

A reappraisal of retrograde cerebral perfusion

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Brain protection during aortic arch surgery by perfusing cold oxygenated blood into the superior vena cava was first reported by Lemole *et al.* In 1990 Ueda and associates first described the routine use of continuous retrograde cerebral perfusion (RCP) in thoracic aortic surgery for the purpose of cerebral protection during the interval of obligatory interruption of anterograde cerebral flow. The beneficial effects of RCP may be its ability to sustain brain hypothermia during hypothermic circulatory arrest (HCA) and removal of embolic material from the arterial circulation of the brain. RCP can offer effective brain protection during HCA for about 40 to 60 minutes. Animal experiments revealed that RCP provided inadequate cerebral perfusion and that neurological recovery was improved with selective antegrade cerebral perfusion (ACP), however, both RCP and ACP provide comparable clinical outcomes regarding both the mortality and stroke rates by risk-adjusted and case-matched comparative study. RCP still remains a valuable adjunct for brain protection during aortic arch repair in particular pathologies and patients.

Keywords: Aortic arch surgery; brain protection; retrograde cerebral perfusion; hypothermic circulatory arrest



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Introduction

Aortic arch surgery has advanced remarkably over the past few decades. Brain protection during the interval in which normal circulation is interrupted is the most critical. As well as preventing ischemic brain injury, the prevention of stroke due to embolization of thrombus or atheromatous debris is essential. Furthermore, many factors are associated with poor neurological outcomes, for example, emergency status, aortic dissection with malperfusion, degree of systemic atheromatous arterial disease, history of cerebrovascular accidents, and renal insufficiency. Therefore, aortic arch surgery is still challenging for surgeons and peri-operative neurological injury remains significant.

In terms of brain and organ protection, antegrade cerebral perfusion (ACP) and hypothermic circulatory arrest (HCA) are the two conventional methods which were utilized for aortic arch surgery in the past. HCA has been widely used since acceptable surgical results were published by Griep *et al.* in 1975 (1-9). The use of HCA simplified

the operative procedure and removed the need for extensive manipulation of the brachiocephalic branches. However, the operation afforded by HCA is imperfect and of limited duration (1-5). The clinical application of continuous retrograde cerebral perfusion (RCP) with HCA for aortic arch surgery was first shown by Ueda and colleagues in 1990 (10). Thereafter, many clinical papers demonstrated the efficacy of RCP and identified a reduction in early mortality and morbidity (11-23). RCP entered routine use as an adjunct for prolonged HCA in the 1990s. Many of those RCP studies reported favorable results compared to historical control series. Although some evidence for enhanced protection by RCP is compelling, it is unclear whether the perceived improvements in mortality and morbidity reflect the direct benefit of RCP or is the result of overall improved surgical and anesthetic techniques (24,25).

History of retrograde perfusion

In 1980, Mills and Ochsner (26) originally used RCP to

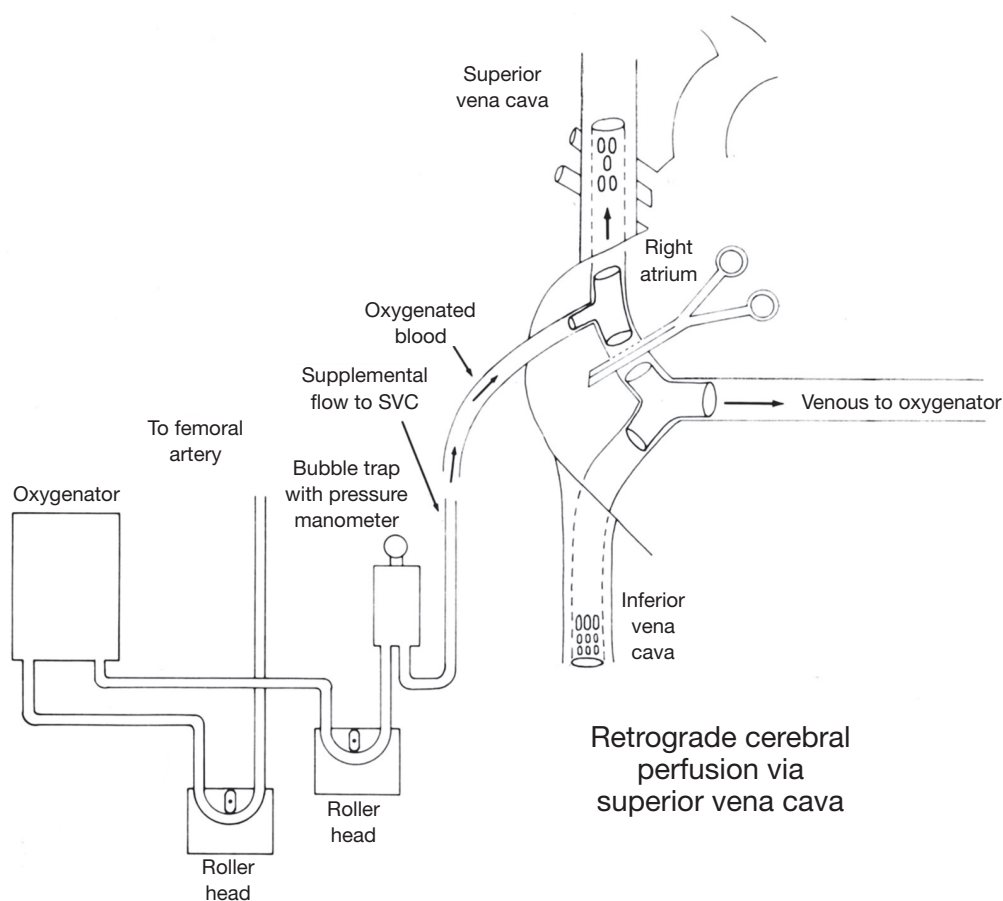


Figure 1 Lemole's circuit of retrograde cerebral perfusion (cited from *J Thorac Cardiovasc Surg* 1982;83:254). After clamping venous drainage, oxygenated blood infused through a side arm in the superior vena caval tubing

treat accidental air embolisms during cardiopulmonary bypass. In 1982, Lemole and colleagues (27) reported the treatment of an acute type A dissection using an intraluminal sutureless graft. They described intermittent RCP only briefly in a part of the discussion section, with a schema of the perfusion circuit (*Figure 1*). RCP into the superior vena cava (SVC) was used every 20 minutes during HCA.

In 1986, unaware of Lemole's paper, RCP was introduced by Ueda and colleagues independently (10). RCP was later extended from an intermittent administration to continuous administration (*Figure 2*) (10-12). RCP flow was always regulated to maintain a pressure of less than 20 mmHg in the internal jugular vein. This was found to provide satisfactory RCP flow in experimental animal models by Usui *et al.* (28). Flow-regulated RCP is not recommended; instead pressure-regulated RCP is favored to reduce the risk of brain edema with sustained jugular

vein pressure over 20 mmHg.

Anatomy of the jugular veins in man and mammals

The venous drainage from the brain in humans differ significantly from that in non-primate mammals. Kalbag (29) precisely described the anatomy and embryology of the cerebral venous system in "Handbook of Neurology Vol. 11" in 1972. Figures entitled "The development of the cranial venous system in man, from the viewpoint of comparative anatomy" (*Figure 3*) by Padget (30) were cited in this chapter. The head and neck are primarily drained by the internal jugular vein which remains predominant in man while in most other mammals, owing to the greater development of the face and neck relative to the brain, it is the external jugular vein that predominates. As the external jugular veins have many valves, venous regurgitation to

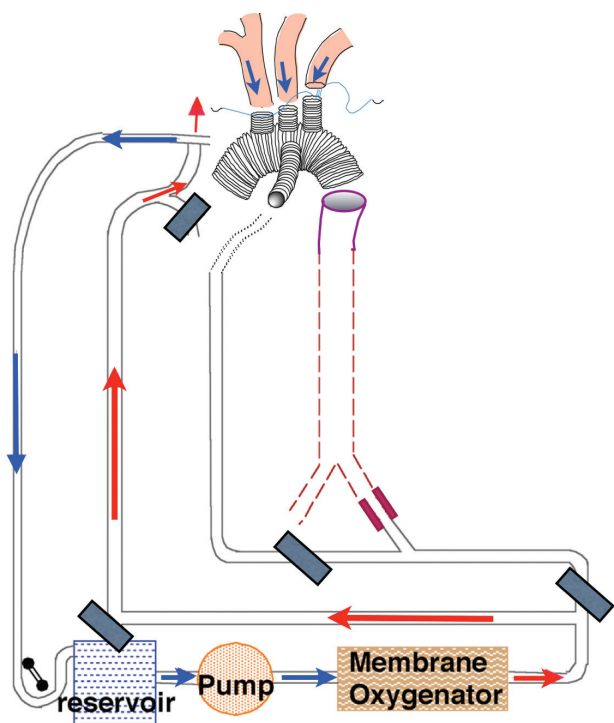


Figure 2 Continuous retrograde cerebral perfusion circuit. Continuous RCP can be started via the bypass connecting arterial and venous tubings by releasing the clamps on the bypass and clamping the inferior vena caval cannula. RCP, retrograde cerebral perfusion

the head is restricted, thereby allowing these non-primate mammals to freely eat and drink while lowering their heads.

On the other hand, the internal jugular veins, which have jugular bulbs with a remnant of venous valves, are the main drainage from the brain in humans. The human internal jugular veins are valved in approximately 90% individuals and studies in cadavers suggest that the valves are competent in 85% (31).

Investigations of RCP pressure and flow

The relationship between perfusion pressure, flow, and metabolism during RCP were investigated. Several papers have consistently demonstrated that RCP via SVC in a variety of animal models delivers only a small proportion of ACP flow in an uneven distribution (32-35). In 1995, Boeckstaens *et al.* measured the cerebral blood flow generated by RCP using a colored microsphere technique in primates (32). After 60 minutes of RCP delivered into the internal jugular veins at a pressure of 20 mmHg, cerebral

blood flow was only 1% of antegrade values. However, as the inferior vena cava (IVC) was allowed to drain freely during the perfusion, preferential perfusion of low resistance venous collateral channels may have accounted for the low flows encountered. The relevance of such studies to human anatomy depends on accurate demonstration of RCP flow.

de Brux *et al.* (31) investigated blood distribution of RCP by colored latex injection into the SVC in adult cadavers. Despite valves in the internal jugular vein, latex injections into cadaver internal jugular veins following instrumentation to render the valves incompetent may still reach the venous sinuses and cerebral venous. Collateral venous systems with lower resistance than the valved internal jugular vein, particularly via the azygos vein, may be responsible for the majority of blood perfusing the brain retrogradely. The status of IVC drainage may have an important role in RCP delivery. Prevention of low pressure run-off via azygos-IVC collaterals may increase the amount of blood flow reaching the brain.

In canine studies with RCP delivery via the maxillary veins (therefore bypassing all the external jugular vein valves), Usui *et al.* (28) demonstrated that return of blood into the aorta was maximal when jugular pressure was 25 mmHg, with a linear relationship between flow and pressure in the range of 15 and 25 mmHg. Rising venous pressure above this did not augment flow despite a rise in cerebrospinal fluid pressure. Nojima *et al.* (36) also found that retrograde flow increased with venous pressures up to 30 mmHg, and significant cerebral edema occurred at 30 mmHg. High SVC pressure has been shown to be damaging, most likely by causing cerebral edema and raised intracranial pressure. They demonstrated that aortic effluent blood volume from brachiocephalic branches was increased if IVC drainage was occluded.

Kawata and colleagues (37,38) introduced a novel RCP method with intermittent pressure augmentation for cerebral protection during aortic surgery. In their animal study, the effect of such brain protection was reinforced by raising the RCP pressure intermittently (every 30 seconds) from 15 mmHg to 45 mmHg in less than 120 minutes HCA at 18 °C. Intermittent augmented pressure effectively dilates and “opens” the cerebral vessels, thereby enabling adequate blood supply to reach the brain while also minimizing brain damage.

Recently, Yang and colleagues (39) investigated the efficacy of a modified RCP protocol by magnetic resonance spectroscopy to track the changes of brain high-energy phosphates. A modified protocol of RCP in pigs with non-occlusion of the IVC, higher perfusion pressure

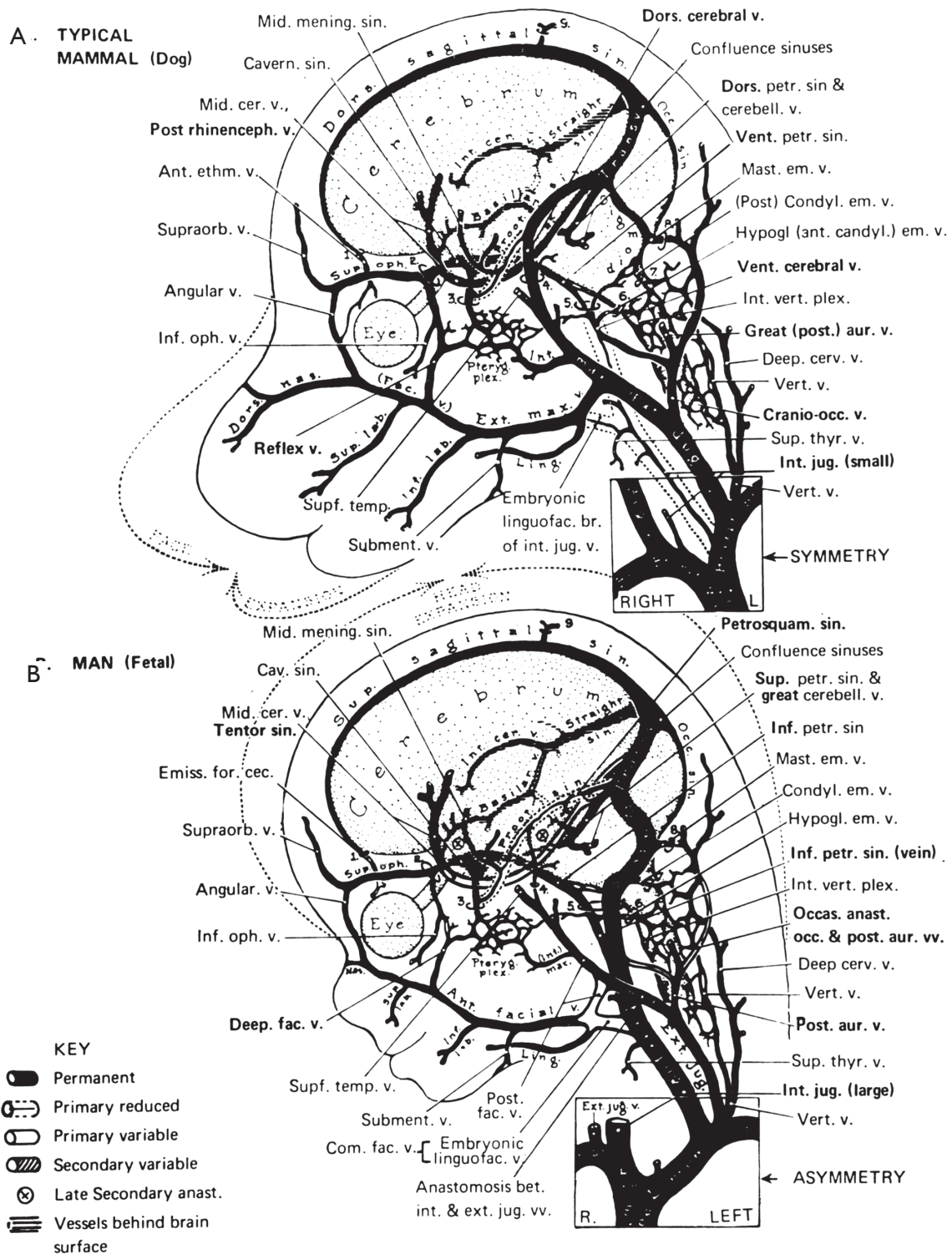


Figure 3 Anatomical figures of craniocervical venous channels by as published by Padget (30). Basic patterns of the craniocervical venous channels in a typical adult mammal (A) and early human fetus (B). In both types the embryonic head and neck are primarily drained by the internal jugular vein which remains predominant in man while in most other mammals owing to the greater development of the face and neck relative to the brain, the external jugular vein predominates. In most mammals essentially all intracranial drainage is received by the dorsal cerebral vein, representing the human petrosquamosal sinus

at 40-50 mmHg, and pH-stat strategy could improve brain tissue perfusion and oxygenation.

Chronic porcine model of RCP

Safi *et al.* used a porcine model of RCP (40). They established three groups of 5 pigs each: group A (control) underwent cardiopulmonary bypass and normothermic circulatory arrest for 1 hour, group B underwent cardiopulmonary bypass and profound HCA (15 °C nasopharyngeal) for 1 hour, and group C underwent the same procedure as group B plus RCP. None of the animals awoke in group A (normoemia). In group B (HCA only), 2 of 5 did not wake, 3 of 5 woke but were unable to stand. All of the group C (HCA with RCP) pigs awoke, 4 of 5 were able to stand, and 1 that was unable to stand could move all limbs. The neurological evaluation of group B showed significantly lower Tarlov scores than group C ($P=0.009$). Group B had a mean wake-up time of 124.6 ± 4.6 versus 29.2 ± 5.1 minutes in group C ($P=0.009$). The late phase circulatory arrest brain oxygenation decreased by $46.0\pm 13.9\%$ in group B, but increased by $26.1\pm 5.4\%$ in group C ($P=0.0013$). The rewarming jugular venous O_2 saturation in group B was $30.8\pm 2.5\%$ versus $56.0\pm 4.4\%$ in group C ($P=0.0011$). They concluded that RCP combined with profound HCA significantly reduces neurologic dysfunction, providing superior brain protection than HCA alone in pigs.

Yerlioglu *et al.* used RCP in a porcine model to evaluate the efficacy of RCP in mitigating the effects of particulate cerebral embolism occurring during cardiac surgery (41). Following embolisation at 20 °C with 250-750 μm albumin-coated polystyrene microspheres, cerebral perfusion was maintained antegradely or retrogradely via the SVC. They speculated that RCP, in addition to its usefulness as an adjunct to HCA, is attractive as a potential means of preventing air and particulate emboli which are the major causes of permanent neurologic injury after cardiac and aortic surgery in adults. They concluded that some pigs recover after embolization and RCP with either minimal or no cerebral injury. The complete recovery of these pigs, without any histopathological evidence of cerebral injury in contrast to the almost invariable neurological impairment and histopathological abnormalities in the antegrade embolism group, suggests that RCP provides some degree of cerebral protection after embolization in the ascending aorta. However, pigs perfused with RCP pressures greater than 40 mmHg had worse neurological outcomes. As a

result, gradually instituting RCP and maintaining the SVC pressures at a level less than 40 mmHg seem to improve the results.

Juvonen and colleagues (42) developed a chronic porcine model to evaluate the efficacy of RCP. Sixty-two pigs were randomly assigned to undergo one of the following for 90 minutes at 20 °C: ACP, conventional RCP, RCP with occlusion of the inferior vena cava (RCP-O), or HCA with the head packed in ice. Complete behavioral recovery was seen in all surviving animals by day 5 after ACP or RCP, but in only 83% after RCP-O and 50% after HCA ($P=0.001$). They demonstrated that conventional RCP without inferior vena caval occlusion results in a significantly better outcome than RCP-O after prolonged HCA, despite more efficient cerebral perfusion during RCP-O, and also provides cerebral protection superior to prolonged HCA alone.

Comments

Various experimental studies on animals have been performed to evaluate the efficacy and limitations of RCP. Published studies revealed that RCP does not provide a sufficient amount of blood flow or oxygen substrate to the brain. However, the interpretation of these findings must bear in mind the different developmental anatomy of the jugular venous system in man compared with other mammals.

Furthermore, there were several controversial factors in the experimental protocols, such as an extended HCA with RCP time up to 90 to 120 minutes and body temperature of 20 °C instead of 18 °C. These experimental protocols seemed to be designed to lead the conclusion of the inferiority of RCP in comparison to ACP. However, it should be appreciated that RCP combined with HCA, even in those intense protocols, revealed a better neuroprotective effect than HCA alone (40-43).

Intraoperative investigation of RCP flow

Human studies of RCP are less clear; there are anecdotal reports of cerebral edema when perfusion pressures exceeding 25 mmHg are adopted. Collapsed cortical veins or functional jugular venous valves may restrict flow at the frequently recommended maximum pressure of 25 mmHg. Ganzel *et al.* (44) have shown that with extensive intraoperative monitoring RCP flow can be safely titrated, with higher driving pressures dependent upon demonstration of a reversal of Doppler flow signal

in the middle cerebral artery. Using multi-modality neurophysiological monitoring they found no evidence of cerebral edema during RCP if SVC pressure was kept at 25 mmHg. Estrera *et al.* (45) described the detection of RCP flow in the middle cerebral arteries during aortic arch surgery. The RCP flow rate was varied depending on the information obtained from bilateral power mode transcranial Doppler ultrasound and bilateral near-infrared spectroscopy (cerebral oximetry). The adequacy of RCP flow was determined by the presence of reversed blood flow in the middle cerebral arteries when power mode transcranial Doppler ultrasound was used. Although a higher “opening” pressure is required, the maintenance flow rate is often below 500 mL/min, maintaining the pressure in the SVC line below 25 mmHg. The information obtained from power mode transcranial Doppler ultrasound was correlated with information obtained with near-infrared spectroscopy.

Paganao *et al.* (46) injected the cerebral perfusion study agent ^{99m}Tc labelled D,L-hexamethyl propylene amine oxime (^{99m}Tc -HMPAO) into the bypass reservoir at commencement of RCP. Continuous intra-operative gamma camera cerebral imaging revealed gradual accumulation of ^{99m}Tc -HMPAO firstly within the jugular bulb, followed by the sagittal and transverse sinuses and subsequently homogenous distribution throughout the gray and white matter. However, quantification of cerebral blood flow by this method was not possible but cumulative activity counts suggested that the actual blood flow was small and only a fraction of that obtained by antegrade perfusion.

Clinical outcomes of aortic arch surgery using RCP

Ueda and colleagues (23) published a retrospective analysis of 249 patients who underwent aortic arch surgery at three Japanese hospitals, where HCA and RCP were used as a routine adjunct, between 1994 and 1996. The pathology of the aortic arch was atherosclerotic aneurysm in 133 patients and dissection in 116. Seventy patients had surgery on an emergency basis. The hospital mortality was 25/249 (10%). Stroke developed in 11 patients (4%). The median duration of RCP was 46 minutes (range, 5 to 95 minutes). Multivariate logistic analysis revealed that pump time ($P=0.0001$), age ($P=0.0001$), and RCP time ($P=0.052$) were the most significant risk factors. The risk factors for mortality and neurological morbidity were pump time ($P=0.0001$), age ($P=0.0002$), urgency of surgery ($P=0.07$),

and RCP time ($P=0.15$).

Coselli *et al.* (20) published their results of aortic arch surgery from 1987 through 1997 using HCA with RCP in 305 patients and without RCP in 204 patients. The in-hospital mortality of 3.9% (12 patients) was significantly improved with RCP. In those without RCP, the in-hospital mortality was 17.2% (35 patients; $P=0.001$). The incidence of permanent stroke in patients undergoing RCP was 2.6% (8 patients), and the incidence for those without RCP was 6.4% (13 patients; $P=0.037$). The variables that were associated with early mortality in the patients with RCP were atherosclerotic heart disease, concomitant coronary artery bypass, aortic cross clamp time, pump time and sepsis. In this retrospective analysis of a large clinical series, RCP was found to significantly and favorably influence in-hospital mortality and the incidence of permanent stroke, although the period of HCA may be tolerable in most patients.

In 1997, Safi and associates (19) demonstrated that the overall 30-day mortality rate was 6% and the incidence of stroke was 4% in 161 patients who underwent surgery for aneurysms of the ascending aorta and transverse arch using HCA and RCP. The use of RCP had a protective effect against stroke (3 of 120 patients or 3%) in comparison to the absence of RCP (4 of 41 patients or 9%; $P<0.049$), and this phenomenon was most significant in patients older than 70 years. The cardiopulmonary bypass time was the sole factor found to be associated with an increased risk of stroke and mortality.

Thereafter, Safi *et al.* (47) revised their surgical results in 2011. They collected a large retrospective dataset from 1991 to 2010, and conducted comprehensive analysis on 1,193 patients who underwent surgery for the ascending aorta and arch. The 30-day mortality rate was 9.3% and the overall stroke rate was 3%. In univariate analysis of risk factors for stroke, the stroke rate was 2.8% with and 4.2% without retrograde cerebral perfusion ($P=0.30$), but when circulatory arrest time exceeded 40 minutes, the stroke rate was 1.7% with and 30% without retrograde cerebral perfusion ($P=0.002$). RCP demonstrated a protective effect against mortality and stroke. They concluded that RCP was associated with a trend towards reduced incidence of hospital mortality and, in patients receiving prolonged hypothermic circulatory arrest, reduced incidence of stroke.

Okita and associates (22) reported similar results and concluded that prolonged HCA and RCP for longer than 60 minutes was not a risk factor for mortality or stroke in patients who underwent aortic arch surgery.

However, the prevalence of transient delirium necessitates further investigation. Their logistic regression analysis demonstrated that the risk factors for mortality were ruptured aneurysm, chronic obstructive pulmonary disease, arterial cannulation in the ascending aorta, and stroke.

Okita *et al.* (48) also conducted a prospective comparative study of brain protection during HCA with RCP or ACP. Sixty consecutive patients who underwent total arch replacement were allocated alternately into two groups: RCP and ACP, each with 30 patients. Hospital mortality occurred in 2 patients in each group. New strokes occurred in 1 (3.3%) of the RCP group and in 2 (6.6%) of the ACP group ($P=0.6$). Both methods of brain protection for patients undergoing total arch replacement resulted in acceptable levels of mortality and morbidity. The incidence of transient neurological dysfunction was significantly higher in the RCP group than in the ACP group (10 patients, 33.3% *vs.* 4 patients, 13.3%; $P=0.05$). Except in patients with strokes, S-100b values were not different in the two groups. There were no intergroup differences in the scores of memory decline, orientation or intellectual function.

Svensson and colleagues (49) conducted a prospective randomized neurocognitive and S-100 study of HCA, RCP, and ACP for aortic arch surgery. Thirty patients who underwent aortic arch operations were randomly assigned to three equal groups for HCA, ACP, and RCP. All patients underwent a battery of 14 neurocognitive tests resulting in 51 subscores per patient at each of four test intervals. Serum S-100 protein levels were measured at more than 12 time intervals, which included before cannulation for cardiopulmonary bypass, going onto cardiopulmonary bypass, at the end of cooling before circulatory arrest, immediately after circulatory arrest, at the end of rewarming, at the conclusion of cardiopulmonary bypass, leaving the operating room, and then at 6, 12, 18, 24, and 48 hours postoperatively. For the randomized patients, the survival rate was 100% and no patient suffered a stroke or seizure. Circulatory arrest (HCA) times were not different (HCA *vs.* ACP *vs.* RCP) for 11 total arch repairs (including 6 elephant trunk; mean, 41.4 ± 15 minutes). The total circulatory arrest time ($P=0.01$) and cardiopulmonary bypass time ($P=0.057$) correlated with the peak serum S-100 levels. Circulatory arrest time correlated inversely with the following neurocognitive scores ($P=0.05$). They recommend that surgeons continue to use HCA by the well established techniques, and RCP or ACP be added on a selective basis according to the expected operative procedure, namely RCP

when a lot of potential embolic material is expected and ACP when prolonged HCA times may occur. Although this study has failed to show added neurocognitive protective benefits with these techniques, in a larger series of patients and with a greater number of strokes there could potentially be some benefit in stroke reduction.

A number of papers demonstrated a spectrum of beneficial, neutral, and detrimental effects of RCP in humans and in experimental animal models. In 2001, Reich and colleagues published a systematic review of evidence-based literature concerning RCP (50). They summarized that the early clinical and laboratory results regarding RCP for thoracic aortic surgery were promising, however it remains unclear whether RCP provides effective cerebral perfusion, metabolic support, washout of embolic material, and improved neurological and neuropsychological outcomes.

In 2004, Barnard *et al.* (51) published a systematic review on brain protection during HCA to determine whether patients undergoing aortic arch surgery benefit from ACP or RCP to reduce neurological injury or mortality. Altogether 408 papers were found using the reported search, of which 16 papers presented the best evidence to answer the clinical question. The author, journal, date and country of publication, patient group studied, study type, relevant outcomes, results, and study weaknesses of these papers were tabulated. They concluded that ACP is superior as an adjunct to HCA when compared to RCP or HCA alone, although clinical evidence for this from prospective clinical trials is weak.

In 2012, Usui and colleagues (52) conducted a comparative study to evaluate up-to-date clinical outcomes of aortic arch surgery between ACP and RCP based on the Japan Adult Cardiovascular Surgery Database. The subjects were confined to cases undergone electively with ACP or RCP for non-dissection aneurysms in the ascending aorta and aortic arch between 2005 and 2008 from 13,467 aortic surgeries. There were 2,209 ACP cases and 583 RCP cases. A risk-adjusted comparison based on 30-day mortality, operative mortality, and major morbidity was assessed by a multivariable logistic regression analysis. A conditional logistic regression analysis was also conducted in 499 propensity matched-pairs with ACP and RCP. 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%); however, RCP resulted in a significantly higher rate of transient neurological dysfunction (3.0% *vs.* 5.8%) and need for dialysis (1.6% *vs.* 4.2%).

Estrera and Safi have consistently reported the beneficial impact of RCP for aortic arch surgery with the largest number of patients (53-57). They recommended the use of 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. They preferred to use RCP with HCA, although RCP was not used in all case. They used ACP, combination of ACP and RCP, or HCA alone, depending on surgical strategy and pathology. "Integrated cerebral perfusion" for HCA during transverse aortic arch repairs has been advocated since 2010 (55).

Conclusions

The significant limitations of HCA to protect the brain during the aortic arch replacement has led to the introduction of RCP as an adjunct to extended the 'safe' duration of arrest period and to eliminate embolisation of air and debris. The technical simplicity of RCP together with a highly favorable impact upon both stroke rate and survival after aortic arch surgery justifies the continued clinical use of RCP in patients requiring HCA lasting about 40 to 60 minutes.

RCP is a beneficial adjunct for aortic arch surgery with 40 to 60 minutes HCA. However, a conversion from ACP to RCP as the adjunct of choice for brain protection is not advocated. ACP is preferable for the complex and extensive aortic arch surgery expected with prolonged HCA. We should realize that the technique of how we perform these adjuncts is important and that RCP still remains a valuable adjunct for cerebral protection in patients with acute dissection or atheromatous cervical branches.

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