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The use of Transcranial Doppler ultrasonography as a 'cerebral stethoscope' for the assessment and treatment of acute stroke

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ABSTRACT Transcranial Doppler ultrasonography is a safe technique, which allows non-invasive assessment of intracerebral blood flow. This article focuses on the recognition of physiological and pathological TCD waveforms. Transcranial Doppler can be used at the bedside aiding the diagnosis of stroke and complementing other imaging modalities. Due to the discovery of a new TCD finding called small vessel knock, TCD may detect small vessel arterial occlusion when conventional angiography is negative. This review provides evidence that TCD increases recanalization of occluded arteries with and without rtPA and preliminary but exciting evidence that TCD targeting of SVK using ultrasound alone can result in clinical recovery. Three cases are shown recovering on film using this new technique. Further trials are planned in acute stroke and other areas of medicine that may be associated with small vessel occlusion. This could establish TCD as one of the most important techniques used in medicine.

KEYWORDS Small vessel occlusion, stroke, TCD, therapy, thrombolysis

LIST OF ABBREVIATIONS Angle of insonation (AI), anterior cerebral artery (ACA), anterior inferior cerebellar arteries (AICA), anterior communicating artery (ACoA), computerised tomography (CT), Fast-Fourier transformation (FFT), first part of the middle cerebral artery (M1), first part of the posterior cerebral artery (P1), harmonic arterial closure (HAC), high intensity transients (HITS), internal carotid artery (ICA), magnetic resonance imaging (MRI), mean flow velocity (MFV), middle cerebral artery (MCA), National Institute of Neurological Disorders and Stroke (NINDS), patent foramen ovale (PFO), posterior cerbral artery (PCA), posterior inferior cerebellar arteries (PICA), recombinant tissue plasminogen activator (rtPA), small vessel knock (SVK), thermal and vibratory sensory analyser (TSA II), thrombolysis in brain ischaemia (TIBI), Transcranial Doppler (TCD), veretebral artery (VA)

DECLARATION OF INTERESTS Patents have been applied for the TCD treatment of small vessel occlusive disease and large vessel closure targeting SVK and HAC waveforms respectively with an exclusive licence for the NHS. Dr Syme is also a consultant with DWL Compumedics.

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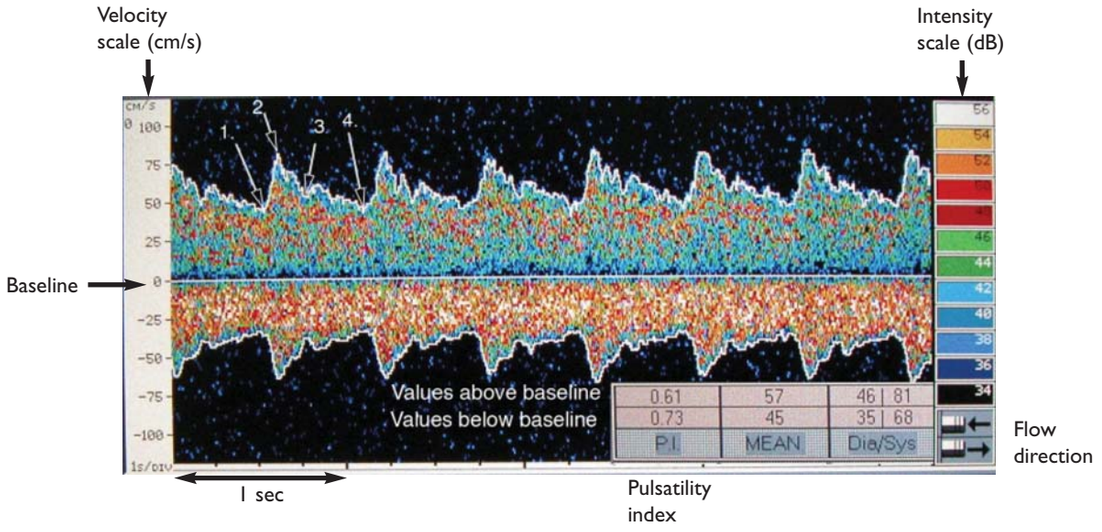
INTRODUCTION

Transcranial Doppler ultrasonography has been shown to aid the diagnosis of acute stroke and allows a non-invasive 'angiogram' to be performed at the bedside. With appropriate interpretation, TCD provides a safe noninvasive powerful addition to other medical imaging and can provide potentially valuable 'bedside' information on the intracerebral vasculature in stroke cases. This article discusses how TCD can establish a diagnosis and/or prognosis in stroke-like presentations when the CT and/or MRI scan is negative or when interpretation of the CT/MRI findings are unclear. It also presents preliminary but exciting evidence that it could be used as a future noninvasive stroke therapy with implications for other areas of medicine.

Basic principles of TCD including ultrasound attenuation, safety issues and insonation technique are briefly discussed. The article then focuses on waveform recognition in cerebrovascular disease, which is the most important aspect of TCD, including the TIBI classification and 'arterial knock' which is an ultrasound feature of occlusion. Other uses of TCD are also briefly discussed, including the detection of emboli and echocontrast studies for investigating cryptogenic stroke and the changes that can be detected in collateral flow secondary to large vessel occlusion. The final section covers the future use of TCD as a potential therapy both in conjunction with rtPA and in isolation. Recent evidence for increased recanalisation with rtPA is presented along with evidence linking small vessel occlusive disease to a new ultrasound finding called 'SVK'. Ultrasound targeting of SVK without rtPA would appear to result in clinical



1 beginning of systole. 2 peak systole. 3 diacrotic notch. 4 end diastole.
1–2 systolic acceleration. 2–3 late systolic deceleration. 3–4 diastolic deceleration.

FIGURE 1 Shows a typical TCD spectra with velocity and intensity scale on the left and right axis respectively and timescale along the base. The wave above and below the baseline reflects flow towards and away from the probe respectively. Changes in the spectra linked to the cardiac cycle are shown. This butterfly appearance is found at the division of the internal carotid into the MCA (above baseline) and the ACA (below baseline). The mean flow velocity in the ACA is normally less than the MCA.

recovery with an extensive therapeutic window. Properly constructed randomised control trials need to be established to confirm these findings.

Stroke physicians should now receive training in the diagnostic uses of TCD, which should be considered a 'cerebral stethoscope' that can be used at the bedside. In the future, TCD examination may become part of the work up of every stroke patient and targeted TCD insonation of abnormal waveforms could become established as an effective non-invasive safe treatment for stroke.

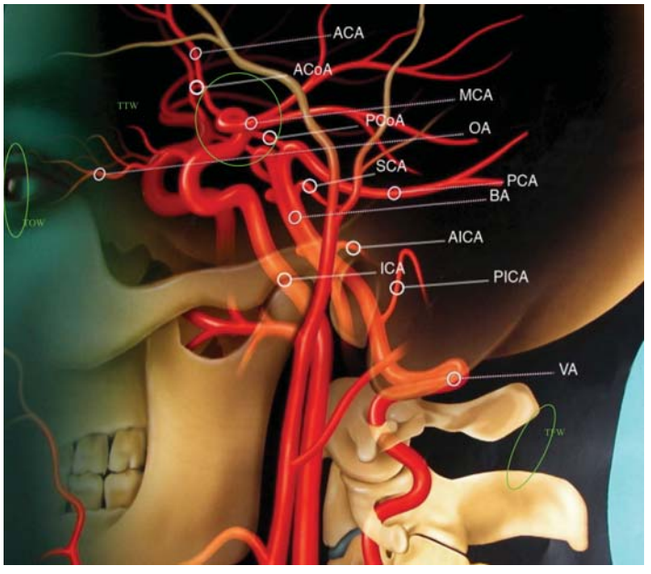
BACKGROUND AND PURPOSE

The Dussik brothers in 1942 carried out tests in Vienna to determine whether the application of ultrasound in underwater technology could be used for medical purposes. They developed a machine called the 'hyperphonograph'[1] which produced sonographic images of the head but this could not be used as a diagnostic tool because of ultrasonic wave attenuation by the skull. In the 1950s, echoencephalography was introduced allowing imaging of the midline structures of the skull,[2] and by the 1970s two-dimensional images of cerebral parenchyma in children were obtained.[3] In 1982, Aaslid and his colleagues developed the first TCD ultrasonography device that could emit ultrasound at 2 MHz allowing penetration of the skull and the measurement of the direction and velocity of blood flow in the basal cerebral vessels and in the circle of Willis.[4] Since then, TCD has been used extensively as a non-invasive method for measuring physiological parameters of blood flow in major intracranial arteries, and for evaluating vascular pathology including subarachnoid haemorrhage[5] and cerebrovascular-occlusive disease.[6,7]

However, TCD has largely remained a research tool and has been confined to specialist centres.[8] It has not gained widespread acceptance in the clinical environment because the technique has been seen as both time-consuming and operator-dependent. The interpretation of signals can be difficult due to anatomical variation within the circle of Willis[9] and the variation of sound penetration through the skull prevents its use in some individuals.[10] Furthermore, both CT and MRI provide detailed structural images, which are not obtained by TCD. However, the recent development of more powerful portable machines has allowed non-invasive examination of the intracerebral vessels at the bedside. Fast-track protocols have been developed for TCD examination in acute stroke and can aid the interpretation of early infarct changes on CT scan allowing the rationale use of rtPA.[7] In addition, there is now evidence that ultrasound promotes recanalisation of large intracerebral arteries and would appear to enhance rtPA recanalisation.[11]

PRINCIPLES

Detailed descriptions of TCD principles can be found in established texts and is beyond the scope of this article.[12,13] Doppler ultrasonography is based on the 'Doppler effect'



ACA	Anterior cerebral artery
ACoA	Anterior communicating artery
AICA	Anterior inferior cerebellar artery
BA	Basilar artery
ICA	Internal carotid artery
MCA	Middle cerebral artery
OA	Opthalmic artery
PCA	Posterior cerebral artery
PCoA	Posterior communicating artery
PICA	Posterior inferior cerebellar artery
VA	Vertebral artery
TOW	Transorbital window
TFW	Transforaminal window
TTW	Transtemporal window

FIGURE 2 Shows the anatomical distribution of intracerebral and extracerebral arteries that can be insonated using a standard TCD machine. The three main TCD insonation windows are also shown. Image courtesy of DWL-Compumedics.

first described by the Austrian Physicist Christian Andreas Doppler in 1842. This effect depends on the principle that the frequency of sound waves reflected from any object remains the same if the object is stationary but increases or decreases if the object moves towards or away from the sound source respectively. This frequency shift is called the Doppler frequency shift and forms the basis of TCD. Ultrasound normally at 1 or 2 MHz is transmitted from a probe through the skull and the probe, which also acts as a receiver, then detects reflected sound from inside the head. Sound travels at a constant 1,540 m/s in tissue, and so varying the time of the pulse allows the probe to detect a signal from different depths measured in millimetres from the skull surface. Arterial flow changes the frequency by kHz and these differences in reflected frequency are then converted into a visible spectrum using FFT. The frequency shift is dependent on the velocity of the flow of red blood cells coming towards or moving away from the probe. The machine uses this frequency shift along with the speed of sound in tissues to calculate the velocity of the moving blood. The spectrum produced consists of a velocity or frequency shift on the Y-axis with time on the X-axis. The spectra also have a colour-coding which represents the intensity at any particular frequency (see Figure 1). The intensity of the signal represents the amount of blood travelling at a given velocity. Both the velocity and intensity reflect flow. It is also important to note that the volume (sample volume) over which the signal is collected is relatively large, and so in most situations the frequency shifts cover the whole cross section of the insonated artery and can include branches of that artery or other arteries feeding that artery. Spectra are therefore composites of all these different signals. During the cardiac cycle the frequency shift also varies due to the change in the velocity of blood. The spectrum therefore resembles the waveform seen using pressure flow monitoring at the aorta or carotid. During isometric contraction, no flow is detected; at ejection there is a fast upstroke in the spectra due to a sudden increase in velocity reaching a maximum at peak systole. The diacrotic notch can then be seen at closure of the aortic valve and then the velocity gradually falls during diastole before the cycle repeats (see Figure 1). Transcranial Doppler spectra obtained from one sample volume is termed single-gated TCD. M mode Doppler[14, 15] is a multi-gated TCD combining TCD spectra from multiple sample volumes along an artery and can cover up to 6 cm of intracerebral vasculature. This can help the inexperienced operator with vessel orientation. However, single-gated TCD remains the most widely used technique and is the most sensitive for detecting abnormal waveforms. Single-gated TCD forms the basis of this review.

The signal received by the probe is also dependent on the angle with which sound hits the artery. This is called the angle of insonation (AI). The maximum signal is obtained when the AI is zero degrees (coming straight to the probe face) and minimal at 90 degrees. The artery of interest is identified from its depth, flow pattern and position and so TCD is a 'blind' technique.[16] In most situations, assumption can be made that the AI is zero. The qualitative changes that occur to the waveform as a result of arterial occlusion, stenosis and spasm are more important than changes in velocity (see below).

One of the biggest problems with TCD is the attenuation of ultrasound by tissue. Grolimund showed that the mean loss of power through the skull was up to 80%.[17] The temporal

area of the skull is the thinnest with less cancellous bone and as a consequence, ultrasound can enter the skull in this area. This provides an ultrasound 'window' to the cerebral circulation, which is called the 'transtemporal window'. This area is found between the angle of the eye and the pinna of the ear above the zygomatic ridge and is the main window for insonating the anterior, middle and posterior cerebral arteries. The other two main windows are the 'transforaminal window' through the foramen magnum insonated from the top of the neck below the occiput and the 'transorbital window' through the eye (see Figure 2).

SAFETY

Ultrasound has an impressive safety record and there have been no reported adverse effects using diagnostic TCD. However, as a result of the known problem of acoustic attenuation by the skull more powerful pulse-wave dopplers have been developed along with increased use of echocontrast agents. This increases the possibility that ultrasound could produce biological effects, which may be hazardous.

The two physical mechanisms, by which ultrasound can produce biological effects, are by non-thermal and thermal means. The main non-thermal effect is ultrasound-induced 'cavitation'. Cavitation can be stable or transient. Stable cavitation refers to the production and motion of bubbles in fluid. This oscillation results in shear stresses to cells but has not been associated with cell damage.[19] Transient 'cavitation' occurs with much higher power where the oscillations become so large that the bubbles suddenly collapse. This has the potential to disrupt cells and has been shown to increase free radicals and cell-mutagenesis in culture. At diagnostic power levels transient cavitation does not occur. Thermal effects occur through attenuation of ultrasonic energy. Attenuation is greater with increasing ultrasound frequency. Superficial heating occurs with higher- and distant heating with lower-frequency instruments respectively. There have been no reports of a thermal hazard using TCD but as a precaution when using the transorbital window the lowest power setting should be used (10% maximum) because of potential effects on the retina.[19]

TECHNIQUE

Detailed descriptions of TCD technique can also be found in established texts.[12, 13] A Transcranial Doppler examination can easily be performed at the bedside. The proximal sections of the arteries that make up the Circle of Willis (see Figure 2) are all 'TCD-visible' if an adequate window can be obtained. Transtemporal and transorbital windows, are normally obtained with the patient supine. The posterior circulation, including both vertebrals, the basilar artery and all relevant branches are examined through the transforaminal window with the patient sitting upright in a chair or on the edge of the bed with again the examiner behind the patient. If the patient cannot sit up, this window can also be found by lying the patient on their side.

Transcranial Doppler is a 'blind' technique and the examiner has to determine which artery is involved based only on probe position, depth of signal and characteristics of the TCD waveform. The middle cerebral artery is identified around 30–60 mm from the skull surface through the transtemporal window and is the most complex artery in the brain with 12 main branches which are seen as composite signals with the main branch. The flow is normally towards the probe but branches can make the signal bidirectional. Distal branches (<30 mm) are not visible. At around 60 mm the ICA divides into the MCA and the ACA, which flows away from the probe and produces a characteristic butterfly appearance (see Figure 1) which for TCD is one of the most important reference points. The Anterior cerebral artery is routinely insonated up to the ACoA but cannot be visualised beyond this point (>75–80 mm). The PCA is insonated normally at 60–65 mm and the top of the basilar artery and superior cerebellar artery at 65–75 mm by directing the probe posteroinferiorly from the MCA/ACA junction. The posterior communicating artery when open is found between the MCA/ACA junction and the PCA. Normally flow is absent in the AcoA and both PcoAs (see 'Collateral Circulation' below).

At depths of 80–90 mm flow in the MCA and PCA on the opposite side can be detected. This is important in order to demonstrate that a 'window' has been obtained in large occlusions of the MCA or PCA when detection of a signal on the ipsilateral side may be difficult and is part of the 'fast-track' MCA occlusion protocol developed by Alexandrov *et al.*[7]

Both vertebral arteries and the basilar artery are insonated from the transforaminal window and normally both the PICA and AICA can be identified.

Anomalies of the Circle of Willis are common and in one study up to 38% of individuals had hypoplastic PcoAs and 7% a foetal blood supply with the PCAs supplying the MCA territory rather than the internal carotid.[20] In addition, the depth at which arterial branches arise can vary between individuals resulting in incorrect identification of an arterial branch and when this knowledge is essential other imaging modalities are required. However, with attention to detail and with waveform recognition TCD can be used at the bedside to help with stroke diagnosis. The neurological history and examination can direct TCD examination to the correct side and site of the brain where abnormal waveforms can be identified. These can be reported in relation to the main arterial branch and depth of insonation, e.g. in a patient with dysphasia, a blunted signal found in a branch

of the left MCA at 50 mm can simply be reported as a left MCA branch blunted waveform at 50 mm using the transtemporal window. Used in this way, TCD can be used as a 'cerebral stethoscope' for stroke physicians providing a non-invasive angiogram at the bedside.

WAVEFORM RECOGNITION

Transcranial Doppler examination requires a basic knowledge of the cerebral vasculature and recognition of the characteristic arterial waveforms obtained from different arteries at different depths. The operator must also know how these waveforms change under different physiological and pathological conditions. One of the most useful parameters to note in TCD waveforms is the pulsatilty of the artery.[21] This is represented by the calculated pulsatility index:

$$\frac{\text{maximum systolic flow velocity} - \text{end-diastolic flow velocity}}{\text{mean flow velocity}}$$

Both flow velocity and PI are affected by blood viscosity and blood pressure.[22] Low viscosity due to severe anaemia or a raised end-tidal CO_2 results in high velocity and reduced pulsatility (Vasomotor reactivity) due to vasodilatation (Figure 3A). This occurs in all arteries and resembles that seen in an artery supplying an AV malformation (low resistance).[23] High blood viscosity and low end-tidal CO_2 do the opposite. High blood pressure increases (Figure 3B) and low blood pressure decreases the PI respectively (cerebral autoregulation) due to vasoconstriction and dilatation. Thus, the brain maintains a constant flow despite these physiological changes. Taking account of these physiological variations is important when interpreting the changes in waveform associated with occlusion, stenosis (see Figures 3C and 3D) or haemorrhage.[24]

Demchuk *et al.*[25] have classified changes found in association with large arterial occlusion, in the TIBI classification which categorizes TCD waveforms found in association with recanalisation during rtPA therapy at or just beyond the site of occlusion. The range of TIBI score is from 0–5, with TIBI 0 absent, 1 minimal, 2 blunted, 3 dampened, 4 stenotic and 5 normal flow, and waveform examples of this are shown in Figure 4. If a clot causes complete obstruction to flow then no frequency shift occurs and so no doppler signal is detectable and is termed absent flow, but care has to be taken that a 'window' has been obtained.[7] However, the complete absence of flow at the clot site tends to be rare since movement of blood around the clot often produces noise around the baseline which is described as minimal flow (Figure 4A). Reverberating flow (Figures 4B and 4C) is another form of minimal flow and can sometimes be detected proximal to the clot. It resembles the arterial signal seen in patients with brain death due to raised intracranial pressure and that found in subclavian steel.[26] Another form of minimal flow can be seen at the clot site, where low intensity systolic flow can be found due to high resistance with no flow during diastole (Figures 4D and 4E). However, this is non-specific since a similar waveform can be found in the presence of an intracerebral haemorrhage, due to raised intracranial pressure (Figure 4F). Distal to the clot, the artery is fully vasodilated and provided flow is present, the arterial signal has a low pulsatility index, velocity and intensity (Figure 4G). This is termed 'blunted flow' and when less severe, 'dampened flow'. These changes distal to a clot are similar in appearance to the arterial waveform found in the MCA associated with severe ipsilateral internal carotid artery stenosis when the collateral blood flow is inadequate (see Figures 3C and 3D). Distal MCA stenosis can be missed with TCD[27] because distal MCA branches are invisible. This will also be the case for distal ACA stenosis. Extracranial stenosis also reduces the sensitivity of TCD for detecting intracranial stenosis due to a reduction in the MFV.[28] However, the waveform changes in stenosis show characteristic changes and TCD estimates of stenotic flow have been shown to correlate well, if not better, with that found using magnetic resonance arteriography[29] and progression of stenosis identified using TCD has also been shown to predict further vascular events.[30] With a tight narrowing (>50% reduction in lumen diameter) due to acute clot or atheroma the velocity increases dramatically at the site of the narrowing (MFV ≥ 80 cm/s and a velocity difference of ≥ 30% compared with the control side).[31] Although the velocity increases due to vessel narrowing, the blood flow is still restricted and so the signal has a lower intensity. There may also be turbulence at the baseline and sometimes a bruit can be detected. However, this waveform is not unique to stenosis (Figures 4H and 4I) and can be found with arterial spasm due to a subarachnoid haemorrhage (Figure 4J) or a small to moderate intracerebral haemorrhage (Figure 4K). Stenosis and spasm can be distinguished by identifying (using a small sample volume) whether the above changes occur over a small arterial segment (stenosis) or over a longer segment and/or involve multiple arteries (spasm). Confusion can also occur when stenotic-like signals occur due to increased collateral flow through hypoplastic communicators. In most situations PIH does not produce spasm but reduces diastolic flow due to a local increase in pressure and apparently normal signals can be obtained in the presence of a haemorrhage. Thus, TCD spectral changes associated with haemorrhage need interpretation by an experienced operator. This is illustrated in Figure 4L and 4M which show the left and right MCA waveforms respectively obtained from a patient with a small basal ganglia haemorrhage on the left. Both these waveforms would be considered to demonstrate normal flow but on closer inspection there is a pulsatility difference between Figures 4L and 4M with increased pulsatility in 4L with a reduced diastolic flow compared with Figure 4M. Thus, when an unexplained difference is pulsatility or a stenotic-like signal is found, the operator should be alerted to the fact that a haemorrhage could be present and further imaging is required before any assumptions can be made about the TCD findings. However, used in conjunction with

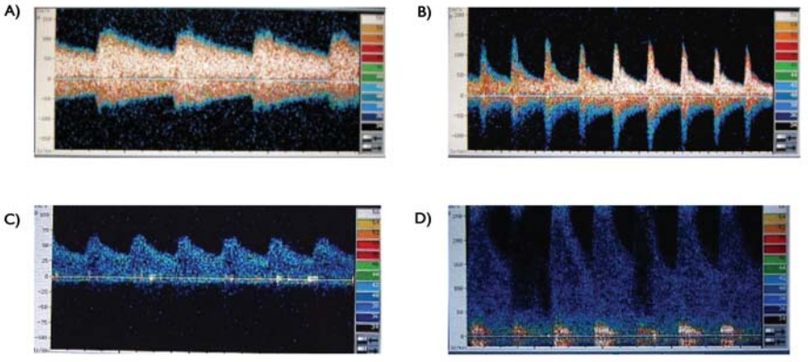


FIGURE 3 A) Lower pulsatilty associated with anaemia; B) Increased pulsatility associated with severe hypertension; C) low pulsatility and intensity in a middle cerebral artery associated with ipsilateral; D) internal carotid artery stenosis (low intensity, high velocity, bruit at baseline).

a CT scan these TCD findings provide extremely useful information for the examining stroke physician.

The Transcranial Doppler signal seen in larger arteries proximal to the clot varies depending on the size of the distal obstruction and proximity to the clot. With small distal branch occlusion the main feeding vessels can be normal (see Figure 1) particularly with good collateral circulation (see below). When larger occlusions occur the signal also becomes dampened (Figure 4N) with a slight reduction in intensity, velocity and PI. With more severe distal obstruction the signal in the larger feeding vessel shows further blunting (Figures 4H (composite blunted waveform at baseline associated with a stenosis), 4O and 4P) with little change in intensity but a further reduction in velocity and pulsatlity. The reduction in pulsatilty is likely to be due to dilatation of the proximal artery and reflects the elasticity of this artery and the availability of open branches or perforators to allow some flow through the artery proximal to the occlusion.

Alexandrov *et al.*[32] have used the TIBI score as a measure of the severity of arterial obstruction but, as discussed above, changes in arterial waveforms vary depending on the proximity to the clot, the size of the clot, the size of the occluded artery and not just the degree of occlusion. This, along with the lack of specificity of certain TIBI waveforms, means that the examiner has to be cautious when using this classification in acute stroke. Furthermore, any assumption about the degree of recanalisation can only be made with a fixed probe position monitoring at a single site.[11] Recanalisation at a proximal artery may also not reflect opening of distal branch occlusion and may explain why no correlation was found between apparent increased ultrasound-associated recanalisation measured using the TIBI score and clinical outcome.[11]

Emboli can also be detected using TCD because they produce unidirectional HITS (>3 dB over background) anywhere in the cardic cycle (see Figure 5A) and have a popping sound.[33] Gaseous and solid emboli have a similar appearance but can be distinguished by slightly different frequency shifts.[34] This characteristic appearance of gaseous emboli can also be used to easily identify right to left shunts in patients with cryptogenic stroke and PFO following agitated saline injection[35] (see Figure 5B). The feeding artery to an arteriovenous malformation has a characteristic waveform with a high velocity and intensity with low pulsatility due to the low pressure in the malformation and resembles that seen in severe anaemia (see Figure 3A).

Systolic high intensity signals can also be found with severely raised intracranial pressure and brain death.[36] This systolic thump has been termed arterial 'knock' because it has a knocking quality. Immediately before a clot, a similar high intensity, low velocity thump can also be detected. This is often associated with diacrotic reflection at aortic valve closure. Figure 5C shows this signal in an occluded internal carotid artery.[31, 37] Since Doppler detects movement, this signal has to be caused by a small movement of the clot away from the probe during systole and movement towards the probe at closure of the aortic valve. The author has described similar signals to that found in internal carotid occlusion in association with small vessel occlusive stroke and has named this 'small vessel knock'. These high intensity signals are also seen at the beginning of systole and at the diacrotic notch, repeating with each cardiac cycle and are found in the 300 Hz region of the spectra which can be filtered by some TCD machines. Although it is unlikely that current imaging technology will allow demonstration of a clot in a small artery causing SVK, the similarity between SVK and knock at proven ICA occlusion mean that both share similar frequency shifts and support the view of the author that SVK is caused by clot movement at small vessel occlusion. Small vessel knock can occur in association with both MRI positive and negative stroke-like deficits[38] and continuous insonation of SVK often reveals an underlying waveform with a pulsatilty and

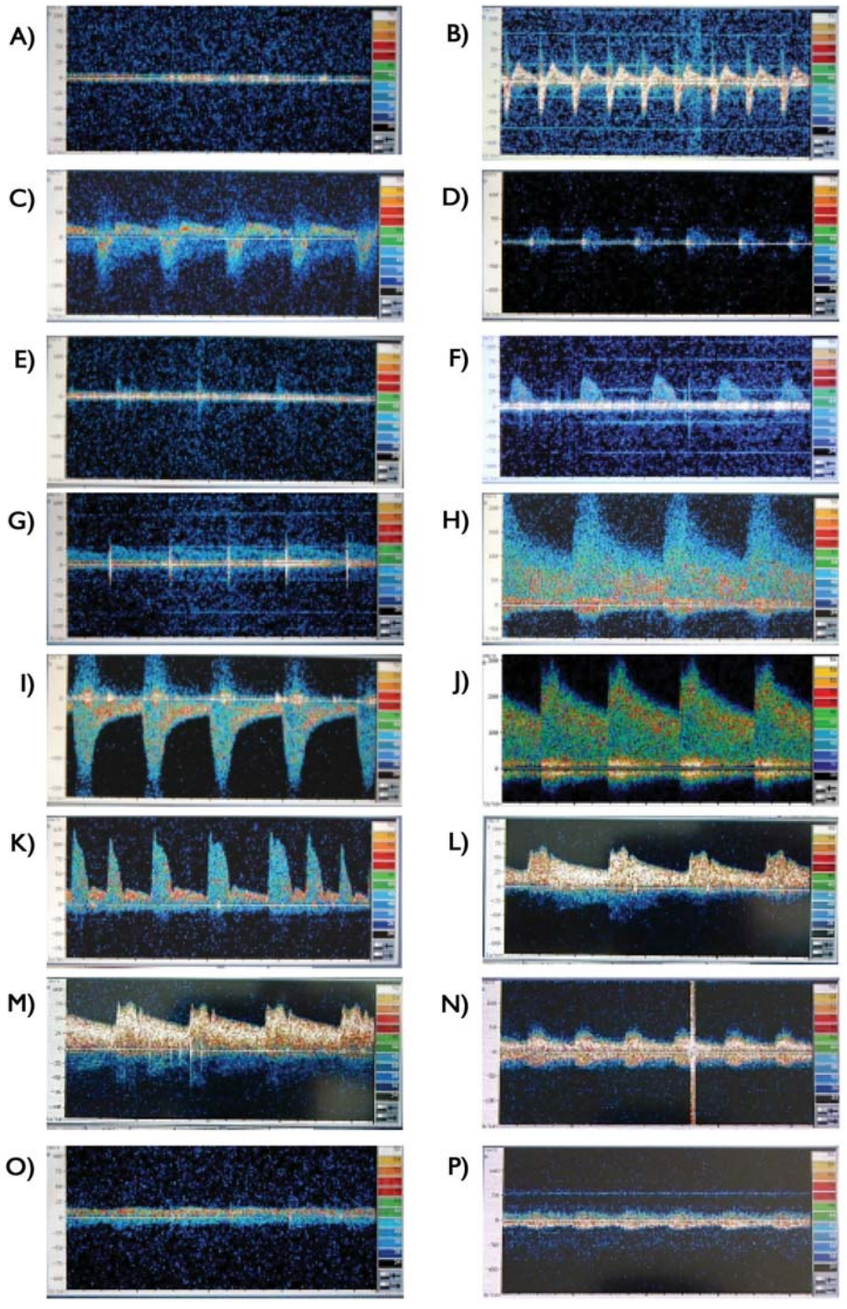


FIGURE 4 A) Absent signal (TIBI 0). No flow can be detected but the noise at the baseline is consistent with an occluded large artery; B) Reverberating flow in a patient with brain death; C) Reverberating flow in the ACA in a patient with innominate artery stenosis. A similar waveform can be found in the basilar artery with subclavian steel; D) Minimal low intensity flow with no diastolic component associated with arterial knock (white triangles) (TIBI 1); E) Minimal flow associated with MCA occlusion; F) Minimal systolic flow with no diastolic component due to a large intracerebral haemorrhage following a brain biopsy of a cerebral metastasis from a Wilms tumour (patient had a successful evacuation and survived); G) Blunted signal (TIBI 2) low pulsatility and intensity associated with arterial knock (white lines); H) MCA stenosis (TIBI 4) with a composite blunted signal (TIBI 2) at the baseline; I) Basilar artery stenosis in a patient with vertebrobasilar insufficiency; J) MCA spasm associated with a subarachnoid haemorrhage. (Image courtesy of the Neurosurgical Unit, Newcastle General Hospital); K) MCA pulsatile flow with poor diastolic flow associated with a PIH; L) Left MCA (TIBI 5) and M) Right MCA (TIBI 5) in the same patient. The diastolic flow is reduced in (L) due to a small PIH in the basal ganglia on the left; N) Dampened MCA proximal high intensity waveform (TIBI 3) associated with an MCA occlusion. This is likely to occur as a result of flow through collaterals and arterial elasticity; O) Blunted low intensity waveform associated with knock (white lines) (TIBI 2) at or just distal to the site of occlusion; P) Blunted MCA proximal high intensity waveform (TIBI 2) which changed to (N) during insonation.

direction of flow consistent with a small arterial signal (see Figures 5K–5N). An example of SVK can be seen in the left vertebral artery of a patient with diplopia (see Figure 5D) and in the ACA of a patient with vascular dementia and widespread MRI evidence of small vessel vascular disease (see Figure 5E).[39,40] It is often hidden by the main arterial waveform (see Figure 5F). The author has also consistently found arterial knock which resembles ICA-occlusive knock in distal branches of the MCA following proximal Middle cerebral artery occlusion (see Figures 4G and 4O). It is the view of the author that knock in its various forms represents the true ultrasound finding of arterial occlusion.[31,37–40]

The author has also found a further high intensity blunted signal resembling a first harmonic with a low pitched humming sound in association with ischaemic occlusion, haemorrhage, tumour and migraine (see Figure 5G). Unlike the normal intensity blunted waveform proximal to occlusion, continuous ultrasound insonation results in changes to this waveform within minutes, resulting in an open artery with increased signal velocity, pulsatility and reduction in intensity (see Figures 5G–5I). The rapidity of opening and high intensity of the artery signal suggests that it is not occluded but would appear to be shut down ('closed'). As a result the author has named this waveform HAC. Harmonic arterial closure may form part of a spectrum of hyperintense waveforms seen in larger arteries proximal to any distal obstruction. All can respond to ultrasound targeting (see Figures 4A, 4P and 4N are from the same patient with MCA occlusion and these changes occurred over 20 minutes of targeted TCD insonation). However, HAC waveforms tend to be smoother than the blunted signal seen in Figure 4A and are much more sensitive to ultrasound.

COLLATERAL CIRCULATION

Apart from the waveform changes associated with either occlusion or haemorrhage at the site of the stroke, blood flow changes can occur distal to the stroke site due to increased collateral flow. This collateral flow is important to reduce infarction size and, following MCA occlusion, can easily be assessed at the bedside using TCD.

The mean flow velocity of the MCA is normally greater than that for the ACA or PCA. With an ipsilateral proximal MCA occlusion (M1 occlusion) the contralateral flow in the ACA may become greater than the contralateral MCA (see Figure 5J), the ACA and ophthalmic artery on the ipsilateral side may show flow reversal and the proximal PCA (P1 component) ipsilaterally may also increase with flow in the PCA>MCA. Bruits or even stenotic-like flow may be detected in the AcoA and the ipsilateral PcoA if they are hypoplastic. With excellent collateral flow, these changes may be all that allows the detection of an occlusion of the ipsilateral MCA and also explains why severe stenosis or occlusion of an ipsilateral internal carotid can be associated with a normal ipsilateral MCA waveform and only a minor stroke or a TIA. Thus, subtle changes of an ipsilateral MCA waveform when associated with the above changes are consistent with an occlusion in this MCA. Furthermore, a normal MCA waveform ipsilaterally does not exclude an extracranial internal carotid occlusion or stenosis. If this is suspected then a carotid duplex examination must be performed. It also follows that if the MCA waveform shows decreased pulsatlity and/or reduction in MFV due to an ipsilateral ICA stenosis then this patient is at higher risk of a cerebral event if the carotid occludes (see Figures 3C and 3D). This compensatory change in flow can be revealed by the TCD operator by raising the end-tidal CO_2 either by increasing the inspiratory CO_2[41] or by a patient breath-holding test.[24,42] A raised end-tidal CO_2 normally increases the MFV through vasomotor reactivity[43] but in areas of ischaemia, where blood is provided from distal sites, this results in only a small increase and may even result in a paradoxical fall in MFV because the distal donor site vasodilates reducing donated blood to the ischaemic site. Following MCA occlusion, anomalies of the circle of Willis[9] can result in a lack of collateral flow, larger hemispheric infarction and even death.[44]

FUTURE TCD THERAPY

Stroke is currently the third biggest cause of mortality and the most important cause of disability in the UK. In the future, an expected reduction in stroke mortality with a predicted increase in the proportion of elderly is likely to increase the burden of stroke worldwide.[45] This makes it essential to find effective acute treatments for stroke. Treatment for primary intracerebral haemorrhagic stroke is mainly supportive and early surgery has not been shown to be beneficial.[46] Current treatments for ischaemic stroke are also poor with aspirin reducing death or dependency in ischaemic stroke at six months by only 1%.[47] Neuroprotective agents have also proved disappointing.[48] The most effective acute treatment is rtPA, which needs to be given within three hours of stroke onset. This is based on one favourable study, the NINDS part 2.[49] Even recombinant tissue plasminogen activator requires eight to nine patients to be treated for recovery of one patient with minimal benefit, and symptomatic haemorrhage can result in 1 in 16 patients. Failure of recovery with rtPA may result from inadequate recanalisation. This review will now focus on exciting new evidence that TCD appears to increase arterial recanalisation by rtPA in large arterial occlusion. This may reduce infarct size or allow smaller doses of rtPA to be given so reducing the haemorrhagic consequences of rtPA. Preliminary evidence will also be presented that TCD in isolation may produce arterial recanalisation and clinical recovery in small vessel occlusive disease.

ULTRASOUND-ENHANCED rtPA THROMBOLYSIS

In a recent randomised control trial, Alexandrov *et. al.* have shown that increased recanalisation of large MCA occlusion (M1) occurs using a combination of exogenous rtPA and diagnostic ultrasound (2 MHz) compared with rtPA alone.[11] The mechanism for this is still unknown. However, it has been shown that high power ultrasound at low frequency (<1 Mhz) can increase clot lysis *in vitro* in the presence of rtPA[50, 51] by increasing rtPA clot penetration and cross link exposure. Alexandrov and his colleagues showed that the combination of ultrasound and rtPA was not associated with an increase in itracerbral haemorrhage and the authors concluded that the combination of ultrasound and rtPA appeared to be safe. All patients in this study had large (M1) occlusions of the middle cerebral artery and insonation focused on the proximal M1 segment. Although there was a trend towards clinical recovery, this was not significant. The lack of clinical recovery, despite increased recanalisation, could be explained by an immediate infarct following large arterial occlusion or by failure to open distal MCA branches (see discussion above). This needs to be determined with appropriate trials (see below).[11]

ULTRASOUND-ENHANCED THROMBOLYSIS WITHOUT rtPA

It has also been shown that minimal fluid stress on endothelial cells can result in increased nitric oxide synthesis[52] and the release of endogenous tPA.[53] This could result in vasodilatation and endogenous thrombolysis with ultrasound alone. In support of this, Cintas *et al.*[54] have reported that patients within six hours of symptom onset with acute MCA main stem occlusion, who were not treated with rtPA showed recanalisation in five of six patients (83%) beginning after a few minutes of continuous exposure to low-intensity ultrasound. This group reviewed previous studies of early spontaneous recanalisation in similar patients not continuously exposed to ultrasound, and found that the rates of recanalization were much lower ranging from 0–18%. However, like Alexandrov *et al.*[11] increased recanalisation of MCA occlusion did not produce clinical recovery. In large arterial occlusion, at least the time to irreversible infarction would appear to be short and measured in hours. Indeed, Transcranial Doppler evidence of recanalisation without recovery suggests that an infarct has already become established. In contrast to large arterial occlusion, the author has reported that targeting SVK (see above) using diagnostic ultrasound (2 MHz, <750 mW) in the absence of rtPA can result in complete clinical recovery of stroke-like deficits over an extensive time window associated with changes to the SVK induced by ultrasound (see Figures 5K–5N).[38] A patient with sudden onset SVK-associated complete hemianaesthesia, including a loss of corneal reflex for 26 hours, can be viewed making a complete recovery during TCD-targeted SVK insonation.[55] A shortened version of this film along with two other cases can be viewed on the College website. (A case of hemianaesthesia; A case of severe dysarthria; A case of diplopia.) These cases are examples linking SVK to small vessel occlusive stroke. Recovery over an extensive time window challenges the time considered for recovery of the ischaemic penumbra following small vessel occlusion which appears to last as long as collateral blood flow keeps the ischaemic tissue alive and arterial remodeling has not taken place. Targeting SVK would also appear to show benefit in all cerebral arterial territories.[38] Recently, it has also been shown that SVK in branches of the vertebral artery is associated with the lateral medullary syndrome with dissociated sensory loss.[38] This has led to a new hypothesis linking common conditions such as irritable bowel syndrome, cardiac syndrome X and reflex sympathetic dystrophy, to SVK in branches of the vertebral arteries.[56]

Figures 5G–5I shows the opening of one of two HAC arteries (other not shown) in a patient who, three months before this, had dissected his left internal carotid sustaining an MCA infarct, hemiplegia and dysphasia. Opening of these HAC vessels resulted in apparent improvement of his dysphasia. The author has published further examples of HAC vessel opening associated with an intracranial haemorrhage and migraine, which resulted in recovery of hemiparesis.[44] These cases, although anecdotal, provide the exciting possibility of TCD reversal of neurological stroke-like deficits due to HAC opening associated with ischaemic and haemorrhagic stroke. Thus, TCD targeting of HAC waveforms may offer future treatment for these conditions. Furthermore, the finding of HAC arteries in association with large arterial occlusion may be linked to the ischaemic penumbra associated with these occlusions.

FUTURE TCD TRIALS

The reason for the failure of significant stroke recovery despite increased recanlisation of the MCA needs to be determined. As discussed above, this could be caused by early infarction or a failure of distal recanalisation. A study designed to target distal branches of the middle cerebral artery following M1 occlusion should now be performed. Targeting 'knock' in the MCA may also produce similar effects to targeting SVK. The development of carbon fibre TCD probes (DWL Compumedics) will also allow the future possibility of insonation during diffusion/perfusion weighted MRI examinations.

A series of randomised control trials are now being designed to determine the effectiveness of ultrasound targeting of SVK in stroke patients. Recently, the author has used a quantitative neurosensory analyzer TSAII (Medoc Ltd) to measure SVK-associated dissociated

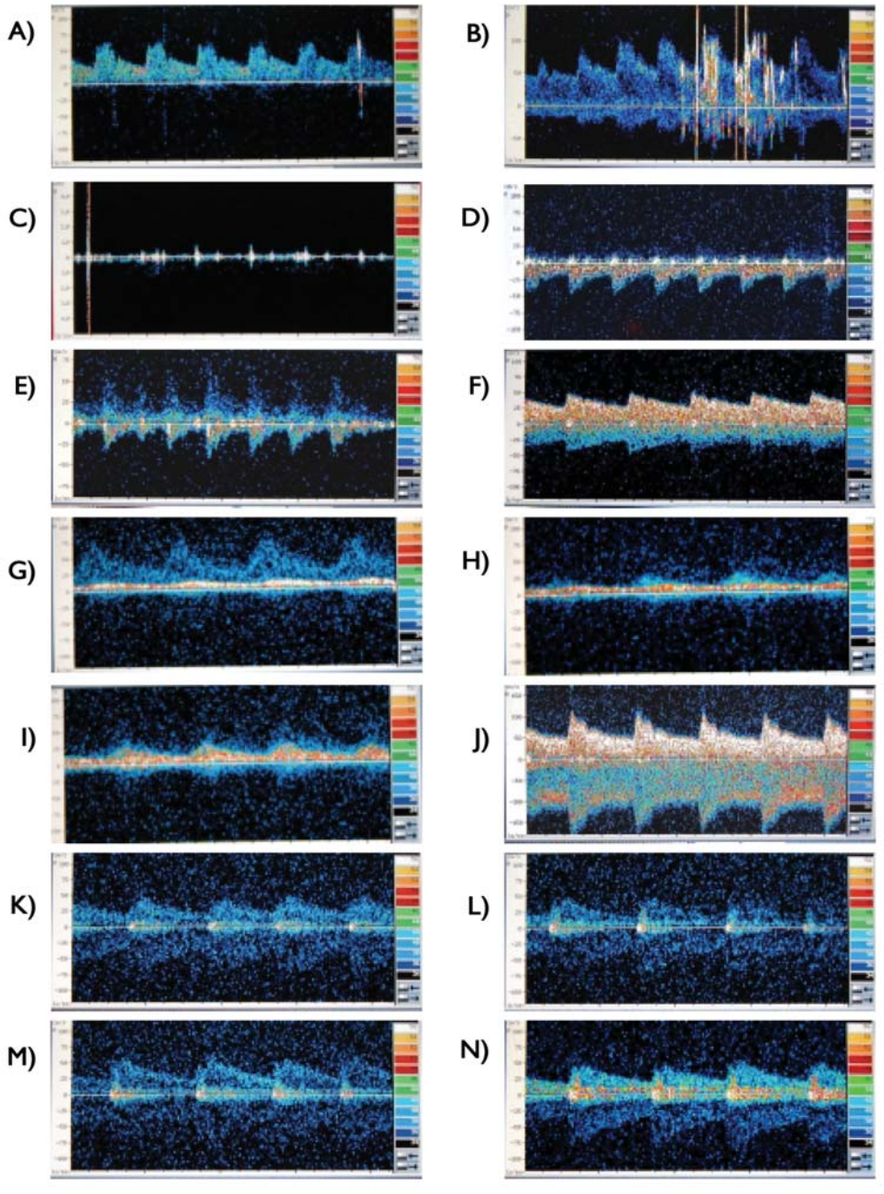


FIGURE 5 A) High intensity transient seen in the spectra of a patient with a mechanical aortic valve. Emboli associated with mechanical valves are normally gaseous due to blood vortexes produced during opening and closing of the valve; B) Echocontrast study in a patient with cryptogenic stroke at the end of a valsalva manoeuvre showing numerous HITs produced by injected intravenous agitated saline. During the valsalva the MFV decreases. At the end of valsalva, the MFV increases above baseline levels. This can be seen in the figure. With a significant right to left communication (PFO), atrial or ventricular septal defect, pulmonary arteriovenous fistula. More than 20 HITs can be seen within five cardiac cycles. This patient had a PFO which was successfully closed; C) Knock occurring at systole and at aortic valve closure in association with ICA occlusion; D) Small vessel knock, white triangles, above the baseline at the start of systole and at the diacrotic notch (seen in the wave below the baseline) due to aortic valve closure in a patient with diplopia. There is no systolic flow in the SVK artery above the baseline. This flow appeared during insonation (not shown) and this was associated with immediate full clinical recovery. To date, this recovery has persisted (currently two years); E) Small vessel knock in the ACA of a patient with vascular dementia; F) Small vessel knock at the baseline hidden in the main spectra of a right VA; G–I) These spectra show a hyper-intense signal occurring at the baseline which changes in appearance within a few minutes of targeted insonation from G to I. This waveform resembles a first harmonic and has been named HAC; J) This shows the MCA/ACA bifurcation as per Figure 1. However, the flow in the ACA (below baseline) is much greater than that in the MCA (above baseline). This patient had recently dissected his contralateral internal carotid artery with MCA occlusion; K–N) These spectra show the changes in SVK with appearance of the underlying occluded artery responsible for the SVK waveform. During 5–10 minutes of continuous insonation the SVK waveform can be seen to change from K to N. These changes are always associated with neurological recovery when the CT/MRI scan is negative.

sensory loss due to lateral medullary ischaemia. Preliminary evidence has been obtained showing reversal of this dissociated sensory loss with SVK targeting. However, the TSAII is still a subjective measure. A trial is proposed to measure the amplitude and latency of evoked potentials in lateral medullary ischaemia[57] associated with SVK. Changes in both amplitude and latency resulting from TCD targeting of SVK will be measured. This study could provide the first objective evidence of neurological recovery using TCD.

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