Retrograde cerebral perfusion (RCP) potentially delivers metabolic substrate to the brain during surgery using hypothermic circulatory arrest (HCA). Serial measurements of O₂ extraction ratio (OER), Pco₂, and pH from the RCP inflow and outflow were used to determine the time course for O₂ delivery in 28 adults undergoing aortic reconstruction using HCA with RCP. HCA was instituted after systemic cooling on cardiopulmonary bypass for 3 min after the electroencephalogram became isoelectric. RCP with oxygenated blood at 10°C was administered at an internal jugular venous pressure of 20–25 mm Hg. Serial analyses of blood oxygen, carbon dioxide, pH, and hemoglobin concentration were made in samples from the RCP inflow (superior vena cava) and outflow (innominate and left carotid arteries) at different times after institution of RCP. Nineteen patients had no strokes, five patients had preoperative strokes, and four patients had intraoperative strokes. In the group of patients without strokes, HCA with RCP was initiated at a mean nasopharyngeal temperature of 14.3°C with mean RCP flow rate of 220 mL/min, which lasted 19–70 min. OER increased over time to a maximal detected value of 0.66 and increased to 0.5 of its maximal detected value 15 min after initiation of HCA. The RCP inflow-outflow gradient for Pco₂ (slope 0.73 mm Hg/min; P < 0.001) and pH (slope 0.007 U/min; P < 0.001) changed linearly over time after initiation of HCA. In the group of patients with preoperative or intraoperative strokes, the OER and the RCP inflow-outflow gradient for Pco₂ changed significantly more slowly over time after HCA compared with the group of patients without strokes. During RCP, continued CO₂ production and increased O₂ extraction over time across the cerebral vascular bed suggest the presence of viable, but possibly ischemic tissue. Reduced cerebral metabolism in infarcted brain regions may explain the decreased rate of O₂ extraction during RCP in patients with strokes. Implications: Examining the time course of oxygen extraction, carbon dioxide production, and pH changes from the retrograde cerebral perfusate provided a means to assess metabolic activity during hypothermic circulatory arrest.

Operative repair of aortic aneurysms or aortic dissections extending into the aortic arch requires temporary interruption of antegrade blood flow through the cerebral vessels. The primary technique used to protect against cerebral injury during the period of circulatory arrest has been deep hypothermia (1,2). Recent clinical reports have suggested that circulation management using retrograde cerebral perfusion (RCP) in combination with hypothermic circulatory arrest (HCA) has decreased the rate of stroke and operative mortality associated with aortic arch operations (3–7). Although this circulation management strategy has been used with increasing frequency, the maximal safe duration that antegrade cerebral perfusion can be interrupted when RCP is used, and the mechanisms by which RCP prevents neuronal injury in this setting have not been established.

Delivery of metabolic substrate to prevent cerebral ischemia and infarction during the temporary interruption of antegrade cerebral perfusion has been one rationale for using RCP. However, existing experimental and clinical studies have not consistently demonstrated that RCP provided sufficient nutrient flow to support cerebral metabolism and prevent cerebral ischemia during HCA. Some experimental models have demonstrated cerebral tissue flow via RCP as high as 33%–50% of that achieved with antegrade perfusion flow rates that were sufficient to support cerebral metabolic requirements (8,9). Other experimental models have failed to demonstrate a significant level of brain blood flow via RCP (10) or the ability of RCP to sustain brain metabolic function during HCA (11–13). Clinical reports in small numbers of patients have demonstrated that RCP used during HCA partially restored cerebral oxygenation (14), provided cerebral cortical blood flow...
that was 10% of baseline (15), or maintained cerebral oxygenation (15). In a previous study, we found that brainstem somatosensory evoked responses could be recorded in some patients during HCA. However, RCP was not sufficient to sustain these brainstem evoked potentials indefinitely during HCA, although it did attenuate the rate at which the amplitude of the brainstem somatosensory evoked potential amplitudes decayed (16).

The purpose of this study was to examine the time course of cerebral metabolic activity during deep hypothermia after interruption of antegrade cerebral perfusion when RCP was used by measuring serial concentrations of oxygen, carbon dioxide, and pH in RCP inflow and outflow specimens. The time course for changes in the oxygen extraction ratio was compared with the known functional changes in brain electrical activity during HCA demonstrated by somatosensory evoked potential (SEP) monitoring (16). Impaired oxygen extraction or carbon dioxide production during RCP could indicate tissue malperfusion or infarction.

Methods

Intraoperative electroencephalogram (EEG) and SEP monitoring together with serial arterial (outflow) and venous (inflow) blood sampling was performed in 28 consecutive patients undergoing aortic reconstruction. Each patient had a formal neurological evaluation with a focused neurological examination before the operation and a complete neurological examination on the first or second day after the operation. Patients with abnormalities on either the initial or immediate postoperative neurological examination were followed with serial examinations. The circulation management strategy used for all patients consisted of: 1) cooling to deep hypothermia for 3 min after an isoelectric EEG and disappearance of the N20-P22 cortical SEP had been achieved; 2) partial exsanguination with interruption of antegrade cerebral perfusion; and 3) RCP (Table 1). Clinical data used for study purposes were acquired according to a protocol approved by the University of Pennsylvania Committee on Studies Involving Human Beings.

All patients were anesthetized with fentanyl (25–75 μg/kg), midazolam (0.03–0.15 mg/kg), isoflurane (0.0–0.5 vol%), and pancuronium (0.25–0.5 mg/kg). No anesthetics were administered into the retrograde cerebral perfusate.

Cardiopulmonary bypass was instituted using standard bicaval cannulation and cannulation of either the left femoral artery, ascending aorta, or aortic arch. A 26F superior vena cava cannula was used to allow greater cephalad flow during RCP and positioned in the superior vena cava so that its tip was just cephalad to the insertion of the ayzygous vein. The left ventricle was vented via the right superior pulmonary vein. Patients were cooled on cardiopulmonary bypass for a minimum of 30 min. Antegrade cerebral perfusion was not interrupted until the EEG became isoelectric (<2 μV for 3 min) and the N20-P22 SEP disappeared (amplitude <0.05 μV) bilaterally. At that time, the patient was partially exsanguinated, the superior vena cava was snared between the right atrium and ayzygous vein, and the cardiopulmonary bypass circuit was converted to a system for delivering RCP (4). RCP with oxygenated blood was adjusted to maintain a right internal jugular venous pressure of 25 mm Hg (transducer zeroed at the level of the left atrium) with the patient in an approximately 10° Trendelenberg position. RCP was interrupted for variable periods of time during deep hypothermia at the onset of HCA while the aortic arch was opened, when an absolutely bloodless operating field was required, when air had to be removed from the venous circulation, and when the arterial cannula was placed into the aortic graft for antegrade perfusion. The temperature of the retrograde perfusate was maintained at 10°C. After completion of aortic arch anastomoses, air was removed from the aorta and graft by allowing it to fill via RCP. After “deairing,” a cross-clamp was placed across the

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>No stroke</th>
<th>Preoperative stroke&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Intraoperative stroke&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>9</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>66 ± 12 (39–80)</td>
<td>75 ± 2 (72–75)</td>
<td>71 ± 4 (65–74)</td>
</tr>
<tr>
<td>HCA temperature (°C)</td>
<td>14.3 ± 1.1 (12.4–16.1)</td>
<td>14.1 ± 1.1 (13.2–15.2)</td>
<td>13.0 ± 3.0 (10.0–16.5)</td>
</tr>
<tr>
<td>Duration of HCA (min)</td>
<td>39 ± 15 (19–70)</td>
<td>44 ± 6 (39–52)</td>
<td>56 ± 34 (30–106)</td>
</tr>
<tr>
<td>Duration of RCP (min)</td>
<td>34 ± 13 (16–61)</td>
<td>36 ± 6 (35–47)</td>
<td>48 ± 27 (27–87)</td>
</tr>
<tr>
<td>Duration of no flow (min)</td>
<td>5 ± 4 (2–14)</td>
<td>5 ± 3 (3–11)</td>
<td>9 ± 7 (3–19)</td>
</tr>
<tr>
<td>Fraction of no-flow time</td>
<td>0.12 ± 0.07 (0.04–0.33)</td>
<td>0.12 ± 0.06 (0.08–0.22)</td>
<td>0.14 ± 0.05 (0.10–0.20)</td>
</tr>
<tr>
<td>RCP flow rate (mL/min)</td>
<td>220 ± 83 (60–360)</td>
<td>152 ± 17 (130–170)</td>
<td>272 ± 34 (230–300)</td>
</tr>
<tr>
<td>Hemoglobin of perfusate (g/dL)</td>
<td>8.0 ± 1.5 (5.8–10.6)</td>
<td>7.2 ± 1.8 (4.2–9.0)</td>
<td>6.7 ± 0.2 (6.5–6.9)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes one patient with both preoperative and intraoperative stroke.
ascending aorta, and standard cardiopulmonary bypass with antegrade cerebral perfusion was reintroduced for the final stage of repair and rewarming. The duration of HCA was defined as the elapsed time from the interruption of antegrade cerebral perfusion to the reintroduction of antegrade cerebral perfusion via the standard cardiopulmonary bypass circuit. The duration of RCP was defined as the sum total of all time periods during HCA that RCP was maintained. The "no-flow" time was defined as the sum total of all time periods during HCA when RCP was not administered. The fraction of no-flow time was the percentage of time during HCA when RCP was not administered.

Serial blood samples were obtained during HCA at different times after the interruption of antegrade cerebral perfusion. At each sampling time, blood was collected simultaneously from the RCP inflow (oxygenated blood entering the superior vena cava) and RCP outflow (blood trickling out of the left carotid or distal innominate arteries). Measurements of PO2, PCO2, pH, and co-oximetry were performed immediately on the blood samples and measured at 37°C. Alpha-stat analysis in which measured values were not temperature-corrected to the patient’s actual body temperature was used. Oxygen content was calculated using the formula:

\[
O_2 \text{ content (vol\%)} = \frac{[Hb] \times 1.36 + 0.003 \times PO_2}{1 + \frac{[Hb] \times 1.36}{1.36}}
\]

where So2 is oxygen saturation (%) of the sample measured by co-oximetry, Hb is the concentration of hemoglobin (g/dL) of the sample measured by co-oximetry, and PO2 is the oxygen tension (mm Hg) in the sample. The oxygen extraction ratio (OER) was calculated from the formula:

\[
OER = \frac{(O_2 \text{ content}_{\text{RCP inflow}} - O_2 \text{ content}_{\text{RCP outflow}})}{O_2 \text{ content}_{\text{RCP inflow}}}
\]

where O2 contentRCP inflow is the calculated oxygen content (vol%) of blood in the RCP perfusate entering the superior vena cava and O2 contentRCP outflow is the oxygen content (vol%) of blood collected from the left carotid or innominate artery.

All measured variables were treated as continuous variables. Repeated-measures analysis of variance was used to test for changes in measured variables during HCA. Spearman rank correlation analysis was used to determine whether patient-specific characteristics such as age, hemoglobin concentration, temperature at the time of HCA, and fraction of no-flow time were related to the changes in PO2, PCO2, or pH of the retrograde outflow. Multiple linear regression analysis was used to test whether the following factors—time after circulatory arrest, preoperative stroke, or intraoperative stroke—affected the OER or the RCP inflow-outflow gradients for SO2, O2 content, PCO2, or pH. Nonlinear regression analysis was performed to quantify further the change in OER over time during HCA with RCP.

Results

Nineteen patients (9 male and 10 female) did not have preoperative or postoperative strokes. Five patients had preoperative strokes, three patients had isolated intraoperative strokes, and one of the five patients with preoperative strokes also had an intraoperative stroke (Table 1). All 19 of the patients without strokes survived the operation. The mean (±sd) age of the patients without stroke was 66 ± 12 yr, duration of HCA was 39 ± 15 min, duration of RCP was 34 ± 13 min, duration of no-flow was 5 ± 4 min, fraction of no-flow time was 0.12 ± 0.07, RCP flow rate was 220 ± 83 mL/min, Hb in the RCP perfusate was 8.0 ± 1.5 g/dL, and nasopharyngeal temperature during HCA was 14.3 ± 1.1°C (Table 1). The mean nasopharyngeal temperature at the onset of HCA was 14.3°C, and at the end of HCA was 14.2°C, a change that was not statistically significant (P = 0.36).

Changes in the PO2 and PCO2 of blood sampled from the RCP inflow and outflow over time after HCA was analyzed from individual patients and from pooled data that included all patients. In 12 of 15 patients (80%) who had blood samples from at least two time points after HCA, the PCO2 in the RCP outflow increased between the first and second measurements (Figure 1A). In four of five patients (80%) who had blood samples from at least three time points after HCA, the PCO2 in the RCP outflow also increased over time. The mean rate of increase in PCO2 in individual patients was 0.24 mm Hg/min with a range of −0.16 to 0.64 mm Hg/min. The mean rate of increase estimated from pooled data that included all patients was 0.43 mm Hg/min.

In 13 of 15 patients (87%) who had blood samples from at least two time points after HCA, the PO2 in the RCP outflow decreased between the first and second measurements (Figure 1B). In four of five patients (80%) who had blood samples from at least three time points after HCA, the PO2 in the RCP outflow also decreased over time. The mean rate of decrease in PO2 over time in individual subjects was 1.5 mm Hg/min, with a range of −0.63 to 4.5 mm Hg/min. The mean rate of decrease estimated on the basis of pooled data from all patients was 1.0 mm Hg/min.

Patient-specific factors did not affect the rate of change in any of the measured variables during HCA with RCP in the group of patients without strokes. The Spearman rank correlation among patient age, nasopharyngeal temperature, hemoglobin concentration,
and fraction of no-flow time during HCA with RCP showed no relation \((P > 0.2)\) to the rate of decrease in \(P_{\text{O}_2}\), the rate of increase in \(P_{\text{CO}_2}\), and the rate of decrease in pH.

Linear regression analysis performed on the pooled data from patients without stroke demonstrated a significant increase in OER (slope = 0.01 min\(^{-1}\), \(r = 0.84\), \(P < 0.001\)) and a decrease in the \(O_2\) saturation of the RCP outflow as a function of time after initiation of HCA (Table 2). In addition, the \(O_2\) content difference, \(P_{\text{CO}_2}\) difference, and pH difference between the RCP inflow and outflow samples increased significantly over time after initiation of HCA in the group of patients without stroke (Table 2, Figure 2). The minimal oxygen content difference measured was 0.6 vol% 4 min after interruption of antegrade cerebral perfusion, and the maximal oxygen content difference measured was 8.8 vol% 53 min after interruption of antegrade cerebral perfusion in the entire group of patients studied (Figure 2). The minimal OER measured was 0.07 at 1 min after interruption of antegrade cerebral perfusion, and the maximal OER measured was 0.66 at 53 min after interruption of antegrade cerebral perfusion in the entire group of patients studied.

Nonlinear regression analysis on the effect of time after HCA on the OER in patients without strokes using a standard bounded monotonic response function yielded the equation \(\text{OER} = 0.82 - 0.71e^{-t/40.3}\) as the best fit with a correlation coefficient of \(r^2 = 0.71\) (Figure 3). According to this model, the OER reaches 0.5 of its maximal value of 0.66 at 15 min after HCA.
The finding that OER across the brachiocephalic vascular bed increased over time after interruption of antegrade cerebral perfusion when RCP was used indicates continuing metabolic activity during HCA. Although samples used for analysis consisted of pooled blood from the brachiocephalic vessels, it is likely that the measurements made on RCP outflow blood specimens did, to some degree, reflect cerebral metabolic activity. Support for this conclusion comes, in part, from the observation that RCP outflow oxygen content, Pco₂, and pH differences were less in patients with strokes compared with patients without strokes. This finding was based on a limited number of measurements but was expected as a consequence of reduced cerebral metabolic activity from cerebral infarction. Additional support for the contention that the RCP outflow measurements provided a measure of cerebral metabolic activity during HCA was the consistent increase in OER that paralleled the decrease in amplitude of brainstem somatosensory evoked potentials over time during HCA that was observed in a previous study (16). The decrease in somatosensory evoked potential amplitudes over time during HCA with RCP in patients without stroke suggests relative cerebral hypoperfusion, rather than infarction, as did the increase in OER (20,21). As displayed in Figure 3, the time for the brainstem somatosensory evoked potential to decrease to half of its initial amplitude was 16 min, which is similar to the 15 min it took for the OER to increase to half its maximal value.

The metabolic changes observed in the study are also consistent with the metabolic changes observed in animal studies in which it was possible to perform direct measurements of cerebral metabolism during HCA with RCP. Significant gradients in oxygen saturation, Po₂, Pco₂, and pH across the cerebral vascular bed were observed after the interruption of antegrade cerebral perfusion in baboons subjected to HCA with RCP (10).
Clinical studies verifying the ability to perfuse the brain via RCP provide further support for the assumption that blood specimens from the RCP outflow were a sampling of blood that had perfused regions of the brain. Methods that have been used to verify the presence of cerebral blood flow during HCA with RCP in humans include intraoperative brain perfusion imaging using technetium Tc 99m-labeled d,L-hexamethyl propylene amine oxime (18), direct measurement of cortical blood flow using laser Doppler flow probes that were placed in a cranial window (15), the demonstration of retrograde blood flow in the middle cerebral artery using transcranial Doppler ultrasonography (19), and the observation of an acute increase in cerebral oxygen saturation with the onset of RCP using near infrared spectroscopy (14).

Sampling blood from the RCP outflow to assess cerebral metabolic activity during HCA may provide a means to determine the safe duration for HCA with RCP by detecting the time point when relative cerebral ischemia becomes cerebral infarction signaled by an acute decrease in the OER. Studies in humans using positron emission tomography to measure regional OER in the brain have demonstrated that symptomatic cerebral ischemia associated with stroke was associated with acute increases in the OER of affected brain regions (20,21). In those studies, the OER of ischemic regions of the brain ranged from 0.54 to 0.67 compared with values that ranged from 0.35 to 0.45 in regions of the brain that were not ischemic (20,21). In contrast, the OER decreased over time in regions of the brain that evolved into infarction, a finding that suggests decreased regional metabolism due to cell death (20). In the extreme case of brain death, the average value for OER measured across the cerebral vascular bed decreased to 0.12 (22). The similarity between the maximal and minimal OER values measured by sampling blood during HCA with RCP and the OER values that had been determined using positron emission tomography suggests that the RCP outflow could be used to assess cerebral metabolism. The decreased rate of increase in the OER and oxygen content difference during HCA with RCP observed in the group of patients with preoperative or intraoperative strokes was also consistent with the contention that the RCP outflow samples provided an assessment of cerebral metabolism during HCA. Although a maximal safe duration for HCA using RCP could not be determined from the data in this study, it is likely that an acute reduction in OER or outflow PCO2 would signal infarction. Further investigation with larger numbers of patients, a wider range of HCA duration, and the inclusion of patients with intraoperative strokes would be required to verify this hypothesis.

An alternative explanation for the time course of changes in oxygen extraction, PCO2, and pH in the RCP outflow specimens was that the transit time of

Figure 2. Changes in the retrograde cerebral perfusion (RCP) inflow-outflow O2 content difference (A) and RCP inflow-outflow PCO2 difference (B) as a function of time after the initiation of hypothermic circulatory arrest (HCA) for patients without strokes (CTR; n = 19), with preoperative stroke (△; n = 4), with intraoperative stroke (●; n = 3), and with both preoperative and intraoperative stroke (●; n = 1). Linear regression analysis (fitted line) indicated a change in RCP inflow-outflow O2 content difference of 0.11 vol%/min (r = 0.82, P < 0.001) and a change in the RCP inflow-outflow PCO2 difference of −0.73 mm Hg/min (r = 0.82, P < 0.001) over time after HCA in patients without stroke.
blood and retrograde cerebral perfusate across the cerebral vascular bed was slow. A slow transit time would mean that the composition of blood sampled from the RCP outflow shortly after the onset of HCA consisted mainly of blood that had been pooled in the arterial circulation that had not perfused capillary beds in the brain. Over time, the composition of blood from the RCP outflow would more closely resemble the composition of blood perfusing capillary beds in the central nervous system. Variable shunting of blood away from cerebral vascular beds toward other vascular beds with lower metabolic activity at the onset of RCP could also explain the lower OER at the beginning of HCA. Finally, changes in oxygen extraction, P\text{CO}_2, and pH in the RCP outflow samples could also reflect metabolic changes outside the central nervous system caused by nonelective perfusion of the upper body via RCP. This consideration prompted the attempt to obtain RCP outflow samples from the distal carotid arteries when possible. However, these reasons would not explain the differences observed in the group of patients who had strokes.

In summary, RCP inflow and outflow blood samples were measured to assess the time course of metabolic changes across the brachiocephalic circulation during HCA when antegrade cerebral perfusion was interrupted. The observation that oxygen extraction was near maximal after 40–60 min of HCA with RCP is consistent with other studies that suggest relative hypoperfusion during RCP. Reduced cerebral metabolism in infarcted regions may explain the lower OER observed in stroke patients and deserves further investigation.

References


Gwenifer C. M. Wilson, MD

Nicholas M. Greene, MD