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Neuroprotection during cardiac surgery

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Abstract
Cerebral injury following cardiac surgery continues to be a significant source of morbidity and mortality after cardiac surgery. A spectrum of injuries ranging from subtle neurocognitive dysfunction to fatal strokes are caused by a complex series of multifactorial mechanisms. Protecting the brain from these injuries has focused on intervening on each of the various etiologic factors. Although numerous studies have focused on a pharmacologic solution, more success has been found with nonpharmacologic strategies, including optimal temperature management and reducing emboli generation.

Key words Cardiac surgery · Cardiopulmonary bypass · Brain · Neuroprotection

Introduction

Although substantial progress has been made in recent decades, cerebral injury remains a continuing source of morbidity and mortality in cardiac surgical patients. Advances have allowed cardiac surgery to be performed on a progressively older and sicker population. Indeed, it is this older, sicker population that is at particular risk for cerebral injury during cardiac surgery [1].

The incidence of cerebral injury spans a spectrum from cognitive loss to overt stroke and varies considerably depending upon the type of injury, as well as the risk status of the patient. The overall stroke rate in the analysis of large cohorts is approximately 2% [2]. Far more common than stroke, however, is cognitive dysfunction. This too has a variable incidence, depending upon the time period at which cognitive function is assessed. In the early postoperative period (days after surgery), the incidence ranges as high as 80%–90%; however, at 2–3 months following surgery the incidence is approximately 40%, dropping to approximately 25% at 1 year [3]. Early cognitive loss, once thought to be transient, has now been demonstrated in longitudinal studies to persist for up to 5 years after cardiac surgery, where the incidence has been reported to be over 40%. Whereas these neurocognitive injuries are less devastating than stroke, the fact that the incidence is 20-fold greater than stroke makes these injuries far more significant in terms of their impact on quality of life and overall healthcare resources utilization.

The precise etiology of cardiac surgery-associated cerebral injury remains incompletely understood. Cerebral microembolization, hypoperfusion, inflammation (both cerebral as well as systemic), cerebral edema, blood-brain barrier dysfunction, and hyperthermia, as well as a genetic susceptibility to injury or genetic inability to repair following injury, have all been implicated [4]. Embolization of particulate and gaseous material into the cerebral microvasculature, resulting in focal areas of cerebral ischemia, has been most well studied [5,6]. However, embolization is not the only means by which the brain can become ischemic. Due to the disordered nature of nonpulsatile cardiopulmonary bypass (CPB), global cerebral hypoperfusion may result [7]. These etiologies support ischemia and its sequelae to be important pathophysiologic events. However, a number of other events do occur in the setting of cardiac surgery that may not rely directly on initiating a cerebral ischemic cascade. Cerebral as well as systemic inflammatory effects can be induced during CPB, leading to injury, both directly and indirectly, to brain cells [8,9]. In addition, cerebral edema documented by magnetic resonance imaging (MRI) scanning in the postoperative period has also been demonstrated [10]. The intraoperative period, which has been the focus of most interventional trials during cardiac surgery, is not the only time period at which injury can occur, however. A hyperthermic response in the early postoperative

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period following cardiac surgery occurs and has been associated with cognitive decline 6 weeks following cardiac surgery [11]. It is unclear, however, whether this hyperthermia is directly responsible for the cognitive decline, or is a result of processes that resulted in the cerebral injury itself, such as injury to hypothalamic thermoregulatory areas.

There is wide variation in the susceptibility to cardiac surgery-associated cerebral injury, as well as variability in the recoverability after these injuries. This variability is, in part, due to the genetic differences among patients. The apolipoprotein genotype (APOE) was one of the first genetic variants linked to cognitive decline after cardiac surgery [12]. It has also been shown to be a factor affecting injury phenotype following a number of other types of cerebral injury [13,14]. This genetic variability likely affects both the susceptibility to injury as well as the ability to recover following injury. It is, however, only one of potentially hundreds of variants that may play a role, which has recently raised doubt as to the significance of its individual effect [15]. More recently, the impact of APOE has been questioned, with the overall impression that it has only a minor if any impact on cognition post-CPB. In the most current studies, genotypes involving inflammation have been implicated in both post-cardiac surgery stroke [16] and cognitive loss [17].

Neuroprotective strategies

Both nonpharmacologic and pharmacologic approaches have been used to reduce cerebral injury after cardiac surgery [18]. The nonpharmacologic strategies largely have centered on minimizing emboli generation (reducing cerebral embolization through arterial filtration, avoidance of aortic atheroma, and optimizing pH management), as well as modulating perioperative temperature. Further technological advances have now become available and show promise in this area, including the use of specially designed aortic cannulae and epiaortic imaging, both designed to further minimize emboli generation.

Pharmacologic neuroprotective strategies have focused upon targeting individual pathways of the ischemic cascade which is activated in the brain during and after ischemia. Although dozens of different agents have been investigated in cardiac surgery, none have proven sufficiently efficacious to warrant widespread clinical application.

Pharmacologic neuroprotection

The ischemic cascade represents a convenient matrix for identifying and discussing drugs that have been studied in cardiac surgery. There are hundreds of different targets (ion channels, receptors, etc.) to which modulating drugs have been developed. Multiplying this by the number of compounds directed at each target makes choosing which is the optimal drug to study in this setting a very difficult problem. Areas that show some promise relate to the unique situation of CPB and its inherent inflammatory processes. Preliminary gene expression work by others [19] and ourselves further suggests that inflammatory and possibly apoptotic pathways should be investigated [20].

Excitotoxicity, modulated through the N-methyl-D-aspartate (NMDA) receptor-mediated pathways, has received much attention in the field of neuroprotection. Although human stroke trials of NMDA antagonists have been limited by distressing side effects, there is a wealth of animal data that suggests that these NMDA receptor antagonists are robust neuroprotective agents, including data from experimental CPB [21,22]. Remacemide, a noncompetitive NMDA antagonist, has been evaluated for neuroprotection during coronary artery bypass grafting (CABG) surgery [23]. In a clinical study by Arrowsmith et al. [23], remacemide was given orally for 4 days prior to CABG. Although, when one examines the data for the presence or absence of a neurocognitive deficit, there appeared to be no difference between groups ($P = 0.6$), examination of the Z scores (a measure of learning ability) showed there was a beneficial effect in the patients who received remacemide ($P = 0.028$). This was the first adequately powered study of a neuroprotective agent in the setting of cardiac surgery that demonstrated a beneficial effect. However, due to the length of time that it took to perform this single-center trial, the initial nonbeneficial preliminary results, as well as the prolonged period of data analysis and review for publication, this drug was not further pursued for this indication.

The excitotoxic theory has spawned a clinical trial focusing on a historically well-tolerated NMDA blocker, magnesium. However, what is most interesting about Mg^{+2} is its ability to affect other pathways as well, potentially involving inflammatory processes. Clinical cardiac surgical trials of this drug are currently underway; however, preliminary data have been published by at least one other research group, identifying it as a potentially important drug for the prevention of neurologic complications of cardiac surgery [24]. Experimental evidence for the benefit of magnesium has not been well delineated; however, another NMDA receptor blocker has proven to be of benefit in experimental cerebral ischemia, but, importantly, also in experimental models of CPB-associated cognitive decline. Xenon gas, which has long been known to possess anesthetic properties [25], which are also thought to be related to antagonism at the excitatory NMDA receptor, has recently been

demonstrated to possess neuroprotective properties [26]. This has been demonstrated in the setting of cerebral ischemia, but most intriguingly, in the setting of animal CPB [21]. These positive experimental results have led to early-phase clinical trials ultimately aimed at protecting the brain [27].

The neuroprotective effects of S(+)-ketamine, a frequently used anesthetic that is also an NMDA-receptor antagonist, were also evaluated in a small (n = 106) study in cardiac surgery patients [28]. The incidence of neurocognitive dysfunction 10 weeks after surgery trended towards being lower in the ketamine group (20%, ketamine vs 25%, controls; $P = 0.54$), but, as the study was underpowered, it was not a significant change. There are no other published trials evaluating ketamine for neuroprotection in this setting.

Intravenous lidocaine, due to its properties as a sodium channel-blocking agent, along with potential anti-inflammatory effects, has been investigated as a neuroprotectant in several cardiac surgical trials. In one study of 55 patients undergoing valvular surgery, a lidocaine infusion (in an anti-arrhythmic dose of $1\,mg{\cdot}min^{-1}$) was begun pre-induction and maintained for 48 h following surgery [29]. Neurocognitive testing was performed preoperatively, then 8 days and 2 and 6 months postoperatively. Compared to placebo, neurocognitive outcome 8 days following the surgery was significantly better in the lidocaine group ($P = 0.025$). A second trial, by Wang et al. [30], also demonstrated a short-term benefit of lidocaine. However, a much larger double-blind randomized trial in cardiac surgery failed to replicate the finding [31]. Currently, lidocaine cannot be recommended as a clinical neuroprotective agent in cardiac surgery.

The use of beta-blockers in patients with cardiac disease is almost a ubiquitous therapy. This therapy, though predominately directed towards the prevention of adverse myocardial events has, in a recent study of neurologic outcomes following cardiac surgery, been demonstrated to be associated with an improvement in neurologic outcome [32]. In this study of over 2000 patients, the neurologic outcomes, represented by stroke, transient ischemic attack, and encephalopathy were studied. Patients receiving beta-blocker therapy had a significantly lower incidence of neurologic deficit versus those not receiving beta-blockers. Although the reasons for this potential benefit are not intuitively obvious, there are several potential reasons why these agents may be efficacious, including modulating both cerebrovascular tone and CPB-related inflammatory events. Recent experimental support for potential neuroprotective effects from beta-blockers has been seen in a study of carvedilol, which is known to have mixed adrenergic antagonist effects, as well as acting as an antioxidant and inhibiting apoptosis [33].

One of the most fascinating agents that has been available for clinical use from the very early days of cardiac surgery, albeit not specifically used in the setting until recent decades, is the serine protease inhibitor, aprotinin. Aprotinin is a nonspecific serine protease inhibitor that was first used in the 1950s for the treatment of pancreatitis. Its current indication in cardiac surgery is for the reduction of blood loss and transfusion. However, in a large multicenter trial of aprotinin in primary or redo CABG and valvular surgery, the group receiving high-dose aprotinin also had a lower stroke rate ($P = 0.032$) [34,35]. Similarly, Frumento et al. [36] retrospectively examined patients at high risk for stroke (due to the presence of significant aortic atheroma); those who received aprotinin had a significantly lower stroke rate. In a recent small (n = 36) study examining the effect of aprotinin on cognitive deficit following CABG surgery, the incidence of cognitive deficit was also reduced in the aprotinin group (58%, aprotinin vs 94% placebo; $P = 0.01$) [37]. However, the high rate in the placebo group, the small size of the study, and methodologic concerns limit the applicability of these cognitive results to broader populations [38].

There has been considerable discussion and investigation as to the potential mechanism for any aprotinin-derived neuroprotection. Initial enthusiasm focused upon its anti-inflammatory effects potentially preventing some of the adverse inflammatory sequelae of cerebral ischemia. Animal investigations in the setting of cerebral ischemia failed to show any direct benefit on either functional or neurohistologic outcome following cerebral ischemia [39]. Indeed, aprotinin may have had its beneficial effects independent of any direct neuroprotective effect through an indirect effect of modulating cerebral emboli. Brooker et al. [40] have identified the cardiotomy suction as a major source of cerebral emboli during CPB. One could extrapolate 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) might also be decreased.

Most recently, however, considerable question has been added to the aprotinin story. Mangano et al. [41], in a study of more than 5000 patients, have reported an increase in strokes in those receiving aprotinin in a retrospective study that used propensity scoring to adjust for the higher overall risk in patients receiving aprotinin. The question as to aprotinin's true effect on cardiac surgery-related neurologic injury will remain unanswered until addressed by a properly conducted and powered prospective randomized trial.

Other inhibitors of the inflammatory cascade, including complement inhibitors have begun to be investigated [42]. The activation of complement is central to

the CPB-associated inflammatory response [43]. In a small ($n = 18$) study using the mini-mental status examination as a simple assessment of cognitive function, patients receiving a complement (C5) inhibitor (h5G1.1-scFv; pexelizumab), demonstrated fewer visuospatial deficits at hospital discharge [44]. Further large-scale (phase III) investigations of this compound (pexelizumab) have been performed to more adequately delineate any potential longer-term neuroprotective effects from this drug in this setting. Mathew et al. [44] studied pexelizumab in a 914-patient study aimed at evaluating its effect on both myocardial outcome and mortality. A secondary endpoint of neurocognitive outcome demonstrated that pexelizumab, although having no effect on global measures of cognition, appeared to have a benefit with respect to the visuospatial domain of cognitive function.

Corticosteroids have long been considered as potential cerebroprotective agents, in part due to their ability to reduce the inflammatory response. Inflammation is considered an important factor in propagating ischemia-mediated brain injury [45,46]. However, with the exception of spinal cord injury [47], they have never been demonstrated to possess any significant clinical neuroprotective properties. Furthermore, the administration of steroids has actually worsened cerebral outcome in a recent large ($n = 10\,000$) noncardiac surgical trial. The CRASH trial investigating head injury demonstrated an increased relative risk of death (1.18 [95% confidence intervals; CI, 1.09–1.27]; $P = 0.0001$) in those receiving high-dose steroids with in 8 h of injury [48,49]. Part of their lack of effect may be due to the hyperglycemia that generally follows their administration. Hyperglycemia, in animal models and several human studies of cerebral injury, has been associated with worsened neurologic outcome [50,51]. The administration of steroids with the intent of conferring some degree of neuroprotection during cardiac surgery cannot be recommended based on current evidence.

Nonpharmacologic neuroprotection

Several well-defined areas of nonpharmacologic neuroprotection warrant addressing. Optimal temperature management, aortic atheroma detection and management, and emboli reduction strategies all hold promise for protecting the brain.

Temperature

A great deal of investigation has focused on the influence of intraoperative temperature on cerebral outcome after cardiac surgery. Hypothermia protects in almost all experimental, and some clinical, paradigms of brain injury [52]. The mechanism by which hypothermia protects is likely multifactorial. Although hypothermia has a measurable effect on suppressing cerebral metabolism (approximately 6%–7% decline per °C) [53], it is likely that its other neuroprotective effect(s) may be mediated by nonmetabolic actions. In the ischemic brain, for example, moderate hypothermia has multimodal effects, including blocking the release of glutamate [54], reducing calcium influx [55], hastening recovery of protein synthesis [56], diminishing membrane-bound protein kinase C activity [57], slowing of the time to onset of ischemia depolarization [58], reducing the formation of reactive oxygen species [59], and suppressing nitric oxide synthase activity [60].

Some of the most meaningful data on CPB temperature and cerebral outcome came from work that had its origins in the late 1980s and early 1990s. It was at that time that the judicious use of warm CPB was undertaken because of its putative myocardial salvaging effects when used with continuous warm cardioplegia [61–64]. However, because CPB was being carried out at higher temperatures than what were considered conventional, the implications on the brain were also studied. Several large studies were undertaken in order to elucidate the effects of temperature management on cerebral outcome after cardiac surgery. The Warm Heart Investigators trial [61], a second trial performed at Emory University [65], and a later trial at Duke University [66], although having several methodological differences, had very similar results with respect to neurocognitive outcome [67,68], but some very divergent results in terms of stroke. In short, none of the studies demonstrated any neuroprotective effect of hypothermia on neurocognitive outcome after cardiac surgery. What the Emory trial did demonstrate, however, was an apparent injurious effect (as manifested by a worse stroke outcome) of what was most likely mild degrees of hyperthermia during CPB. Neither the Warm Heart Investigators trial nor the Duke trial showed any effect of temperature on stroke per se. These data suggested that active warming to maintain temperatures at (or greater) than 37°C may pose an unnecessary risk of stroke.

Just as hypothermia has some likely protective effects on the brain, hyperthermia, in an opposite and disproportionate fashion, has some injurious effects. Although the studies referred to previously [61,65,66] demonstrated no neuroprotective effect, there is emerging evidence that if some degree of neuroprotection is afforded by hypothermia, it may be negated by the obligatory rewarming period that must ensue [69]. Indeed, Grigore et al. [69] demonstrated that, when compared to conventional faster rewarming, slower rewarming resulted in a lower incidence of neurocognitive dysfunction 6 weeks after cardiac surgery. These slower rewarming rates led to lower peak cerebral temperatures during rewarming, consistent with past observations

that rapid rewarming can lead to an overshoot in cerebral temperature, resulting in inadvertent cerebral hyperthermia [70]. By reducing this rewarming rate, one reduces the overshoot in temperature and may prevent the negative effects of cerebral hyperthermia. Consistent with the concept that preventing some of the rewarming may be protective was a study by Nathan et al. [71] that demonstrated a neurocognitive benefit for patients who were maintained between 34°C and 36°C for a prolonged (12-h) period postoperatively. That trial may have had its beneficial effect via the avoidance of cerebral hyperthermia during rewarming, rather than via the prolonged hypothermia [71].

The postoperative period is a relatively understudied time period with respect to temperature management and cerebral injury in cardiac surgery patients. We have recently demonstrated that hyperthermia commonly occurs during the first 24 h after CABG and that there is a direct relationship between postoperative fever and cognitive loss at 6 weeks after surgery [11]. The postoperative period therefore represents an important time period in which to intervene with a potential (albeit as yet unproven) strategy of preventing post-CABG fever and subsequent cognitive loss.

pH management

Alpha-stat is the most often utilized blood gas management convention for adult CPB. Alpha-stat management maintains normal cerebral blood flow (CBF) autoregulation with the coupling of cerebral metabolism ($CMRO_2$) to CBF, allowing for adequate oxygen delivery while minimizing the potential for emboli. Studies by Murkin [72] and Newman et al. [73] have outlined significant neurocognitive advantages of alpha-stat over pH-stat management. During pH stat management (where CO2 is added to the fresh oxygenator gas flow), a higher than needed for the brain's metabolic requirements CBF results. This luxury perfusion risks excessive delivery of emboli to the brain. Except for congenital heart surgery, where the majority of recent outcome data support the utilization of pH-stat management[91,92] (due to its ability to maintain brain cooling homogeneity prior to circulating arrest), adult outcome data support the use of alpha-stat pH management.

Emboli reduction

With convincing evidence that patients are likely exposed to thousands of cerebral emboli during surgery and that this embolic shower is associated with cerebral injury [6], numerous strategies have been proposed to reduce this damaging embolic load. There are multiple sources of emboli, both particulate and gaseous, during the normal conduct of cardiac surgery. The CPB circuit itself contributes to this load through the generation of particulate emboli, in the form of platelet-fibrin aggregates and other debris produced within the circuit itself. Gaseous emboli can be created, or augmented if already present, in the circuit due to factors such as turbulence-related cavitation, and vacuum-assisted venous drainage contributing to this gaseous emboli process [74]. The intrinsic ability of the circuit to allow air entrained from the venous return cannula to pass through the oxygenator itself varies considerably between manufacturers but remains a significant source for air in the circuit. As significant quantities of air can be entrained into the heart itself from the surgical field, flooding the field with CO_2 has been touted as being effective in reducing this emboli source [75]. Its ability to specifically reduce cerebral injury has not been well studied.

Blood that is returned to the venous reservoir from the surgical field though the use of the cardiotomy suction may significantly contribute to the particulate load in the CPB circuit. This has been demonstrated to significantly increase the cerebral emboli load [40]. The use of blood salvage devices (i.e., cell-saver) to process the blood prior to returning it to the venous reservoir may minimize the amount of particulate/lipid-laden material, which likely originates from the sternotomy itself, that is available for embolization. Most of this material is likely either small enough in size or so significantly deformable that it can pass through standard arterial line filters. Although small preliminary studies have proven that there may be a potential benefit to the use of the cell saver [76], one must balance the ability of the cell-saver to decrease the amount of particulate matter getting into the circuit with its side effects, if used excessively, of reducing both platelet and coagulation factors through its intrinsic washing processes. The right balance likely lies in using the cell-saver up to a certain, as yet undefined, volume of processed blood and then returning to using the cardiotomy return. This area has not been studied with respect to cognitive outcome, but studies are underway.

Pulsatile perfusion

Nonpulsatile CPB is the most commonly practiced form of artificial perfusion and has been examined in several studies. Although inherently nonphysiologic, there is a paucity of data to suggest that pulsatile flow during clinical CPB is beneficial compared to nonpulsatile bypass. In a study (n = 316) by Murkin [72], the effect of pulsatile versus nonpulsatile CPB on neurologic and neuropsychologic outcomes was examined, but demonstrated no significant differences in outcome.[87] However, a significant limitation to most pulsatility studies is that true "physiologic" pulsatility is almost never accomplished. Instead, variations of sinusoidal pulse waveforms are produced that clearly do not match the hydrodynamics of normal physiologic pulsation.

Although there is hope that newer pulsatile technologies, better reproducing normal biologic pulsatility, may have some benefit,[89] the majority of studies to date do not present enough convincing evidence to suggest that routine pulsatile flow during CPB is warranted.

Atheroma management

The aorta itself is a significant source of injurious embolic material, largely represented by atheromatous aortic debris that can embolize to various vascular beds, including the brain. There are multiple techniques that can be used to minimize atheromatous material being liberated from the aortic wall and embolizing into the cerebral circulation. These range from optimizing the placement of the aortic cannula in an area relatively devoid of plaque [77] to the use of specialized cannulae that cause less "sandblasting" of the aortic wall. The use of transesophageal echocardiography (TEE) and epiaortic scanning has allowed for the "knowledgeable avoidance" of the atheromatous ascending aorta, with respect to cannulation, clamping, and proximal vein graft anastomosis placement [77]. Alternative aortic cannulae and the use of different locations possess the ability to decrease the embolization of atheromatous plaque. The avoidance of partial-occlusion clamping for proximal anastomosis, using single-step automated anastomotic devices, and the use of alternatives to cross-clamping all possess the ability to mitigate injury due to embolization. Hammon et al. [78] have recently demonstrated that avoiding manipulation of the aorta by using only a single clamp application can significantly reduce postoperative cognitive loss. In addition, specialized cannulae that contain filtering technologies and other means to deflect emboli to more distal sites have been developed and are being studied [79]. Optimizing the management of the atheromatous aorta will see further development in future years.

Glycemic control

Hyperglycemia is a common occurrence during the conduct of CPB. In addition to the exogenous administration of glucose-containing solutions (dextrose-containing cardioplegia and pump prime) [80] and the stress response to surgery and CPB, marked by significant increases in circulating catecholamines (epinephrine and norepinephrine) and cortisol [81,82], hypothermia-induced insulin resistance is common. All of these result in significant peripheral insulin resistance and marked increases in glycemic conditions [83–85]. Hyperglycemia, variably defined as a serum glucose of more than 180–200 $mg \cdot dl^{-1}$ (approximately > 11 $mmol \cdot l^{-1}$) occurs in as many as 75% of patients. Patients with pre-existing diabetes mellitus have an even higher incidence [86].

Multiple investigations have examined the adverse sequelae (such as perioperative infection [87,88]) associated with hyperglycemia during cardiac surgery. There is emerging clinical and experimental evidence implicating hyperglycemia with various immunomodulatory effects, particularly in those patients with critical illness [89,90]. In particular, hyperglycemia has been demonstrated to reduce white blood-cell function, most notably that of macrophages and neutrophils [91]. In addition to its immunomodulatory effects, hyperglycemia, because of its osmotic effects, also has an impact on the kidney, acting as a potent osmotic diuretic. However, little work has focused on its potential impact on longer-term renal impairment, which has been demonstrated in certain subsets of patients after cardiac surgery [92,93].

With respect to neurologic outcome, multiple studies outside the cardiac surgical setting have demonstrated relationships between hyperglycemia and worse outcome after cerebral injury [94–96]. Experimentally, there are considerable data confirming the link between hyperglycemia and adverse cerebral outcome after stroke [49,51,97,98]. The potential mechanisms for hyperglycemia's association with adverse neurologic outcome are several-fold. Firstly, higher glucose levels lead to a higher degree of substrate availability for the production of lactate during the anaerobic metabolism that is consequent on cerebral ischemia [99–101]. The resulting intracellular acidosis then interferes with glycolysis, protein synthesis, homeostasis, enzyme function, and other critical intracellular processes [101–103]. In addition, hyperglycemia has been shown to increase the release of excitotoxic amino acids (glutamate and aspartate) during cerebral ischemia. The release of these amino acids is a key mediator in the ischemic cascade; the presence of hyperglycemia augments this injurious response [104,105]. Furthermore, there is potentially some evidence suggesting that the presence of hyperglycemia itself may enhance the inflammatory response [106]. As it is already known that CPB has a much enhanced inflammatory response [43,107], and that inflammation may mediate several adverse outcomes, including cerebral ones, the additional hyperglycemia-mediated inflammation may cause further injury. With the cerebral ischemia that has the potential to occur during cardiac surgery, this may be one potential mechanism that explains why an adverse cerebral outcome would be expected to be linked with hyperglycemia during cardiac surgery.

The link between hyperglycemia and adverse neurologic outcome is not clear, however [108]. Most studies have been small and underpowered to demonstrate any meaningful associations between adverse cerebral outcome and hyperglycemia during cardiac surgery. A

notable exception is a study ($n = 709$) of patients undergoing CABG with CPB where cognitive function was assessed both pre- and post operatively (6 weeks). The incidence of cognitive deficit was compared between those with hyperglycemia versus those who were not hyperglycemic. The hyperglycemic patients had a cognitive deficit rate of 40%, versus 29% in the normoglycemic group (odds ratio [OR], 1.85; 95% CI, 1.1–3.0; $P = 0.0165$) [86].

Attenuating the hyperglycemic response to cardiac surgery has proven difficult, with even high insulin doses more often than not failing to return glucose levels to normal during surgery. In a study by Chaney et al. [109], not only was normoglycemia difficult to attain during cardiac surgery, but with the high insulin doses administered during surgery, the incidence of hypoglycemia in the post-bypass period was excessive. In addition, excessive insulin can also result in hypokalemia, due to its enhancement of potassium transmembrane transport mechanisms. The most recent data examining the ability of reducing hyperglycemia in order to decrease the incidence of neurologic injury was published by Butterworth et al. [110]. This study did not demonstrate any beneficial effect of insulin therapy on neurologic and neurobehavioral outcome, but significant hyperglycemia remained in both their cohorts, proving once again how difficult precise glycemic control is with current glucose monitoring and insulin therapy strategies.

Off-pump cardiac surgery

Although it is logical to assume that the elimination of the CPB apparatus with off-pump coronary bypass surgery (OPCAB) would reduce some of the cerebral injury associated with cardiac surgery, it is unlikely that it will eliminate these injuries altogether, particularly as cognitive dysfunction has still been documented in OPCAB patients. The largest trial comparing OPCAB to conventional on-pump CABG surgery failed to demonstrate a decrease in neurocognitive decline at 1 year after surgery [111]. The reasons for this are unclear, but may be partly explained by the complex pathophysiology involved. For example, if inflammatory processes play a role in mediating cardiac surgery-related brain injury, then OPCAB, with its continued use of sternotomy, heparin administration [112], and wide hemodynamic swings, may be a significant reason as to why cognitive dysfunction is still seen. In addition, traditional embolic theories are still valid, as ascending aortic manipulation, with its ensuing particulate embolization, is still commonly used. In addition, significant hemodynamic compromise, due to manipulation of the heart, can lead to hypotension that has been associated with significant jugular venous desaturation [113]. This type of desaturation was demonstrated by Croughwell et al. [114] to be associated with cognitive decline.

Large prospective studies will help in both determining if off-pump procedures will have lower neurologic complications, but also in regard to which patient population this procedure should be optimally targeted. For example, is the patient who is at high risk for neurologic injury the best choice for OPCAB, where a compromise of potentially incomplete adequate revascularization may be made in order to prevent debilitating stroke? Or, conversely, should OPCAB be performed in a younger patient, in whom the risk of neurologic complications is lower, but who would have the most to gain from the longest possible patency (probably from conventional CABG)? Understanding the balance between optimizing neurologic outcome and coronary outcome is critical, and this is the focus of several recent studies. Al-Ruzzeh et al. [115] have re-examined the issue of potential OPCAB benefits in a more recent study ($n = 168$) that better controlled for some of the aortic manipulative limitations. They demonstrated better neurocognitive function without any compromise in coronary angiographic outcome in the OPCAB group. The precise role of OPCAB continues to be a dynamic area of research.

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