

REVIEW ARTICLES

Transcranial Doppler ultrasonography in anaesthesia and intensive care

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Transcranial Doppler ultrasonography (TCD) was introduced in 1982 by Aaslid and colleagues⁵ as a non-invasive technique for monitoring blood flow velocity (FV) in the basal cerebral arteries. It is now increasingly being used in anaesthesia and intensive care for research as well as in clinical practice. The purpose of this review is to present: the basic concepts of TCD; the current status of the information obtained; its use of assessment of vascular reactivity; and applications in anaesthesia and intensive care.

Basic concepts

TCD is based on the use of a range-gated, pulsed-Doppler ultrasonic beam of 2 MHz frequency.⁵ The ultrasonic beam crosses the intact skull at points known as 'windows' and is reflected back from the moving erythrocytes in its path. The difference between the transmitted signal and the received signal is called the Doppler shift, and can be expressed by the formula:¹

$$\text{Doppler frequency shift} = 2 \times V \times Ft \times \cos\theta / C$$

where *V* is the velocity of the reflector (red cells), *Ft* is the transmitted frequency, *C* is the speed of sound in soft tissue, and $\cos\theta$ is the correction factor based on the angle of insonation (θ). In TCD, *Ft* (2 MHz) and *C* (1540 m s⁻¹) remain constant; therefore, frequency shift depends mainly on the blood FV and the angle of insonation of the TCD probe.

TCD ultrasound is pulsed.¹ This means that a pulse of ultrasound is sent out and then there is a period of 'listening'. The time interval from pulse emission to receiving will determine the depth from which any Doppler frequency shift is detected. Thus, the depth of insonated structures can be adjusted by altering the interval between emitting and receiving the TCD signal.

Within a vessel, different erythrocytes move at different speeds. The Doppler signal obtained from blood flowing

in vessels is therefore, a mixture of different frequency components. Transcranial Doppler machines use spectral analysis and present three-dimensional Doppler data in a two-dimensional format. Time is represented on the horizontal scale, frequency shift (velocity) on the vertical scale, and signal intensity as the relative brightness or colour (Fig. 1). For calculating FV, a 'spectral envelope' corresponding to the maximum FV throughout the cardiac cycle is created. This has the advantage of being relatively straightforward to create even when the signal to noise ratio is low. It also compensates for curved vessels, as the segment most closely in line with the ultrasound beam has the highest Doppler shift.¹ Once this outline is created, the spectral detail is largely ignored. Different parameters are then measured from the 'spectral envelope' (Fig. 1).

Information obtained using TCD

Technique

With TCD, three 'windows' (temporal, orbital and foramen magnum) can be used to insonate different cerebral arteries. The middle cerebral artery (MCA) is most commonly insonated because of the ease of access through the temporal window and the quality of the signal. Also the MCA carries 50–60% of the ipsilateral carotid artery blood flow,¹⁰⁵ and thus can be taken to represent blood flow to the hemisphere.

Various authors have described slightly different approaches to insonate the MCA, and readers are referred to standard texts for complete descriptions.¹⁰⁶ The subject usually lies supine. Acoustic gel is applied to the area to be examined and the probe is applied with consistent gentle force to the skin. The temporal window is defined as an area delineated by a line drawn from the tragus to the lateral canthus of the eye, and the area 2 cm above this. Moving the probe slowly and systematically over the whole area,

the examiner searches for a signal, initially starting at a depth of 50 mm. Initially, the area is scanned with the probe perpendicular to the skull. If a faint signal is found, then slight adjustments of the angle between the probe and skull may allow an optimal signal to be obtained. Some practitioners find the audio signal useful in initial identification of the vessel. If no signal is found then the process is repeated using depths from 45 to 70 mm. Having identified the vessel, the examiner should attempt to follow the vessel toward the bifurcation of the internal carotid artery (ICA) into the MCA and anterior cerebral artery. This provides greater confidence that the vessel is indeed the MCA. The bifurcation of the ICA is usually identified at a depth of 60–65 mm; the typical Doppler signal at this point has FV pulse wave images above and below the zero line of reference, representing the flow directions towards (MCA) and away (anterior cerebral artery), respectively. The depth of insonation is then reduced back to 45–55 mm following the positive deflection of the MCA FV waveform. The point of maximum deflection is taken for measurements. Insonation of the MCA can be further confirmed by the ability to follow the signal for at least 10 mm, and reduction in FV with compression of the ipsilateral carotid artery.¹⁰⁶ It is possible to find the anterior and posterior cerebral arteries through the temporal window, but it is usually possible to distinguish these from the MCA (Table 1). Finding the MCA takes some practice, but in competent hands is possible in 90% of subjects. Magnetic resonance (MR) studies have shown that using standard criteria the MCA segment with the highest blood FV is the initial segment of the vessel (M1

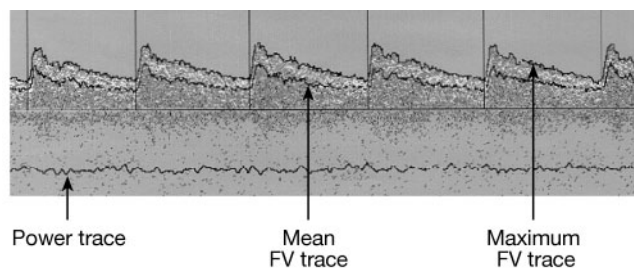


Fig 1 A typical MCA FV spectral display from transcranial Doppler ultrasound. Each waveform is 'enveloped' in the outer black line that is drawn electronically to represent the maximum velocity profile of each cardiac cycle; the inner black line represents the mean velocity profile. In clinical practice, systolic, diastolic, and mean FV are usually calculated from the maximum velocity profile. The lower black trace represents the power of the reflected Doppler signal.

Table 1 Typical patterns for identification of cerebral arteries. These are 'normal' patterns expected in individuals with 'normal' Circle of Willis anatomy and without vascular or intracranial pathology. Individual examinations may differ

Vessel	Probe direction	Depth (mm)	Direction of flow	Ipsilateral carotid compression	Contralateral carotid compression
Anterior cerebral artery	Anterior	60–75	Away	Flow reversal	Increased velocity
MCA	Perpendicular	35–60	Toward	Reduced velocity	No change
Posterior cerebral artery	Posterior	55–70	Toward	No change or increased velocity	No change

segment—main stem), and the proximal portions of the major MCA divisions.⁸⁸

Blood FV

From the FV waveform, systolic, diastolic and time-averaged mean values can be calculated. The mean FV shows least variation and is commonly used. The values for mean MCA FV in healthy adults range from 35 to 90 cm s⁻¹ under normal physiological conditions.¹²⁷ This variability, despite constant cerebral blood flow (CBF), is mainly the reflection of variability in the diameter of the MCA or the angle of insonation. Also, there is a considerable degree of variation both between subjects and within subjects measured at different times.^{58–70} This should be borne in mind when single values are documented, or when changes are claimed over time without changes in vessel diameter or angle of insonation being excluded.

In the short term, MCA FV varies cyclically by around 10%.⁴⁰ Side to side variation has been assessed and differences of more than 14% should be considered abnormal.¹²⁷ Day to day variation should be less than 10 cm s⁻¹ in 95% of individuals. Inter-observer variability has been reported as around 7.5% on the same day, and around 13% on different days.⁷⁰

Age influences MCA FV. At birth, MCA FV is approximately 24 cm s⁻¹ increasing to 100 cm s⁻¹ at 4–6 yr. Thereafter, it decreases steadily to about 40 cm s⁻¹ in the seventh decade.⁵⁸ MCA FV is affected by subject arousal, exercise,⁵³ menstrual cycle,¹² pregnancy,¹¹ and haematocrit,¹³ and these factors should be taken into consideration when changes in MCA FV are assessed.

Measures of cerebrovascular resistance

Analysis of FV waveform has been performed in a number of ways to allow estimation of the cerebrovascular resistance (CVR). Three indices of CVR have been widely used:

- (i) The resistance index (RI) described by Pourcelot,¹²⁸

$$RI = (FVs - FVd) / FVs;$$

- (ii) The pulsatility index (PI) of Gosling and King,⁴³

$$PI = (FVs - FVd) / FVm; \text{ and}$$

- (iii) The ratio of cerebral perfusion pressure (CPP) to FV: CPP/FV. This relies on the assumption that FV and CBF correlate well.

PI has been frequently used in the past. Normal PI ranges from 0.6 to 1.1. The main advantage of PI is that, being a ratio, it is not affected by the angle of insonation. However, both PI and RI may be influenced by a large number of factors including arterial pressure, vascular compliance and $P_{a_{CO_2}}$.²⁷ Furthermore, decreases in CPP, which would be expected to reduce PI may, in fact, increase it. The interplay of these factors is difficult to interpret and this limits the meaningful use of PI or RI in a clinical or research setting.

Measures of vessel diameter

If CBF can be assumed to be constant, then changes in MCA FV will be proportional to changes in the cross-sectional area of MCA. However, in both aneurysmal and traumatic subarachnoid haemorrhage, vasospasm may coexist with hyperaemia or oligoemia. One approach has been to measure FV in both the MCA and ipsilateral ICA and to use the ratio between the two as an index of vasospasm.⁶⁶ In theory, the ratio should remain constant even if overall ICA flow increases as a result of cerebral hyperaemia. However, inconsistent probe positioning over either artery may introduce errors. In an attempt to quantify the area of the insonated vessel, Giller and colleagues³⁹ have produced an area index (AI). Within the spectral envelope, each velocity has an intensity (colour on the display) that is proportional to the volume of blood with that velocity. The flow for that 'volume' of blood is thus proportional to the product of its velocity and acoustic intensity. Summing these individual flows will give a flow index (FI) proportional to total flow. Given the axiomatic relationship between flow volume, FV, and cross-sectional area, an AI can be defined as FI/mean velocity.

Limitations of TCD

FV vs blood flow

Most importantly, TCD gives information only about blood FV and not blood flow; the two are related as

$$FV = \text{blood flow volume} / \text{blood vessel diameter}.^{39}$$

Assumptions about the changes in one factor will only hold if the other remains constant. To date there is no widely accepted, reliable method of assessing vessel diameter using TCD. The corollary of the relationship between diameter and flow is such that if flow remains constant while the diameter decreases, the FV will increase. This forms the basis for using TCD to diagnose areas of vessel stenosis or spasm.

Angle of insonation

The TCD velocity spectrum outline represents the blood having the highest velocity in the segment of vessel being studied. The observed velocity is inversely proportional to the cosine of the angle of incidence between the ultrasound beam

and the velocity vector. If the angle of incidence is 0° the cosine is 1, and at an angle of 15° , the cosine remains more than 0.96. So within this range, any error caused by change in insonant angle is less than 4%. However, increasing the angle to 30° results in an error of up to 15%.⁵ Because of this, conclusions based on absolute values of FV measured on different occasions should only be made if the probe has been fixed in position throughout the study period. The power of the reflected Doppler signal is related to the total flow observed by the Doppler: this is therefore related to the angle of insonation, vessel area, and haematocrit.¹³ Some workers have taken the power of the reflected Doppler signal as a marker of a constant angle during a study.³⁹ This should be treated with caution if changes in vessel diameter or haematocrit may have occurred.

Acoustic window

The technical limitation of TCD is the absence of adequate acoustic windows, which occur in around 8% of subjects. Inadequate windows are more common in women and in older subjects.⁵² This has resulted in the development of a 1 MHz ultrasound probe to overcome this problem, which allows better penetration through bone. Early reports suggest that the proportion of individuals without acoustic windows with 1 MHz is the same as with 2 MHz probes, though some subjects are better with one probe than the other;²³ detection of emboli may be superior but overall signal quality is worse, and time to achieve a signal is longer.²³

Comparison of TCD with other techniques of assessing CBF

A number of studies have compared CBF measurement as determined by techniques such as administration of i.v. xenon,²⁰ the Kety-Schmidt method,⁹⁷ Fick principle,¹²³ and magnetic resonance imaging (MRI),¹²⁹ with TCD estimation of FV in order to ascertain whether FV can be used to assess changes in CBF.

Correlation between absolute CBF and CBFV values is poor with wide between-patient variation. However, changes in response to hypercapnia correlate well. The correlation is less good for hypocapnia. In subjects having a carotid endarterectomy, spontaneous fluctuations in arterial pressure, metaraminol and thiopental all cause an almost parallel change in ipsilateral MCA and ICA FV.⁶⁵ The changes in hemisphere blood flow have been found to be reflected in MCA FV in a proportional manner, suggesting that MCA diameter remains constant.⁹⁴

Several other workers have demonstrated that MCA diameter does not change over a range of arterial pressures and arterial partial pressures of carbon dioxide. Ter Minassian and colleagues¹²³ measured global CBF from changes in $AVDO_2$ and compared this with MCA FV in head injured patients. Their findings suggested that moderate variations in

$P_{a_{CO_2}}$ and CPP do not appear to affect the diameter of the MCA in this clinical setting. Marked hypocapnia may cause MCA vasodilation, although the direct effects of large changes in $P_{a_{CO_2}}$ on cerebral metabolism confound interpretation of this finding. Giller³⁷ measured the diameter of basal cerebral arteries directly at craniotomy and found no significant change with changes in arterial carbon dioxide. Valdueza and colleagues¹²⁹ found that within the limits of resolution of their magnetic resonance imaging matrix, MCA diameter did not change with hypocapnia and reduced CBF. These studies confirm that MCA is resistant to changes in diameter under a wide variety of physiological influences, and therefore changes in FV in these circumstances are more likely to reflect changes in blood flow.

The relationship between FV and CBF may be influenced by the underlying intracranial pathology. Brauer and colleagues¹⁴ studied 32 patients with pathology varying from brain oedema secondary to closed head injury to cerebral vascular malformations. Using acetazolamide or changes in $P_{a_{CO_2}}$, they found a correlation coefficient of 0.82 for relative changes in CBF vs MCA FV. However, subgroups formed of patients classified according to diagnosis showed wide data dispersion with poor correlation between flow and FV. This poor subgroup correlation may have been a result of the relatively arbitrary assigning of patients to groups and the relatively small numbers in each group ($n=16-38$). Further work is needed to determine the precise relationships between CBF and MCA FV in distinct intracranial pathological states. Nuttall and colleagues⁹⁷ compared CBF measured using the Kety-Schmidt method with MCA FV during cardiopulmonary bypass and hypothermia. They found little correlation either between absolute values of CBF and MCA FV or direction of change in these parameters. However, the range of CBF and MCA FV was small, so this may represent variability of both techniques rather than a failure of TCD.

Advantages of TCD over other estimates of CBF

Despite its limitations, TCD has numerous advantages. It can be performed using portable equipment, avoiding the need to move the patient. Once the learning curve has been passed, it is easy to use. It can provide continuous information, and does not involve use of radioactive substances. It can also provide more than just summary measures of flow, with information available from analysis of the waveform. It is particularly useful for investigation of vasoreactivity because of the rapid response and continuous online beat-to-beat information. Non-flow related measurements such as microemboli could also be monitored.

Cerebral vascular reactivity

The ability of the cerebral vascular bed to undergo constriction or dilatation in response to various stimuli is termed

vascular reactivity. When the stimulus is the change in perfusion pressure, the vascular response is cerebral autoregulation. It has long been known that CBF remains constant over a range of mean arterial pressures, approximately 60–160 mm Hg.¹⁰⁰ This is believed to be a protective mechanism to ameliorate the effects of surges in arterial pressure caused by movement and changes in posture. Outside this range, flow becomes proportional to pressure, with the consequent risks of hypoperfusion at low arterial pressure (<60 mm Hg) and oedema/haemorrhage at high arterial pressure (>160 mm Hg).¹⁰⁰ Although the exact mechanism of autoregulation is unclear, the underlying effect is vasodilation and vasoconstriction of the resistance vessels distal to the feeding arteries. This process is rapid being complete within seconds.³ It is not instantaneous however, which allows assessment of autoregulation using dynamic tests.³

CBF is also responsive to $P_{a_{CO_2}}$; with a linear change in CBF with $P_{a_{CO_2}}$ over the range 3–9 kPa. This represents part of the flow metabolism coupling that occurs in the cerebral circulation. Of note, this carbon dioxide reactivity may be altered in certain pathological conditions, most commonly head injury.⁷³

As TCD provides continuous information about changes in CBFV during changes in arterial pressure or $P_{a_{CO_2}}$, it has been used to create a dynamic assessment of the cerebrovascular system that is relevant to normal physiology.

Measurement of cerebral autoregulation using TCD

All the methods of assessing cerebral autoregulation assess the changes in FV secondary to the changes in CPP. The autoregulatory phenomenon has different properties, which form the basis of these tests; these properties are speed of autoregulation, the degree to which FV remains constant despite changes in perfusion pressure between the limits of autoregulation (i.e. the gradient of the autoregulatory plateau), and the limits of autoregulation.⁹⁸ The traditional approach has been to measure changes in CBF during a range of arterial pressure changes in order to reproduce an autoregulatory curve defining the limits of autoregulation and the gradient of the autoregulatory plateau.^{100 125} The method is time-consuming, and involves extreme changes in arterial pressure and the use of vasoactive agents; vasoactive agents may themselves affect autoregulation. For these reasons, simpler, preferably non-pharmacological, methods have been evolved for research and clinical use.

Static autoregulation

This refers to the assessment of the autoregulatory plateau over a small range of arterial pressure change. Using TCD, MCA FV is measured under normal physiological conditions and then repeated, once a steady state has been reached, following a 20–30 mm Hg increase in mean arterial pressure induced by a phenylephrine infusion. The index

of autoregulation is calculated as the per cent change in the CVR (calculated as mean arterial pressure/FV) per per cent change in the mean arterial pressure. If autoregulation is intact, FV change should be negligible and the value of the index should be 1. A value of autoregulatory index less than 0.4 suggests impaired autoregulation.⁹⁸

This method has been used extensively in the study of anaesthetic agents as well as in critical care situations.^{79 83 120 125} However, the data related to intra-individual or inter-individual variability with this method are limited.

Dynamic autoregulation

These tests describe the FV response to sudden changes in perfusion pressure, induced by a number of methods. The thigh-cuff method, first described by Aaslid in 1989,³ has been extensively used in anaesthesia and intensive care research.^{32 119 122 126}

In the thigh-cuff method, the MCA FV is measured continuously whilst the arterial pressure is lowered transiently, in a step-wise manner, by rapidly deflating bilateral thigh tourniquets.^{3 72} Normally, both FV and mean arterial pressure decrease initially, but because of intact autoregulation, FV recovers quicker than the mean arterial pressure (Fig. 2). If autoregulation is impaired, FV recovery follows passively the recovery in mean arterial pressure. An autoregulation index (ARI) is calculated based on the goodness of fit between the observed changes in FV and those predicted if autoregulation were as fast as possible (ARI=9) or absent (ARI=0). A normal value has been quoted as 5 (SD 1).¹²⁶ The method essentially assesses the speed of autoregulation and its validity has been confirmed in human subjects.¹²⁶ Unlike cardiac baroreceptor responsiveness, cerebrovascular response to this test appears to be unaffected by age.¹⁸ The main advantages are only a transient change in the mean arterial pressure without the use

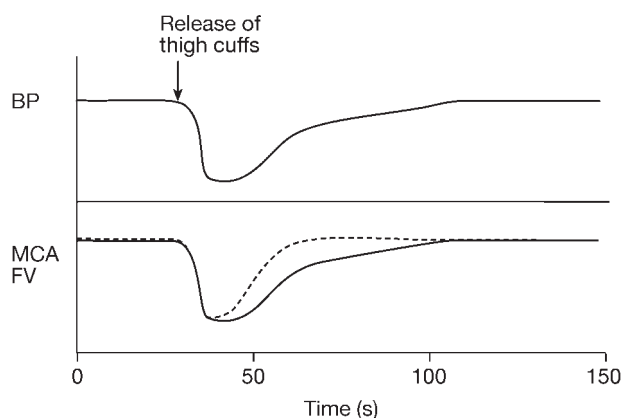


Fig 2 Diagrammatic representation of thigh-cuff method. Paired recordings of mean arterial pressure (BP) and MCA FV. On release of the thigh cuffs, arterial pressure decreases and then returns to baseline. The solid line demonstrates absent autoregulation. The MCA FV follows the changes in arterial pressure closely. The MCA FV returns to baseline before the arterial pressure. The dashed line demonstrates the presence of autoregulation.

of any vasoactive agents. The method, however, is cumbersome and the variability is much higher than other methods. Because of high variability, repeated measurements are recommended.⁷²

Transient hyperaemic response (THR) test

The THR test, first described by Giller,³⁵ has been extensively used in research and the clinical arena.^{19 111} The test involves a continuous record of the MCA FV. A brief compression (3–10 s) of the ipsilateral common carotid artery is commenced, which results in a sudden reduction in the MCA FV and presumably perfusion pressure. This provokes vasodilatation (if autoregulation is intact) in the vascular bed distal to the MCA. Thus, a transient increase in the MCA FV is seen on release of the compression.¹⁹ The test has been validated against measurement of static autoregulation.¹²⁵ Two autoregulatory indices have been described. The THR ratio (THRR) is the ratio between the FV after release of compression and the FV before onset of compression (Fig. 3). The strength of autoregulation (SA) is calculated by normalizing the THRR for changes in the mean arterial pressure of the MCA at the onset of compression.¹⁹

In theory, the THR test assesses both the gradient as well as the limits of the autoregulatory plateau without differentiating between the two.¹⁹

The test has been used to study anaesthetic agents as well as in the critical care situation. The variability (coefficient of variation <10%) is much lower than the other tests, making it suitable for comparisons.¹¹³ The main advantages are reproducibility, simplicity, and lack of pharmacological intervention. The main disadvantage is risk of embolization of carotid artery atheroma. Thus, this test is contraindicated in patients with carotid artery disease, although various studies have demonstrated a good safety record even in at risk patients.³⁴

The relative merits of different tests of autoregulation are not entirely clear. When both dynamic and static measurements were made in normal human subjects, the results of both were the same.¹²⁶ THR and thigh-cuff tests correlate in healthy volunteers,¹¹³ and both thigh-cuff and static

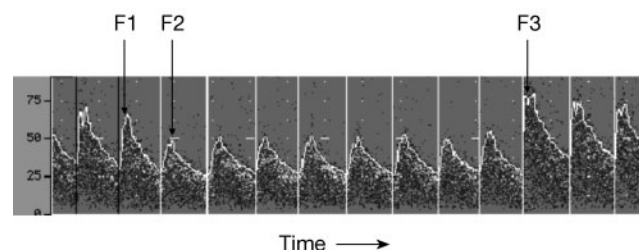


Fig 3 THR test. Following onset of ipsilateral carotid artery compression, there is an immediate decrease in MCA FV followed by a gradual increase as a result of autoregulation. On release, there is a brief overshoot because of the compensatory vasodilatation. F1, FV immediately before compression. F2, FV immediately after compression. F3, FV on release of compression. THRR is defined as: F3/F1.

autoregulation tests correlate with THR when compared directly using volatile anaesthetic agents.^{119 125} However, two advantages have been suggested for the dynamic and THR tests. First, these allow continuous monitoring of the autoregulatory response and secondly, these do not require any medications to change arterial pressure.⁹⁵ Importantly, in view of the earlier discussion of flow compared with FV measurements, relative changes in MCA FV have been shown to accurately reflect changes in ICA flow during dynamic autoregulation testing.⁹⁵

Other methods

Other methods of assessing autoregulation have been described including: phase shift with respiration, standing, and spontaneous changes over a longer period. These have not been widely used in anaesthesia or intensive care, mainly because the changes in arterial pressure induced are small and so the signal to noise ratio is low.

Carbon dioxide reactivity

The changes in CBF in response to changes in $P_{a_{CO_2}}$, induced either by changes in ventilatory pattern, inspired carbon dioxide or acetazolamide administration are well documented. These are mirrored by changes in MCA FV. Evidence from direct measurement of MCA diameter during craniotomy,³⁷ with changes in carbon dioxide and MRI measurements,¹²⁹ suggest that MCA diameter changes by less than 2%, so allowing TCD MCA FV to be used as a valid surrogate for changes in CBF. Stepwise changes in arterial $P_{a_{CO_2}}$ of around 1 kPa can be used to elicit significant MCA FV changes. Cerebral reactivity to carbon dioxide (CRCO₂) is reproducible over time.⁸⁰ Caution must be exercised, however, if CRCO₂ appears to be reduced as most studies use end-expired carbon dioxide as a surrogate for arterial carbon dioxide. The method of inducing hypocapnia may influence $P_{a_{CO_2}}$ in volunteers, and the alveolar-arterial carbon dioxide gradient may not be constant if other physiological variables have been changed.⁸¹ Generally accepted values for CRCO₂ are 2.5–5% change in FV per mm Hg (or 25–35% per kPa) change in arterial $P_{a_{CO_2}}$. Chronic hypercapnia, as in lung disease, does not change baseline MCA FV but does reduce CRCO₂.²¹ Sleep apnoea, however, appears to augment the response to hypercapnia and hypocapnia.⁶⁸ Increased age reduces CRCO₂⁶⁷ as does hypertension.⁷¹

Non-invasive estimation of CPP and zero flow pressure

Aaslid described a method of estimating cerebral perfusion pressure (eCPP) using TCD for the first time.⁴ The following formula was used:

$$eCPP = FV_m \times A1 / F1$$

(F1=amplitude of the fundamental frequency components of FV and A1=amplitude of the fundamental frequency

components of arterial pressure, where the fundamental frequency is determined by fast Fourier analysis of the waveform, and is equivalent to the heart rate. A sine wave based on this frequency would have the same mean value as the original waveform—the amplitude of this fundamental frequency is less susceptible to artefactual variation than the original pulse pressure.) Using this method in 10 patients undergoing routine ventricular infusion tests (because of supratentorial hydrocephalus) changes in eCPP strongly correlated with the changes in calculated CPP (mean arterial pressure–ICP).

In clinical practice, ICP is commonly taken to represent the effective downstream pressure in the cerebral circulation. This is based on the implication that collapsible cerebral veins with Starling resistor properties primarily determine effective downstream pressure. Thus, as is suggested for the lung, the resistance to flow may be determined by the pressure external to the vessel (ICP), rather than the downstream intravascular pressure (central venous pressure). The cerebral circulation would stop if the mean arterial pressure equals effective downstream pressure. The effective downstream pressure has also been termed critical closing pressure (implying that small vessels will close at this pressure) or zero-flow pressure (ZFP); this can be estimated by using the relationship $eCPP = \text{mean arterial pressure (Bpm)} - \text{effective downstream pressure (or ZFP)}$.

Since Aaslid's study,⁴ a number of methods have been described to estimate CPP and ZFP

$$\begin{aligned} eCPP &= FV_m \times (BP_m - BP_d) / (FV_m - FV_d),^{10} \\ ZFP &= BP_s - [FV_s \times (BP_s - BP_d) / (FV_s - FV_d)],^{26} \\ ZFP &= [(BP_d \times FV_s) - (BP_s \times FV_d)] / (FV_s - FV_d),^{84} \\ ZFP &= BP_m - [(BP_m \times FV_d / FV_m) + 14].^{107} \end{aligned}$$

Most of these methods are based on systolic, diastolic, or mean flow velocities (FVs, FVd, FVm) as related to systolic, diastolic, or mean arterial pressures (BPs, BPd, Bpm). The basic principle remains the same, that is perfusion pressure = flow × resistance. In most of the formulae, the flow is represented by FV, and the resistance is represented by the ratio between instantaneous pressure and flow, or the ratio between changes in pressure and flow during the cardiac cycle. Michel and colleagues,⁸⁴ and Aaslid and colleagues,⁴ both used the harmonic components of the waveforms to account for impedance effects. In theory, any relationship between pressure and flow in an elastic vessel during pulsatile flow, whether based on systolic, diastolic, or mean values during the cardiac cycle, when extended to the point of ZFP (which is never measured directly), assumes that the vessel's elastic behaviour remains constant throughout its diameter. This assumption remains to be proven.

Weyland and colleagues¹³² have shown that effective downstream pressure can be reasonably assessed from instantaneous pressure–FV plots by extrapolation to ZFP. Using this approach, in the absence of intracranial hypertension, ZFP is

not always the same as the ICP, suggesting that a second Starling resistor is acting, probably at the pre-capillary arteriolar position. This approach has shown a good correlation between ZFP and ICP in patients with intracranial hypertension.¹⁶

Non-invasive estimation of CPP has tremendous potential for use in the management of patients with head injury, intracranial hypertension, sub-arachnoid haemorrhage, and stroke. However, more work is needed as none of the recently described methods are fully validated; in particular, it is not clear from the existing literature as to which formula is most appropriate under given pathophysiological conditions. Recently, bench model studies suggest that Belfort's formula can reliably estimate changes in ZFP related to either changes in simulated intracranial pressure, or changes in systemic vascular compliance.¹¹⁶ In another recent study in human volunteers, where intracranial pressure can be assumed to be normal, changes in ZFP, subsequent to changes in end-tidal carbon dioxide, were reliably predicted and estimated by Belfort's formula.⁴⁸ The results of this study were similar to those published by Weyland and colleagues;¹³² one can conclude that arterial tone is the main determinant of downstream pressure of cerebral perfusion in patients or subjects without intracranial hypertension.

Studies that have attempted to evaluate whether ZFP can reliably estimate ICP have produced conflicting results,¹⁶ perhaps because they overlooked the role of arteriolar tone in determining ZFP. Validation of these different methods and their relative merits is awaited. Present, limited data would suggest that methods described by Weyland,¹³² Belfort,¹⁰ Czosnyka,²⁶ Schmidt,¹⁰⁷ and Michel,⁸⁵ although not accurate in estimating absolute ICP, can be reliably used to assess the changes in eCPP and ZFP within individuals. Although CPP, measured as mean arterial pressure ICP, is prognostic in head injury, further work is needed to clarify whether the same applies to TCD estimated CPP.

Detection of emboli

When emboli pass through an insonated vessel, a characteristic distortion of the signal occurs, often described as a chirruping sound. This is a result of signals of high intensity, but with a narrow frequency range. The current gold standard for embolic detection is human expert opinion. However, recent trials with online and offline software analysis have reported sensitivity and specificity matching a panel of experts.²⁴ Embolic detection is essentially a dichotomous variable, although altering the signal intensity decibel threshold can vary detection. Studies use thresholds from 0 to 40 dB.¹⁰³ Currently, the ability of TCD to differentiate between gaseous and particulate emboli is poor, but several groups are working on systems to overcome this.¹⁰³ A consensus document for detection and recording of emboli has been published recently.¹⁰³

Applications of TCD in intensive care

Head injury

Although a number of studies have indicated the mean MCA FV measured over time during the study period, only two studies have set out to define the changes in MCA FV that occur on a daily basis following head injury. Steiger and colleagues¹¹⁷ recorded ICA and MCA FV in 86 patients with Glasgow coma scale 3–12. These followed a typical pattern in which the FV in both vessels was decreased during the initial 24 h following trauma. Internal carotid artery FV then increased slowly to a maximum on day 5, whilst MCA velocities reached a maximum between days 5 and 7. The values then normalized over the following week. Martin and colleagues found a similar pattern in 125 patients with severe head trauma.⁷⁴ In this study, three distinct pulsatility phases occurring during the first 2 weeks after injury were described. Phase 1 occurred on the day of injury and was associated with a low CBF, normal MCA FV and normal AVDO₂. In phase 2 (1–2 days post-injury), the hyperaemic phase, CBF was increased, MCA FV increased and AVDO₂ decreased. In phase 3 (days 4–15), the vasospastic phase, CBF decreased further and MCA FV further increased. The time-courses noted in this study are broadly in keeping with other reports. Together these indicate that the peak MCA FV occurs at around 9–11 days. Basilar artery velocities are also increased in head injury, and may be higher (>60 cm s⁻¹) in more severe injuries and with traumatic vasospasm.¹¹⁴ Hadani and colleagues⁴⁶ examined basilar artery FV following head injury using TCD. They found that basilar artery FV gradually increased, beginning on day 2, as for MCA FV but reached a peak on days 4–5 after injury, somewhat earlier than the increase in flow seen in the MCA. No attempt was made to distinguish between hyperaemia and vasospasm and this may be a potential area for further studies. It is therefore possible that a normal MCA FV may be misleading regarding actual intracranial haemodynamics. However, the highest velocity recorded, whether a result of hyperaemia or to vasospasm, is an independent predictor of outcome from head injury.¹³⁹

Czosnyka and colleagues have published data from (semi)-continuous monitoring of MCA FV in combination with invasive intracranial and arterial pressure measurement. In calculating the regression of CPP on MCA FV (mean and systolic), they have assessed the ability of severely head injured patients to autoregulate in response to spontaneous fluctuations in arterial pressure. They found that loss of autoregulation early (within 2 days of insult) was correlated with poor outcome,²⁵ although other studies have found no correlation.⁹⁵ Similarly, disruption of THR autoregulation is correlated both with poor clinical state at presentation and outcome.¹¹² Moderate hyperventilation (PE'co₂ down from 5 to 3.7 kPa) improves autoregulation (thigh-cuff) in head injury,⁹⁶ but this has not been translated into clinical benefit.⁹¹ There is some evidence that hyperventilation and mannitol are only effective in lowering ICP when autoregulation

is intact.⁹⁰ Minor head injuries also disturb autoregulation although this has not been correlated without outcome.¹²⁰

These studies have significant implications for the interpretation of changes in MCA FV after head injuries. They highlight the continuously changing nature of cerebral haemodynamics in these subjects, and reinforce the need to use TCD in combination with other monitoring modalities to gain an overall understanding of changes in perfusion and oxygenation, and how these can be optimized with different interventions.

Subarachnoid haemorrhage

Transcranial Doppler in subarachnoid haemorrhage (SAH) is used to diagnose changes in vessel diameter as well as changes in flow. However, if velocities do not increase this may be a reflection of changes in vessel diameter as well as reductions in flow. Delayed narrowing or vasospasm of cerebral arteries occurs in around 50% of patients with aneurysmal subarachnoid haemorrhage. It usually occurs between 2 and 17 days after the initial event. Around a quarter of patients will have a neurological deficit as a result of vasospasm by day 14.⁵⁴

Angiography is viewed as the gold standard for assessing vasospasm. However, it has a significant risk of stroke,¹³⁸ and is not practical for repeated testing. Transcranial Doppler has therefore been widely used as a complement, although not replacement, for angiography.

At the most basic level, TCD data can be analysed in terms of FV,² with a cut off for diagnosing vasospasm of around 120–140 cm s⁻¹. If these values are used, TCD of the MCA has a relatively high specificity (85–100%) but low sensitivity (59–94%) compared with angiography¹¹⁰ (i.e. if vasospasm is diagnosed on the basis of TCD, then it is probably real, but negative results do not rule out its presence). Higher MCA FV (>200 cm s⁻¹) is associated with poorer computed tomography (CT) grade of SAH and worse outcome.¹⁰⁸ However, false negatives may occur. High grade SAH is associated with lower CBF and hence lower MCA FV. Very high MCA FV may therefore not be seen. Proximal lesions (e.g. in the internal carotid artery) may obscure clinically significant distal vasospasm.

Repeated testing of all accessible vessels improves sensitivity and allows earlier detection of possible vasospasm. Correction for $P_{a_{CO_2}}$ and haematocrit may be required if artificial ventilation or haemodilution are in progress. Using age-specific values for 'normal' FV may improve sensitivity further.¹¹⁰ A rapid increase in FV (>65 cm s⁻¹ over 24 h) is associated with a poorer outcome, and has been suggested as an indication for initiation of treatment with haemodilution, hypertension, and hyperventilation ('triple H' therapy).

Loss of autoregulation assessed by THR is associated with poorer outcome.¹¹¹ The Lindegaard index (MCA FV/ICA FV) has been used to predict the presence of vasospasm. A ratio of less than 3 is rarely found in patients with

vasospasm, and ratios of greater than 6 may distinguish moderate from severe MCA vasospasm. The overall sensitivity and specificity seem to be similar to that of MCA FV alone.¹¹⁰ Giller and colleagues have published one series³⁹ demonstrating good sensitivity and specificity of FI and AI for detecting angiographically confirmed changes in cross-sectional area associated with subarachnoid haemorrhage. However, because FI is exquisitely sensitive to probe position and technique (as a result of changes in reflected Doppler power), any changes observed must be treated with caution.

Giller's work is encouraging but is probably not sufficiently refined for widespread clinical use.³⁹ Combining mean velocities with other indices such as the presence of the dichrotic notch or the PI may provide greater sensitivity, but at present TCD cannot be regarded as a replacement for angiography.⁶⁹

At least some of the neurological deterioration seen after aneurysmal clipping may represent microemboli. One series has found that embolus detection with TCD, although rare, correlated with new ischaemic areas on CT.³⁸

Liver failure

Intracranial hypertension and cerebral dysautoregulation may complicate acute⁶⁰ and chronic liver failure,¹¹⁸ and cirrhosis.⁶² This may be a consequence of disturbed flow-metabolism coupling. Neurological complications are common and prognostically significant. Hypotension secondary to systemic vasodilation is also common and may lead to a reduced CPP even without intracranial hypertension. Studies from Larsen's group have demonstrated an absence of autoregulation in fulminant hepatic failure similar to that seen with traumatic brain injuries.⁶⁰ MCA FV and its changes are proportional to CBF in fulminant hepatic failure and during reperfusion following liver transplant, indicating that MCA diameter does not change significantly.⁶¹ Thus, TCD can be used to assess cerebral reactivity with a degree of confidence in these patients. Transcranial Doppler has been shown to be predictive of brain stem death in fulminant hepatic failure.⁶³ As with head injuries, however, there is little evidence that monitoring makes a difference to outcome.

Brain stem death

Transcranial Doppler is not a formal part of brain stem death testing in the UK, nor in the USA. However, when performed, it shows 100% specificity and 96% sensitivity.⁴⁷ Typical flow patterns are: reduced or absent diastolic flow, reverberant flow and short systolic spikes (Fig. 4).³³ However, these patterns may also be seen temporarily following bolus administration of sedatives. PI is high with markedly reduced systolic flows. It may be useful in demonstrating cerebral circulatory arrest when sedative drugs preclude formal testing.³⁰ Even if 'typical' patterns are seen with TCD, the

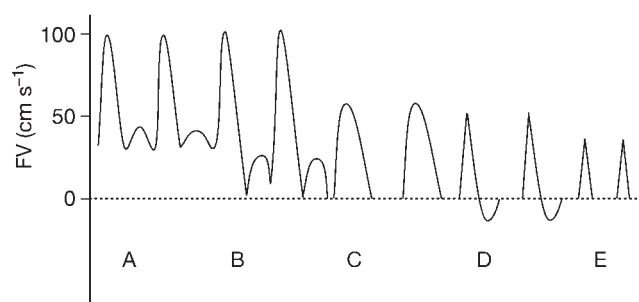


Fig 4 Diagrammatic representation of TCD traces in brain death. (A) Normal TCD waveform. (B–E) Waveforms seen in brain death. (B) Low diastolic velocity. (C) Zero diastolic velocity. (D) Reverberating flow. (E) Short systolic spikes.

diagnosis of brain stem death remains a clinical one based on clear inclusion and exclusion criteria.

Applications of TCD in anaesthesia

Neurosurgery

Transcranial Doppler has been shown to be useful in some areas of neurosurgical and neuroanaesthesia practice. It provides good detection of microemboli, which may influence surgical or anaesthetic technique. It also gives information about post-surgical blood FV, which may direct haemodynamic management after vascular surgery. Some tumour surgery and aneurysm surgery requires sacrifice or temporary occlusion of the carotid artery. The MCA FV response to manual occlusion of the carotid has been shown to be a good predictor of tolerance of sacrifice or occlusion.³⁶ Some caution is needed in analysing data during tumour surgery as tumours are associated with higher MCA FV.

Carotid endarterectomy

Monitoring for carotid endarterectomy is directed mainly towards detection of cerebral ischaemia during cross clamping, indicating when a shunt is needed, and detection of microemboli. Transcranial Doppler provides information about ipsilateral reduction in flow. Transcranial Doppler appears to be about as sensitive and specific at detecting flow ischaemia as EEG,³¹ or near infra-red spectroscopy,⁵⁵ although it may not be as sensitive as the intraoperative response of the awake patient.¹⁷ Severe reductions in FV (>90%) at the onset of clamping and an increase in PI (>100%) at the release are associated with intra- and postoperative stroke.⁶ Some authors have found a reduced rate of postoperative stroke when using these criteria to aggressively treat postoperative hyperaemia.²⁸ McCarthy and colleagues⁸² concluded that using MCA FV less than 30 cm s⁻¹, a clamp/pre-clamp ratio less than 0.6 or reduction of MCA FV more than 50% were not reliable methods for

detecting cerebral ischaemia, despite sensitivities of 83–92% and specificities of 49–77%. Transcranial Doppler guided use of shunts appears not to influence morbidity.⁹² This may be because the determinant of morbidity is not the use of intraoperative shunts, but the ability of the cerebral circulation to autoregulate when flow is restored. Using TCD to assess autoregulation rather than just FV may be the next step forward, but this is as yet unproven. Some work has been done with CRCO₂ as a predictive variable. Patients with normal CRCO₂ are less likely to need a shunt intraoperatively,¹³⁰ but this was not related to changes in outcome. Impaired CRCO₂ before operation does not correlate with intraoperative ischaemia assessed by sensory evoked potentials.¹²⁴ CRCO₂ and cerebrovascular reserve in response to acetazolamide²² are both shown to improve after carotid endarterectomy. Transcranial Doppler may be a useful tool for the assessment of neurological deterioration after surgery. The main differential diagnoses of stroke post-endarterectomy are carotid occlusion or haemorrhage secondary to hyperperfusion. TCD may be of value in distinguishing between them.³⁶

Microemboli may be detected both by visual/audio inspection of the signal and using automated analysis. Various studies have found an association between embolic rates and the risk of clinical neurological events and or changes on CT/MRI,^{6, 92} although higher embolic rates during the percutaneous transluminal angioplasty are not matched by worse neuropsychological sequelae.²² The presence of emboli during initial dissection and wound closure appears to be more important in predicting adverse events than emboli during clamping or shunting, probably because of the different pathophysiology.⁶ Emboli occurring during dissection may also be a marker of a prognostically poor group rather than a preventable event, although it is also associated with excessive handling of the carotid artery, which may be amenable to changes in surgical technique.¹¹⁵ Emboli during closure may be amenable to changes in surgical technique as this may be a result of residual atheroma and early platelet aggregation. Transcranial Doppler has been used as a guide to administration of Dextran-40 as an anti-embolic therapy after operation, with some encouraging reductions in thrombotic stroke rates.³¹

Although TCD has not been conclusively shown to improve outcome after carotid endarterectomy, it at least provides some real-time feedback to the surgical/anaesthetic team on both haemodynamics and microemboli, which may allow alterations in technique.

Cardiac surgery

Extra-corporeal circulation¹⁵ and hypothermia²⁹ both disturb autoregulation. Various studies have used TCD as an embolic monitor, and some¹⁰¹ have correlated reduced microemboli with improved outcome, in terms of length of intensive therapy unit stay and neuropsychological tests. Correlation

between TCD estimates of CBF, and Kety-Schmidt⁹⁷ and xenon clearance⁴⁴ calculation of CBF, is poor in bypass conditions. However, there are limited data on tests of autoregulation, which have a theoretical advantage of smaller inter-patient variability.

Obstetrics

Marked cardiovascular changes are seen in both normal and pathological pregnancy. Various studies have been carried out to assess whether these changes affect the cerebral circulation as well. Transcranial Doppler has been used most commonly because of its non-invasive, non-radioactive and repeatable nature.

Compared with age-matched controls, healthy pregnant women have reduced mean MCA FV.^{109 135} This is most marked in the third trimester and is because of a reduction in systolic FV.¹³⁵ Diastolic FV does not change.¹³⁵ eCPP is increased over control values.¹⁰⁹ Vascular reactivity as assessed by THR¹⁰⁹ and CRCO₂¹⁰⁹ remains unchanged. Epidural anaesthesia has no effect on MCA FV, but reduces eCPP.¹³⁷

The evidence for pre-eclampsia is less clear, perhaps reflecting a heterogeneous disease that changes with time, analogous to head injury. MCA FV is higher than in normal pregnancy,¹⁰⁹ and has been shown to be similar to non-pregnant controls.¹⁰⁹ eCPP has been found to be the same,¹⁰⁹ or increased¹³⁶ compared with matched pregnant subjects. Vascular reactivity as assessed by THR¹⁰⁹ is unchanged compared with non-pregnant controls. CRCO₂ is unchanged¹⁰⁹ compared with values during normal pregnancy. Magnesium,^{10 93} but not phenytoin⁹³ reduces eCPP.

Anaesthetic agents

Transcranial Doppler is ideal for investigating the effects of anaesthetic agents on cerebral haemodynamics because of its repeatability. Studies have been carried out using static (vasopressors), dynamic and THR autoregulation tests.

I.V. induction. I.V. induction agents depress CMRO₂ without affecting flow-metabolism coupling, thus CBF and MCA FV decrease in a dose-dependent fashion.^{56 102} Propofol has little effect on autoregulation or CRCO₂, although hypercapnia may impair autoregulation at around 8 kPa.^{50 79 83} One report has demonstrated a reversal of loss of autoregulation in head injury. Whether this translates into improved outcome in head injured patients is not known.⁷⁵

Ketamine has an 'excitatory effect' tending to increase MCA FV.⁸⁰ However, when this excitatory effect is blunted by pre-existing anaesthesia, ketamine appears to act like other i.v. anaesthetics with a decrease in CBF/MCA FV and preservation of flow metabolism coupling.⁸⁰

Volatile anaesthetic agents. Volatile anaesthetic agents have two opposing effects on CBF, and methods of assessing CBF with TCD have found contradictory results. These

agents act to reduce CBF/CBFV by reducing CMRO₂, and also to increase CBF/CBFV by a direct vasodilatory action on the resistance vessels.^{59 76 86} There does not appear to be any tachyphylaxis to this effect in humans.⁵⁹ Which effect is seen depends largely on the conditions in which the agents are tested and the dose used (Table 2). Sevoflurane has the least effect on MCA FV and tests of autoregulation, desflurane has the greatest, and isoflurane is intermediate.^{45 51 78 119 122}

Nitrous oxide. Nitrous oxide, when used alone, at concentrations of 30–60% increases MCA FV and CBF.⁴² It may also increase MCA FV and disrupt autoregulation when added to volatile anaesthetic agents or propofol.^{8 77} This may be in part a result of 'cerebral stimulation'.⁷⁷

Muscle relaxants. There are limited data available about the effects of neuromuscular blocking drugs. Using succinylcholine, no change in MCA FV has been found in patients with neurological injury.⁵⁷

Opioids. Transcranial Doppler has been used to delineate the effects of opioids, both alone and in combination with other anaesthetic agents. If other factors are kept constant (particularly mean arterial pressure and Pa_{CO₂}) then moderate doses of opioids have no significant effect on MCA FV. At high dose (3 µg kg⁻¹ min⁻¹), remifentanyl reduces MCA FV by a presumed central mechanism.⁹⁹ High dose sufentanil also reduces MCA FV.⁴⁹

Vasoactive agents. There has not been much work on the effects of vasoactive agents on MCA FV, autoregulation, CRCO₂, eCPP, or ZFP, despite their widespread use in the static tests. Norepinephrine,¹³³ dobutamine, and dopexamine⁸⁹ have been shown to have no effect on autoregulation and CRCO₂ in volunteers and in patients anaesthetized with isoflurane and propofol.¹²¹ Norepinephrine has, however, been shown to increase estimated ZFP.⁶⁴ Although this is

Table 2 The effect of anaesthetic agents on cerebral haemodynamics assessed by Transcranial Doppler. (+) Small increase, (++) moderate increase, (+++) large increase, (–) small decrease, (–) moderate decrease, (–) large decrease, (=) no change. *Effect of 1.0 minimum alveolar concentration (MAC) sevoflurane, **effect of 1.5 MAC sevoflurane, ***effect of nitrous oxide with 1.0 MAC volatile, †effect of nitrous oxide with high dose volatile, ††effect of ketamine alone, †††effect of ketamine in presence of isoflurane. For references see text

Drug	MCA FV	Autoregulation			
		THR	Static	Thigh cuff	CRCO ₂
Isoflurane	++		--	--	–
Sevoflurane	+*/=**	=	=	–	=
Desflurane	+++	–	----	--	=
Nitrous oxide (alone)	+	–			–
Nitrous oxide (added to propofol)	+	=			
Nitrous oxide (added to volatile)	+***=†	–***/=†			
Thiopental	–				
Ketamine	+††_†††				
Etomidate	–				=
Propofol	–	+	=	=	=

early work, it may suggest that increases in effective CPP with norepinephrine administration may be overestimated by taking ICP as the downstream pressure.

Glyceryl trinitrate. Glyceryl trinitrate has been studied using both THR,¹³⁴ and thigh-cuff tests,³² and appears not to affect autoregulation. It does however lower ZFP,¹³⁴ so arterial hypotension caused by glyceryl trinitrate may not reduce eCPP. Prostaglandin E1, another hypotensive agent, does not affect autoregulation as assessed by thigh-cuff tests.³² Hypotensive doses of sodium nitroprusside reduce CRCO₂.⁷⁸

Future developments

The relative ease of use and non-invasive nature of TCD for obtaining information about FV, CPP, vascular reactivity, and emboli makes it a very attractive tool in the management of a wide variety of neurological disorders in anaesthesia and intensive care. However, concerns remain about its reliability. Expanding the use of TCD will depend on the following developments.

- The situations and reasons where MCA FV is not proportional to CBF need to be more clearly defined.
- A clinically robust and reliable measure of insonated vessel area to allow distinction between vasospasm and hyperaemia is required.
- A wider understanding of the effects of individual vasoactive agents on TCD indices and tests of vasoreactivity is required to address their relative merits in patients with neurological disease.
- A clinically robust and reliable measure of eCPP and ZFP will allow new insights into the effects of anaesthetics and vasoactive agents on cerebral perfusion in patients with or without neurological disease.

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