Cerebral Blood Flow and Metabolism During Cardiopulmonary Bypass

Randall M. Schell, MD, Frank H. Kern, MD, William J. Greeley, MD, Scott R. Schulman, MD, Peter E. Frasco, MD, Narda D. Croughwell, CRNA, Mark Newman, MD, and J.G. Reves, MD

Duke University Medical Center, Department of Anesthesiology, The Heart Center, Durham, North Carolina

Since the 1950s, cardiopulmonary bypass (CPB) has evolved from a high-risk technology with 50% mortality into a safe and effective procedure performed routinely at many hospitals throughout the world. Yet despite the successful application of this technology and nearly 40 yr of investigation, the effect of CPB on human physiology remains incompletely understood. Marked changes in systemic flow, temperature, perfusion pressure, arterial blood gases, and hematocrit are artificially controlled and regulated by the perfusion team and are never completely normal. Of great concern is the effect these physiologic changes have on the brain.

Recent reports suggest that neuropsychologic dysfunction may occur in ~20-70% of patients after cardiac surgery with cardiopulmonary bypass and frank stroke in ~2-5%. As progress was made in myocardial protection with a decrease in overall mortality rates for cardiac surgery (1), morbidity, especially inadequate brain protection with resultant neuropsychologic dysfunction, has become a more prominent concern. We recently have reviewed the subject of central nervous system injury after cardiac surgery (2,3), and concluded that although the cause(s) of cerebral injury has not been elucidated fully, further investigations of the effects of CPB on cerebral blood flow and cerebral metabolism are still needed. This knowledge serves as the scientific basis for the control of physiologic variables during CPB.

CBF/CMR Physiology

The brain is dependent on mitochondrial aerobic oxidation of glucose for energy. Approximately 60% of this energy is utilized to maintain and restore ionic gradients necessary for depolarization and repolarization of neuronal membranes and 40% to maintain cellular integrity (4,5). The brain stores little glucose and contains low concentrations of ATP; therefore, maintenance of an adequate CBF and metabolic substrate is critical. Although the brain comprises only 2% of body weight, its high metabolic rate requires 15% of the cardiac output. In the unanesthetized patient, cerebral metabolism (CMRO₂) is ~3.5 mL/100 g/min. Global CBF is ~50 mL/100 g/min, 80% of the flow directed to gray matter and 20% to white matter (Table 1) (6). The brain normally extracts approximately 25% of the oxygen supplied. CBF and CMRO₂ are not uniform throughout the brain, as would be predicted from the fluctuating states of cerebral activity. Cerebral blood flow is regulated to supply the metabolic needs of regional areas of the brain. Changes in cerebral metabolism are associated with parallel changes in CBF. This is termed "flow-metabolism coupling" and is part of the process of cerebral autoregulation. Perfusion pressure-flow autoregulation also exists. This form of autoregulation maintains a constant CBF over a wide range of systemic perfusion pressures (assuming CMRO₂ remains constant). If CBF is independent of the perfusion pressure within the autoregulatory range, then pressure-flow autoregulation is intact. If CBF parallels changes in the MAP (within the normal autoregulatory range), pressure-flow autoregulation is lost. Many physiologic variables influence CBF and/or CMRO₂ including brain temperature, Paco₂, Paco₂, blood viscosity, mean arterial pressure outside the autoregulatory range,
intracranial pressure (ICP), and central venous pressure (Table 2).

**CBF**

In humans, CBF varies linearly with the Paco2 in the range of ~20–80 mm Hg. Within the range of normal Paco2 values there is an ~1 mL/100 g/min change in CBF for each 1 mm Hg parallel change in Paco2 in adults (7). Carbon dioxide is a potent cerebrovasodilator.

CBF is not affected by the Pao2 except during unphysiologic Pao2 values. Pao2 values less than 50 mm Hg cause cerebrovasodilation, which overrides metabolism and pressure-flow autoregulation (8). Very high Pao2 values slightly increase cerebrovascular resistance and decrease CBF.

CBF increases with decreasing viscosity (hematocrit) (9–11).

**CMR**

Cerebral metabolism decreases exponentially with reductions in temperature. On average CMRO2 is reduced ~7% for each degree centigrade decrease in body temperature. The multiple by which the rates of cerebral metabolic processes decrease for each 10°C decrease in temperature (Q10) for adults during CPB is 2.8 (12). The type and depth of anesthesia also affect the CMRO2.

**Cerebral Perfusion Pressure (CPP)**

Despite marked changes in MAP and cardiac output, cerebral autoregulation maintains a constant CBF by varying cerebrovascular resistance (CVR). CPP depends on MAP and ICP (CPP = MAP – ICP or venous pressure) thus, MAP is the predominant determinant of CPP (5,6).

**CBF and Cerebral Ischemia**

Cerebral ischemia occurs when the CBF is too low to meet the neuronal demand for oxygen and glucose. The degree of CBF reduction and the length of time the brain is without adequate oxygen delivery are the primary determinants of ischemic injury. At normothermia, thresholds (13) of CBF have been described (Table 3) where electroencephalogram (EEG) silence, ionic failure, and cell death occur. These thresholds are altered dramatically by hypothermia and anesthetics. For example, during moderate hypothermic CPB, CBF may be as low as 10–20 mL/100 g/min (14); however, CMRO2 may be only ~0.5 mL/100 g/min (12,15). At moderate hypothermia, oxygen demand is reduced significantly and these flows exceed cerebral metabolic demand, as reflected by very narrow arterial venous oxygen gradients.

**Pharmacologic Agents and CBF/CMRO2**

**Anesthetics and CBF/CMRO2**

Anesthetic agents and the depth of anesthesia directly affect CMRO2 and CBF. The anesthetic should be standardized when CBF and CMR measurements are obtained. We will review briefly the effects of commonly used anesthetics on CBF, CMRO2, and cerebral autoregulation.

**Opioids.** During cardiac anesthesia, opioids are rarely administered as the sole anesthetic but rather in combination with a hypnotic and amnesic drug such as midazolam or isoflurane. The effect of narcotic anesthesia on CBF and/or CMR02 has not been elucidated fully and is confounded frequently by other non-opioid anesthetics. Human studies suggest that fentanyl and sufentanil affect a modest reduction in CBF and CMR02 while maintaining cerebral autoregulation (16–18).

In morphine-lorazepam-premedicated subjects receiving an anesthetic induction with 10 µg/kg sufentanil, CBF and CMRO2 were reduced by 25% and 21%, respectively (16). Similarly, a 25% reduction in CBF was demonstrated with 100 µg/kg fentanyl and 0.4 mg/kg diazepam anesthesia induction (17). When low-dose sufentanil (0.5 µg/kg) was administered as a single agent to unpremedicated healthy volunteers, a significant effect on CBF could not be demonstrated (18).
served when isoflurane is added. Increasing the MAC (minimum alveolar concentration) isoflurane can induce an isoelectric EEG (27). 

Cerebral vascular reactivity to Paco2 (28). At clinically relevant concentrations (=2.0 minimum alveolar concentration), isoflurane increases CBF and cerebral blood volume and decreases cerebral vascular resistance and CMR02 while maintaining cerebral autoregulation (29,30). In the canine model, CMR02 could only be reduced to 2.9 mL/100 g/min (24), and 4.0 mL/100 g/min (25) with midazolam. In a separate study, a CMR02 of 2.2 mL/100 g/min was obtained with large doses of thiopental. Although midazolam reduces CBF and CMRO2, it is less than the reduction obtained with thiopental. When fentanyl and midazolam were used for induction and maintenance of anesthesia for cardiac surgery (7 pg/kg and 200 µg/kg respectively), followed by an infusion (0.15 µg/kg/min and 3 µg/kg/min), CBF decreased by 38% and oxygen consumption was lowered by 22% (26.)

Isoflurane. In contrast with the parallel reduction in CMRO2 and CBF that occur with most intravenous anesthetic agents, volatile anesthetics produce a dose-related reduction in CMRO2 but an increase in CBF (27). Thus inhalation anesthetics might be considered to abolish metabolic autoregulation. Among the volatile anesthetics, isoflurane is the least potent cerebral vasodilator but the most potent depressant of CMR02. In a dose-dependent manner, isoflurane increases CBF and cerebral blood volume and decreases cerebral vascular resistance and CMRO2 while maintaining cerebral vascular reactivity to Paco2 (28). At clinically relevant concentrations (=2.0 minimum alveolar concentration [MAC]) isoflurane can induce an isoelectric EEG (27).

During CPB, pressure-flow autoregulation is preserved when isoflurane is added. Increasing the MAP by at least 20% with phenylephrine did not alter CBF in isoflurane (0.6%, 1.2%) anesthetized subjects (29).

Barbiturates. Barbiturates produce a dose-dependent decrease in CMRO2 and CBF and an increase in cerebral vascular resistance. The reduction in CMRO2 with barbiturates plateaued at ~50% of control when the EEG was isoelectric in dogs (4). The effectiveness of cerebral protection with barbiturates during cardiac surgery with cardiopulmonary bypass is controversial (30,31).

Nonanesthetic Pharmacologic Agents and CBF/CMR02

Vasoactive agents characteristically produce their effects on CBF and CMR02 by altering hemodynamics rather than by a direct effect on the brain. 

Vasoconstrictors. Catecholamines influence CBF through changes in MAP and systemic vascular resistance. When the MAP is above or below the pressure-flow autoregulatory threshold, increasing the MAP increases CBF. A high proportion of the cardiac output is directed toward the brain as temperature is lowered on CPB. This may be augmented by direct vasoconstrictors such as methoxamine and phenylephrine (pure α1-adrenergic agonists). It appears that if the blood-brain barrier is intact and the MAP is within the autoregulatory range, pure α1, β, and mixed catecholamine agonists (epinephrine, norepinephrine) have little effect on CBF and CMR02 (6).

Phenylephrine. The α1-adrenergic agonist phenylephrine is administered frequently to increase the MAP during CPB. However, the systemic MAP (≥30 mm Hg) does not correlate with CBF during hypothermic nonpulsatile CPB when a-stat blood gas management is employed (14). When phenylephrine is administered under these conditions, cerebral autoregulation (pressure-flow) is intact and CBF will not change with changes in MAP (32). However, when CO2 is added to the CPB circuit (pH-stat blood gas management), CBF rises in parallel with MAP (perfusion pressure-dependent) (15,32).

Vasodilators

Nitroprusside. Sodium nitroprusside (SNP) predominantly acts on resistance vessels and is a cerebrovasodilator (33,34). Laboratory experiments suggest that species and experimental condition may determine the effect of SNP-induced hypotension on CBF. However, CBF in most cases is unchanged, even at low MAP levels. CBF and CMRO2 are unchanged in humans during SNP-induced hypotension (MAP ~50 mm Hg) (35–37). However, the level at which changes in MAP affect changes in CBF in individual patients (loss of pressure-flow autoregulation) potentially may be altered by the presence of longstanding hypertension (altered autoregulation), Paco2 level, anesthetic state, and other concurrent diseases (i.e., cerebrovascular disease). When the MAP was decreased from ~75 mm Hg to ~50 mm Hg with SNP during hypothermic CPB in humans, there was a significant decline in CBF in both a-stat (17–13 mL/100 g/min) and pH-stat (25–17 mL/100 g/
Table 4. Cerebral Blood Flow (CBF) Measurement Techniques Compared

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kety-Schmidt</td>
<td>• Very accurate</td>
<td>• Labor-intensive</td>
</tr>
<tr>
<td></td>
<td>• Classic reference method</td>
<td>• High radiation dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Not continuous measurement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Global measurement of CBF</td>
</tr>
<tr>
<td>131Xe Clearance</td>
<td>• Very accurate</td>
<td>• Radioactive tracer (low dose)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Intermittent rather than continuous measurement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Global measurement of CBF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Electrocautery interference</td>
</tr>
<tr>
<td>TCD</td>
<td>• Noninvasive</td>
<td>• Assumes steady state conditions for duration of sampling period</td>
</tr>
<tr>
<td></td>
<td>• Continuous</td>
<td></td>
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</tbody>
</table>

TCD = transcranial Doppler; 133Xe = radioactive xenon.

min) blood gas-managed patients. This change became insignificant when the data were corrected for the spontaneous decline in CBF that was observed throughout CPB (38). SNP may not have a direct cerebral vasodilatory effect during nonpulsatile moderate hypothermic CPB in humans anesthetized with fentanyl (39).

Nitroglycerine. Nitroglycerine acts predominantly on capacitance vessels. In dogs, CBF and CMRO2 remain unchanged until the MAP was reduced to ~40 mm Hg (40,41). In the doses typically used for the treatment of myocardial ischemia, and when the MAP is within the autoregulatory range, no significant effect on CBF and CMRO2 is expected.

CBF Measurement Methods

Kety-Schmidt

Most intraoperative methods for determining CBF (Table 4) are based on the Fick principle. The classic reference method of measuring CBF was described by Kety and Schmidt (42). It requires the administration of a freely diffusible, insoluble, inert tracer substance (e.g., 133Xenon, N2O) and sampling from the cerebral venous system (catheter in the jugular bulb) and arterial blood during its washin or washout from the brain. If the time until equilibration of arterial and cerebral venous tracer substance is calculated, blood-brain partition coefficient of the tracer known, and steady state conditions during the study period obtained, a quantitative determination of CBF can be made. The greater the CBF, the less time it takes for the arterial and cerebral venous concentrations to equilibrate.

Xenon Clearance

The 133Xenon clearance technique is a simple, noninvasive method of determining CBF which has been validated against the continuous Kety-Schmidt method (43), and is used widely for CBF measurements during CPB. Simply stated, 133Xenon is injected into the arterial circulation (arterial inflow tubing of CPB circuit, aorta, or common carotid artery) and extracranial detectors are used to count the emitted γ-radiation. CBF is calculated from the clearance of γ-radiation from the brain by using the area under the curve or the initial slope index (ISI) method (44), where:

\[
\text{CBF ISI (mL/100 g/min)} = -\log \text{slope} \cdot \text{Ag} \cdot 100
\]

where slope is equal to the natural logarithm of the 133Xenon clearance (Linear regression) during the first minute, Ag = gray-matter blood partition coefficient for 133Xenon, corrected for temperature and hematocrit (45), and 100 converts the flow value to standard units (mL/100 g/min).

Transcranial Doppler (TCD)

Transcranial Doppler sonography was introduced by Aaslid et al. (46), and may be used to assess the circulation of the major intracranial vessels. TCD sonography uses the Doppler principle to detect shifts in frequency of reflected signals from blood in motion to calculate flow velocity. Because the diameter of the large cerebral arteries are relatively constant, even with changes in Paco2 and CPP (47,48), flow velocity should be representative of CBF. However, quantitative CBF values cannot be obtained, as blood flow through a vessel is equal to the mean blood flow velocity multiplied by the cross-sectional area of that vessel, which is unknown. Despite this limitation, cerebral blood flow velocity has correlated well (r = 0.80–0.93) (49), with established techniques of measuring CBF. TCD has been utilized during cardiovascular surgery to detect microemboli, to study CBF autoregulation, and to monitor cerebral blood flow velocity (50,51). Typically, the temporal ultrasonic window (1–5 cm anterior to the ear...
and just above the zygomatic arch) is used to interro-
gate the middle cerebral artery for velocity measure-
ments.

Cerebral Metabolic Rate Measurements
(Table 5)

CMRO2

If the cerebral arteriovenous content difference is de-
termined for a substrate, CMR for that substrate (ox-
ygen, glucose) can be calculated. Retrograde cannula-
tion of the jugular venous bulb is a safe and technically
simple method of obtaining the cerebral equivalent of
"mixed venous" blood (52). The CMRO2 may then be
determined by multiplying the oxygen content differ-
ence between the arterial (radial artery) and cerebral
venous specimen with the concurrent measurement of
CBF. CMRO2 (mL/100 g/min) is then:

\[
CMRO_2 = CBF \times (1.39 \times Hb[Sao_2 - Svo_2] + 0.003 [Pao_2 - Pvo_2])/100
\]

where Sao2 and Svo2 are the arterial and venous oxygen
saturation of the radial arterial and jugular venous bulb
blood, respectively. Hb is hemoglobin and Pvo2 is jugh-
ular venous oxygen tension. The blood obtained from
the jugular bulb is the effluent from all regions of the
brain. Consequently, the oxygen content and saturation
difference between the arterial and jugular bulb blood
is a global average and may not reflect areas of regional
cerebral ischemia/hypoperfusion. A normal or ele-
vated jugular venous saturation does not necessarily
ensure adequate cerebral blood flow, but a low satu-
rature suggests possible cerebral ischemia. Intermitt-
ent, or continuous (53), determinations of the jugular
venous oxyhemoglobin saturation allow assessment of
overall adequacy of cerebral oxygen supply and de-
mand. The confounding effect of varying hematocrit,
temperature, and vessel wall artifact, secondary to con-
tact of the catheter with the wall of the jugular bulb
requiring frequent calibration, limits jugular oximeter
catheter use.

Spectroscopy

Near-infrared spectroscopy (NIR) (54–57), and nuclear
magnetic resonance (58) (NMR), are noninvasive meth-
ods of monitoring brain oxygen saturation. The prin-
ciple of NIR spectroscopy is based on the ready trans-
mision of near-infrared wavelengths of light through
biological tissue and attenuation attributed to oxyhe-
moglobin, deoxyhemoglobin, and oxidized cyto-
chrome c oxidase. Changes in the wavelength of near-
infrared light that penetrates the skull and is
transmitted through, or reflected from, brain tissue are
proportional to the relative concentrations of oxy- and
dehydrateryhemoglobin. Near-infrared spectroscopy has
been used to monitor cerebral oxygenation during car-
diac surgery with cardiopulmonary bypass (55,59), and
during periods of hypothermic arrest (60). It functions
well during circulatory arrest, low flow states, and hy-
pothemia. It is conceivable that cerebral oxygenation
during CPB will soon be monitored (optical spectro-
scopy) as routinely as arterial oxygen saturation is with
pulse oximetry. Refinements of this technique may
make CBF determinations clinically feasible.

Mechanisms of Cerebral Injury During
CPB

Recent studies have demonstrated a disturbingly high
incidence of perioperative stroke and cognitive dys-
function (determined by postoperative psychometric
testing) in patients that have undergone cardiac sur-
gery with CPB. Factors associated with an increased
incidence of central nervous system (CNS) dysfunction
include: intracardiac versus extracardiac procedures,
the duration of CPB, the use of bubble oxygenators,
absence of an arterial filter, concurrent cerebrovascular
disease, and advanced age (2).

During CPB, cerebral ischemia may be due to global
hypoperfusion (e.g., cerebral perfusion pressure [CPP]
below the autoregulatory threshold) or focal occlusion

Table 5. Cerebral Metabolism Measurement Techniques

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMRO2</td>
<td>Gold standard for global metabolism</td>
<td>Requires retrograde jugular catheter</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Requires CBF measurement (radiation exposure)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Is a global measure and may not detect regional</td>
</tr>
<tr>
<td></td>
<td></td>
<td>changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intermittent sampling</td>
</tr>
<tr>
<td>NIR</td>
<td>Continuous measure</td>
<td>Not quantitative measure of CMRO2</td>
</tr>
<tr>
<td>NMR</td>
<td>Measures ATP directly</td>
<td>Requires NMR technology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not clinically applicable</td>
</tr>
</tbody>
</table>

ATP = adenosine triphosphate; CBF = cerebral blood flow; CMRO2 = cerebral metabolic rate for oxygen; NIR = near-infrared spectroscopy; NMR = nuclear magnetic resonance.
of the cerebral vasculature due to emboli. Focal ischemia appears to produce the preponderance of neurologic events that occur during cardiac surgery. Microemboli can be found in all patients (arterial-line blood) undergoing CPB (61,62). These microemboli have been detected by middle cerebral artery transcranial doppler and retinal angiographic techniques (51,63). The anatomical correlate of the neurologic deficits resulting from microemboli after cardiac surgery may be focal dilatations or very small aneurysms in terminal arterial and capillaries of the cerebral circulation. Debris from the surgical field and embolization of ventricular air likely account for the incidence of neurologic injury following open cardiac procedures.

Echocardiography is one technology which may be used to reduce the risk of microemboli. Echocardiography can predict an aortic cannulation site free from atherosclerotic plaques and identify residual intracardiac air which may be evacuated before aortic cross-clamp removal, thereby decreasing the risk of significant cerebral emboli (70,71).

Global hypoperfusion may likewise be a mechanism for cerebral injury following cardiac surgery. CPB is associated with periods of low systemic flow and reduced perfusion pressure, reduced hemoglobin levels resulting in decreased oxygen content, altered cerebral autoregulation, and changing cerebral metabolic demands (temperature). These factors may affect the relationship of CBF and CMRO₂. Reductions in the CBF/CMRO₂ ratio may place the brain at greater risk for cerebral hypoperfusion. Maintaining an appropriate flow-metabolism ratio presumably is essential to reducing neuropsychologic morbidity following CPB.

**Preoperative Clinical Conditions**

The preoperative identification of one or more of the following clinical conditions may uniquely affect CBF and CMR during CPB and require alterations in the routine clinical management of the patient (see also Table 6).

<table>
<thead>
<tr>
<th>Table 6. Perioperative Factors Adversely Affecting Normal Cerebral Autoregulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hypertension</td>
</tr>
<tr>
<td>2. Insulin-dependent diabetes</td>
</tr>
<tr>
<td>3. Cerebrovascular disease</td>
</tr>
<tr>
<td>4. Temperature (deep hypothermia)</td>
</tr>
<tr>
<td>5. pH-stat blood gas management</td>
</tr>
<tr>
<td>6. Extremes of age</td>
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</tbody>
</table>

**Hypertension**

Cerebral blood flow remains constant in normal humans between a cerebral perfusion pressure of approximately 50–150 mm Hg. Over this range, alterations in CPP are accompanied by compensatory changes in cerebral vascular resistance to normalize CBF. Uncontrolled hypertension however, leads to a shift of this autoregulatory curve to the right (72). This is most likely due to structural thickening and luminal narrowing of cerebral resistance vessels (73). Although pressure-flow autoregulation is not lost, CBF becomes pressure-dependent at both extremes of the autoregulatory curve. Long-term antihypertensive therapy, especially in young patients, may reverse this autoregulatory adaptation to hypertension (74). Pressure-flow autoregulation may return toward normal after several weeks in treated hypertensive patients (5). Whether these changes are reversible in the elderly, chronically hypertensive patient is unknown (75).

The lower limit of the autoregulatory threshold in individual hypertensive patients will vary; therefore, a higher perfusion pressure on CPB may be required to assure adequate cerebral perfusion.

**Insulin-dependent Diabetes**

Insulin-dependent diabetic patients placed on cardiopulmonary bypass have evidence of impaired metabolism-flow autoregulation (76).

In an investigation of 23 patients, it was demonstrated that diabetic patients do not increase CBF like nondiabetic patients when the perfusate temperature is increased (76). To compensate for failure to deliver more oxygen at normothermia, more oxygen was extracted from the blood (decreased jugular venous saturation). Greater extraction of oxygen is a normal compensatory mechanism to assure adequate O₂ delivery when metabolism-flow autoregulation fails to maintain CBF.

**Aging**

Age appears to be a major risk factor contributing to a negative neurologic outcome after cardiac surgery (1,2,77,78). Although aging is associated with reductions in both CMRO₂ and CBF (79,80), the response of the cerebral circulation to changes in arterial pressure and Paco₂ appear to be intact (81–83). In a study of the effect of age on CBF and cerebral blood flow autoregulation during cardiopulmonary bypass, age did not appear to interfere with pressure-flow autoregulation (80). The sample size was small (n = 20) and the results of the investigation are considered preliminary.

The mechanism(s) of increased neurologic risk with aging is unknown but may involve increased microemboli, cerebrovascular disease, and/or aberrations in...
Table 7. Effect of Hypothermia on the Cerebral Metabolic Rate for Oxygen (CMRO₂) and Cerebral Blood Flow (CBF) During Cardiopulmonary Bypass (CPB)

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>CMRO₂ (Mean) (mL/100 g/min)</th>
<th>CBF (Mean) (mL/100 g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake/normal (5, 6) 37</td>
<td>~3.5</td>
<td>~50</td>
</tr>
<tr>
<td>Murkin (15) ~35 (pre-bypass) 26</td>
<td>1.67</td>
<td>25</td>
</tr>
<tr>
<td>Govier (14) 34.5 ± 1.1 (pre-bypass) 28 ± 3.6 26.1 ± 1.7</td>
<td>1.4 ± 0.34</td>
<td>35 ± 9.0</td>
</tr>
<tr>
<td>Croughwell (12) 37 ± 0.7 27 ± 2.0</td>
<td>0.5 ± 0.2</td>
<td>21 ± 6.8</td>
</tr>
</tbody>
</table>

Values are mean or mean ± SD when available.

Cerebral autoregulation with incomplete global ischemia.

Cerebrovascular Disease

In most clinical series, prior cerebrovascular event or transient ischemic attack is associated with an increased risk of neurologic morbidity following CPB. The effect of bilateral carotid artery disease on CBF during CPB has been investigated. In a study of CBF during CPB (moderate hypothermia and MAP > 50 mm Hg) in 24 patients with cerebrovascular disease, seven with severe bilateral carotid artery disease, no difference in CBF was observed between the study and control group. CBF measured in the group with bilateral carotid artery disease was similar in each hemisphere and was normal (84). The effect of bilateral 80% carotid obstruction in a 66-yr-old patient undergoing cardiac surgery was investigated, and marked reductions in perfusion pressure were not accompanied by abnormally low global cerebral blood flow measurements using 133Xenon clearance (85). Although global CBF remained intact in these studies, the presence of extracranial obstructive vascular disease in cardiac surgery patients, and its impact on care, await further investigation and the development of better techniques to assess regional CBF and metabolism during cardiopulmonary bypass.

Factors During Cardiopulmonary Bypass That Affect CBF/CMRO₂

Temperature

The brain temperature is an important determinant of cerebral blood flow during CPB. CBF and CMRO₂ are markedly reduced by hypothermia (Table 7).

When the major external factors manipulated during cardiopulmonary perfusion are evaluated (cerebral perfusion pressure, pump flow, Paco₂ and temperature), temperature is the single most important element influencing CBF during CPB (14,86,87).

CMRO₂. Hypothermia is characteristically utilized for brain protection during CPB because it reduces cerebral metabolism ~7%/°C and prolongs the brain's tolerance for ischemia. The CMR may be divided into a component associated with electrophysiologic function (60%) and another for maintenance of cellular integrity (40%) (4,88). Hypothermia is unique, as it proportionally decreases the rate of energy use associated with both of these components of CMR. The relationship of temperature to CMRO₂ in man can be computed and is expressed as the Qlo, or the multiple by which the rate of global metabolism decreases for each 10°C reduction in body temperature. In adult patients undergoing cardiac surgery (12), the median Qlo was 2.8 and a mathematical expression of the effect of temperature on CMRO₂ was expressed as:

\[
CMRO₂ = 0.021 e^{0.1147 \times T_{NP}}
\]

where T_{NP} is the nasopharyngeal temperature in °C. In infants and children undergoing congenital heart surgery (87), the Q₁₀ was 3.6 and the mathematical expression of the relationship:

\[
CMRO₂ = 0.019 e^{0.1171 \times T_{NP}}
\]

These relationships of temperature to oxidative metabolism can be used to compute the duration of cerebral protection afforded by hypothermia (i.e., circulatory arrest), assuming that the sole protective effect of hypothermia is related to a change in CMRO₂ (87–90).

CBF and Flow-Metabolism Coupling. Because hypothermia reduces CMRO₂ and autoregulation of CBF typically is coupled to metabolism, hypothermia also reduces CBF. In humans, an awake CMRO₂ of ~3–4 mL/100 g/min is coupled to a CBF of ~45–80 mL/100 g/min for a CBF/CMRO₂ ratio of ~15–20 (5). Hypothermia reduces CBF linearly (Figure 1A) and CMRO₂ exponentially (Figure 1B). The ratio of CBF/CMRO₂ increases with decreasing temperatures, so that at moderate hypothermia the ratio of CBF/CMRO₂ is increased. This results in luxuriant brain blood flow
and adequacy of organ perfusion as determined by other calorically for cerebral protection during cardiac sur-

vascularization, a study comparing the effects of differ-
ng levels of hypothermia on neurologic outcome.

...The systemic flow rate during CPB customarily is

and acid-base balance (14,94,95). Although pump flow rates in adults characteristically range between ~1.6–

2.4 L/min/m² (~40–70 mL/kg/min) no standard flow rate is optimal for cerebral perfusion under all clinical conditions.

In the unanesthetized and normothermic state, the
brain receives ~15% of the cardiac output. During steady state hypothemic CPB, mean cerebral blood flow was ~600 mL/min at a CPB flow of 2.4 L/min/m². Cerebral oxygen consumption remained constant to a flow of 1.6 L/min/m² at which point the cerebral flow fell to ~400 mL/min (96). Using Q₁₀ data from adults during hypothemic CPB (12), a reduction in pump flow rate down to 0.6 L/min/m² should sustain cerebral metabolic demands at a temperature of 27°C.

The effect of varying pump flow rate on CBF with α-stat blood gas management has been investigated. In a subgroup of 10 patients in which Paco₂ (33–45 mm Hg), temperature (26–29°C), and MAP (45–70 mm Hg) were held relatively constant, randomly applied pump flow rates between 1.0–2.0 L/min/m² had no statistically significant effect on CBF (Figure 2) (14). This is because autoregulation is preserved during nonpulsatile hypothemic CPB. CBF is maintained during reduced systemic perfusion, due to the differential effects of cerebral and systemic vascular resistance during hypothemic CPB. Although cerebral vascular resistance increases, systemic vascular resistance increases to a much greater extent. The net result is a redistribution of blood flow toward the brain and the preservation of cerebral blood flow (95,97).

pH-stat has differing effects on CBF and CMRO₂. In one study where moderate hypothemic CPB and pH-stat blood gas management were used, CBF increased linearly with increases in pump flow rates from 1.4–2.4 L/min/m² (40–70 mL/kg/min) without a significant change in MAP (98). In an attempt to discern the implications of differing blood gas management strategies on the response of the cerebral vasculature to changing pump flow rates, several studies have been conducted. At conventional flow rates using moderate hypothemic CPB, it appears that differences between α-stat and pH-stat management are negligible under many clinical conditions and neurologic outcome differences are indistinguishable (99).

The effect of blood gas management on the CBF response to changing systemic flow and pressure recently was investigated in rabbits during nonpulsatile hypothemic CPB at systemic flows of 50, 70, and 100 mL/kg/min. At 100 mL/kg/min flows, the pH-stat animals had a greater global CBF and there was a strong suggestion that blood gas management affected the CBF response to decreased systemic flow and pressure. When bypass flow was decreased from 100 to 70 mL/
kg/min, CBF was unchanged in the α-stat, but decreased in the pH-stat group, suggesting attenuated autoregulatory responses in the latter group. In the pH-stat animals, bypass flow rate appeared to have an effect on CBF independent of arterial pressure. However, at flow rates of 50–70 mL/kg/min, the CBF and its variation with flow and pressure were indistinguishable between the groups (100). In a study of 24 patients during hypothermic (27°C) nonpulsatile CPB, perfusion flow rates of 1.75 or 2.25 L/min/m² with either α-stat or pH-stat had no effect on CBF, CVR, and CMRO₂. Therefore, CBF and CMRO₂ were independent of perfusion flow rate (Figure 3) under these frequently encountered clinical conditions (101).

Low Flow. Guidelines for the safe implementation of low flow CPB are not readily available. In a canine model at 20°C a flow rate of 15 (102), and 25 mL/kg/min (103), resulted in inadequate cerebral perfusion. At 15°C, a flow rate of 10 mL/kg/min for up to 2 h in 8-wk-old sheep maintained normal brain pH and ATP levels. At 5 mL/kg/min, brain pH fell and ATP levels decreased (104). By comparing the reduction in CMRO₂ with hypothermia with proportional reductions in pump flow rate estimates of minimal acceptable flow rates may be predicted for children (92).

The critical flow below which ischemic injury to the brain will occur is dependent on such variables as temperature, hematocrit, depth of anesthesia, and the degree of oxygen saturation. Monitoring cerebral oxygen saturation with jugular venous bulb oximeters (53), intermittent sampling of jugular venous blood, and infrared cerebral spectroscopy may help identify those patients whose cerebral oxygen demand exceeds oxygen delivery.

Cerebral Perfusion Pressure (CPP)

The cerebral perfusion pressure usually is expressed as mean arterial pressure minus the intracranial or central venous pressure. Assuming that the central venous pressure is 0 mm Hg during cardiopulmonary bypass, and that the ICP is constant and normal, changes in arterial blood pressure probably reflect changes in CPP. Mean arterial blood pressure does not correlate with cerebral blood flow during hypothermic, nonpulsatile cardiopulmonary bypass (Figure 4). Pressure-flow autoregulation, as discussed previously, remains intact to a MAP as low as 30 mm Hg if α-stat arterial blood gas management is employed (14,15). Thus, mean arterial pressures within the range of 30–100 mm Hg do not change CBF in α-stat managed patients. In pH-stat managed patients CBF increases with increases in MAP (15). A study of 34 patients during steady state hypothermic CPB at a pump flow rate of 2.4 L/min/m² demonstrated that left common carotid arterial flow was
not affected by common carotid arterial pressures between 40–80 mm Hg (96).

During moderate hypothermic CPB using α-stat blood gas management in children, Grolee et al. have shown that over a range of mean arterial pressures (15–80 mm Hg), pressure-flow autoregulation remains intact (105). However, pressure-flow autoregulation was disrupted with profound hypothermia and after deep hypothermic circulatory arrest.

Because cerebral oxygen delivery and demand, rather than CPP, is of primary importance, the routine practice of maintaining a perfusion pressure >50 mm Hg with α-agonists (phenylephrine) throughout hypothermic CPB (α-stat) may not be necessary for most patients (106). However, in those patients with altered autoregulation (chronic hypertension, insulin-dependent diabetes) or severe cerebrovascular disease the lower level of CPP at which a change in CPP affects a change in CBF is unknown. Compensatory mechanisms for decreased cerebral O₂ delivery would be cerebral vasodilation and increased oxygen extraction (decreased jugular venous oxygen saturation). The absolute CPP and pump flow necessary to avoid the need for compensatory mechanisms is likely to vary between patients and be altered by other factors such as temperature, hematocrit, and anesthetic state.

**Acid-Base Management**

The arterial Pco₂ decreases ≈4.5%/°C and pH increases ≈0.015 units/°C secondary to increased carbon dioxide solubility in aqueous solutions at moderate hypothermic temperatures. The net result is a decrease in Paco₂ and increased pH ("respiratory alkalosis") when the patients' temperature-corrected arterial blood gases are analyzed at low temperatures. During CPB and hypothermia, Paco₂ may be managed by either a pH-stat approach in which the goal is a pH of 7.40 corrected for the patients temperature (temperature-corrected), or a-stat where the goal is a blood pH of 7.40 when measured at 37°C and uncorrected for the patients temperature (temperature-uncorrected). α-Stat management of arterial blood gases may maintain a more normal intracellular pH (brain), preserve intracellular electrochemical neutrality, and improve the efficiency of intracellular enzymatic function (Table 8) (107).

CBF increases with increasing arterial CO₂ tension in awake and anesthetized patients as well as those supported by CPB. Hypercarbia may (108) or may not (109) independently decrease cerebral oxygen consumption during CPB. Cerebral vasoreactivity to Paco₂ defined as ∆CBF/∆Paco₂ is ≈1.2 mL/100 g/min/mm Hg during both hypothermic and normothermic CPB (110,111). This vasoreactivity is preserved during moderate hypothermic nonpulsatile CPB with α-stat blood gas management. At deep hypothermic temperatures, cerebrovasoreactivity to Paco₂ is present but appears to be slightly attenuated (112). Blood gas management using pH-stat results in increased Paco₂ and CBF in excess of cerebral metabolic demand (luxuriant flow). Pressure-flow and metabolism-flow autoregulation is impaired. With pH-stat, CBF increases in response to increasing MAP (32), and increasing Paco₂ increases CBF/CMRO₂ ratio (113). With α-stat, CBF is independent of ∆MAP and ∆CBF is dependent on CMRO₂ (15). Although α-stat results in lower Paco₂ and CBF during hypothermic CPB, CBF still exceeds brain oxygen consumption (relative hyperperfusion). In the early postoperative period after CPB using α-stat blood gas management, cerebral autoregulation and CO₂ responsiveness appear to be preserved (114).
Table 8. Comparison of pH-Stat and a-Stat Blood Gas Management at Moderate and Deep Hypothermia

<table>
<thead>
<tr>
<th></th>
<th>pH-Stat</th>
<th>a-Stat</th>
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<tbody>
<tr>
<td>Moderate hypothermic CPB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial pH</td>
<td>≈7.32</td>
<td>≈7.40</td>
</tr>
<tr>
<td>CBF/CMRO₂ ratio</td>
<td>↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Pressure-flow autoregulation</td>
<td>Lost</td>
<td>Intact</td>
</tr>
<tr>
<td>Deep hypothermic CPB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial pH</td>
<td>≈7.10</td>
<td>≈7.40</td>
</tr>
<tr>
<td>CBF/CMRO₂ ratio</td>
<td>↑↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Pressure-flow autoregulation</td>
<td>Lost</td>
<td>Lost</td>
</tr>
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</table>

*CPB = cardiopulmonary bypass; CBF = cerebral blood flow; CMRO₂ = cerebral metabolic rate for oxygen.*

As previously discussed, deep hypothermia uncouples pressure-flow autoregulation such that CBF becomes pressure-dependent (115). This implies that at very low temperatures the cerebrovasculature may not be able to vasodilate if cerebral metabolic needs increase. Although CBF remains responsive to ΔPaco₂ at deep hypothermia (18–22°C) and age <1-yr-old diminish this reactivity (112).

Theoretically, the patient managed with pH-stat may have an acidic brain pH during rewarming creating a metabolic debt that, if combined with decreased oxygen delivery after separation from bypass (low cardiac output), produces an increased potential for neurologic injury. Moreover, the inability to autoregulate CBF at lower perfusion pressures theoretically may increase the risk of incomplete global ischemia. The excessive CBF associated with pH-stat may increase the proportion of embolic material (particulate, air) to the brain rather than to the systemic circulation. Finally, if focal cerebral ischemia occurs (embolic) one could also postulate that a concurrent elevation in Paco₂ could increase the risk of regional ischemia by producing vasodilation of nonischemic cerebral vasculature reducing flow to ischemic vascular beds ("steal"). In a recent study (116), intracerebral steal could not be demonstrated in nine patients with cerebrovascular disease undergoing hypothermic CPB with elevated Paco₂ tensions. a-Stat management may theoretically be advantageous in certain subsets of patients (e.g., cerebrovascular disease, altered cerebral autoregulation) by better preserving cerebral autoregulation.

Therefore, under many clinical circumstances using mild-moderate hypothermia and flows of 50–70 mL/kg/min (~1.8–2.4 L/min/m²), the differences in CBF and CBF dynamics between a-stat or pH-stat blood gas strategies may be slight. Mean differences in Paco₂ between a-stat and pH-stat management at 30°C are only approximately 6-7 mm Hg, and pH differences 0.06, becoming more disparate at deep hypothermic temperatures (107). At bypass flow rates of 50 and 70 mL/kg/min, there were no significant differences in global CBF or in the CBF response to decreased pump flow and pressure between a-stat and pH-stat managed rabbits on CPB at 25°C (100). Moreover, a recent prospective randomized study of a-stat and pH-stat management of arterial blood gases during hypothermic CPB did not demonstrate any discernible difference in postoperative neuropsychologic outcome between these CO₂ management strategies at moderate hypothermic CPB (99,113). Although these studies support pH-stat management as an alternative blood gas management strategy during moderate hypothermic CPB in adult patients, more severe decreases in temperature may be less well tolerated.

Hemodilution

The viscosity of the blood influences CBF. The hematocrit is the primary factor influencing blood viscosity and decreasing viscosity with hemodilution increases CBF (9–11). Because blood viscosity increases with hypothermia, hemodilution routinely is utilized during hypothermic CPB. Measurements of CBF made during hemodiluted hypothermic CPB must be corrected for changes in both temperature and hematocrit (45).

Delivery of oxygen to the brain is defined by the equation CDRO₂ (O₂ delivery) = CBF × arterial oxygen content. Decreasing the hemoglobin level will reduce oxygen content and delivery if there is not a reciprocal change in CBF. During hypothermic CPB with hemodilution, both CMRO₂ and CBF are reduced. However, the "optimal hematocrit" to ensure both adequate O₂ delivery and optimal blood rheology through the cerebral microcirculation is confounded by the complex interaction of many variables (microcirculatory rheology, temperature, anesthetic effects, etc). Extremes of hemodilution which may improve microvascular flow must be weighed against maintenance of oxygen carrying capacity. A compensatory increase in cerebral blood flow (vasodilation) and increased oxygen extraction (low jugular venous saturation) may be required if the normothermic hematocrit is markedly depressed. The scenario of an occluded cerebral artery (embolic) and extreme hemodilution in a normothermic patient (following cardiopulmonary bypass) with a limited collateral circulation might impair oxygen delivery and cause greater tissue damage. Under these conditions, the compensatory mechanisms of increased flow and oxygen extraction may not meet regional cerebral oxygen demand. In one study of an analysis of factors predisposing to neurologic injury in patients (n = 312) undergoing coronary bypass surgery, the hemoglobin level at the end of the operation and the absolute drop in hemoglobin during the procedure was one variable showing a significant correlation with CNS complications (117).
Pulsatile Versus Nonpulsatile Perfusion

The institution of nonpulsatile bypass may reduce CBF and CMRO₂ independently (118). The relative contribution of nonpulsatile cerebral perfusion during CPB to CNS injury is unknown, and the debate over the merits of pulsatile perfusion continues. However, evidence for microvasculature dysfunction with nonpulsatile perfusion can be found in many studies. In a study using normothermic pulsatile CPB, capillary flow in the microvasculature of the omentum was maintained, whereas with nonpulsatile perfusion, flow slowed and virtually ceased. At flow rates of 60 and 75 mL/kg/min pulsatile perfusion resulted in a higher pH, reduced base deficit, and improved total body oxygen consumption compared with nonpulsatile perfusion (119). Cerebral capillary collapse, intravascular sludging in the conjunctiva and cerebral circulation, and neuropathologic changes in arterial boundary zones (120), have been demonstrated in dogs undergoing nonpulsatile perfusion and eliminated in dogs perfused with pulsatile flow.

Nonpulsatile perfusion may unfavorably alter cerebral microcirculatory flow, whereas pulsatile flow may minimize the cerebral microcirculatory shunt during CPB. A study of 23 patients undergoing CPB with either pulsatile or nonpulsatile perfusion demonstrated a lower CVR in the pulsed patients. Although there was no difference in CMRO₂ between the groups during and just after CPB, the cerebral arterial venous oxygen difference of the pulsatile group was greater. This suggests that pulsatile flow may attenuate the microcirculatory shunt that occurs with CPB (121). Although these differences are small, pulsatile perfusion may provide better perfusion at marginal pump flow rates such as low flow hypothermic CPB. Improvements in brain pH, Pco₂, and Po₂ have been demonstrated in a canine model when nonpulsatile perfusion was compared with pulsatile perfusion at a flow rate of 25 mL/kg/min (103,122).

At lower flow rates, and with longer perfusion periods, pulsatile assistance may be more beneficial (122). However, the effect of pulsatile perfusion on CMRO₂ and CBF under frequently encountered clinical conditions is likely far outweighed by other perfusion variables (i.e., temperature, Paco₂).

Time on Cardiopulmonary Bypass

It has been suggested that CPB is associated with cerebral microvascular obstruction from accumulated microemboli and/or progressive cerebral vasoconstriction. A decline in CBF with time on CPB was first suggested in 1988 (32). In adult patients undergoing hypothermic (28°C) CPB, CBF was determined after the aorta was cross-clamped and body temperature stabilized for at least 5 min. A repeat CBF determination was made after 20–30 min and a decline in CBF of ≈1%/min was observed. In this study, nasopharyngeal temperature remained constant. However, as the CBF determinations were made shortly after aortic cross-clamp, brain temperature (not reflected in NPT) and CMRO₂ may have declined concomitantly. However, the observed time-dependent reduction in CBF was not accompanied by a concomitant decline in CMRO₂, suggesting that the ability of CBF to meet metabolic demand decreases with time on CPB (123). Using multivariate statistical methods, time on CPB had no effect on CPB in another study (14).

A recent canine study from the same investigative group did not support the clinical observation. CBF was measured with radioactive microspheres for a longer study period (270 min vs 30 min) in a normothermic (n = 10) and hypothermic (28°C) (n = 11) group during stable CPB. At 90, 150, and 210 min, CBF did not decline during stable hypothermia. In normothermic animals, CBF remained constant with only an insignificant decrease overall (124). During low-flow (0.5 L/min/m²) hypothermic (18°C) CPB, CBF also did not change with time (125). If a time-dependent decline in CBF occurred when the systemic flows (low flow CPB) are only 25% of full-flow CPB, the risk of inadequate cerebral perfusion with time on CPB would be increased.

Longer cooling periods may be required for brain temperature equilibration and stable reproducible conditions for CBF determinations (100,109). In a rabbit CPB model using microsphere methodology for CBF determinations, CBF and CMRO₂ did not change between 30 and 90 min of CPB at normothermia and between 60 and 90 min in hypothermic (27°C) animals. However, 41 ± 6 min were required for cortical temperature equilibration (109).

Although time has been suggested as an etiology for a decrease in CBF, this may reflect the inability of superficial temperature monitoring to adequately reflect true brain temperature. We do not believe that duration of CPB, per se is associated with a reduction in CBF because CBF returns to control levels with rewarming (14,15,105). The role that the duration of CPB plays on the intraoperative CBF/CMRO₂ measurements and etiology of postoperative neuropsychologic deficits after cardiac surgery awaits further investigation.

Glucose Management

Although the absolute glucose level may not directly affect CBF and CMRO₂ during CPB, elevated glucose levels at the time of neuronal ischemia may increase cerebral injury. When the cellular demand for oxygen
exceeds supply, anaerobic glycolytic conversion of glucose to lactate occurs, producing an increased intracellular hydrogen ion and lactate concentration. With complete cerebral ischemia (e.g., TCA), the intracellular lactate concentration is proportional to the cerebral stores of glucose at the time of the insult. The intracellular cerebral stores, as well as the continued delivery of glucose to anaerobically metabolizing brain, may make lactate concentrations greater with incomplete global ischemia (126,127). Inefficient production, as well as rapid depletion of ATP, occurs with anaerobic glycolysis. Increased intracellular acidosis enhances neuronal cell injury. Experimental models of global ischemia consistently have demonstrated glucose-induced enhancement of ischemic injury (128). However, the association between glucose levels and neurologic injury after focal ischemia has been inconsistent (128).

Because cardiac surgery with CPB is associated with inhibition of insulin secretion and hyperglycemia (129,130), and a concurrent risk of global and/or focal cerebral ischemia, maintaining euglycemia is recommended. Although maintenance of euglycemia during CPB seems a simple and beneficial goal, there is little evidence that neurologic outcome is worse with hyperglycemia during CPB and/or TCA. A study of 60 patients undergoing moderate hypothermic, nonpulsatile CPB found no effect of relative hyperglycemia (221 ± 58 mg/dL, mean ± so) on postoperative neuropsychologic performance. However, the range of blood glucose levels was relatively narrow 103–379 mg/dL (131). Recently glucose-containing pump priming solutions (D2 LR, 20 mL/kg) were compared with a nonglucose-containing prime. Although measured serum glucose levels were three to four times higher with the glucose prime, no increase in gross neurologic injury could be demonstrated (132). The lack of formalized neuropsychologic testing, however, limits these results. A recent retrospective study evaluated the role of hyperglycemia in 34 children undergoing deep hypothermic circulatory arrest. The hyperglycemic patients trended toward a worse neurologic outcome, although this did not reach statistical significance (133).

Insulin-dependent diabetics lose the normal coupling of cerebral blood flow and metabolism during hypothermic CPB. Due to the inability to increase CBF like nondiabetics, oxygen extraction increases when the perfusate temperature is increased (76). These patients may be at increased risk for cerebral ischemia during low-flow or low-pressure CPB.

The critical level of hyperglycemia at which insulin therapy should be initiated is unknown. Because there is a normal hysteresis between brain and systemic glucose levels after insulin therapy, the time that should be allowed between treatment of a patient with hyperglycemia and the period of neurologic risk is unknown.

Rewarming/After CPB

Following moderate hypothermic continuous CPB, CMRO2 and CBF return to or exceed prebypass levels in nondiabetic adults (15,96,134,135). Adult patients with diabetes, however, lose cerebral flow-metabolism autoregulation. They fail to increase CBF to meet metabolic needs during the rewarming period of CPB (76).

Warming from moderate hypothermic CPB has been associated with jugular venous desaturation (JvSat < 50%) as detected by intermittent jugular bulb sampling (136), and with continuous oximeter catheters in the jugular bulb (53). JvSat reflects the balance of cerebral oxygen supply and demand. Increased oxygen extraction, and therefore, lower JvSat would be the compensatory response when oxygen demand is increased more than oxygen supply. Although Jv desaturation (JvSat < 50%) recently was identified in 25% of patients at normothermia following hypothermic CPB, it was not associated with impaired postoperative neuropsychologic test performance (136,137).

Cerebral autoregulation and CO2 responsiveness are preserved after CPB (138). The CBF response to changes in arterial Paco2 or mean arterial pressure are maintained in the immediate (3–8 h) post-CPB period (114).

Cerebral blood flow, CMRO2, and oxygen extraction increase above pre-bypass measurements in children following continuous flow CPB. There is a cerebral hyperemic response with increased oxygen extraction and metabolism after a period of hypothermic, hemodiluted nonpulsatile perfusion. However, after CPB with deep hypothermic TCA, the CBF and CMRO2 are below baseline measurements, although flow-metabolism coupling remains intact. The lack of a hyperemic response to cerebral hypoxia and acidosis is abnormal, suggesting microcirculatory dysfunction after TCA (86,87,105,115).

Summary

Although much has been learned about cerebral physiology during CPB in the past decade, the role of alterations in CBF and CMRO2 during CPB and the unfortunately common occurrence of neuropsychologic injury still is understood incompletely. It is apparent that during CPB temperature, anesthetic depth, CMRO2, and Paco2 are the major factors that effect CBF. The systemic pressure, pump flow, and flow character (pulsatile versus nonpulsatile) have little influence on CBF within the bounds of usual clinical practice. Although cerebral autoregulation is characteristically
preserved during CPB, untreated hypertension, profound hypothermia, pH-stat blood gas management, diabetes, and certain neurologic disorders may impair this important link between cerebral blood flow nutrient supply and metabolic demand (Figure 5).

During stable moderate hypothermic CPB with α-stat management of arterial blood gases, hypothermia is the most important factor altering cerebral metabolic parameters. Autoregulation is intact and CBF follows cerebral metabolism. Despite wide variations in perfusion flow and systemic arterial pressure, CBF is unchanged. Populations of patients have been identified with altered cerebral autoregulation. To what degree the impairment of cerebral autoregulation contributes to postoperative neuropsychologic dysfunction is unknown.

It must be emphasized that not the absolute level of CBF, but the appropriateness of oxygen delivery to demand is paramount. However, the assumption that the control of cerebral oxygen and nutrient supply and demand will prevent neurologic injury during CPB is simplistic (90). A better understanding of CBF, CMRO₂, autoregulation and mechanism(s) of cerebral injury during CPB has lead to a scientific basis for many of the decisions made regarding extracorporeal perfusion.

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