Selective Antegrade Cerebral Perfusion Attenuates Brain Metabolic Deficit in Aortic Arch Surgery

A Prospective Randomized Trial

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Background—Aortic arch surgery has a high incidence of brain injury. This may in part be caused by a cerebral metabolic deficit observed after hypothermic circulatory arrest (HCA). We hypothesized that selective antegrade cerebral perfusion (SACP) would attenuate this phenomenon.

Methods and Results—In a prospective randomized trial, 42 adult patients were allocated to either HCA (22) or SACP. HCA occurred at a nasopharyngeal temperature of 15°C and SACP at a corporeal temperature of 25°C with cerebral perfusion at 15°C. Paired arterial and jugular venous samples were taken before and after arrest. Continuous transcranial Doppler monitoring of middle cerebral artery velocity (MCAV) was performed. Neuropsychometric testing was performed preoperatively and at 6 and 12 weeks postoperatively. There were 3 hospital deaths (7.1%), 2 strokes (4.8%), and 6 episodes of transient neurological deficit (14.3%). From before to after arrest, jugular bulb pO2 changed by 21.67 mm Hg (26.4) in the HCA group versus 2.27 mm Hg (18.8) in the SACP group (P<0.007). Oxygen extraction changed by 1.7 mL/dL (1.3) in the HCA group versus 1 mL/dL (2.4) in the SACP group (P<0.001). MCAV increased by 6.25 cm/s (9.1) in the HCA group and 19.2 cm/s (10.1) in the SACP group (P=0.001). Incidence of neuropsychometric deficit at 6 weeks was 6/12 (50%) in HCA patients and 8/10 (80%) in SACP patients (P=0.2), and at 12 weeks was 6/16 (38%) in HCA patients and 4/11 (36%) in SACP patients (P=1).

Conclusions—SACP attenuates the metabolic changes seen after HCA. Further studies are required to assess optimal perfusion conditions and clinical outcome. (Circulation. 2004;110[suppl II]:II-231–II-236.)

Key Words: aneurysm ■ aorta ■ brain ■ cerebral ischemia ■ perfusion

Hypothermic circulatory arrest (HCA) is a cerebral protective technique used during aortic arch surgery. Its premise is that hypothermia reduces brain metabolic activity, allowing a period of arrest during which arch reconstruction may be performed. However, there are finite time constraints to the arrest period. The incidence of overt neurological injury increases after 40 minutes and even shorter arrest periods are associated with a disturbing incidence of transient neurological and neuropsychometric deficit.1–4

Selective antegrade cerebral perfusion (SACP) via the innominate and left common carotid arteries has long been used as an adjunctive cerebral protective technique.5,6 Intuitively, antegrade perfusion to the brain during this otherwise ischemic period is beneficial, and the use of a cold cerebral perfusate during a corporeal arrest period at moderate hypothermia may potentially have other advantages. It allows brain cooling while achieving a potential reduction in the prolonged cooling and rewarming times required for profound hypothermia. At risk, however, is a possible increase in the embolic load to the brain. Recently, excellent clinical results in terms of mortality and neurological deficit have been reported by several groups using SACP7–11 that suggest superiority over either HCA alone or HCA supplemented by retrograde cerebral perfusion.

Any studies using stroke as an outcome measure would require vast numbers of patients. Although a high incidence of neuropsychometric deficit after HCA has previously been demonstrated,3,4,12 large numbers would also be required to demonstrate a clinical difference between groups. Cerebral blood flow and transcranial oxygen extraction have been used in a number of studies as surrogate markers of cerebral metabolism.13,14 Immediately after a period of HCA, there is a significant increase in both oxygen extraction and indices of cerebral blood flow.15–17 These changes may indicate the metabolic response of the brain to ischemia. There have been no previous randomized clinical studies between HCA and SACP examining indices of cerebral metabolism. Our aim was to investigate pre- and postarrest cerebral metabolism in HCA and SACP.
Patients and Methods

The study was approved by the local research ethics committee and all patients gave informed consent. Patients undergoing elective or emergency aortic arch surgery via a median sternotomy potentially requiring hypothermic circulatory arrest were considered. Forty-two patients were assigned to HCA or SACP. Computerized randomization schedules, stratified for age (younger than 50, 50 to 70, and older than 70) and anticipated extent of arch repair (as a surrogate for HCA duration) were used, with randomization disclosure to the operating surgeon just before sternotomy. Recruitment took place between June 2001 and January 2003.

Anesthetic and Perfusion Protocol

Anesthesia was induced using etomidate, pancuronium, and fentanyl, and was maintained using intravenous propofol and alfentanil. Standard monitoring, with bilateral upper limb arterial lines together with a retrograde jugular bulb catheter to allow jugular venous blood sampling, was used. The position of the jugular bulb line was later checked by skull x-ray. Jugular bulb temperature was measured using a calibrated thermocouple (Columbus instruments) and connected to a digital thermometer. Cardiopulmonary bypass (CPB) management was performed according to our previous protocol.17 Flows were maintained at 2.4 L/min per m² during normothermia and reduced to 1.6 L/min per m² at 15°C. A mean systemic blood pressure of 55 to 70 mm Hg was maintained using alpha agonists or glyceryl trinitrate as necessary. Antegrade cold blood cardioplegia was used. Cooling and rewarming gradients of up to 7°C between arterial inflow and nasopharyngeal temperature were allowed. Topical head cooling was used and intravenous dexamethasone 100 mg and mannitol 1 g/kg were administered in all cases before circulatory arrest. The patients were placed in a head-down tilt position for HCA and SACP. HCA was performed after achieving a nasopharyngeal (NP) temperature of 15°C. SACP, with a 15°C blood perfusate, was undertaken during cerebral circulatory arrest at a NP temperature of 25°C. Rewarming after arrest was commenced 5 minutes after the re-establishment of CPB. Rewarming was achieved at a NP temperature of 36°C limiting arterial inflow temperature to 37.5°C (maximum). Aprotinin was used during rewarming, 2 MU into the CPB pump, and then 0.5 MU per hour intravenously.

Selective Antegrade Cerebral Perfusion Protocol and Technique

SACP flow was generated using a shunt from the main roller pump and delivered via the cardioplegia heat exchanger circuit (Figure 1). We aimed to achieve SACP flow of 10 mL/kg per min equating to average normothermic brain blood flow.5,8,18 Two modified retrograde cardioplegia cannulae (Chase Medical) were inserted into the innominate and left common carotid arteries.8 SACP flow was adjusted to achieve a right radial pressure of 50 to 70 mm Hg. Flow was maintained at 8 to 12 mL/kg per min. A Fogarty balloon catheter was used to occlude the left subclavian artery.

Operative Technique

The intended site of arterial return was the distal aortic arch, but femoral cannulation was used if this was not possible. Extended open distal anastomosis was defined as a single bevelled anastomosis replacing the undersurface of the transverse aortic arch. Arch replacement was defined as a procedure requiring separate re-implantation of all or some epi-aortic vessels. During anastomotic completion, 4°C cold saline was instilled into the graft, allowing rigorous de-airing and aspiration of particulate material. Orthograde perfusion was then established via a graft side-arm (Antello; Sulzer Vascutek), allowing air-drill completion and recommencement of CPB. The presence of arch atheroma was defined as the observation of friable atheromatous plaques, generating particulate matter during suture placement or manipulation. Transesophageal echocardiographic atheroma assessment was not available.

Metabolic Sampling

Paired arterial and jugular venous samples were taken before and after arrest. The postarrest sample was taken immediately after recommencement of CPB. Samples were analyzed using a Bayer Rapid laboratory 865 blood gas analyser. Oxygen content measurements were corrected for temperature.

Transcranial Doppler

Continuous bilateral transcranial Doppler monitoring of the middle cerebral artery for velocity and embolus detection were performed (Multidop X4; DWL). Emboli were counted off-line by 2 trained observers.

Neurological Examination

All patients underwent neurological examinations according to the National Institutes for Health Stroke Scale (NIHSS) by an independent trained neurological observer. All patients underwent a pre-operative assessment, a brief neurological examination on day 1, then a further NIHSS on days 5 to 7 postoperatively. Stroke was defined as a focal neurological deficit persisting >24 hours and confirmed by CT scanning. Transient neurological deficit was defined as a temporary nonfocal deficit including obtundation, seizures, confusion, or psychosis.

Neuropsychometric Testing

Neuropsychometric testing was performed by a blinded, trained investigator preoperatively and at 6 and 12 weeks postoperatively. A standard test battery was used according to the international consensus statement.19 Neuropsychometric deficit was defined as a 20% decline in ≥2 tests.

Statistical Methods

The study had an 80% power to detect a change in oxygen extraction of 0.5 mL/dL at a significance level of 5%.17 Data were computer-
TABLE 1. Demographic Details, Aortic Pathology, and Procedures Performed

<table>
<thead>
<tr>
<th>Procedure</th>
<th>HCA* (%)</th>
<th>SACP† (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range)</td>
<td>60 (23–78)</td>
<td>67 (46–84)</td>
<td>0.13</td>
</tr>
<tr>
<td>Male:Female</td>
<td>14:8</td>
<td>12:8</td>
<td>1</td>
</tr>
<tr>
<td>Redo procedure</td>
<td>1</td>
<td>3</td>
<td>0.33</td>
</tr>
<tr>
<td>Arch atheroma</td>
<td>6</td>
<td>7</td>
<td>0.74</td>
</tr>
<tr>
<td>Femoral cannulation</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Marfan</td>
<td>3</td>
<td>0</td>
<td>0.23</td>
</tr>
<tr>
<td>Degenerative aneurysm</td>
<td>17</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Acute dissection</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Chronic dissection</td>
<td>2</td>
<td>3</td>
<td>0.66</td>
</tr>
<tr>
<td>Aneurysm of aberrant right subclavian artery</td>
<td>0</td>
<td>1</td>
<td>0.48</td>
</tr>
<tr>
<td>Ascending aortic replacement</td>
<td>12</td>
<td>5</td>
<td>0.07</td>
</tr>
<tr>
<td>Extended open distal anastomosis</td>
<td>0</td>
<td>3</td>
<td>0.1</td>
</tr>
<tr>
<td>Arch replacement</td>
<td>9</td>
<td>11</td>
<td>0.54</td>
</tr>
<tr>
<td>Arch + descending aortic replacement</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total aortic replacement</td>
<td>0</td>
<td>1</td>
<td>0.48</td>
</tr>
<tr>
<td>Concomitant coronary artery bypass grafts</td>
<td>2</td>
<td>5</td>
<td>0.23</td>
</tr>
</tbody>
</table>

 stored on a commercial database and analyzed using SPSS 11.0 for Windows. Categorical data were compared using χ² or Fisher exact tests as appropriate. Continuous data are presented as mean and SD or median and interquartile range. Because the sample size was small, all continuous data were analyzed nonparametrically (Mann–Whitney U test). Statistical significance was assigned when P<0.05. The denominator for percentages takes into account missing data.

Results

There were 21 patients randomized to each group. One patient randomized to SACP underwent HCA because of an inability to isolate the left subclavian artery. This patient was subsequently analyzed as part of the HCA group.

Demographics, aortic pathology, and procedure performed are detailed in Table 1.

There were 3 in-hospital deaths (mortality rate, 7.1%), all of whom had undergone SACP. Two deaths were caused by multiorgan failure, and 1 was caused by sudden late cardiac tamponade. A further HCA patient died after leaving hospital before the 12-week neuropsychometric follow-up.

Mean cardiopulmonary bypass, aortic cross-clamp, HCA, SACP, and cooling times are shown in Table 2. Despite randomization and a similar procedure profile, SACP patients had a longer cerebral protection time.

Metabolic Data

Prearrest metabolic data are shown in Table 3. By study design, prearrest nasopharyngeal temperature was significantly lower in the HCA group. The groups were comparable in terms of prearrest hematocrit. Arterial pH was significantly lower in the SACP group, and arterial pO₂, pCO₂, and transcranial O₂ extraction were significantly higher.

Postarrest metabolic data are shown in Table 4. After arrest, the nasopharyngeal temperature of the SACP group had decreased. Hematocrit remained comparable.

Figure 2a and 2b represent the prearrest to postarrest changes in jugular bulb pO₂ and oxygen extraction for the 2 groups. Jugular venous pO₂ decreased significantly prearrest to postarrest in the HCA group (31.68 mm Hg to 10 mm Hg) (P<0.001) but was unchanged in the SACP group (24.8 mm Hg to 25.57 mm Hg) (P=0.95). The 2 groups behaved significantly differently (P=0.007). Transcranial oxygen extraction changes also differed between groups (P<0.001). Extraction increased from 1.22 mL/dL to 2.95 mL/dL in the HCA group (P<0.001), but decreased from 3.2 mL/dL to 2.38 mL/dL in the SACP group (P<0.04).

Transcranial Doppler Data

In 5 patients (3 HCA), it was not possible to obtain adequate middle cerebral artery velocity (MCAV) monitoring. Prearrest MCAV was similar in both groups (11.1 cm/s [SD 5.7]) HCA and 14 cm/s (SD 6.4) SACP (P=0.08). During SACP, mean MCAV was 21.9 cm/s (SD 12.7). MCAV increased significantly in both groups before to after arrest. Postarrest MCAVs were 16.6 cm/s (SD 11.2) in the HCA group and 16.6 cm/s (SD 11.2) in the SACP group (P=0.95).

TABLE 2. Cardiopulmonary Bypass Details

<table>
<thead>
<tr>
<th>Procedure</th>
<th>HCA* (SD)</th>
<th>SACP† (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiopulmonary bypass time</td>
<td>221 minutes (63.7)</td>
<td>203 (41.8)</td>
<td>0.554</td>
</tr>
<tr>
<td>Aortic cross clamp time</td>
<td>145 minutes (42.4)</td>
<td>152 (23.7)</td>
<td>0.271</td>
</tr>
<tr>
<td>Hypothermic circulatory arrest time</td>
<td>33 minutes (19.4)</td>
<td>8 (2.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Selective antegrade cerebral perfusion time</td>
<td>39 (17.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cerebral protection time (HCA+SACP)</td>
<td>33 minutes (19.4)</td>
<td>47 (17.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Cooling time</td>
<td>74 minutes (18.4)</td>
<td>46 (24.2)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Hypothermic circulatory arrest.
†Selective antegrade cerebral perfusion.

TABLE 3. Prearrest Metabolic Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HCA* (SD)</th>
<th>SACP† (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngeal temperature</td>
<td>15.3°C (0.7)</td>
<td>24.9°C (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>26.7 (4.8)</td>
<td>25.8 (4.5)</td>
<td>0.545</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.67 (0.05)</td>
<td>7.6 (0.06)</td>
<td>0.001</td>
</tr>
<tr>
<td>Arterial pO₂ (mm Hg)</td>
<td>230.2 (51.8)</td>
<td>261.2 (54.5)</td>
<td>0.036</td>
</tr>
<tr>
<td>Arterial pCO₂ (mm Hg)</td>
<td>13.89 (1.7)</td>
<td>19.58 (2.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Jugular venous pO₂ (mm Hg)</td>
<td>31.68 (25.5)</td>
<td>24.8 (15.9)</td>
<td>0.592</td>
</tr>
<tr>
<td>O₂ extraction (mL/dL)</td>
<td>1.22 (0.7)</td>
<td>3.32 (2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Hypothermic circulatory arrest.
†Selective antegrade cerebral perfusion.
33.3 cm/s (SD 13.1) in the SACP group ($P<0.001$). The increase was therefore much greater in the SACP group (+6.3 cm/s [SD 9.1]) versus +19.2 cm/s (SD 10.1; $P=0.001$) (Figure 3). At 5 minutes postarrest, when mean nasopharyngeal temperature was 16.5°C in both groups, this difference was sustained (HCA 20.4 cm/s [SD 11.1]) versus SACP 43.6 cm/s (SD 17.1) ($P<0.001$).

The total number of emboli detected was not different (HCA median 152, interquartile range 68 to 189, versus SACP median 160, interquartile range 99 to 250) ($P=0.59$).

**Neurological and Neuropsychometric Data**

Two HCA patients experienced a stroke. Six patients had postoperative transient neurological deficit, (5 SACP: 4 obtundation, 1 temporary visual field deficit; 1 HCA: confusion). Five of the 6 patients with transient neurological deficit required additional surgical intervention for bleeding. Neuropsychometric data accrual was incomplete. Three initial and 4 follow-up tests could not be performed for logistical reasons. Six patients were unable to complete initial testing. Eight postoperative evaluations could not be performed because of incomplete patient compliance or refusal.

At 6 weeks, 6/13 (46%) of the HCA group had a neuropsychometric deficit, versus 8/10 (80%) of the SACP group ($P=0.2$). At 12 weeks, 6/16 (38%) of the HCA group had a neuropsychometric deficit versus 4/11 (36%) of the SACP group ($P=1$). The incidence of neuropsychometric deficit in the overall cohort decreased between the time points, although not significantly ($P=0.66$).

**Discussion**

This study demonstrates that SACP attenuates the increase in transcranial oxygen extraction at the end of a period of HCA. Transcranial oxygen extraction, a surrogate marker of cerebral metabolism,$^{13,14}$ is relatively simple to measure. Previous studies, including our own,$^{15-17}$ have detected a reduction in jugular venous pO$_2$ and an increase in transcranial oxygen extraction immediately after the circulatory arrest period. This was confirmed in the HCA group of this study. This phenomenon may reflect the cerebral hyperemic response to ischemia during arrest. In the SACP group, we detected no decrease in jugular venous pO$_2$ and a reduction in transcranial oxygen extraction when reinstituting total body perfusion. This decrease in oxygen extraction in the SACP group may be caused by the cooling effect of SACP (Tables 3 and 4), causing a decrease in cerebral metabolism.

The prearrest metabolic data demonstrate a higher pO$_2$, pCO$_2$, and oxygen extraction in the SACP group. This could be explained by the higher prearrest temperature in this group (25°C versus 15°C), which was part of the study design.
We used transcranial Doppler monitoring of MCAV as a noninvasive surrogate of relative cerebral flow.\textsuperscript{20} Middle cerebral artery diameter is reported not to change with hypothermia\textsuperscript{21,22}. We detected an increase in cerebral blood flow after HCA. This is in accordance with previous studies and corroborates the hypothesis of postarrest hyperemia.\textsuperscript{23,24} In the SACP group, the increase in MCAV was significantly greater than in the HCA group. This exaggerated hyperemic response may be explained by differing brain perfusate conditions at the recommencement of CPB including higher differential temperature, greater acidity, and higher CO\textsubscript{2} content, reflecting the temperature differential between the groups at the onset of corporeal arrest. The significance of this finding is unknown but could increase vulnerability to any embolic load.

Theoretically, SACP may increase embolic load during cannulation. However, the actual number of emboli detected in both groups was similar and relatively small.\textsuperscript{25} We used a SACP flow rate of 10 mL/kg per min, chosen on the basis of successful clinical outcomes in large series of SACP procedures.\textsuperscript{7,8} We acknowledge, however, in light of our results, that this flow rate may be greater than that required to safely maintain perfusion at 15°C to 25°C,\textsuperscript{26} and could be detrimental in terms of potential for increased embolic load and raised intracranial pressure. No previous randomized clinical studies have examined the optimum flow conditions for SACP.

The overall cerebral protection time (SACP+HCA) was longer in the SACP group, despite a similar procedure profile. We attribute this to 2 factors. First, the use of SACP necessitates a brief but finite HCA period for cannula manipulation. Second, there were slightly greater numbers of total arch and extended procedures in this group. Despite this increase in cerebral protection time, SACP remained able to reduce oxygen extraction.

Our study was not powered to detect differences in clinical outcomes. The overall incidence of neurological injury in terms of stroke, transient neurological deficit, and neuropsychometric deficit in this study is comparable with the reported literature,\textsuperscript{1,4,12} but it is higher than that observed in 1 previous randomized study.\textsuperscript{29} However, the sample size in that study was also small and a different battery of tests was used. Our test battery is widely used, but the high incidence of failure to complete tests suggests that it may be too complex for this patient group. A concern is the incidence of transient neurological deficit in our SACP group. It is possible that this may be because of the large rewarming gradient after arrest with this SACP technique, because moderate corporeal hypothermia was used with the aim of reducing the complications of profound hypothermia.\textsuperscript{30} Neurological change was predominantly seen in cases complicated by perioperative hemorrhage, a known risk factor for neurological morbidity.

**Study Limitations**

Although the study was adequately powered for metabolic endpoints, its small sample size precludes extrapolation of the clinical outcome data. We acknowledge the difference in nasopharyngeal temperature between the 2 groups and the fact that this is a significant confounding variable. The use of moderate corporeal hypothermia during SACP was to mitigate other adverse consequences of profound hypothermia. However, the metabolic calculations were temperature-corrected, and the data represent prearrest to postarrest differences rather than absolute values.

**Conclusions**

SACP may attenuate the cerebral metabolic deficit seen after HCA, and concerns over its greater embolic load appear unsubstantiated. Further studies are required to demonstrate any clinical difference between HCA and SACP in terms of neurological or neuropsychometric outcome. Investigation is also required to define optimal flow rate and driving pressure and whether these parameters should be adjusted intraoperatively. Finally, if SACP is undertaken using profoundly hypothermic temperatures, the ideal temperature of corporeal arrest and post-SACP reperfusion need to be determined.

**Acknowledgments**

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