac surgery remains unclear. This should be the focus of further research. Although it is uncertain whether any effective neuroprotection will ever be found, what is clear is that it will not be found without considerable investment of time and money.

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