Neuroprotective Strategies in Repair and Replacement of the Aortic Arch

Frank Manetta, MD, FICA¹ Clancy W. Mullan, BS¹ Michael A. Catalano, BS¹

¹Department of Cardiovascular and Thoracic Surgery, Barbara and Donald Zucker School of Medicine at Hofstra/Northwell, Manhasset, New York

Address for correspondence Frank Manetta, MD, FICA, 300 Community Drive, Manhasset, New York 11030 (e-mail: fmanetta@northwell.edu).

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Abstract

Keywords

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Aortic arch surgery is a technical challenge, and cerebral protection during distal anastomosis is a continued topic of controversy and discussion. The physiologic effects of hypothermic arrest and adjunctive cerebral perfusion have yet to be fully defined, and the optimal strategies are still undetermined. This review highlights the historical context, physiological rationale, and clinical efficacy of various neuroprotective strategies during arch operations.

Surgeries of the aortic arch are among the most technically demanding, and they are among the very few that involve direct manipulation of the head and neck vessels. As such, the risk of neurological injury and the need for neuroprotection, during these operations is substantial, and protective strategies remain an active area of research and debate within the cardiothoracic surgical community. Neurologic injury is frequently categorized as either temporary (or transient) neurological dysfunction (TND), which includes delirium, seizures, disorientation, agitation, etc. without clinical or radiographic evidence of residual damage, or permanent neurological dysfunction (PND), such as cerebral vascular accident, paralysis, or paresthesia.

The overall risk of a patient suffering either TND or PND remains significant in the modern era, amounting to approximate risks of 5.2 and 3.4%, respectively.¹ Furthermore, PND or TND after cardiac surgery increases length of intensive care unit (ICU) stay, length of hospitalization, length of stay, readmission rates, and mortality.^{2–5} The review that follows will provide some degree of physiological and historical framework for neuroprotective strategies for surgeries of the aortic arch including pharmacologic and hypothermic methods, will review the clinical studies of these strategies, and will discuss some of the many unanswered questions within the field.

Cerebral Metabolism and Ischemia

Despite accounting for only 2% of the body's weight, the brain receives 15% of the cardiac output, ~45 to 60 mL per gram of tissue per minute at perfusion pressures >70 mm Hg,⁶ and uses 20% of the available oxygen at rest.⁷ Furthermore, there is little-to-no glucose storage in the brain, which put it at risk of rapid adenosine triphosphate (ATP) depletion during ischemia. The mechanistic effects of ischemia are complicated, and the significant events are summarized hereto provide pharmacologic context.

Maintenance of the neuronal electrochemical gradient is the principle driver of cerebral metabolic demand, and nutrient deprivation leads to rapid accumulation of H⁺ and waste and neuronal and glial death. Using a neonatal swine model, Mavroudis et al demonstrated mitochondrial dysfunction after deep hypothermic circulatory arrest (DHCA), including reduced complex I function, increased reactive oxygen species, and reduced oxidative phosphorylation.⁸ With the concomitant increased lipolysis, the increased levels of free fatty acids then contribute to cell membrane damage and radical oxygen species production.⁹

Ultimately, ATP depletion leads to a decrease in intracellular pH, which displaces calcium and increases the level of free calcium ions. As the ATP-dependent Na/K channels

become increasingly dysfunctional, calcium continues to rise, causing initiating cell death via numerous mechanisms including protein kinase C delta, tumor necrosis factor, and Bcl-2-related pathways.¹⁰

Baumgartner et al elucidated additional mechanistic details of cerebral damage after HCA using a canine animal model, describing the release of excitatory neurotransmitters including glutamate and the upregulation of nitric oxide synthase.¹¹ The ensuing excitotoxicity contributes to further neuronal damage via necrotic, necroptotic, and apoptotic mechanisms.¹²

Pharmacologic Neuroprotection

Given the degree of molecular activity that occurs during ischemia, pharmacologic intervention has generated substantial interest as a therapeutic avenue,^{13,14} and many drugs that may protect against residual neuronal activity and reduce oxygen consumption have been trialed, especially as an adjunctive measure to hypothermia. Early work considered the possibility of barbiturates,¹⁵ which showed promise in animal models by reducing excitotoxic damage but has produced conflicting evidence in man.^{16,17} Since that time, other interventions have been studied, the most notable of which are detailed here and summarized in ►Table 1.

Corticosteroids

Corticosteroids have long been employed as a means to reduce post-cardiopulmonary bypass (CPB) cytokine

Table 1 Mechanistic targets of various proposed neuroprotective agents used in cardiac surgery

Drug	Proposed mechanisms
Barbiturates	Reduce excitotoxicity Reduce calcium influx Reduce ROS
Corticosteroids	Anti-inflammatory properties Reduce cerebral edema Improve cerebral blood flow
Inhaled anesthetics	Reduce excitotoxicity Reduce calcium influx Inhibit apoptosis Reduce ROS Anti-inflammatory properties Improve cerebral blood flow
Propofol	Reduce excitotoxicity Reduce ROS Anti-inflammatory properties Inhibit apoptosis
Lidocaine	Stabilize electrochemical membrane Reduce metabolic rate Improve cerebral blood flow Anti-inflammatory properties
Magnesium	Stabilize electrochemical membrane Reduce excitotoxicity Reduce intracellular calcium release
Mannitol	Reduce cerebral edema Reduce ROS

Abbreviation: ROS, radical oxygen species.

response and β -adrenergic desensitization.^{18,19} Shum-Tim et al demonstrated improved neural immunohistochemical outcomes in neonatal swine using systemic methylprednisolone after HCA.²⁰ Langley et al corroborated this evidence in infant swine by demonstrating improved cerebral blood flow (CBF) recovery after hypothermic arrest.²¹

The clinical evidence is mostly from studies of acute spinal cord injury, despite the drastically different mechanism of injury, and even that is weak.¹³ A Cochrane review including 466 patients by Sandercock and Soane demonstrated insufficient evidence for use of corticosteroids in acute ischemic stroke.²² Conversely, there is evidence that corticosteroid-related hyperglycemia may exacerbate ischemic neurological injury.²³

Inhaled Anesthetics

In animal models, isoflurane, sevoflurane, and desflurane have been found to reduce excitotoxicity,²⁴ improve calcium regulation,²⁵ reduce cerebral necrosis,²⁶ and improve histologic outcomes.²⁷ The clinical evidence for these medications is growing, with some evidence of reduced serum inflammatory markers, improved postoperative neurocognitive function, and CBF,²⁸ though studies in HCA are sparse.

Propofol

Animal models have demonstrated possible neuroprotection with propofol via excitotoxin mediation, antioxidant properties, anti-inflammatory nature, or antiapoptotic mechanisms.²⁹ A recent clinical trial by Mahajan et al demonstrated similar minimal status exam outcomes for 66 patients undergoing cerebral aneurysm clipping treated with propofol versus controls; however, this study may have been underpowered for detection of differences via such an insensitive tool.³⁰

Lidocaine

Lidocaine has been explored for its potential to protect the neural electrochemical gradient, reduce neuronal metabolism, improve CBF, and provide anti-inflammatory effects.³¹ Clinical evidence is mixed, with some evidence that lidocaine provides some degree of neuroprotection, especially for transient ischemia,^{32,33} but other studies demonstrating no effect.³⁴ Overall, the consensus appears to be a desire for further study, as lidocaine may be proven to provide clinically relevant neuroprotection.

Magnesium

Magnesium is frequently utilized for its role in stabilizing electrochemical gradients, its role in inhibiting glutamate activity at the N-methyl-D-aspartate receptor, and its ability to reduce intracellular calcium release.³⁵ While there is some clinical evidence for the role of magnesium in neuroprotection in both cardiac surgery and stroke literature,³⁶ including a randomized controlled trial (RCT) by Bhudia et al including 350 patients undergoing CPB that demonstrated improved short-term neurologic function but no benefit at 3 months,³⁷ a recent randomized, double-blinded, placebo-controlled study of 389 patients by Mathew et al failed to produce a clinical effect of perioperative magnesium administration.³⁸

Mannitol

Cerebral edema has been identified as an independent risk factor for postoperative neurocognitive decline.³⁰ As such, osmotic therapy, such as mannitol, is a promising avenue for treatment. In a study of 2,137 patients from the German Registry for Acute Aortic Dissection Type A by Krüger et al, mannitol was associated with a significant reduction of 30-day mortality, from 18.7% in controls to 8.9% with mannitol.³⁹ Overall, despite the promise of animal models, the level of evidence for pharmacologic neuroprotective strategies remains very weak, with few large randomized trials having been performed.

Hypothermic Circulatory Arrest

Hypothermia as an intraoperative management strategy in cardiac surgery was first successfully employed in 1953, when Lewis and Taufic performed an atrial septal defect repair under hypothermic conditions.⁴⁰ Despite the advent of modern surgical treatment of aortic aneurysms in the 1950s by Drs. Cooley and DeBakey,⁴¹ it was not until 1975 when Griep et al first employed hypothermia in arch replacement.⁴² Thankfully, the development of this technique had been furthered in the Soviet Union, led by Eugenij Meshalkin⁴³ and others who found its utility in congenital cardiac operations.⁴⁴

Physiologic Effects of Hypothermia

Hypothermia reduces molecular motion, which, in turn, reduces the metabolic rate, free radical production, and postischemic cerebral edema,^{45,46} though not without risks, including coagulopathy, increased CPB times,⁴⁷ and increased post-HCA cerebral vascular resistance.⁴⁶

McCullough et al described cerebral metabolic suppression in 1999 using 37 patients undergoing HCA and found the temperature coefficient (Q10), or the ratio of metabolic rates at each 10°C interval, to be 2.3, meaning that the cerebral metabolic rate is reduced to 37% by 25°C, 16% by 15°C, and 11% by 10°C. This provided a starting point calculation for estimating the safe maximal duration of HCA of 5 minutes at normothermia, 14 minutes at 25°C, 31 minutes at 15°C, and 45 minutes at 10°C.⁴⁸ However, the Q10 may not be constant, and it is believed to correlate inversely with temperature, as longer arrest times have been reported. The rate of cooling is also relevant to cerebral protection, with large temperature differentials leading to nonuniform cooling and areas of warm, vulnerable brain (► **Table 2**).^{6,49}

Table 2 Metabolic rates and estimated arrest limits at various temperatures based on the Q10 of 2.3, which was calculated by McCullough et al (1999)⁴⁸

Level of hypothermia	Temperature (°C)	Calculated metabolic rate (% normothermia)	Estimated safe arrest limit (min)
Normothermia	36–38	100	5
Mild	28.1–34	48–78	6–10
Moderate	20.1–28	24–47	11–21
Deep	14.1–20	15–24	21–33
Profound	<14	<15	>33

Hypothermia has significant hematologic effects, as well. Principally, blood viscosity increases with decrease in temperature, which is mitigated by dilutional effects of CPB.^{50,51} However, animal models have demonstrated superior brain outcomes when hematocrit is maintained more than 20%, which may be due to preserved mitochondrial function.⁵² Some data from animal models suggest a higher hematocrit of 30%, which previously was believed to reduce cerebral microcirculation.⁵³

Finally, hypothermia increases the buffering capacity of blood and CSF, resulting in CO₂ absorption changes.⁵⁴ The addition of further CO₂ thus produces a relative alkalosis, leading to cerebral vasodilation and increased CBF that improve perfusion of deep brain structures.^{6,49}

Risk of Hypothermic Arrest

A rough appreciation for the limits of physiologic tolerance of hypothermia can be gleaned from the most extreme accidental hypothermia cases with full recovery. The longest reported arrest time without cardiopulmonary resuscitation was reported in 1982 at 70 minutes in a 42-year-old man.⁵⁵ In a 1955 case, a 51-year-old woman was cooled to a core temperature of 9°C, the lowest reported temperature with survival, in an attempt to treat metastatic ovarian carcinoma.⁵⁶

These cases correlate with the clinical findings of the safe limits of HCA, the levels of which are defined as mild (28.1–36°C), moderate (20.1–28°C) (MHCA), deep (14.1–20°C), and profound (<14°C).⁵⁷ For instance, Reich et al found that DHCA times more than 25 minutes were associated with TND, prolonged hospitalizations, and long-term neurocognitive functional decline,⁵⁸ and Ergin et al later demonstrated that post-DHCA TND, relatively minor neurologic injury, may be a harbinger of long-term cerebral dysfunction.⁵⁹

The principle drawback of DHCA is the time constraint placed on the surgeon. Svensson et al demonstrated that DHCA time correlates well with TND and PND, with stroke risk increasing after 40 minutes of arrest time. Furthermore, stroke was identified as a significant predictor of increased risk of early mortality.⁶⁰ This is consistent with animal models. Mezrow et al additionally found that, compared with 45 minutes of HCA time, animals undergoing 90 minutes of HCA demonstrated prolonged increases in cerebral vascular resistance, increased mortality, and worsened short-term postoperative behavioral outcomes.⁶¹

While any patient undergoing these operations is at some degree of risk, Czerny et al identified risk factors by univariate analysis for permanent neurologic injury that include type A dissection, emergency surgery, preoperative hemodynamic instability, use and duration of DHCA, retrograde cerebral perfusion (RCP), and duration of CPB; however, use of DHCA was the only risk factor identified by multivariate analysis.⁶² However, compared with the perfusion strategies that are described later, DHCA offers the significant advantage of being technically simple, requiring no additional time or cannulation, and may be effective for short arrest times.

A retrospective study by Gega et al including 394 patients found that DHCA provided sufficient neuroprotection if arrest times were kept below 45 minutes, at which point the stroke rate rose from 4.3 to 13.1%, though the authors found the majority of these to be embolic in nature rather than ischemic.⁶³ In analyzing a subgroup of patients with cognitively demanding professions, Percy et al found that patients requiring DHCA for distal anastomosis had similar outcomes to patients with less extensive operations.⁶⁴ However, other studies have found conflicting evidence of neurologic dysfunction, including an early study by Reich et al of 149 patients that found DHCA times more than 25 minutes were associated with memory and fine motor deficits.⁵⁸

While a similar study has yet to be performed for surgery of the aortic arch, a study by Likosky et al of 388 patients with stroke after isolated CABG found 62.1% to be embolic in nature.⁶⁵ Based on multiple individual studies, there appear to be two distinct etiologies for PND and TND. It seems likely that PND is primarily caused by embolic phenomena, whereas TND may be related to global hypoperfusion and ischemia-reperfusion injury.^{50,63,66–68}

Cerebral Perfusion Strategies

Two strategies of continued cerebral perfusion during arrest exist: RCP via the venous system and antegrade cerebral perfusion (ACP) via the carotid arteries. These perfusion strategies were developed to prolong circulatory arrest times, and controversy ensued regarding the superiority of one strategy over the other. The body of evidence has grown to favor ACP over RCP, which has led 50% of surgeons to prefer ACP compared with the 6% who prefer RCP.⁶⁹

Retrograde Cerebral Perfusion

RCP involves cannulation of the superior vena cava, connection of the arterial and venous bypass cannulas, and perfusion through the venous sinus system at a flow rate required to maintain jugular venous pressure between 20 and 25 mm Hg.^{69–71} This is believed to provide a greater degree of hypothermia, due to the large capacity of the dural sinuses, flush embolic debris, and provide perfusion of the cerebral parenchyma.⁷² However, in a porcine model comparing ACP and RCP, Ye et al found that India ink delivered via RCP primarily returned via the IVC rather than the head vessels and that RCP animals had 90% fewer stained capillaries than ACP animals.⁷³ Other animal models have demonstrated conflicting metabolic benefits to RCP, as reviewed by Reich et al.⁷⁰

Early clinical evidence revealed an increased safe DHCA window compared with DHCA alone,^{66,74} and a recent retrospective, single-surgeon study by Girardi et al demonstrated adequate protection in hemiarch and total arch replacement operations, with PND rates of 1.3 and 1.9%, respectively.⁷⁵ While RCP increases the limits of DHCA, Ueda et al identified an upper limit of 80 minutes before DHCA with RCP risks an increase in mortality.⁷⁶ Later, Okita et al demonstrated increased prevalence of TND with RCP and correlation between the degree of TND and the length of DHCA with RCP.⁷⁷

Controversy stems from whether RCP provides benefit or not, with some concern that it may even do harm. Harrington et al found worsened neuropsychometric outcomes at 6 and 12 weeks with RCP and DHCA versus DHCA alone.⁷⁸ Another study by Moon et al⁷⁹ compared DHCA and RCP and found no mortality benefit to RCP over DHCA alone. Additionally, multiple animal models have demonstrated increased cerebral edema with RCP,^{80,81} though this has not been substantiated in human trials. Estrera et al observed that transcranial Doppler (TCD) measurement of cerebral arterial flow exhibited no decreased in pulsatility index or end diastolic velocities that would correlate with increased cerebral edema.⁸²

Antegrade Cerebral Perfusion

ACP was first described by Cooley and DeBakey in 1956 using normothermic perfusion via the right common carotid to resect an ascending aortic aneurysm.⁸³ Debate has continued regarding the efficacy of ACP versus RCP. An early prospective study of 32 patients by Tanoue et al found reduced MCA flow by TCD during arrest with RCP compared with ACP, and they also detected increased flow after RCP termination, indicative of reactive hyperemia.⁸⁴ Another prospective study by Okita et al of 60 patients found decreased rates of TND with ACP relative to RCP,⁷⁸ a finding supported by a later retrospective study of 717 that found reduced rates of TND with ACP in prolonged arrest times.⁶⁷

In an analysis of 8,169 patients undergoing total arch replacement, Okita et al found increased ICU time and endotracheal intubation duration for HCA/RCP versus ACP but comparable mortality, TND, and PND.⁸⁵ Most recently, a meta-analysis of retrospective studies including 7,023 patients showed decreased TND with ACP but similar rates of PND, early death, and stroke.⁸⁶ Although ACP clearly provides some advantages and allows for prolongation of circulatory arrest times,⁸⁶ it is not without risks, including vessel injury from manipulation, embolism, and the added difficulty of additional cannulas in the surgical field.^{87,88}

Laterality in Antegrade Perfusion

Controversy exists regarding the value of bilateral versus unilateral ACP. Hesitation to rely on unilateral perfusion (uACP) primarily arises from fears that the contralateral hemisphere may not be perfused during arrest in the 15% of patients who have an incomplete circle of Willis.⁸⁹ However, collateral supply does exist via the external, craniofacial vessels, and the vertebral arteries. Additionally, the left vertebral artery arises from aortic arch in 10%, which may result in arterial steal;

however, this is manageable with clamping of the left-sided head vessels.^{90,91}

The risks of bilateral perfusion (bACP) strategies, which include cannulation of the right axillary combined with left carotid^{92,93} or cannulation of all three supra-aortic vessels,⁹⁴ include those accompanying added manipulation of the head vessels, including dissection, embolism, and intimal damage.⁹¹ A meta-analysis of 3,548 patients comparing the two strategies found that bACP offers the advantage of arrest times up to 86 to over 164 minutes, comparing favorably to 30 to 50 minutes for uACP.⁹⁵ However, a more recent meta-analysis of retrospective studies including 5,100 patients by Angeloni et al found comparable rates of mortality, PND, and TND between bACP and uACP.⁹¹

Mild-to-Moderate Hypothermia

A significant advantage to ACP strategies may be that they allow for milder hypothermia during arrest periods, reducing total bypass time, the physiologic changes, and the end organ dysfunction that accompany deep hypothermia and its required cooling and warming times on CPB.^{96–102} A study of 733 patients undergoing total arch repair with MHCA by Leshnower et al established the technique's safety,¹⁰² and a recent retrospective, all comers study by El-Sayed Ahmad et al of 587 consecutive aortic arch surgery patients, reported 5% TND, 6% PND, and 6% mortality with MHCA.¹⁰³ A study of 377 patients by Kamiya et al found decreased postoperative C-reactive protein levels with MHCA.¹⁰⁰

However, as favor has grown for MHCA with ACP, some have questioned its efficacy in protecting the spinal cord and visceral organs. Using a porcine model, Etz et al demonstrated insufficient spinal cord blood flow using MHCA with ACP to preserve cord function for prolonged arrest periods,¹⁰⁴ although Strauch et al had previously described the spinal cord protection offered by even mild hypothermia compared with normothermia.¹⁰⁵ It is unknown whether MHCA compares satisfactorily to deeper hypothermia during periods of arrest.

With regard to the viscera, Khaladj et al found, in a porcine model, that hypothermia at 30°C resulted in higher serum lactate levels and more histologic findings of bowel wall inflammation compared with arrest at 20°C.¹⁰⁶ In another porcine experiment, Haldenwang et al demonstrated elevated inflammatory markers in ACP compared with animals with ACP plus continued lower body perfusion.¹⁰⁷ These findings were alarming in their suggestion that milder hypothermia may create need for trade-off between visceral and cerebral maintenance.

Interestingly, however, human studies are much more promising. A retrospective study by Arnaoutakis et al found that MHCA was not associated with worse renal outcomes.¹⁰⁸ Another retrospective study by Numata et al found similar mortality and PND with arrest above and below 28°C but significantly reduced rates of postoperative renal failure requiring dialysis and postoperative respiratory failure with prolonged ventilation in patients with arrest temperatures more than 28°C.¹⁰⁹ Other studies have demonstrated safety and promising outcomes for MHCA with regard to mortality, neurologic injury, dialysis-dependent renal failure, CPB times, neurologic injury, and serum ischemic markers.^{97,110,111} A recent

meta-analysis including 1,783 patients found no advantages to DHCA over MHCA.¹¹² Despite this growing body of evidence, there are no prospective, randomized trials, yet, to study differences between DHCA and milder hypothermic strategies.

Cardiopulmonary Bypass Cannulation

The optimal bypass cannulation strategy for protecting the brain remains a contentious issue, as well. Numerous cannulation techniques have been trialed in aortic surgery, including cannulation of the aorta and femoral, iliac, axillary, innominate, carotid, and subclavian arteries.⁵⁷ Among these, femoral, direct aortic, and axillary have been the most studied.

Femoral arterial cannulation remains a common choice, especially in situations demanding rapid arterial access.⁵⁷ Numerous studies have found risk in this strategy, both to the brain and locally, including distal ischemia, compartment syndrome, and local dissection. Westaby et al found an increased incidence of PND compared with direct aortic cannulation, possibly due to atheromatous debris in the aorta.¹¹³ Later, multivariate analysis of 501 patients undergoing aortic arch surgery by Khaladj et al found femoral cannulation to be an independent risk factor for mortality.¹¹⁴

Compared with femoral cannulation, cannulation strategies that preserve antegrade flow through the thoracic aorta are believed to be superior.^{113,115,116} Direct aortic cannulation is the most obvious of these techniques but can be difficult in dissection, aneurysm, or thrombus, any of which may prevent adequate cerebral perfusion. Aortic cannulation may also further complicate an aneurysmal aorta.¹¹⁶ Aortic cannulation likely provides only a modest improvement in outcomes versus femoral cannulation, as found in a recent meta-analysis by Benedetto et al.^{115,117} However, numerous individual studies have found no risk reduction versus femoral cannulation strategies.^{66,118–122}

Perfusion via axillary cannulation has increasingly gained favor, with a growing body of evidence supporting its superiority.^{115,116,122–125} A retrospective, propensity-matched analysis by Svensson et al demonstrated decreased PND and in-hospital mortality with axillary versus direct aortic cannulation.¹²⁶ A later retrospective study by Etz et al found superior outcomes in atherosclerotic aneurysms and all-cause proximal aortic surgery, despite these patients being older and more likely to have coronary disease and chronic obstructive pulmonary disease.¹¹⁶ Another recent meta-analysis of retrospective studies by Benedetto et al demonstrated 65 and 39% absolute risk reductions for mortality and PND, respectively, comparing axillary cannulation to femoral cannulation, which compares favorably with 7 and 8% respective reductions with aortic cannulation. In addition to superior CPB outcomes, axillary cannulation allows for a rapid transition to ACP during periods of circulatory arrest.

Neurophysiologic Intraoperative Monitoring

Due to the significant individual variability in tolerating hypothermia, including individual buffering capacities,

glucose tolerances, and basal metabolic rates,¹²⁷ optimal intraoperative, real-time monitoring of cerebral protection is an area of active discovery. Furthermore, standard temperature measurement locations may not correlate well with cerebral temperature, though nasopharyngeal, esophageal, and pulmonary arterial temperatures exhibit the best correlation.¹²⁸ While incomplete cooling is obviously problematic, cold injury also results in some degree of cerebral edema due to breakdown of the blood-brain barrier.^{129,130} As such, accurate and timely monitoring of temperature, malperfusion, and continued cerebral activity is a necessity in surgery of the aortic arch.

Electroencephalography

Electroencephalography (EEG) is considered the gold standard monitoring strategy for complete cerebral metabolic and electrocerebral inactivity during hypothermia and the identification of cerebral injury.^{131–133} Additionally, nasopharyngeal temperatures are variable at the point of electrocerebral silence; therefore, in the absence of EEG monitoring, fixed temperature targets less than 12.5°C or cooling time >50 minutes are required.^{49,134} Interestingly, Stecker et al showed that the temperature at which continuous EEG activity and somatosensory evoked potentials (SEPs, discussed later) returned correlated with postoperative neurological impairment.¹³⁵ A significant disadvantage of EEG is the effect of anesthetic choice on EEG activity, with, for instance, propofol and barbiturates producing a burst-suppression pattern at clinically relevant dosages.¹³⁶

Somatosensory Evoked Potentials

SEP monitoring is a tool that monitors brain stem and cortical activity after electrical stimulation of peripheral nerves, most often alternating median nerve stimulation. The measured potentials are mapped to various regions of the brain and allow monitoring of specific areas for cerebral and brain stem activity. However, these regions do not correlate well with complete ECI, with some disappearing prior to ECI and other, typically subcortical structures, persisting past ECI.¹³⁶ In one study of 32 patients by Guérit et al, SEPs monitoring provided adequate information to determine the level of hypothermia at which neurological injury after HCA may be prevented,¹³⁷ which was later corroborated in a larger study of 62 patients by Ghariani et al.¹³⁸ As previously mentioned, delayed return of SEP during rewarming correlates to neurological injury.¹³⁵

Bilateral Transcranial Doppler

TCD provides real-time measurement of blood velocity in the middle cerebral artery using temporal ultrasonography. This strategy is advantageous in that it is continuous and provides bilateral monitoring of actual blood flow to the brain, which may be valuable in unilateral perfusion strategies.^{139,140}

Near-Infrared Reflectance Spectroscopy

Near-infrared reflectance spectroscopy (NIRS) is a technology that monitors regional cerebral O₂ saturation by using transcranial near-infrared light to measure the ratio of oxygenation to deoxygenated hemoglobin.¹⁴¹ This technology is sensitive

for the detection of low-flow states and changes in oxygen saturation,¹⁴² and, as such, it is especially valuable in elderly and patients with cerebrovascular disease.¹⁴¹

Despite its theoretical value and isolated studies demonstrating clinical efficacy,^{142–145} systematic reviews and meta-analyses have yet to find clinical advantage to NIRS monitoring, including a recent meta-analysis of 51,698 adult cardiac surgery patients by Zheng et al, which found no consistent benefit to stroke, postoperative neurocognitive decline, or delirium with NIRS monitoring and subsequent intervention.¹⁴⁰ In their discussion of the topic, Zheng et al noted that the technology is limited by the variability in available devices and the lack of a universal definition of cerebral desaturation, with some authors using relative desaturation and others using an absolute value. However, in aortic surgery with selective cerebral perfusion, NIRS is able to detect flow disruption effectively, as demonstrated by Urbanski et al.¹⁴⁶

A study by Yu et al found that a combination of TCD, measuring CBF, and NIRS, measuring hemoglobin saturation, may be effective in determining true oxygen delivery to the brain during selective cerebral perfusion at flow rates as low as 5 mL/kg/min,¹⁴⁷ work which was supported by a later study by Wang et al.¹⁴⁸ Thus, the utility of NIRS may be application specific.

Cerebral Venous Oxygen Saturation Monitoring

Monitoring of the cerebral venous oxygen saturation was an early technique in cerebral metabolic monitoring during CPB and hypothermia, and it involves placing an oximeter in the jugular bulb. This method allows real-time temperature and saturation monitoring. Technically simple and capable of detecting global cerebral metabolic activity, venous oxygen saturation is not able to detect focal ischemic injury.¹⁴⁹ With the advent of NIRS monitoring, which is also capable of estimating jugular bulb oxygen saturation,¹⁵⁰ this invasive method is now interesting for historical purposes only.

Acid-Base Monitoring

Detection of acidemia during circulatory arrest as a marker of cerebral ischemia is critical. Two monitoring strategies predominate: α -stat and pH-stat.¹⁵¹ α -stat protocols are based on maintaining a constant pH at normothermia, or, rather, avoiding correction of the patient's measured pH during the normal increase that accompanies hypothermia. The decreased dissociation of hydrogen ions leads to an alkalosis, which results in reduced CBF and oxyhemoglobin unloading in tissue. As such, α -stat management maintains a relationship between cerebral metabolism and blood flow and may reduce microembolic injury.^{152,153}

In contrast, pH-stat monitoring maintains a constant pH at the patient's temperature, targeting a pCO₂ of 40 and pH of 7.4 by reduced sweep gas flow or the addition of CO₂ to the air intake. This produces a respiratory acidosis, cerebral vasodilation, and a decoupling of CBF from metabolic demand. Ultimately, this produces pressure-dependent cerebral perfusion, hyperemia, and edema.^{6,153}

While controversy persists and complex pH monitoring strategies exist, such as using pH-stat during periods of

circulatory arrest to improve perfusion of deep brain structures while using α -stat management otherwise,¹⁴ consensus^{154–156} generally favors α -stat management during adult cardiac surgeries for reasons including reduced postoperative acidosis,¹⁵⁷ improved metabolic suppression,¹⁵⁸ and improved cognitive function,¹⁵⁹ though pH-stat monitoring continues to be favored for pediatric operations.^{160,161}

Debates and Unknowns

Retrograde versus Antegrade Perfusion

Although ACP best approximates physiologic cerebral perfusion, may be especially useful with longer arrest times and greater operative complexity, and has been found efficacious in various intraoperative and postoperative measures,^{67,84,162–165} numerous individual studies and meta-analyses have found conflicting evidence, demonstrating similar, or even superior, outcomes with other strategies.^{76,86,166–171} A significant weakness of this body of literature is that the majority of studies to date have been retrospective and/or limited in the number of patients included.^{67,169,172} Additionally, improvements in techniques over time and lack of adequate controls make comparisons between studies difficult.^{86,167}

To date, there have been five publications regarding prospective, randomized trials to compare ACP and RCP.^{78,84,165,166,173} These are limited by small enrollment sizes (30–121 patients), describe variable outcomes, and have produced conflicting results. A high-quality, multi-institutional, randomized, controlled trial is needed to settle the debate, but the innumerable institutional-, surgeon-, and patient-specific factors make this an extraordinarily difficult study to design.

Depth of Hypothermia

It is unknown whether milder hypothermia provides adequate protection of the entire central nervous system and the visceral organs. While the evidence is promising,^{97–102} there remain significant concerns. A high-quality trial comparing the strategies is warranted, preferably one that includes major outcomes (mortality, PND, renal failure, etc.) along with serum biomarkers, transfusion requirements, and other outcomes measures that may better elucidate the differences between the strategies.

Cannulation

Innominate cannulation is a relatively recent approach to providing cerebral perfusion during ACP and may avoid the added time and potential for local injury with axillary cannulation.¹⁷⁴ Debate regarding its comparability to axillary cannulation followed, which led to the design of the ACE CardioLink-3 randomized trial. This prospective study will evaluate diffusion-weighted magnetic resonance imaging before and after elective proximal aortic arch surgery to identify new ischemic lesions and will likely be published this year.¹⁷⁵

Antegrade Flow Rate

As previously discussed, NIRS monitoring, possibly when combined with TCD, has demonstrated good CBF at flow rates

as low as 5 mL/kg/min.^{147,148} Using a porcine model of ACP using α -stat management, Halstead et al demonstrated that lower intracranial pressures may provide neurologic benefit, as measured by reduced post-CPB oxygen metabolism and neurobehavioral outcomes, compared with higher pressures.¹⁷⁶ Another porcine study suggested flow rates of 6 mL/kg/min as the ischemic limit in ACP.¹⁷⁷

Most prior studies have ranged from 250 mL to 1 L per minute, which is significantly higher than these thresholds and depends on the cannulation strategy, demonstrate similar outcomes throughout the range,^{93,125,139,156,178–183} though no meta-analysis of the topic has been conducted. It is possible that higher flow rates could contribute to arterial trauma and/or cerebral edema, so optimization of flow rates could further reduce rates of neurologic injury.

Acid–Base Management

While pH-stat and α -stat both offer relative advantages, most aortic surgeons prefer α -stat management to preserve autoregulation of CBF and to mitigate embolic risk.^{14,158,184} Though, pH-stat may improve subcortical perfusion during HCA.¹⁸⁵ However, no multi-institutional RCT has demonstrated a survival or neurologic benefit to one monitoring strategy over the other.

Electroencephalography

Although EEG is considered the gold-standard modality for intraoperative detection of cerebral electrical and metabolic suppression,¹³² its effects on outcomes in aortic arch surgery have not been studied nor has it been directly compared with other monitoring strategies. The advantage lies in detecting the true point of electrocerebral inactivity, which occurs over a large range of temperatures.¹⁸⁶ However, given the growing climate of cost-awareness in surgery, a cost-benefit analysis of EEG versus other monitoring strategies during aortic surgery may be warranted.

NIRS Standardization

There is no universal definition of abnormal NIRS readings during aortic arch surgery, though most studies define abnormal as a relative decrease of 20% or absolute saturation of <50%, which is borrowed from studies of carotid endarterectomy.¹⁴¹ Both animal and human studies of the appropriate cutoff values for NIRS are needed to better define what is significant desaturation.

Conclusion

The physiology of cerebral ischemia is a complex issue that is not completely understood, as evidenced by the lack of a definitive management strategy. While mannitol may have a role in reducing cerebral edema and short-term mortality, overall evidence for pharmacologic neuroprotection is weak. The various strategies for instituting CPB likely have their own appropriate indications, though axillary cannulation appears to provide superior outcomes to alternate strategies, and upcoming clinical trial data may provide a stronger argument for axillary cannulation in the institution of cerebral perfusion.

In circulatory arrest, four strategies predominate in the literature, DHCA, DHCA with either adjunctive RCP or ACP, and, most recently, MHCA with adjunctive ACP. However, the evidence does not clearly support one strategy over the others, especially given the lack of high powered, prospective, randomized, multi-institutional studies. Until these studies are performed, it is likely that uniform institutional strategy and a coherent, multidisciplinary approach to cerebral protection provides optimal clinical outcomes.

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