Cardiopulmonary Bypass Management and Neurologic Outcomes: An Evidence-Based Appraisal of Current Practices

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Neurologic complications after cardiac surgery are of growing importance for an aging surgical population. In this review, we provide a critical appraisal of the impact of current cardiopulmonary bypass (CPB) management strategies on neurologic complications. Other than the use of 20–40 μm arterial line filters and membrane oxygenators, newer modifications of the basic CPB apparatus or the use of specialized equipment or procedures (including hypothermia and "tight" glucose control) have unproven benefit on neurologic outcomes. Epiaortic ultrasound can be considered for ascending aorta manipulations to avoid atheroma, although available clinical trials assessing this maneuver are limited. Current approaches for managing flow, arterial blood pressure, and pH during CPB are supported by data from clinical investigations, but these studies included few elderly or high-risk patients and predated many other contemporary practices. Although there are promising data on the benefits of some drugs blocking excitatory amino acid signaling pathways and inflammation, there are currently no drugs that can be recommended for neuroprotection during CPB. Together, the reviewed data highlight the deficiencies of the current knowledge base that physicians are dependent on to guide patient care during CPB. Multicenter clinical trials assessing measures to reduce the frequency of neurologic complications are needed to develop evidence-based strategies to avoid increasing patient morbidity and mortality.

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Cardiopulmonary bypass (CPB) has been used to assist cardiac surgery for more than 50 yr since its introduction by John H. Gibbon, Jr. in 1953 (1). Despite resurgent interest in "off-pump" surgery, CPB still plays a vital role for the majority (~80%) of coronary artery bypass graft (CABG) surgeries and for all open chamber procedures (2,3). Technological improvements with CPB and other advances over the last half century have allowed the benefits of cardiac surgery to be extended to older patients with a greater burden of comorbidity (3). Complications from surgery, thus, are of growing importance for this aging and high-risk surgical population. Neurologic complications are of particular concern because of their impact on duration of hospitalization, mortality, health care costs, and quality of life (4–12). The purpose of this review is to perform a critical appraisal of the impact of current CPB management strategies on neurologic complications in an effort to optimize patient care and outcomes. We will first review relevant literature and then synthesize recommendations using objective evidence-based methodology.

NEUROLOGIC COMPLICATIONS: MANIFESTATIONS AND MECHANISMS

Brain injury from cardiac surgery is manifest as a spectrum of disorders, including stroke, encephalopathy, and cognitive dysfunction. Stroke is the most obvious clinical manifestation, occurring in 1% to 3% of patients in most series (4–9,12). By far, cognitive dysfunction is the most common neurologic complication, affecting 30% to 65% of patients 1 mo postoperatively and between 20% to 40% of patients 5 mo later (10,11–19). The broad range in reported incidence reflects differences in both the patients studied and methodologic approaches to diagnosis (18,20,21). The finding of a relationship between early postoperative cognitive dysfunction and long-term cognitive decline further underscores the importance of this complication and the need for strategies to lessen its occurrence (10). Clinical variables identifying risk for neurologic complications include advanced patient age, systolic

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hypertension, prior stroke, diabetes, female sex, and atherosclerosis of the ascending aorta (5–8,10,12,18,19). Preliminary data linking certain genetic polymorphisms with perioperative stroke and cognitive decline hold promise for both an enhanced understanding of the mechanisms of these disorders and a potential means for identifying individual susceptibility (22,23).

Cerebral embolism and hypoperfusion exacerbated by ischemia/reperfusion injury are believed to be the primary causes of perioperative brain injury (4–7, 12–16, 19, 24–29). The clinical manifestations depend on the location of brain injury, whether the ischemia is regional or global, and whether it is transient or permanent. Regional cerebral ischemia is characterized by a central core of neurons at highest risk for death surrounded by a region of vulnerable but viable neurons ("ischemic penumbra") (30). In global ischemia the entire brain is at risk, although certain regions are especially susceptible. These include memory-processing areas (CA-1 and CA-4 areas of the hippocampus), the thalamic reticular nucleus, cortical layers III, V, and VI, and cerebellar Purkinje cells (30,31).

Cerebral macro- and microembolism (emboli <200 μm in size that block arterioles) have been documented during and after cardiac surgery by retinal fluorescein angiography, transcranial Doppler (TCD) monitoring, sensitive magnetic resonance imaging (Fig. 1), and at autopsy (12–15,24–27,32). Macroemboli are typically composed of atheromatous material suggested to arise mainly from the aorta (5,24,25). Microemboli are either particulate or gaseous in composition. The latter are introduced into the CPB circuit via incomplete de-airing, venous cannulation, perfusionist interventions, and from left-sided open cardiac chambers (33–35). The finding of a relationship between cerebral microembolic load during CPB and cognitive dysfunction after CABG surgery supports cerebral microembolism as a cause of cognitive dysfunction (12–15,34). In patients undergoing valvular surgery where embolic counts are higher, though, this relationship has not been confirmed (36,37). These data suggest that vulnerability to cognitive dysfunction is determined more by composition than by absolute number of microemboli. Lipogenous material found in small cerebral vessels at autopsy in humans who had undergone cardiac surgery, and in dogs after CPB, is implicated (27,38). In animal experiments, the lipid emboli were found to primarily arise from pericardial suction aspirate returned in the CPB circuit. Presently, the connection between lipid emboli and postoperative cognitive dysfunction is inferential and not definitive because the data are from dogs or human autopsy (i.e., no cognitive testing performed).

Mechanistic paradigms for surgery-related brain injury are challenged by data showing that avoiding CPB (off-pump surgery), although substantially decreasing TCD microembolic signals, does not eliminate cognitive dysfunction (39-41). The finding of cognitive dysfunction after noncardiac surgery further supports the notion that these disorders have a complex, and likely multifactorial, etiology (42). Of increasing relevance in an aging surgical population may be the role of cerebral hypoperfusion. Reduced cerebral blood flow (CBF) during CPB might be a primary cause of ischemic brain injury or it might exacerbate injury by impairing microembolism clearance (4,7,40,43–45). At particular risk for cerebral hypoperfusion are the growing number of patients with advanced cerebrovascular disease and prior stroke. Prior brain infarction is found in 40% or more of patients when magnetic resonance imaging is obtained before cardiac surgery (32). The infarcts are usually clinically asymptomatic, accompanied by cerebral arterial stenosis, and are associated with risk for perioperative stroke and cognitive dysfunction.

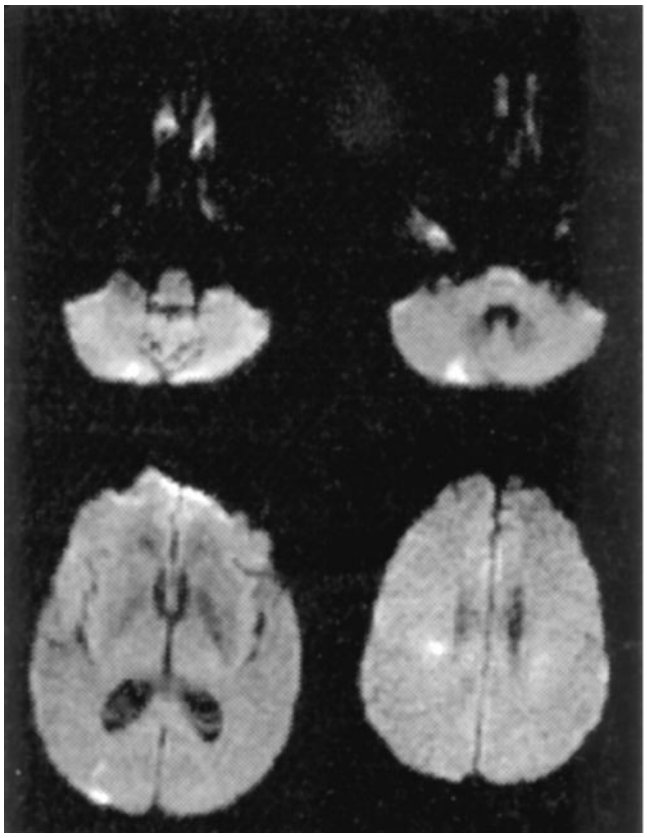

Figure 1. Diffusion-weighted magnetic resonance image (MRI) (DWI) image of a patient after coronary artery bypass graft surgery. DWI imaging is a sensitive means for detecting brain injury within hours of the event. In this patient, preoperative MRI results (not shown) demonstrated a small DWI lesion in the right corona radiata. This lesion, along with two new DWI lesions (inferior cerebellar hemisphere seen in the top image and left posterior cerebral cortex seen in the bottom image) were detected in "watershed" brain areas despite the absence of an overt neurologic deficit. Watershed brain injury may result from cerebral embolism and/or hypoperfusion. Reprinted with permission from Restrepo et al. (32).

In general, the aims of neuroprotection during CPB are to prevent the occurrence of injury (i.e., reduce

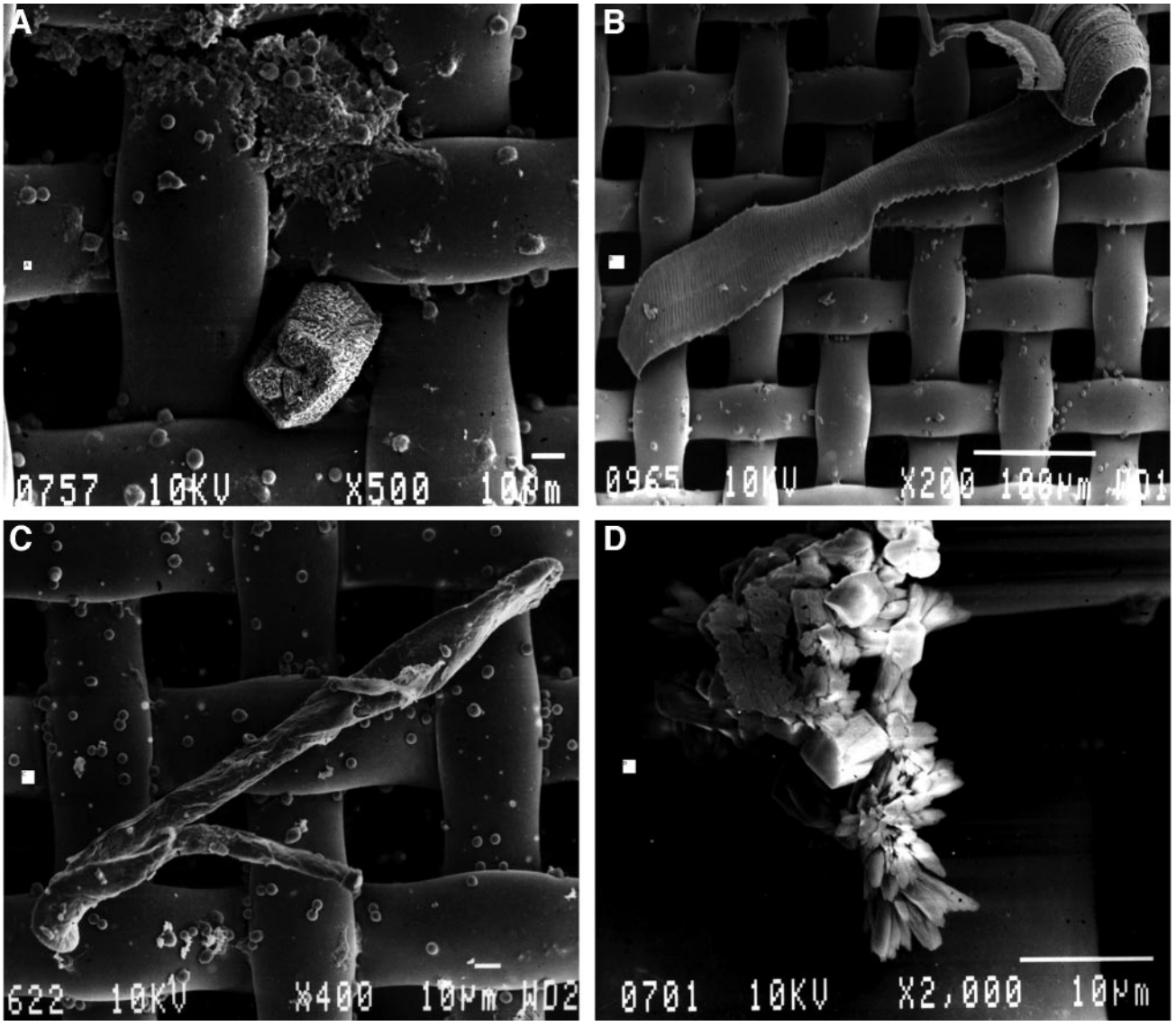

Figure 2. Scanning electron micrographs of 40-micron arterial line filters after clinically uneventful cardiopulmonary bypass. A) A large piece of possibly crystalline material can be seen embedded in the filter mesh. An adherent mass of fibrinous material incorporating erythrocytes can also be seen. B) A particle measuring some 80 × 600 um thought to be spallated silicone rubber. C) A particle thought to be an exogenous, organic fiber. D) A complex crystalline deposit. Courtesy of Department of Perfusion, Middlesex Hospital, London, UK and Pall Biomedical, Portsmouth, UK.

cerebral embolism and/or hypoperfusion) and to increase the tolerance of neurons to ischemia. Approaches include physical interventions, physiologic manipulations, and pharmacologic therapy.

BASIC CPB EQUIPMENT AND NEUROLOGIC OUTCOMES

Early studies of CPB equipment confirmed lower TCD embolic signals and improved cognitive outcomes with the use of membrane compared with bubble oxygenators and with the use of arterial line filters (13,46–48). Figure 2 demonstrates potential embolic material captured by CPB inline filters after otherwise uncomplicated cardiac surgery. Concern about the inefficiency of standard inline filters for removing lipid globules linked to cerebral arterioloar emboli has prompted investigations of other types of filters. Experimentally, leukocyte depleting filters attenuate organ damage by removal of inflammatory mediators during CPB (49). During CABG surgery, leukocyte-depleting filtration led to reduced TCD microembolic signals, but there were minimal effects on postoperative cognitive function (50). In a canine experiment, leukocyte-depleting filters did not reduce lipogenous cerebral arteriolar embolism compared with standard filtration (51). Cerebral microemboli at autopsy, though, were reduced in number by processing pericardial suction contents with a "cell saver" thus removing lipid globules. Whether these latter findings can be extrapolated to humans is currently unknown. A concern is that processing large quantities of pericardial blood could lead to increased bleeding and

transfusion rates because the discarded supernatant is rich in platelets and coagulation factors. The risks versus benefits of discarding or processing pericardial aspirate thus remains to be clinically defined.

One source of the systemic inflammatory response during cardiac surgery is the contact of blood with the foreign surfaces of the CPB circuit, leading to the activation of platelets, leukocytes, and the complement, kallikrein, and coagulation cascades (29,52–57). Multiple technologies have been proposed for modifying the surfaces of the CPB circuit to enhance biocompatibility including coating with heparin, poly-2-methoxyethylacrylate, trillium, synthetic protein, and other compounds (53–60). Further, use of centrifugal versus roller CPB pumps has been proposed to reduce cellular damage, as has the use of a closed versus open reservoir system to minimize the air-blood surface interface (61,62).

Heparin-bonded CPB circuits, clinically available for more than two decades, have perhaps been the most widely studied modification. The use of the latter during CPB in humans have been demonstrated to reduce contact activation and inflammation that could potentially reduce organ ischemia-reperfusion injury (53–57). In two small, randomized studies heparin-bonded CPB circuits either had no impact or led to minor improvements in postoperative cognitive function compared with standard CPB circuits (63,64). Cognitive performance after surgery was not correlated with markers of intraoperative inflammatory activation. In a randomized trial of 300 low-risk patients, the use of either covalently heparin-bonded (Carmeda Bioactive Surface; Medtronic Inc., Anaheim, CA) or ionically heparin-bonded (Duraflo II; Baxter Healthcare Corp, Bentley Division, Irvine, CA) CPB circuits during CABG surgery did not influence the frequency of postoperative memory impairment or release of the brain glial protein $S100B_2$ compared with nonheparin-bonded circuits (65).

ANTICOAGULATION

Patient-specific anticoagulation protocols decrease coagulation factor consumption and platelet activation during CPB, which, in turn, could conceivably influence platelet-thrombus microemboli formation (66). Whether this approach to anticoagulation can affect neurologic outcomes has not been extensively investigated.

MANAGEMENT OF ATHEROSCLEROSIS OF THE ASCENDING AORTA

Atherosclerosis of the thoracic aorta is an important predictor of stroke and cognitive dysfunction (5–7,12,24,67,68). Surgical manipulations of the aorta for cannulation, cross-clamping, and proximal bypass graft anastomosis could lead to cerebral atheroembolism. High-velocity flow patterns generated at the orifice of the CPB aortic cannula might further lead to a "sand-blasting" effect promoting disruption of atheroma (69,70). In the past, the diagnosis of an atheromatous aorta was made using direct palpation by the surgeon. Epiaortic ultrasound is now more sensitive than either palpation or transesophageal echocardiography for detecting this condition (Fig. 3) (12,71–73).

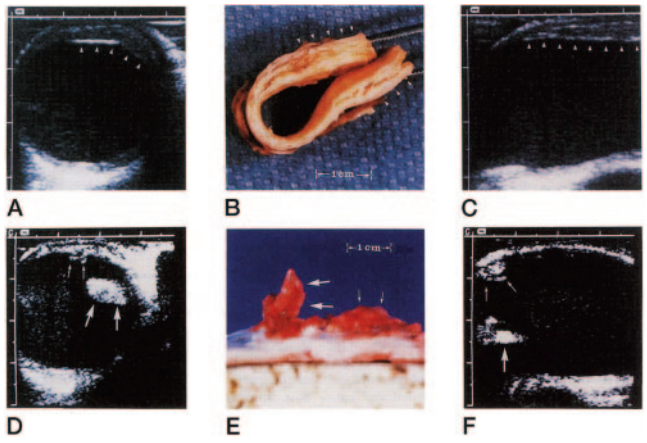

Figure 3. Epiaortic ultrasound images and pathologic specimen depicting atherosclerosis of the ascending aorta. Transverse (panel A) and longitudinal (panel C) ultrasound scans demonstrate circumferential intimal thickening particularly anteriorly (arrows). Pathologic specimen (panel B) confirms the diagnosis. Transverse (panel D) and longitudinal (panel F) images from a second patient demonstrate intimal thickening (small arrows) and large sessile atheroma confirmed with the pathologic specimen (panel E). The pathologic specimens were made available when the patients underwent replacement of the ascending aorta. Reprinted with permission from Dávila-Román et al. (73).

Table 1. Proposed Strategies for the Management of Atherosclerosis of the Ascending Aorta

- Epiaortic ultrasound guidance to avoid atheroma during aortic manipulations
- Avoid partial aortic occlusion cross-clamp ("single cross-clamp" technique)
- Internal mammary artery for proximal bypass graft anastamosis (Y graft) to avoid aortic manipulation
- Axillary artery, innominate artery, or distal aortic arch cannulation rather than ascending aorta cannulation for CPB
- Modified aortic cannula (e.g., low-velocity jetting profile or deployable intra-aortic filter)
- Conversion to "off-pump" CABG with Y graft anastamosis for "no-touch technique"
- Replacement of the ascending aorta under circulatory arrest when atherosclerosis is severe and widespread

CPB = cardiopulmonary bypass; CABG = coronary artery bypass grafts.

Proposed strategies for management of the atherosclerotic aorta are listed in Table 1 (5,74–79). Using epiaortic ultrasound to identify and then avoid ascending aorta atheroma with surgical manipulations has been shown, in large observational case series, to be associated with a low stroke rate even in high-risk patients (5). In a small study the use of epiaortic ultrasound and a "no-touch" technique was found to

lead to less cognitive dysfunction 2 mo after surgery compared with controls (75). Reduced frequency of postoperative cognitive dysfunction and low stroke rates have been reported after adoption of perioperative practices that included epiaortic-guided aortic manipulations and other management strategies including avoiding partial aortic clamping using a "single" aortic cross-clamping approach (76,77,79,80).

Aortic cannula with a more uniform dispersion of CPB flow reduces aortic sandblasting and, at least experimentally, reduces cerebral microembolization (69,70). The use of long aortic cannula (7 cm) was found to result in less turbulence in the aortic arch during CPB than with a short cannula (1.5 cm) (81). Other modifications include cannula with a deployable intraaortic filter and cannula that preferentially divert microemboli away from the aortic arch (82,83). In a multicenter randomized study, particulate emboli were captured in 96.8% of cases in which an intraaortic filter was deployed before aortic cross-clamp removal (82). There was no difference in the frequency of the composite endpoint of mortality, stroke, and transient cerebral ischemic events between the filter and the standard cannula groups.

SURGICAL FIELD CO_2 INSUFFLATION

Carbon dioxide is 50 times heavier and 25 times more soluble in blood than air (84). Consequently, insufflation of CO_2 into the surgical field displaces air decreasing the nitrogen content of gaseous emboli (85–89). Emboli composed of CO_2 have a shorter lifespan in the microcirculation than nitrogen containing emboli limiting arteriolar-capillary obstruction and cerebral injury (86). Although CO_2 insufflation reduces echocardiographically detected intracardiac and aortic microemboli, improvement in cognitive outcomes has not been demonstrated using this technique (85,87–89).

CBF DURING CPB

Systemic flow during CPB is empirically determined depending on body surface area and temperature, and then it is adjusted based on indicators of adequate systemic tissue perfusion (Svo_2, pH). Proposed methods to assess adequacy of brain perfusion during CPB include electroencephalogram (EEG), TCD, jugular venous oxygen saturation ($Sjvo_2$), and near-infrared spectroscopy monitoring (90–92). Whether use of any of these methods leads to improved neurologic outcomes awaits rigorous investigation. Accordingly, there are presently no widely accepted monitors to judge the adequacy of global or regional CBF during CPB. Sufficient CBF is assumed based in part on data showing that cerebral autoregulation remains intact with CPB flows of 1.6 to 2.4 $L/min/m^2$ (using α-stat pH management) (93,94). That is, these data suggest that CBF is unchanged over a range of arterial blood pressures during CPB even at mean pressures as low as 30 mm Hg. A mean arterial blood pressure of 50 mm Hg is commonly viewed as the minimal acceptable arterial blood pressure during CPB (93). This fails to consider that cerebral autoregulation has wide individual variation, is altered in many common conditions (e.g., hypertension, diabetes, prior or acute stroke), is not entirely pressure-independent, is impaired in brain areas dependent on collateral perfusion, and is derived in clinical studies using disputed statistical methods (93–102). Indeed, reductions in $Sjvo_2$, occur in 17% to 23% of patients during CPB, and they are associated with impaired tissue oxygenation and cognitive dysfunction (16,103). In some patients, thus, CBF is inadequate to meet cerebral oxygen demands during at least portions of CPB.

Data supporting a minimal mean arterial blood pressure of 50 mm Hg (or lower) during CPB are inconsistent, derived from studies that included few patients at risk for brain injury, or are based on retrospective analysis (93,94,104–107). Whether the data can be extrapolated to contemporary high-risk surgical patients is, thus, not clear. Gold et al. (44) found fewer myocardial and neurologic complications after CABG surgery when targeted mean arterial blood pressure during CPB was between 80 to 100 mm Hg rather than 50 to 60 mm Hg (4.8% versus 12.9%; $P = 0.026$). Actual arterial blood pressure during CPB in the "high blood pressure" group was often below the targeted levels. Further, there was insufficient power to evaluate the effect of the arterial blood pressure targets on stroke alone, and there was no relation between arterial pressure and cognitive outcomes 6 mo after surgery (rates of cognitive decline were low in both groups, 11% to 12%). Retrospective analysis suggests that a mean arterial blood pressure >50 mm Hg during CPB might benefit patients at risk for neurologic complications because of advanced age or atherosclerosis of the aorta (67,105). The optimal arterial blood pressure targets during CPB in such patients are undefined.

CPB FLOW CHARACTERISTICS

The most widely used method of CPB perfusion is nonpulsatile flow. This is, in part, by default as a result of past engineering difficulties that have been somewhat overcome with modern computer-controlled CPB pumps that allow for reliable generation of pulsatile flow (94). Compared with nonpulsatile flow, pulsatile flow attenuates neurohumoral responses to CPB, reduces vascular resistance, increases visceral blood flow, and improves renal and liver function (94). In dog experimental models, pulsatile CPB perfusion increases CBF and brain oxygenation compared with nonpulsatile flow (108–111). These findings, however, were not confirmed in animals that lack the extensive external-to-internal carotid artery collateralization seen in canines (112,113). Nevertheless, the higher energy imparted by pulsatility leads to more

Table 2. Putative Benefits of Pulsatile CPB Flow Compared with Nonpulsatile Flow

- Increased capillary patency
- Less venous "sludging"
- Enhanced lymphatic drainage reducing edema
- Enhanced nitric oxide and attenuated endothelin-1 release reducing cerebral vascular resistance
- Attenuation of inflammatory response to CPB
- Increased regional CBF after hypothermic circulatory arrest leading to increased tissue oxygenation and metabolism
- Increased CBF when blood flow is pressure dependent (i.e. impaired autoregulation)
- Lower neuropathologic score in ischemic penumbra after experimental stroke
- Less neuronal cell loss to CA1 hippocampal region and caudate nucleus after global cerebral ischemia
- Decreased number of $Sjvo_2$ desaturations

CPB = cardiopulmonary bypass; CBF = cerebral blood flow; $Sjvo_2$ = jugular venous oxygen saturation.

efficient distribution of blood flow to the microcirculation that could enhance flow to ischemic brain areas (94,114–119). The putative neuroprotective effects of pulsatile CPB flow are listed in Table 2 (109,111,120–128).

Clinical studies that have examined the impact of pulsatile CPB flow on neurologic outcomes have contradictory conclusions (4,129–134). This can be attributed to the varying methods to generate pulsatility, use of limited psychometric testing, nonrandomized and retrospective study design, and inadequate study power in these reports. In a single center study, 316 patients were randomized to pH-stat or α-stat pH management and to pulsatile or nonpulsatile CPB flow (134). Pulsatile flow had no effect on the incidence of cognitive dysfunction, but it led to less myocardial infarction and death. There were few elderly patients with risk factors for brain injury in that study, and mean arterial blood pressure during CPB ranged between 57 and 61 mm Hg. Thus, whether pulsatile flow offers advantages over nonpulsatile CPB for elderly and patients at high risk for neurologic complications has not been clearly evaluated.

ACID-BASE MANAGEMENT

As body temperature decreases, the solubility of CO_2 in blood increases resulting in a decreased $Paco_2$ and increased pH (but unchanged total CO_2 content) (135,136). For decades, pH-stat management was used during hypothermic CPB, whereby the temperature-corrected (to the patient's low body temperature) blood pH and $Paco_2$ were kept at 7.4 and 40 mm Hg, respectively. That is, laboratory analysis of blood gases is performed at 37°C, requiring calculation of the actual "corrected" $Paco_2$ and pH at the patient's specific body temperature. This can be done automatically by most blood gas machines, with a standard equation, or by reference to tables. The desired $Paco_2$ and pH is maintained by adjusting gas flow ("sweep") and/or by adding CO_2 to the CPB circuit. In poikilothermic animals (e.g., reptiles) blood CO_2 content remains constant over a range of temperatures and the slope of the change in pH versus change in temperature is similar to that of the neutral pH of water (pN) (135,136). The buffer responsible for this effect is the α-imidazole moiety of protein-bound histidine, which changes its pKa in parallel to the change in pN. This phenomenon is thought to preserve cellular metabolism during hypothermia maintaining the cellular pH near the optimum for enzyme function. In contrast, hibernating mammals use a pH-stat strategy induced by hypoventilation. The resultant larger intracellular CO_2 content and hydrogen ion concentration reduces cellular metabolism of some tissues (135,136).

Based in part on physiologic arguments and its clinical simplicity, the α-stat strategy was adopted in the late 1980s for adults and pediatric patients for managing mild (>25°C) hypothermic CPB. With this method hypothermia-induced hypocarbia and alkalemia are not corrected; the aim is a $Paco_2$ of 40 mm Hg and pH of 7.4 measured at 37°C. Nonetheless, CBF during hypothermic CPB is linearly related to CO_2 content such that CBF is higher with pH-stat compared with α-stat management (137–142). For example, CBF decreases 40% during CPB at 26°C using α-stat management but remains similar to baseline with pH-stat management (141). Because CBF and cerebral metabolic rate for oxygen ($CMRO_2$) remain "coupled" using α-stat (but not pH-stat) management, reduced CBF is explained to be compensatory to reduced cerebral metabolism. $Sjvo_2$ is higher with pH-stat compared with α-stat management but the frequency of desaturations during rewarming in a small study did not differ (143). A concern is that higher CBF with pH-stat management may increase cerebral microembolism and cause cerebral arterial "steal" (137,140,144,145). The former has not been conclusively confirmed, and redistribution of CBF from low-flow to high-flow brain areas resulting from increased CO_2 content was not found in patients with cerebrovascular disease during hypothermic CPB (146).

In addition to maintaining CBF, the larger CO_2 content associated with pH-stat management has other potential neuroprotective effects including: a) inducing a rightward shift of the oxy-hemoglobin dissociation curve promoting O_2 unloading to tissues, b) reducing $CMRO_2$ and increased neuronal tolerance to ischemia, and c) modulating the *N*-methyl-D-aspartate receptor that limits the neurotoxic effects of excitatory amino acids (EAA) (142,147–149). In a rodent stroke model, hypocapnia was associated with increased ischemic cerebral injury compared with mild hypercarbia (150,151). Clinical investigations have shown less morbidity and earlier return of first EEG activity after deep hypothermic CPB using pH-stat rather than α-stat management during repair of complex congenital heart abnormalities (152). In the

Table 3. Prospectively Randomized Clinical Trials of the Effects of Acid-Base Management During CPB on Neurologic Complications After Cardiac Surgery

Study	n	Findings
Murkin et al (134)	316	Frequency of cognitive impairment no different between α-stat and pH-stat management using primary endpoints. Subsequent analysis suggested a benefit with α-stat when CPB duration >90 min ($P = 0.047$ versus pH-stat). Whether there was correction for multiple comparisons is not clearly stated.
Bashein et al (154)	86	No difference in psychometric endpoints 7 mo after CABG surgery for patients undergoing CPB with α-stat or pH-stat management.
Stephan et al (155)	65	Neurologic deficits (mostly cerebellar and cranial nerve deficits) more common 7 days after surgery with pH-stat versus α-stat management. Psychometric testing was not performed and long-term results were not reported.
Patel et al (156)	70	Frequency of cognitive dysfunction 6 wk after CABG surgery was not different between groups undergoing CPB with pH-stat versus α-stat management using predefined endpoints. Patients with cerebrovascular disease or diabetes were excluded from study. A benefit of α-stat management was found when the definition of cognitive decline was changed during *post hoc* data analysis from >2 SD decline from baseline on >2 tests to decline on >3 tests.

CPB = cardiopulmonary bypass; CABG = coronary artery bypass graft.

latter study, though, there were no differences in neurologic examinations in the infants randomized to pH-stat versus α-stat management, and neurodevelopment 1 yr after surgery was not markedly affected by pH-management (153). Randomized trials of α-stat versus pH-stat management during hypothermic CPB in adults have produced conflicting results and provide few data for patients at high risk for neurologic injury (Table 3) (134,154–156). The available data are further limited by the small number of patients studied, the use of bubble oxygenators in one study, the reporting of only short-term neurologic endpoints, or the use of *post hoc* statistical analyses when the primary endpoints did not differ for patients randomized to the different pH management strategies.

HEMATOCRIT

In the past, a common teaching for CPB management was that hemodilution is necessary during hypothermia to reduce blood viscosity and thus ensure microcirculatory flow (157). These benefits might be offset by reduced oxygen-carrying capacity of diluted blood. Laboratory investigations contradict this practice, demonstrating that cerebral microcirculatory flow (intravital microscopy assessments) is not impaired during experimental hypothermic CPB with hematocrit levels as high as 30% (158). During rewarming, higher hematocrit reduced white cell/endothelial activation, whereas hematocrit <10% resulted in inadequate tissue oxygenation. Observational data now suggest that there is a strong relationship between lower hematocrit level and risk-adjusted operative mortality (159,160). In these retrospective analyses, though, whether lower hematocrit is merely a marker for other factors associated with operative mortality or whether it is casually related is unknown.

For the most part, investigations examining whether low hematocrit levels during CPB increase the risk for neurologic outcomes have been limited to observational studies. DeFoe et al. (160), for example, reported a review of 6980 patients undergoing CABG surgery enrolled in the Northern New England Cardiovascular Disease Study Group database. Although nadir hematocrit was related to need for intraaortic balloon counterpulsation, return to CPB after initial weaning, and risk for in-hospital mortality, it was not significantly associated with risk for stroke. Mathew et al. (161) performed a prospective trial of 107 patients randomizing adults undergoing cardiac surgery to a minimal hematocrit on CPB of 27% or 15% to 17%. The study was halted by the safety monitoring committee because of increased adverse event rates in the lower hematocrit group compared with the controls. Profound hemodilution (minimal hematocrit of 15% to 17%) was found to be associated with greater cognitive decline 6 wk after CABG surgery, especially in the elderly. Jonas et al. (162) randomized infants to hematocrits of either 21% or 28% at the start of low-flow hypothermic CPB. Postoperatively low cardiac index and lactatemia were found in the low hematocrit groups. Psychometric development was superior 1 yr after surgery in the high versus low hematocrit group.

BLOOD GLUCOSE CONTROL

Hyperglycemia is common perioperatively, even in nondiabetics, for multiple reasons related to the stress response to hypothermic CPB (163). Experimentally, hyperglycemia worsens cerebral infarction via numerous mechanisms (164–166). Clinical reports have clearly shown a relationship between even moderate hyperglycemia (>140 mg/dL) and worse neurologic outcome and mortality after both global and regional brain ischemia in nonsurgical patients (167–170). Hyperglycemia appears to increase recruitment of ischemic penumbral tissue into the infarction but has little impact on irreversibly ischemic neurons (170). The influence of hyperglycemia on neurologic outcome after cardiac surgery is less clear (106,107,171,172). Laboratory data suggest that insulin possesses neuroprotective properties beyond decreasing glucose (173–175). Nonetheless, there are few clinical data showing that prevention of hyperglycemia actually

improves neurologic outcome. There was no relationship between hyperglycemia (glucose >150 mg/dL) and neurodevelopment outcomes after arterial switch surgery for D-transposition of the great arteries, but hypoglycemia (glucose <50 mg/dL) was associated with slower EEG recovery after surgery and seizures (176). Recently, Butterworth et al. (177) reported that insulin infusion in nondiabetic patients with glucose concentrations >100 mg/dL during CPB had no effect on the frequency of new neurological, neuroophtalmologic, or neurobehavioral deficits 4 to 8 days, 6 wk, and 6 mo after CABG surgery compared with placebo. Similar to other reports, maintaining normoglycemia with insulin during CPB was difficult (171). In the study by Butterworth et al. (177), 42% of insulin-treated and 40% of placebo-treated patients had at least one glucose level >200 mg/dL, whereas initial glucose on arrival to the intensive care unit (ICU) was similar between treatment groups (placebo group, 179 ± 60 mg/dL versus insulin group, 178 ± 57 mg/dL). Thus, whether maintaining lower glucose levels during CPB in known or unknown diabetics improves neurologic outcomes is not known.

Regardless of any neuroprotective effect, insulin administration during cardiac surgery improves neutrophil function, and it is suggested, based on retrospective analysis, to reduce sternal wound infections (178,179). Furthermore, maintenance of glucose between 80 and 110 mg/dL with the IV infusion of insulin in surgical ICU patients shortened the duration of mechanical ventilation and decreased morbidity compared with standard therapy (insulin when glucose >215 mg/dL) (180). Mortality was less frequent for patients in the intensive insulin treatment group compared with standard treatment (20.2% versus 10.6%; $P = 0.005$) but only for patients who remained in the ICU for >5 days. Whether intensive insulin therapy started *intraoperatively* can have similar benefits has not yet been demonstrated.

HYPOTHERMIA

Hypothermia reduces the size of experimental brain infarction and its use in victims of out-of-hospital cardiac arrest leads to improved neurologic outcomes and survival (181–184). The neuroprotective effects of even modest (2°C to 5°C) temperature reductions include decreased $CMRO_2$, reduced EAA release, attenuation of Ca^{2+} accumulation, and other mechanisms (185–192). Though commonly used for neuroprotection during CPB, hypothermia is often absent during some critical periods of brain injury (e.g., aortic cannulation) and the practice of rewarming at the conclusion of surgery might lead to inadvertent cerebral hyperthermia (16,193). The latter is attributable to the proximity of the aortic cannula to the cerebral vessels and to unrecognized cerebral hyperthermia because standard temperature monitoring underestimates brain temperature (193). Hyperthermia worsens ischemic brain injury by increasing $CMRO_2$, promoting EAA release, and other deleterious mechanisms (181,194–198). Keeping the gradient between the aortic perfusate and nasopharyngeal temperature ≤2°C has been shown to be associated with improved cognitive function compared with conventional rewarming (199).

The benefits of hypothermic CPB were debated in the 1990s, when the use of normothermic cardioplegia was proposed to improve cardiac outcomes after CABG surgery (200–205). A concern was that by avoiding hypothermia during "warm heart surgery," the risk for brain injury would increase. The data were inconsistent, though, with some studies showing no added risk and others indicating increased rates of stroke or postoperative cognitive decline after normothermic versus hypothermic CPB. Differences in outcomes might have resulted from varied temperature management strategies that ranged from allowing the body temperature to "drift" (which might lead to actual mild hypothermia) to active warming to maintain normothermia (which might lead to inadvertent cerebral hyperthermia). In a carefully controlled study where temperature drift and inadvertent hyperthermia were avoided, hypothermia was not found to reduce the frequency of neurocognitive dysfunction after CABG surgery compared with normothermia (206). Recent meta-analysis concluded that there is no evidence of a neurologic protective effect of hypothermic CPB, but the limitations to the existing data preclude definitive conclusions (207).

Hyperthermia is prevalent the first 48 h after CABG surgery using CPB, a finding of relevance because many strokes occur in the postoperative period (7,208,209). Grocott et al. (208) found an association between peak body temperature within 24 h of CABG surgery and cognitive decline 6 wk postoperatively. Postoperative temperature increase might be related to the inflammatory response associated with CPB or, conversely, to thermal dysregulation from brain injury (29,210). Nathan et al. (211,212) reported that rewarming from mild hypothermia to 34°C was associated with fewer cognitive deficits both 1 wk and 3 mo after CABG surgery compared with rewarming to a body temperature of 37°C, suggesting a benefit for mild postoperative hypothermia.

PHARMACOLOGIC NEUROPROTECTION: PATHOPHYSIOLOGIC TARGETS

It is anticipated that an understanding of the molecular and genetic mechanisms of ischemic neuronal injury will provide targets for neuroprotection (Fig. 4). The brain requires a constant supply of oxygen and glucose for cellular metabolism. During ischemia, cellular energy stores are rapidly depleted, leading to ionic pump failure and membrane depolarization with EAA release (30,31). A series of cellular events follows (i.e., the "ischemic cascade"), leading to cell death. Although necessary for restoring oxygen and metabolic substrate supply, reperfusion can exacerbate

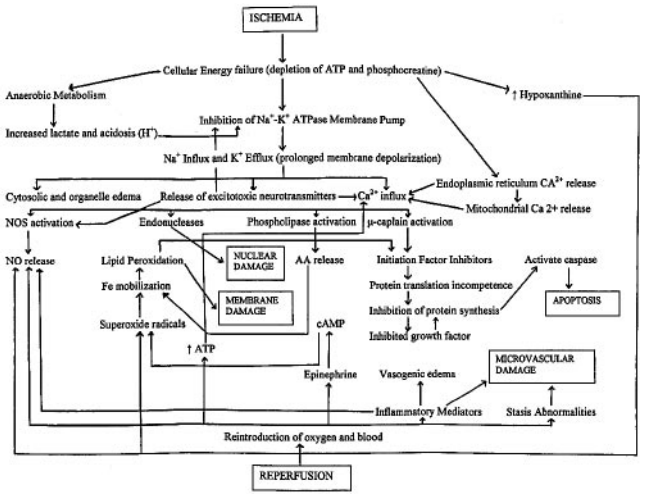

Figure 4. Diagram depicting the multiple, interrelated biochemical and molecular pathways resulting from brain ischemia and reperfusion. Enhanced understanding of molecular and genetic mechanisms of brain ischemia is the foundation for the development of neuroprotective therapies. Reprinted with permission from (30).

neuronal injury by inducing the generation of oxygen-derived free radicals and by other mechanisms (30,31,213). Protein synthesis, necessary for DNA repair and cellular recovery, declines as a result of energy depletion (30,214,215). Cerebral ischemia further leads to activation of genes encoding apoptosis (30,216–218). Even ischemia below the threshold for necrotic cell death may trigger apoptosis, leading to neuronal cell death (219,220). A further understanding of apoptotic pathways may provide a potential target for neuroprotection (221).

PHARMACOLOGIC NEUROPROTECTION: CLINICAL TRIALS

Several neuroprotective drugs have been investigated in patients undergoing cardiac surgery with mostly disappointing results, despite a sound experimental rationale for each drug (Table 4) (222–235). Anesthetic drugs in particular have been the focus of investigations based in part on the hypothesis that anesthesia-induced reduction in $CMRO_2$ increases tolerance to cerebral ischemia (236,237). Nussmeier et al. (222) found that thiopental, at a dose sufficient for EEG suppression during CPB, reduced the incidence of neuropsychiatric complications 10 days after open-chamber surgery compared with placebo. These findings were not confirmed by Zaidan et al. (223) in patients undergoing CABG surgery. The disparate results might be explained by differences in types of surgery, approach to temperature management, and CPB equipment (bubble versus membrane oxygenator; arterial line filtration). In a further study, Roach et al. (224) reported that EEG suppression with propofol during CPB did not reduce the incidence of cognitive dysfunction compared with controls. Volatile anesthetics have neuroprotective properties in laboratory models of ischemic brain injury, but these drugs have not been evaluated in clinical trials of patients undergoing cardiac surgery (236,237). Regardless, based on the available data, pharmacologic reduction in $CMRO_2$ with anesthetics, as a means for brain protection during cardiac surgery, has thus far been an ineffective strategy (238).

Other trials report encouraging results with drugs targeting EAA and inflammatory pathways. Arrowsmith et al. (228) found that the *N*-methyl-D-aspartate receptor antagonist remacemide used during cardiac surgery improved some measures of postoperative psychometric performance compared with placebo, although the frequency of cognitive dysfunction using the primary endpoint was unaffected. Mitchell et al. (232) and Wang et al. (233) found that in antiarrhythmic doses, lidocaine improved short-term neurocognitive function compared with placebo. In the latter study, psychometric testing was limited to the immediate postoperative period, whereas only 42 patients were available for analysis in the former study. Further, in the study by Mitchell et al. (232) significant differences between treatment groups were limited to the number of patients with decrements on one psychometric scale, but there were no differences when considering more rigorous definitions of cognitive dysfunction. More recently, Mathew et al. (235) reported that pexelizumab, a humanized monoclonal antibody against the C5 complement component, led to less visuo-spatial impairment up to 1 mo after surgery compared with placebo, but the overall incidence of cognitive dysfunction was no different.

In a study designed to evaluate the efficacy of aprotinin for reducing blood transfusion during cardiac surgery, Levy et al. (230) found that stroke occurred less often in treated than in control patients. Retrospective data analysis of a larger number of patients enrolled in placebo-controlled trials of aprotinin have confirmed these results (239–241). In a small, randomized study, less frequency of cognitive deficits 6 wk after CABG surgery was observed in patients receiving aprotinin compared with those receiving placebo (231). The mechanism(s) for the potential brain protective effects of aprotinin are not known but are speculated to include the antiinflammatory effects of the drug. Alternatively, the blood loss-sparing effects of aprotinin might have limited the volume of pericardial aspirate indirectly implicated in cerebral microembolism, or it might have limited platelet transfusions that in retrospective analysis were associated with stroke (38,242). Regardless, stroke was a secondary endpoint in the studies reporting potential neuroprotection with aprotinin. It must be further acknowledged that the stroke rate in the placebo group of the study by Levy et al. (230) (7.7%) was higher than that usually reported after CABG surgery (2%–3%), which may have inadvertently overemphasized the potential stroke-decreasing effects of aprotinin (4–9).

Table 4. Randomized, Placebo-Controlled, Trials of Pharmacologic Neuroprotection for Adults Undergoing Cardiac Surgery

Drug	Proposed primary mechanism	Author	*n*	Type of surgery	Main findings
Thiopental	↓ $CMRO_2$	Nussmeier et al (222)	182	Valvular	Thiopental ↓ cognitive complications 10 days after surgery.
		Zaidan et al (223)	300	CABG	No difference in neurologic outcomes thiopental versus placebo.
Propofol	↓ $CMRO_2$	Roach et al (224)	225	Valvular	No difference in cognitive complications 5–7 days or 50–70 days after surgery propofol versus controls.
Nimodipine	Ca^{++} channel blocker	Legault et al (225)	150	Valvular	Study terminated early due to higher mortality in treated versus control group; no evidence of benefit with nimodipine on cognitive outcomes.
Prostacylin	↓ platelet aggregation, ↓ inflammation	Fish et al (226)	100	CABG	No difference in cognitive outcomes 2 wk after surgery between treated and control patients.
GM1 ganglioside	↓ EAA signaling	Grieco et al (227)	29	CABG ± valvular	Pilot study finding no difference cognitive outcomes between treated and control patients.
Remacemide	NMDA receptor antagonist	Arrowsmith et al (228)	171	CABG	Remacemide led to better performance on 3 of 10 psychometric measures and better global cognitive function.
Pegorgotein	Antioxidant	Butterworth et al (229)	67	CABG	Study stopped before completion; no drug benefit in reducing the rate of neurocognitive dysfunction.
Aprotinin	Mechanism(s) unknown; maybe due to ↓ inflammation/ ↓ pericardial aspirate	Levy et al (230)	287	CABG	No strokes in "high" and "low" dose aprotinin groups versus controls ($n = 5$) and "pump" prime only ($n = 1$) groups ($P = 0.01$).
		Harmon et al (231)	36	CABG	Cognitive deficits 6 weeks after surgery lower in aprotinin versus placebo group (23% versus 55%, $P < 0.05$).
Lidocaine	Na+ channel blockade; membrane stabilization/ ↓ EAA release	Mitchell et al (232)	55	Valvular	Neurocognitive outcome better 10 days and 10 wk after surgery in lidocaine versus placebo group but not at 6 mo.
		Wang et al (233)	42	CABG	Improved neurocognitive function 9 days after surgery with lidocaine versus placebo.
Clomethiazole	GABA receptor agonist	Kong et al (234)	219	CABG	No difference in neurocognitive function 4–7 wk after surgery in clomethiazole versus placebo groups.
Pexelizumab	↓ C5a and C5b-9	Mathew (235)	800	CABG	Pexelizumab had no effect on global cognition but did lower decline in the visuo-spatial domain compared with placebo.

$CMRO_2$ = cerebral metabolic rate for oxygen; CABG = coronary artery bypass grafts; EAA = excitatory amino acid; NMDA = *N*-methyl-D-aspartate; GABA = gamma-aminobutyric acid.

One explanation for the failure of many neuroprotective drugs in clinical trials, despite supportive laboratory data, is that the treatment often targets only a single pathway of cell injury in a pathologic process that is very complex (243). Further, it is now known that many drugs may afford protection from initial ischemic injury but not delayed neuronal death (236,237,244). The disappointing clinical findings thus might be explained by the targeting of only initial ischemic injury and not delayed death (e.g., as the result of apoptosis or inflammation). Therapy beyond the immediate operative period with a combination of compounds blocking acute and delayed ischemic injury pathways may prove more fruitful but remains to be clinically investigated (245).

The ultimate extent of brain injury depends on the duration of ischemia. In nonsurgical patients, fibrinolytic drugs given within 3 h of stroke onset limits brain injury, improves functional outcomes, and decreases mortality (246). Although IV fibrinolytic drugs might be contraindicated in surgical patients, the feasibility of selective *intraarterial* thrombolysis in patients with acute stroke after cardiac surgery has been demonstrated (247). This approach requires prompt diagnosis and rapid access to a skilled neuroradiology team.

EVALUATION OF THE EVIDENCE AND CONCLUSIONS

Evidence-based reviews are often the product of multidisciplinary working groups typically commissioned by professional organizations with a goal of synthesizing recommendations for clinical care. In addition to evaluation of data from randomized clinical trials, clinical observational studies, and well controlled laboratory investigations, these working groups often rely on "expert opinion" to develop consensus statements when there is a paucity of data. In an attempt to

Table 5. Criteria for Evidence-Based Ratings Adapted from the American Heart Association as used in the International Guidelines for Advanced Cardiac Life Support

Class of rating	Criteria
Class I: interventions are always acceptable, proven safe, and definitely useful.	More than one randomized, controlled trial that is considered of excellent quality with robust and consistently positive results supporting intervention.
Class IIa: interventions are acceptable, safe, and useful. Considered the standard of care: reasonably prudent physicians can choose. Considered the intervention of choice by majority of experts.	Number of studies of good to very good quality with a positive result. Weight of evidence/expert opinion more strongly favor intervention that for Class IIb recommendation. Magnitude of benefit higher than Class IIb recommendation.
Class IIb: interventions are acceptable, safe, and useful. Considered "within" the standard of care: reasonably prudent physicians can choose. Considered optional or alternative intervention by majority of experts.	Level of evidence low to intermediate. Only a few studies of fair or poor quality support its use. Weight of evidence/expert opinion less favor of usefulness/efficacy. Results not always positive.
Class Indeterminate: interventions can still be used but insufficient evidence to suggest efficacy.	Evidence found but available studies have one or more shortcomings. Intervention is promising but studies fail to address relevant clinical outcomes, are inconsistent, noncompelling, or have inconsistent results.
Class III: no evidence of efficacy and/or studies suggest them.	Positive evidence is completely absent or evidence strongly suggestive of harm.

From International Guidelines 2000 Writing Group (248).

Table 6. Evidence-Based Ratings for Pharmacologic and Nonpharmacologic Neuroprotection during Cardiopulmonary Bypass (see Text and Table 5 for Criteria)

Intervention	Rating
Heparin-bonded CPB circuits	Class Indeterminate
Epiaortic ultrasound-guided changes in surgical approach	Class IIb
Modified aortic cannula	Class Indeterminate
Leukocyte-depleting filters	Class Indeterminate
Cell-saver processing of pericardial aspirate	Class Indeterminate
CO_2 wound insufflation	Class Indeterminate
Maintaining "higher" MAP targets (i.e., > than lower target of 50 mm Hg)	Class IIb for patients at high risk for neurologic injury
Non-pulsatile (versus pulsatile) perfusion	Class IIb (Class Indeterminate for patients at high risk for neurologic injury)
α-stat (versus pH-stat) acid base management	Class IIb (Class Indeterminate for patients at high risk for neurologic injury)
Minimal hematocrit target during CPB of >27%*	Class Indeterminate
Thiopental, propofol, nimodipine, prostacylin, GM1 ganglioside, pegorgotein, clomethiazole	Class III
Remacemide, lidocaine, aprotinin, pexelizumab	Class Indeterminate
"Tight" glucose intraoperative control	Class Indeterminate
Hypothermia	Class Indeterminate

*The optimal hematocrit during CPB is not defined by available data. A hematocrit of >27% chosen as indicative of "high" hematocrit based on its use in available randomized trials (see text).
CPB = cardiopulmonary bypass; MAP = mean arterial blood pressure.

provide objectivity to our review we used methods similar to the American Heart Association in their evidence-based recommendations (Table 5) (248). Our aims, though, were to focus on investigations in cardiac surgical patients rather than lower levels of evidence (e.g., laboratory studies, opinion). We included studies that evaluated the endpoints of stroke and/or cognitive dysfunction but not those primarily using only surrogate outcomes (e.g., TCD, serum markers of brain injury). Based on these assumptions, we rate proposed neuroprotective interventions based on our review (Table 6). These ratings are intended as objective evaluations of the existing literature rather than strict clinical recommendations *per se*.

Studies examining neuroprotective CPB strategies have many limitations, including different definitions of adverse events, varied timepoints of neurologic assessments, and inadequate statistical power (12,20,21). Arguably, the greatest limitation is the under-representation of patients who are at high risk for neurologic injury (e.g., advanced age, prior stroke, atherosclerosis of the ascending aorta) in the available studies. Extrapolating the results of studies comprised of mostly low-risk patients to contemporary practices composed of older and higher risk patients therefore is difficult. Thus, we consider in our ratings (Table 6) whether the data apply to patients at high risk for perioperative neurologic complications (5-8,10,12,18,19). Further, we assume that CPB using membrane oxygenators and arterial line filtration are the standard of care.

Presently, no neuroprotective strategy during CPB

achieves a Class I rating. When considering the available data, several management approaches are given Class IIb ratings, although the use of nonpulsatile CPB versus pulsatile CPB and α-stat versus pH stat acid-base management have not been thoroughly tested in patients at high risk for neurologic injury. While avoiding hyperglycemia during CPB is a laudable goal, there are few data showing benefits of this treatment on neurologic outcomes. Although there are promising data for several interventions, most are not supported by robust and reproducible results from well conducted clinical trials and thus are given Class Indeterminate rating. Many of the drugs evaluated for neuroprotection are given a Class III rating because of the absence of positive efficacy evidence and/or data showing higher rates of adverse events. Whether thiopental should be regarded as a Class III versus a Class Indeterminate intervention could be considered controversial. Although widely used before hypothermic circulatory arrest, there are few clinical data showing that large doses of thiopental improve neurologic outcome, and its use is associated with adverse effects (e.g., hypotension, increased need for inotropic drugs, delayed awakening making early neurologic assessments difficult). Of note, the available data do not support a definite benefit (or risk) of mild hypothermia for reducing neurologic complications after cardiac surgery.

Cardiac surgery is one of the most frequently performed operations worldwide (>709,000 procedures annually in the United States alone) (2). The current knowledge base that physicians are dependent on to guide patient care during CPB is clearly and alarmingly deficient. Recently, a Working Group from the National Heart, Lung, and Blood Institute on Future Directions in Cardiac Surgery has acknowledged that there is a need for a better understanding of the mechanisms of neurologic complications and a need for development of methods for its prevention (249). Their suggestion for the formation of a Cardiovascular Surgery Clinical Network to conduct multicenter clinical trials, including those aimed at reducing the frequency of perioperative stroke and cognitive dysfunction, holds promise for more definitive data in the future. Given the magnitude of the effect of perioperative neurologic complications on patient morbidity, mortality, and health care costs, funding for such initiatives should be a high priority.

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