Brain protection in open arch surgery

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This review outlines the history of aortic arch surgery and examines classifications of hypothermia and mechanisms of perioperative neurological injuries. Risk factors for these neurological insults are explored, as well as cerebral monitoring systems available to mitigate such injuries. Furthermore, a comparative literature analysis evaluates outcomes among deep hypothermic circulatory arrest, retrograde cerebral perfusion, and antegrade cerebral perfusion. Finally, technical considerations for cerebral perfusion delivery and contemporary trends in temperature management are discussed.

Keywords: Aortic arch surgery; brain protection; antegrade cerebral perfusion (ACP); deep hypothermic circulatory arrest (DHCA); retrograde cerebral perfusion (RCP)

Submitted Mar 16, 2026. Accepted for publication Jul 28, 2026. Published online Jul 31, 2026.
doi: 10.21037/acs-2026-0072-aar
View this article at: https://dx.doi.org/10.21037/acs-2026-0072-aar

Introduction

As the number of open surgical and endovascular treatments for aortic arch lesions has increased, there has been a concomitant improvement in the outcomes of these interventions. However, further progress is required, particularly in high-risk cohorts such as elderly patients, those with a shaggy aorta, or those presenting with secondary cerebral malperfusion due to aortic dissection.

History of brain protection in aortic surgery

Methods for cerebral protection during aortic arch surgery were pursued by DeBakey and others even before the advent of cardiopulmonary bypass (CPB). Initial approaches relied on extra-anatomical bypass grafting to isolate the cerebral circulation prior to the integration of CPB (1). Although antegrade pulsatile cerebral perfusion under normothermic conditions theoretically offers optimal neuroprotection, early experience with antegrade cerebral perfusion (ACP) during the 1960s and 1970s was hampered by unsatisfactory clinical outcomes.

In 1950, Bigelow and colleagues introduced the concept of whole-body hypothermia by surface cooling and proposed applying this method to cardiac surgery (2). Using surface cooling, Lewis and associates reported successful repair of an atrial septal defect in a 5-year-old girl in 1953, and in the same year, Gibbon successfully performed the first open heart surgery using the CPB machine in an 18-year-old girl with an atrial septal defect (3,4). Asano *et al.* first reported a successful ACP in repairing the atrial septal defect in 1956 (5).

Use of hypothermic circulatory arrest (HCA) in combination with CPB in adults was first reported by Barnard and associates in 1963. Two patients with aneurysms of the ascending aorta and aortic arch underwent replacement of the aortic segments using hypothermia of 10 ℃ during circulatory arrest (6). In 1964, Borst and colleagues reported successful repair of an arteriovenous fistula involving the aortic arch using a brief period of HCA (7). In 1969, Lillehei and colleagues reported use of partial CPB, HCA, and circulatory arrest for managing ruptured mycotic aneurysms (8). The first series of patients with aneurysms of the aortic arch that were successfully resected during profound HCA was reported by Griepp and colleagues in 1975 (9).

Ueda *et al.* first reported that retrograde cerebral perfusion (RCP) provides a new approach that can augment cerebral protection during circulatory arrest (10). In our previous experience, RCP is clearly effective in

maintaining cerebral hypothermia, and preventing air from reaching the terminal vessels of the brain (11). Coselli *et al.* reported that patients who had RCP during deep HCA had a lower mortality and stroke rate than those who did not undergo deep HCA (DHCA) with RCP among their 479 patients (12). Safi *et al.* demonstrated that the use of RCP had a protective effect against stroke (13).

On the other hand, Frist *et al.* revived the concept of ACP and reported 90% survival after arch replacement using unilateral ACP under moderate hypothermia in 1986 (14). In 1989, Bachet *et al.* described the "cerebroplegia" method as cold ACP (15). Kazui *et al.* demonstrated ACP using a four-branched graft technique and reported no neurological sequelae and three early deaths in 32 patients with arch aneurysm (16). Nowadays, ACP has become the standard method of brain protection in complex aortic arch surgery.

Definition of hypothermia

There has been expert consensus regarding the grade of hypothermia, with profound hypothermia defined as ≤14 ℃, deep hypothermia as 14.1–20 ℃, moderate hypothermia ranges as 20.1–28 ℃ (low-moderate hypothermia 20.1–24 ℃, high-moderate hypothermia 24.1–28.0 ℃), and mild hypothermia as 28.1–34 ℃ (17). Most clinical studies of the relationship of temperature to the safety of a given circulatory arrest time are flawed by a lack of information about the temperature of the brain itself and by the variety of sites of temperature measurement (18). The temperature of the tympanic membrane and nasopharynx most closely resembles the mean temperature of the brain; however, a general consensus was made to use the rectal temperature as the core temperature.

Temperature and duration

Both experimental and clinical evidence indicate that a 45-minute arrest period is safe for at least 70% of subjects (17). Any damage occurring within this timeframe is typically structural and does not lead to permanent functional impairment. Most patients exhibit structural evidence of damage from 60 minutes of arrest, but only about 10% to 20% had evident functional damage, which was transient. Svensson *et al.* evaluated 656 patients after aortic surgery using DHCA and concluded that the occurrence of stroke was observed to increase after 40 minutes of circulatory arrest, and the mortality rate increased markedly after 65 minutes of circulatory arrest (19). Coselli and colleagues found no clinical evidence of brain damage attributed to HCA (mean nasopharyngeal temperature 16.9 ℃; range, 10.1–24.1 ℃) in 56 patients with arrest times ranging from 14 to 109 minutes (median 36 minutes) (12). In contrast, Gega and colleagues, in a study of 394 patients undergoing aortic arch replacement, reported 8 strokes [13%; confidence limit (CL): 8.6–18%] among 61 patients in whom the duration of HCA exceeded 40 minutes. Only 10 strokes (3.3%; CL: 2.3–4.3%) occurred among the remaining 333 patients with shorter intervals of circulatory arrest (20). The arch-first technique using a branched arch graft with a shorter period of HCA proposed by Spielvogel and associates became a popular procedure when RCP was applied during total arch replacement (21).

However, the higher prevalence of transient neurological deficit indicated the need for caution against liberal use of RCP. Hagle *et al.* reported that the incidence of TND increased if the duration of RCP exceeded 25 minutes and that longer ACP increased TND incidence as well (22). Ergin and associates reported that TND can occur in up to 20% of survivors of operations on the thoracic aorta where HCA is used. Incremental risk factors associated with developing this complication are duration of HCA and increasing patient age (23). Prevalence of temporary neurologic dysfunction increases substantially among patients in whom the duration of circulatory arrest exceeds 60 minutes. Our data indicated that patients who had a duration of RCP over 40 minutes in arch surgery had over 25% incidence of postoperative delirium (11).

Definition of cerebral complication

Studies of brain injuries following aortic arch surgery demonstrate marked heterogeneity in definitions. Terminology ranges from broad descriptors like "postoperative brain damage" and "cerebral complications" to specific classifications distinguishing focal from non-focal injuries, permanent from temporary dysfunction, and clinical presentations such as stroke, coma, hemiplegia, and neurocognitive deficits. The neurologic complications associated with aortic arch surgery historically have been categorized as permanent neurologic dysfunction and temporary neurologic dysfunction. Taylor and associates reported that incidence rates for stroke are around 2% to 3%, with increased risk in elderly patients and other high-risk groups (24). This relatively low incidence of what is

Table 1 Risk factors for hospital mortality

Variables	Hazard ratio	P value
Age (years)	1.08	<0.001
eGFR (mL/min/1.73 m^2)	0.98	0.012
Organ malperfusion	5.13	0.009
CPB time	1.01	0.002

CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate.

universally recognized as a serious complication may be contrasted with the much higher reported incidence of cognitive defects assessed by neuropsychological testing. The incidence of cognitive defects is as high as 60% at 8 days postoperative, with a reduction to 25% to 30% incidence at 8 weeks and 12 months. There are a variety of mechanisms by which the brain may be injured during an operation with CPB, including reduced cerebral blood flow, micro-embolism and macro-embolism, and a systemic inflammatory response.

High-risk patients of cerebral complications after arch surgery

Shaggy aorta is a severe arteriosclerotic state first described by Hollier and colleagues in 1991 as widespread, very atheromatous lesions in the aorta (25). It is characterized by sparse mural thrombi, but extensive, protuberant, irregular-surfaced atheromas. Diagnosis is mainly made by contrast-enhanced CT scans. Several grading systems of the aortic shagginess were proposed, including the thickness of the atheroma and the area or length of the lesions. We reported that highly shaggy lesions in the aortic arch or in the thoracoabdominal aorta have been identified as a risk factor for adverse neurological outcomes of the brain or spinal cord (26).

Leukoaraiosis is a patchy, punctate, or confluent hyperintensity in the white matter and deep gray nuclei on a T2-weighted image. This white matter hyperintensity reflects chronic ischemic damage to myelin and axon (27). Several studies demonstrated that there is a significant relationship between increased stroke risk and leukoaraiosis.

Between October 1999 and March 2018, we performed 665 total arch replacements at Kobe University (28). Three hundred ninety-nine patients had non-dissecting arch aneurysms, 149 had acute aortic dissection, and 107 had chronic dissection. Mean age at operation was 73.6±0.4 years, and the JapanSCORE for early mortality was 8.1%±8.4%. Six hundred and six patients had ACP, and 59 patients had circulatory arrest with RCP as a brain protection method. The CPB time, cardiac ischemia time, ACP time, and circulatory arrest of the lower body time were 193±68, 93±47, 101±39, and 44±17 minutes, respectively. Hospital mortality was 5.2%, 4.5%, 9.4%, 1.9% in the overall cohort, non-dissection cohort, acute dissection cohort, and chronic dissection cohort, respectively. Postoperative PND occurred in 3.7%, 2.5%, 8.7%, 0.9% in the overall cohort, non-dissection cohort, acute dissection cohort, and chronic dissection cohort, respectively. Postoperative TND occurred in 9.8%, 9.5%, 12.8%, 6.5% in the whole patient population, non-dissection population, acute dissection population, and chronic dissection population, respectively. Significant risk factors on multivariable analysis for hospital mortality included higher age at operation, low estimated glomerular filtration rate (eGFR), patients with organ malperfusion syndrome, and longer CPB time (*Table 1*). Risk factors for PND included severe white matter change by brain MRI, patients with shaggy aorta, and longer CPB time (*Table 2*); risk factors for TND included shaggy aorta, significant stenosis in the carotid artery, moderate or severe white matter change, and longer CPB time (*Table 3*). Five-year survival at 5 and 10 years was 73%±2% and 54%±3%, respectively, which was inferior to that of the matched normal Japanese population (*Figure 1*). Significant risk factors for late mortality were higher age at operation, low eGFR, patients who had concurrent other procedures, occurrence of PND, patients who required tracheostomy, and occurrence of acute kidney injury at operation (*Table 4*). Long-term survival was clearly stratified by preoperative renal function (*Figure 2*) (29), and a similar trend was found in accordance with preoperative respiratory function (*Figure 3*).

Table 2 Risk factors for PND

Variables	Hazard ratio	P value
Severe WMC	7.6	0.01
Shaggy aorta	7.6	0.02
CPB time	1.01	0.01

CPB, cardiopulmonary bypass; PND, permanent neurological dysfunction; WMC, white matter change.

Table 3 Risk factors for TND

Variables	OR	P value
Shaggy aorta	4.4	0.026
Carotid artery disease	5.5	0.01
WMC ≥ moderate	3.62	0.05
CPB time	1.02	0.008

CPB, cardiopulmonary bypass; OR, odds ratio; TND, transient neurological dysfunction; WMC, white matter change.

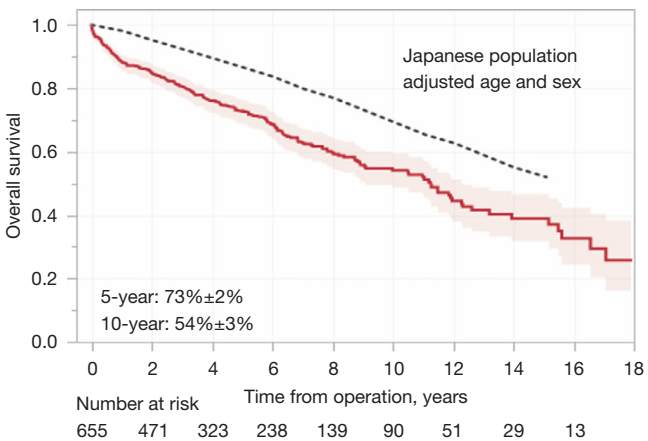


Figure 1 Overall survival of patients who underwent total arch replacement with four-branch graft.

Table 4 Risk factors for late mortality

Variables	Hazard ratio	P value
Age (years)	1.06	<0.001
eGFR (mL/min/1.73 m^2)	0.98	<0.001
Concurrent procedures	1.47	0.043
Permanent neurologic deficit	3.31	<0.001
Tracheostomy	2.38	<0.001
Acute kidney injury	2.53	<0.001

eGFR, estimated glomerular filtration rate.

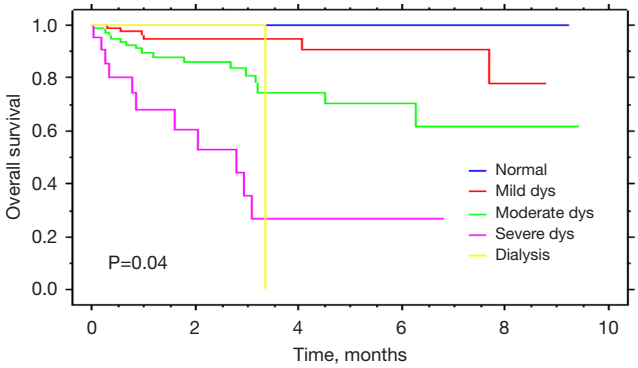
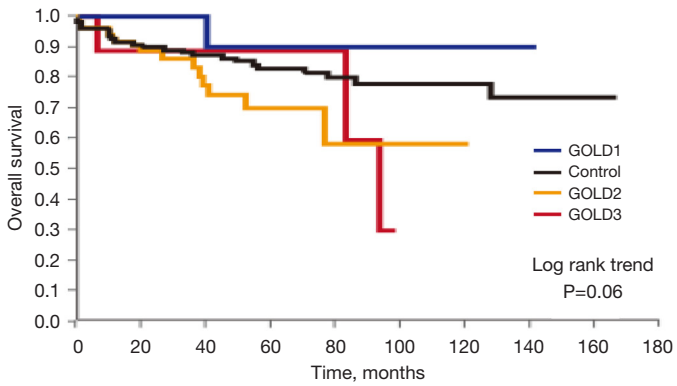


Figure 2 Survival stratified by preoperative renal dysfunction. dys, dysfunction.



Number at risk

	Control	169	120	92	73	49
GOLD1	Mild	21	16	12	5	4
GOLD2	Moderate	52	36	27	13	6
GOLD3	Severe	18	13	6	4	3

Figure 3 Survival stratified by COPD, GOLD classification. COPD, chronic pulmonary obstructive disease; GOLD, Global Initiative for Obstructive Lung Disease.

Monitoring

Transesophageal echocardiography (TEE) and epiaortic echo

TEE is an essential tool for monitoring cardiac function and detecting intracardiac air bubbles. The epiaortic ultrasound is routinely used to identify aortic atherosclerotic plaques and wall calcifications to determine optimal aortic cross-clamping and cannulation sites.

Arterial pressure

Multiple arterial lines are required, especially during circulatory arrest with ACP. Ideally, bilateral radial artery pressure and an arterial line in the lower body are monitored, and the perfusion line pressure of the ACP is also monitored. The optimal mean arterial pressure (MAP) is typically the same as routine CPB except for patients with intra- or extra-cranial arterial obstructions.

Electroencephalography (EEG)

Ideally, electrocerebral silence on EEG indicates minimal cerebral metabolic demand. However, the duration of cooling required to reach electrocerebral silence is variable in adult aortic surgery. More than 30% of patients exhibited brain activity on EEG even at a temperature of 18 ℃. Another limitation of EEG is that it monitors only the superficial layers of the cerebral cortex; ischemia in deep brain regions, including the subcortex, is undetected. Many

factors can affect the sensitivity of EEG in detecting brain ischemia, including prior cerebral ischemia, anesthetic medications, hypothermia, CPB, and electrical cautery. Furthermore, EEG interpretation is subjective in nature. As such, EEG monitoring is less used in clinical settings nowadays except for special pediatric cases (30).

Bispectral index (BIS)

The BIS is a simpler and an easier processed EEG monitor; however, this modality is mainly used for detecting intraoperative awareness and depth of anesthesia, not for the prediction of brain ischemia and embolism, for the same reasons as the EEG.

Transcranial Doppler (TCD)

TCD is used to measure blood flow in the middle cerebral artery and can be used to optimize ACP during circulatory arrest, especially in patients who have an incomplete circle of Willis. However, TCD measurement requires a sonographer's expertise and depends on the images acquired through a small window. TCD is a very sensitive tool for detecting arterial embolism during cardiac surgery; however, it is usually too late to intervene (31).

Near-infrared spectroscopy (NIRS)

NIRS can determine the regional cerebral oxygen saturation by measuring the different absorptive properties of saturated and unsaturated hemoglobin (Hb) in the near-infrared spectrum (600–900 nm). The definition of cerebral desaturation in cardiac surgery has been a decrease in regional cerebral oxygen saturation of over 20% from baseline or a decrease below 50%. NIRS has several limitations, as it primarily monitors the anterior brain with a maximal depth of 1 to 2 cm. Usually, NIRS monitors assume a fixed distribution of blood volumes between arterial and venous blood (25–30% arterial to 70–75% venous) and variability in arteriovenous blood distribution is ignored. NIRS is not accurate for cerebral oxygenation during circulatory arrest with RCP. Like other brain monitoring, the NIRS measurements vary according to the regional cortical blood oxygen content, cerebral metabolic rate, and cerebral blood flow, temperature, hemodilution, partial pressure of oxygen and partial pressure of carbon dioxide. No randomized clinical trials have shown superiority of using NIRS, and there has been no data to support a threshold level or duration of NIRS-detected brain hypoxia that can be tolerated without detrimental neurologic events (32).

Avoiding brain embolism

One of the major causes of newly developed post-operative stroke is emboli originating from atherosclerosis and thrombi at sites of aortic clamping, vascular anastomosis, and aortic or cerebral perfusion cannula (33). Meticulous search for atheroma or thrombi of the aorta using CT, echocardiogram, or intra-operative direct echocardiogram, can provide important information for selecting the sites of cannulation and clamping. In an experimental study, Fukuda *et al.* confirmed that directing the cannula tip toward the aortic root generated slower and less turbulent flow in the transverse arch of glass models of both healthy and aneurysmal aortic arches (34). Sometimes the atheromatous aorta precludes cannulation in the ascending aorta, and peripheral arterial cannulation from the axillary artery or femoral artery is selected. However, axillary arterial cannulation sometimes causes atheroemboli from an atheromatous lesion at the orifice of the brachiocephalic artery. Moreover, retrograde embolization by debris from femoral artery cannulation is a well-recognized phenomenon.

French reports indicated that the majority of permanent neurologic injuries were due to strokes resulting from embolic phenomena and were not directly related to the method of brain protection (35). Computed tomographic scans demonstrated that 62% of these strokes were embolic in origin and 38% were related to hypoperfusion. In an autopsy study, Amerenco and associates reported that the prevalence of ulcerated plaques in the aortic arch was 28% in 183 patients with cerebral infarcts and 20% of 56 patients with brain hemorrhage (36). Blauth and associates demonstrated a direct correlation between age, severe atherosclerosis of the ascending aorta and atheroemboli (33). Our previous data showed that the prevalence of atheroma or ulcerative plaques was most prevalent at the anterior of the aortic arch, concentrated around the root of the arch vessels (37).

Wareing *et al.* modified their technique for cardiac procedures according to intraoperative echography, including alterations in the site of aortic cannulation, aortic clamping, attachment of the vein grafts, and cannulation for infusion of cardioplegia, or even performed HCA without clamping the aorta (38). Manipulation of the atheromatous

aorta should be avoided to prevent atheroembolism.

Shiiya and colleagues proposed a strategy of avoiding cerebral athero-emboli during CPB and ACP in such patients by performing early isolation of the arch vessels (39). They started ACP from the right and left axillary, and direct left common carotid artery perfusion before starting the systemic perfusion.

ACP *vs.* deep HCA/RCP

Many studies, including randomized trials or meta-analyses, showed that ACP provided superior neurological outcomes compared to DHCA (27,40-58). Bilateral ACP achieved the lowest pooled disabling stroke rate, and the neuroprotective advantage of ACP increased with longer circulatory arrest durations. Operative mortality was driven primarily by patient-specific factors (e.g., acute dissection, age) rather than the choice of perfusion technique, which showed inconsistent mortality benefits. For shorter circulatory arrests (<20 minutes) in hemiarch repairs, contemporary DHCA at 20–24 ℃ provides adequate cerebral protection with acceptable outcomes. However, for total arch replacements, complex repairs requiring prolonged arrest times (>30 minutes), or acute type A dissections, ACP offers superior neuroprotection with maintained cerebral oxygenation at moderate hypothermia.

The most important advantage of ACP is that it provides the luxury of time, allowing for deliberate repair of complicated arch aneurysms. However, there have been several criticisms of ACP, including the longer time required for arch repair, as well as cannulation-origin embolism, and uneven distribution of intracranial blood flow. Di Eusanio *et al.* (40) demonstrated that ACP of >90 minutes is not associated with an increased risk of mortality or a negative neurological outcome. Girardi and colleagues reported that in 879 patients who underwent arch replacement (671 hemiarch, 208 total arch replacement) with DHCA (18 ℃) with RCP, the total arch patients had longer duration of DHCA (39 *vs.* 21 minutes, P<0.001) and RCP (37 *vs.* 19 minutes, P<0.001). However, the incidence of TND (3.0% *vs.* 2.4%) and PND (1.3% *vs.* 1.9%) was similar for both techniques (46). Mortality was greater in the hemiarch group (4.8% *vs.* 0.5%). Leontyev and colleagues reported that the ACP was associated with a significant reduction in in-hospital mortality and occurrence of PND, even in three-quarters of 925 patients who underwent hemiarch grafting (42).

There have been few randomized comparative studies and many retrospective studies comparing DHCA and ACP. We evaluated 60 consecutive total arch replacements allocated randomly to DHCA or ACP and concluded that both DHCA and ACP resulted in acceptable levels of mortality and morbidity, but the prevalence of TND was significantly higher with DHCA (43). Hagl *et al.* retrospectively analyzed the outcomes among 717 survivors of ascending and aortic arch surgery and determined that the method of brain protection did not influence the incidence of stroke; however, ACP did result in a significantly reduced the incidence of TND (22). Svensson *et al.* analyzed postoperative neurocognitive function and serum s-100 proteins in a prospective randomized manner and found essentially no differences among the ACP, DHCA, and DHCA/RCP groups (59). Hage also reported an additional randomized study that in 121 patients who underwent total arch replacement using RCP (n=60) or ACP (n=61) brain perfusion during HCA (50). Thirty-day mortality was 0.8% (1/121), and clinical stroke was evident in 1 patient (0.8%). A similar prevalence of neurologic events after RCP and ACP (22/60, 37% and 15/61, 25%, respectively) was noted. A meta-analysis of 5,060 patients in 15 studies by Hu *et al.* disclosed that the incidence of postoperative stroke and TND were similar between ACP and RCP (60). Another meta-analysis by Tian *et al.* revealed that stroke rates were significantly lower in patients undergoing ACP compared with those in patients who had DHCA (58). We extracted data from 8,169 patients who underwent elective surgery of the total aortic arch replacement from 2009 to 2012 using the Japanese Adult Cardiovascular Database, and compared clinical outcomes of patients who had ACP and RCP (52). Mean age at surgery was 70.5±10.1 and 68.3±11.6 years, respectively. In this patient cohort, 86.0% of all patients had ACP, and 14.1% had DHCA +/– RCP. A propensity-matched analysis of 1,141 patients showed that there was essentially no difference regarding post-operative survival or neurological outcome, except for prolonged ventilation time and ICU stay in the RCP group. The Canadian multi-center (the Canadian Thoracic Aortic Collaborative) in 2,520 patients who underwent aortic arch repair with HCA between 2002 and 2018 in 11 centers disclosed that ACP was found to be protective against mortality, stroke, and composite outcomes, as compared with HCA alone (51). RCP yielded similar outcomes as compared to ACP.

Cerebral perfusion flow rates during ACP

Cerebral perfusion flow rate and pressure have been

extensively investigated by means of animal experiments and by clinical experience. Early perfusion protocols were complicated by cerebral over-perfusion, as the maintenance of physiologic normothermic flow rates (1,000–1,200 mL/min) induced cerebral edema. Soma and associates set different flow rates for each arch vessel as 11.2, 8.5, 7.0, and 3.9 mL/kg/minutes in the right axillary artery, right common carotid artery, left common carotid artery, and left subclavian artery, respectively (61). Kazui and colleagues standardized the amount of brain perfusion as the ACP flow was maintained at 10 to 15 mL/kg/min and pressure at 50 mmHg (41). Bachet and colleagues set a lower flow (400 to 500 mL/min) and higher pressure (70 mmHg) at lower core temperature (10 to 12 ℃) (15). Kuwabara (62) and Matsuda (63) independently found that adequate brain perfusion flow was 10 to 15 mL/kg/min, measuring jugular or caval venous oxygen saturation.

Bilateral or unilateral perfusion

Controversies still exist regarding the use of unilateral brain perfusion, bilateral perfusion, or triple perfusion, as patient cohorts in most clinical studies comprise a mixture of hemiarch and total arch replacements (*Table 5*). Urbanski *et al.* using only one cannula to perfuse the whole brain, reported a low incidence of postoperative stroke (64). Many surgeons perfuse only the brachiocephalic and left common carotid artery, omitting the left subclavian artery. However, the incompleteness of the circle of Willis has been reported as 20% to 30% in the normal population, and sometimes the vertebral arteries are hypoplastic or stenotic, especially in elderly patients. Additionally, the left subclavian artery is often a supplier of the collateral vessels to the spinal cord. We have always used three cannulae, which were inserted into each arch vessel from inside the arch without snaring. A meta-analysis of ACP by Angeloni *et al.* demonstrated that the superiority of bilateral brain perfusion was greater as the time of brain perfusion increased than that of unilateral perfusion (65). Another meta-analysis of 222 studies of brain protection in aortic arch surgery assessed outcome differences between the perfusing options (57). A total of 43,720 patients were included, 38% of patients had acute aortic dissection, and 40 % had total arch replacement. Postoperative early mortality was 6.6%, 9.1%, 7.8%, 9.2% in the unilateral ACP, bilateral ACP, RCP and DHCA groups, respectively. The incidence of postoperative stroke was 4.8%, 7.3%, 6.4%, 6.3% in unilateral ACP, bilateral ACP, RCP and DHCA groups, respectively. A functional assessment of the circle of Willis using the TCD disclosed that the risk of ischemic brain damage due to malperfusion is estimated to be substantially higher during right unilateral ACP than during bilateral ACP.

Warmer body temperature

Contemporary clinical practice has shifted away from utilizing deep hypothermia as the target systemic temperature during ACP. Deep hypothermia tends to be associated with more coagulopathy and lung injury. However, mild hypothermia is not adequate for the protection of the brain, spinal cord, and viscera, especially when unilateral ACP is applied. The optimal core temperature in the setting of ACP has been reported to be between 20 and 28 ℃. Kamiya *et al.* reported that the temperature during HCA could be safely increased to 28 ℃ with a high ACP flow rate, and that the incidence of neurological events was not increased (66). In our experience, the lowest temperature was between 20 and 23 ℃, and CA and ACP duration was 42.4±27.8 and 97.3±31.4 minutes, respectively (27). In addition, careful attention must be paid to protecting the spinal cord and visceral organs during circulatory arrest of the lower body under moderate hypothermia or normothermia. A Canadian multi-center study showed that a propensity score analysis of 647 matched patients who had arch surgery identified nadir temperature >24 ℃ as a predictor of lower mortality, stroke, composite of mortality or stroke and composite outcomes (50). A meta-analysis consisting of nine comparative studies to analyze postoperative outcomes in arch surgery using DHCA or moderate HCA disclosed that the stroke rates were significantly lower in patients undergoing MHCA + ACP, while comparable results were observed with TND, mortality, renal failure or bleeding (60).

Uneven cooling of the brain is likely a risk factor for brain damage, although evidence is largely indirect. However, the damage might be related to the shorter period of cooling with cold blood, resulting in uneven brain cooling. Luehr and colleagues noted a considerably higher prevalence of major neurologic events after circulatory arrest when core cooling by CPB alone was used, compared with surface cooling first to 28 ℃, followed by core cooling (67). A reasonable presumption is that more rapid core cooling resulted in uneven cooling of the brain. We always take at least 15 to 20 minutes to cool the patients until the target temperature is reached. Additional application of the brain cooling jacket is a useful adjunct.

Table 5 Arch replacement

Author	Study period	Center	Number	Dissection	Emergent/urgent	Hemiarch	TAR	Brain protection	Lowest temperature (℃)	TND (%)	PND (%)	Mortality (%)
Di Eusanio (39)	1995–2001	Nieuwegein	413	116 (28%)	125 (30%)	214	138	Bi ACP	22–26	5.1	3.7	9.4
Kazui (40)	1986–2001	Hamamatsu	330	89 (27%)	99 (30%)	0	330	Bi ACP	22	4.2	2.4	11.2
												(1997–2001: 3.2)
Okita (42)	1997–1999	Osaka	60, prospective	O	o	0	60	Bi ACP: 30	20–25	13.3	6.6	6.6
								RCP: 30	18	33.3	3.3	6.6
Leontyev (41)	1995–2014	Leipzig	925	69 (7.7%)	185 (20%)	715	210	ACP 701 (Uni 184, Bi 517)	28	9.8	6.0	4.4
								RCP/CA: 224	23	11.2	17.9	9.4
Hagl (21)	1986–1999	Mt Sinai	717	322 (14%)	259 (36%)	569	145	DHCA 588, RCP 43, ACP 86	10–13	11.2	5.5	10.1
Shimizu (43)	2001–2011	Tokyo	203	69 (34%)	45 (22.2%)	0	203	Bi ACP	25–26		2.5	3.9
												(elective: 1.9)
Minatoya (44)	2001–2015	Osaka	1005	230 (22.8%)	252 (25.7%)	0	1,005	Bi ACP	<25 (47.5%)	6.4	3.6	5.2
									25–28 (52.5%)			
Ikeno (26)	1999–2016	Kobe	655	256 (39%)	209 (32%)	0	655	Bi ACP	23.5 (tympanic)	8.7	3.7	5.2
									26.9 (rectal)			(elective: 2.1)
Girardi (45)	1997–2013	Cornell	879	198 (25%)	346 (51.6%)	671		RCP	18	3	1.3	4.8
				28 (13.5%)	74 (35.6%)		208			2.4	1.9	
Ahmed (46)	2000–2015	Frankfurt	587	219 (37%)		386	201	Uni ACP: 393	28	5	6	6
								Bi ACP: 194				
Khullar (47)	2003–2014	Rochester	567		88 (20.5%)	429		ACP: 51	19	2.6	2.8	4
					41 (31%)		129	ACP: 93		3.9	2.4	5.4
Preventza (48)	2005–2014	Houston	665	0	0	479	186	Uni ACP: 165	20–24	3.9	2.4	5.1
								Bi ACP: 500	24–28			
Svensson (49)	2003–2010	Cleveland	121, RCT	0	0	0	121	ACP: 61	<20	24	0.8	0.8
								RCP: 60				
Hage (50)	2002–2018	Canada, multi-C	842, matched	422	428	637	62	ACP: 421	18–25	3.2	8.1	10.2
								RCP: 421		5.6	11.9	13.6
Okita (51)	2009–2012	Japan, multi-C	2282, matched	0	0	0	2,282	ACP: 1,141	24.2	4.4	8.6	7.1
								RCP: 1,141	21.2	4.1	6.7	6
Kamenskaya (52)	2011–2012	Novosvirsk	58, RCT					ACP: 29	23–24	13.7	6.8	
								RCP: 29		37.8	17.2	
Matalanis (53)	1996–2000	Melboune	62					DHCA: 14				8.0
								RCP: 23				
								ACP: 25			8.0%	6.4

Table 5 (*continued*)

Table 5 (*continued*)

Author	Study period	Center	Number	Dissection	Emergent/urgent	Hemiarch	TAR	Brain protection	Lowest temperature (℃)	TND (%)	PND (%)	Mortality (%)
Di Eusanio (54)	1996–2013	Bologna	623	289 (46%)	240 (39%)	282	335	Bi ACP	24.5	8.2	6.9	15.1
Hameed (55)	2020 (published)	NA	26,968 (meta-analysis)					ACP				0.63
								DHCA				1
								RCP				0.66
Abjigitova (56)	2021 (published)	NA	45,720 (meta-analysis; 222 studies)					Uni ACP	25.8		4.8	6.6
								Bi ACP			7.3	9.1
								RCP			6.4	7.8
								DHCA			6.3	9.2
Tian (57)	2013 (published)	NA	1,018 (meta-analysis)					ACP: 370				
								DHCA: 648				
Hu (59)	2013 (published)	Wuhan	5,060 (meta-analysis)					ACP: 2,855		7.5	7.2	5.2
								RCP: 1,897		8.7	4.7	5.2

ACP, antegrade cerebral perfusion; Bi, bilateral; CA, circulatory arrest; DHCA, deep hypothermic circulatory arrest; NA, not applicable; PND, permanent neurological dysfunction; RCP, retrograde cerebral perfusion; RCT, randomized clinical trial; TAR, total arch replacement; TND, transient neurological dysfunction; Uni, unilateral.

The effect of rewarming on cerebral metabolism after HCA has not been elucidated in the literature. In our study (68), rewarming speed affected the severity of TND among patients who had postoperative TND. Regional SO2 was significantly decreased during the early rewarming phase in the patients with postoperative TND. Rungatscher and associates, showed a delay in return of cerebral metabolic rate for oxygen to baseline values during rewarming after moderate hypothermic CPB, in contrast to the very prompt recovery of cerebral blood flow (69). This phenomenon indicates the correlation between cerebral desaturation during the early rewarming phase and cerebral damage. Proposed re-warming speed should be less than 0.1 ℃/minutes; however, our recent data suggested that slower rewarming (<0.08 ℃/minutes) is accompanied by worse neurological outcomes.

Acknowledgments

None.

Footnote

Funding: None.

Conflicts of Interest: The author has no conflicts of interest to declare.

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Cite this article as: Okita Y. Brain protection in open arch surgery. Ann Cardiothorac Surg 2026;15(4):48. doi: 10.21037/acs-2026-0072-aar