11 MEASURING CEREBRAL BLOOD FLOW AND METABOLISM

Alois Zauner and J. Paul Muizelaar

11.1 Overview of CBF measurements

11.1.1 INTRODUCTION
The optimal method for measuring cerebral blood flow (CBF) has yet to be discovered. Because of the anatomical difficulties inherent in accessing the central nervous system, quantitative measurements of cerebral blood flow are difficult. An ideal method for measuring CBF should provide all the following.

- Quantitative results
- High spatial resolution
- Continuous measurements, if clinically required
- No influence on the normal brain function
- No or minimal risk to the patient
- Cost-effectiveness
- Application in the clinical setting

The first well-recognized CBF studies on humans were performed by Kety and Schmidt in the 1940s using nitrous oxide (N₂O) gas. The measurement of CBF was based on the principle that the rate of uptake and clearance of an inert diffusible gas is proportional to blood flow. The tissue concentration of the tracer at equilibrium must therefore be dependent on blood flow rather than diffusibility. The Kety and Schmidt equation can be used for calculating CBF using N₂O, krypton-85 and xenon-133. In fact, complete equilibrium of N₂O between arterial blood, brain tissue and venous blood occurs slowly or not at all. Thus CBF calculated from a short saturation period will overestimate CBF (Hoyer, 1985).

The Kety and Schmidt equation (1948) is:

\[ C(t) = f \int C_u(u)e^{-k(t-u)}du \]

where:
- \( C(t) \) = total amount of tracer delivered to tissue between time zero and \( t \);
- \( u \) = tissue concentration of the tracer at time \( t \);
- \( C_u(u) \) = input function, i.e. the amount of tracer delivered to the brain, an integral of the arterial concentration from 0 to \( t \).

In the 1960s extracranial recordings of the uptake and clearance of radioisotopes for measuring local CBF became available using krypton-85 and xenon-133 (¹³³Xe; Lassen and Ingvar, 1961). Krypton-85 is a weak beta emitter and has been abandoned, whereas xenon-133, a strong gamma emitter, has been widely used in humans. Xenon-133 is a freely diffusible inert gas that does not interfere with cerebral metabolism. Elimination occurs very rapidly and almost completely through the lungs.

11.1.2 CLINICAL METHODS FOR MEASURING CBF AND BRAIN METABOLISM
Even 50 years after the first quantitative clinical measurements, CBF is not routinely measured in neurosurgery or neurology. This is surprising considering its potential importance in the management of patients with severe head injury, stroke and subarachnoid hemorrhage.

Clinical measurements of CBF and metabolism can be divided into:

- Quantitative measurements;
- Qualitative measurements;
- Indirect measurements of CBF and metabolism;
- Measurements of cerebral metabolism.

The most important techniques for obtaining CBF are explained in detail below.

(a) Quantitative measurements
Quantitative CBF measurements mainly use xenon-133, either injected into a carotid artery or intravenously, or given by inhalation (Bruce et al., 1973; Obrist et al., 1975; Agnoli et al., 1969). The stable (non-radioactive) xenon technique uses repeated computer tomography scanning (Winkler et al., 1977;
Sheinberg can be used for tests of autoregulation and CO$_2$ absolute) CBF in a small brain volume (1 mm$^3$) and al.

barrier after trauma (Bullock SPECT may also be used to study the blood–brain use. This may change as newer tracers are developed. visual interpretation of SPECT images is of clinical
tation (CMRO$_2$ help to determine the status of cerebral
reactivity (Bolognese

visual interpretation of SPECT images is of clinical use. This may change as newer tracers are developed. SPECT may also be used to study the blood–brain barrier after trauma (Bullock et al., 1990; Schröder et al., 1994).

Laser Doppler measures the local, relative (not absolute) CBF in a small brain volume (1 mm$^3$) and can be used for tests of autoregulation and CO$_2$ reactivity (Bolognese et al., 1993).

The recently developed thermal diffusion technique is based on the thermal conductivity of cortical tissue, allowing continuous recordings of CBF in a small region of the cortex (Carter, 1991). Indirect methods for obtaining information on CBF and metabolism include jugular venous oximetry, transcranial Doppler sonography and near-infrared spectroscopy.

Continuous monitoring of jugular venous oxygen saturation ($S_jvO_2$) assesses global cerebral oxygenation. Episodes of cerebral desaturation can be detected which would not been seen otherwise. Intermittent calculations of arteriovenous oxygen difference (AVDO$_2$) and the metabolic rate of oxygen consumption (CMRO$_2$) help to determine the status of cerebral oxygen metabolism (Chapter 5; Cruz et al., 1991; Sheinberg et al., 1992).

Transcranial Doppler sonography (TCD), a non-invasive bedside test, is now more frequently used in intensive care settings (Chan, Dearden and Miller, 1993; Steiger et al., 1994). Doppler sonography is described in detail in Chapter 13.

Near-infrared spectroscopy (NIRS) is another non-invasive monitoring now being evaluated for its clinical value in detecting changes in brain oxygenation, CBF and cerebral blood volume. NIRS depends upon the relative transparency of biological tissue to light in the near-infrared spectrum. The absorption of oxyhemoglobin, deoxyhemoglobin and oxidized cytochrome can be detected transcranially. NIRS is most widely used to assess neonatal cerebral hemodynamics and appears reliable and useful in this setting. In adults only certain brain areas can be monitored because bone thickness produces a scattering of the light spectrum (Elwell et al., 1993; Gopinath et al., 1993). Intracerebral microdialysis is undergoing clinical evaluation for measuring certain products of cerebral metabolism. With this method extracellular brain tissue electrolytes, excitatory amino acids, glucose and lactate can be measured (Persson and Hillered, 1992; Bullock et al., 1994; Zauner and Bullock, 1995). Continuous ‘on line’ pH measurements in the dialysate are also possible and need further evaluation. The measurement of cerebral $P_{O_2}$, $P_{CO_2}$, pH and temperature with one fiberoptic sensor is another application still in the experimental stage that may find a place in managing head-injured patients (Zauner, Bullock and Young, 1995; Zauner et al., 1995).

11.2 Xenon CBF measurements

11.2.1 THE XENON-133 METHOD

Whatever the route of administration, this method depends on direct monitoring of the radioactive tracer concentration by external recording with multiple scintillation detectors placed against the scalp. Assessment of regional CBF in a number of brain areas is possible depending on the number and location of the detectors, but such information is not truly topographic and it is degraded by various methodological artifacts. The reader is referred to Wood et al. (Jaggi and Obrist, 1987; Ewing et al., 1987) for a detailed review.

(a) The intracarotid xenon-133 method

A bolus of xenon-133 is injected into one internal carotid artery and the peak count rate measured by external detectors reflects the isotope concentration in brain tissue. CBF can be calculated from the clearance curve as the ‘height/area under the curve’, providing the ‘mean’ CBF (non-compartmental index; Meier and Zierler, 1954). By calculating the initial slope index a fast and a slow compartment can be differentiated in normal brain. However this may not be valid in injured brain (Risberg et al., 1975).

Over the last decade the intracarotid xenon method has been increasingly displaced by less invasive techniques using inhalational xenon-133 or stable xenon-enhanced computer tomography.

(b) The non-invasive xenon-133 methods

The modified intravenous xenon-133 injection method developed by Austin et al. (1972) and the inhalation
methodology developed by Obrist et al. (1975) are two less invasive radioactive xenon techniques. In contrast to the intracarotid method, they result in greater scalp and extracerebral contamination, which needs correction. Assessment of the arterial isotope input can be achieved by monitoring the xenon-133 concentration in end-tidal air. There is a close relationship between end-tidal air xenon-133 and arterial concentration if pulmonary diffusion is normal (Hausen et al., 1990). All these factors depend on a reliable mathematical model for calculating CBF.

Because of the instability of compartmental analyses in patients after severe head injury, other blood flow indices, such as CBF_{15} and CBF_{in}, equivalent to the CBF in patients after severe head injury, other blood flow model for calculating CBF.

All these factors depend on a reliable mathematical model for calculating CBF.

In our studies, severely head-injured patients studied with the inhalation method inhaled a gas mixture containing 5–8 mCi \(^{133}\)Xe/l for 1 minute. Those studied with the intravenous injection technique were injected with xenon-133 dissolved in saline (0.3 mCi/kg body weight). Immediately following the injection, ventilation was interrupted for 20 seconds to prevent large amounts of xenon from being expired during its first passage through the pulmonary circulation.

After xenon-133 administration, radioactivity from the brain was monitored for 15 minutes (CBF_{15}). A system with 16 detectors concentrically arranged in a Plexiglass helmet or a portable instrument with ten probes may be used (Bouma et al., 1991).

For better comparison, CBF_{15} values are often recalculated to a \( P_{aCO_2} \) of 34 mmHg, assuming the CO\(_2\) response to be 3% change in CBF per 1 mmHg change in \( P_{aCO_2} \). Normal CBF values in young volunteers with a \( P_{aCO_2} \) of 34 mmHg are 44.1 ± 5.6 ml/100 g/min and increase to about 50 ml/100 g/min at a \( P_{aCO_2} \) of 40 mmHg (Obrist et al., 1984).

Advantages of this technique are quantitative results, repeatable measurements, a portable bedside system and cost-effectiveness. The limitations of non-invasive CBF measurements are the inability to detect small regions of low CBF and poor spatial resolution, especially for deep brain structures.

11.2.2 STABLE-XENON-ENHANCED COMPUTED TOMOGRAPHY

(a) Methodology

The technical limitations and the poor spatial resolution of the non-invasive xenon-133 method were reasons for searching for better ways of measuring CBF with xenon as the diffusible tracer.

Sequential CT scanning allows visualization and quantification of time-dependent changes following the administration of a contrast medium. Winkler et al. proposed in 1977 that the radiodensity of xenon, which is close to that of iodine, would provide CT enhancement in proportion to blood flow. Thus for CBF measurements stable non-radioactive xenon can be inhaled during CT scanning.

Commercially available software can be easily added to a standard CT scanner. In studying patients with severe head injury, good teamwork is required between neurosurgery, neuroradiology and intensivists.

CBF is computed by measuring the brain tissue uptake during arterial build-up of xenon. The end-tidal xenon concentration is assumed to be in equilibrium with the concentration in arterial blood. Subsequently, the time-dependent change in arterial xenon concentration is obtained and can be converted to equivalent CT units (Obrist et al., 1975). Additionally, a correction for the hematocrit is required. The relationship for the hematocrit is shown in the following equation:

\[
C_a(t) = k X_e(t) (1 + 1.1 hct)
\]

\( C_a(t) \) = arterial xenon concentration; \( k \) is a conversion constant; \( X_e(t) \) = end-tidal xenon concentration; \( hct \) = hematocrit.

The baseline images are averaged and subtracted from the enhanced images obtained during xenon inhalation, producing a sequence of raw enhanced images. CBF is calculated by using the Kety and Schmidt equation on a pixel by pixel basis (Kety and Schmidt, 1948). CBF images are generated by computed flow values which are converted into Hounsfield units. Software post-processing techniques and smoothing procedures reduce image artifacts. A confidence image for each CBF image yields information about the quality and reliability of the CBF assessment. Most centers use 6–12 minute xenon washin protocols for calculating CBF (Bouma et al., 1991; Got, Yonas and Good, 1989; Good, Got and Yonas, 1992; Nakano et al., 1992). Xenon washin and washout (clearance) protocols have the advantage of capturing more data points, which increases the accuracy of blood flow measurements and a shorter inhalation time of xenon. Fatouris et al. showed that a 3 minutes washin, i.e. 3 minutes of xenon inhalation only, and 3 minutes washout procedure is superior to 6 minutes washin alone, especially if low blood flow is present (Fatouris et al., 1995a).

(b) Clinical studies

At the Medical College of Virginia, CT-CBF measurement for severely head-injured patients (GCS 8 or less) is a routine diagnostic procedure. The first CBF scan is usually performed on admission following a regular diagnostic head scan, unless the patient is clinically unstable or needs the immediate evacuation of a
hematoma or any other emergency surgical treatment. Prior to CT-CBF scanning, arterial blood gas analysis and hematocrit are required. To avoid artifacts, the patient must not move during the study and sedation and/or muscle paralysis may be necessary. At present an 8 minute xenon washin study is performed. As noted above, a 3 minute washin and 3 minute washout protocol is currently being investigated. Two baseline non-enhanced scans are obtained at three levels of the brain determined from the diagnostic CT scan. A gas mixture containing 30% xenon and 30–60% oxygen is than delivered for 8 minutes via a specially designed enhancer connected between the respirator and patient. Eight sequential CT scans at each level are obtained during the 8 minute period using a rapid sequence CT technique. Xenon end-tidal values are obtained and recorded during the study. End-tidal $PCO_2$ is measured with a capnograph and $O_2$ saturation is monitored using a pulse oximeter. Blood pressure and intracranial pressure may be continuously monitored throughout the study and in some patients transcranial Doppler measurements are also performed prior to or during the study. CBF studies add about 15–30 minutes to a regular CT scan. Follow-up CBF studies are performed between days 3 and 5 or as needed, to distinguish brain ischemia from hyperemia. Depending on the clinical situation cerebral blood volume (CBV) may also be measured by injecting 50 ml iodinated non-ionic contrast material intravenously after completing the xenon study. CBV is calculated by multiplying CBF by the mean transit time (MTT) for contrast (see below). CBF images are analyzed according to regions of interest (ROIs) immediately after the measurements. Hemispherical or regional values are calculated by outlining these structures using drawing tools on the CT screen.

(c) Advantages and limitations of the stable xenon technique

Quantitative, non-invasive blood flow measurements in the superficial cortex as well as in deeper structures, such as brain stem and basal ganglia, can be studied. The direct correlation with anatomy on the baseline CT images enables easy recognition of specific regions of interest. Problems associated with the xenon-133 technique, such as extracerebral contamination and the 'look-through phenomenon' do not occur with this technique. Added to a regular CT scan, it can be undertaken in severely head-injured patients without putting them at risk, although careful monitoring of blood pressure, $O_2$ saturation, ICP and end-tidal $CO_2$ is necessary.

There are several reports of the direct effects of xenon inhalation on CBF and ICP. At greater than 50% concentration, xenon is an anesthetic agent and may cause respiratory depression and cerebral vasodilation thereby increasing ICP (Bruce et al., 1973; Giller, Purdy and Lindstrom, 1990; Takasago et al., 1992; Obrist, Jaggi and Harel, 1985; Winkler and Turski, 1985). By using shorter xenon inhalation times (washin and washout procedures) and a maximal xenon concentration of 32%, a compromise can be achieved between xenon side effects and accuracy – which depends on sufficient enhancement for a good signal-to-noise ratio. The radiation exposure of approximately 8–28cGy per studied level must be also considered (Good, Got and Yonas, 1992). In an awake or agitated patient head motion is another limitation, whereas in the comatose head-injured patient, with proper sedation and head fixation, this is usually not a problem.

(d) Cerebral blood volume (dynamic CT technique)

In patients with severe head injury, cerebral blood volume (CBV) is of great interest, especially if ICP is raised as a result of brain edema and/or vascular engorgement. Increased CBV may accompany high, normal or low CBF, suggesting that CBF and CBV are not simply related (Grubb et al., 1978; Muizelaar et al., 1989; Phelps et al., 1979). The ratio of CBF/CBV may help to differentiate between irreversible and reversible ischemia in some patients (Leblanc et al., 1987; Powers and Raichle, 1985).

With CT scan times of 2 seconds and very short interscan delays it is possible to assess the kinetics of the first passage of an i.v. bolus of iodine contrast through brain tissue. The mean transit time (MTT) of the bolus through the cerebral vasculature can then be estimated and CBV be calculated as $CBV = CBF \times MTT$.

The MCV method is manually to inject a bolus of 50 ml of iodinated non-ionic contrast medium through an i.v. line in less than 5 seconds. The hemispheres or any other regions, excluding major vessels and the ventricular system, may be chosen as ROIs and the mean Hounsfield number in each region is calculated. The CT enhancement versus time curves are fitted to a gamma variate function:

$$C(t) = k(t - t_a)^{\alpha - (t - t_a)/\beta}$$

where $t = $ time after injection; $t_a = $ indicator appearance time; $k$, $\alpha$, $\beta$ are fit parameters; $C(t) = $ indicator concentration that is proportional to the CT number.

The arrival time, as well as a cut-off point on the downslope to avoid recirculation, must be specified by the operator or computed automatically. The use of a gamma variate function greatly simplifies the computation of the MTT. The interval between the first and second inflection points, which is the inflection width...
(IW) of the time density curve can be used as an estimate of MTT. The IW represents the transit time of the densest part of the bolus and this is close to the MTT (Axel, 1980; Oldendorf, 1964; Bouma et al., 1992; Fatouros et al., 1995b).

In summary, a CT-based method for measuring CBV is practicable, by combining CBF measurements with the stable xenon CT technique and using the inflection width following an intravenous iodine bolus as the cerebral transit time. However, additional work is required to further validate this method.

11.3 Further direct clinical methods for obtaining CBF

11.3.1 THERMAL DIFFUSION TECHNIQUE

The thermal diffusion measurement of cortical CBF (CoBF) is based on the thermal conductivity of cortical tissue (Carter et al., 1982; Dickman et al., 1991). A sensor consisting of two small flat gold plates, one of which is neutral and the other heated, is placed through a burr hole or craniotomy on a region of interest of the cortex. The CoBF in ml/100 g/min is estimated from the temperature difference between these two plates. If CoBF increases, the temperature difference between the two plates becomes smaller, the heat loss being conducted through the capillary bed. A microprocessor continuously converts the temperature difference to CBF in ml/100 g/min. Placement of the sensor over large surface vessels should be avoided.

Cortical blood flow measurements have been used in patients following subarachnoid hemorrhage and head injury, as well as after surgery for tumors, arteriovenous malformations or epilepsy (Carter, 1991; Carter et al., 1982; Dickman et al., 1982). In head-injured patients, continuous monitoring of CoBF may assist in differentiating cortical ischemia from hyperemia, and permit autoregulation and CO2 reactivity tests to be done. Hyperventilation during increased ICP may be monitored with less risk of inducing ischemia. A correlation between CoBF and whole brain CBF measured by the Kety and Schmidt N2O method has been shown (Carter, Weinand and Oommen, 1993; Robertson, 1993). Although CoBF is not representative of blood flow in the whole hemisphere or in deeper regions of the brain, continuous measurements of relative changes in the days after severe head injury may be of great value in guiding clinical management.

11.3.2 LASER DOPPLER FLOWMETRY

Laser Doppler flowmetry (LDF) is a new method for continuous measurement of local microcirculatory blood flow. The method is based on the principle of Doppler shift (Chapter 13). Monochromatic laser light reflected from stationary tissue remains unchanged in frequency. When it is reflected from moving blood cells it undergoes a frequency shift and therefore light reflected from the microcirculation measures the movements of red blood cells (Frerichs and Feuerstein, 1990; Meyerson et al., 1991). Monochromatic laser light, wavelength 600–780 nm, which is above the maximal absorption of hemoglobin and below the absorption of water, is used. The magnitude and frequency distribution of the wavelength changes are directly related to the number and velocity of red blood cells but unrelated to the direction of their movement. The light is carried by a fiberoptic probe and the reflected light is converted into an electrical signal from which several values are derived. The flux (an arbitrary flow unit) represents the movement and concentration of blood cells through the microvasculature. It is derived from the concentration of moving blood cells (CMBC) in the measured volume multiplied by the mean velocity. All three values, flux, CMBC and velocity, are continuously recorded and can be displayed by a computer (Bolognese et al., 1993).

Absolute CBF in ml/100 g/min can be theoretically estimated from LDF measurements, but must be interpreted with great caution. LDF measures the local flow within a very small sample volume of approximately 1 mm³, depending on the type of laser being used, and varies markedly with the location of the probe and its relationship to the microvasculature (Meyerson et al., 1991; Haberl, Villringer and Dirnagl, 1993). At present the measurement of relative values and their changes over time seems to be more accurate than relying on absolute values.

LDF has been developed for bedside monitoring (Meyerson et al., 1991; Bolognese et al., 1993) and requires surgical implanting. The device may be used alone or with other intracranial monitoring devices (Meyerson et al., 1991; Bolognese et al., 1993; Haberl, Villringer and Dirnagl, 1993; Steinmeier, Bondar and Bauhuf, 1993). In patients with severe head injury, LDF can be used to assess CO2 reactivity and the state of autoregulation (Le Bihan and Turner, 1992).

11.3.3 MAGNETIC RESONANCE IMAGING FOR CBF MEASUREMENTS (CHAPTER 14)

The washin and washout kinetics of exogenously administered MRI-detectable tracers, such as 2H-water, 19F-trifluoromethane and gadolinium permit measurements of cerebral perfusion (Zhang, Williams and Koretsky, 1993). Most of these tracers are still under investigation and MRI studies for calculating CBF in acute clinical settings such as head injury are not yet possible.
Recently a technique for proton magnetic resonance imaging (MRI) has been developed using water as the freely diffusible tracer. This technique involves labeling the water proton nuclear spins in the arterial blood by continuously inverting them in the neck region before they enter the brain. This permits the calculation of CBF (Williams et al., 1992). Le Bihan et al. have taken another approach for calculating CBF (Le Bihan and Turner, 1992). They have focused on the capability of magnetic resonance to image and measure molecular diffusion and capillary blood flow or perfusion. By using diffusion imaging techniques, perfusion can be measured non-invasively on the basis of intravoxel incoherent motion (IVIM). This MRI model considers that capillary segments are randomly oriented in each voxel and the perfusion seen by the IVIM technique is quantified in terms of active capillary density or average blood flow velocity rather than as ml/100 g/min.

At present for patients with severe head injury CBF measurements using MRI are in an experimental stage, but MRI has great potential and warrants further exploration.

11.4 Indirect methods for obtaining CBF and metabolism

11.4.1 Jugular Venous Oximetry

Jugular bulb oxygen saturation can be used to calculate AVDO2 and to monitor cerebral oxygenation. The cerebral metabolic rate for oxygen (CMRO2) can be calculated as:

\[ \text{CMRO}_2 = \text{CBF} \times \text{AVDO}_2. \]

Under physiological conditions CBF and CMRO2 are coupled and the ratio of these two parameters, and AVDO2 remains constant (Robertson et al., 1989). The normal value for AVDO2 is approximately 6.5 ml O2/100 ml blood and for CMRO2 3.2 ml O2/100 g/min (Muizelaar and Schröder, 1994). In about 45% of patients who are comatose following severe head injury, CMRO2 and CBF remain normally coupled (Obrist et al., 1984). Only in these patients does a high AVDO2 indicate low CBF relative to CMRO2, as the brain compensates for the decreased CBF by extracting a greater amount of oxygen, and conversely a low AVDO2 indicates increased CBF (Robertson et al., 1989). Cruz has suggested that measuring the cerebral oxygen extraction, i.e. the difference between arterial and jugular bulb oxyhemoglobin saturation, is more accurate than AVDO2 especially in the presence of anemia (Cruz, 1993a).

Fiberoptic catheters that measure jugular venous oxygen saturation (S\textsubscript{\text{jvO}_2}) continuously in the jugular bulb are a major advance over intermittent jugular monitoring (Cruz, 1993a, b; Sheinberg et al., 1992). A no. 4 or 5G fiberoptic oxygen saturation catheter is inserted percutaneously in a retrograde direction into the internal jugular vein. The tip of the catheter must be placed within the jugular bulb and its position verified by X-ray or CT-scan. The catheter must be calibrated before and after insertion and thereafter every 8 hours by drawing a blood sample from the catheter and measuring the oxygen saturation on a co-oximeter. The reflected light intensity of the fiberoptic device must be checked regularly. It depends on correct placement of the catheter tip within the lumen and will be reduced if the catheter becomes attached to the vein wall. S\textsubscript{jvO}_2 in normal individuals is 65%. However, in comatose patients with severe head injury, readings over 50% are considered normal (Sheinberg et al., 1992). An S\textsubscript{jvO}_2 less than 50% and AVDO2 above normal indicate ischemia or a mismatch between CBF and metabolism. Because arterial oxygen saturation and arterial hemoglobin affect cerebral metabolism and oxygenation, they must also be taken into consideration (Cruz, 1993a, b). Whenever S\textsubscript{jvO}_2 drops below 50% for more than 15 minutes, the cause of the desaturation must be sought. First, the light intensity of the catheter should be checked and the catheter calibrated by co-oximeter. If both are within the normal range then cerebral desaturation has occurred. Episodes of cerebral desaturation occur most frequently within the first 48 hours after injury, most often in relation to high ICP (Muizelaar and Schröder, 1994; Sheinberg et al., 1982).

There are several limitations with jugular bulb oximetry.

- It measures the global saturation of one hemisphere only.
- S\textsubscript{jvO}_2 may not decrease during raised ICP until tentorial herniation has occurred (Sheinberg et al., 1982).
- There is contamination with blood from the contralateral hemisphere and from extracranial venous blood.

A previous study found that almost 50% of readings that suggested desaturation were incorrect (Sheinberg et al., 1982), usually as a result of low light intensity.

At present jugular venous oximetry is the only method available to give continuous monitoring of cerebral oxygenation and metabolism. Even though the technique can be time-consuming, several authors have found it helpful in management, even though experience at the Medical College of Virginia has, in comparison, been disappointing. In the near future cerebral tissue O2 and CO2 measurements may prove to be a better way of monitoring comatose patients (Zauner and Bullock, 1995; Zauner et al., 1995).
11.4.2 TRANSCRANIAL DOPPLER SONOGRAPHY

Transcranial Doppler sonography is discussed in detail in Chapter 13.

The technique was introduced in 1982 by Aaslid, Markwalder and Nornes (1982). Using a 2 MHz pulsed Doppler it is possible to penetrate the skull at certain areas and to record the blood flow velocity from the major basal cerebral arteries. The most frequent measurement site is transtemporal (via the ‘temporal window’), where the middle cerebral artery, internal carotid artery and anterior cerebral artery can be identified (McCormick et al., 1991). Vessel identification depends on the cranial window used, the depth of the sample volume, the flow direction and the spatial relationships of vessels. The vertebral arteries and the basilar artery may be insonated through the foramen magnum.

A standard nomenclature has become accepted, in which peak systolic velocity refers to the highest velocity during systole and the end-diastolic velocity represents the maximum velocity at the end of the diastole. The mean velocity is the time averaged maximum velocity during the cardiac cycle.

**Blood flow velocity does not give direct information on CBF. In an artery with a lumen area A (cm²), the blood flow Q (ml/s) and cross sectional average blood velocity V (cm/s) are related by the following equation:**

\[ Q = V A. \]

However cross-sectional blood velocity is difficult to measure, since the anatomy of cerebral arteries is very complex. Blood flow velocity is further influenced by several factors, including arterial blood pressure, ICP, hematocrit, \( P_{\text{CO}_2} \) and the status of autoregulation, thus making a direct comparison of flow velocity and CBF very complex. All these factors may be altered in severe brain injury and may make Doppler measurements difficult to interpret (Steiger et al., 1994).

11.4.3 NEAR-INFRARED SPECTROSCOPY

Near-infrared spectroscopy (NIRS) was recently developed as a continuous bedside technique suitable for clinical use particularly in neonates. Near-infrared light with a wavelength between 650–1100 nm can penetrate the scalp, skull and brain (Jöbsis, 1977; McCormick et al., 1991). Penetration into brain tissue is limited by the thickness of the skull. In adults it extends for a few centimeters only, whereas in neonates penetration is much deeper. Thus relative changes in CBF and cerebral oxygenation can be investigated transcranially by means of the transparency and absorption of oxyhemoglobin, deoxyhemoglobin and oxidized cytochrome in the near-infrared spectrum. The absorption of hemoglobin occurs at a wavelength between 670 and 760 nm, whereas oxidized cytochrome aa3 is detected near 830 nm. No separation into arterial, venous or capillary compartments in the measured brain areas can be discerned. Recent studies in adults have reported that NIRS is at least as sensitive in detecting progressive human cerebral hypoxia as EEG (McCormick et al., 1991). Gopinath et al. (1993) have also found NIRS useful in detecting and localizing intracranial hematomas. Potential limitations of this application are that only acute hematomas could be found and that bilateral hematomas might not be detected.

With further refinement NIRS may prove to be useful in managing patients with severe head injury in the intensive care unit or the emergency room, both to detect brain oxygen desaturation in selected areas and localize intracranial hematomas. At present, NIRS is more reliable in neonates than in adults.

11.5 Direct measurement of cerebral metabolism

11.5.1 INTRACEREBRAL MICRODIALYSIS

Intracerebral microdialysis enables endogenous substances in the extracellular fluid (ECF) of the brain to be retrieved. Many experimental studies have suggested that excitatory amino acids (EAAs), neurotransmitters, electrolytes and energy-related metabolites are released in abnormal quantities after severe head injury. EAAs such as glutamate and aspartate have toxic effects on cell membranes and cause cell damage particularly in states of prolonged ischemia (Ungerstedt, 1991; Beneviste and Hiittemeier, 1990). The membranes of microdialysis probes in current use have a length of 4–10 mm and a diameter of 0.5 mm. They may be implanted during surgery or together with an ICP monitoring device (Persson and Hillered, 1992; Bullock et al., 1994). The probe is perfused with sterile normal saline or Ringer’s solution using a microinjection pump (2 μl/min). The dialysate is collected in vials over a defined interval (for example: 30 min = 60 μl) in a cooled fraction collector. In our studies the probe is left in place for 4 days. The samples are analyzed by high performance liquid chromatography for EAAs, lactate and glucose, and by flame photometry for electrolytes (Bullock et al., 1994, 1995; Zauner and Bullock, 1995). In the first 50 patients with severe head injury, there was a six- to eightfold increase in EAAs if there were no secondary ischemic events. However, if secondary ischemia occurred, EAA release was 20–50 times greater than normal and persisted over days (Figure 11.1; Persson and Hillered, 1992; Bullock et al., 1994, 1995; Zauner and Bullock, 1995). An increase in ECF K⁺ following
severe head injury was also seen and correlated with the increase of glutamate. In ischemia, a rise in ECF K⁺ and an influx of Ca²⁺ is thought to trigger glutamate release and activation of cation and anion conductance. (Bullock et al., 1995). A marked reduction in ECF glucose can be seen after head trauma. This is most probably due to low CBF and increased anaerobic metabolism (Figure 11.2).

11.5.2 POSITRON EMISSION TOPOGRAPHY

Positron emission topography (PET) scanning is currently the most versatile and widely used functional imaging modality for the human brain, both in health and disease. The theory and methodologies of the technique are beyond the scope of this chapter and the reader is directed to Alavi et al., 1982, 1996; Huang et al., 1980; Phelps, Mazziotta and Huang, 1982; and Heiss et al., 1984. However, in spite of the enormous cost and complexity of PET scanning, it has made little impact on either research or clinical practice in the neurosciences. Since the isotopes must be obtained on-line from a cyclotron, PET scan studies need to be planned and scheduled well in advance. Patients need to be stable and in close physical proximity to the scanner and this limits its utility in patients with acute head injuries. The anatomical resolution of detail is quite limited, being about 0.5 cm³, which is similar to that of SPECT scans.

Despite these limitations, the technique has been applied to studies in patients with head injury. CBF and metabolism were studied in stable patients during the first and second weeks after head injury (Langfitt et al., 1986). There were uniform reductions in both CBF and metabolism, the most profound reductions being found in the parietal and occipital lobes. More
recently, elegant studies of glucose metabolism using fluorodeoxyglucose found that in about one-third of 13 patients cerebral metabolism for glucose was increased within 48 hours of injury. The greatest increases were seen in zones surrounding focal cerebral contusions and adjacent to hematomas (Hovda et al., 1995). These findings accord exactly with animal studies. At later time points, however, glucose metabolism had decreased by 30–40%, also in accord with findings in animal studies. It appears, therefore, that

![Figure 11.2 Methods of placement of a microdialysis probe.](image)

![Figure 11.3 Instrumentarium used for placement of a triple lumen bolt (drill bit, taper), together with the multiparameter sensor, microdialysis probe and triple lumen blot itself.](image)
there is a initial phase of hypermetabolism for glucose after trauma, which is followed by a phase of hypometabolism. The potential of PET scanning to demonstrate changes in neurotransmitter metabolism and protein synthesis has yet to be fully realized.

11.6 Comprehensive neuromonitoring

There are now a number of monitoring and diagnostic devices that have been developed for use in comatose patients. They include devices for ICP monitoring, jugular bulb oximetry, CBF measurement, transcranial Doppler sonography and EEG. However none of these techniques is ideal, and only indirect information on cerebral oxygen delivery and metabolism can be obtained from them.

At the Medical College of Virginia, a comprehensive neuromonitoring system is being developed that includes an ICP monitor with a microdialysis probe and a combined sensor for measuring brain oxygenation, CO₂ generation, and temperature (Zauner, Bullock and Young, 1995; Zauner et al., 1995) With this system it is possible to continuously measure ICP, CPP, brain oxygen, CO₂ pH and temperature, as well as brain chemistry for glucose, lactate, ions and amino acids, for several days after injury (Figure 11.i). The three measuring devices are secured to a three lumen bolt for skull and brain fixation. This system is being assessed in patients with severe head injury but further work is needed to establish its value in intensive care management.

11.7 References
