BRAIN METABOLISM AND CEREBRAL BLOOD FLOW

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General Introduction

Under normal circumstances foodstuffs are broken down into fat, protein and the carbohydrate glucose, from which the body's supply of energy is produced through a series of reactions primarily involving metabolism with oxygen (figure 1.1.).

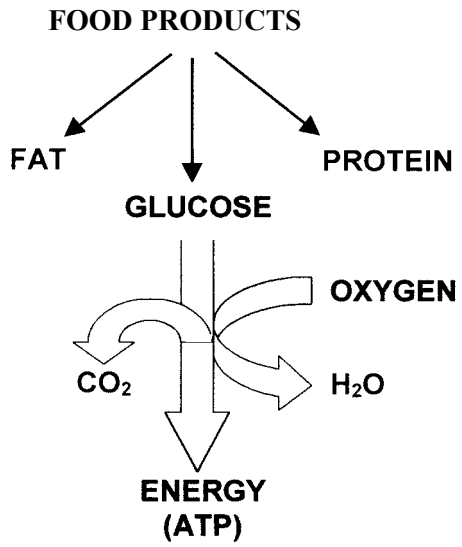
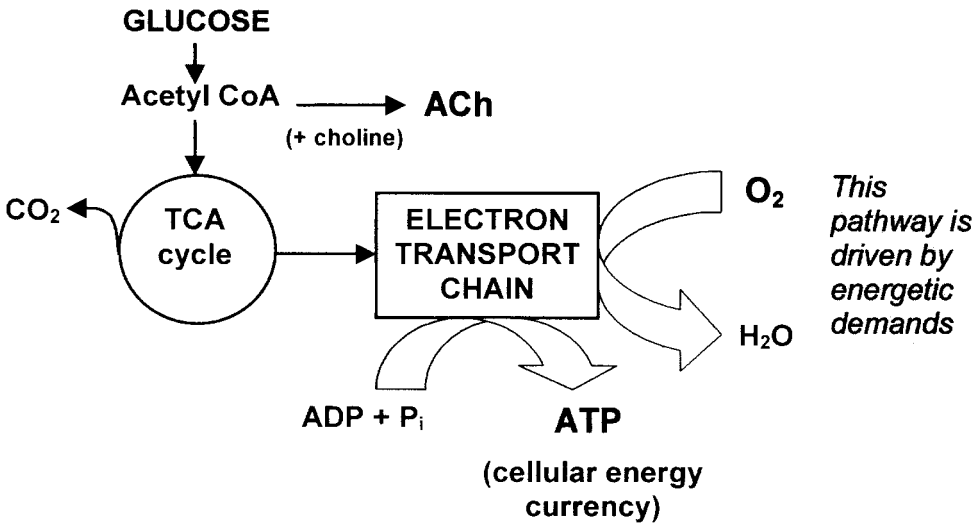


Figure conversion of food to energy in the body.

As its primary energy source, constant supplies of glucose and oxygen are critical to brain function, and a lack in these energy sources leads to cognitive impairments. Examples in which a reduction of these sources may occur are ageing, high altitude and the hypoglycaemic phase of diabetes. There is increasing evidence that enhancing the brains potential for metabolic activity is reflected by an augmentation of cognitive performance. For example; for glucose, cognitive performance over a number of tasks correlates with blood glucose levels, irrespective of resting, basal level. One possible explanation for the enhancing effects of glucose administration on cognition is that it leads to increased levels of acetylcholine (ACh) synthesis (Figure 1).



Outline of the relationship between glucose metabolism, acetylcholine synthesis and energy production.

The increase in fuel supply leads to an upgrade in adenosine triphosphate (ATP) production at times of high demand and therefor lead to an improvement in cognitive performance known as cognitive enhancement.

Oxygen has no substitute as a nutrient. In higher animals the amount of oxygen used for the synthesis of a great variety of important chemical compounds that act as regulators and constituents of cellular metabolism is minor compared to that consumed for energy production.

The brain weight is 2% of total body weight, but the brain attracts 15% of the cardiac output and consumes 20% of the total oxygen used by the body, and 75% of the glucose released rom the liver at rest. Its stores of glycogen, creatine phosphate and ATP are minute, and would last only about 2 min at normal consumption rates. If supplies were suddenly cut off, optimal functioning would be impaired long before this, within a few seconds. The brain therefore relies on a constant supply of glucose, oxygen and blood to remove waste products. Blood exits the brain at a PO2 of 35 mmHg, but that leaving grey matter areas may be at 17 mm Hg, equivalent to that leaving the myocardium. In rats, total anoxemia produces an isoelectric EEG in 60 sec. Hypoxemia has less drastic effects, but ischemia is worse, because glucose as well as O2 delivery is reduced, and wastes also can build up. The maximal period of total ischemia compatible with recovery is 30 min in the brainstem and about 5 min in the

cerebral hemispheres. An O2 consumption rate of *c*. 3.5 ml/100 g/min is maintained down to plasma glucose levels of *c.* 20 mg/dl, below which O2 consumption falls. At plasma glucose levels of *c.* 8 mg/dl, EEG changes and coma may occur. The brain almost exclusively burns glucose, aerobically, as a fuel (normal RQ *c.* 0.97). During fasting however, ketone bodies may enter the brain via a specific carrier, and be used. Deficient protein intake has little effect on brain protein metabolism in the adult, the brain protein being spared relative to muscle. Perhaps related to this, the capacity for gluconeogenesis in brain is very restricted.

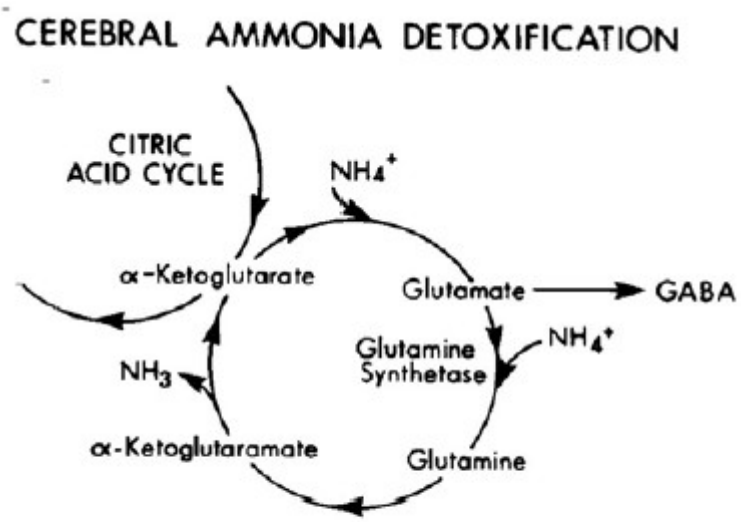
The Energy Requirements, Production and Utilisation in the Brain.

The brain relies solely on the oxidative metabolism of glucose for its energy requirements. At rest the brain consumes roughly 17 calories per 100 grams of brain tissue per minute. The normal arterial concentration of glucose is 5.5mM/L, and the normal level of oxygen is equivalent to 0.12mM/L. As 6 molecules of oxygen are required to oxidise 1 molecule of glucose, then from the standpoint of supplying these metabolic needs, the concentration of glucose is 275 times greater than that of oxygen in the extracellular fluid at the surface of the cell. Thus oxygen turnover is the highest amongst the essential nutrients. Such times of high cellular demand for energy as mentioned above, may outstrip the supply of oxygen and the cells may have to fall back (to some degree) on anaerobic metabolism. This provides less energy and leads to the accumulation of toxic end products, but allows a level of baseline cellular metabolism until physiological responses can restore supply to the required levels.

A vast part of the brain's metabolism goes into the regulation of ionic gradients in neurones and glial cells, and into the synthesis of neurotransmitter substances.

Much of the glucose taken up is used in amino acid synthesis, and quickly appears in glutamic acid, aspartic acid, alanine and GABA. Essential amino acids except lysine compete for a Large Neutral Amino-Acid transporter in the Blood-Brain Barrier. Lysine is carried by a Basic Amino-Acid transporter. Macro-nutrients (*e.g.*glucose, amino acids) are transported into brain by selective carriers on endothelial cells of the brain capillaries. Glucose is carried by facilitated transport, and amino acids by active transport. Micro-nutrients (*e.g.* vitamins) are selectively transported into brain by carriers on cells of the choroid plexus. Ammonia produced as a by-product of protein metabolism in brain, is combined with glutamate in glial cells, to form glutamine, which is at a higher concentration in venous blood leaving the brain, than in arterial blood. The glutamine may be transferred to synaptic terminals, and converted to glutamate by mitochondrial *glutaminase*. -ketoglutarate

from the Krebs Cycle also contributes to glutamate formation. Glutamate in turn may be conveted to GABA by glutamic acid decarboxylase, or to glycine (below) by transamination. Tyrosine is an essential amino-acid in brain, since phenylalanine cannot be converted to tyrosine there. Although the synthesis of many transmitters is regulated by feedback inhibition, dietary levels of precursors, notably tryptophan (serotonin precursor), and oerhaps l-dopa (dopamine precursor) can influence brain levels of the respective neurotransmitters. Choline in the diet can also promote ACh synthesis.



Key: NH_4^+:ammonium ion
NH_3 :ammonia
GABA: ɣ-aminobutyric acid

How is the Energy For Neural Function Produced ?

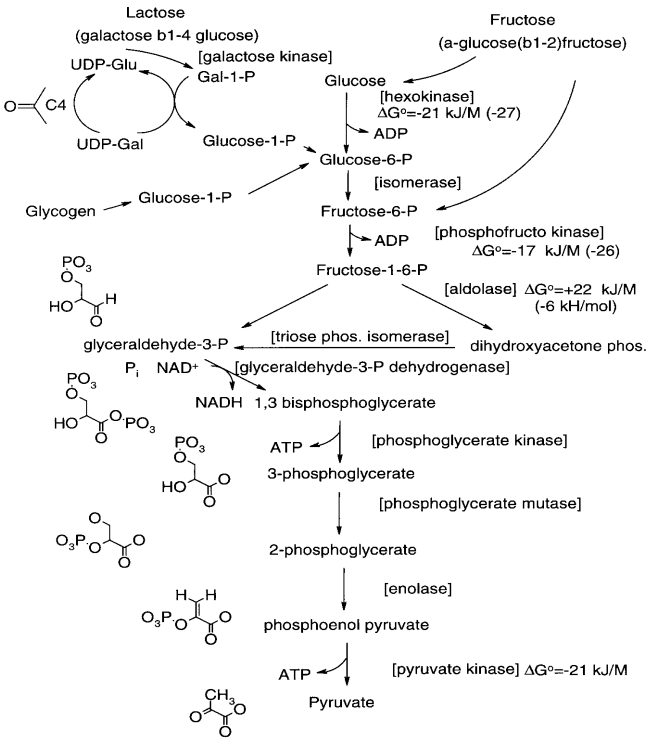
Glucose

As mentioned earlier, brain energy is almost exclusively derived from the oxidative metabolism of glucose. Glucose is obtained from two sources; the breakdown of glycogen stored in astrocytes, and from glucose within the blood serum. Synthesis and degradation of glycogen appears to be linked generally to the level of membrane activity, with most metabolism occuring in the grey rather than the white matter; and specifically to synaptic transmission, synaptic excitation and inhibition, transmitter synthesis and protein phosphorylation. Glycogen provides only a small part of the glucose required by the brain, the amount stored and the length of time that the brain can survive using glycogen as an exclusive energy source is not known. The brain is therefore mainly dependent on a constant

supply of glucose provided by the blood which is than transported across the blood brain barrier via carriers contained within the blood capillary endothelial cells which transport glucose into the extracellular space of the brain. Once inside the extracellular space glucose is then carried into neurons and glia by specific membrane-bound glucose transport systems driven by concentration gradients. Once glucose has entered cells it undergoes the process of glycolysis in the cytosol which leads to the main product of glycolysis, pyruvate. This later enters the tricarboxylic cycle in mitochondria and through a complex series of reactions leads to the production of ATP, difened by some the "universal energy currency".

Glycolysis

Firstly glucose is phosphorylated into glucose-6- phosphate by the enzyme hexokinase, a reaction that consumes one molecule of ATP. Glucose-6-phosphate so produced is available to three possible processes: 1) as the substrate for glycogen synthesis; 2) as a substrate for glucose-6-phosphate dehydrogenase which initiates the pentose shunt pathway; or 3) it can be further metabolised along the glycolytic pathway. The remainder of the reactions involved in glycolysis result in the production of pyruvate.



The key reactions involved in glycolysis

The rate of glycolysis is regulated at three points.

1) The regulation of hexokinase activity.

2)The regulation of the activity of the enzyme phosphofructokinase, which is enhanced by increased concentrations of ADP, AMP and inorganic phosphate and is inhibited by increased concentrations of ATP.

3)The activity of the enzyme pyruvate kinase which is also enhanced by high ADP concentrations and inhibited by high ATP concentrations.

The Tricarboxylic Acid Cycle

The enzymes that catalyze the reactions of the trycarboxylic acid (TCA) cycle are located in the mitochondria. The membrane of the mitochondria is not permeable to pyruvate which is therefore transported across the membrane by a special carrier system. Once inside the mitochondrion pyruvate is decarboxylated and combines with coenzyme A to produce acetylcoenzyme A (Acetyl Co A), which carries a two-carbon unit and two molecules of CO_2. The rest of the metabolism of glucose is made up of the conversion of acetyl Co A into CO_2, NADH and $FADH_2$, which can be described by:

$CH_3CO\sim SCoA + 3NAD^+ + FAD + GDP + P_i + H_2O$ □ $CoASH + 2CO_2 + 3NADH + FADH_2 + GTP + 2H^+$

Where NAD^+/ NADH = Nicotinamide Adenine Dinucleotide ; $FAD/FADH_2$ = Flavin Adenine Dinucleotide ; GDP = Guanosine 5-Diphosphate, and GTP = Guanosine 5-Triphosphate.

The tricarboxylic acid cycle is connected to a number of side paths, including the GABA shunt, and the synthesis of acetylcholine - one neurotransmitter involved in memory formation and attention. The TCA cycle and all its associated side paths behave as one interconnected series of reactions into which the pyruvate enters. As a result both pyruvate and acetyl Co A can become trapped for undetermined periods of time as one of the intermediaries or products of one of these side paths, rather than being processed directly into the end products outlined above.

The most important purpose of the TCA cycle however is the production of NADH and $FADH_2$, which then feed electrons into the electron transfer chain to produce energy in the form of ATP.

Oxidative Phosphorylation

The phosphorylation of ADP to ATP is the key to this sysytem, and can be defined by the equation :

$ADP^{3-} + P_i^{2-} + H^+ \rightarrow ATP^{4-} + H_2O$

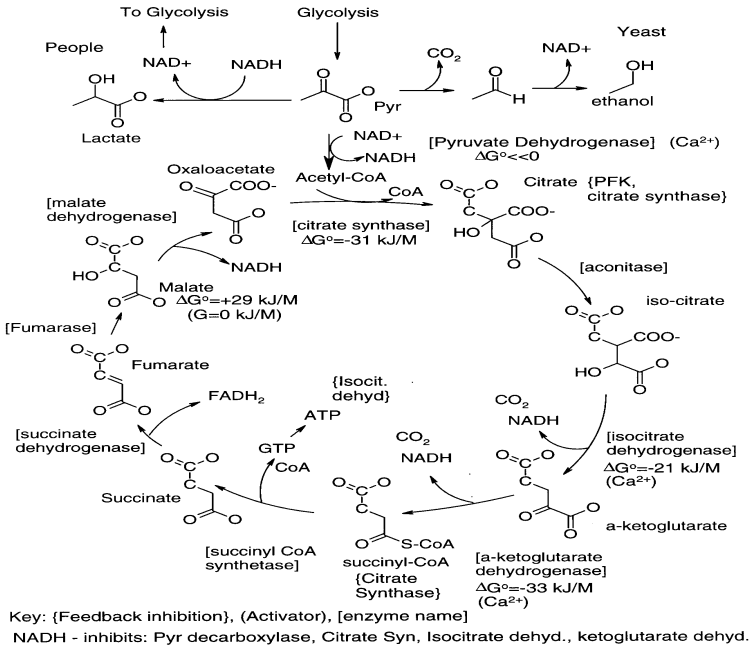
Where ADP = adenosine di phosphate; P_i = inorganic phosphate, and H^+ = proton.

Under normal physiological conditions about 95% of ATP is produced by this mitochondrial oxidative phosphorylation, while 0-5% is derived from lactate production. The electron transfer chain in oxidative phosphorylation is in reality a series of enzymes which are, by virtue of their molecular constitution, able to accept electrons. The complete system is quite complex (Figure 1.4), but the electron transfer chain has two main functions :

1) To pump H^+ ions across the inner mitochondrial membrane. This leads to a H^+ gradient which acts as the driving force for the conversion (phosphorylation) of ADP to ATP.

2) The completion of the oxidation of glucose through the transfer of electrons to molecular oxygen, the most powerful electron acceptor.

The final reaction of the electron transfer chain is the movement of an electron to cytochrome aa3 and then to oxygen to form O_2 which is then able to react with $2H^+$ from within the mitochondrial space to form H_2O. Under resting conditions the rate of this chain of reactions is limited by the availability of reduced cytochrome aa3 (which is usually only partly oxidised), as oxygen diffuses readily accross the mitochondrial membrane (Roland 1993). However under times of cognitive demand it has been suggested that oxygen may be rate limiting, and indeed metabolism may be transiently forced into the anaerobic route leading to increased levels of lactate production.



The key reactions in the Tricarboxylic Acid (TCA) or Krebs Cycle

Oxygen

The brain needs a constant supply of oxygen in order to maintain the oxidative metabolism of glucose. Although lactate and pyruvate can substitute for glucose as alternative substrates for metabolism there is no such alternative for oxygen, and as the brain does not store oxygen, even a transient disruption of supply can have deleterious consequences.

Currently it is not known exactly how much oxygen is consumed during neural activation. Positron emission tomography (PET) studies have been employed to show that the brain initially resorts to glycolysis to meet the increased energy demands during heightened activation. The debate on wether the brain resorts first to glycolysis or O2 consumption during functional activation is still ongoing. Magistretti and Pellerin (1997) propose a model that is consistent with an initial glycolytic processing of glucose occurring in astrocytes during activation, resulting in a transient lactate overproduction, followed by a recoupling phase with increased oxygen consumption.

Where is the Energy Consumed?

We know from *In vivo* and *in vitro* experiments have that most of the ATP consumption in the resting brain is linked to the sodium/potassium (Na^+/K^+) pump. Ion pumps are responsible for the establishment and maintenance of ionic gradients across neural cell membranes that allow for the passage of action potentials. The most important is the sodium pump or Na^+/K^+

ATP-ase which transports two K^+ ions into the cell and three Na^+ ions out of the cell for each ATP molecule consumed. This results in the inside of the neurons and glia being more negatively charged than the extracellular space.

The exact proportion of energy consumed by the sodium pump during brain activation is not known, but it is estimated that the ATP consumption during excitatory post synaptic potentials (EPSPs) and inhibitory post synaptic potentials (IPSPs) is greater than that during the passage of action potentials.

How is Energy Production Linked to Neuronal Activity?

As it appears that sodium pump activity may be the key factor in energy consumption during neuronal activity, it would be of great functional value for the production of ATP to be regulated in order to ensure the continuous efficacy of the pump, and such a situation would appear to exist. Neuronal activity starts with depolarisation which leads to the opening of the sodium and other voltage-gated channels. This results in increased work for the sodium pump to re-establish the ionic gradient. The re-uptake of neurotransmitters will increase its activity further. These events result in increased hydrolysis of ATP by the pump, leading to a decrease in the ratio of □ ATP□ / □ ADP□ □ $P_{i□}$ which acts as the stimulus for oxidative phosphorylation, and as a consequence an increase in ATP production. A combination of the effect of the activation of rate limiting enzymes in glycolysis and the TCA cycle leads to an upgrade in TCA cycle activity and consequently an increase in NADH production which in turn stimulates the electron transfer chain. Through this mechanism ATP production is maintained at a high level during a high rate of sodium pump activity. Once the level of sodium pump activity reduces, the level of available ATP rises and the above regulatory controls reduce oxidative phosphorylation, and the TCA cycle and glycolytic rate are slowed.

What Evidence Suggests that Brain Activation Increases the Regional Metabolic Rate?

Metabolic rate is not uniform across the brain, or even within single neurons. Research has demonstrated that changes in the metabolic rate associated with neuronal activity are localised to regions that have a large concentration of synapses, at axon terminals and dendrites, and to the axonal processes but not the cell bodies. Prolonged increases in neuronal activity can also increase the number of mitochondria in active neurons. It is a logical conclusion therefore that the density of mitochondria, and so the capacity for metabolism, reflects the long term activity level of the cell.

Regulation of Metabolism by Regional Cerebral Blood Flow

The heart pumps blood to the main cerebral arteries which subdivide into smaller arterioles and capillaries. The pressure waves created by the heart's pumping, i.e. phasic cardiac output are changed into a steady state arterial blood pressure by elasticity of the blood vessels. The brain receives 15% of the resting cardiac output (700ml/min in the adult) and accounts for 20% of basal oxygen consumption. Mean resting cerebral blood flow in young adults is about 50ml/100g brain per minute. This mean value represents two very different categories of flow: 70 and 20ml/100g per min for grey and white matter respectively (Menon 1995). Blood supply to the brain is provided by two internal carotid arteries and the basilar artery, which divides into the two posterior cerebral arteries. Importantly, the brain's blood pressure is independent of the rest of the body. The cerebral circulation is protected from systemic blood pressure surges by a specially designed branching system and resistance elements in the two types of blood vessels. The arteries and arterioles are innervated with nerve fibres which regulate their degree of contraction and hence blood pressure. For neurons and glia, the blood pressure and flow is not relevant. The important factor is whether the cells can get more glucose and oxygen at times of high demand; a factor referred to as regional cerebral blood flow (rCBF).

There are two ways in which rCBF can be increased: either by allowing more blood to pass through at the same velocity or by allowing the same volume of blood to pass through at a higher velocity. The former is the most important since it has been shown that the number of capillaries in any localised region of the brain significantly correlates with the number of synapses in the region but not with the number of cell bodies. Additionally, the density of capillaries in the brain is closely related to the density of the mitochondrial enzyme cytochrome oxidase, with more capillaries in areas rich in cytochrome oxidase. At times of high demand capillaries respond in such a way as to match supply with demand. Effectively rCBF, capillary volume and regional metabolic rate interact in such a way that more capillaries are recruited when there is a high metabolic rate, and so the rCBF increases to supply the increased demand for glucose and oxygen. There are several theories relating to the mechanism responsible for the opening of capillaries in response to increased metabolic demand and one of these involves Nitric oxide (NO). NO relaxes blood vessels and is produced by endothelial cells in response to a range of substances including acetylcholine, adenosine mono-phosphate (AMP), ADP and ATP. It is an ideal candidate for regulating rCBF, having a half life of seven seconds and an effect that disappears as soon as production

ceases. However, little is known about the distribution of NO in the brain and it remains to be seen if rCBF matches NO concentration.

At present there is no single substance that can be held responsible for regulating variations in rCBF at the tissue level. It is clear however a close relationship exists between changes in rCBF and changes in regional metabolism, and that these changes can be coupled to neuronal activity.

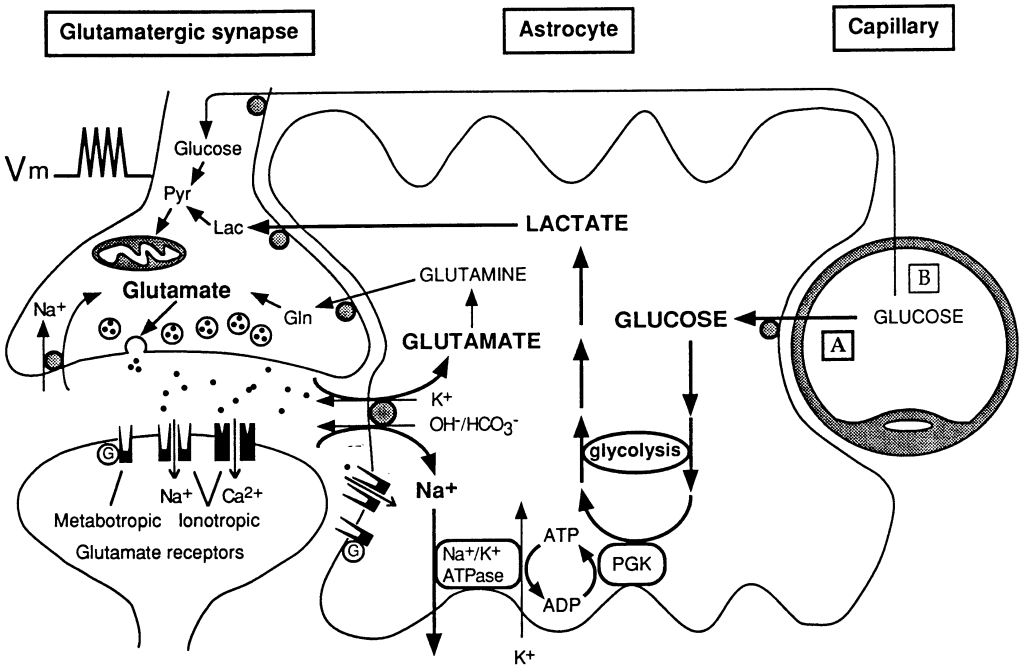
It is possible that several factors interact to mediate the relationship between neuronal activity, neuronal metabolism, and tissue blood flow. It appears that no single compound can be said to regulate rCBF under all conditions.

Brain Oxygen Consumption and Cognitive Functioning

Brain Imaging Studies

Signals detected using functional brain imaging techniques are based on the coupling between neuronal activity and energy metabolism. Positron emission tomography (PET) detects blood flow, oxygen consumption and glucose utilisation associated with localised neuronal activity. Functional magnetic resonance imaging (fMRI) is thought to detect the blood oxygen level as at least part of its signal, whereas magnetic resonance spectroscopy (MRS) identifies the spatiotemporal pattern of glucose or lactate levels. Although these offer a higher degree of sophistication than earlier imaging techniques, the exact mechanisms and cell types involved in coupling and generating metabolic signals are still debated. Recent research has suggested that there may be a degree of uncoupling of supply and demand in the early stages of neuronal activation. MRS in humans has revealed that during physiological stimulation of the activation of the visual system, a transient lactate peak is observed in the primary visual cortex (Prichard et al. 1991). These MRS data would support the proposition that there is transient anaerobic glycolytic processing of glucose during neuronal activation. PET analyses have indicated that oxygen consumption in activated brain areas does not increase in tandem with blood flow and glucose utilisation, suggesting an activity-dependent glycolytic processing of glucose in the early period of brain activation. On the other hand, other researchers have found that the degree of uncoupling between glucose metabolism and oxygen consumption during activation may actually vary, and may even not occur, depending on the type of stimulation used.

At present, the critical question of how much oxygen is consumed during brain activation remains unresolved. However a model proposed by Pellerin and Magistretti (1994), based on studies at the cellular level (below) would be consistent with an initial burst of glycolytic metabolism of glucose occurring in astrocytes, resulting in a transient lactate overproduction, followed immediately by a recoupling phase during which the lactate would be oxidised by neurons.



Schematic of the mechanism for glutamate-induced glycolysis in astrocytes durind physiological activation. From Pellerin and Magistretti (1994).

The spatiotemporal 'window' during which the lactate peak could be detected by MRS would depend on the speed of the recoupling process, and the sensitivity and resolution of the measuring technique employed. Such a model would support the hypothesis that during the processing of information in cognitive tasks, supplemental oxygen supply may compensate for a transient shortfall and augment energy production at a time of high demand, thereby leading to more efficient processing and hence improved performance.

Compromised Oxygen Delivery and Cognitive Dysfunction

Ischemia

Ischemia may be defined as an inadequate supply of oxygen supply in relation to demand, and in general terms is caused by an interruption in blood supply. Cerebral ischemia associated with systemic hypotension classically produces maximal lesions in areas where

the zones of blood supply from two vessels meet, resulting in 'watershed' infarctions. However anatomical variations lead to a wide range of possible consequences (Menon 1995)

Cerebral Blood Flow (CBF)

The blood receives 15% of the resting cardiac output (700ml/min in the adult) and accounts for 20% of basal 02 consumption. Mean resting cerebral blood flow (CBF) in young adults is about 50 ml/100gr/min., (70ml and 20ml/100g/min for grey and white matter respectively).

MICROCIRCULATION

The cerebral circulation is protected from systemic blood pressure surges by a complex branching system and two resistance elements: the first of these lies in the large cerebral arteries and the second in vessels of diameter less than 100μm.

Functional activation of the brain is thought to result in capillary recruitment, implying that some parts of the capillary network are non-functional during rest. However, recent evidence suggests that all capillaries may be persistantly open and recruitment involves changes in capillary flow rates with homogenization of the perfusion rate in a network.

CBV

Most of the intracranial blood volume (200ml) is contained in the venous sinuses and pial veins, the capacitance vessels of the cerebral circulation. In accord with the Monroe-Kelly doctrine, (intracranial volume=brain tissue+CSF+Blood), a reducion in the venous blood volume can buffer rises in volume of the other intracranial contents. Conversely, when compensatory mechanisms to control intracranial pressure (ICP) have been exhausted, even small increases in CBV can result in step rises in ICP. Mettere fig qui PVI curve.

The position of the system on this curve can be expressed in terms of the pressure-volume index (PVI), which is defined as the change in intracranial volume that produces a 10-fold increase in ICP. The higher the ICP (or lower the compliance) the lesser the volume needed to produce this effect.

CPP

The inflow pressure to the brain is equal to the mean arterial pressure (MAP) measured at the level of the brain. The outflow pressure from the intracranial cavity depends on the ICP,

since the collapse of the intracranial veins is prevented by the maintainance of an intraluminal pressure 2-5 mmHg above ICP. The difference between the MAP and the ICP thus provides an estimate of the effective cerebral perfusion pressure (CPP):

CPP = MAP – ICP

Cerebral blood flow is dependent on pressure and the vascular resistance

Flow = pressure 7 resistance

Inside the scull, intracranial pressure must be taken into account

CBF = CPP / CVR

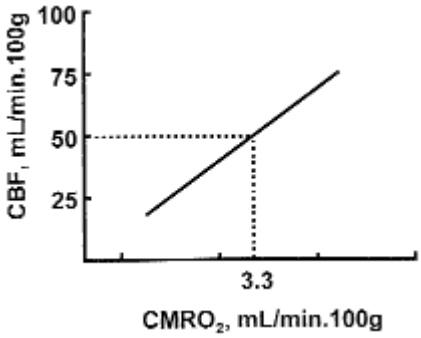
PHYSIOLOGICAL DETERMINANTS OF rCBF AND rCBV

The cerebral circulation is regulated by four primary factors: metabolic stimuli, pressure autoregulation, chemical stimuli, and neural stimuli.

Metabolic regulation

Flow-Metabolism Coupling

Cerebral metabolic regulation (sometimes called metabolic autoregulation) is the mechanism of adaptation of CBF to the metabolic demands of the brain. CBF is thus linked to brain function and metabolism so that CBF varies in parallel with $CMRO_2$.



Coupling between CBF and $CMRO_2$. Corresponding normal CBF and $CMRO_2$ values are represented in dashed lines.

This coupling of flow to metabolism is a rapid and precise regulation so that local increases in metabolic demand can be rapidly met by a local increase in CBF and substrate delivery. Several vasoactive metabolic mediators have been proposed for cerebral regulation, including hydrogen ion, potassium, CO_2, adenosine, glycolytic intermediates, phospholipid metabolites, and, more recently, nitric oxide (NO). In humans, flow-metabolism coupling is evident during a variety of motor and cognitive tasks that can be mapped using CBF techniques.

The global relationship between CBF and $CMRO_2$ can be expressed by the Fick equation where $DajO_2$ is the arterio-jugular content difference for oxygen:

$CMRO_2 = DajO_2 \times CBF$ or $DajO_2 = CMRO_2 / CBF$.

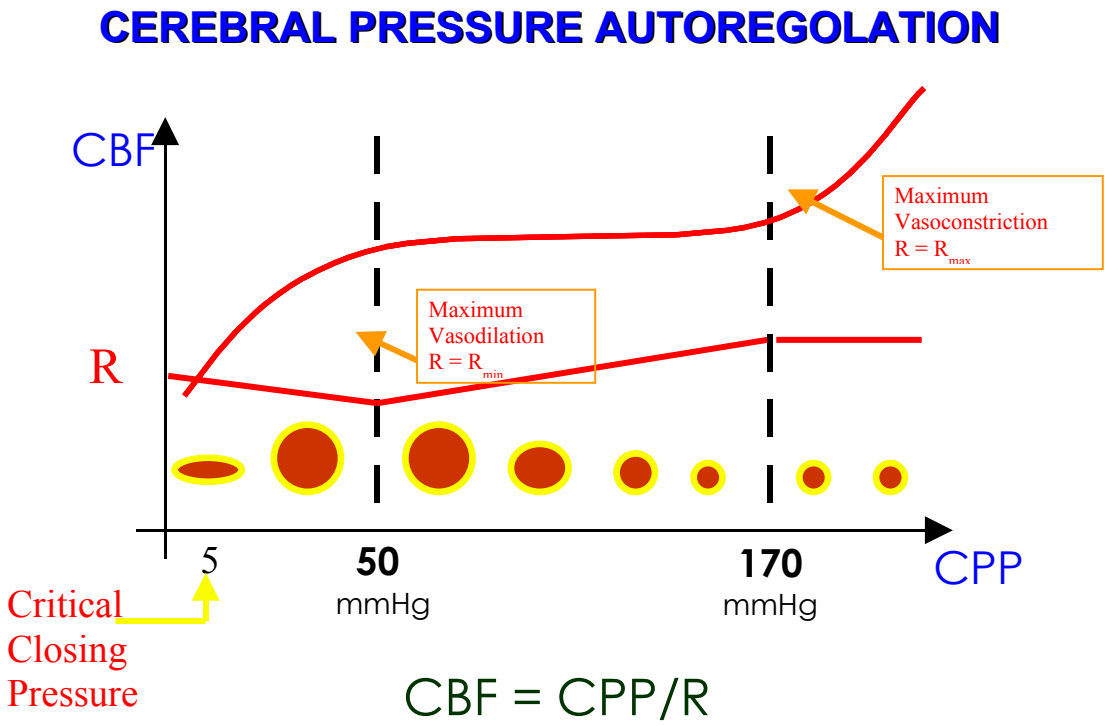
In brain injury, CBF and metabolism may be dissociated. Because of reduced synaptic activity, $CMRO_2$ consistently falls in proportion to coma depth, whereas CBF varies independently. Hence, CBF may exceed metabolic requirements, resulting in hyperaemia.

Until recently, the icreases in rCBF and 02 consumption produced during functional activation were thought to be closely coupled to the cerebral metabolic rate of utilization of 02 (CMR02) and glucose (CMRglu). However, it has now been clearly shown that increases in rCBF during functional activation tend to track glucose utilization but may be far in exess of the increase in 02 consumption. This results in regional anaerobic glucose utilization and a consequent local decrease in 02 extraction ratio and increase in local hemoglobin saturation. The cellular mechanisms underlying these observations are elucidated by recent publications which have highlighted the role played by astrocytes in the regulation of cerebral metabolism. These data suggest that astrocytes utilize glucose glycolitically and produce lactate which is then transfered to neurones, where it serves as a fuel in the citric acid cycle. Astrocytic glucose utilization and lactate production appear to be, in large part, coupled by the astrocytic reuptake of glutamate released at excitatory synapses.

Pressure Autoregulation

Coronary and cerebral circulations are predominantly regulated by local control.
In case of cardiac output insufficiency (e.g. hemorrhage), blood flow to coronary and cerebral circulations is preserved while blood flow to other organs is reduced.
Cerebral pressure autoregulation minimises deviations in cerebral blood flow (CBF) when cerebral perfusion pressure (CPP) changes by altering the cerebral vascular resistance (CVR). In clinical and experimental studies the ability of this physiologic system to maintain relatively constant CBF within a CPP of 50-170 mmHg has been convincingly documented. This mechanism is distinct from flow-metabolism coupling and cerebral vascular reactivity to carbon dioxide. While the former matches CBF to metabolism, the latter changes vascular tone in response to changes in arterial carbon dioxide tension ($PaCO_2$).
Cerebral pressure autoregulation is a complex process composed of several physiologic mechanisms operating at different rates. The restoration of CBF after abrupt changes in CPP is probably the result of changes in CVR by two components: a rapid response sensitive to

pressure pulsations followed by a slow response to changes in mean perfusion pressure. Sympathetic nervous system activity and $PaCO_2$ modulate these responses. While increased sympathetic tone and hypocapnia respectively increases and shifts the autoregulatory range at the upper and lower limits, hypercapnia and vasodilatory agents such as the inhalational anaesthetic agents reduce the autoregulatory range. A modification of the autoregulatory response is also observed in patients with chronic hypertension, where the response is preserved but the lower and the upper limits are shifted to higher levels of CPP. In circumstances where autoregulation is impaired, small variations in arterial blood pressure or CPP may lead to secondary brain hypoperfusion, progressing to ischaemia, oedema and infarction if not corrected. Furthermore, impaired autoregulatory response may be a sign of exhaustion of cerebral vascular compensatory reserve, and has been correlated with outcome.



As the benefits of detecting impaired cerebral pressure autoregulation become more evident, the need for reliable clinical tests for the assessment of this response becomes greater. The benefits of exploring new methods of assessment of cerebral pressure autoregulation can and has led to other benefits such as the ability to non-invasively estimate CPP.

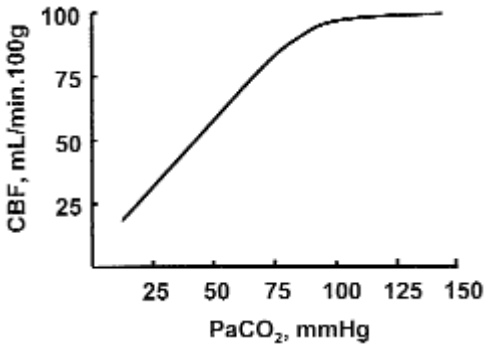
Ideally the method for evaluating cerebral autoregulation should have accuracy as well as a good temporal resolution. Transcranial Doppler ultrasonography (TCD), a non-invasive, continuous measure of CBF velocity in the conductance vessels of the cerebral circulation, has made the clinical assessment of cerebral pressure autoregulation more feasible. Furthermore, by integrating TCD into multimodal monitoring, a multifaceted picture of changes in cerebral haemodynamics over time and in response to stimuli can be obtained.

Chemical stimuli

Chemical stimuli include arterial blood gases and circulating vasoactive substances, and also cerebrospinal fluid (CSF) gases and neurotransmitters.

Arterial PCO_2

Because of its powerful vasodilator effect on the cerebral vasculature, CO_2 is a major determinant of CBF.



Changes in CBF in relationship with P_aCO_2.

At normotension CBF increases almost linearly when arterial PCO_2 ($PaCO_2$) increases from 20 to 80 mmHg, global CBF varying by about 2 to 4 % for each mmHg change in $PaCO_2$.

Grubb et al studied the CBF/PaCO2 responce curve in primates and demonstrated thatthe CBF changed by approximately 1.8 ml/100g/min for each mmHg change in PaCO2. However, in the same experiment, the CBV/PaCO2 curve was much flatter (about 0.04 ml/100g/mmHg (0.3ml/100g/KPa) change in PaCO2). It follows from these figures that whil a reduction in PaCO2 from 40 to 30 mmHg would result in about a 40% reduction in CBF (from a baseline of about 50ml/100g/min), it would only result in a 0.4% reduction in intracranial volume. This may seem trivial but in the presence of intracranial hypertention,

the resultant 5ml decrease in intracranial volume in an adult brain could result in a halving of ICP since the system operates on the steep part of the intracranial compliance curve.

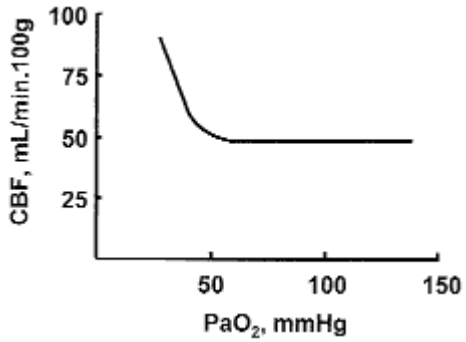
The effects of $PaCO_2$ on the cerebral circulation are regulated by a complex and interrelated system of mediators. The initial stimulus of CO_2 -induced vasodilation is a decrease in brain extracellular pH, further mediated by nitric oxide, prostanoids, cyclic nucleotides, potassium channels, and a decrease in intracellular calcium concentration as a final common mediator.

Arteriolar tone has an important influence on how $PaCO_2$ affects CBF. Moderate hypotension impairs the response of the cerebral circulation to changes in $PaCO_2$, and severe hypotension abolishes it altogether. Similarly, $PaCO_2$ modifies pressure autoregulation, and from hypercapnia to hypocapnia there is a widening of the autoregulation plateau.

The response of the cerebral vessels to CO_2 is used by anaesthesiologists and intensivists to decrease CBF; and therefore reduce cerebral blood volume and ICP. Numerous studies on CO_2 reactivity have generally demonstrated that the response is preserved during intravenous or inhalation anaesthesia. CO_2 reactivity has also been used to assess adequacy of brain perfusion in patients with internal carotid artery stenosis, or cerebrovascular disease. In severe head injury, intact CO_2 vasoreactivity is a good predictor of the effectiveness of hyperventilation (which should be reserved only for temporary emergency situations) or barbiturate therapy in controlling elevated ICP in individual patients. Furthermore, impaired cerebral CO_2 vasoreactivity is associated with a poor outcome in patients with severe head injury.

Arterial PO2 (hypoxic vasodilation)

Moderate changes in arterial PO_2 (PaO_2) do not significantly alter CBF.



Relationship between CBF and PaO_2 showing almost no effect on CBF in the normoxaemic range. CBF is greater if PaO_2 is less than 50 mmHg.

Nevertheless, CBF increases once PaO_2 drops below 50 mmHg so that cerebral oxygen delivery remains constant. However, recent TCD data from humans suggest cerebral thresholds for cerebral vasodilation as high as 64mmhg (SaO2 of 90%). This non linear behaviour is because tissue oxygen delivery governs CBF and the sigmoid shape of the hemoglobin-O2 dissociation curve means that the relationship between CaO2 (arterial O2 content) and CBF is inversely linear. These vasodilater responses to hypoxaemia appear to show little adaption with time but may be substantially modulated by PaCO2 leves. NO does not appear to play a role in the vasodilatory response to hypoxia.

Hypoxia acts directly on cerebral tissue to promote the release of adenosine, and in some cases prostanoids which contribute significantly to cerebral vasodilation. Hypoxia also acts directly on cerebrovascular smooth muscle to produce hyperpolarisation and reduce calcium uptake, both mechanisms enhancing vasodilation. Hypoxia also appears to promote release of both relaxing and constricting factors from the endothelium, the combined effect of which can either promote or attenuate vasodilation depending on the artery and species under study. In addition to chemical stimuli in blood, chemical stimuli present in the CSF such as neurotransmitters can also affect cerebral haemodynamics. Neurotransmitters can reach vasoactive levels in perivascular CSF as a results of synaptic overflow during neuronal activation or in pathological conditions.

Autonomic Nervous System

A major difference between other systemic circulations and the cerebral circulation is the relative lack of humoral and autonomic control on normal cerebrovascular tone. Hence, a maximal stimulation of the sympathetic or parasympathetic nerves alters CBF only slightly. Furthermore, there is considerable evidence that indicates there are age-related differences in cerebral resistance vessels to neural stimuli. For example, both in vivo and in vitro, cerebrovascular constrictor responses to noradrenaline or electrical transmural stimuli are greater in foetal and neonatal animals than in adult animals. The mechanism for the age-related decrease is unclear, but could be the result of such factors as loss of number or affinity of alpha-adrenergic receptors with development. However, changes in cerebrovascular sensitivity to alpha-adrenergic stimuli may not occur with age in all species. Electrical or reflex activation of sympathetic nerves reduces CBF in adult rabbits. Sympathetic nerves protect the cerebral circulation from hyperaemia associated with even modest elevations in arterial blood pressure.

The autonomic nervous system mainly affects the larger cerebral vessels, up to and including the proximalparts of the anterior, middle and posterior cerebral arteries. β1-adrenergic stimulation results in vasodilation while α2-adrenergic stimulation vasoconstricts these vessels. The effect of systemically administered α or β-agonists is less significant. However significant vasoconstriction can be produced by extremely high concentrations of catecholamines (e.g. in hemorrhage) or centrally acting α2-agonists (e.g. dexamedetomidine).

Other factors regulating CBF

Cardiac output

Although cardiac output *per se* hardly influences CBF in normal conditions, it may significantly influence flow to ischaemic regions. However, studies examining the possible relationship between a change in cardiac output and a change in CBF have, for the most part, assessed the effect of drugs that increase cardiac output during either normotension or induced hypertension. Improving cerebral perfusion by volume loading is indirectly accomplished by improving blood rheology and directly accomplished by increasing systemic arterial pressure and preventing occult decreases in systemic pressure in hypovolaemic patients.

Hematocrit

Since blood viscosity is a major determinant of vascular resistance, CBF is inversely related with haematocrit. Nevertheless, a continuing controversy questions whether CBF is purely rheologic or a function of changes in oxygen delivery to the tissue. Muizelaar and co-workers have claimed that viscosity directly participates in cerebral haemodynamic autoregulation, so called viscosity autoregulation. Some recent studies in the setting of vasospasm following subarachnoid hemorrhage have suggested that modest hemodilution to a hematocrit of 30-35% may improve neurological outcome by improving rheological characteristics and incresing rCBF. However this may result in a reduction in O2 delivery if maximal vasodilation is already present and since clinical results in the setting of acute ischemia have not been uniformly successful, this approach must be viewed with caution.

Anesthetics and CBF

Both inhaled and intravenous anesthetics can modulate CBF. This topic will be addressed further on in this booklet.

MONITORING CBF

The benefits of monitoring CBF in the brain-injured patient are becoming more apparent. In addition to avoiding the dangers of transferring critically ill patients for "single time point" measurements in the CT or PET scanner, continuous bedside monitoring may detect transient ischaemic events. Furthermore, continuous assessment of CBF permits rapid diagnoses and early therapeutic interventions, which may improve outcome. Unfortunately, many of the techniques for the bedside measurement of CBF are either cumbersome, have a large inter-observer bias, or depend on various assumptions for calculating CBF, and hence, are indirect or open to criticism. The most important available techniques, bedside and non, are the following:

- KETY SCHMIDT METHOD, AVDO2
- JUGULAR THERMODILUTION TECHNIQUE
- LASER DOPPLER FLOWMETRY
- NEAR INFRARED SPECTROSCOPY
- TRANSCRANIAL DOPPLER ULTRASONOGRAPHY
- RADIOACTIVE TRACER CLEARANCE TECHNIQUES, XENON (intracarotid, intravenous, inhaled)
- PET, SPECT
- MRI

KETY SCHMIDT METHOD

The first practical quantitative method of measuring cerebral blood flow, and now regarded as the gold standard, is the technique described by Kety and Schmidt in 1945. All CBF measurement techniques in use today are either derived from this method, or have been validated against it. This method, adapted from the original technique for the measurement of pulmonary blood flow, is based on the Fick principle. Briefly, this states that the amount of a substance taken up or eliminated by an organ is equal to the difference between the amount in the arterial blood and the amount in the venous blood supplying that organ, in the same time period.

Thus for the brain:

$$QBt = QAt - QVt$$

Where QBt is the quantity of tracer taken up by the brain in time t, QAt is the quantity of tracer delivered to the brain by arterial blood in time t, and QVt is the amount of tracer removed by cerebral venous blood in time t.

TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

The transcranial Doppler ultrasonography (TCD) is a non-invasive monitor which calculates red blood cells (FV) in the large vessels at the base of the brain using the Doppler shift principle . The most commonly insonated vessel is the middle cerebral artery (MCA) which carries about 75-80% of the ipsilateral carotid artery blood flow and thus is representative of hemispheric CBF. TCD measures velocity and not flow, and therefore, changes in FV only represent true changes in CBF when both the angle of insonation and the diameter of the vessel insonated remain constant. There is also ample evidence suggesting that the diameter of the MCA does not change significantly with changes in arterial pressure, carbon dioxide partial pressure or the use of anaesthetic or vasoactive agents. Hence, it is generally accepted that during steady state anaesthesia, changes in FV reflect corresponding changes in cortical CBF. New methods are being applied using TCD in order to measure estimated Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP) and Critical Closing Pressure (CCP) with very promising results.