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SPECIAL EDITION

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Brain protection in aortic arch aneurysm: antegrade or retrograde?

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Abstract
During open aortic arch repair, there is an interruption of cerebral perfusion and to prevent neurological sequelae, the hypothermic circulatory arrest has been established to provide sufficient brain protection coupled with adjuncts including retrograde and antegrade cerebral perfusion. To date, brain protection during open aortic arch repair is a contested topic as to which provides superior brain protection with little evidence existing to suggest supremacy of one modality over the other. This article reviews current literature reflecting on key and emerging studies in brain protection and their associated outcomes in patients undergoing open aortic arch surgery.

Keywords Aorta · Aneurysm · Cerebral perfusion · Brain protection · Aortic arch · Circulatory arrest · Thoracic aortic surgery

An overview of the history of aortic arch surgery and brain protection

The first documented human total aortic arch repair was performed as early as 1955 by the Dr Denton Cooley [1], who used a combination of hypothermia and temporary shunts to accomplish a degree of hypothermia. However, despite the measures to protect the brain during surgery, the patient developed post-operative stroke. In 1975, Dr Griepp published a case series of 4 patients who underwent successful aortic arch aneurysms repair with hypothermia using a combination of surface cooling and cardiopulmonary bypass [2]. However, following this key study, it was further recognized that hypothermia alone for brain protection still led to a high incidence of stroke and this led to the development of antegrade cerebral perfusion (ACP) and retrograde cerebral perfusion (RCP) which are used as adjuncts to DHCA today.

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Brain protection during aortic arch surgery

There are three main methods to protect the brain, either with deep hypothermic circulatory arrest alone or additive of adjuncts such as antegrade cerebral perfusion (ACP) or retrograde cerebral perfusion (RCP); nevertheless, the optimal method for brain protection remains controversial and disputed [3]. The reported incidence of neurological complications following aortic arch surgery ranges between 3–16%, because the nervous tissue has a high susceptibility to ischaemic injuries [4].

Deep hypothermic circulatory arrest safety

Deep hypothermic circulatory arrest (DHCA) is a technique where body temperature is cooled down to as low as 18 °C to preserve organ function and reduce metabolic demand [2–4]. The efficacy and safety of such circulatory arrest are limited; it is likely of no more than 45 min at 10 °C, especially in elderly people [5]. It has been demonstrated that any duration of hypothermic circulatory arrest more than 25 min is associated with increased risk of transient neurologic and fine motor deficits [6]; however, Griepp et al. demonstrated that such adverse outcomes occur only when the duration of HCA exceeds 60 min [5]. A study by Percy et al. [6] which included 394 patients who underwent ascending and aortic

arch repair, concluded that patients with HCA time of over 40 min experienced a higher rate of stroke (13.1%). Similarly, an increased rate of neurological complications has been demonstrated by Di Eusanio et al. [7] and Sakamoto et al. [8] when the duration of DHCA exceeds 25 min. Yet, with all these studies, there is no consensus about the exact cut off time for DHCA especially in the presence of adjuncts of ACP and RCP.

Temperature controversy

In the present time with the presence of many single centre experiences of using various temperature methods ranging from mild to deep HCA, there is a lack of high quality published evidence in the literature to support the use of any degrees during HCA except the DHCA [9, 10]. Majority of the moderate hypothermic circulatory arrest (MHCA) and Mild HCA studies are not considered as high clinical evidence and they do not qualify to be used as a strong base for building a standard protocol for practice. In two large studies by Svensson et al. [11] and Gega et al. [10], they have reported an acceptable rate of mortality at 6.1 and 6.13%, respectively; after using DHCA with ACP or RCP in complex aortic surgery patients, such reports have been boosted in 2010 when Milewski et al. [12] published their study of 682 patients who underwent DHCA for complex aortic surgery and reported a mortality and stroke rate of 2.8%. On the other hand, the use of a lesser degree of hypothermia is based purely on evidence from experienced centres and lack of any randomized trial; however, such data demonstrated the successful use of such method only together with adjuvant use of ACP [13–16].

Delivery mechanism

Retrograde cerebral perfusion

Retrograde cerebral perfusion (RCP) came to prominence during the early 1990s [17, 18] although it was intermittently used during the early 1980s [19, 20]. The first reported use of retrograde cerebral perfusion was 1980 by Mills and Ochsner [19] who used this technique to successfully treat air embolism during cardiopulmonary bypass. Shortly after, Lemole et al. in 1982 [19] reported the use of intermittent RCP every 20 min during HCA for a patient with acute type A aortic dissection. Importantly, the clinical use and advantages of using RCP have been extensively studied both in humans and at experimental levels to evaluate the efficacy of using RCP in protecting the brain during HCA. Based on the results and outcomes of such studies, RCP became a recognized cerebral protection adjunct in aortic arch surgery [21–23].

RCP is performed with the retrograde perfusion of the brain through the venous system initially via the superior vena cava and later the cerebral microvasculature. Its main advantages are the ability to maintain cerebral hypothermia during HCA as well as the removal of emboli from the arterial circuit [18].

Considerations to pressure include provision of a good flow through the jugular veins enough to give perfusion of the brain including both the opening and maintaining pressure. Safi and colleagues in 2013 [24] reported that the standard flow of 500 cc/min at a jugular pressure between 15 and 25 mmHg is not adequate to provide enough cerebral protection, as it was practiced before, and therefore an opening pressure of 31 mmHg is required to establish the flow to overcome the jugular venous valves and the capacitance vessels [24, 25], while the required pressure thereafter to maintain the flow to its regular rate to be between 15 and 25 mmHg [24, 26].

A large series by Estrera et al. [27] published in 2008 included 1107 cases; of these, RCP was used in 82% of cases, while ACP combined ACP and RCP, or DHCA alone were used in the remaining 18% of the cases; they reported a mortality rate of 9.9% and stroke rate of 2.7% using RCP with a flow rate of below 500 cc/min and maintaining the pressure in superior vena cava of below 25 mm Hg. RCP was the only independent factor in protecting against both stroke and early death.

In 1996, Ueda et al. studied 249 patients who underwent aortic arch surgery using HCA and RCP as a routine adjunct and the hospital mortality was 10%; RCP time contribution for mortality and neurological deficits was not significant ($p = 0.15$). A year later, the above results were complemented by Coselli et al. [28] as they reported a mortality rate of 3.9% in their cohort of 305 patients that had aortic arch surgery using RCP compared to non-RCP technique in 204 patients with a mortality rate of 17.2% ($p = 0.001$), and much lower incidence of stroke rate in RCP group of patients (2.6 vs 6.4%, respectively, $p = 0.037$). Therefore, in this large clinical retrospective series, RCP was found to significantly and favourably influence in-hospital mortality and the incidence of permanent stroke.

In two large series by Safi et al. [29], it was demonstrated that the use of RCP is a protective mechanism against stroke and mortality especially in patients above the age of 70 years and those who received a prolonged period of circulatory arrest. Safi's results were matched by Okita et al. [30] and Girardi et al. [31] in which they also concluded that prolonged period of HCA over 60 min and performing more complex aortic surgery, respectively, while using RCP, as an adjunct is not a risk factor for stroke or mortality in patients undergoing aortic arch surgery.

Despite no recognized guidelines to suggest RCP as a mandatory adjunct for aortic arch surgery due to lack of high-level evidence, the current international trend supports the use of RCP based on clinical observations, anatomic and experimental data. Interestingly, some centres limit the use of RCP to the prevention of neurologic injury in patients at high risk of embolic strokes although this basis is not recommended by any guidelines or consensus.

Although not mandatory but strongly recommended, transcranial Doppler scanning to direct the retrograde perfusion, as well as cerebral oximetry by bilateral near-infrared spectroscopy to demonstrate RCP in the cerebral vessels [24, 25, 28, 32, 33]. However, further studies provided many limitations to such technique as only 0.01% of the blood infused into the superior vena cava crosses the capillaries of the brain tissues and can contribute to the degree of cerebral oedema by increasing the perfusion pressure [34].

Antegrade cerebral protection gains momentum

Antegrade cerebral perfusion in combination with DHCA significantly reduces the incidence of neurologic consequences, not only so but such technique provides a safer extension of the operating time; therefore, a DHCA time of up to 90 min gives the surgeon an upper hand while operating on complex aortic surgery cases [7]. Antegrade cerebral perfusion emerged during mid-1980, the technique of ACP was introduced by Frist et al. [35], and was brought into clinical practice by Bachet et al. [36] in Europe and then Kazui et al. followed pursuit in Japan [37]. The use of ACP gained momentum after its establishment of neuroprotective benefits when used in conjunction with deep hypothermic circulatory arrest and having a significant reduction in the incidence of neurologic complications [11, 37]. Disadvantages of using such technique are the technical complexities that require manipulation of the major neck and aortic vessels for appropriate cannulation site, especially in cases of complex aortic arch surgeries or severely atherosclerotic aortic arch aneurysms and thus perhaps reduced visibility for the operating surgeon [38]. Important considerations when employing ACP are selective ACP, unilateral or bilateral ACP.

Harrington et al. [39] compared two groups of patients, 22 patients were allocated to using HCA alone and 20 allocated to use HCA and ACP. Their study showed that ACP attenuates the increase in oxygen extraction at the end of the HCA period through improved jugular venous oxygenation; however, the study was underpowered and there was no significant difference in early or late clinical outcomes between both groups.

In a large retrospective study by Di Eusanio et al. published in 2002 [40] included 413 patients who underwent surgery on thoracic aorta with ACP as adjunct, the mean cerebral perfusion time was s 63.00 ± 38.7 min (range 16–220 min), the hospital mortality was 9.4%, and temporary and permanent neurological deficit occurred in 5.1 vs 3.6%, respectively. In this study, they concluded that use of ACP for 90 min or more as an adjunct to HCA will provide adequate brain protection without increasing the risk of hospital mortality or poorer neurological outcomes; those findings were strengthened in a subsequent study by the same author that was published in 2003 [7].

The question of bilateral or unilateral antegrade cerebral perfusion?

The use of ACP has expanded and further challenged by adding more complexity to it, whether with unilateral ACP or bilateral ACP to provide a thorough brain perfusion and subsequent neuroprotection, yet debates still exist on cannulating and perfusing the appropriate number of vessels [41, 42]. It is imperative to bear in mind that cannulating diseased vessels is a risk factor that can contribute significantly to higher rate of neurological complications and therefore mortality [43].

In current practice, there are no recognized guidelines as to which method offers superior brain protection and the choice of unilateral or bilateral ACP is mainly based on surgeon preference and discretion.

Potential advantages of using unilateral ACP are provision of sufficient neuroprotection during aortic arch surgery in patients who have no prior neck vessel pathologies and there is sufficient backflow from the contralateral carotid artery or there is no evidence of cerebral malperfusion on near-infrared spectroscopy (NIRS) study [43]. However, bilateral ACP is perhaps useful in patients who have prior stroke, carotid artery stenosis, or evidence of cerebrovascular anomalies (incomplete circle of Willis) [44].

In a study by Urbanski et al. [45] he reported a satisfactory clinical outcomes including mortality and neurological outcomes for unilateral ACP. On the contrary, many surgeons prefer to use bilateral ACP to ensure adequate bihemispherical perfusion [44, 46]. Angeloni et al. [47] in their meta-analysis showed similar rate of postoperative mortality of 9.2% for bilateral ACP while 8.6% for unilateral ACP ($p=0.78$), and the same insignificance was noted in the incidence of permanent neurological deficits 6.5% for bilateral ACP vs 6.1% for unilateral ACP use ($p=0.80$); however, the rate of temporary neurological deficits was slightly higher in bilateral ACP than unilateral ACP (8.8 vs 7.1%, $p=0.46$). Therefore, the bottom line outcome was that there was no superiority of bilateral ACP over unilateral ACP in terms of clinical outcomes, in bilateral ACP group of patients, and this was possible due to the additive manipulation of neck vessels while trying to establish bilateral ACP. Nevertheless,

the use of ACP in aortic arch surgery has its own advantages, especially when it comes into operating on complex aortic arch and several studies support the idea of using ACP in such circumstances [46, 59].

Which is superior:antegrade or retrograde?

At present, only four prospective randomized controlled trials (RCT) compared the use of ACP vs RCP [48–51], in the largest of which Okita et al. [48] randomized 60 patients into 30 patients to receive ACP and 30 patients to receive RCP. There was a significant incidence of total neurological complications in patients who received ACP when compared to RCP group (33 vs 13%, respectively, $p < 0.05$). However, it is important to note that no significant difference was found for mortality rate, stroke rate or other neurocognitive deficits. Another RCT was performed by Tanoue et al. [49] where a total of 32 patients were randomized to ACP or RCP (17 and 15 patients, respectively); it was identified that cerebral blood flow is significantly improved in patients undergoing ACP than those who had RCP through transcranial doppler. Importantly, in the RCP group, only three patients showed the signs of reversal of cerebral blood flow, although such low rate is perhaps contributed to the technique used for RCP with the pressure utilized in the RCP circuit to 15–25 mmHg. Furthermore, the duration of cerebral perfusion was significantly different between groups, 71 min in ACP group and 38 min in the RCP group ($p = 0.0047$). Despite this, there were no reported differences in the clinical outcomes between both groups. The most recent RCT is by Svensson et al. [50], in which 121 patients were randomized to receive retrograde ($n = 60$) and antegrade ($n = 61$) cerebral perfusion during total aortic arch replacement. In their study, they have concluded that there is no superiority of ACP over RCP and both have similar neurologic outcomes. Svensson et al. [51] conducted a prospective randomized neurocognitive study for 30 patients that equally underwent HCA, RCP, and ACP for aortic arch surgery. In this study, there was no difference in circulatory arrest times (HCA vs ACP vs RCP) and the survival rate was 100% for randomized patients. Svensson et al. recommended from this study the use of HCA and for RCP or ACP to be added on a selective basis. RCP was recommended above ACP when a potential embolic material is expected and ACP when prolonged HCA times may be required.

In an observational non-randomized study of 13,467 patients, Usui et al. [52] concluded that ACP was not superior to RCP in protecting the brain and provided the same rate of neurological complications. A risk-adjusted analysis showed no significant differences between the ACP and RCP groups regarding 30-day mortality (3.5 vs. 2.6%), operative mortality (5.3 vs. 4.1%), or stroke (6.8 vs. 3.1%). Propensity-matched pairs also revealed no significant differences between ACP and RCP regarding 30-day mortality (3.4 vs. 2.4%), operative mortality (3.8 vs. 3.4%), or stroke rate (5.0 vs. 3.0%). Fleck et al. [53] studied the factors affecting the temporary neurological deficits after aortic surgery using DHCA as solo neuroprotection or in adjunct with ACP or RCP and concluded that incidence of temporary neurological deficits did not differ in using ACP or RCP. The same outcomes of no difference have been observed in a separate study by Mueller et al. [54]. Hagl et al. [55] and Neri et al. [56] have also concluded in their study that ACP is not superior to RCP when used in conjunct with HCA. In a more recent systematic review of 5060 patients by Hu et al. [57] comparing cerebral protection using ACP or RCP in aortic arch surgery, they found no difference in neurological outcomes using either techniques and the choice of ACP or RCP is dependent on the intra-operative findings. While on the contrary, Perreas et al. [58] analysed 259 patients retrospectively who had either DHCA plus RCP ($n = 207$) or MHCA plus ACP ($n = 52$) for ascending and aortic arch surgery and they concluded that MHCA plus ACP patients had lower rate of postoperative neurologic complications and comparative outcomes at 30-day and mid-term mortality rates. In a very recent study, Okita et al. [59] analysed 8169 patients who underwent elective total aortic arch replacement using either DHCA with RCP or ACP. There was no significant difference in operative mortality between ACP and DHCA/RCP group of patients (3.2 vs 4.0%), neither in the incidence of stroke 6.7 vs 8.6% nor in transient neurological disorders (4.1 vs 4.4%), respectively. The only statistical difference was that patients with DHCA/RCP had longer intensive care stay (> 8 days: 24.2 vs 15.6%). The ultimate conclusion was that using ACP could be of advantage in complex aortic arch surgeries.

Internationally, there is a growing trend toward the use of ACP over RCP. This is anecdotally based on evidence to suggest the likelihood of just providing sufficient cooling than enough nutrition to the brain tissues [44], and the efficacy of this technique might be impaired by the presence of the valves in the jugular veins which require higher perfusion pressure and as such may contribute to raised intracranial pressure and ultimately cerebral oedema [60]; therefore, when it comes to complex aortic procedures, the use of ACP is preferred over RCP due to the reasons mentioned above, this has been supported by several studies [46, 59, 61, 62]. In a large study analysis by Zierer et al. [62] in which they analysed 1002 consecutive patients who underwent complex aortic arch repair using ACP with mild HCA, they concluded that using ACP, up to 90 min, in complex aortic surgery with mild HCA is safe and provides good clinical and neurological outcomes. Table 1 provides summary of the key papers included in this study.

Table 1 Summary of the key articles included in this study

Author	Focus of the study	Number of patients	Article type	Brief outcome
Bashir et al. [2]	Cerebral protection in hemi-arch surgery	125	Retrospective study	DHCA alone is not suffice to give appropriate neuroprotection
Percy et al. [5]	DHCA and full preservation of cognitive abilities	29	Retrospective study	Straight DHCA provides adequate neuroprotection during short to moderate-duration circulatory arrest
Di Eusanio et al. [6]	DHCA and ACP during proximal aortic surgery	289	Retrospective study	Combination of DHCA and ACP provides acceptable hospital mortality and neurologic outcomes in ascending-hemi arch replacement
Ziganshin et al. [8]	Straight DHCA during aortic arch surgery	490	Retrospective study	Straight DHCA is a safe and effective technique of cerebral protection during aortic arch surgery. At experienced centres, up to 50 min of DHCA can be considered safe without additional neurological sequelae
Gega et al. [9]	Straight DHCA during complex aortic surgeries	394	Retrospective study	Straight DHCA without adjunctive perfusion suffices as a sole means of cerebral protection. Stroke and seizure rates are low. Cognitive function outcomes are excellent
Milewski et al. [11]	ACP and RCP in elective aortic arch surgery	776	Retrospective study	No superiority of ACP/MHCA over RCP/DHCA in terms of clinical outcomes
Leshnower et al. [12]	MHCA and uSACP in aortic arch surgery	412	Retrospective study	Use of MHCA with uSACP provides sufficient neuroprotection during elective and emergency aortic arch surgery
Leshnower et al. [13]	MHCA vs Mild HCA and uSACP in aortic arch surgery	708	Retrospective study	Hemi-arch replacement can safely be performed at mild HCA with uSACP with satisfactory neurological protection
Pacini et al. [15]	MHCA and SACP in aortic arch surgery in elderly	95	Retrospective study	MHCA and SACP in elderly patients undergoing elective aortic arch surgery provide excellent results regarding mortality and neurological outcome
Estrera et al. [27]	RCP in ascending and arch replacement	1107	Retrospective study	The use of RCP combined with DHCA provides lower rate of mortality and stroke
Okita et al. [30]	DHCA and RCP in aortic arch surgery	148	Retrospective study	Prolonged (>60 min) DHCA and RCP are not risk factors for mortality and stroke
Girardi et al. [31]	RCP and DCHA in aortic arch surgery	879	Retrospective study	RCP is a safe and effective method for neuroprotection during aortic arch surgery
Estrera et al. [32]	RCP alone, RCP and ACP with extended HCA in aortic arch surgery	64	Retrospective study	Combined ACP and RCP do not provide superiority, in terms of clinical outcomes, to RCP used alone when combined with HCA
Harrington et al. [39]	SACP during aortic arch surgery	42	Randomized controlled study	SACP attenuates metabolic changes seen after use of HCA
Di Eusanio et al. [40]	ACP in thoracic aorta surgery	413	Retrospective study	ACP is an effective neuroprotection method; perfusion times of over 90 min were not associated with increased mortality or poor neurological outcome
Aytekin et al. [41]	uACP and MHCA in thoracic aortic surgery	30	Prospective study	uACP and MHCA are safe techniques and provide good clinical outcomes
Urbanski et al. [45]	ACP and mild-moderate HCA in elective aortic arch surgery	347	Retrospective study	Mild-moderate HCA together with ACP is safe and effective organ protection methods during aortic arch surgery

Table 1 (continued)

Author	Focus of the study	Number of patients	Article type	Brief outcome
Angeloni et al. [47]	Unilateral vs bilateral ACP with HCA during complex aortic surgery	5100	Meta-analysis	No difference in clinical outcomes in using uACP or bACP during complex aortic surgeries
Okita et al. [48]	RCP or SACP with DHCA in total aortic arch replacement	60	Randomized controlled study	Both RCP and SACP provide similar clinical outcomes
Svensson et al. [50]	Neurological assessment following ACP or RCP with DHCA during total aortic arch replacement	121	Outcomes from a randomized controlled study	Similar neurological outcomes in using either ACP or RCP with DHCA during total aortic arch replacement
Svensson et al. [51]	DHCA, ACP or RCP in aortic arch surgery	139	Randomized controlled study	No neurocognitive superiority in using ACP or RCP over DHCA, similar outcomes observed in all techniques
Usui et al. [52]	ACP or RCP in ascending and aortic arch surgery	2792	Randomized controlled study	Both RCP and ACP provide clinically comparable outcomes in terms of stroke and mortality rates
Fleck et al. [53]	DHCA with ACP or RCP in ascending aorta replacement	160	Retrospective study	DHCA was the predicting factor of transient neurological dysfunction postoperatively, regardless of using either ACP or RCP
Mueller et al. [54]	DHCA, ACP or RCP in aortic arch surgery	64	Retrospective study	No superiority of DHCA, ACP or RCP in terms of neurological outcomes postoperatively
Hagl et al. [55]	DHCA with ACP or RCP in ascending–aortic arch surgery	717	Retrospective study	Use of ACP reduces the incidence of postoperative transient neurological dysfunction
Hu et al. [57]	ACP or RCP combined with DHCA in aortic arch surgery	5060	Meta-analysis	ACP and RCP provide similar neurological outcomes when combined with DHCA
Perreas et al. [58]	DHCA/RCP or MHCA/ACP in ascending–hemiarch aortic surgery	259	Retrospective study	MHCA/ACP is associated with a lower rate of neurological complications, decreased 30-day and mid-term mortality
Okita et al. [59]	ACP or DHCA with or without RCP in aortic arch surgery	8,169	Retrospective study	DHCA/RCP and ACP had comparable clinical outcomes with regard to mortality and stroke rates
Zierer et al. [61]	SACP and mild HCA in aortic arch surgery	1,002	Retrospective study	ACP and mild HCA (up to 90 min) provide safe clinical and neurological outcomes in complex aortic surgeries
Shihata et al. [62]	SACP vs non-Antegrade cerebral perfusion	124	Retrospective study	ACP was associated with improved survival and neurologic outcomes, especially for complex aortic arch repair cases

ACP = antegrade cerebral perfusion, RCP = retrograde cerebral perfusion, DHCA = deep hypothermic circulatory arrest, MHCA = moderate hypothermic circulatory arrest, uSACP = unilateral selective Antegrade cerebral perfusion, HCA = hypothermic circulatory arrest, uACP = unilateral antegrade cerebral perfusion,

At present, there is no reliable evidence to recommend either technique as superior. Whether this important question will be answered in the future several confounding factors will need to be addressed when designing any comparative study, which include in ACP the cannulation sites, delivery in the perfusate (unilateral or bilateral), as well as amount of the perfusate and for RCP the deliverance of continuous or intermittent and the flow and pressure of the RCP circuit. Additionally, this is even further complicated by the degree of hypothermia used for aortic arch repair. It should also be noted that surgeon volume and experience in aortic surgery play a pivotal role in morbidity and mortality.

Conclusion

The clinical outcomes from aortic arch surgery since the introduction of deep hypothermic circulatory arrest have improved dramatically through the introduction of many sophisticated adjunct measures to protect the brain. Deep hypothermic circulatory arrest with or without retrograde or antegrade cerebral perfusion could provide sufficient brain protection during complex aortic surgeries. Nevertheless, each of the three brain protection techniques has its own advantage and disadvantages, yet there is no gold standard method to be used in protecting the brain during aortic arch surgery and choice of the technique for brain protection remains surgeon and centre preference. This will require a large international multicentre randomized trial to set the corner stone of current controversies and present an international consensus.

Compliance with ethical standards

Conflict of interest There are no conflicts of interest or sources of support.

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