The brain uses approximately 20% of the total body oxygen consumption, receiving 15% of the total cardiac output. As with other major organ systems, the brain is subject to autoregulatory influences and adjusts for environmental changes to prevent oxygen deprivation. Such oxygen deprivation can lead to devastating physical and cognitive dysfunction.

Knowledge of cerebral blood flow and metabolism is essential to understanding the effect of ischemic insults on the brain. In all ischemic conditions, neuronal damage can extend far beyond the initial insult if attention is not paid to maximizing oxygen delivery to threatened areas. Therefore a working knowledge of cerebrovascular physiology can help the physician apply appropriate treatments during ischemic insults with the ultimate goal of preserving and promoting good functional outcomes.

**CEREBRAL BLOOD FLOW**

Cerebral blood flow (CBF) is defined as the velocity of blood through the cerebral circulation. CBF is expressed as milliliters per 100 g of brain tissue per minute. Once CBF is determined, other metabolic parameters can be calculated, such as the cerebral metabolic rate of oxygen consumption (CMRO₂) and oxygen delivery. A summary of pertinent physiological formulas is listed in Table 4-1.

Global CBF is approximately 50 ml/100g/min. Gray matter blood flow is approximately 3 to 4 times greater than white matter. Newborn blood flow is approximately 40 ml/100g/min. In infants and children, CBF is generally higher, increasing to 108 ml/100 g/min by 2 to 4 years of age, and can remain above 100 into adolescence. “Hyperemia” occurring in children after head injury may actually be a relative state of ischemia given the higher normative values (Table 4-2).

According to Ohm’s law, flow is directly related to perfusion pressure (inflow minus outflow) and inversely related to cerebrovascular resistance. The main resistance vessels are the small arteries and pial arterioles, the smallest of which are capable of dilating to up to 300% of their original diameters. These vessels may account for up to 85% of the total cerebrovascular resistance.

CBF is maintained according to Poiseuille’s law, which relates flow to physiological and anatomical variables within the cerebrovascular system.

\[
Q = \frac{\Delta P \pi r^4}{81 \eta}
\]

Flow (Q) is directly proportional to the pressure gradient, or differential (ΔP), which is synonymous with the cerebral perfusion pressure (CPP), and the fourth power of the vessel radius (r²). Flow is also inversely proportional to the length of the vascular tree (l), a constant, and the blood viscosity (η), which can vary under certain circumstances.

Autoregulation is the maintenance of constant CBF in the face of physiological changes, mainly brain perfusion. Altering elements of Poiseuille’s law can help improve blood flow in ischemic states such as head injury or vasospasm.
<table>
<thead>
<tr>
<th>Parameters (Units)*</th>
<th>Formula</th>
<th>Conversion Factor</th>
<th>Normal Values</th>
<th>Head Injury Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF (ml/100 g/min)</td>
<td>1.34 · Hb · SaO2 + .0031 · PaO2</td>
<td>$\frac{CaO_2 \ (ml/dl)}{2.24} = CaO_2 \ (\mu mol/ml)$</td>
<td>54 ± 12</td>
<td>52 ± 12</td>
</tr>
<tr>
<td>Cjvo2 (ml/dl)</td>
<td>1.34 · Hb · Sjvo2 + .0031 · Pjvo2</td>
<td>$\frac{Cjvo_2 \ (ml/dl)}{2.24} = Cjvo_2 \ (\mu mol/ml)$</td>
<td>19.6 ± 1.2</td>
<td>16.9 ± 1.5</td>
</tr>
<tr>
<td>AVDO2 (ml/dl)</td>
<td>$\frac{CaO_2 \ (ml/dl) - Cjvo_2 \ (ml/dl)}{2.24} = AVDO_2 \ (\mu mol/ml)$</td>
<td>6.3 ± 1.2</td>
<td>6.7 ± 0.8</td>
<td>6.5 ± 1.8</td>
</tr>
<tr>
<td>CMRO2 (ml/100 g/min)</td>
<td>$\frac{AVDO_2 \ (ml/dl) \cdot CBF \ (ml/100 \ g/min)}{100}$</td>
<td>$\frac{CMRO_2 \ (ml/100 \ g/min)}{2.24} = CMRO_2 \ (\mu mol/110 \ g/min)$</td>
<td>3.3 ± 0.4</td>
<td>3.3 ± 0.6</td>
</tr>
<tr>
<td>O2ER (%)</td>
<td>$\frac{AVDO_2 \ (ml/dl) \cdot 100%}{CaO_2}$</td>
<td>34 ± 4</td>
<td>31 ± 10</td>
<td></td>
</tr>
<tr>
<td>AVDG (ml/dl)</td>
<td>ArtGluc (ml/dl) − JVGluc (ml/dl)</td>
<td>$\frac{AVDG \ (ml/dl)}{18} = AVDG \ (\mu mol/ml)$</td>
<td>9.6 ± 1.7</td>
<td>11.0 ± 2.3</td>
</tr>
<tr>
<td>CMRG (ml/100 g/min)</td>
<td>$\frac{AVDG \ (ml/dl) \cdot CBF \ (ml/100 \ g/min)}{100}$</td>
<td>$\frac{CMRG \ (ml/100 \ g/min)}{18} = CMRG \ (\mu mol/g/min)$</td>
<td>5.5 ± 1.1</td>
<td>3.5 ± 2.4</td>
</tr>
<tr>
<td>AVDL (ml/dl)</td>
<td>ArtLact (ml/dl) − JVLact (ml/dl)</td>
<td>$\frac{AVDL \ (ml/dl)}{9} = AVDL \ (\mu mol/ml)$</td>
<td>-1.70 ± .9</td>
<td>-0.5 ± 0.9</td>
</tr>
<tr>
<td>CMRL (ml/100 g/min)</td>
<td>$\frac{AVDL \ (ml/dl) \cdot CBF \ (ml/100 \ g/min)}{100}$</td>
<td>$\frac{CMRL \ (ml/100 \ g/min)}{9} = CMRL \ (\mu mol/g/min)$</td>
<td>-0.23 ± 0.37</td>
<td>-0.25 ± 0.73</td>
</tr>
<tr>
<td>LOI</td>
<td>$\frac{-AVDL \ (\mu mol/ml)}{AVDO_2 \ (\mu mol/ml)}$</td>
<td>0.06 ± 0.03</td>
<td>0.02 ± 0.05</td>
<td></td>
</tr>
</tbody>
</table>


*All average values are given in the units used in the first column.

O2ER can also be calculated by the formula $1 - \frac{Sjvo_2}{SaO_2}$ or $\frac{SaO_2 - Sjvo_2}{SaO_2} \cdot 100\%$.

CaO2, arterial oxygen content; Cjvo2, jugular venous oxygen content; SaO2, arterial oxygen saturation; Sjvo2, jugular venous oxygen saturation; Hb, hemoglobin concentration; PaO2, arterial PO2; Pjvo2, jugular venous PO2; AVDO2, arterial venous oxygen difference; O2ER, oxygen extraction ratio; ArtGluc, arterial glucose concentration; JVGluc, jugular venous glucose concentration; AVDG, arterial venous glucose difference; CMRG, cerebral metabolic rate of glucose; ArtLact, arterial lactate concentration; JVLact, jugular venous lactate concentration; AVDL, arterial venous lactate difference; CMRL, cerebral metabolic rate of lactate; LOI, lactate oxygen index.
Cerebrovascular Pathophysiology and Monitoring in the Neurosurgical Intensive Care Unit

Components of Poiseuille’s Law

Cerebral Perfusion Pressure (ΔP)
Cerebral perfusion pressure is also referred to as the transmural pressure gradient. CPP is the differential pressure of arterial inflow and venous outflow, the latter usually equaling the intracranial pressure (ICP). CPP can also be defined as the differential mean pressure within the arterial vessel (MAP) and the pressure surrounding the vessel wall (ICP).

Dewey and colleagues further defined CPP as the MAP minus the critical closing pressure, which is determined by ICP and vascular smooth muscle tone. When ischemia results in maximal vessel dilation, the smooth muscles are maximally relaxed (zero tone). When the ICP approaches MAP, the vessel collapses at CPP less than 10 mm Hg, resulting in blood flow cessation (Figure 4-1, bottom panel). At relatively high shear rates (<10 sec⁻¹), viscosity is inconstant on the hematocrit. At low shear rates, erythrocyte aggregation occurs, which is reversible at elevated shear rates.

Vascular Radius (r⁴)
As stated previously, small arteries and arterioles are capable of dilating and constricting in response to altered blood flow. As CPP decreases below 50 mm Hg, vascular smooth muscle begins to relax and vessels dilate to increase the volume of blood traveling within them, improving oxygen delivery. If CPP is raised above 50, vessels begin to constrict to decrease blood volume to match the decreasing oxygen demand until a steady-state diameter is reached (Figure 4-1, top and middle panels). The adjustment of vessel diameter regulates the inflow according to metabolic demands. Other environmental factors can affect vascular muscle tone such as sympathetic and parasympathetic innervation, nitric oxide, adenosine, hypoxia, anemia, and hypercarbia/hypocarbia.

Blood Viscosity (η)
Cerebral blood flow is inversely proportional to whole blood viscosity. However, blood is a non-Newtonian fluid, containing proteinaceous elements that are capable of aggregating in low-flow states. Therefore the relationship of blood flow and viscosity is not strictly linear under all conditions.

Viscosity, expressed in centipoise units, measures a liquid’s resistance to flow. Blood traveling through vessels is subject to laminar flow, meaning the velocity is faster in the periphery than in the center. Shear rate (sec⁻¹) is the velocity gradient within the vessel and is directly proportional to velocity and inversely proportional to the radius. At higher blood velocities/shear rates, the viscosity is less, thus defining the inverse relationship between shear rate and viscosity. At relatively high shear rates (<10 sec⁻¹), viscosity is inconstant on the hematocrit. At low shear rates, erythrocyte aggregation occurs, which is reversible at elevated shear rates.

Manipulating blood viscosity is an integral part of hypertensive, hypervolemic, hemodilution (triple-H) therapy of cerebral vasospasm and subarachnoid hemorrhage. This therapy uses decreased hematocrit to improve blood rheology, which optimizes flow and deformation of blood elements through different diameter blood vessels. Increasing blood flow with pressors in addition to hemodilution can help push blood through the microvasculature more efficiently.

Pharmacological agents such as mannitol, dextran, albumin, and hetastarch help improve hemorheology by promoting intravascular volume expansion, or hemodilution. These agents, especially dextran, can prevent red blood cell (RBC) aggregation while traveling through the microvasculature. It is in these small vessels where viscosity contributes the most to Poiseuille’s CBF equation, especially in ischemic states.

CEREBRAL AUTOREGULATION

According to a landmark review by Lassen in 1959, “cerebral perfusion is controlled very efficiently by homeostatic regulation of the perfusion pressure and the so-called cerebral vascular resistance.” Autoregulation therefore refers to the maintenance of a relatively constant CBF during fluctuations in CPP. Constant CBF is maintained over a MAP range of 60 to 160 mm Hg. Cellular metabolism also influences vascular radius and consequently autoregulation. Through autoregulation the brain protects itself from ischemia. At the extreme, Cushing’s response provides a physiological attempt to improve CBF during times of critical ischemia.

---

**Table 4-2** Normal CBF Values According to Age

<table>
<thead>
<tr>
<th>Age</th>
<th>CBF (ml/100g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>40</td>
</tr>
<tr>
<td>6 months</td>
<td>65</td>
</tr>
<tr>
<td>1 year</td>
<td>80</td>
</tr>
<tr>
<td>2-4 years</td>
<td>108</td>
</tr>
<tr>
<td>8 years</td>
<td>85</td>
</tr>
<tr>
<td>14 years</td>
<td>70</td>
</tr>
<tr>
<td>Adult</td>
<td>50</td>
</tr>
</tbody>
</table>

---
Limits of Autoregulation

Figure 4-1 (bottom panel) demonstrates a small decrease in CBF as the CPP values fall to 50 mm Hg, which can be considered the lower limit of autoregulation.\(^{6,26}\) As CPP declines, vascular radius reaches its peak, the point of maximal dilation (Figure 4-1, middle panel). Below this threshold, vessels collapse and cerebral blood flow declines. Below this lower limit of autoregulation, cerebral blood volume (CBV) decreases proportionately with the blood pressure. As perfusion is restored, CBV increases until smooth muscle responsivity is restored and constricts to maintain constant blood flow. CBV thus decreases. Therefore CBV does not increase proportionately with increased blood flow within the autoregulatory range, but in fact decreases until a steady state is reached (Figure 4-1, top panel).\(^{26}\)
Increasing perfusion at the upper limit of autoregulation results in passive dilation of many of the autoregulatory pial arterioles, leading to increased CBF and decreased CVR. Kontos demonstrated that smaller vessels dilate more than larger ones. Fusiform microaneurysms were found in smaller vessels in cats subjected to induced hypertension to greater than 200 mm Hg. Above this level, dilatory responses were largely irreversible. Such responses can lead to blood brain barrier disruption, cerebral edema, or intracranial bleeding.

Vasoresponsivity

Vasoresponsivity is the ability of blood vessels to dilate or constrict in response to environmental influences. Such factors include CPP fluctuations, hypoxia, and hypocarbia/hypercarbia. By determining the CBF response to such stimuli, assessment of the brain’s ability to autoregulate can be made. The brain may lose this ability if subject to critical, irreversible ischemia. Such loss can occur either regionally or globally.

Blood vessel diameter does change in the face of CPP alterations. Normal latency is approximately 5 to 10 seconds. In pathological states such as head injury, responsivity is delayed. Manipulation of CPP may result in an initial rise in ICP as blood volume transiently increases proportionately, then decreases as vessels vasoconstrict.

Carbon dioxide vasoresponsivity is defined by a 3% change in CBF per 1 mm Hg change in PCO2. By using induced hypocarbia, responsivity can be assessed both globally and regionally during various tests for CBF determination. Acetazolamide is also used for this purpose. In dosages greater than 10 mg/kg, acetazolamide inhibits carbonic anhydrase in the erythrocyte. Vorstrup and colleagues demonstrated a 53% to 75% increase in CBF in patients given acetazolamide. Although the exact mechanism is uncertain, RBC carbonic anhydrase inhibition results in a decrease in brain pH by impeding CO2 removal through the circulation. Acetazolamide has been found to be equal or superior to CO2-induced vasomotor reactivity.

Vasoresponsivity may still be present despite autoregulatory impairment. Impaired autoregulation can be seen in head injury, subarachnoid hemorrhage, and other global ischemic insults. In severe head injury, focal and global autoregulation may still be intact. Global, severe, and persistent autoregulation eventually leads to autoregulatory loss. This loss is evidenced by passive changes in ICP with blood pressure caused by passive increases in CBV.

Theories of Autoregulation

Although the above discussion assumes that autoregulation is largely incumbent on vascular smooth muscle tone and the response to pressure changes, various theories have been proposed for the autoregulatory mechanism, such as myogenic, neurogenic, and metabolic.

The myogenic theory proposes that vascular smooth muscle reacts to changes in stretch forces, or the transmural pressure. The metabolic theory, as defined by Kontos, states that cell metabolites arising from blood flow changes alter vascular diameter. Hydrogen, potassium, and adenosine have been shown to have vasoactive properties under conditions of hypoxia, ischemia, or cortical activation.

The endothelial cell may have a strong influence on vessel caliber. Reduced CBF stimulates endothelium-derived relaxing factor (EDRF) release, identified as the vasodilator nitric oxide (NO) or an NO-containing compound. Prostaglandins are also vasodilators. Endothelin and thromboxane A2 are vasoconstrictors. Arguments against the metabolic theory are primarily based on the longer delay in activation compared with the normal autoregulatory latency.

In neurogenetic theory, perivascular sympathetic and parasympathetic nerves may have autoregulatory effects. Evidence suggests that these factors are not essential for autoregulation. It is likely that all three mechanisms work in concert to regulate blood flow. Certainly, although pressure change is the primary factor in vasoactivity, chemical and molecular contributions as a consequence of pressure changes are also very important.

Ischemic Penumbra and Ischemic Thresholds

The ischemic penumbra refers to the ischemic zone of brain tissue surrounding a core area of infarction or severe ischemia. As CBF decreases, less oxygen is carried to neurons, resulting in a decrease in mitochondrial adenosine triphosphate (ATP) production and ATP depletion. This depletion leads to lactic acid, free radical, lipid peroxidase, and other toxic metabolites production. Sodium and calcium influx and potassium efflux are also noted, eventually resulting in membrane breakdown and cell death. Just before this point, slowing and eventual cessation of synaptic transmission occurs without cell breakdown. This phenomenon occurs at 8 to 23 ml/100g/min. Cortical potentials cease at 16 to 18 ml/100 g/min.

In the penumbral range, lactic acid accumulates, ATP production remains normal, and the Na+/K+ pump is intact. Blood flow restoration in this ischemic range can result in neuronal recovery as evidenced by the return of cortical evoked responses. After suffering an ischemic stroke, optimal cerebral perfusion can help limit the extent of functional impairment.

Return of function also depends on the duration of ischemia at various levels of CBF. For example, flows ranging from 18 to 23 ml/100g/min can be tolerated...
for up to 2 weeks, 10 to 12 ml/100g/min for less than 3 hours, and 8 ml/100 g/min for about 1 hour until neuronal death occurs.16 The ischemic threshold can be raised by hyperglycemia, chronic hypertension, head injury, and vasospasm and lowered by certain anesthetic agents (isoflurane) and other neuroprotective drugs.16

Cushing’s Response

The classic Cushing’s triad—hypertension, bradycardia, and respiratory depression—can occur with significant intracranial hypertension.21 As ICP rises to significant levels, nearing the MAP (with a concomitant dangerous decrease in CPP), the systemic blood pressure (BP) becomes elevated to a systolic BP greater than 200 mm Hg. This hypertension results from peripheral vasoconstriction and catecholamine release.47 Brainstem/medullary ischemia results in bradycardia.78,81

In a series of animal experiments, Schrader and colleagues78,80 demonstrated that expanding infra- and supratentorial masses resulted in progressive brainstem ischemia. Supratentorial mass expansion led to ischemia traveling in a rostral-caudal direction. Cushing’s response resulted from ischemia extending to the lower pons.78 The hypertensive response increased the ability of the brain to tolerate the expanding mass.78 During Cushing’s response, there is decreased blood flow to peripheral tissues but increased flow to the myocardium and adrenals.33,80,95 Harris and colleagues33 found that blood levels of epinephrine, norepinephrine, and arginine vasopressin were increased in fetal sheep. Blood flow increased in organs vital for sustaining and increasing blood pressure. As a result, Cushing’s response helped to maintain adequate blood flow and tissue oxygenation during periods of ischemia.5,51,80

Cushing’s response is the physiological response to life-threatening cerebral ischemia and is the body’s attempt to preserve neuronal function through CBF improvement. Failure to recognize this critical need often leads to inappropriate antihypertensive therapy, which may precipitate irreversible neuronal damage.

METHODS OF CBF MEASUREMENT

Bedside Measurements

Kety-Schmidt/Nitrous Oxide Technique

The Kety-Schmidt technique, first described in 1945,38 uses nitrous oxide (N2O), a diffusible gas, for global CBF measurement. This examination is based on the Fick principle, which states that the amount of inert substance taken up by the brain is equal to the difference between substance delivery through the arterial system and removal by the venous system. After inhalation, N2O reaches equilibrium between arterial blood, venous blood, and brain; arterial and jugular venous samples are obtained and analyzed for N2O concentration over time. The integral of the arteriovenous difference is used to calculate CBF. CMRO2 can also be calculated given the knowledge of arteriovenous oxygen difference (AVDO2) and CBF.25,74

The Kety-Schmidt method is inexpensive and can be repeated multiple times. However, this method does not allow for regional CBF measurement or change detection, which may exist in disease processes such as traumatic brain injury, infarction, and vasospasm.

Xenon-133

Bedside regional CBF monitoring has been performed for many years using radioactive Xenon-133 (Xe-133), a low gamma emitter. Xe-133 has a half-life of approximately 5 days and is freely diffusible throughout the brain. Approximately 90% is cleared by first pass through the lungs, preventing recirculation in the brain. Bedside collimated scintillators are used to gather data about Xe-133 washout. The washout curve is approximately 15 minutes and is composed of two major compartments—fast (gray matter) and slow (white matter).23 The two compartments can be analyzed separately. Regional CBF is calculated via several methods, a more detailed review of which can be found in Anderson.1 Xe-133 can be administered invasively (intrararterially) or noninvasively (inhaled gas).68 The gas form is soluble in normal saline. Given the small doses used, radiation exposure risk to the patient and medical staff is small.

Bedside Xe-133 CBF monitoring provides regional CBF measurements, allowing the clinician to evaluate several areas in both hemispheres simultaneously. Spacial resolution, however, is poor. The “look-through” phenomenon overestimates areas of low or no flow as a result of uptake in the immediately surrounding tissues.1 CBF in deep hemisphere structures, brainstem, and cerebellum are obscured by surface uptake detection.23 Despite various artifactual interferences, regional CBF changes can be easily recognized, making this technique useful in the clinical setting.

CBF Imaging

MR Diffusion and Perfusion408

Magnetic resonance (MR) diffusion imaging uses the apparent diffusion coefficient (ADC) of water to qualitatively evaluate areas of low blood flow. Diffusion imaging has been used in patients with ischemic stroke. Areas with low ADC values are bright (Figure 4-2). Such changes can be seen as early as 10 minutes after the occlusive event and as late as 1 week, recovering to baseline in 5 to 10 days.

MR perfusion imaging uses intravenous contrast such as gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA). Such imaging provides a map of
cerebral blood volume by measuring the magnetic field gradient between the blood vessel lumen and surrounding tissue over time on the first pass of contrast agent. Low areas of CBV indicate poor perfusion.

Combined diffusion and perfusion imaging may allow for ischemic penumbra visualization as areas of perfusion-diffusion mismatch. This is because perfusion cannot distinguish between reversible and irreversible ischemia, whereas acute diffusion imaging might underestimate the ultimate infarct volume.

**Xenon-CT**

Stable xenon computed tomography (Xe-CT) involves inhalation of 28% to 33% stable xenon gas. Xenon, a general anesthetic in high concentrations, crosses the blood-brain barrier easily because of its lipid solubility. Combining CT with the radiodense Xe allows for a cross-sectional view of Xe concentration in various regions within the brain, as well as globally. The 33% concentration is a safe, nonanesthetic concentration. Xenon washout takes 20 minutes, after which the test can be repeated. Using a region of interest (ROI), the exact CBF can be calculated by computer. Because the test is repeatable within a relatively short period, vasoresponsivity can be assessed by methods such as hypercarbia or acetazolamide. Care must be taken to avoid motion artifact and Xe gas leakage around the mask. Spiral CT scanning has improved Xe-CT images.

Xe-CT is commercially available (Diversified Diagnostic Products, Houston, Tex.). This technology is particularly useful in conditions in which regional CBF quantification is useful in directing management. Such conditions include cerebrovascular surgery, head injury, stroke, and subarachnoid hemorrhage.*

**SPECT**

Single photo emission tomography (SPECT) employs radioactive tracers to measure CBF using tomographic images (Figure 4-3, A-C) through the detection of scattered photons. Regional and global CBF can be visualized. Various agents have been used, including Xe-133 gas, I-123, and various compounds of technecium-99m. Of these, only Xe-133 gas provides quantitative CBF measurements. Xe-133 also allows for multiple rapid measurements. I-123 must be imaged rapidly because of its quick redistribution within the brain. The brain retention half-life is 60 minute to 6 hours, depending on the compound.

Tc-99m compounds are the most widely used because of their availability and lower expense. Redistribution is slower, and brain retention half-life can be up to 24 to 28 hours, limiting the temporal resolution of each study. Tests for cerebrovascular reserve can also be done using SPECT technology. However, only qualitative blood flow assessments can be made. Stroke, brain death determination, and epilepsy are among the applications for SPECT blood flow studies.

**PET**

Positron emission tomography (PET) uses gamma ray (positron)–emitting nuclides, which produce two photons when captured by electrons. PET provides quantitative evaluation of the flowing parameters: CBF, CBV, CMRO₂, oxygen extraction fraction (OEF), cerebrovascular mean transit time (t-CBV/CBF), and cerebral metabolic rate of glucose consumption (CMRG). PET thus uniquely gives dynamic information in blood flow and metabolism. ¹⁵O-labeled gases, carbon dioxide, oxygen, and carbon monoxide are used for CBF, CBV, CMRO₂, OEF, and mean transit time. ¹⁸F-fluoro-2-deoxy-D-glucose (¹⁸FDG) is used for CMRG. Non–steady-state ¹⁵O-labeled water can also be used to measure CBF.

PET measurements of CBF, OEF, and CMRO₂ can demonstrate ischemic penumbral areas and be used to augment flow. Although PET is a well-rounded, multifaceted technique for evaluating cerebral hemodynamics and metabolism, limited availability and expense restrict its usage in routine clinical practice.

**Continuous CBF Monitoring**
Continuous regional CBF monitoring can be adapted for bedside monitoring. Applications include head injury, intraoperative aneurysm/arteriovenous malformation (AVM) resection, subarachnoid hemorrhage, and epilepsy. Such monitoring can alert the clinician to...
changes in regional CBF and allow for minute-to-minute hemodynamic alterations.

**Thermal Diffusion Flowmetry**
Thermal diffusion flowmetry uses a temperature gradient on the sensor to calculate the cerebral blood flow. The sensor contains two gold plates, one heated, one neutral. The heat dissipates to the neutral plate and this temperature difference (dT) is converted to flow in ml/100g/min. Blood flow is inversely proportional to dT. Therefore the higher the blood flow, the lower the temperature difference between the heated and neutral plates. Although correlating with global CBF as measured by N2O technique, this method does not correlate well with Xe-CT regional or global values.

The sensor comes as a flat silicone plate for intraoperative or postoperative monitoring. A “trauma bolt” has been developed for placement inside a standard burrhole (Flowtronics, Inc., Phoenix, Ariz.). Each plate must touch relatively normal cortex, avoiding large surface vessels. The confidence factor helps determine whether both plates are in contact with the cortical surface. Once the heater is turned off, both plates should be at the same temperature. A confidence factor of 0.8 and above is considered reliable for use. Sioutos and colleagues found that in 56 severely head-injured patients, 66% had reliable data with a confidence factor greater than or equal to 0.75.

**Laser Doppler Flowmetry**
Laser Doppler flowmetry estimates regional cerebral blood flow by using low-power laser light through cerebral tissue. Photons are randomly scattered by moving blood cells in capillary-sized vessels and are Doppler shifted. The proportion of Doppler-shifted light, which scatters back to the photo sensor, gives information regarding the blood cell velocity and blood volume in “arbitrary units.” These values poorly correlate with absolute CBF.

The laser Doppler probes can be placed on the cortical surface or within the brain parenchyma. As in thermal diffusion, avoidance of macroscopic vessels is key. The special resolution is 1 mm, the smallest of all regional CBF methods, which may be a significant disadvantage. Other problems include the susceptibility to motion artifact, reducing reliability; fluctuation of signal without obvious cause; and tissue and capillary density. However, because of the high temporal resolution, allowing for a high frequency of data collection during continuous monitoring, changes in blood flow can be ascertained and treated quickly.

**Indirect CBF Measurements**

**Transcranial Doppler Sonography**
Transcranial Doppler sonography (TCD) is a useful, noninvasive bedside method for inferring blood flow. TCD measures blood flow velocity in intracranial vessels. Depending on the clinical circumstances, increased or decreased velocity can indicate low or compromised blood flow.

Cerebral blood flow can be mathematically calculated if certain parameters are known and constant. Such parameters include vessel cross-sectional area and the angle of incidence between arterial blood flow and the ultrasonic beam. However, in pathological states, such parameters may vary over time and with environmental conditions, rendering CBF calculations unreliable.

TCD uses the Doppler principle to measure blood flow velocity via ultrasonic waves, which reflect off moving red blood cells. The transducer emits these waves at a known frequency, usually 2 MHz. A wave form is generated with a systolic peak, dicrotic notch, and diastole. Mean velocities are used and are determined as the area under the curve.

Intracranial vessels are sonoated through three “windows” (Table 4-3). The transtemporal window lies within the temporal squama just above the zygoma,

<table>
<thead>
<tr>
<th>Window</th>
<th>Vessel</th>
<th>Depth (mm)</th>
<th>Normal Vm (cm/sec)</th>
<th>Direction of flow*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transtemporal</td>
<td>MCA</td>
<td>45-55</td>
<td>60 ± 12</td>
<td>Toward</td>
</tr>
<tr>
<td></td>
<td>ACA</td>
<td>55-75</td>
<td>50 ± 12</td>
<td>Away</td>
</tr>
<tr>
<td></td>
<td>PCA</td>
<td>65-80</td>
<td>40 ± 11</td>
<td>Toward/away</td>
</tr>
<tr>
<td>Transorbital</td>
<td>OA</td>
<td>30-55</td>
<td>20 ± 10</td>
<td>Toward</td>
</tr>
<tr>
<td></td>
<td>ICA</td>
<td>55-70</td>
<td>50 ± 15</td>
<td>Toward/away</td>
</tr>
<tr>
<td>Transforamental</td>
<td>VA</td>
<td>65-85</td>
<td>40 ± 10</td>
<td>Away</td>
</tr>
<tr>
<td></td>
<td>BA</td>
<td>&gt;85</td>
<td>40 ± 10</td>
<td>Away</td>
</tr>
</tbody>
</table>


*In relation to transducer.

Vm, Mean velocity; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; OA, opthalmic artery; ICA, internal carotid artery; VA, vertebral artery; BA, basilar artery.
the thinnest portion of the temporal bone, and allows for anterior circulation insonation. The suboccipital/foramen magnum window studies the vertebrobasilar system. The orbital approach insonates the ophthalmic and cavernous carotid arteries. This window is especially useful in diagnosing proximal carotid occlusions, which, as a result of external carotid collateralization, demonstrate flow reversal in the ophthalmic artery.

Blood flow velocity is inversely related to the vessel radius. Velocities can therefore be increased in vasospasm (Figure 4-4). Other factors, such as fever, anemia, hypoxia, dominant vessels, and vasopressor therapy, can also result in increased blood velocity. Blood flow and velocities are higher in young patients and lower in the elderly. Cessation of cerebral blood flow, or brain death, can be identified as small spikes with reversal of diastole in intracranial vessels and high-spiked systolic flow with reversal of diastolic flow in the extracranial carotid artery, indicating high-flow resistance (Figure 4-5). The pulsatility index (PI) is an indicator of flow resistance and is calculated as the systolic minus the diastolic velocities divided by the mean. Normal PI is 0.7 to 1.1. High PI may indicate atherosclerosis, intracranial hypertension, or brain death.

The Lindegaard ratio can help discern between elevated flow velocities caused by high-flow states and vasospasm. This ratio is calculated as the mean middle cerebral artery divided by the mean extracranial internal carotid artery velocities. Ratios greater than 3 correlate with angiographic spasm, whereas 6 and above indicate severe spasm. Mean velocities of 200 cm/sec are consistent with severe vasospasm. Severely compromised blood flow is usually indicated by clinical deficits.

TCD can provide continuous, real-time blood flow velocities intraoperatively during carotid endarterectomies to detect altered middle cerebral artery blood flow during cross clamping or from emboli. AVM flow velocities and collateral flow patterns in patients with

![Figure 4-4](image)

**Figure 4-4** Transcranial Doppler tracing of a patient with middle cerebral artery spasm (*top panel*). The mean velocity is 160 cm/sec, representing moderate vasospasm. A later study (*bottom panel*) demonstrated resolution of the middle cerebral spasm (mean velocity, 66 cm/sec).
stenotic or occlusive vascular disease can also be determined. Noting velocity changes over time is helpful. Recently, transcranial color duplex sonography has been available for greater anatomical viewing of blood vessels, their diameter, and flow velocities.

Inaccuracies in TCD arise when the angle of insonation is greater than 15 degrees. By catching the edge of the blood vessel, as opposed to the center, the velocity can be underestimated. It has been observed that the resistance index (V_s - V_d/V_s) often remains constant through each vessel when the angle of insonation is correct. Turbulence at branch points can overestimate velocities. Thick temporal squamae make insonation difficult. Vertebrobasilar ectasia can create difficulty finding wave forms at certain depths.

**Brain Oxymetry**

Brain oxymetry measures oxygen delivery to the brain, which is an indirect measure of cerebral blood flow. Oxymetry best reflects the balance between brain oxygen supply and demand, or metabolism, and is discussed in further detail later in this chapter.

**CEREBRAL METABOLISM**

As stated previously, the brain uses 20% to 25% of the total body oxygen consumption. During aerobic metabolism, 1 mole of glucose plus 2 moles of oxygen combine through a series of well-known pathways (glycolytic, citric acid cycle, electron transport chain) to ultimately yield 38 moles of ATP. ATP provides energy for cellular metabolism, including maintenance of membrane integrity and protein synthesis. Under normal circumstances, less than 10% of glycolysis occurs under aerobic conditions, converting 1 mole of glucose into 2 moles of ATP plus 2 moles of lactic acid. Such metabolism results in less energy production and lactate accumulation, ultimately leading to acidosis and cellular breakdown if allowed to become the predominant pathway. For the neuron, 55% of the en-
nergy metabolism is used for nerve conduction and synaptic transmission, whereas 45% is for cellular maintenance. Gray matter consumes nearly twice as much glucose and oxygen as white matter.\textsuperscript{73}

Knowledge of CBF is critical to assessing the state of cerebral metabolism. The metabolic parameters include the cerebral oxygen delivery (DO\textsubscript{2}), CMRO\textsubscript{2}, CMRG, and cerebral metabolic rate of lactate consumption (CMRL). Oxygen delivery is the product of the arterial oxygen content, which takes hemoglobin levels into account, and the CBF. Determination of the metabolic rates of consumption or production requires comparison of the cerebral arterial and venous substrate content. Jugular bulb sampling is the most common method of obtaining the venous blood.

The arteriovenous oxygen difference compares the oxygen content of the arterial and venous blood. The normal value is approximately 6.5 ml/dl\textsuperscript{74,75} because the jugular oxygen content is usually less than arterial. The brain extracts oxygen from the arterial supply as the metabolic demand dictates. The oxygen extraction ratio (O\textsubscript{2}ER) indicates the state of cerebral metabolism independent of the hemoglobin by using the ratio of arterial and venous oxygen saturation. Normal O\textsubscript{2}ER is approximately 35%. This parameter may arguably be more “stable,” or reliable, than the AVDO\textsubscript{2} in assessing cerebral metabolism supply and demand.\textsuperscript{19,20} In ischemic states the brain extracts as much oxygen as needed for metabolism, resulting in an increase in AVDO\textsubscript{2} and O\textsubscript{2}ER, at least initially. Metabolic activity (demand) therefore exceeds the oxygen supply (CBF). When blood flow and oxygen delivery exceed the metabolic demand, AVDO\textsubscript{2} and O\textsubscript{2}ER are decreased, resulting in hyperemia, or luxury perfusion. As is apparent, these parameters (AVDO\textsubscript{2} and O\textsubscript{2}ER) do not require CBF and can be performed inexpensively and frequently.

CMRO\textsubscript{2} is calculated from the product of CBF and AVDO\textsubscript{2}. The CMRO\textsubscript{2} is 3.4 ml/100g/min, or 1.5 \mu mole/g/min. CMRO\textsubscript{2} can be increased by 10% per 1°C temperature elevation and decreased by 5% per 1°C temperature decrease.\textsuperscript{73} CMRG and CMRL are calculated in a similar fashion as CMRO\textsubscript{2}, using the arterial and venous contents of glucose and lactate, respectively. Normal average CMRG is 5.5 ml/100g/min. Normal average CMRL is -0.23 ml/100g/min, indicating a small degree of baseline lactate production. An increase in lactate production (more negative) indicates possible ischemia. An increase in the lactate/oxygen index (LOI), determined by the ratio of AVDLactate (AVDL) to AVDO\textsubscript{2} to greater than 0.8 is an indicator of increased anaerobic metabolism.\textsuperscript{73,75} This parameter can be easily obtained without knowledge of CBF.

Robertson and colleagues\textsuperscript{75} identified a pattern relating O\textsubscript{2} consumption to blood flow in severely head-injured patients. Two states were identified when ischemia was present. The first, “compensated hypoperfusion,” related low CBF to an increase in AVDO\textsubscript{2} while CMRO\textsubscript{2} remained unchanged and CMRL was normal. An increase in brain O\textsubscript{2} extraction, demonstrated by an increased AVDO\textsubscript{2} allowed the total O\textsubscript{2} consumption to remain constant. With persistently low CBF (the “ischemic/infarct” state) the brain is no longer able to extract enough oxygen to maintain normal metabolic function. Therefore, lactate production increases and AVDO\textsubscript{2} decreases, possibly because of the decreased total volume of brain able to extract O\textsubscript{2}. The authors concluded that as long as the lactate/oxygen index remains normal, AVDO\textsubscript{2} can predict the status of cerebral blood flow through an inverse relationship. When ischemia/infarction sets in, the relationship is not reliable and direct CBF measurements are required.

**Hypoglycemia/Hyperglycemia**

Experimental and clinical evidence suggest that preexisting hyperglycemia exacerbates neuronal injury in ischemia states.\textsuperscript{67,70,71,102} Diabetics and nondiabetics with elevated glucose levels may have worse outcomes after stroke.\textsuperscript{70,102} Lactic acid production had long been postulated as the mechanism.\textsuperscript{71} Nakai and colleagues\textsuperscript{47} found that significantly decreased tissue pH is ischemic hemisphere in hyperglycemic rates. Other possible causes are reduction in regional cerebral blood flow\textsuperscript{27,67} and increased glutamate levels.\textsuperscript{48}

Not all experimental studies have shown a negative effect of hyperglycemia, especially in focal, permanent ischemic damage.\textsuperscript{31,109} Schurr and colleagues\textsuperscript{83} found that glucose loading 15 minutes before experimental ischemia resulted in increased neuronal damage. However, preloading with glucose 120 minutes before the ischemia decreased delayed neuronal damage over the 15-minute subjects and control animals. Both groups exhibited similar lactate levels despite their different outcomes.

Hypoglycemia is usually well tolerated in normal brain metabolism.\textsuperscript{69} Mild hypoglycemia may offer some neuronal protection during ischemia.\textsuperscript{70,69} There has been recent interest in using insulin as a neuroprotective agent.\textsuperscript{49} The glucose insulin in stroke trial (GIST) is currently underway.\textsuperscript{64}

**CBF/METABOLIC COUPLING**

CBF/metabolic coupling refers to the matching of oxygen and glucose supply (CBF) with utilization (metabolism/consumption). Normally these functions are closely related and change proportionately. During cortical activation, increase in glucose and oxygen consumption is matched with a concomitant increase in blood flow. The reverse is true during hypothermia, anesthesia, or when using high-dose barbiturates.
Several mediators for coupling have been postulated. Among these are vasodilators: hydrogen ion and lactic acid produced by anaerobic metabolism; increased extracellular potassium concentration: prostacyclin; adenosine from ATP breakdown; and nitric oxide. Arachidonic acid derivatives such as thromboxane \( \Lambda_2 \) are vasoconstrictors.

Neuronally derived nitric oxide may contribute to physiologic coupling. Nitric oxide is a vasodilator produced by nitric oxide synthase, whose action is stimulated by \( N \)-methyl-D-aspartate (NMDA) receptor activation by the excitatory amino acid glutamate. The latter is released in increased amounts during ischemia. Adenosine has been identified as a potentially significant mediator of physiological coupling. Adenosine is a purine derivative formed by ATP breakdown and a potent vasodilator. Adenosine production is increased in ischemia, hypoxia, seizures, and states of hypermetabolism. During carotid endarterectomy, jugular adenosine concentrations increased in patients experiencing ischemia during carotid cross-clamping. Adenosine may play a key role in hyperemia and uncoupling during the later phases of head injury. After release, adenosine acts on the \( \Lambda_2 \) vascular smooth muscle receptor. A neuroprotective role has also been identified because adenosine may attenuate ischemic brain injury through \( \Lambda_1 \) receptor activation. This activation may inhibit excitatory amino acid release, thereby preventing calcium influx.

Hypothermia in severe head injury provides an example of the decoupling of CBF and metabolism in pathological states. Early CBF decrease and increases in CMRO\(_2\), CMRG, and CMRL have been demonstrated. Hypothermia lowers CMRO\(_2\), thereby promoting improved CBF/metabolic coupling. Early prophylactic hypothermia has been shown in some studies to improve outcomes from severe head injury (SHI).

**METABOLIC MONITORING TECHNIQUES**

**Brain Oxymetry**

**Near-Infrared Spectroscopy**

Near-infrared spectroscopy (NIRS) is a continuous, noninvasive method, having been used during carotid endarterectomies, head injury, cerebral embolic events, and seizures to detect changes in brain oxygen supply and demand. Hemoglobin and cytochrome oxidase, which carry oxygen, have well-developed absorption spectra. Oxyhemoglobin concentration can be used as a “tracer” to determine CBF. Information can be mathematically applied to calculate CBF and CBV. NIRS does not require pulsatile flow.

Near-infrared light (650 to 1000 nm) emanates from emitters placed on the scalp, penetrating to a depth of 2.5 cm. This light is reflected back to a sensor. The temporal resolution is approximately 0.5 seconds. Scalp ischemia can influence measurements, although the significance of bone blood flow is uncertain. NIRS was found to correlate well with jugular venous oxygen measurements.

**Tissue \( P_{O_2} \)**

Partial oxygen pressure in tissue (TP\(_{O_2}\)) is measured through a sensor coupled with an oxygen pressure measuring instrument, which can be intraparenchymal, on the cortical surface or in the CSF. Using such monitors, differences in TP\(_{O_2}\) have been noted in pathological (edematous) brain tissue and normal cortex. Mass and colleagues found that Cushing’s response resulted in good TP\(_{O_2}\) maintenance in experimental intracranial hypertension. Such devices may be useful and minimally invasive for monitoring for cerebral ischemia.

**Multi-Modality Monitoring**

Currently, monitoring systems such as Neurotrend (Diametrics, Inc., Codman, Raynham, Mass.) measure multiple parameters including \( P_{O_2}, P_{CO_2}, \) pH, and temperature to infer blood flow and metabolic status. This technology combines optical fibers with indicators, such as fluorescent ruthenium (\( P_{O_2} \)), phenol red (pH), and phenol red plus carbonate (\( P_{CO_2} \)). Temperature is measured through a copper thermocoupled system (personal communication, Codman, Raynham, Mass.).

Multimodality monitoring has been applied to head injury and aneurysm and hematoma surgery. Zauner and colleagues found that severely head-injured patients who died or remained vegetative had statistically significant decreases in tissue \( P_{O_2} \), increased \( P_{CO_2} \), and decreased pH compared with patients who had favorable outcomes.

**Jugular Bulb Oxymetry**

Assessing cerebral metabolism is incumbent on knowledge of venous oxygen content, which retrograde jugular bulb sampling can provide. Although such sampling cannot give direct information about blood flow, it provides knowledge of the delicate balance between supply and demand. Measuring jugular venous oxygen saturation (S\(_{jvO_2}\)) provides a quick, easy estimate of the brain’s metabolic needs at any point.

**Technique**

The apex of the triangle formed by the two heads of the sternocleidomastoid muscle forms the landmark for jugular bulb catheter insertion. The carotid artery, lying medial to the internal jugular vein, is palpated and gently displaced. Under sterile conditions, a 23-gauge needle finds the internal jugular vein,
aiming cephalad, toward the mastoid process. A large-bore needle then cannulates the vein at a 30-degree angle, and, using the Seldinger technique, a 20-gauge single-lumen central venous pressure catheter is inserted in a retrograde fashion until light resistance is felt. This resistance occurs approximately 12 to 16 cm from the insertion site and represents the jugular bulb at the foramen jugulare. It is helpful to estimate the distance between the insertion site and the mastoid process a priori. Once resistance is felt, the catheter is withdrawn 0.5 cm. This is especially important when using a fiberoptic catheter, because the \( S_jvO_2 \) reading is inaccurate if the light source abuts the wall of the foramen. The catheter must lie within 2 cm of the jugular bulb or the extracerebral circulation will contaminate the venous blood. An anteroposterior skull and neck radiograph confirms the catheter tip location medial to the mastoid process. Complications include catheter malposition, carotid artery puncture, infection, or thrombosis.

Usually 80% to 90% of venous blood drains through the superior sagittal sinus to the dominant (usually right) transverse sinus and internal jugular vein. There is little difference between the \( O_2 \) content of the left and right jugular veins. Perhaps with focal hemispheric lesions, the ipsilateral jugular might be most representative. In general, most practitioners place the catheter within the right jugular unless there is clearly representative. In general, most practitioners place the catheter within the right jugular unless there is clearly lateralizing pathology. When in doubt, manual jugular compression can be performed while observing for intracranial hypertension. The dominant jugular usually causes a greater ICP rise.

**\( S_jvO_2 \) Information**  
\( S_jvO_2 \) monitoring at the jugular bulb is an indication of global cerebral metabolism and does not demonstrate regional changes. The normal \( S_jvO_2 \) range is 60% to 80%. A low oxygen saturation (\(<50\%\)) indicates a critically ischemic or hypoxic state, resulting in increased cerebral oxygen extraction, usually before cell death sets in. Also, a low \( S_jvO_2 \) represents either supply from hyperventilation, anesthesia, or intracranial hypertension or increased metabolic demand such as hyperthermia, agitation, or seizures.

High \( S_jvO_2 \) (\( >85\% \) to 90%) indicates a hyperemic state in which oxygen delivery exceeds cellular metabolic needs. Increased \( S_jvO_2 \) may also result from vasodilation (e.g., sepsis, acetazolamide challenge), hypercarbia, increased \( PaCO_2 \) late ischemia, and cerebral blood flow cessation (brain death). Decreased metabolic need resulting from hypothermia; agents such as propofol, barbiturates, and anesthetic gases; and paralysis can also raise \( S_jvO_2 \).

**Continuous \( S_jvO_2 \) Monitoring**  
Continuous fiberoptic \( S_jvO_2 \) monitoring is helpful during situations in which critical global ischemic is anticipated. Such situations include severe head injury, especially in those patients experiencing intracranial hypertension; subarachnoid hemorrhage; cardiac bypass; and cerebrovascular, tumor, or hematoma surgery.

A specially designed fiberoptic catheter or pediatric pulmonary artery catheter has been used for the above purpose. The optical fiber transmits two or three wavelengths at 1-ms intervals, reflecting along a receiving fiber to a photosensor. The catheters are pre-calibrated and may also be calibrated in vivo using oximeter data obtained from a jugular bulb sample. Anything that decreases fiberoptic light intensity, such as abutting the jugular foramen, decreases the apparent \( S_jvO_2 \) reading. Therefore, most abnormal readings are confirmed with simultaneous blood sampling. An increase in \( O_2 \) saturation might indicate catheter pull-out proximal to the jugular bulb, resulting in extracranial venous contamination. Withdrawing blood slowly from the catheter, when properly positioned, also reduces such contamination. Fiberoptic catheter maintenance is labor intensive. Alternatively, intermittent sampling can be performed at regular intervals or during crises to assess the metabolic state. However, improved time resolution with continuous monitoring affords quicker assessment and the ability to perform hemodynamic or metabolic alterations to optimize the balance between supply and demand.

Sheinberg and colleagues used continuous \( S_jvO_2 \) monitoring in 45 patients with severe head injury. The authors noted an excellent correlation between jugular venous samples and fiberoptic catheter values \( (r = 0.87, p \leq 0.01) \) when light intensity was sufficient. Oxygen desaturations were due to intracranial hypertension, hyperventilation/hypocarbia, hypotension, and vasospasm. Increasing \( PaCO_2 \) in hyperventilated patients improved \( S_jvO_2 \).

Therapeutic maneuvers for intracranial hypertension, such as CPP therapy and hyperventilation, can be more safely performed with \( S_jvO_2 \) monitoring. Improving low CBF through CPP increase may result in positive changes in \( S_jvO_2 \) when global ischemia is present. This information can also help identify the lower CPP limit required to restore adequate oxygen supply. An algorithm for treating jugular oxygen desaturation is provided in Figure 4-6.

**Microdialysis**  
Microdialysis analyzes the concentration of metabolic byproducts in the extracellular space. Such byproducts include lactate, glutamate, pyruvate, aspartate, \( Na^+ \), and \( K^+ \). This technique uses a small probe and membrane continuously perfused with a physiological solution. At various intervals, dialysate is collected in aliquots and frozen for analysis. High-performance liquid chromatography (HPLC) is used for the final
analysis. Microdialysis has been used in experimental and clinical head injury and subarachnoid hemorrhage to determine the effects of ischemic insults on brain metabolism. Knowledge of lactate production and glutamate release may help in thwarting the ischemic process through intervention. However, at present, high cost and maintenance prohibit its use in general clinical practice.

**MRI Spectroscopy/PET**

Magnetic resonance spectroscopy analyzes regional metabolism. This technology depends on the magnetic spin moment of nuclei such as 1H. Within a specified area of interest, metabolites such as glutamate, aspartate, choline, and lactate can be measured. The aforementioned PET demonstrates and quantifies cerebral metabolism, which is useful in patients with epilepsy and tumors, among other applications. Cortical activation representing increased metabolism can also be visualized with new functional MRI techniques.

**REFERENCES**


