Selective cerebral perfusion for cerebral protection: what we do know

David Spielvogel, Gilbert H. L. Tang

Department of Surgery, Section of Cardiothoracic Surgery, New York Medical College, Westchester Medical Center, Valhalla, New York, USA
Corresponding to: David Spielvogel, MD, Professor. Cardiothoracic Surgery, Westchester Medical Center, 100 Woods Road, Macy 114W, Valhalla, NY 10595, USA. Email: SpielvogelD@wcmc.com.

Selective antegrade cerebral perfusion (SACP) for aortic arch surgery has evolved considerably since it was first reported. Various pressure rates have been investigated through animal models, as has the effect of warmer perfusate temperatures and hematocrit. Clinical research into pH management, the role of unilateral and bilateral perfusion, and core temperatures have further refined the procedure. We recommend the following protocol for SACP: perfusion pressure between 40-60 mmHg, flow rates between 6-10 mL/kg/min, and perfusate temperature of 20-28 ℃; core cooling to 18-30 ℃ contingent on duration of arrest; alpha-stat pH management; hematocrit between 25-30%; near infrared spectroscopy to monitor cerebral perfusion; and bilateral perfusion when prolonged durations of SACP is anticipated.

Keywords: Selective antegrade cerebral perfusion; neuroprotection; arch surgery; surgical protocol

DeBakey reported the first series of 138 aortic arch replacements using selective cerebral perfusion in 1962 (1). Primarily two methods for cerebral perfusion were utilized: the first, a constructed passive shunt from the ascending to descending aorta with limbs for carotid artery perfusion and the second, use of cardiopulmonary bypass (CPB) and bilateral normothermic carotid artery perfusion. Although encouraged by some success, the overall mortality was 22% with the stroke rate not reported. The first description of antegrade cerebral perfusion from the axillary artery was reported by Panday *et al*. (2), whereby a pre-emptive right subclavian to left carotid bypass allowed right axillary perfusion to circulate to the brain and femoral artery cannulation to the corpus during aortic arch replacement - a clever technique that avoids cannulation of the brachiocephalic vessels. Frist and associates (3) published a series by the Stanford group of ten patients operated on using a combination of low-flow CPB and moderate (25-28 ℃) hypothermic selective antegrade cerebral perfusion (SACP); mortality was 30%, but no patients suffered a stroke. Other early champions of hypothermic selective antegrade cerebral perfusion included Matsuda, Kazui and Bachet. Matsuda *et al*. (4) used deep hypothermia (16-20 ℃) and SACP in 34 patients with 3 deaths and one stroke. Kazui *et al*. demonstrated a technique for arch replacement with branched grafts using hypothermic SACP at 25 ℃ with 9.1% early mortality and no strokes in 11 patients (5). This remains to be one of the most widely practiced techniques today. Bachet *et al*. reported a series of 54 aortic arch reconstructions using deep hypothermic SACP (6-12 ℃) and moderate systemic hypothermia with outstanding results; a temporary neurological dysfunction (TND) rate of 3.7%, stroke rate of 1.8%, and mortality of 13% (6). This method originally described by Guilmet (7) was termed "cold cerebroplegia". Finally, Dr. Kouchoukos published a series of extensive thoracic aortic aneurysm resections utilizing the "arch first" technique with limit circulatory arrest to the brain, right axillary artery perfusion and excellent neurological outcomes (8).

As clinical use of SACP increased, refinement of the formulation was increasingly necessary. Examination of experimental work in perfusion pressure, flow, temperature,

pH management, and hematocrit helped define safe parameters for delivery of SACP. In terms of unilateral versus bilateral cerebral perfusion, the right brachial or axillary artery, the common carotid artery, or the direct cannulation of the brachiocephalic vessel all demonstrate efficacy when delivered within safe parameters. Lastly, whilst the brain is being perfused, one must not forget about the lower body, particularly the ischemic tolerance of the spinal cord.

The optimal pressure for the delivery of hypothermic SACP in the porcine model was described by Halstead *et al.* (9) and Haldenwang *et al.* (10). Dividing experimental animals into three groups with SACP delivered at 50, 70 and 90 mmHg at 20 ℃, a pattern of increasing cerebral blood flow with increasing pressure led initially to similar cerebral metabolic suppression, but an elevated metabolic rate in the post-CPB period in the 90 mmHg group. An accompanying rise in intracranial pressure (ICP) throughout the SACP interval led to inferior neurobehavioral recovery in the chronic model. As a note of caution when applying these findings clinically, many older patients have chronic hypertension and atherosclerotic cerebrovascular disease, which may affect autoregulation and possibly the uncoupling during hypothermic perfusion. For this reason some investigators focus on cerebral blood flow, preferring to search for the ideal upper and lower limits. For Haldenwang *et al.* (10), using two groups of animals separated into 8 and 18 mL/kg/min hypothermic SACP, a similar pattern emerged showing equivalent cerebral metabolic suppression. However, the high perfusion pressure group demonstrated increased "luxury" regional blood flow with elevated ICP and sagittal sinus pressure (SSP), markers for poorer cerebral preservation. Two studies defined the lower limit of hypothermic SACP; Tanaka *et al.* (11), in a canine model, decreased 25 ℃ SACP from 100% baseline cerebral blood flow (CBF) towards zero, while concurrently evaluating cerebral function with continuous somatosensory evoked potentials (SSEP) monitoring and ultimately histological outcomes. Maintaining CBF at 100% of baseline and decreasing it to 50% revealed no signs of cerebral compromise. However, a decrease in flow to 25% of baseline (mean arterial pressure of 25 mmHg) demonstrated loss of SSEP and mild cellular injury. A recent study by Jonsson *et al.* (12) using hypothermic (20 ℃) SACP, beginning at 8 mL/kg/min and a controlled stepwise reduction to 6, 4 and 2 mL/kg/min, exhibited rising cerebral lactate in magnetic resonance spectroscopy

and decreased venous saturations below the 6 mL/kg/min threshold. Clinically, Shimizu *et al.* (13) directly monitored the flow distribution through three cannulas in the brachiocephalic, left carotid, and left subclavian arteries during hypothermic (<25 ℃) SCP. The target pressure at the tip of the cannulas ranged between 30 and 50 mmHg, with flow adjusted accordingly. Total flow rates and flow ratios in the supraaortic vessels were 5.8, 3.3, 3.4 mL/kg/min and 46.5%, 26.5%, and 27.0%, respectively. Total flow in these vessels was significantly lower in patients with adverse neurologic events (732 *vs.* 806 mL/min). The authors suggest that flow rates >10 mL/kg/min may be necessary when SCP at moderate hypothermia is used.

The success of SACP in total aortic replacement has led to a generalized trend for warmer temperatures by many experienced centers. A study by Khaladj *et al.* (14) used a porcine model of SACP for 90 minutes at 10, 20 and 30 ℃, and compared outcomes to HCA alone. Consistently higher ICP occurred in the 30 ℃ group during SACP and with reperfusion when compared to baseline and the 20 ℃ animals. The moderate hypothermia (20 ℃) animals showed sufficient cerebral metabolic suppression, and earlier recovery of EEG with significantly less expression of HSP-72 (heat shock protein 72 kDa). A recent study by Numata *et al.*, suggests that as compared to colder temperatures, SCP at >28 ℃ results in low mortality and incidence of permanent neurologic injury (6.1%) without compromising end-organ function (15).

Controversy persists over the pH management of hypothermic SACP. Some studies in children suggest a benefit of pH-stat over alpha-stat, but this is unsubstantiated in adults. Halstead *et al.* (16), comparing strategies in a porcine model, found that alpha-stat animals exhibited better suppression of cerebral metabolic rate of oxygen ($CMRO_2$), with lower cerebral blood flow and improved early neurobehavioral recovery. Dr. Kazui's group examined the effect of old cerebral infarct during hypothermic SACP (17). A rise of serum lactate, VADL, and glutamate all indicate additional ischemia of the chronic penumbra of the old cerebral injury. This area relies on collateral circulation with disturbed autoregulation and possible pressure/flow dependency. Elevated serum glutamate is associated with early neurologic deterioration after acute ischemic stroke (18). Ohkura *et al.* (19), using the same cerebral infarction model, demonstrated the attenuation of chronic ischemia of the infarct penumbra using pH-stat management during hypothermic SACP. pH-stat management may provide better protection against cerebral

ischemia after previous stroke when compared to alpha-stat. These results should be interpreted with caution as patients with old CVA's from atherosclerotic cerebrovascular disease may not have normal CO_2 reactivity.

Experimental animal studies comparing low hematocrit (20%) and high hematocrit (30%) hypothermic SACP suggest a benefit to the higher group (20). The 20% group produces higher cerebral blood flow during SACP with equivalent levels of cerebral metabolic suppression, once again demonstrating "luxury" perfusion and the possible attendant increased embolic load. Intracranial pressure showed a trend towards lower values in the high hematocrit animals with better and earlier neurobehavioral recovery.

The delivery of SACP can be unilateral or bilateral. The dependence of unilateral perfusion on the integrity of the Circle of Willis (CoW) is debatable. Merkkola and associated (21) performing anatomic autopsies on 98 brains using a 0.5 mm threshold for sufficient arterial diameter determined that 14% of specimens were unsuited for unilateral perfusion due to deficient anterior communicating artery or left posterior communicating artery. CT angiography was recommended for identification of high risk patients needing bilateral SACP. An additional study from Papantchev et al. (22) suggested that up to 42.4% of eastern Europeans have some incomplete anatomic variation of the Circle of Willis affecting the use of unilateral SACP. Besides pre-operative CT angiography, the authors suggest the use of near infrared spectroscopy (NIRS), transcranial Doppler (TCD), and EEG to assess cerebral perfusion.

The importance of the secondary collateral vessels, such as the ophthalmic artery, leptomeningeal vessels and external carotid arteries, may be underestimated. Urbanski and associates (23) published a series of 99 patients with unilateral left common carotid SACP at 30 ℃, with only one CVA. The average perfusion time was 18 min but pre-operative CT angiography documented complete CoW in only 60% of patients. All the patients received TCD, EEG, SSEP, and bilateral radial arterial lines. The authors discounted the need for pre-operative CT angiography of the CoW and emphasized the role of extracranial collaterals. Leshnower et al. (24) corroborated the clinical findings with a series of 412 patients undergoing a combination of hemiarch and total arch procedures with unilateral hypothermic SACP at 26 ℃ for up to 45 minutes, with a stroke rate of 3.6%. In a follow-up manuscript, Urbanski et al. (25) documented the outstanding results of 347 patients (77 total arch replacements) using unilateral SACP at 28 ℃

for an average of 34 minutes via the left or right common carotid arteries or innominate artery; the overall stroke rate was 0.9% and TND rate of 2.3%. For shorter intervals of SCP (<40 min), Lu et al. (26) confirmed the non-inferiority of unilateral hypothermic (16-20 ℃) SCP as compared to bilateral SCP. In the largest series to date, of 1,002 patients, Zierer and colleagues (27) compared unilateral vs. bilateral SCP combined with mild hypothermia (28-30 ℃) and found no difference in TND, PND or risk to the lower body. This included 318 total arch replacements with SCP performed for 36±19 minutes (range, 9-135 minutes). A trend was seen towards reduced PND rate with unilateral SCP (2%) vs. bilateral SCP (4%). Nonetheless, concern remains when the duration of SACP is longer than 50 minutes as is necessary for some techniques of total aortic arch replacement. Krahenbuhl et al. (28) followed 292 patients after aortic arch surgery with a combination of deep hypothermic circulatory arrest (DHCA), and unilateral or bilateral cerebral perfusion. Using the SF-36 health survey questionnaire, mid-term follow-up indicated better quality of life in patients with SACP times greater than 40 minutes treated with bilateral SACP. Review of 17 manuscripts involving 3,548 patients by Malvindi et al. (29), using a threshold neurological injury rates of <5%, found 599 patients treated with unilateral SACP for less than 50 minutes and 2,949 patients perfused with bilateral SACP for more than 86 minutes. They recommend the use of bilateral hypothermic SACP if the anticipated interval will be >50 minutes.

A consequence of performing aortic arch repair at warmer temperatures is the vulnerability of the viscera, and in particular, the spinal cord. In the past, using deep hypothermia, and with little knowledge of the spinal cord's tolerance to ischemia, one could be relatively certain that the interval necessary for aortic arch replacement and the "elephant trunk" procedure would produce no significant spinal injury. A study by Kamiya et al. (30) divided aortic arch patients into two groups based on deep versus moderate hypothermic lower body ischemia. The overall paraplegia rate was 2.1% (8/337) patients. A subgroup analysis of 11 patients with lower body circulatory arrest >60 minutes at moderate temperatures (25-28 ℃) showed 2 cases of paraplegia (18.2%). An elegant study by Etz et al. (31), using a porcine model for SACP at 28 ℃ for 90 and 120 minutes with fluorescent microspheres, determined spinal cord blood flow. After the initiation of SACP, blood flow was nearly absent below the T4-T13 region. Recovered animals showed evidence of paraparesis/paraplegia in both time

intervals, but was more severe in the 120-minute group. Histological specimens demonstrated moderate to severe ischemic lumbar spinal cord damage even in the animals that regained normal function. The severity increased distally and in the 120-minute SACP group. As such, the margin of safety may not be as great as has been widely assumed.

After a review of clinical application and experimental strategy, the following recommendations for the use of non-pulsatile SACP are proposed: perfusion pressure should remain between 40 to 60 mmHg, with a detrimental effect at higher pressures; flow rates ranging from 6 to 10 mL/kg/min depending on the selection of temperature, with higher flows unnecessary; core cooling to between 18 to 30 ℃, contingent on the duration of lower body circulatory arrest and the ability to institute lower body perfusion if the duration is prolonged; SACP temperature delivered within the 20 to 28 ℃ range; CPB pH management using alpha-stat; hematocrit between 25% and 30%; NIRS monitoring to detect cannula migration or inadequate perfusion of the left hemisphere with unilateral SACP; and with prolonged unilateral SACP, consider a second cannula for direct support of the contralateral side. Finally, the current warming trend in aortic arch surgery places the spinal cord at risk during SACP. This is probably not an all-or-none phenomenon, with prolonged ischemia injuring some motor neurons that are possibly undetectable on routine clinical exam.

Acknowledgements

References

1. DeBakey ME, Henly WS, Cooley DA, et al. Aneurysms of the aortic arch: factors influencing operative risk. Surg Clin North Am 1962;42:1543-54.
2. Panday SR, Parulkar GB, Chaukar AP, et al. Simplified technique for aortic arch replacement. First-stage right subclavian-to-left carotid artery bypass. Ann Thorac Surg 1974;18:186-90.
3. Frist WH, Baldwin JC, Starnes VA, et al. A reconsideration of cerebral perfusion in aortic arch replacement. Ann Thorac Surg 1986;42:273-81.
4. Matsuda H, Nakano S, Shirakura R, et al. Surgery for aortic arch aneurysm with selective cerebral perfusion and hypothermic cardiopulmonary bypass. Circulation 1989;80:I243-8.

5. Kazui T, Inoue N, Komatsu S. Surgical treatment of aneurysms of the transverse aortic arch. J Cardiovasc Surg (Torino) 1989;30:402-6.
6. Bachet J, Guilmet D, Goudot B, et al. Cold cerebroplegia. A new technique of cerebral protection during operations on the transverse aortic arch. J Thorac Cardiovasc Surg 1991;102:85-93; discussion 93-4.
7. Guilmet D, Roux PM, Bachet J, et al. A new technic of cerebral protection. Surgery of the aortic arch. Presse Med 1986;15:1096-8.
8. Kouchoukos NT, Masetti P. Total aortic arch replacement with a branched graft and limited circulatory arrest of the brain. J Thorac Cardiovasc Surg 2004;128:233-7.
9. Halstead JC, Meier M, Wurm M, et al. Optimizing selective cerebral perfusion: deleterious effects of high perfusion pressures. J Thorac Cardiovasc Surg 2008;135:784-91.
10. Haldenwang PL, Strauch JT, Amann I, et al. Impact of pump flow rate during selective cerebral perfusion on cerebral hemodynamics and metabolism. Ann Thorac Surg 2010;90:1975-84.
11. Tanaka H, Kazui T, Sato H, et al. Experimental study on the optimum flow rate and pressure for selective cerebral perfusion. Ann Thorac Surg 1995;59:651-7.
12. Jonsson O, Morell A, Zemgulis V, et al. Minimal safe arterial blood flow during selective antegrade cerebral perfusion at 20° centigrade. Ann Thorac Surg 2011;91:1198-205.
13. Shimizu H, Matayoshi T, Morita M, et al. Total arch replacement under flow monitoring during selective cerebral perfusion using a single pump. Ann Thorac Surg 2013;95:29-34.
14. Khaladj N, Peterss S, Oetjen P, et al. Hypothermic circulatory arrest with moderate, deep or profound hypothermic selective antegrade cerebral perfusion: which temperature provides best brain protection? Eur J Cardiothorac Surg 2006;30:492-8.
15. Numata S, Tsutsumi Y, Monta O, et al. Aortic arch repair with antegrade selective cerebral perfusion using mild to moderate hypothermia of more than 28°C. Ann Thorac Surg 2012;94:90-5; discussion 95-6.
16. Halstead JC, Spielvogel D, Meier DM, et al. Optimal pH strategy for selective cerebral perfusion. Eur J Cardiothorac Surg 2005;28:266-73; discussion 273.
17. Washiyama N, Kazui T, Takinami M, et al. Experimental study on the effect of antegrade cerebral perfusion on brains with old cerebral infarction. J Thorac Cardiovasc Surg 2001;122:734-40.

18. Campos F, Pérez-Mato M, Agulla J, et al. Glutamate excitoxicity is the key molecular mechanism which is influenced by body temperature during the acute phase of brain stroke. PLoS One 2012;7:e44191.

19. Ohkura K, Kazui T, Yamamoto S, et al. Comparison of pH management during antegrade selective cerebral perfusion in canine models with old cerebral infarction. J Thorac Cardiovasc Surg 2004;128:378-85.

20. Halstead JC, Wurm M, Meier DM, et al. Avoidance of hemodilution during selective cerebral perfusion enhances neurobehavioral outcome in a survival porcine model. Eur J Cardiothorac Surg 2007;32:514-20.

21. Merkkola P, Tulla H, Ronkainen A, et al. Incomplete circle of Willis and right axillary artery perfusion. Ann Thorac Surg 2006;82:74-9.

22. Papantchev V, Hristov S, Todorova D, et al. Some variations of the circle of Willis, important for cerebral protection in aortic surgery--a study in Eastern Europeans. Eur J Cardiothorac Surg 2007;31:982-9.

23. Urbanski PP, Lenos A, Blume JC, et al. Does anatomical completeness of the circle of Willis correlate with sufficient cross-perfusion during unilateral cerebral perfusion? Eur J Cardiothorac Surg 2008;33:402-8.

24. Leshnower BG, Myung RJ, Kilgo PD, et al. Moderate hypothermia and unilateral selective antegrade cerebral perfusion: a contemporary cerebral protection strategy for aortic arch surgery. Ann Thorac Surg 2010;90:547-54.

25. Urbanski PP, Lenos A, Zacher M, et al. Unilateral cerebral perfusion: right versus left. Eur J Cardiothorac Surg 2010;37:1332-6.

26. Lu S, Sun X, Hong T, et al. Bilateral versus unilateral antegrade cerebral perfusion in arch reconstruction for aortic dissection. Ann Thorac Surg 2012;93:1917-20.

27. Zierer A, El-Sayed Ahmad A, Papadopoulos N, et al. Selective antegrade cerebral perfusion and mild (28 ℃-30 ℃) systemic hypothermic circulatory arrest for aortic arch replacement: results from 1002 patients. J Thorac Cardiovasc Surg 2012;144:1042-49.

28. Krähenbühl ES, Clément M, Reineke D, et al. Antegrade cerebral protection in thoracic aortic surgery: lessons from the past decade. Eur J Cardiothorac Surg 2010;38:46-51.

29. Malvindi PG, Scrascia G, Vitale N. Is unilateral antegrade cerebral perfusion equivalent to bilateral cerebral perfusion for patients undergoing aortic arch surgery? Interact Cardiovasc Thorac Surg 2008;7:891-7.

30. Kamiya H, Hagl C, Kropivnitskaya I, et al. The safety of moderate hypothermic lower body circulatory arrest with selective cerebral perfusion: a propensity score analysis. J Thorac Cardiovasc Surg 2007;133:501-9.

31. Etz CD, Luehr M, Kari FA, et al. Selective cerebral perfusion at 28 degrees C--is the spinal cord safe? Eur J Cardiothorac Surg 2009;36:946-55.