

# 5 Brain metabolism and cerebral blood flow

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## 5.1 The basic principles of brain metabolism and blood flow

### 5.1.1 CEREBRAL HEMODYNAMICS

#### (a) Anatomical and physiological considerations

Cerebral blood flow is influenced and regulated by a number of factors, including arterial blood pressure, intracranial pressure, venous outflow, blood viscosity,  $P_{aCO_2}$  and  $P_{aO_2}$ , collateral flow, vasoreactivity and the status of cerebral autoregulation. The regulation of vascular resistance lies mainly in the arterioles and precapillary segments (Auer and Loew, 1983). It is important to note that cerebral metabolism is the major determinant of regional blood flow.

#### *Anatomy*

Each carotid artery contributes approximately 40% to the total cerebral perfusion, the remaining 20% coming from the two vertebral arteries, which fuse to form the basilar artery. Autopsy studies, however, show that there are many variations in the vascular anatomy and a 'normal circle of Willis' was seen in only 52% of brains (Alpers, Berry and Paddison, 1959). Collateral channels occur on the pial surface or within the brain itself. These channels cross the arterial boundary zones (sometimes termed 'watershed' zones) and the severity of focal ischemia after systemic hypotension or occlusion of a major vessel is determined by these collaterals.

The major fraction of venous blood draining from the brain is collected in the transverse sinuses which, together with the inferior petrosal sinuses, form the internal jugular veins. The cerebral venous drainage territories are not sharply delineated and overlap. It is estimated that approximately 70% of blood in each internal jugular vein originates in the ipsilateral and 30% in the contralateral hemisphere. Approximately 3% of blood in the internal jugular vein is from

extracranial sources, mainly via the superior petrosal sinus (Jennett, Miller and Harper, 1976).

The distribution of capillaries is functionally organized throughout the central nervous system. The capillary density may provide an anatomical indicator of oxidative metabolism. Brain areas with high basal levels of glucose metabolism contain a high density of capillaries. Some 90% of cerebral capillaries are continuously perfused and 10% are subject to recruitment in response to metabolic and other stimuli (Sokoloff *et al.*, 1977). A close relationship exists between aerobic metabolism and the microvasculature.

#### (b) Cerebral perfusion pressure and cerebrovascular resistance

The net driving force for the cerebral circulation is defined as the cerebral perfusion pressure (CPP), which is the mean arterial blood pressure (MABP) minus the cerebral venous pressure. If the pressure within the thin-walled cortical veins and the bridging veins in the subarachnoid space is equal to or less than the external (CSF) pressure, the veins may collapse and increase the resistance to flow. Under most circumstances, however, the pressure in these veins is slightly above extravascular, (that is intracranial pressure), in order to permit continuous flow. The venous sinuses do not collapse completely because of their stiff walls. Because of the close relationship between cerebral venous pressure and ICP, CPP is generally defined as the difference between arterial pressure and ICP. In a normal brain, changes in CPP between 50 and 130 mmHg produce only minimal changes in CBF. A constant flow in this range of CPP is maintained by an increase or decrease in vascular resistance (Harper, 1966). Outside this range, cerebral vasodilatation or vasoconstriction cannot maintain a normal cerebral blood flow (CBF). *Following ischemia, trauma or subarachnoid hemorrhage, the normal autoregulatory relationship may be lost or its range altered such that a CPP of about 70 mmHg may be needed to prevent*

*ischemic brain damage. A mean systemic blood pressure of 60 mmHg, which is satisfactory in the normal individual, may result in a profound fall in CBF, such that ischemic brain damage may occur after only 15–30 minutes.*

Thus,  $CPP = MABP - ICP$  and  $CBF = CPP/CVR$

where CVR is cerebrovascular resistance.

Blood is a non-Newtonian fluid and viscosity is velocity-dependent. This, with the pressure loss across cerebral circulation and the complex geometry of the brain circulation, makes it difficult to calculate CVR. However, although the law of Poiseuille describes steady laminar flow of Newtonian fluids in cylindrical tubes, it can be used to describe CBF and the CVR.

$$F = P / [(8 - \mu l) / (r^4)]$$

( $P$  = pressure;  $F$  = flow;  $\mu$  = viscosity;  $l$  = length;  $r$  = radius).

Since vascular resistance is inversely proportional to the fourth power of the vessel diameter, a modest change in cerebral vessel diameter will produce a marked change in flow resistance

Most resistance to the cerebral circulation lies within the arterioles and precapillary sphincters. There is a pressure drop from 90 mmHg in the conductance arteries to 20–30 mmHg in the capillaries across these resistance vessels. The resistance arterioles are able to regulate their own diameter through their vasomotor smooth muscle. They are supplied with a complex peptidergic nerve fiber network with cell bodies in various brain-stem nuclei such as the dorsal raphe nuclei.

### (c) Effects of hematocrit on CBF

Blood viscosity is determined by a number of factors, including erythrocyte size and concentration, shear rate, temperature, pH, plasma protein level and plasma lipid concentration. Clinical studies show an inverse relationship between CBF and hematocrit. *A hematocrit of 47% is associated with a significantly reduced CBF, whereas lowering the hematocrit within the physiological range, e.g. by volume expansion, increases CBF.* (Kuschinsky *et al.*, 1972; Humphrey *et al.*, 1979) *A similar inverse relationship can be seen between red cell concentration and CBF* (Thomas *et al.*, 1977). On the other hand, reduced CBF increases blood viscosity and stasis may occur. A fall in  $P_{O_2}$  and pH increases red cell stiffness and may decrease CBF further. In normal brain, autoregulatory mechanisms can compensate for changes in blood viscosity by changing the cerebrovascular resistance. These changes take place in the resistance, not the conductance vessels (Hudak *et al.*, 1989; Giller *et al.*, 1993; Muizelaar *et al.*, 1992). If viscosity increases, vasodilation occurs to overcome the increase in cerebrovascular resistance.

## 5.1.2 REGULATION OF CBF

### (a) Arterial gas tension and cerebral vasoreactivity

Minimal changes in arterial  $P_{CO_2}$  lead to variations of the cerebral perfusion.  $CO_2$  molecules are highly diffusible and pass the blood–brain barrier easily. The glycolytic pathway, the major energy-producing source in the brain, produces six moles of  $CO_2$  per mole of glucose. Hypercapnia relaxes cerebrovascular smooth muscles, whereas hypocapnia produces vasoconstriction. *An arterial  $P_{CO_2}$  of 20–25 mmHg may reduce the CBF by 40–50%, and conversely an increase in  $P_{CO_2}$  over 50 mmHg increases CBF by more than 50%.* (Olesen, Paulson and Lassen, 1971) *These changes in CBF due to alterations in  $CO_2$  occur almost immediately in healthy brain, but the response may be altered after head injury* (Bouma and Muizelaar, 1992).

Carbon dioxide induces changes in the hydrogen ion concentration (modulating extracellular pH), and it is most likely this which acts on the smooth muscle, rather than  $P_{CO_2}$  (Kontos, Raper and Patterson, 1977; Wahl *et al.*, 1970). Experimental studies have shown that  $HCO_3^-$  solutions decrease CBF whereas low  $HCO_3^-$  solutions increase CBF, supporting the importance of tissue pH (Cameron and Caronna, 1976). Various brain structures have different densities of perfused capillaries, but the number of perfused capillaries is unchanged during hypercapnia (although blood flow is increased) compared to normocapnia (Gobel *et al.*, 1989). Extracellular pH may also modulate the action of vasomotor agents such as norepinephrine (noradrenalin). In isolated pial vessels, the contractile response induced by catecholamines was reduced by 50% at a pH of 7.0 (Edvinsson and Sercombe, 1976). Certain pharmacological agents and therapeutic techniques influence cerebrovascular reactivity via changes in gas tension. The carbonic anhydrase inhibitor acetazolamide decreases extracellular brain pH at a constant arterial  $P_{CO_2}$ , and increases normocapnic CBF. However this effect lasts only for a short time (Ehrenreich *et al.*, 1961; Heuser *et al.*, 1975). Barbiturates depress cerebrovascular reactivity but the mechanisms involved are not well understood. Barbiturates lower both cerebral metabolism and CBF and may reduce  $CO_2$  reactivity (Kassell *et al.*, 1981; Edvinsson and McCulloch, 1981). *In clinical studies, diminished  $CO_2$  reactivity is associated with a worse prognosis and with decreased effectiveness of barbiturates* (Cold, 1989; Nordstrom *et al.*, 1988; Bouma and Muizelaar, 1992; Muizelaar *et al.*, 1991; Giller *et al.*, 1993). *If vasoreactivity is preserved, patients with high ICP may respond to barbiturate therapy with further reduction in energy consumption and reduced CBF and volume. In these patients with preserved reactivity, prolonged hyperventilation may diminish*

*brain oxygen delivery and it must be used with caution (Muizelaar et al., 1991).*

### (b) Autoregulation and CBF

In the normal brain CBF remains relatively constant despite changes in the systemic blood pressure and CPP. These vascular responses are also true for changes in CPP due to ICP increase. This phenomenon, called cerebral autoregulation, has a range of between 40 and 160 mmHg. The limits of autoregulation are not fixed and are influenced by both pharmacological agents and pathological conditions (systemic as well as intracranial). Autoregulation describes a pressure–flow homeostatic relationship of the cerebral circulation and several hypotheses have been formulated to explain it. However, it is most probably controlled and regulated by the interplay of several mechanisms.

#### *The metabolic hypothesis*

This proposes that a reduction in CBF results in the release of chemical mediators. Regional CBF is then regulated by constriction and dilation of cerebral arterioles and opening and closing of precapillary sphincters in the metarterioles, which are responsible for distribution of blood through the cerebrovascular bed. But a coupling of CBF autoregulation to vasoactive metabolites or molecules is not well defined. CO<sub>2</sub>, O<sub>2</sub>, K<sup>+</sup>, Ca<sup>2+</sup>, H<sup>+</sup> and adenosine have all been proposed as playing a role (Kuschinsky and Wahl, 1978). Hypercapnia and hypoxia are powerful stimulants for CBF increase. Adenosine, which is formed from ATP breakdown during energy consumption, is a potent vasodilator. It increases with reduction in blood pressure, but the role of adenosine and adenosine phosphorylated derivatives in controlling CBF is still unsolved (Winn *et al.*, 1980; Kontos, 1985). Tissue oxygen pressure may also be a metabolic component of the control of cerebral autoregulation. This O<sub>2</sub>-sensitive mechanism will cause cerebral arteriolar dilation in response to increased venous pressure, an effect which can be reversed by local hyperoxia (Wei and Kontos, 1988).

#### *The myogenic hypothesis*

The short latency of the autoregulatory response is considered to be an argument in favor of a myogenic mechanism, whereby smooth muscle cells of small arteries and arterioles constrict or dilate in response to changes in transmural pressure. A rapid change in intravascular pressure alters the state of the actin and myosin filaments within the smooth muscle cells. Experimentally, changes in arterial transmural pressure correlate positively with changes in smooth

muscle action potentials and membrane potentials which lead to spontaneous activation (Harder *et al.*, 1989; Kontos *et al.*, 1978).

Endothelial-cell-related factors have also been implicated in autoregulation. Endothelium-derived relaxing factor (EDRF) has been identified as nitric oxide (NO) or a NO-containing substance produced in cerebral blood vessels. EDRF action is mediated by the activation of guanylate cyclase and formation of cyclic GMP. Ca<sup>2+</sup>/calmodulin activates NO synthetase, which generates NO from L-arginine. Stimulated neurons and glia also produce NO and may mediate local vasodilation (Furchgott and Vanhoutte, 1989; Faraci, 1993; Kim and Vanhoutte, 1990). An impaired endothelium-dependent response with decreased production of EDRF but increased release of endothelium-derived contracting factors, such as endothelin and arachidonic acid, has been found in subarachnoid hemorrhage. Endothelin is an extremely potent and long-lasting vasoconstrictor peptide. In experimental focal cerebral ischemia, activation of nitric oxide synthetase with a burst of NO and activation of guanylate cyclase has been found (Kader *et al.*, 1993).

### 5.1.3 CEREBRAL ENERGY METABOLISM

#### (a) Cerebral energy generation

*The brain comprises only 2% of body weight, but receives 15% of cardiac output and uses 20% of total body oxygen and 25% of total body glucose. Within normal levels of global CBF the brain extracts about 50% of the oxygen and 10% of the glucose from arterial blood. High-energy phosphates, predominantly adenosine triphosphate (ATP), are the most important energy source for the brain. ATP is produced almost entirely by the oxidative metabolism of glucose.*

Complete aerobic oxidation of one molecule of glucose yields 38 molecules of ATP (via the glycolytic and tricarboxylic acid pathway), whereas anaerobic breakdown of one molecule of glucose produces only two molecules of ATP. Carbon dioxide, the end-product of aerobic oxidation, is easily eliminated from the brain and crosses the blood–brain barrier (BBB). On the other hand lactic acid, the end-product of anaerobic glycolysis, is toxic to neurons and decreases the pH. A severalfold increase in cerebral tissue lactate concentration can be seen in ischemic animal models, where a low level of cerebral perfusion provides some glucose but insufficient oxygen. Experimental data show that gray matter uses about three times more glucose than white matter, although there are considerable inter-regional variations (Abrams *et al.*, 1984; Phelps, Mazziotta and Schelbert, 1986).

It is speculated that neurons consume about 75% of all oxygen in the CNS. About 80% of all energy generated may be necessary for the maintenance of ionic gradients. Glial cells, which make up almost 50% of the brain volume, have a much lower metabolic rate and account for less than 10% of total cerebral metabolism (Siesjö, 1984).

#### (b) The effect of the blood–brain barrier on brain metabolism

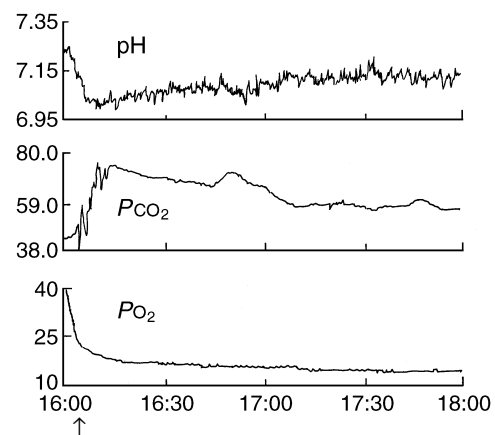
*The blood–brain barrier comprises morphological and functional mechanisms that restrict or facilitate the passage of substances from blood to brain. Endothelial cells of cerebral capillaries are sealed together by tight junctions. They contain a large number of mitochondria and pinocytotic vesicles that facilitate the transport of substances into the brain.* Astrocytes also play an important role in the normal functioning of the BBB. The uptake of a substance by the brain depends on its polarity, the presence of carrier mechanisms, pH, enzymes and the size of the molecules. The endothelial cells are not simply a barrier between cerebrovascular smooth muscle and the blood. Endothelium produces vasoactive substances (see above), such as endothelin-1 which is a potent vasoconstrictor of cerebral arteries, and vasodilators, NO and acetylcholine (Faraci, 1993; Robinson and McCulloch, 1990). Endothelial cells are also part of the mechanism of hemodynamic regulation via their responses to changes in transmural pressure (Harder *et al.*, 1989). Oxygen passes from the blood to the brain by diffusion, whereas glucose crosses the BBB via a saturable mechanism that is activated by hypoxia or hypoglycemia. Blood–brain barrier mechanisms may be disturbed by head injury but little is known about the long-term effects of BBB dysfunction in human head injury (Sokrab *et al.*, 1988).

#### (c) Brain tissue oxygen and carbon dioxide

Brain function and tissue integrity are highly dependent on a continuous supply of oxygen and clearance of CO<sub>2</sub>. Tissue oxygenation is the product of the blood flow and arterial O<sub>2</sub> content. *The percentage of hemoglobin carrying oxygen depends on several factors, the most important of which is the partial pressure of oxygen (P<sub>O<sub>2</sub></sub>). The affinity of oxygen for hemoglobin is increased by decrease in temperature, hydrogen ion concentration (increased pH) or P<sub>CO<sub>2</sub></sub>, shifting the oxyhemoglobin curve to the left so that release of oxygen into tissue is decreased. Conversely, the release of oxygen into tissue is increased when the curve is shifted to the right. However hypoxemia shifts the dissociation curve to the right, decreases O<sub>2</sub> loading and consequently reduces O<sub>2</sub> unloading in the*

*tissue.* Because the movement of oxygen depends on partial pressure gradients, the cells furthest away from capillaries are most vulnerable to hypoxia. Oxygen delivery is also dependent on CBF. Leniger-Follert *et al.* (1975) found, in cats, that brain P<sub>O<sub>2</sub></sub> remained constant if the blood pressure was kept between 50–150 mmHg. However, below a blood pressure of 50 mmHg there was a dramatic drop in brain P<sub>O<sub>2</sub></sub>. Local P<sub>O<sub>2</sub></sub> may be regulated by vasoconstriction during increased arterial oxygen supply. However, local regulation is abolished by tissue anoxia or by adding CO<sub>2</sub> to the inspired air (Leniger-Follert, Groncowski and Danz, 1984; Leusen, Weyne and Demester, 1980; Lübbers, 1968).

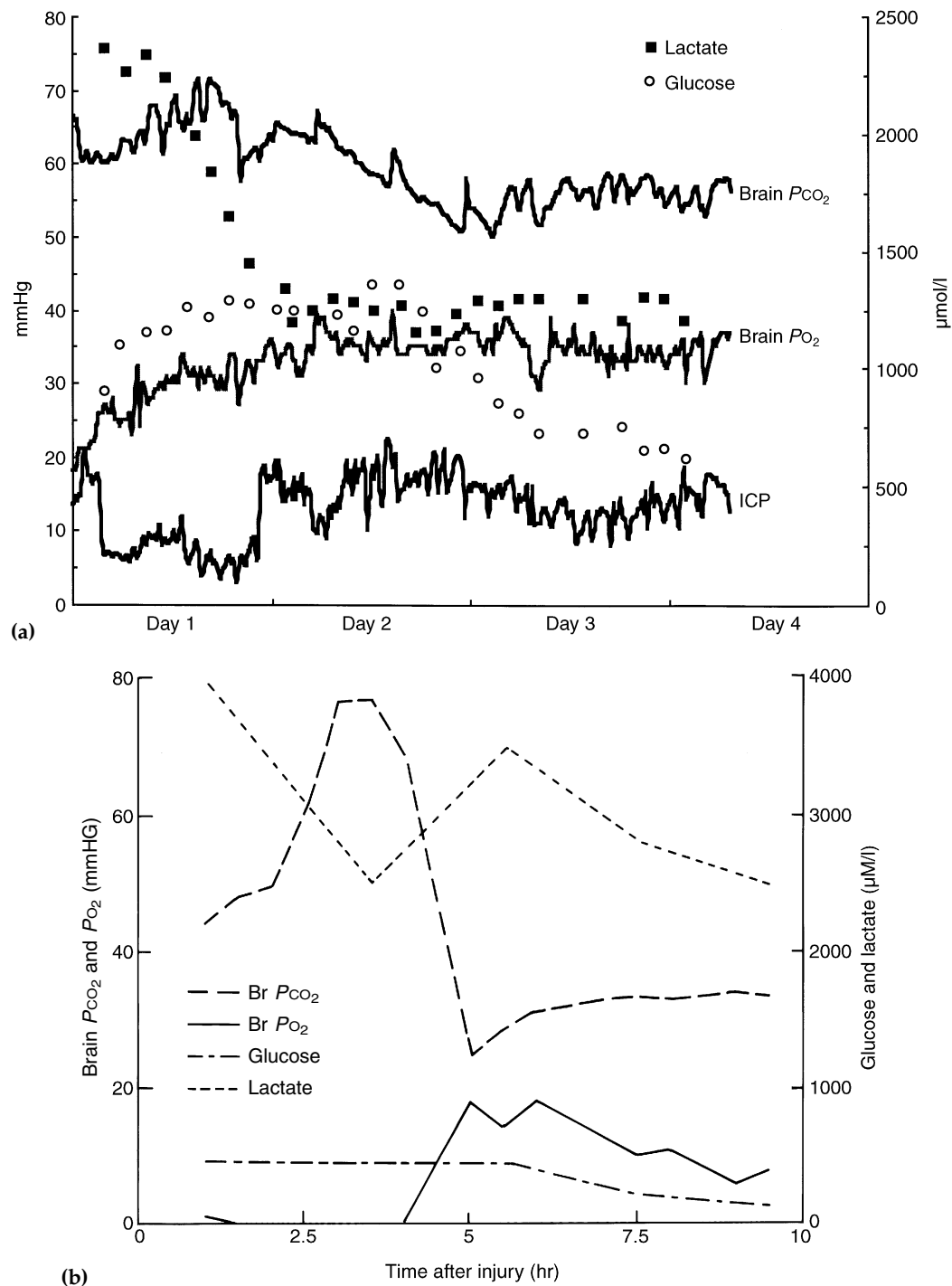
Several research groups have investigated continuous oxygen measurements in brain tissue. Major drawbacks in the past were the considerable drifting of oxygen sensors over time and the labor-intensive calibration procedures (Fleckenstein *et al.*, 1990). In their animal studies, Maas *et al.* (1993) found a brain tissue oxygen of 28 mmHg under normocapnia and normal CPP, but when CPP was lowered to 40 mmHg or less there was a sharp decline in brain tissue oxygen tension. Recently a multiparameter probe has become available for measuring brain P<sub>O<sub>2</sub></sub>, P<sub>CO<sub>2</sub></sub>, pH and temperature in one combined sensor. Studies at the Medical College of Virginia have demonstrated stable tissue P<sub>O<sub>2</sub></sub> (42 ± 9 mmHg), P<sub>CO<sub>2</sub></sub> (58 ± 14 mmHg) and pH (7.0 ± 0.2; Zauner *et al.*, 1995). Hypoxemia, hypocapnia and hypercapnia significantly changed tissue P<sub>CO<sub>2</sub></sub>, whereas P<sub>O<sub>2</sub></sub> was markedly changed during hypoxemia and hypocapnia. On occluding the middle cerebral artery to produce focal ischemia, P<sub>O<sub>2</sub></sub> fell to 19 ± 6 mmHg (–53%) immediately and stayed low throughout the experiment, whereas P<sub>CO<sub>2</sub></sub> increased to 71 ± 11 mmHg (+20%; Zauner *et al.*, 1995; Figure 5.1).



**Figure 5.1** Example of changes in brain oxygen, P<sub>CO<sub>2</sub></sub> and pH in a feline model of focal ischemia (middle cerebral artery occlusion), using a multiparameter probe. The onset of middle cerebral artery occlusion is shown by the arrow.

This technique was applied to 18 severely head-injured patients. In patients who made good recoveries following severe head injury, brain  $P_{O_2}$  was  $35 \pm 8$  mmHg, brain  $P_{CO_2}$  was  $50 \pm 9$  mmHg, brain pH was  $7.12 \pm 0.15$  and brain temperature was  $37.8 \pm 0.8^\circ\text{C}$ .

However, patients with poor outcome (died or vegetative state) had a brain tissue oxygen of  $15 \pm 6$  mmHg, a brain  $P_{CO_2}$  of  $67 \pm 23$  mmHg, a brain pH of  $6.95 \pm 0.4$  and a brain temperature of  $36.3 \pm 2.4^\circ\text{C}$  (Zauner, Bullock and Young, 1995a; Figure 5.2).



**Figure 5.2** (a) Brain  $P_{O_2}$ ,  $P_{CO_2}$ , lactate, glucose and ICP plotted against time in a patient with good outcome. The brain  $P_{O_2}$  increases in the first 24 hours after injury. Note the drop in brain lactate in the first 36 hours after injury. (b) Brain  $P_{O_2}$ ,  $P_{CO_2}$ , and dialysate glucose and lactate in a patient with arterial hypoxemia ( $P_{aO_2}$ -55 mmHg on admission to ICU). Note that brain  $CO_2$  was very high (pulmonary contusions). Hyperventilation at  $F_{iO_2}$  1.0 failed to improve brain  $P_{O_2}$  to  $>20$  mmHg, and dialysate lactate remains very high. (The patient died 9.5 hours after monitoring commenced.)

## 5.1.4 NEUROTRANSMITTERS AND CBF

**(a) Metabolic effects of neurotransmitters**

The close relationship between regional CBF and glucose utilization is generally accepted. CBF increases with increased neuronal activity and also during tissue hypoxia. It is thought that  $P_{CO_2}$ , pH and adenosine serve as coupling factors, but the mechanisms involved cannot be fully explained. Extracellular  $K^+$  affects membrane function and cerebrovascular tone (Kuschinsky *et al.*, 1972). Astrocytes may play a role by raising  $K^+$  concentration around cerebral arterioles.

The role of neurotransmitters with vasomotor effects on cerebral vessels and cerebral metabolism is less well understood. The presence of dopamine receptors ( $D_2$ ) in neurons and cerebral blood vessels suggests that they can increase CBF and glucose metabolism (Sharkey and McCulloch, 1995). Different cerebral regions have a variable amount of  $\alpha$ - and  $\beta$ -adrenoreceptors. *The literature reports a diversity of roles for catecholamines and both vasoconstriction and vasodilation have been reported. It seems that the systemic application of catecholamines has little direct effect on cerebral metabolism. However, if the blood-brain barrier is disrupted, CBF and cerebral metabolic rate of oxygen are increased (Edvinsson, 1982).* The effect of gamma-aminobutyric acid (GABA), one of the most widely distributed neurotransmitters in the human brain, on CBF and metabolism is not known. Both increased and decreased regional CBF have been reported after systemic administration (Alborch *et al.*, 1984; Kelly and McCulloch, 1983).

An intrinsic neuronal pathway that may influence and partially regulate the cerebral circulation and metabolism has received attention, although the results of experimental studies are diverse. For example, electrical stimulation of the cerebellar fastigial nucleus increased cerebral cortical blood flow, but no change in local metabolism and glucose utilization was observed (Nakai *et al.*, 1983).

## 5.2 Normal values for CBF and metabolism

The most widely used clinical techniques for measuring CBF are described in detail in Chapter 11. In summary, quantitative blood flow measurement is available using:

- stable xenon-enhanced computer tomography;
- inhalational i.v. xenon-133;
- PET scanning;
- MRI angiography and flow measurement by oxy-hemoglobin spectral shifts, and contrast indication

transit times – this is currently being investigated for use in patients with acute severe head injuries;

- SPECT (Section 9.5);
- laser Doppler flowmetry and the thermal diffusion techniques – these are useful for monitoring progressive changes but they are essentially qualitative;
- transcranial Doppler sonography;
- near-infrared spectroscopy – the last two methods are non-invasive and are being used more frequently at the bedside, but they do not measure CBF directly, and their value in the intensive care management needs further evaluation;
- continuous monitoring of jugular venous oxygen saturation to give an assessment of global cerebral oxygenation and an indirect indication of CBF;
- brain tissue sensors for oxygen and carbon dioxide – these allow direct substrate delivery measurements but are still undergoing experimental evaluation.

The normal values for xenon CBF and jugular bulb oximetry are summarized below. Other techniques, which measure relative quantitative or qualitative changes, are described in Chapter 11.

## 5.2.1 XENON CBF MEASUREMENTS

A wide range in CBF values has been reported for different brain locations measured by the stable (non-radioactive) xenon and the xenon-133 methods (Risberg *et al.*, 1975; Austine *et al.*, 1972; Gur, Yonas and Good, 1989; Gur, Good and Yonas, 1992; Nakano *et al.*, 1992). Dettmers found a mean hemispheric CBF value of  $44.4 \pm 5.7$  ml/100 g/min in 17 normal volunteers (mean age 29 years; Dettmers *et al.*, 1992). In a recent series of nine healthy volunteers of similar age, we found that the mean hemispheric CBF was  $54.9 \pm 9.0$ . Different clinical approaches for CBF evaluation necessitate the differentiation of various brain compartments. Meyer *et al.* reported a CBF of  $52.8 \pm 10.9$ ,  $57.7 \pm 15.2$  and  $15.8 \pm 3.3$  ml/100 g/min for frontal cortex, thalamus and frontal white matter respectively in 22 neurologically normal volunteers. They also noted a decline in cortical gray matter blood flow with advancing age (Meyer *et al.*, 1992). The variations in CBF using stable xenon in different studies are most likely due to the limitations in the spatial resolution of computed tomography, the use of different xenon concentrations and different durations of xenon inhalation, as well as biological variation. Most of the current stable xenon equipment and calculations are for adult patients, and less is known about CBF in infants and children. However, Suzuki *et al.* used the intravenous xenon-133 clearance method to study CBF in 80 children, aged from 1 week to 15 years (Suzuki, 1990). *Within the first weeks of life CBF was*

20–60 ml/100 g/min. Between 6 months and 1 year mean CBF was  $74 \pm 10$  and between 1 and 2 years  $101 \pm 12$ . There was a peak of  $108 \pm 5$  between 2 and 4 years, followed by a slow decline to  $90 \pm 10$  between 4 and 9 years, and a further decline to  $71 \pm 12$  ml/100 g/min between the ages of 9 and 15.

As noted earlier, the brain has little storage capabilities for ATP and glucose and virtually no reserves of oxygen. Therefore CBF must be tightly coupled to cerebral metabolism. At a normal serum glucose concentration, the influx of glucose to the brain is twice the glucose utilization. However, if serum glucose falls below  $2.5 \mu\text{mol/ml}$  the availability of glucose to the brain is reduced (Robinson and Rapoport, 1986). The average cerebral metabolic rate for glucose (CMRG) in adults is  $0.325 \mu\text{mol/g/min}$  (Hatazawa *et al.*, 1988). *In normal brain more than 90% of glucose usage is met by aerobic metabolism and the remaining by anaerobic glycolysis, which yields lactate as the end product (Hatazawa et al., 1988).* The cerebral metabolic rate of lactate (CMRL) can be positive or negative depending on whether there is uptake or excretion of lactate by the brain. Normally under aerobic conditions, the CMRL is  $-0.02 \mu\text{mol/g/min}$  (Ritter and Robertson, 1994). The normal cerebral metabolic rate for oxygen (CMRO<sub>2</sub>) in healthy adults ranges from 1.8–3.9 ml of oxygen/100 g/min (mean  $3.4 = 1.5 \mu\text{mol/g/min}$ ; Muizelaar and Schröder, 1994). *After head injury CMRO<sub>2</sub> is often reduced to an average of  $0.9 \mu\text{mol/g/min}$ . Less than  $0.6 \mu\text{mol/g/min}$  is insufficient to maintain normal cellular function (Ritter and Robertson, 1994). The cerebral arteriovenous oxygen difference (AVDO<sub>2</sub>), representing the amount of oxygen extracted by the brain, ranges from 4.5–8.5 ml (mean 6.5) O<sub>2</sub>/100 ml of blood. In a normal coupled relationship between AVDO<sub>2</sub> and CBF (AVDO<sub>2</sub> = CMRO<sub>2</sub>/CBF), AVDO<sub>2</sub> remains unchanged when the CMRO<sub>2</sub> changes. However if CMRO<sub>2</sub> remains constant, changes in AVDO<sub>2</sub> reflect uncoupled changes in CBF (Robertson et al., 1989). If CBF decreases following head injury, AVDO<sub>2</sub> will increase as the brain compensates by extracting a greater amount of oxygen. A further uncompensated decline in CBF leads to ischemia and a fall in CMRO<sub>2</sub> and an increase in the cerebral lactate production.*

The average jugular venous saturation (S<sub>jv</sub>O<sub>2</sub>) in normal adults is 65%, ranging from 55–71%. However in comatose patients, values greater than 50% are considered normal (Cruz, 1993a, b; Sheinberg *et al.*, 1992). Whenever S<sub>jv</sub>O<sub>2</sub> drops below 50% for more than 15 minutes, the cause must be sought (Sheinberg *et al.*, 1992). If technical errors are excluded, a decline in S<sub>jv</sub>O<sub>2</sub> may be caused by a low P<sub>a</sub>O<sub>2</sub>, prolonged hyperventilation, decreased CPP (<70 mmHg), vasospasm or, very occasionally, low hemoglobin (Gopinath *et al.*, 1994).

### 5.3 CBF and metabolism following head injury

The severity of injury to the brain resulting from mechanical trauma depends not only on the structural damage inflicted by the impact, but also on complex pathophysiological events occurring in the first hours or days. In the past a distinction has been made between primary and secondary injury. Current research is seeking ways of intervening before or during the secondary events to correct metabolic derangements.

A classification of head injury based on initial CT findings was introduced by the Traumatic Coma Data Bank (TCDB; Marshall *et al.*, 1991). This classification shows a strong relationship between CT appearance, mortality and the frequency of increased ICP in the early phase of injury. It is also helpful in the early prediction of outcome in these patients. The stable xenon technique can be performed at the same time as a diagnostic CT scan, thus allowing a better interpretation of the CBF results.

In keeping with the known heterogeneity of traumatic brain injury, considerable variations in CBF values, ranging from abnormally low to abnormally high flow, are found. There is little information on the time course and significance of CBF changes in the early hours following brain injury. Both very low and very high blood flow values have been associated with poor outcome. Low CBF represents either a state of ischemia or reduced brain metabolism and is seen especially in patients with severe head injury. On the other hand, hyperemia or luxury perfusion due to uncontrolled vasodilation contributes to brain swelling and high ICP and may also be associated with poor outcome (Obrist *et al.*, 1984; Bouma and Muizelaar, 1992).

#### 5.3.1 CEREBRAL ISCHEMIA AFTER SEVERE HEAD INJURY

Decreased CBF is frequently seen following severe head injury. It may be secondary to depressed metabolism rather than a sign of cerebral ischemia (Obrist *et al.*, 1984; Adams and Graham, 1972). Many of the earlier studies of CBF and AVDO<sub>2</sub> were performed several hours after injury and in several of these reports, CBF values below the threshold of ischemia (18 ml/100 g/min) and critically high values of AVDO<sub>2</sub>, indicative of ischemia, were extremely rare (Obrist *et al.*, 1984; Bouma and Muizelaar, 1992; Adams and Graham, 1972; Jones *et al.*, 1981; Bruce *et al.*, 1973; Muizelaar and Schröder, 1994). Autopsy studies, however, have indicated that cerebral ischemic damage is present in 80% of patients dying from severe head injury (Adams and Graham, 1972; Jennett *et al.*, 1973). Furthermore, experimental work suggests that head

injury enhances the vulnerability of brain tissue to ischemia and that this vulnerability persists for at least 24 hours following the injury (Jenkins *et al.*, 1989).

Using the stable xenon CT technique with the initial diagnostic CT scan, Schröder *et al.* (1995) confirmed that the threshold for global ischemia of 18 ml/100 g/min was accurate and that most patients with CBF values below this value will develop low-density changes on CT scans and die within 48 hours. They assumed that these very low CBF values last for a few hours only and are therefore missed in studies performed beyond 4 hours after injury. *It is generally assumed that if CBF stays above 18 ml/100 g/min but below 20–25 ml/100 g/min neurons will survive but may not function. However, recent research suggests that infarction will ensue with a CBF of 5 ml/100 g/min sustained for more than 1.5 hours, 10 ml/100 g/min for more than 3 hours, 15 ml/100 g/min for more than 3.5 hours or 18 ml/100 g/min for more than 4 hours (Obrist *et al.*, 1984; Bouma *et al.*, 1991, 1992; Heiss, Hayakawa and Waltz, 1976; Schröder, Muizelaar and Kota, 1994).*

CMRO<sub>2</sub> is typically reduced after severe head injury to 0.6–1.2 μmol/g/min. This decrease in metabolic requirements may protect against cerebral ischemia caused by the injury (Ritter and Robertson, 1994). Salvant and Muizelaar suggested that a parallel reduction in CBF and CMRO<sub>2</sub> without an increase in AVDO<sub>2</sub> is consistent with diminished cerebral metabolic requirements or reduced capacity for oxidative metabolism (Salvant and Muizelaar, 1993). If CBF falls below the ischemic level of 18 ml/100 g/min, CMRO<sub>2</sub> is low and AVDO<sub>2</sub> is increased, usually to over 4–8 ml/100 ml blood, as the brain compensates by extracting a greater amount of oxygen (Ritter and Robertson, 1994; Obrist *et al.*, 1984; Robertson, Narayan and Gokaslan, 1989). If ischemia continues, an increase in CSF lactate and CMRL is observed. Very high cerebral lactate levels can be seen in patients who die early after severe head injury (Robertson, Narayan and Gokaslan, 1989). *In theory, it is possible to differentiate viable brain at severe risk for ischemia (low CBF, high AVDO<sub>2</sub>, low CMRO<sub>2</sub>), from compensating and 'low-risk' brain (low CBF, normal AVDO<sub>2</sub>, low CMRO<sub>2</sub>), and from irreversible brain damage (low CBF, low AVDO<sub>2</sub>, very low CMRO<sub>2</sub>; Muizelaar and Schröder, 1994).*

With the ability to measure global cerebral oxygen saturation via a jugular bulb catheter either continuously or by intermittent blood samples, cerebral desaturation (defined as a sustained jugular bulb oxygen saturation less than 55% for more than 15 minutes) might theoretically be detected early (Sheinberg *et al.*, 1992). However in some studies, more than 50% of the fiberoptic catheter readings are not reliable and major improvements in the equipment are needed

to make this technique more widely applicable. Our studies with continuous brain tissue P<sub>O</sub><sub>2</sub>, P<sub>CO</sub><sub>2</sub>, pH and temperature monitoring via a single fiber suggest that this may be a better way to continuously monitor cerebral oxygenation and metabolism (Zauner *et al.*, 1995; Zauner, Bullock and Young, 1995a, b, c).

### 5.3.2 CEREBRAL HYPEREMIA AFTER SEVERE HEAD INJURY

Hyperemia is defined as CBF in excess of metabolic demands and is frequently seen in severely head-injured patients. When CBF is reduced, CBF and CMRO<sub>2</sub> often stay coupled, whereas in hyperemia uncoupling of CBF and metabolism is more likely (Obrist *et al.*, 1984; Bruce *et al.*, 1973; Enevoldsen *et al.*, 1976). *Although the etiology is unknown, hyperemia implies one of:*

- *metabolic derangement;*
- *vasodilation due to loss of vasomotor tone;*
- *severe tissue acidosis (Obrist *et al.*, 1984; Bouma and Muizelaar, 1992; Lassen, 1966; Langfitt, Weinstein and Kassell, 1965).*

Hyperemia after severe brain injury usually follows a period of reduced CBF or increased ICP. It may start approximately 48 hours after injury and last from a few hours to 7–10 days (Bouma and Muizelaar, 1992). Hyperemia is frequently seen shortly after removal of an epidural or acute subdural hematoma (Schröder, Muizelaar and Kota, 1994). *Pressure–volume index (PVI) and cerebral blood volume (CBV) studies have suggested that the association between hyperemia and ICP is probably due to an increase in cerebral blood volume rather than CBF (Bouma and Muizelaar, 1992; Marmarou *et al.*, 1987).*

These observations suggest the usefulness of combined studies of CBV and CBF with the xenon-enhanced computed tomography (Chapter 11) in acute severely head-injured patients.

*According to Obrist *et al.* (1984), in patients with head injury CBF below 33 ml/100 g/min at a P<sub>a</sub>CO<sub>2</sub> of 34 mmHg should be considered to be reduced, and all values above this level are hyperemic. CBF between 33 and 55 ml/100 g/min represents relative hyperemia and above 55 ml/100 g/min, absolute hyperemia.*

Previous studies have reported hyperemia in more than 50% of patients after severe head injury, generally associated with high ICP and uncoupling of CBF and CMRO<sub>2</sub> (Obrist *et al.*, 1984; Bouma and Muizelaar, 1992). In children hyperemia was found even more frequently in some studies, but others found no increased incidence for hyperemia in children aged 3–18, nor a relationship between ICP and CBF (Bouma and Muizelaar, 1992; Salvant and Muizelaar, 1993; Muizelaar, Marmarou and Desalles, 1989; Muizelaar *et*



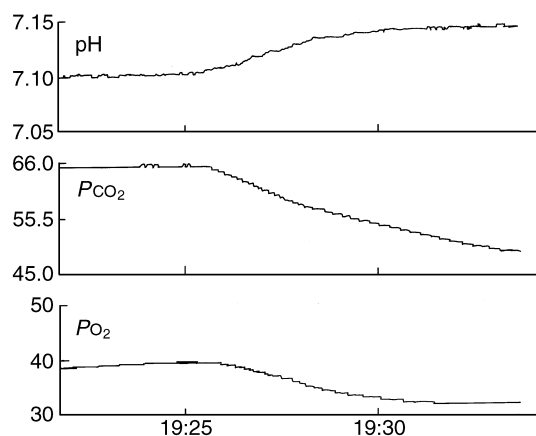
*al.*, 1989a, b; Sharples *et al.*, 1995). Children normally have a higher CBF depending on their age (see above), and this must be taken into consideration.

### 5.3.3 CEREBROVASCULAR REACTIVITY AFTER SEVERE HEAD INJURY

Under normal physiological conditions there is a 3–6% change in CBF per mmHg  $P_{aCO_2}$  (Obrist *et al.*, 1984; Bouma and Muizelaar, 1992; Enevoldsen *et al.*, 1976). *In most patients with severe head injury, some depression of CO<sub>2</sub> reactivity is seen for some time (Bouma and Muizelaar, 1992). Diminished CO<sub>2</sub> reactivity is associated with a poor outcome and is most probably a reflection of the severity of the injury rather than a causative mechanism.* Reduced CO<sub>2</sub> reactivity is also associated with decreased effectiveness of barbiturate therapy in the control of raised ICP (Messeter *et al.*, 1986). A xenon-enhanced CBF study in 17 severely head-injured patients found that hemispheric CO<sub>2</sub> reactivity ranged from 1.3–8.5% per mmHg change in  $P_{aCO_2}$  (Bouma and Muizelaar, 1992).

*Prolonged hyperventilation may decrease brain oxygenation and must be used with caution and only for a short period of time (Muizelaar et al., 1991). In the future, measuring brain tissue PO<sub>2</sub> and PCO<sub>2</sub> may allow P<sub>aCO<sub>2</sub></sub> to be adjusted more accurately and safely (Zauner, Bullock and Young, 1995a; Zauner et al., 1995; Figure 5.3).*

Current knowledge on the status of cerebral autoregulation following severe head injury is inconclusive. In general, pressure autoregulation is usually intact for the first hours after injury but may deteriorate in



**Figure 5.3** Changes in brain  $PO_2$ ,  $PCO_2$  and pH in the human brain during hyperventilation after severe head injury. Brain  $PO_2$  is lowered during hyperventilation, resulting in decreased substrate delivery, although this remains above threshold levels ( $\geq 20$  mmHg). Brain  $PCO_2$  follows the washout of arterial  $CO_2$ , resulting in an increase in the pH of the brain tissue.

many patients (Obrist *et al.*, 1984; Bouma and Muizelaar, 1992; Enevoldsen *et al.*, 1976; Lassen, 1966; Muizelaar, Marmarou and Desalles, 1989). However, conclusions regarding the outcome of patients according to the status of autoregulation should be made with great caution. Bouma and Muizelaar performed 158 autoregulation tests, using CBF measurements and an alpha-adrenergic agonist, on 117 severely head-injured patients. They found autoregulation to be intact in 51% and defective in 49% (Bouma and Muizelaar, 1992). They concluded that the presence or absence of pressure autoregulation had no specific temporal profile, nor a clear relationship to clinical status or outcome. This has also been the finding in head-injured children (Muizelaar *et al.*, 1989b; Sharples *et al.*, 1995). However, the status of autoregulation is important for determining the most appropriate blood pressure and CPP in a particular patient, and may influence the choice of treatment for raised ICP. For example, mannitol may be more effective if autoregulation is intact (Bouma and Muizelaar, 1992).

### 5.3.4 POST-TRAUMATIC CEREBRAL HYPERMETABOLISM FOR GLUCOSE

Positron emission tomography has been used to measure brain metabolism after human head injury. Uniformly reduced glucose metabolism has been reported, although marked regional variations were present in two studies performed more than 1 week after injury (Alavi *et al.*, 1986; Langfitt *et al.*, 1986). *Recently Hovda et al. (1995) have found striking increases in regional glucose utilization in post-traumatic studies performed within the first few days of injury. This was seen especially in the underlying brain after hematoma removal. This early post-traumatic hyperglycolysis may result from cellular efforts to re-establish ionic gradients. Thus the hyperemic zones seen in some patients may represent an appropriate response to metabolic needs.*

## 5.4 References

- Abrams, R. M., Ito, M., Frisinger, J. E. *et al.* (1984) Local cerebral glucose utilisation in fetal and neonatal sheep. *American Journal of Physiology*, **246**, R608–R618.
- Adams, J. H. and Graham, D. I. (1972) The pathology of blunt head injury, in *Scientific Foundations of Neurology*, (eds M. Critchley, J. L. O'Leary and B. Jennett), Heinemann, London, pp. 488–491.
- Alavi, A., Dann, R., Chawluk, J. *et al.* (1986) Positron emission tomography imaging of regional cerebral glucose metabolism. *Seminars in Nuclear Medicine*, **16**, 2–34.
- Alborch, E., Torregrosa, G., Terrasa, J. C. *et al.* (1984) GABA receptors mediate cerebral vasodilation in the anaesthetised goat. *Brain Research*, **321**, 103–110.
- Alpers, B. J., Berry, R. O. and Paddison, R. M. (1959) Anatomical studies in the circle of Willis in normal brains. *Archives of Neurology and Psychiatry*, **81**, 409–418.
- Auer, L. M. and Loew, F. (1983) *The Cerebral Veins. An Experimental and Critical Update*, Springer-Verlag, Vienna.

- Austine, G., Horn, N., Rouhe, S. *et al.* (1972) Description and early results of an intravenous radioisotope technique for measuring regional cerebral blood flow in man. *European Neurology*, 43–51.
- Bouma, G. J. and Muizelaar, J. P. (1992) Cerebral blood flow, cerebral blood volume, and cerebrovascular reactivity after severe head injury. *Journal of Neurotrauma*, 9(Suppl. 1), S333–S348.
- Bouma, G. J., Muizelaar, J. P., Choi, S. C. *et al.* (1991) Cerebral circulation and metabolism after severe traumatic brain injury: the elusive role of ischaemia. *Journal of Neurosurgery*, 75, 685–693.
- Bouma, G. J., Muizelaar, J. P., Stringer, W. A. *et al.* (1992) Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computed tomography. *Journal of Neurosurgery*, 77, 360–368.
- Bruce, D. A., Langfitt, T. W., Miller, J. D. *et al.* (1973) Regional cerebral blood flow, intracranial pressure and brain metabolism in comatose patients. *Journal of Neurosurgery*, 38, 131–144.
- Cameron, I. R. and Caronna, J. (1976) The effect of local changes in potassium and bicarbonate concentration on hypothalamic blood flow in the rabbit. *Journal of Physiology*, 262, 415–430.
- Cold, G. E. (1989) Measurements of CO<sub>2</sub> reactivity and barbiturate reactivity in patients with severe head injury. *Acta Neurochirurgica*, 98, 153–163.
- Cruz, J. (1993a) Cerebral oxygenation – monitoring and management. *Acta Neurochirurgica (Supplement)*, 59, 86–90.
- Cruz, J. (1993b) On-line monitoring of global cerebral hypoxia in acute brain injury: relationship to intracranial hypertension. *Journal of Neurosurgery*, 79, 228–233.
- Dettmers, C., Broich, K., Hartmann, A. *et al.* (1992) Estimated values in normal subjects, in *Cerebral Blood Flow Measurements with Stable Xenon-enhanced Computer Tomography*, (ed. H. Yonas), Raven Press, New York.
- Edvinsson, L. (1982) Sympathetic control of cerebral circulation. *Trends in Neuroscience*, 8, 425–429.
- Edvinsson, L. and McCulloch, J. (1981) Effects of phenobarbital on contractile responses of feline cerebral arteries. *Journal of Cerebral Blood Flow and Metabolism*, 1, 437–440.
- Edvinsson, L. and Sercombe, R. (1976) Influence of pH and pCO<sub>2</sub> on alpha-receptor mediated contraction in brain vessels. *Acta Physiologica Scandinavica*, 97, 325–331.
- Ehrenreich, D. L., Burns, R. A., Alman, F. N. *et al.* (1961) Influence of acetazolamid on cerebral blood flow. *Archives of Neurology*, 5, 227–232.
- Enevoldsen, E. M., Cold, G. E., Jensen, F. T. *et al.* (1976) Dynamic changes in regional cerebral blood flow, intraventricular pressure, cerebrospinal fluid pH and lactate levels during the acute phase of head injury. *Journal of Neurosurgery*, 44, 191–214.
- Faraci, F. M. (1993) Endothelium-derived vasoactive factors and regulation of the cerebral circulation. *Neurosurgery*, 33, 648–658.
- Fleckenstein, W., Maas, A. I., Nollert, G. and de Long, D. A. (1990) Oxygen pressure in cerebrospinal fluid, in *Clinical Oxygen Pressure Measurement 11*, (eds A. M. Ehrly, W. Fleckenstein and H. Landgraf), Blackwell, Berlin, pp. 368–393.
- Furchgott, R. F. and Vanhoutte, P. M. (1989) Endothelium-derived relaxing and contracting factors. *FASEB Journal*, 3, 2007–2018.
- Giller, C. A., Bowman, G., Dyer, H. *et al.* (1993) Cerebral arterial diameters during changes in blood pressure and carbon dioxide during craniotomy. *Neurosurgery*, 32, 737–742.
- Gobel, U., Theilen, H. and Kuschinsky, W. (1990) Congruence of total and perfused capillary network in rat brains. *Circulation Research*, 66, 271–281.
- Gobel, U., Klein, B., Schrock, H. and Kuschinsky, W. (1989) Lack of capillary recruitment in the brains of awake rats during hypercapnia. *Journal of Cerebral Blood Flow and Metabolism*, 9, 491–499.
- Good, W. F., Gur, D. and Yonas, H. (1992) Technical aspects, in *Cerebral Blood Flow Measurements with Stable Xenon-enhanced Computer Tomography*, (ed. H. Yonas), Raven Press, New York.
- Gopinath, S. P., Robertson, C. S., Contant, C. F. *et al.* (1994) Jugular venous desaturation and outcome after head injury. *Journal of Neurology, Neurosurgery and Psychiatry*, 57, 717–723.
- Gur, D., Yonas, H. and Good, W. F. (1989) Local cerebral blood flow by xenon-enhanced CT: current status, potential improvements, and future directions. *Cerebrovascular Brain Metabolism Review*, 1, 68–96.
- Harder, D. R., Kausner, K., Roman, R. J. *et al.* (1989) Mechanism of pressure-induced myogenic activation of cerebral and renal arteries: role of the endothelium. *Journal of Hypertension*, 7, S11–S15.
- Harper, A. M. (1966) Autoregulation of cerebral blood flow: influence of the arterial blood pressure on the blood flow through the cerebral cortex. *Journal of Neurology, Neurosurgery and Psychiatry*, 29, 398–403.
- Hatazawa, J., Ito, M., Matusuzawa, T. *et al.* (1988) Measurement of the ratio of cerebral oxygen consumption to glucose utilisation by positron emission tomography: its consistency with the values determined by the Kety-Schmidt method in normal volunteers. *Journal of Cerebral Blood Flow and Metabolism*, 8, 426–432.
- Heiss, W. D., Hayakawa, T. and Waltz, A. G. (1976) Cortical neuronal function during ischaemia. *Archives of Neurology*, 33, 813–820.
- Heuser, D., Astrup, J., Lassen, N. A. *et al.* (1975) Brain carbonic acid acidosis after acetazolamide. *Acta Physiologica Scandinavica*, 93, 385–390.
- Hovda, D. A., Lee, S. M., Smith, M. L. *et al.* (1995) The neurochemical and metabolic cascade following brain injury: moving from animal models to man. *Journal of Neurotrauma*, 12, 903–906.
- Hudak, M. L., Jones, M. D., Popel, A. S. *et al.* (1989) Hemodilution causes size-dependent constriction of pial arterioles in the cat. *American Journal of Physiology*, 257, H912–H917.
- Humphrey, P. R. D., Marshall, J., Russel, R. W. R. *et al.* (1979) Cerebral blood flow and viscosity in relative polycythemia. *Lancet*, i, 873–876.
- Jenkins, L. W., Moszynski, K., Lyeth, B. *et al.* (1989) Increased vulnerability of the mildly traumatized rat brain to cerebral ischaemia: the use of controlled secondary ischaemia as a research tool to identify common or different mechanisms contributing to mechanical and ischaemic brain injury. *Brain Research*, 477, 211–224.
- Jennett, B., Miller, J. D. and Harper, A. M. (1976) *Effect of Carotid Artery Surgery on Cerebral Blood Flow*, Excerpta Medica, Amsterdam.
- Jennett, B., Graham, D. I., Adams, H. P. *et al.* (1973) Ischemic brain damage after fatal blunt head injury, in *Cerebrovascular Diseases, 8th Conference*, (eds F. H. McDowall and R. W. Brennan), Grune & Stratton, New York, pp. 163–176.
- Jones, T. H., Morawetz, R. B., Crowell, R. M. *et al.* (1981) Thresholds of focal cerebral ischaemia in awake monkeys. *Journal of Neurosurgery*, 36, 463–470.
- Kader, A., Frazzini, V., Solomon, R. A. and Trifiletti, R. R. (1993) Nitric oxide production during focal cerebral ischaemia in rats. *Stroke*, 24, 1709–1716.
- Kassell, N. F., Hitchon, P. W., Gerk, M. K. *et al.* (1981) Influence of changes in arterial pCO<sub>2</sub> on cerebral blood flow and metabolism during high-dose barbiturate therapy in dogs. *Journal of Neurosurgery*, 54, 615–619.
- Kelly, P. A. and McCulloch, J. (1983) The effect of the GABA agonist muscimol upon the relationship between local cerebral blood flow and glucose utilisation. *Brain Research*, 258, 338–342.
- Kim, P. and Vanhoutte, P. M. (1990) Endothelium dependent relaxations and chronic vasospasm after subarachnoid hemorrhage. *Blood Vessel*, 27, 263–268.
- Kontos, H. A. (1985) Oxygen radicals in cerebral vascular injury. *Circulation Research*, H57, 508–516.
- Kontos, H. A., Raper, A. J. and Patterson, J. L. (1977) Analysis of vasoactivity and local pH, pCO<sub>2</sub> and bicarbonate on pial vessels. *Stroke*, 8, 358–360.
- Kontos, H. A., Wei, E. P., Navari, R. M. *et al.* (1978) Responses of cerebral arteries and arterioles to acute hypotension and hypertension. *American Journal of Physiology*, 234, H371–H383.
- Kuschinsky, W. and Wahl, M. (1978) Local chemical and neurogenic regulation of cerebral vascular resistance. *Physiology Reviews*, 58, 656–689.
- Kuschinsky, W., Wahl, M., Bosse, O. *et al.* (1972) Perivascular potassium and pH as determinants of local pial arterial diameter in cats: a microapplication study. *Circulation Research*, 31, 240–247.
- Langfitt, T. W., Weinstein, J. D. and Kassell, N. F. (1965) Cerebral vasomotor paralysis produced by intracranial hypertension. *Neurology*, 15, 622–641.
- Langfitt, T. W., Obrist, W. D., Alavi, A. *et al.* (1986) Computerized tomography, magnetic resonance imaging, and positron emission tomography in the study of brain trauma. *Journal of Neurosurgery*, 64, 760–767.
- Lassen, N. A. (1966) The luxury perfusion syndrome and its possible relation to acute metabolic acidosis localised within the brain. *Lancet*, ii, 1113–1115.
- Leniger-Follert, E., Gronczewski, J. and Danz, C. (1984) Regulation of microflow in the cat brain during insulin induced hypoglycemia. *Advances in Experimental Medical Biology*, 169, 297–303.
- Leniger-Follert, E., Lübbers, D. W. *et al.* (1975) Regulation of local tissue P<sub>O<sub>2</sub></sub> of the brain cortex at different arterial O<sub>2</sub> pressures. *Pflugers Archiv*, 359, 81–95.
- Leusen, I. R., Weyne, J. J. and Demeester, G. M. (1980) Regulation of acid-base equilibrium of cerebrospinal fluid, in *Neurobiology of Cerebrospinal Fluid*, (ed. J. H. Wood), pp. 25–42.
- Lübbers, D. W. (1968) The oxygen pressure field in the brain, in *Oxygen Transport in Blood and Tissue*, (eds D. W. Lübbers, U. C. Loft, G. Thews and E. Witzleb), Springer-Verlag, Berlin, pp. 67–92.
- Maas, A. I. R., Fleckenstein, W., de Long, D. A. and van Santbrink, H. (1993) Monitoring cerebral oxygenation: experimental studies and preliminary clinical results of continuous monitoring of cerebrospinal fluid and brain tissue oxygen tension. *Acta Neurochirurgica (Supplement)*, 59, 50–57.
- Marmarou, A., Maset, A. I., Ward, J. D. *et al.* (1987) Contribution of CSF and vascular factors to elevation of ICP in severely head injured patients. *Journal of Neurosurgery*, 66, 883–890.
- Marshall, L. F., Gautille, T., Klauber, M. R. *et al.* (1991) The outcome of severe closed head injury. *Journal of Neurosurgery*, 75, S28–S36.
- Messester, K., Nordstrom, C. H., Sundberg, H. M. *et al.* (1986) Cerebral hemodynamics in patients with acute severe head trauma. *Journal of Neurosurgery*, 64, 231–237.
- Meyer, I. S., Imai, A., Ichijo, M. *et al.* (1992) Local cerebral blood flow and local lambda values change with normal advancing age, in *Cerebral Blood Flow Measurements with Stable Xenon-enhanced Computer Tomography*, (ed. H. Yonas), Raven Press, New York.
- Muizelaar, J. P., Marmarou, A. and Desalles, A. A. (1989a) ICP and PVI with blood pressure alterations and relation with CBF autoregulation, in *Intracranial Pressure VII*, (eds J. T. Hoff and A. L. Betz), Springer-Verlag, Berlin, pp. 825–828.
- Muizelaar, J. P. and Schröder, M. L. (1994) Overview of monitoring of cerebral blood flow and metabolism after severe head injury. *Canadian Journal of the Neurological Sciences*, 21, S6–S11.

- Muizelaar, J. P., Marmarou, A., Desalles, A. A. *et al.* (1989b) Cerebral blood flow and metabolism in severely head-injured children. Part I: Relation with GCS, outcome, ICP and PVI. *Journal of Neurosurgery*, **71**, 63–71.
- Muizelaar, J. P., Ward, J. D., Marmarou, A. *et al.* (1989) Cerebral blood flow and metabolism in severely head injured children. Part II: Autoregulation. *Journal of Neurosurgery*, **71**, 72–76.
- Muizelaar, J. P., Marmarou, A., Ward, J. D. *et al.* (1991) Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. *Journal of Neurosurgery*, **75**, 731–739.
- Muizelaar, J. P., Bouma, G. J., Levasseur, J. E. *et al.* (1992) Effect of hematocrit variations on cerebral blood flow and basilar artery diameter in vivo. *American Journal of Physiology*, **262**, H949–H954.
- Nakai, M., Iadecola, C., Ruggiero, D. *et al.* (1983) Electrical stimulation of cerebellar fastigial nucleus increases cortical blood flow without change in local metabolism: evidence for an intrinsic system in brain for primary vasodilation. *Brain Research*, **260**, 35–49.
- Nakano, S., Yamashita, T., Kashiwagi, S. *et al.* (1992) in *Cerebral Blood Flow Measurements with Stable Xenon-enhanced Computer Tomography*, (ed. H. Yonas), Raven Press, New York.
- Nordstrom, C. H., Messeter, K., Sundbarg, G. *et al.* (1988) Cerebral blood flow, vasoreactivity, and oxygen consumption during barbiturate therapy in severe traumatic brain lesions. *Journal of Neurosurgery*, **68**, 424–431.
- Obrist, W. D., Langfitt, T. W., Jaggi, J. L. *et al.* (1984) Cerebral blood flow and metabolism in comatose patients with acute head injury. *Journal of Neurosurgery*, **61**, 241–253.
- Olesen, J., Paulson, O. B., Lassen, N. A. (1971) Regional cerebral blood flow in man determined by the initial slope of the clearance of intra-arterially injected <sup>133</sup>Xe. *Stroke*, **2**, 519–540.
- Phelps, M. E., Mazziotta, J. C., Schelbert, H. R. (1986) *Positron Emission Tomography and Autoradiography, Principles and Applications for the Brain and Heart*, Raven Press, New York.
- Risberg, J., Ali, Z., Wilson, E. M. *et al.* (1975) Regional cerebral blood flow by <sup>133</sup>xenon inhalation: preliminary evaluation of an initial slope index in patients with unstable flow compartments. *Stroke*, **6**, 142–148.
- Ritter, A. M. and Robertson, C. S. (1994) Cerebral metabolism. *Neurosurgical Intensive Care*, **5**, 633–645.
- Robertson, C., Grossman, R., Goodman, C. *et al.* (1987) The predictive value of cerebral anerobic metabolism with cerebral infarction after head injury. *Journal of Neurosurgery*, **67**, 361–366.
- Robertson, C. S., Narayan, R. K., Gokaslan, Z. L. *et al.* (1989) Cerebral arteriovenous oxygen difference as an estimate of cerebral blood flow in comatose patients. *Journal of Neurosurgery*, **70**, 222–230.
- Robinson, M. J. and McCulloch, J. (1990) Contractile responses to endothelin in feline cortical vessels in situ. *Journal of Cerebral Blood Flow and Metabolism*, **10**, 285–289.
- Robinson, P. and Rapoport, S. (1986) Glucose transport and metabolism in the brain. *American Journal of Physiology*, **250**, R127–R136.
- Salvant, J. and Muizelaar, J. (1993) Changes in cerebral blood flow and metabolism related to the presence of subdural hematoma. *Neurosurgery*, **33**, 387–391.
- Schröder, M. L., Muizelaar, J. P. and Kota, A. J. (1994) Documented reversal of global ischaemia immediately after removal of an acute subdural hematoma. *Journal of Neurosurgery*, **80**, 324–327.
- Schröder, M. L., Muizelaar, J. P., Kota, A. J. *et al.* (1995) Thresholds for cerebral ischaemia after severe head injury: relationship with late CT findings and outcome. *Journal of Neurotrauma*.
- Sharkey, J. and McCulloch, J. (1995) Relationship between local cerebral blood flow and glucose utilisation with selective dopamine receptor agonists. *Journal of Cerebral Blood Flow and Metabolism*, **5**(Suppl.), 537–538.
- Sharples, P. M., Stuart, A. G., Matheras, D. S. *et al.* (1995) Cerebral blood flow and metabolism in severely head injured children. Part I: Relationship to age, GCS, outcome, ICP and time after injury. *Journal of Neurology, Neurosurgery and Psychiatry*, **59**, 145–152.
- Sheinberg, M., Kanter, M. J., Robertson, C. S. *et al.* (1992) Continuous monitoring of jugular venous oxygen saturation in head-injured patients. *Journal of Neurosurgery*, **76**, 212–217.
- Siesjö, B. K. (1984) Cerebral circulation and metabolism. *Journal of Neurosurgery*, **60**, 883–908.
- Sokoloff, L., Reivich, M., Kennedy, C. *et al.* (1977) The <sup>14</sup>C deoxyglucose method for measurement of local cerebral glucose utilisation: theory, procedure and normal values in the conscious and anesthetized albino rat. *Journal of Neurochemistry*, **28**: 897–916.
- Sokrab, T., Johansson, B., Kalimo, H. *et al.* (1988) A transient hypertensive opening of the blood-brain barrier can lead to brain damage. *Acta Neuropathologica*, **75**, 557–565.
- Suzuki, K. (1990) The changes of regional cerebral blood flow with advancing age in children. *Nagoya Medical Journal*, **34**, 159–170.
- Thomas, D. J., DuBoulay, G. H., Marshall, J. *et al.* (1977) Effect of hematocrit on cerebral blood flow in man. *Lancet*, **ii**, 941–943.
- Wahl, M., Deetjen, P., Thurau, K. *et al.* (1970) Micropuncture evaluation of the importance of perivascular pH for the arteriolar diameter on the brain surface. *Pflugers Archiv*, **316**, 152–163.
- Wei, E. P. and Kontos, H. A. (1988) Increased venous pressure causes myogenic constriction of cerebral arterioles during local hyperoxia. *Circulation Research*, **55**, 249–252.
- Winn, H. R., Welsh, J. E., Rubio, R. *et al.* (1980) Brain adenosine production in rat during sustained alteration in systemic blood pressure. *American Journal of Physiology*, **239**, H636–H641.
- Zauner, A., Bullock, R. and Young, H. F. (1995a) Continuous brain oxygen, CO<sub>2</sub>, pH and temperature monitoring in neurosurgical patients. *Neurosurgery*, **37**, 570 (abstract).
- Zauner, A., Bullock, R. and Young, H. F. (1995b) Continuous monitoring of oxygen, CO<sub>2</sub>, pH and temperature in brain tissue, using a single sensor. *Journal of Neurotrauma*, **12**, 468 (abstract).
- Zauner, A., Bullock, R. and Young, H. F. (1995c) Brain oxygen, CO<sub>2</sub>, and cerebral blood flow measurements in focal ischaemia. *Journal of Cerebral Blood Flow and Metabolism*, **15**(Suppl. 1), S297 (abstract).
- Zauner, A., Bullock, R., Di, X. *et al.* (1995) Brain oxygen, CO<sub>2</sub>, pH, and temperature monitoring: evaluation in the feline brain. *Neurosurgery*, **37**, 1168–1177.

