Cerebral Blood Flow Measurement for Neurological Assessments: Functional Transcranial Doppler Ultrasound

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Edward J. Truemper and Gregory R. Bashford

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E.J. Truemper
Department of Pediatrics, Division of Pediatric Critical Care Medicine, Children's Hospital and Medical Center, Omaha, NE, USA
e-mail: etruemper@childrensomaha.org

G.R. Bashford (✉)
Department of Biological Systems Engineering, University of Nebraska-Lincoln, Lincoln, NE, USA
e-mail: gbashford2@unl.edu

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Abstract

Transcranial Doppler (TCD) is a special type of ultrasound developed to measure cerebral blood flow (CBF) and subsequently shown to be valuable in an increasingly larger number of clinical applications. Physically, TCD operates in the same way and is as safe as ultrasound imaging used during pregnancy. Changes in CBF in response to controlled stimuli have been shown to be valuable indicators of a variety of pathological conditions. In addition to measuring CBF, TCD can detect the passage of emboli in the bloodstream due to a stark difference in acoustic properties when emboli pass through the ultrasound beam. This unmistakable change in ultrasound signal echo between emboli and blood is due to density and acoustic impedance differences. The TCD signal is processed in real-time for visual display and measurement of cerebral blood flow velocities (CBFV). Two scanning techniques, the free-hand and continuous monitoring techniques, are the two primary methods for performing TCD. The free-hand technique is suitable for short-term monitoring (30 min or less) but is not effective for continuous monitoring due to operator fatigue and inconsistent transducer placement. The second method, continuous TCD monitoring, requires a fixation apparatus to hold the Doppler probe(s) in a static location at the scalp insonation site. Due to its low cost, real-time measurement capability, and easy portability, TCD has remained a valuable imaging tool when compared to more costly and stationary modalities. More recently, TCD has been used in conjunction with cerebral function tests (functional TCD, or fTCD) as a proxy for neuronal activity for indication in an ever-increasing number of brain studies. The future of TCD and fTCD as biomarkers for neurological assessment is exciting indeed.

Keywords

Transcranial Doppler • Cerebrovascular disease • Ultrasound • Emboli • Functional TCD • Autoregulation

Abbreviations

ACA	Anterior cerebral artery
AD	Alzheimer's disease
BCA	Basal cerebral artery
BH	Breath holding
CBF	Cerebral blood flow
CBFV	Cerebral blood flow velocities
CVR	Cerebrovascular reactivity
fTCD	Functional transcranial Doppler
ICA	Internal carotid artery
MCA	Middle cerebral artery
MCI	Mild cognitive impairment
MHz	Megahertz (one million cycles/s)
mW	milliWatts
mW/cm^2	milliWatts per centimeter squared (acoustic intensity)
PCA	Posterior cerebral artery

PI	Pulsatility index
RI	Resistivity index
SAH	Subarachnoid hemorrhage
TBI	Traumatic brain injury
TCD	Transcranial Doppler

Key Facts of Transcranial Doppler

- Despite the term "Doppler," TCD technology does not use the physical Doppler principle to detect blood flow.
- Transcranial Doppler can measure blood flow in the deepest parts of the brain; in fact, care must be taken when setting the depth to ensure flow information is coming from the correct side of the brain.
- TCD has no known side effects; it uses non-ionizing energy (mechanical sound waves) at very low power and is thus safe and painless.
- TCD can be used with fixation devices, allowing for measurement of blood flow even when subjects are moving.
- About 8 % of the population have temporal windows that attenuate sound too much to acquire a strong enough signal – research continues for overcoming this limitation.
- More complex forms of TCD machines can produce two-dimensional images of the flow in the brain, in addition to the velocity-time spectrum.

Definitions

Basal cerebral arteries The major arteries emanating from the base of the brain carrying and distributing the majority of blood flow to various lobes.

Circle of Willis A vascular "roundabout" fed by the internal carotid arteries and the basilar arteries and diverting blood to various areas of the brain via other basal arteries such as the MCA, PCA, and ACA.

Diastolic velocity (or end diastolic velocity) In one cardiac cycle, the blood flow velocity existing at the end of the relaxation phase of the heart, just before contraction. This value changes throughout the vasculature and is measured at a specific location by TCD.

Mean velocity In one cardiac cycle, the time-averaged velocity of the TCD envelope.

Pulsatility index (PI) The difference between peak systolic velocity and end diastolic velocity divided by the mean velocity.

Resistivity index (RI) The difference between peak systolic velocity and end diastolic velocity divided by the peak systolic velocity; a measure of the impedance the blood flow "sees" as it is flowing at the point of insonation.

Systolic velocity (or peak systolic velocity) In one cardiac cycle, the maximum blood flow velocity achieved due to the contraction phase of the heart. This value changes throughout the vasculature and is measured at a specific location by TCD.

TCD envelope The trace of maximum velocity at each point in time of a Doppler spectrum, from which hemodynamic parameters and indices are measured.

Introduction

First developed by Rune Aaslid in 1982 (Aaslid et al. 1982), transcranial Doppler (TCD) has steadfastly achieved an important diagnostic niche in the diagnosis and management of a large variety of cerebrovascular disorders. TCD applications almost exclusively center on examining the basal cerebral arteries (BCAs) and several of the tributaries that comprise the circle of Willis (Fig. 1). The unifying principles comprise a low-intensity, focused, pulsed acoustic wave with frequency on the order of 1–2 MHz, aimed toward the location of desired vessel. Successful insonation provides vessel depth and continuous flow velocity information for the blood flow within the insonated portion of the vessel. This Doppler-derived data is converted into audible and visual signals to guide the technician to achieve the maximum signal intensity and thereby a representation of the aggregate velocities at that point within the vessel. Visual imaging of the entire spectra is encapsulated into flow velocity envelopes that mirror each cardiac cycle. Changing the location of the probe results in interrogation of adjacent vessel territories; angling the probe in the direction of the vessel and changing beam depth of focus allows the technician to insonate all of the vessels that compromise the circle of Willis.

TCD has yet to be superseded by other more elaborate techniques. Despite marked advances in other neuroimaging techniques such as magnetic resonance imaging (MRI) with diffusion-weighted scanning, computed tomography, and MRI angiography in helping to decipher the impact of vascular disorders on cerebral perfusion and related injury mechanisms, TCD remains an increasingly important neuroimaging adjunct because of its high temporal resolution and easy portability to the bedside of critically ill patients with severe neurologic injury. The technique also proves valuable real-time continuous evaluation of flow characteristics and velocity patterns during dynamic clinical conditions where perturbations in cerebral blood flow (CBF) can be severe and rapid correction with medical treatment is necessary. Since the technique provides for continuous visual inspection, mapping the circle of Willis can provide data on CBF disturbances produced by, e.g., vasospasm, vascular stenosis, compensatory flow patterns, and hyperperfusion. Currently, TCD is the only technique that is able to detect emboli as they transit through the blood vessel.

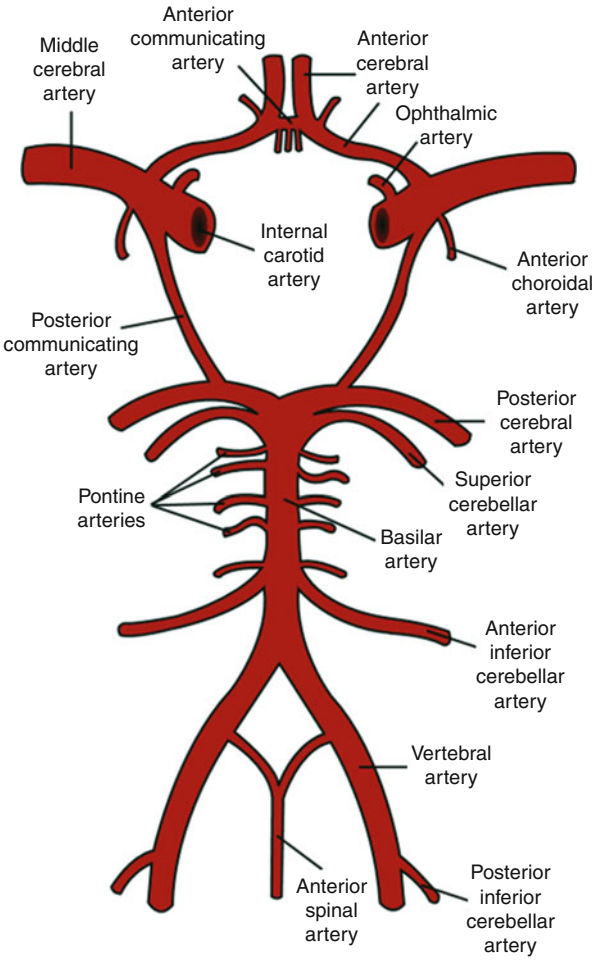

Fig. 1 The Circle of Willis is the central vascular hub within the cerebral arterial circulation. Blood is supplied by the basilar artery and internal carotid arteries and delivered to the Circle of Willis, where several vessels branch off to supply blood throughout the brain. Of note, the middle cerebral artery, anterior cerebral artery, and posterior artery branch off the Circle of Willis to carry blood to their perfusion territories. Image is public domain

This chapter reviews the physical mechanisms of the TCD modality, followed by current clinical indications. Some rapidly evolving usages, especially in the fields of early-onset disease diagnosis and neurocognitive assessment, are discussed at the end of the chapter.

Physical Principles

Sound Generation

This section provides an overview of the physical principles used in transcranial Doppler; for a more detailed treatment, refer to ▶ Chap. 44, "Ultrasonic Measurement of Blood Flow Velocity and Applications for Cardiovascular Assessments" in this

volume. TCD uses similar physical principles that apply to all acoustic imaging systems. Ultrasound uses mechanical wave propagation that is above the audible range (>20,000 Hz). Ultrasound instrumentation utilizes the piezoelectric effect whereby electrical energy is converted to an oscillating ultrasonic wave through expansion and contraction of a piezoelectric crystal due to cyclical changes in polarity of the electrical impulse. The ultrasound frequency is fixed by the physical features of the piezoelectric crystal, and for TCD, this frequency may range from 2 MHz in adult examinations (Kumar and Alexandrov 2015) to 5–10 MHz in infants (American Institute of Ultrasound in Medicine 2012) and even 16 MHz in neurosurgical applications. Commercial instrumentation can focus the Doppler beam at the desired distance as well as control the range of acquisition ("sample volume" or "gate") at the location of its intended vascular target. Reflected ultrasound energy returns back to the piezoelectric element, exerting mechanical force on the crystal, which produces voltage proportional to the mechanical forces exerted on the crystal by ultrasonic energy.

Measurement of Doppler Spectrum

Transcranial Doppler ultrasound operates on the principles of pulsed-wave Doppler ultrasound. In pulsed-wave Doppler, a very short pulse of mechanical sound energy is emitted by the transducer. The pulse of sound is reflected off of small scatterers in the blood vessel being insonated, such as red blood cells, and returns to the transducer, where it is detected. The velocity of the small scatterers in the blood has an effect on the time it takes for subsequent pulses to return to the transducer. By measuring the change in return time from one pulse to the next, the velocity of scatterers in the blood can be estimated via the Doppler equation. The velocity versus time display in TCD contains a range of velocities at every moment in time, representing the range of velocities present in the insonated artery. The TCD waveform, often referred to as the **TCD envelope**, is defined as a wave that traces the maximum velocity present in the velocity versus time display at any moment in time (Fig. 2). Other blood flow velocity parameters may be measured from the TCD envelope, including **systolic velocity** (V_s, the maximum velocity present in the envelope waveform over one heartbeat cycle), **diastolic velocity** (V_d, the minimum velocity present in the envelope waveform over one heartbeat cycle), **mean velocity** (V_m, the average of the envelope waveform over one heartbeat cycle), Gosling's **pulsatility index** ($PI = (V_s - C_d)/V_m$) (Gosling and King 1974), and Pourcelot's **resistivity index** ($RI = (V_s - V_d)/V_s$, (Petersen et al. 1997). The significance of PI and RI, as well as V_s, V_d, and V_m, will be discussed below under "Interpreting Doppler Spectra."

Other Considerations: Aliasing, Sample Volume, and Doppler Angle

Due to the principles of pulsed-wave Doppler, several conditions are required to ensure accurate TCD spectra. The first condition is that the pulse repetition frequency (PRF) is high enough to avoid "aliasing," which occurs when blood flow

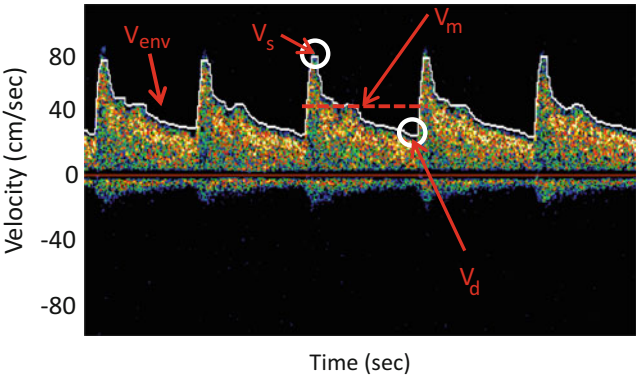

Fig. 2 Example TCD output with the spectral flow envelope (V_{env}) shown outlined in white. Note the pulsatile nature of the blood flow velocity versus time. Systolic velocity (V_s), diastolic velocity (V_d) and mean velocity (V_m) are marked for one heartbeat cycle

velocities are measured which are not actually present in the artery. This can be avoided by increasing the PRF or decreasing the maximum velocity present in the velocity versus time display. A second condition is that the sample volume should be small enough to ensure that only the artery of interest is being insonated; too large of a sample volume can cause the TCD spectra from several adjacent arteries to be displayed as one spectrum. It is usually best to start with a large sample volume when initially searching for arteries and then decrease the sample volume once the desired signal is found. Finally, it is important to remember that due to the Doppler equation, the velocities displayed in the velocity versus time spectrum will only be accurate up to a factor of cos(θ) (Deppe et al. 2004). Therefore, the actual velocity present in the artery will always be greater than or equal to the velocity displayed on the TCD machine, and the amount of difference will depend on the transducer's position and angle relative to the artery being insonated.

Factors Affecting Signal Strength

Other factors that are important in generating spectra that accurately reflect the flow metrics through the insonated vessel include intensity, impedance, and attenuation. Intensity is defined as the ultrasound energy flux measured in watts over the cross-sectional area of the beam. In TCD applications, power adjustment is necessary to achieve penetration through the insonation site to achieve adequate return signal strength. Factors that affect intensity include beam width, depth of insonation, and tissue density. The presence or absence of bone at the site of insonation proves to be a chief factor determining the acoustic intensity necessary to obtain adequate signal. As little as 5–10 mW/cm^2 is required to achieve an adequate spectral examination through the anterior fontanelle, foramen magnum, or orbit, whereas 50–200 mW/cm^2 is required through the transtemporal window in most children and adults. Increased

bone density such as hyperossification in patients with sickle cell disease may require intensity as high as 700 mW/cm^2. In clinical practice, acoustic transmission also requires ensuring a suitable probe-tissue interface. Failure to use a suitable acoustic liquid gel to eliminate air and ensure a smooth interface can lead to marked attenuation, reflection, and scattering of the acoustic energy by more than 99 %, precluding an effective examination.

Safety

Although ultrasound is a very safe imaging modality, it is good practice to limit patient exposure, both in terms of the power used and insonation time (American Institute of Ultrasound in Medicine 2012). When conducting TCD examinations, some clinicians will initially set power to a high value; this shortens the time needed to find the blood vessel of interest and can therefore decrease the overall dose of mechanical energy received. However, once the vessel is found, power is immediately reduced to the minimum amount needed to achieve a usable signal in accordance with the ALARA (As Low As Reasonably Achievable) principle (Wells 2006).

Interpreting Doppler Spectra

Training is necessary to interpret TCD spectra. Information of clinical use may be obtained from the velocity parameters (defined above) such as V_s, V_d, V_m, the pulsatility, and the resistivity indices, as well as from other characteristics of the TCD envelope. The shape of the envelope provides information about resistance distal to the point being insonated and, along with direction of flow, the depth of the insonated region, and velocity parameters such as V_m, PI, and RI, allows artery identification (for a list of normal velocity values, PI values, and depths, see (Alexandrov and Neumyer 2004). A large difference between V_s and V_d indicates high distal resistance, and a small difference between V_s and V_d indicates low resistance. The pulsatility index (PI) and resistivity index (RI) also capture information about resistance distal to the point being insonated (Petersen et al. 1997; Naqvi et al. 2013). Normal values for the PI are 0.5–1.19, with values less than 0.5 indicating distal vasodilation and values greater than 1.19 indicating distal vasoconstriction or occlusion; normal values for the RI are slightly less than for the PI, with values $>$0.8 indicating distal vasoconstriction or occlusion (Naqvi et al. 2013).

Changes in cerebral blood flow velocity are well-correlated with changes in CBF, as long as the diameter of the vessel being insonated does not change significantly, which is often the case for the basal cerebral arteries (Deppe et al. 2004).

The direction of flow (toward or away from the transducer) allows artery identification and may also allow detection of abnormalities, such as a steal (will show reversal of blood flow, as blood intended for one vessel is instead sent to a different vessel) or a totally occluded artery (low but equal velocities in opposite directions during systole and diastole). Typical Doppler spectra for several basal arteries in

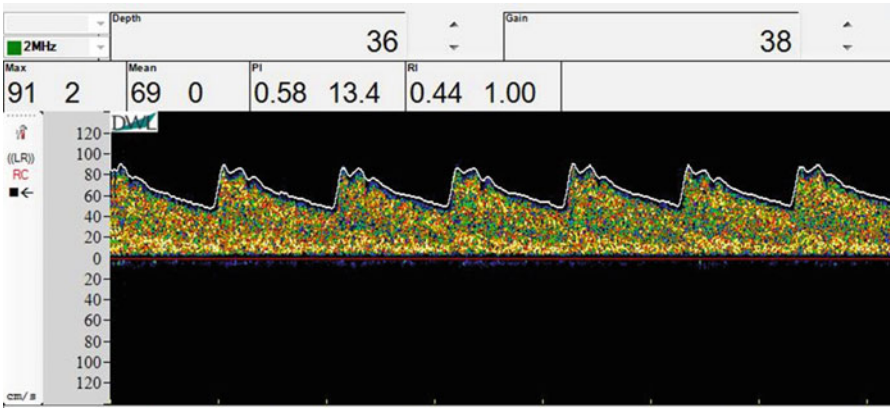

Fig. 3 Healthy blood flow through the distal middle cerebral artery is visible in the TCD spectra. Note the relatively shallow insonation depth of 36 mm

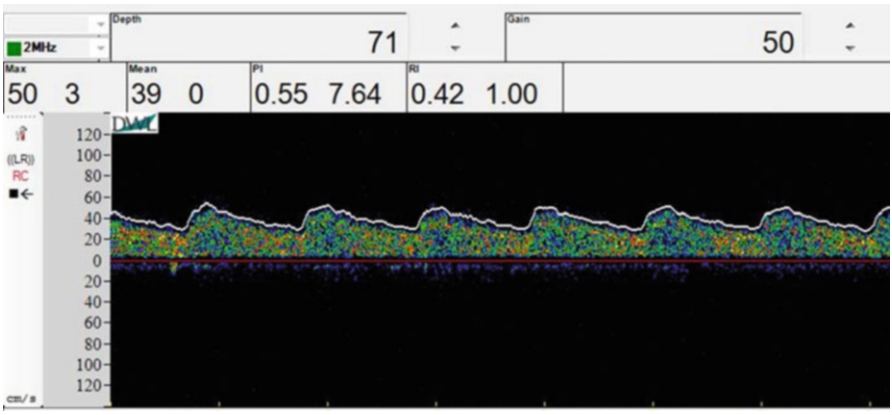

Fig. 4 TCD spectrum of posterior cerebral artery, showing low-resistance flow. Note the lower maximum and mean velocities than are present in the middle cerebral artery (the first numbers under the headings "max," "mean," "PI," and "RI" refer to flow towards the transducer); also note the depth of 71 mm

healthy subjects are shown in Figs. 3, 4, 5, 6, 7, and 8. These spectra demonstrate the differences in the hemodynamic parameters described above that are seen within the normal brain.

Current Clinical Use

The most common method of assessing the circle of Willis is using a handheld method where a well-trained technician controls power amplitude, depth of insonation, sample volume, and the angle of insonation. Technicians must have

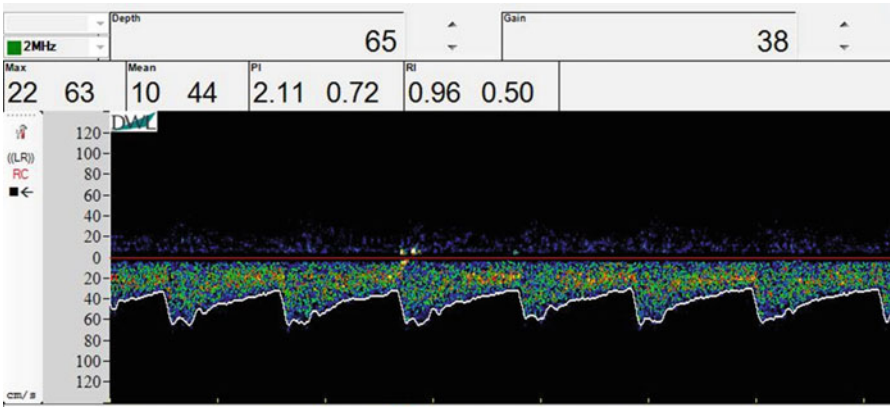

Fig. 5 TCD spectrum of anterior cerebral artery (ACA). Note the retrograde flow (towards the transducer, below the *red baseline*). The second values under the headings of maximum velocity, mean velocity, pulsatility index (PI), and resistivity index (RI) refer to blood flow towards the transducer

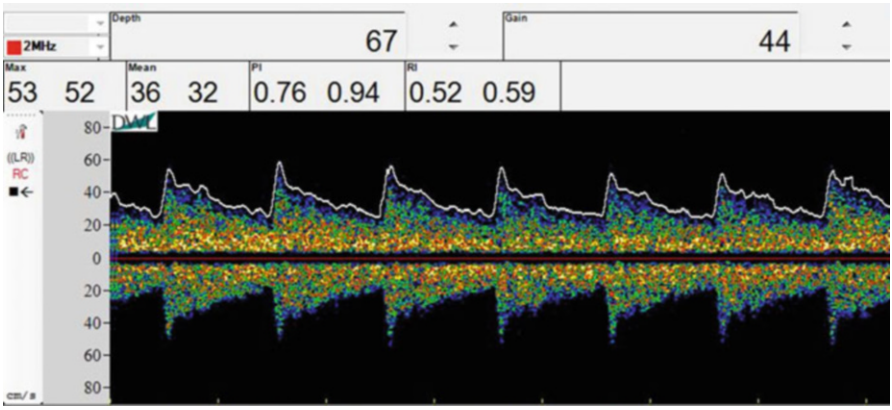

Fig. 6 TCD spectrum of the bifurcation of the anterior cerebral artery (ACA) and middle cerebral artery (MCA), showing both anterograde (towards the transducer) and retrograde (away from the transducer) flow at the same depth. The bifurcation is a landmark used in TCD examinations. When locating the bifurcation, the depth and angle should be adjusted until the signal with the brightest spectrum in both directions is found

considerable knowledge of the anatomy and variation of the circle of Willis, vessel depth in relation to the insonation window, vessels that can be interrogated via each of the windows, and creation of suitable visual displays of the spectral analysis of the reflected acoustic data. Technicians should have extensive experience in assessing the circle of Willis when assessing each of the BCAs.

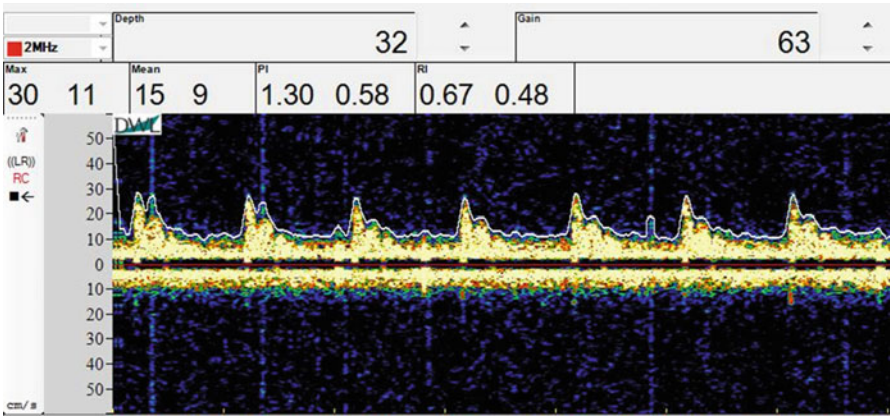

Fig. 7 TCD spectra of the ophthalmic artery. Note the elevated PI and RI values, indicating higher resistance. Additionally, note the distinctly increased flow velocity during systole as compared to diastole. Greater visibility of background noise due was caused by applying a high gain to obtain an optimal flow envelope

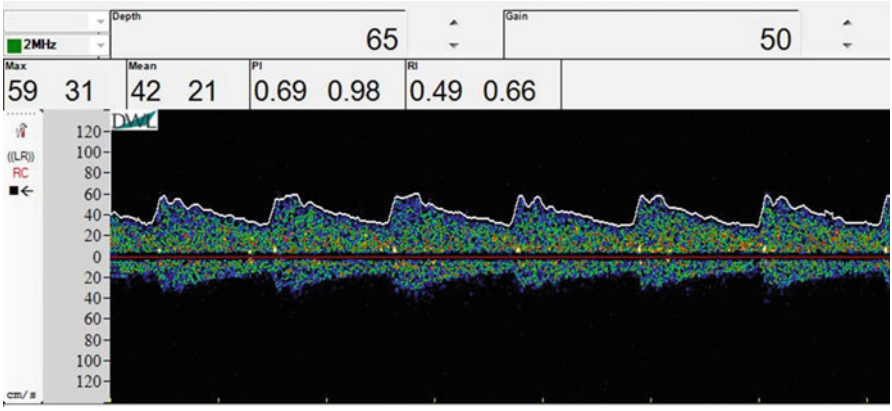

Fig. 8 TCD spectrum of the internal carotid artery, indicating both positive and negative flow velocities, suggesting blood flow in two directions. Low resistance flow is shown by the relatively small difference between the systolic velocity and the diastolic velocity

Emboli

As early as 1998, there was consensus that emboli detection via TCD is important (Ringelstein et al. 1998), and several studies have confirmed negative neurological outcomes in adults are correlated with emboli (e.g., Stump et al. 1999). Tragically, brain injury (both short-term and long-term) is the most common complication of cardiac surgery in pediatric patients (Hirsch et al. 2012; Su and Undar 2010). Its cause is

hypothesized to involve many factors, including alterations in cerebral flow and metabolism that lead to poor oxygenation of tissue and cell death. While many of these factors have been studied, the role of cerebral emboli generated by cardiopulmonary bypass and the surgical procedure is poorly understood, especially in infants and children. It is known that during cardiac surgery, emboli, which include tissue fragments, air bubbles, platelet thrombi, fibrin plugs, or microscopic flakes of catheters and vascular tubing, are inadvertently introduced into the systemic circulation. It is also known that once emboli enter the bloodstream, they can move into the brain and create dangerous blockages of cerebral vessels that lead to neurological damage.

TCD is an ideal modality for monitoring emboli passage through blood vessels because of the sharp echo signature emboli produce in the Doppler spectrum. The signature is clearly identifiable both visually and aurally, producing audible "chirps" that give real-time feedback to clinicians of timing and number of emboli. Research continues for robust algorithms for discrimination of emboli (between gaseous and particulate), as well as sizing of emboli.

Traumatic Brain Injury

Traumatic brain injury (TBI) is a growing medical concern, affecting approximately 1.7 million people in the United States every year (Centers for Disease Control and Prevention 2010). Nearly 80 % of TBI patients are seen in a hospital emergency room, resulting in approximately 275,000 hospitalizations and over 50,000 deaths each year. Tragically, an estimated 5.3 million Americans live with disabilities resulting from traumatic brain injury. Patients with severe traumatic brain injury have a significant risk of hemorrhage and cerebral edema.

A subgroup of these patients will develop associated bleeding complications including epidural, subdural, intracerebral, and subarachnoid hemorrhage (SAH), which can induce a secondary brain injury from ischemia or infarction within a vascular territory (stroke). The mechanism of injury is associated when a damaged vessel bleeds into the space between the arachnoid membrane and the pia mater. The same event can also occur when a developmental anomaly within the vascular wall (aneurysm) ruptures and blood extravasates within the same space. Visible bleeding detected by neuroimaging may not be identified in up to 15 % of cases (Raya and Diringer 2014). The extravascular blood produces a secondary injury to the blood vessel that results in varying levels of cerebral vasospasm, which causes constriction of the affected blood vessel and restricting of CBF in the distal cerebral territory fed by the blood vessel. The vasospasm is often delayed from 3 to 14 days after the bleeding event. Hemorrhage-associated vasospasm is capable of producing progressive decline in neurologic function, coma extensive cerebral infarction, and sometimes brain death (Rigamonti et al. 2008). Currently, the gold standard for vasospasm diagnosis is cerebral angiography. However, this procedure does not allow for bedside monitoring, which is needed for unstable critically ill patients with

vasospasm SAH. Recently, TCD has emerged as an inexpensive, noninvasive tool used for bedside monitoring of vasospasm after SAH (Marshall et al. 2010). Close monitoring of patients with TCD following SAH permits early treatment of the development of narrowing cerebral arteries through medication.

Cerebral edema is swelling in parenchymal brain tissue due to increased intracranial pressure from fluid accumulation as a result of a severe TBI or any nontraumatic ischemic event. It is a potential cause of the devastating consequence of cerebral herniation, which if not quickly corrected leads to either a vegetative state or death (Asil et al. 2003; Arch and Sheth 2014). TCD may be used in two situations for detection of cerebral swelling: in its conventional way, measuring blood flow in cerebral arteries, looking for decreased flow as a result of pressure from edema in the territories being fed by the insonated blood vessels, and also as a monitor of intracranial pressure, which is related to hemodynamic indices. TCD studies have shown a correlation between PI and cerebral edema (Muttagin et al. 1993). Cerebral swelling from direct brain injury typically occurs within the first 1–3 days after the inciting event, far earlier than witnessed with brain injury as a result of cerebral vasospasm. Rising resistance indices within one or more vessels during the time frame of the two mechanisms of injury is useful in detecting these two vascular complications, and necessary interventional therapies can be delivered to ameliorate or reverse permanent cerebral damage that can ensue.

Sickle Cell Disease

Sickle cell disease (SCD) is a life-threatening genetic disorder that affects nearly 100,000 individuals in the United States (Yawn et al. 2014) and is associated with life-threatening cerebral complications. Cerebral complications primarily result from progressive vascular stenosis principally located at the juncture of the intracranial component of the internal carotid artery, middle cerebral artery, and anterior cerebral artery. Progressive stenosis results in a gradual attenuation of CBF to the distribution of the anterior circulatory territories that comprise more that 80–85 % of the cerebral hemispheres. A subset of the SCD population develop a particularly aggressive course and can suffer cerebral infarction as early as 4 years of age and continue to suffer new cerebral infarction as the disease progresses. The primary therapy to control disease progression is long-term blood transfusions to reduce the sickle cell percentage of the blood to less than 30 % (Yawn et al. 2014). In order to avoid wasting valuable blood resources and exposing the entire SCD population to repeated blood transfusions, screening for stenosis is the ideal method to identify the population at risk for stroke. TCD can identify with high-fidelity children with sickle cell disease who develop a risk of stroke (Adams et al. 1992). Annual TCD monitoring with intervention in cases with high TCD velocities (more than 200 cm/s) is the standard of care in children with sickle cell disease and has been shown to effectively reduce the incidence of stroke (Sloan et al. 2004).

Cardiac Right-to-Left Shunts

Patent foramen ovale is a relatively common residual congenital cardiac defect with an incidence of about 5 % in the general population (Wu et al. 2004). The presence of an intracardiac shunt has long been considered an emerging cause of cardioembolic cerebral infarction (Arboix and Alio 2012). It is unclear whether or not it is causal to stroke or transient ischemic attack (Katsanos et al. 2014). TCD has been used to detect with a high degree of fidelity right-to-left shunts (RLS) such as patent foramen ovale, atrial septal defect, and patent ductus arteriosus. A meta-analysis showed weighted mean sensitivity and specificity of 97 % and 93 %, respectively, when using TCD to detect RLS, using transesophageal echocardiography (TEE) as the standard (Mojadidi et al. 2014), and a preliminary study showed that, when TCD and TEE or transthoracic echocardiography were both performed, 25 % of the population TCD detected an RLS that the other method did not (de Havenon et al. 2015).

Brain Death

The concept of brain death was first introduced in 1959, marked as the "irreversible cessation of all functions of the entire brain" (Wijdicks 2001). According to the most recent report of the Quality Standards Subcommittee of the American Academy of Neurology (Wijdicks et al. 2010), in addition to cerebral angiography and electroencephalography (EEG), TCD is listed as a method of ancillary testing for the determination of brain death (Wijdicks et al. 2010). Abnormalities that may be identified in the MCA suggesting the event of brain death include reverberating flow or small systolic peaks during early systole (Wijdicks et al. 2010). The main advantage of TCD in comparison to EEG or cerebral angiography is the diagnostic power for early confirmation of brain death. Early confirmation of brain death gives families time to cope and reach closure and improves the opportunity to consider organ donation.

Potential Applications to Prognosis and Other Diseases or Conditions

Functional TCD

The relationship between neural activity and cerebral blood flow has long been known since first described by Fulton (1928). Later studies have confirmed a close relationship between brain activity and blood flow (Raichle et al. 1975; Heiss and Podreka 1978; Kuschinsky 1991). Cerebral blood flow (CBF) is regulated by the vasodilation and vasoconstriction of small cerebral arteries (Huber and Handa 1967) and cerebral precapillaries and arterioles (Itoh and Suzuki 2012). Currently, functional magnetic resonance imaging (fMRI) is a popular technique used to measure hemodynamic changes that can be related to neural activation (e.g., see (Hurschler

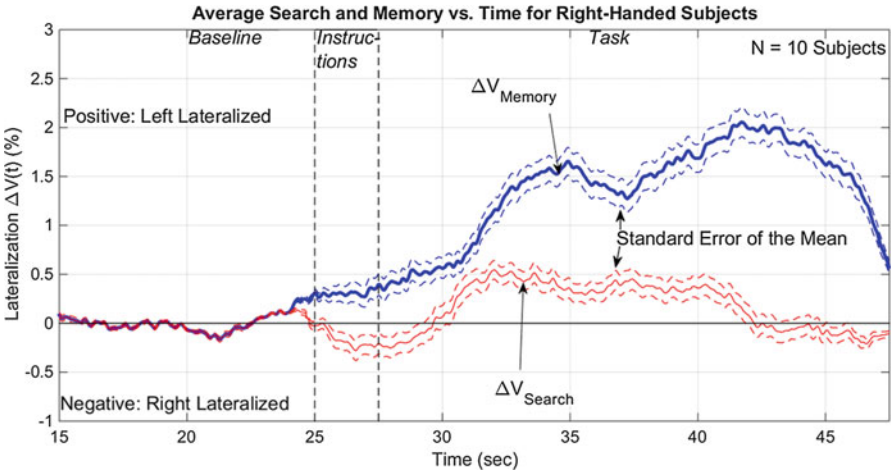

Fig. 9 Example of the use of functional TCD to measure the lateralization in response to two different stimuli: a search task and a memory task. The average lateralization versus time for the two tasks ($\Delta V_{Search}(t)$ and $\Delta V_{Memory}(t)$) is shown by *solid lines*. *Dashed lines* above and below *solid lines* represent +/− 1 standard error of the mean. The experiment consisted of a baseline period in which no stimuli were presented, an instruction period in which subjects had to read instructions, and a task period in which subjects were shown a visual scene on a computer screen and asked to perform the appropriate task (Hage et al. 2015)

et al. 2015; Greve et al. 2013; Poldrack 2012), but this technique has the disadvantages of high cost and having limited time resolution for imaging transient changes in hemodynamics (Marxen et al. 2012).

After describing TCD in 1982, Aaslid was able to show an increase in CBFV in the posterior cerebral artery in response to a visual stimulus (Aaslid 1987), one of the first demonstrations of "functional" TCD (fTCD). One important application of fTCD was in determining hemisphere dominance, eventually replacing the Wada test, which is an invasive test administered before epilepsy surgery in order to determine the dominant hemisphere for language in a patient (Knecht et al. 1998). Studies have also shown that fTCD can provide very accurate information on neural activation and lateralization during cognitive tasks; for example, on verbal tasks (Knecht et al. 1996, 1998; Meyer et al. 2014; Deppe et al. 2004; Vingerhoets and Stroobant 1999), visuospatial tasks such as design comparison and mental rotation of figures (Vingerhoets and Stroobant 1999), and perceptual speed and visual discrimination tasks (Schmidt et al. 1999). Most recently, studies have shown the ability of TCD to determine lateralization (Fig. 9) in visual memory and visual search tasks simultaneously (Hage et al. 2015). Some studies have shown right lateralization of blood flow in the MCA during emotional responses to negative stimuli, suggesting that the right hemisphere is more active in processing emotional stimuli than the left; it has also been shown that this right lateralization in response to emotional stimuli is absent in Parkinson's disease patients (Troisi et al. 1999, 2002). Future work may extend this study of lateralization in the processing of emotions to depressed patients.

Alzheimer's Disease

Currently, dementia affects more than 44 million people worldwide (Alzheimer's Disease International 2014). Alzheimer's disease (AD) is the leading cause of dementia, where approximately 50–75 % of all dementia cases are caused by AD. There is no single test to diagnose AD. However, a variety of approaches and tools are available to help make a diagnosis (Alzheimer's Association 2015). Current diagnostic tools and measures are either invasive (cerebrospinal fluid (CSF) proteins) or expensive (Pittsburgh compound B (PIB) brain scan) (Laske et al. 2015). TCD is a noninvasive, cost-effective tool, and studies have shown that TCD may be a very promising screening tool for AD. CBFV, pulsatility index (PI), and cerebrovascular reactivity (CVR) are the most studied parameters for AD diagnosis with TCD (Tomek et al. 2014).

Compared with healthy control subjects, research using TCD suggests that individuals with AD and mild cognitive impairment (MCI) have significantly lower CBFV and higher PI values, particularly in the middle cerebral artery (Stefani et al. 2009). Moreover, a longitudinal study showed that subjects with greater CBFV velocity were less likely to develop Alzheimer's disease (Ruitenberg et al. 2005).

CVR is a change in CBVF in response to a vasodilatory or vasoconstrictive stimulus (Fierstra et al. 2013). The primary types of vasoactive stimuli include the injection of acetazolamide (Markus and Harrison 1992), the breathing of a 5 % carbon dioxide gas mixture, and the breath-holding method. The most commonly used stimulus utilized to measure CVR with transcranial Doppler is the breath-holding (BH) test. In this method, CVR is calculated by the following formula (Shim et al. 2014)

$$\frac{(\text{Average CBFV before BH}) - (\text{maximum CBFV during BH})}{\text{average CBFV before BH}} \times 100\% \quad (1)$$

Studies indicate not only significantly lower CVR values in AD and MCI patients versus controls but additionally show significantly lower CVR values in AD versus MCI (Shim et al. 2014). This method is accurate enough to distinguish between AD and MCI. This accuracy may be used for future applications in distinguishing the preclinical stage of Alzheimer's disease.

Mild Traumatic Brain Injury and Concussion

Concussion (a subset of TBI) affects hundreds of thousands of high school, college, and professional athletes each year (Len et al. 2011; Alsalaheen et al. 2010). An estimated 300,000 sports-related concussions occur annually in high school alone (Marar et al. 2012). Concussions are a complex pathophysiological process that can have long-term consequences on an athlete's brain function, balance, and behavior (McCrory et al. 2013).

Some studies suggest that normal CVR responses may be disrupted immediately after concussion (Len et al. 2011; Dewitt and Prough 2003). TCD provides a useful method for assessing CVR impairment after concussion. Combining transcranial Doppler technology with standard postural control feedback measurement methods could offer an objective, quantitative tool for clinical use as an improved concussion-screening protocol. The ability to simultaneously and synchronously acquire cerebral hemodynamic data and postural control data has recently been shown (Honaker et al. 2015).

Summary Points

- Transcranial Doppler is a subset of the conventional diagnostic ultrasound modality that is specifically designed to measure blood flow in cerebral arteries.
- Transcranial Doppler is equivalent to pulsed-wave (PW) Doppler in conventional ultrasound, operating at a low frequency (1–2 MHz) in order to penetrate the cranium.
- Compared to other brain-imaging modalities, TCD is inexpensive, easily portable, and provides real-time (on the order of 100 samples per second) blood flow velocity data.
- The dynamic nature of transcranial Doppler, and the ease of capturing fast transient blood flow responses due to artificial stimuli, allow for diagnosis of a variety of pathologies affecting cerebral autoregulation.
- Because blood flow has been shown to be correlated with neural function, TCD can be used in a variety of ways to locate and quantitate brain activity.

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