Rapid Rewarming Causes an Increase in the Cerebral Metabolic Rate for Oxygen that Is Temporarily Unmatched by Cerebral Blood Flow

A Study during Cardiopulmonary Bypass in Rabbits

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Background: Jugular venous hemoglobin desaturation during the rewarming phase of cardiopulmonary bypass is associated with adverse neuropsychologic outcome and may indicate a pathologic mismatch between cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMR0₂). In some studies, rapid rewarming from hypothermic cardiopulmonary bypass results in greater jugular venous hemoglobin desaturation. The authors wished to determine if rewarming rate influences the temperature dependence of CBF and CMR0₂.

Methods: Anesthetized New Zealand white rabbits, cooled to 25°C on cardiopulmonary bypass, were randomized to one of two rewarming groups. In the fast group (n = 9), aortic blood temperature was made normothermic within 4 min. In the slow group (n = 9), aortic blood temperature was made normothermic over 25 min. Cerebral blood flow (microspheres) and CMR0₂ (Fick) were determined at baseline (25°C), and at brain temperatures of 28°, 31°, 34°, and 37°C during rewarming.

Results: Systemic physiologic variables appeared similar between groups. At a brain temperature of 28°C, CMR0₂ was 47% greater in the fast rewarming group than in the slow group (2.2 ± 0.5 vs 1.5 ± 0.2 ml O₂ g⁻¹ min⁻¹, respectively; P = 0.01), whereas CBF did not differ (48 ± 18 vs. 49 ± 8 ml · 100 g⁻¹ · min⁻¹, respectively; P = 0.47). Throughout rewarming, CBF increased as a function of brain temperature but was indistinguishable between groups. Cerebral metabolic rate for oxygen differences between groups decreased as brain temperatures increased.

Conclusions: Cerebral venous hemoglobin desaturation with rapid rewarming is caused by an increase in CMR0₂ that is temporaril greater than the increase in CBF. This mismatch may indicate a transient abnormality in flow-metabolism coupling, or the effect of temperature gradients on oxygen transfer from hemoglobin to brain. (Key words: Brain: cerebral blood flow; rewarming; temperature. Metabolism: flow-metabolism coupling; temperature. Surgery, cardiac: cardiopulmonary bypass.)

THIRTY to 60% of cardiac surgery patients have impaired cognitive and neuropsychologic performance in the first postoperative week.1,2 Although neuropsychologic impairment tends to improve with time, 10–30% of cardiac surgery patients have measurable deterioration of their cognitive status months to years after undergoing surgery.3–5 Microemboli, of either gas6 or particulates,7,8 certainly contribute to these cognitive changes. Nevertheless, the diffuse, nonfocal nature of neuropsychologic impairment also is consistent with a period of globally impaired cerebral oxygenation, most likely during cardiopulmonary bypass (CPB).

Evidence that such a period exists has recently been provided by several groups who observed that jugular venous hemoglobin saturation decreases, sometimes markedly, during the rewarming phase of CPB.9–14 Croughwell et al.2 and Newman et al.13 reported an association between the magnitude of rewarming-induced jugular venous hemoglobin desaturation and the severity of postoperative neuropsychologic dysfunction. Consequently, it has been suggested that jugular venous hemoglobin desaturation indicates there is a clinically significant “mismatch” between cerebral oxygen consumption and delivery during the rewarming phase of CPB. In some studies, the magnitude of this mismatch also appeared to be related to rewarming...
rate. Nakajima et al.12 and van der Linden et al.14 both noted that jugular venous desaturation was greater with greater rewarming rates.

Greater jugular venous hemoglobin desaturation with faster rewarming can be explained two ways. At any given brain temperature during rewarming, either: (1) fast rewarming results in greater cerebral metabolic rate for oxygen (CMRO₂) than slow rewarming, but cerebral blood flows (CBF) do not differ; or (2) fast rewarming results in lesser CBF than slow rewarming, but CMRO₂ does not differ. To distinguish between these possibilities, we used a rabbit model of CPB. We hypothesized that CBF/CMRO₂ differences between fast and slow rewarming (if present) would be greatest when rewarming rates differed most greatly.

Materials and Methods

Study Design

Experimental protocols were approved by the Animal Care and Use Committee of the University of Iowa in accordance with the “Guide for the Care and Use of Laboratory Animals” (National Institutes of Health Publication No. 85-23, revised 1985).

We planned to serially measure CBF and CMRO₂ at predetermined brain temperatures during fast and slow rewarming (25–37°C). With multiple measurements, we recognized the potential for a large number of CBF and CMRO₂ comparisons. Given CBF and CMRO₂ variances from previous experiments, a prohibitively high number of animals would have been required to avoid a type II error, were all potential comparisons to be made. Because we hypothesized that CBF/CMRO₂ differences between fast and slow rewarming would be greatest when brain rewarming rates differed most greatly, an a priori decision was made to formally compare CBF and CMRO₂ between groups only at the point of maximal difference in brain rewarming rate. Based on our mathematical model of brain heat transport during CPB,15 we expected this would occur at the first measurement point during rewarming (specifically, at a brain temperature of 28°C; see Protocol later). However, because the behavior of CBF and CMRO₂ during the remaining warming period was of interest, later data points were obtained.

Basic Preparation

Twenty New Zealand white rabbits (weight, 4–5 kg) were randomly preassigned to one of two groups, according to whether they would undergo fast or slow rewarming during CPB. Anesthesia was induced by inhalation of 3–5% isoflurane in oxygen. After local infiltration with 1% lidocaine, a tracheotomy was performed and the trachea was intubated with a 3.0-mm cuffed endotracheal tube. Thereafter, the animals’ lungs were mechanically ventilated to achieve normocarbia, and anesthesia was maintained with 2% isoflurane in oxygen for the remainder of pre-CPB preparation, monitored by a calibrated agent analyzer (Datex-Puritan-Bennett, Helsinki, Finland). Animals were paralyzed with an infusion of 2 mg/ml, 4 ml·kg⁻¹·h⁻¹ succinylcholine/lactated Ringer’s solution via a 22-G car vein catheter and positioned prone. After a midline sagittal scalp incision, a 2-mm burr hole was drilled over the right frontoparietal cortex, and a calibrated 1-mm thermocouple (K-type, L-08419-02, Cole Parmer, Chicago, IL) was inserted under the cranium to rest on the dural surface overlying cerebral cortex. The response time of this thermocouple (25–37°C) was less than 1 s. A posterior midline craniectomy was performed, exposing the confluens sinuorum. Heparin was administered as a bolus (200 IU/kg intravenously) and was added to the succinylcholine/lactated Ringer’s infusion to give a maintenance dose of 200 IU·kg⁻¹·h⁻¹. The tip of a saline-filled polyethylene catheter (PE-90, Intramedic, Parsippany, NJ) was placed in the confluens sinuorum, permitting collection of cerebral venous blood. Anatomic and physiologic studies in the rabbit have shown that venous blood at this site is derived almost entirely from cerebral cortex, with no detectable extracerebral contamination.16 The thermocouple and cerebral venous catheter were secured with bone wax and fast-drying cyanacrylate cement, and the animals were placed supine.

The tip of a saline-filled catheter (PE-90), introduced via the right external jugular vein, was advanced to the superior vena cava to measure central venous pressure. An incision was made 2–3 mm inferior to the midpoint of the mandibular ramus, and the facial artery was cannulated retrograde (i.e., toward the aortic arch) with a saline-filled catheter (PE-50) for arterial pressure monitoring. Both subclavian arteries were cannulated (saline-filled PE-160) for microsphere reference blood sampling. These catheters also were used to collect arterial blood. To monitor arterial blood temperature, a calibrated 1-mm thermocouple (as above) was introduced via the left subclavian artery so that its tip was in the aortic arch.
A midline abdominal incision was made. Viscera were packed away from the operative field with saline-soaked gauze and the distal abdominal aorta was isolated. The sternum was divided in the midline, the thymus was retracted, and a pledgeted 4-0 silk pursestring suture was placed in the right atrium. After systemic anticoagulation with heparin (300 IU/kg, intravenous), the distal aorta was ligated at the bifurcation and cannulated retrograde with a 10-French pediatric arterial perfusion cannula (Biomedicus, Eden Prairie, MN) 7–10 mm superior to the distal aortic bifurcation. A 21-French venous cannula (Polystan, Ballerup, Denmark) was placed in the right atrium. The aortic and right atrial cannulas were connected to the perfusion circuit, and CPB was initiated as described later. Approximately 30 min before CPB, isoflurane, maintenance fluids, and the succinylcholine/heparin infusion were discontinued. Anesthesia was maintained for the rest of the experiment with fentanyl (100 μg/kg bolus, 150 μg·kg⁻¹·h⁻¹ infusion) and diazepam (2 mg/kg bolus, 3 mg·kg⁻¹·h⁻¹ infusion). Muscle relaxation was achieved with 0.2 mg/kg pancuronium.

Cardiopulmonary Bypass

The CPB circuit consisted of a venous reservoir, membrane oxygenator (Capiq 308, Terumo, Piscataway, NJ), variable-temperature water pump (VWR Scientific, San Francisco, CA), and centrifugal pump (model 540, Biomedicus, BP-50 pump head). Circuit priming fluid consisted of 300 ml 6.5% (weight/volume) high molecular weight hydroxyethyl starch (McGaw, Irvine, CA) in 0.7% sodium chloride, 18 mM sodium bicarbonate, 250 mg CaCl₂, and 1,000 IU heparin. The priming fluid was circulated through a 40-μm filter for 15–20 min before addition of ~150 ml fresh, filtered, packed rabbit erythrocytes, achieving a priming hemoglobin concentration of 6–10 g/dl (OSM3; rabbit absorption coefficients; Radiometer, Copenhagen, Denmark).

Cardiopulmonary bypass was initiated and maintained throughout the entire experiment at a systemic flow rate of 100 ml·kg⁻¹·min⁻¹, monitored with a calibrated in-line electromagnentic flow meter (Biomedicus, TX-40P). The pulmonary artery was clamped to ensure complete venous outflow to the CPB circuit. To prevent left ventricular ejection and/or distention, the tip of a 14-G catheter was placed transapically in the left ventricle to permit drainage to the venous reservoir. Systemic cooling began with onset of CPB with water to the heat exchanger being maintained at 25°C. The oxygenator was ventilated with a variable mixture of oxygen and nitrogen to maintain Pa₄CO₂ near 40 mmHg and PaO₂ near 250 mmHg when measured at an electrode temperature of 37°C (α-stat acid-base management) (LI1304, Instrumentation Laboratory, Lexington, MA). Blood from the surgical field was returned to the venous reservoir after passing through a 40-μm filter. Before rewarming, sodium bicarbonate was given to maintain a base excess greater than -4 mEq/l, calculated at 37°C. No bicarbonate was given during rewarming to prevent abrupt changes in Pa₄CO₂. Rabbit erythrocytes were given to maintain a hemoglobin concentration near 7 g/dl. No pharmacologic or mechanical means were used to control arterial pressure at any time during the experiment.

Protocol

All animals were cooled to 25°C and were maintained at this temperature for the first 50 min of CPB. Animals were randomly assigned to either fast (n = 10) or slow (n = 10) rewarming. At 50 min of CPB, heat exchanger water tubing was clamped. In the fast group, the temperature of the water bath was increased to 40°C, where it remained for the duration of the experiment. In the slow group, the temperature of the water bath was increased to 30°C (subsequent adjustments described later). At 55 min of CPB (brain temperature still 25°C), the following were recorded: arterial pressure, central venous pressure, systemic flow rate, brain (epidural) temperature, and aortic blood temperature. Concurrent with these measurements, CBF was determined (as described later) and arterial and cerebral venous blood was collected for blood gas analysis and measurement of oxyhemoglobin saturation.

At exactly 60 min of CPB, rewarming was initiated by release of clamps from the heat exchanger water tubing. In animals assigned to fast rewarming, water bath temperature remained at 40°C. In animals assigned to slow rewarming, water bath temperature was increased from 30°C to 35°C at 10 min of rewarming, and increased to 40°C at 20 min of rewarming. At target brain temperatures of 28°C, 31°C, 34°C, and 37°C, the duration of rewarming was recorded and all physiologic measurements described above were repeated. At no time was surface heating or cooling employed. When brain temperature was ≥36.6°C, the experiment was considered complete. Animals were killed by discontinuation of CPB and intracardiac injection of saturated potassium chloride solution.
Cerebral Blood Flow and Cerebral Metabolic Rate for Oxygen Measurements

Cerebral blood flow was measured by the radioactive microsphere technique. Isotopes used included $^{48}$Sc, $^{89}$Sr, $^{99}$Nb, $^{111}$Sn, and $^{141}$Ce (New England Nuclear, Boston, MA). Stock microspheres (200 μl, ~0.9 million microspheres), vigorously mixed for 5 min before withdrawal, were diluted in 1.5 ml suspending solution (10% dextran-40 in normal saline with 0.5% (vol/vol) Tween-80) and mixed for an additional 60 s before injection. Microspheres were injected over 30 s into the arterial perfusion line approximately 25 cm proximal to the distal tip of the aortic cannula. Starting 30 s before microsphere injection, and continuing ≥90 s thereafter, blood was simultaneously withdrawn from each subclavian arterial catheter via a calibrated withdrawal pump (1.96 ml/min). Because of the need for rapid sampling, all reference blood was collected in two (right and left) 30-ml syringes, rather than separate syringes for each isotope. In instances where time between CBF determinations was <3 or >4 min, reference blood was continuously, rather than intermittently, collected.

After the experiment, the brain was removed and dissected into the following regions: right and left cerebral cortex, cerebellum, mid brain, and medulla. Fresh tissue samples were weighed, placed in counting tubes and, with reference blood samples, each counted for 5 min in a sodium iodide well-type gamma counter (Minaxi γ Auto-Gamma 5000, Packard Instruments, Meriden, CT). Isotope separation, background, overlap corrections, and CBF calculations (ml · 100 g⁻¹ · min⁻¹) were performed by standard techniques. Weight-averaged values for right and left cortical CBF were used to calculate mean cortical CBF.

Arterial and cerebral venous oxygen content (ml O₂/dl) was calculated as (1.39 × percent saturation × hemoglobin concentration (g/dl)) + (PO₂ × 0.003). Cerebral oxygen extraction ratio was calculated as the arterial-cerebral venous oxygen content difference, divided by arterial oxygen content. Cerebral metabolic rate for oxygen (ml O₂·100 g⁻¹·min⁻¹) was calculated as the product of mean cortical CBF and the arterial-cerebral venous oxygen content difference.

Statistics

One animal from each group was omitted before analysis. One animal from the fast group was deleted because of inadequate microsphere mixing. One animal from the slow group was deleted because of inadequate microsphere mixing and cerebral venous sampling problems. Hence, data from nine animals in each group were analyzed.

Right and left microsphere reference counts appeared to be normally distributed, permitting linear regression analysis to test adequacy of microsphere mixing and distribution. In contrast, box and whisker plots suggested that many variables were not normally distributed. Consequently, all physiologic variables were summarized using their median ± quartile deviation, the latter equaling half the difference between the first and third quartiles. Systemic physiologic variables were assessed qualitatively to preserve statistical power to detect differences in CBF and CMRO₂.

Analyses were performed using Systat statistical software. Cerebral blood flow and CMRO₂ at 28°C were compared between groups using independent samples, two-sided t tests, with separate variances. Cerebral blood flow appeared to follow a normal distribution. Cerebral metabolic rate for oxygen appeared to follow a log-normal distribution. Thus, CMRO₂ was log-transformed before analysis. All statistical assumptions were satisfied, and there were no outliers.

Results

Microsphere Validation

Paired right and left microsphere reference counts were well matched ($r^2 = 0.967$, slope = 1.10, intercept ($-279$ cpm) not significantly different than zero), indicating adequate microsphere mixing and uniform distribution. There were no right-left CBF asymmetries between the cerebral hemispheres.

Systemic Variables

Systemic physiologic variables are summarized in table 1. As intended, aortic blood temperature rapidly increased to normothermic values in the fast group (~4 min) whereas, in the slow group, 25–30 min were required. There were no physiologically meaningful differences between groups, or over time, with respect to the following variables: mean arterial pressure, central venous pressure, arterial pH level, PaO₂, PaCO₂, arterial hemoglobin concentration, or oxygen content.

Cerebral Physiology

Cerebral physiologic variables are summarized in table 2. Cerebral blood flow, oxygen extraction ratio, and CMRO₂ are shown as functions of brain temperature.
Table 1. Systemic Physiologic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>25</th>
<th>28</th>
<th>31</th>
<th>34</th>
<th>37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic blood temperature (°C)</td>
<td>Fast</td>
<td>25.5 (0.4)</td>
<td>36.8 (1.3)</td>
<td>37.5 (1.0)</td>
<td>37.9 (0.8)</td>
<td>38.3 (0.7)</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>26.0 (0.3)</td>
<td>29.3 (0.7)</td>
<td>33.6 (0.6)</td>
<td>36.5 (0.7)</td>
<td>37.7 (0.4)</td>
</tr>
<tr>
<td>Rewarming time (min)</td>
<td>Fast</td>
<td>3.7 (0.5)</td>
<td>6.0 (0.7)</td>
<td>9.1 (1.3)</td>
<td>15.6 (1.9)</td>
<td>33.6 (1.9)</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>8.5 (1.9)</td>
<td>18.5 (0.7)</td>
<td>25.4 (1.4)</td>
<td>36.5 (0.7)</td>
<td>37.7 (0.4)</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>Fast</td>
<td>81 (14)</td>
<td>71 (13)</td>
<td>91 (13)</td>
<td>92 (13)</td>
<td>98 (18)</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>86 (8)</td>
<td>78 (6)</td>
<td>84 (9)</td>
<td>84 (9)</td>
<td>98 (18)</td>
</tr>
<tr>
<td>Central venous pressure (mmHg)</td>
<td>Fast</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>pHs</td>
<td>Fast</td>
<td>7.39 (0.02)</td>
<td>7.41 (0.02)</td>
<td>7.41 (0.02)</td>
<td>7.40 (0.02)</td>
<td>7.36 (0.03)</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>7.43 (0.01)</td>
<td>7.41 (0.01)</td>
<td>7.36 (0.01)</td>
<td>7.36 (0.01)</td>
<td>7.32 (0.02)</td>
</tr>
<tr>
<td>(P_{aO_2}) (mmHg)</td>
<td>Fast</td>
<td>267 (11)</td>
<td>253 (45)</td>
<td>270 (52)</td>
<td>298 (57)</td>
<td>221 (26)</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>247 (7)</td>
<td>245 (73)</td>
<td>290 (37)</td>
<td>190 (54)</td>
<td>186 (33)</td>
</tr>
<tr>
<td>(P_{aCO_2}) (mmHg)</td>
<td>Fast</td>
<td>40 (2)</td>
<td>37 (1)</td>
<td>36 (2)</td>
<td>36 (2)</td>
<td>38 (2)</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>37 (2)</td>
<td>36 (2)</td>
<td>38 (1)</td>
<td>39 (1)</td>
<td>43 (1)</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>Fast</td>
<td>6.6 (0.5)</td>
<td>6.9 (0.6)</td>
<td>6.9 (0.6)</td>
<td>7.0 (0.4)</td>
<td>7.0 (0.3)</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>6.9 (0.3)</td>
<td>7.0 (0.1)</td>
<td>7.0 (0.3)</td>
<td>7.0 (0.4)</td>
<td>7.2 (0.2)</td>
</tr>
<tr>
<td>Arterial oxygen content (ml O2/dl)</td>
<td>Fast</td>
<td>9.8 (0.6)</td>
<td>10.0 (0.9)</td>
<td>10.0 (0.9)</td>
<td>10.3 (0.8)</td>
<td>10.5 (0.4)</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>10.1 (0.4)</td>
<td>10.5 (0.3)</td>
<td>10.4 (0.3)</td>
<td>10.1 (0.3)</td>
<td>10.3 (0.4)</td>
</tr>
</tbody>
</table>

Values are median and quartile deviation (parentheses); n = 9.

in figure 1. At prewarming baseline (25°C), CBF, CMRO2, and oxygen extraction ratio appear to have been equivalent between groups. In the fast group, times to achieve target temperatures were 32–46% of those in the slow group. In the fast group, blood-brain temperature gradients were greater than those in the slow group, the difference between groups being most marked at a brain temperature of 28°C (8.5 ± 1.5°C vs. 1.5 ± 0.7°C, respectively). At a brain temperature of 28°C, CMRO2 was 47% greater in the fast group than in the slow group (2.2 ± 0.5 vs. 1.5 ± 0.2 ml O2·100 g−1·min−1, respectively; P = 0.01), whereas CBF did not differ between groups (48 ± 18 vs. 49 ± 8 ml·100 g−1·min−1, respectively; P = 0.47).

Throughout the rest of rewarming, CBF remained indistinguishable between groups. In contrast, the CMRO2 difference between groups decreased as brain temperature increased. At 31°C, median CMRO2 was ~35% greater in the fast group. At 34°C, median CMRO2 was only 10% greater in the fast group, and by 37°C, median CMRO2 was equivalent between groups.

Discussion

During rewarming, CBF appeared to vary solely with brain temperature, independent of blood temperature, blood-brain temperature gradients, and rate of rewarming. In contrast, at equivalent brain temperatures, CMRO2 was greater during fast rewarming than during slow rewarming. Cerebral metabolic rate for oxygen differences between groups were greatest when blood-brain temperature gradients differed most greatly between groups. The disparate effect of rewarming rate on CBF and CMRO2 was associated with greater oxygen extraction in the fast rewarming group (figure 1 and table 2). Clinically, greater oxygen extraction would correspond to greater levels of jugular venous desaturation. Thus, in this experiment, the "abnormality" in the relationship between brain blood flow and metabolism during rewarming appears to have been caused by an increase in CMRO2, that was "unmatched" by an increase in CBF.

The Effect of Rewarming on Cerebral Metabolism

To our knowledge, this experiment is the first to observe that CMRO2 varies not only with brain temperature but with rewarming rate as well. The phenomenon is very short-lived and would be undetectable by methods of CBF and CMR determination requiring more than a few minutes. Hence, current techniques to measure brain blood flow and metabolism during clinical CPB do not have sufficient temporal resolution to observe this phenomenon. Because the microsphere "bolus" is trapped in brain on the first pass,31 the time over
BRAIN BLOOD FLOW AND METABOLISM WITH REWARMING

Table 2. Cerebral Physiologic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Target Brain Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Brain temperature (°C)</td>
<td>Fast 25.2 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Slow 25.3 (0.3)</td>
</tr>
<tr>
<td>Blood-brain temperature difference (°C)</td>
<td>Fast 0.4 (0.3)</td>
</tr>
<tr>
<td></td>
<td>Slow 0.6 (0.1)</td>
</tr>
<tr>
<td>Cerebral venous oxygen content (ml O₂/dl)</td>
<td>Fast 6.7 (0.7)</td>
</tr>
<tr>
<td></td>
<td>Slow 6.6 (0.4)</td>
</tr>
<tr>
<td>Arterial-cerebral venous oxygen content difference (ml O₂/dl)</td>
<td>Fast 3.9 (0.7)</td>
</tr>
<tr>
<td></td>
<td>Slow 3.1 (0.3)</td>
</tr>
<tr>
<td>Cerebral oxygen extraction ratio</td>
<td>Fast 0.37 (0.06)</td>
</tr>
<tr>
<td></td>
<td>Slow 0.32 (0.02)</td>
</tr>
<tr>
<td>Cerebral blood flow (ml - 100 g⁻¹·min⁻¹)</td>
<td>Fast 35 (6)</td>
</tr>
<tr>
<td></td>
<td>Slow 43 (7)</td>
</tr>
<tr>
<td>Cerebral metabolic rate for oxygen (ml O₂·100 g⁻¹·min⁻¹)</td>
<td>Fast 1.2 (0.3)</td>
</tr>
<tr>
<td></td>
<td>Slow 1.3 (0.2)</td>
</tr>
</tbody>
</table>

Values are median and quartile deviation (parentheses); in each group, n = 9.
* Cerebral metabolic rate for oxygen greater in fast group. P = 0.01.

which each CBF determination is made is largely determined by the microsphere administration time; in this experiment, 30 s. We employ correction techniques that compensate for the partial overlap of energy spectra among isotopes. This permits pooled collection of reference blood samples, making separate collections for each isotope unnecessary. By pooling reference blood samples and correcting for overlap, it is possible to make rapid serial measurements of CBF by the microsphere technique, limited only by the time necessary to inject microspheres.

A possible explanation for increased CMRO₂ in the rapid rewarming group is that brain temperature was underestimated by the epidural thermocouple, (i.e., that underlying cerebral cortex was actually warmer than indicated). We consider this unlikely. Cerebral blood flow values were derived almost entirely from cerebral cortex. Given the strong temperature dependence of CBF, the equivalency of CBF between fast and slow rewarming groups suggests brain temperatures were, indeed, equivalent between groups. Recently, Stone et al. reported that, during CPB cooling and warming in baboons, epidural and cortical temperatures were indistinguishable.²² In our experiment, the epidural thermocouple was placed directly over cortex in what was, essentially, a closed-skull preparation. Given the low thermal conductivity of bone, the effect of ambient temperature to decrease surface (cortical) temperature in open-skull preparations would be small. Also, given the small distances for thermal diffusion, the magnitude of temperature gradients within the cortical mantle would be expected to be very small. Based on a Q₁₀ of 2.6 in this experiment, if at 28°C, mean cortical temperature in the fast group would have had to have been 4°C warmer than indicated to explain the observed CMRO₂ difference between groups. Given our methods and findings, a measurement error of this magnitude is unreasonably large.

Although human studies are not currently able to directly observe CMR transients during rapid rewarming, clinical studies have observed electrophysiologic differences between cooling and rewarming during CPB. Markand et al. noted that cortical evoked potential latencies increased linearly with nasopharyngeal temperature during cooling. With rewarming, however, evoked potential latencies and amplitudes returned to normothermic values very quickly, well before nasopharyngeal temperature normalized.²³ Similar observations have been reported by Russ et al.²⁴ Markand’s data indicate that the differential effect of cooling versus rewarming is greatest at the level of thalamic relay nuclei, with transmission ofafferent input from periphery to cortex being far greater during warming. Enhancement of synaptic activity with rewarming.
would seem likely to result in an increase in brain metabolism. Hence, we speculate that the increase in CMRO₂ with rapid rewarming may have been caused by facilitated transmission of afferent input to the brain, or some other form of generalized “alerting” response. Higher blood temperatures with rapid rewarming also might cause a primary increase in afferent input, a result of stimulation of vascular and/or hypothalamic temperature sensors.

Flow-metabolism “Mismatch” during Rewarming

Typically, CBF varies proportionately with cerebral metabolic rate. This phenomenon is referred to as flow-metabolism coupling. It is hypothesized that various mediators, such as nitric oxide, adenosine, or potassium are released by neurons, glial cells, and/or perivascular nerves in response to an increase in neuronal metabolism. These mediators cause cerebrovascular smooth muscle to relax, producing an increase in CBF proportional to the increase in neuronal metabolism. To date, studies of this process have been conducted under steady-state normothermic conditions. During rewarming, and most especially rapid rewarming, a unique situation exists: brain, blood, and the cerebral vasculature may all be at different temperatures. Thus, the mismatch of flow and metabolism in the early stages of rewarming may be the result of differing temperatures at one (or more) of the steps involved in flow/metabolism coupling.

For example, the mismatch of flow and metabolism could be caused by an inability of a cold cerebral vasculature to respond to vasodilatory stimuli. Indeed, Ogura et al. have shown hypothermic cerebral microvessels are, in fact, less responsive to vasodilatory stimuli. However, this does not seem like a likely explanation for our results when one considers that flow/metabolism mismatch occurred only in the rapid rewarming group — where blood temperature, and presumably vessel temperature, was considerably greater than in the slow rewarming group. However, Ogura’s data also show that cerebral microvessels also have an initial contractile response to an acute increase in temperature. In vitro, vessels exposed to step changes in temperature (from 37°C to 40°C, 42.5°C, or 45°C) exhibit graded constrictions for 2–4 min before dilating. Perhaps then, in the fast rewarming group, the direct (but transient) constrictive effect of an abrupt increase in vessel temperature may have overwhelmed other factors that would have increased CBF in proportion to CMRO₂. Another explanation for the apparent failure
of CBF to increase in response to increased CMR_o2 during rapid rewarming could be a relative failure of hypothermic brain (neurons/glia) to produce vasodilatory mediators in response to increased CMR. Perhaps neural production of vasodilatory substances is determined more by brain temperature than by CMR per se. The close relationship between CBF and brain temperature in this experiment supports this latter hypothesis.

Still another possible explanation for the mismatch of flow and metabolism during rapid rewarming is that there was, in fact, no “mismatch” at all. Using a mathematical model of oxygen transfer from blood to brain, we have shown that oxygen transfer is highly dependent on hemoglobin oxygen affinity. When blood is cooled, oxygen transfer from hemoglobin to brain is progressively impaired, resulting in increased hemoglobin oxygen affinity (decreased hemoglobin P_50). A corollary to this prediction is that warm blood, with decreased oxygen affinity (increased P_50), should facilitate oxygen transfer from hemoglobin to brain. This facilitation should be most marked when blood is warm and brain is cold. In this situation, enhanced oxygen off-loading from hemoglobin would result in cerebral venous blood with less oxygen (i.e., a greater degree of desaturation). In the fast rewarming group, aortic blood was normothermic less than 4 min after starting rewarming. Although CMR_o2 was greater with fast rewarming, we speculate that an increase in hemoglobin P_50 may have facilitated oxygen transfer from hemoglobin to brain (i.e., increased cerebral oxygen extraction). Consequently, increased brain oxygen requirements could be met without an increase in CBF over that needed with lesser CMR_o2 (but with colder blood). Thus, increased extraction in the fast rewarming group could simply be a manifestation of facilitated blood-brain oxygen transfer, instead of a pathologic mismatch of flow and metabolism. In other words, it is possible that, in the fast rewarming group, the apparent failure of CBF to increase in proportion to CMR_o2 was not because it could not, but because it did not need to.

If this last explanation for our findings were correct, then, contrary to current thinking, cerebral venous hemoglobin desaturation with rewarming would not necessarily be a manifestation of impaired cerebral oxygenation (or flow/metabolism mismatch), but rather, would simply be the result of the concomitant effects of changing blood temperature on CMR_o2 and blood-brain oxygen transfer. Nevertheless, were rewarming-induced desaturation entirely accounted for by this mechanism, one would not expect cerebral venous hemoglobin desaturation to be associated with neuropsychological impairment, as observed by Croughwell et al. and Newman et al. Of note, in these two studies, patients who had the greatest degree of rewarming-induced jugular venous hemoglobin desaturation could, in general, be identified before rewarming was initiated. This suggests patients having the greatest degree of rewarming-induced cerebral venous hemoglobin desaturation had some preexisting cerebrovascular abnormality. Thus, it is possible that increased neuropsychological impairment in patients with marked cerebral venous hemoglobin desaturation was caused by abnormalities in flow/metabolism coupling (and/or brain injury) that were present before rewarming, rather than rewarming-induced jugular venous hemoglobin desaturation per se. Thus, in the studies by Croughwell et al. and Newman et al., warming-induced jugular venous hemoglobin desaturation may have been a marker of a brain that was injured before rewarming, and it is this injury, not the desaturation, that was responsible for postoperative neuropsychological impairment. If true, one would predict changing the magnitude of jugular venous hemoglobin saturation, either by changing rewarming rate or pharmacologically reducing CMR during rewarming, should have no effect on neuropsychological outcome. In support of this hypothesis, Newman et al. recently reported that rewarming rate had no independent effect on postoperative neuropsychological outcome.

In summary, during rewarming from 25°C to 37°C in a rabbit model of CPB, CBF depended solely on brain temperature. In contrast, at equivalent brain temperatures, CMR_o2 and brain oxygen extraction were greater with fast- than with slow-rewarming, particularly in the early phase of rewarming. Hence, cerebral venous hemoglobin desaturation with rapid rewarming is caused by an increase in CMR_o2, which is unmatched by an increase in CBF. This mismatch may indicate a transient abnormality in flow-metabolism coupling, or the effect of temperature gradients on oxygen transfer from hemoglobin to brain.

References

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