# Transcranial Doppler ultrasound

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Transcranial Doppler ultrasound allows measurements of blood flow velocity to be made from the basal intracerebral vessels The major advantages of transcranial Doppler ultrasound are that it is non-invasive, relatively cheap, can be performed with portable machines, allows monitoring for prolonged periods, and has a high temporal resolution making it ideal for studying dynamic cerebrovascular responses. In addition it has recently been demonstrated that it can be used to detect circulating cerebral emboli, these cannot be detected by any other currently available imaging modality.



Transcranial Doppler ultrasound (TCD) allows measurements of blood flow velocity to be made from the basal intracerebral vessels. Although Doppler ultrasound was first applied to patients in the 1960s,[1] it was not appreciated for many years that sufficient ultrasound could pass through the skull to allow recording from intracerebral vessels. It was only in the 1980s that successful insonation of the middle cerebral artery was described by Aaslid *et al*[2]. To enable sufficient transmission of ultrasound through the skull, a low frequency transducer (usually 2 MHz) is used. This has the consequence that the spatial resolution is poor and, therefore, the technique is primarily useful for giving Doppler information on blood flow velocity. Duplex machines, which provide a two dimensional B-mode image of the intracranial structures, have been developed more recently, but the spatial resolution is of low quality and provides limited clinically useful information. Even using state-of-the-art TCD ultrasound equipment, it is impossible to successfully insonate the intracerebral vessels in approximately 10% of individuals due to the lack of an acoustic window; this proportion is increased in black individuals and with increasing age. A number of acoustic windows are used to provide access to different intracerebral vessels[3]. Most commonly, a temporal window above the zygomatic arch is used, through which the terminal internal carotid artery, middle cerebral artery, anterior cerebral artery, and proximal posterior cerebral artery can be insonated. The distal vertebral arteries and basilar artery can be insonated via an occipital window. Access can be obtained to the distal internal carotid artery and the ophthalmic artery via the orbit.

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**Table 1** Major uses of transcranial Doppler ultrasound

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| Detection of intra-cranial stenosis | |
| | Atheromatous stenosis |
| | Acute stroke |
| | Sickle cell disease |
| | Subarachnoid haemorrhage |
| Evaluation of the presence or absence of collateral flow channels | |
| Measurement of dynamic cerebrovascular responses | |
| | Carbon dioxide reactivity |
| | Dynamic autoregulation |
| | Vasoneuronal coupling |
| Intra-operative monitoring | |
| | Carotid endarterectomy |
| | Cardiopulmonary bypass |
| | Interventional neuroradiological procedures |
| Embolic signal detection | |

Major advantages of TCD are that it is non-invasive, relatively cheap, can be performed with portable machines, allows monitoring for prolonged periods, and has a high temporal resolution making it ideal for studying dynamic cerebrovascular responses. In addition, it has recently been demonstrated that it can be used to detect circulating cerebral emboli; these cannot be detected by any other currently available imaging modality. The major uses of TCD are shown in Table 1.

## Detection of intracranial stenosis

TCD is widely used in many countries for detection of intracranial stenoses usually caused by atheromatous disease. Stenosis can be identified by the presence of a high velocity jet and is most commonly detected in the middle cerebral artery[4]. One difficulty with using conventional TCD ultrasound is that one cannot correct for the angle between the ultrasound beam and the direction of flow. This is less of a problem for the middle cerebral artery where the angle is usually less than 20°, but it means that the sensitivity for detecting middle cerebral artery stenoses is reduced, particularly in subjects in whom the angle is at the upper end of the normal range. Using duplex TCD systems it is possible to determine and correct for this angle[5]. Intracranial stenoses can be detected in a number of patients with acute stroke, but it has been argued that the finding does not alter management and, therefore, in many countries TCD is not routinely used in acute stroke. There is some

evidence that intracranial stenoses may be better treated with warfarin than aspirin[6], and, if this is confirmed, the importance of detecting such stenoses will be increased. Recently, this use of TCD has been challenged by magnetic resonance angiography. Both have potential advantages, but a major use of TCD is in ill patients with acute stroke or where serial monitoring is required. It has also been shown in an elegant study that, in patients with acute stroke, the presence of both middle cerebral artery occlusion and the subsequent time course of its recanalisation can be monitored using TCD[7]. Using TCD to identify individuals with acute stroke who have persisting middle cerebral artery occlusion, and who, therefore, might be particularly suitable for thrombolysis, is attractive. However, no large thrombolysis studies using it as a screening tool have yet been performed.

TCD is ideally suited to situations where repeated measurements are required. This potential use is illustrated by a recent stroke prevention study in sickle cell disease study[8]. Children with sickle cell disease are at markedly increased risk of stroke, which frequently occurs secondary to intra-cranial stenosis. TCD was used to identify children with sickle cell disease who had middle cerebral artery stenoses, and in a prospective study it was shown that these individuals were at markedly increased stroke risk[8]. In a follow on study, sickle cell children with intracranial stenoses, as detected by TCD, were randomised to either exchange transfusion or no additional treatment[9]. There was a very marked reduction in strokes during follow-up in the actively treated group.

Subarachnoid haemorrhage is another situation where the ability to perform repeated measurements is useful, primarily for the detection of vasospasm, which can be identified by TCD[10].

## Evaluation of the presence or absence of collateral flow channels

TCD ultrasound can be used to identify the directionality of flow within collateral pathways[3] and provides useful information about whether collateral supply is adequate in cases of arterial occlusion. For example, in carotid artery occlusion the directionality of ophthalmic artery flow will indicate whether blood is being shunted from the extracranial circulation into the intracranial circulation. The technique can also be used to demonstrate the integrity of the circle of Willis. In practice, dynamic techniques such as carbon dioxide reactivity (as discussed below) may give a better global estimate of the adequacy of collateral supply.

## Measurement of dynamic cerebrovascular responses

A major advantage of TCD is its very high temporal resolution. This makes it ideal to study rapid changes in cerebral haemodynamics. This has led to its use in the measurement of cerebral autoregulation. One potential problem in this setting is that TCD measures blood flow velocity and not absolute blood flow. Therefore, it is only a valid method to estimate changes in cerebral blood flow if the vessel diameter does not change during the intervention. It has been demonstrated using angiography that there is very little or no change in the middle cerebral artery diameter during carbon dioxide inhalation at the concentrations used during carbon dioxide reactivity measurements[11]. Therefore, in this setting, it appears a valid technique. Similarly, the middle cerebral artery does not change in diameter following certain drugs. However, some drugs, particularly those affecting the nitric oxide system, can cause marked changes in middle cerebral artery diameter. For example, nitric oxide synthase inhibition in man resulted in a 30% reduction in cerebral blood flow, as determined by absolute carotid artery volume flow. In contrast, there was no change in middle cerebral artery blood flow[12]. This is consistent with vasoconstriction in the middle cerebral artery, and similar studies using nitric oxide donors have suggested that marked vasodilation can occur[13].

Carbon dioxide reactivity has been widely used as a surrogate measure of autoregulation, particularly in patients with carotid stenosis, as a way to determine the adequacy of collateral supply. Middle cerebral artery blood flow velocity is measured while the patient breathes air, and then while they breathe a mixture of 5–8% carbon dioxide in air. The percentage change in blood flow velocity is then calculated[14]. If a concentration of carbon dioxide is used which does not maximally vasodilate (*i.e.* 5 or 6%), the change in blood flow velocity is divided by the change in end tidal carbon dioxide, an estimate of the partial pressure of carbon dioxide in the blood. A proportion of patients with carotid stenosis and occlusion have impaired carbon dioxide reactivity, and this is primarily seen in individuals with poor collateral supply[14]. An improvement is seen after carotid endarterectomy[15]. Studies have demonstrated that, in patients with carotid occlusion, impaired reactivity identifies individuals at particularly high risk of future stroke or TIA[16]. There is less firm data as to whether the same technique identifies individuals with carotid stenosis who are at high risk. If so, it may be a useful technique to identify high-risk asymptomatic patients with carotid stenosis for endarterectomy. One potential problem with the technique is that high doses of carbon dioxide can result in hypertension and, in some patients, this results in a 'passive' rise in cerebral artery blood flow velocity. This can sometimes obscure impaired autoregulation[17]. For this

reason, it is recommended that a non-invasive technique such as a Finapres is used to monitor blood pressure during the procedure. An alternative vasodilatory stimulus which is frequently used is acetazolamide, a carbonic anhydrase inhibitor[18]. However, some studies have suggested that the results are less reproducible than those obtained using carbon dioxide as a vasodilator[19].

Carbon dioxide reactivity is an indirect measure of autoregulation. More recently, a direct measure of cerebral autoregulation has been developed by Aaslid *et al*[20]. Following a sudden stepwise drop in blood pressure, cerebral blood flow drops suddenly and then returns to normal. The rate of rise of blood flow is greater than that of systemic blood pressure, and this difference is caused by the cerebral autoregulatory response. A sudden stepwise blood pressure drop can be induced by inflating leg cuffs, and then suddenly deflating them, resulting in a reactive hyperaemia. Middle cerebral artery blood flow velocity can be recorded by TCD and blood pressure non-invasively monitored at the same time by a Finapres or other similar method. The rate of rise of the two parameters can then be compared to derive an autoregulatory index[20]. There has been concern that the stepwise drop in blood pressure might alter middle cerebral artery diameter. However, validation studies have shown that an autoregulatory index measured in this way correlates well with that measured using carotid artery flow monitoring, which provides an absolute measure of blood flow[21]. A good correlation has been found between dynamic autoregulation, estimated using this method, and estimates of static autoregulation[22]. Therefore, the technique does appear to be valid, and impaired autoregulation has been found both in patients with head injury[21] and in a subgroup of patients with carotid artery stenosis[23]. This technique may be useful at identifying those individuals at high risk who may benefit from revascularisation. It may also allow identification of individuals with carotid stenosis or occlusion who have a particularly poor collateral supply, and in whom lowering of blood pressure to the normal range could precipitate cerebral ischaemia.

Vasoneuronal coupling describes the increase in regional blood flow seen in response to neuronal activity. An estimate of this can also be obtained using TCD. Using the high temporal resolution of TCD, the rise in cerebral blood flow velocity in the artery supplying a particular brain region can be determined while that brain region is activated. Most commonly the occipital cortex is activated, using a flashing visual stimulus, while posterior artery blood flow velocity is recorded[24]. By averaging over a number of stimuli, a reliable measurement can be obtained. Using a language activation task, and recording from both middle cerebral arteries, the technique may allow hemispheric dominance for language to be determined[25,26]. Using other activation tasks, the technique has also been used to study mechanisms of recovery following

stroke[27]. However, the application of TCD here is limited by its poor spatial resolution, and the mechanisms of neural recovery following stroke may be better answered using positron emission tomography or functional magnetic resonance imaging.

## Intra-operative monitoring

The non-invasive nature of TCD and its high temporal resolution make it ideally suited to intra-operative monitoring. In this context, it is most used during carotid endarterectomy[28]. In a proportion of patients during cross clamping, if collateral supply is inadequate, middle cerebral artery blood flow can drop dramatically and there is a danger of cerebral ischaemia. In such patients, it is necessary to insert a shunt. One method of identifying individuals who require shunt insertion is to continuously monitor middle cerebral artery blood flow velocity during the operation, and only insert a shunt in individuals in whom it falls below a particular threshold on cross-clamping. Monitoring can also identify individuals in whom the potential problems arise such as shunt kinking. The technique is also used to monitor for embolisation occurring during both carotid endarterectomy and cardiopulmonary bypass as discussed below.

## Embolic signal detection

Doppler ultrasound has the unique ability to detect emboli as they pass through the circulation. Due to increased scattering and reflection of ultrasound from the embolus, compared with the surrounding red blood cells, an embolus appears as a short duration high intensity signal within the Doppler flow spectrum. It has been appreciated since the 1960s that gas bubbles can be detected using ultrasound[29], and the technique has been applied to both decompression sickness and cardiopulmonary bypass to detect gaseous emboli[30,31]. However, it was only in 1990 that it was appreciated that solid emboli, composed of thrombus or platelet aggregates, could also be detected. While recording during carotid endarterectomy for air emboli introduced during the operation, Spencer and colleagues noted that similar embolic signals occurred prior to arterial opening, *i.e.* before any air could be introduced into the system[32]. They deduced these must be solid emboli dislodged from the carotid plaque during surgical manipulation. Although there was initial scepticism, subsequent *in vitro* and *in vivo* studies have demonstrated that the technique is highly sensitive and specific[33–35]. Embolic signals have been detected in patients with a wide variety of potential embolic sources

including carotid artery stenosis, atrial fibrillation, and valvular heart disease[36]. Conventionally, recordings are made from the middle cerebral artery. The low frequency transducer used for TCD increases the embolic-to-background blood signal ratio and, therefore, makes them easier to detect[37]. In addition, prolonged recording can be performed using simple headpieces. Good interobserver reproducibility in identifying embolic signals has been reported[38] and recent consensus criteria have been developed for applying this technique in clinical practice[39].

Most work has been performed in carotid artery stenosis. Asymptomatic embolic signals are surprisingly frequent and are usually detected in 20–50% of patients with symptomatic carotid stenosis if recordings are performed for an hour[40–45]. Their presence has been shown to correlate with known markers of increased risk including symptomatic status[40,41], time since last symptoms[45–47], and plaque ulceration determined either histologically[48] or on angiography[43,44]. Recently, small studies have suggested that asymptomatic embolisation may be an independent predictor of future stroke risk[49–51] and this is being tested in larger multicentre studies.

Asymptomatic embolic signal detection has a number of potential uses. It may allow identification of individuals at high risk of stroke for targeted pharmacological or surgical therapy. For example, operating on an asymptomatic carotid stenosis has a poor risk-benefit ratio. Eighty-five patients have to be operated on to prevent one stroke over a one-year period[52]. Identifying a high-risk group of individuals would improve both cost-benefit and risk-benefit ratios. Embolic signal detection may also be useful in monitoring the effectiveness of antithrombotic therapy in individuals. It may also be useful in monitoring during interventional procedures. For example, it has been demonstrated that embolic signals during the dissection phase of carotid endarterectomy (before arterial opening) correlate with both new peri-operative MRI infarcts[53] and neuropsychological decline[54]. Intra-operative use of the technique may aid the surgeon in reducing embolisation. Furthermore, embolisation in the postoperative period has been associated with early postoperative stroke and TIA risk[55]. It has been suggested that the technique may allow the identification of individuals in this setting who require more aggressive postoperative antithrombotic measures such as a Dextran infusion[56].

Embolic signal detection may also prove useful in evaluating new antithrombotic and antiplatelet therapies. Currently, these are evaluated in large expensive clinical trials with an endpoint of stroke. For example, the recent CAPRIE trial recruited approximately 20,000 patients and only just achieved a significant result[57]. There is a wide gulf between *ex vivo* assessment of platelet function and clinical effectiveness, and animal models are not always truly representative of the situation occurring in man. Because asymptomatic embolic signals are much more frequent than stroke and TIA, they provide a surrogate endpoint which can be used to

test the effectiveness of novel therapies. For this application, a situation is required where embolisation is frequent, and asymptomatic emboli have clinical significance. The setting of the postoperative period following carotid endarterectomy has been used. It was possible to show the highly significant antithromboembolic effect of a novel and potentially platelet-specific nitric oxide donor, S-nitrosothiol, in only 12 cases and 12 controls using this technique[58].

Asymptomatic embolic signal detection may also be useful in patients with acute stroke both in identifying the stroke subtype and mechanism, in localising the embolic source by recording from multiple sites along the arterial tree simultaneously, and possibly in identifying individuals at high risk of recurrent stroke[59]. Particularly in patients with carotid artery stenosis and acute stroke, continued embolisation is frequent even at 2 weeks post-stroke[59,60].

## Other recent advances

Recently, duplex ultrasound machines have been adapted for transcranial imaging. The B-mode modality does allow some delineation of structure, and lesions such as intracranial haemorrhage and mid-line shift have been identified; however, the spatial resolution is much inferior to computed tomography or magnetic resonance imaging. Nevertheless, this imaging modality does have advantages for studying intracerebral vessels, primarily due to the use of the colour coded modality. It can be easier to identify certain intracranial arteries, and this can help in determining whether they are absent or merely difficult to identify due to a poor acoustic window. It allows the sample volume to be placed in the vessel of interest and the Doppler angle to be adjusted manually so that angle corrected flow velocity can be determined[61]. The technique has also been used to study other intracranial vascular structures such as the pulsatility of intracranial aneurysms[62].

A major problem with TCD remains the lack of an acoustic window in approximately 10% of individuals. The use of ultrasonic contrast agents can overcome this problem[63]. An intravenous injection is given of an agent containing stabilised microbubbles. This passes into the intracranial arterial circulation, and results in increased back-scattering and signal intensity. Using this technique in combination with colour flow duplex imaging the anatomy of the complete circle of Willis can be visualised.

## Conclusions

In its early days, TCD ultrasound was primarily used to identify intracranial stenoses. With the advent of magnetic resonance angiography,

TCD is less used for this indication by many units. However, its non-invasive nature and high temporal resolution make it ideal to for the study of cerebral hemodynamics, to monitor during interventional procedures, or where repeated measurements are required particularly in sick patients. It also offers the only technique by which asymptomatic emboli can be detected non-invasively.

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