Advances in Transcranial Doppler Ultrasonography

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Current Neurology and Neuroscience Reports 2009, **9**:46–54
Current Medicine Group LLC ISSN 1528-4042

Transcranial Doppler ultrasonography (TCD) is the only noninvasive real-time neuroimaging modality for the evaluation of characteristics of blood flow in basal intracerebral vessels that adds physiologic information to structural imaging. TCD has been rapidly evolving from a simple noninvasive diagnostic tool to an imaging modality with a broad spectrum of clinical applications. In acute stroke, TCD can provide rapid information about vascular stenosis and occlusion, the hemodynamic status of the cerebral circulation, and real-time monitoring of recanalization. Extended applications such as vasomotor reactivity testing, emboli monitoring, and right-to-left shunt detection help clinicians ascertain stroke mechanisms at the bedside, plan and monitor treatment, and determine prognosis. In the neurointensive care unit, TCD is useful for detecting increased intracranial pressure and confirming cerebral circulatory arrest. TCD is of established value for screening children with sickle cell disease and detecting and monitoring vasospasm after spontaneous subarachnoid hemorrhage.

Introduction

The pathophysiology of acute ischemic stroke is heterogeneous. Neurovascular imaging is essential for accurate delineation of the stroke mechanism and the development of acute stroke therapies [1]. Several studies have evaluated digital subtraction angiography (DSA), contrast-enhanced CT angiography (CTA), magnetic resonance angiography (MRA), and ultrasound in the acute stroke setting [2]. Rapid identification of the location and severity of arterial obstruction aids triage of acute stroke patients.

Transcranial Doppler ultrasonography (TCD) is the only noninvasive real-time modality for evaluation of characteristics of blood flow in basal intracerebral vessels that adds physiologic information to structural imaging [3••,4–6,7••]. TCD is relatively inexpensive, can be performed at the bedside, and allows monitoring both in acute emergency settings and for prolonged periods, with a high temporal resolution making it ideal for studying dynamic cerebrovascular responses. For the vascular neurologist or neurointensivist with experience in cerebrovascular ultrasound, small and portable TCD devices serve as a "stethoscope for the brain"; they are an extension of the clinical neurologic examination. CTA and MRA are alternative modalities for assessment of vessel patency in acute stroke [8]. However, in contrast to TCD, CTA and MRA are "snapshots in time" and are unable to provide continuous information about arterial patency and cerebral hemodynamics in diverse clinical settings.

Two major limitations of TCD impede its more widespread use. It is highly operator dependent, with the handheld technique requiring detailed three-dimensional knowledge of cerebrovascular anatomy. TCD also is hampered by the 10% to 15% rate of inadequate temporal windows most commonly seen in blacks, Asians, and elderly female patients [2]. This is related to thickness and porosity of the temporal bone attenuating ultrasound energy transmission. A newer technology called power motion-mode (or M-mode) TCD (PMD/TCD) appears to improve window detection and simplifies operator dependence of TCD by providing multigate flow information simultaneously in the power M-mode display [9,10]. PMD/TCD facilitates temporal window location and alignment of the ultrasound beam to allow visualization of blood flow from multiple vessels simultaneously without sound or spectral clues (Fig. 1).

The American Society of Neuroimaging's Practice Guidelines Committee recently developed guidelines for TCD performance based on literature analysis and extensive personal experience [3••]. These guidelines describe complete diagnostic spectral TCD examination for patients with cerebrovascular diseases. Although there is a significant individual variability of the circle of Willis

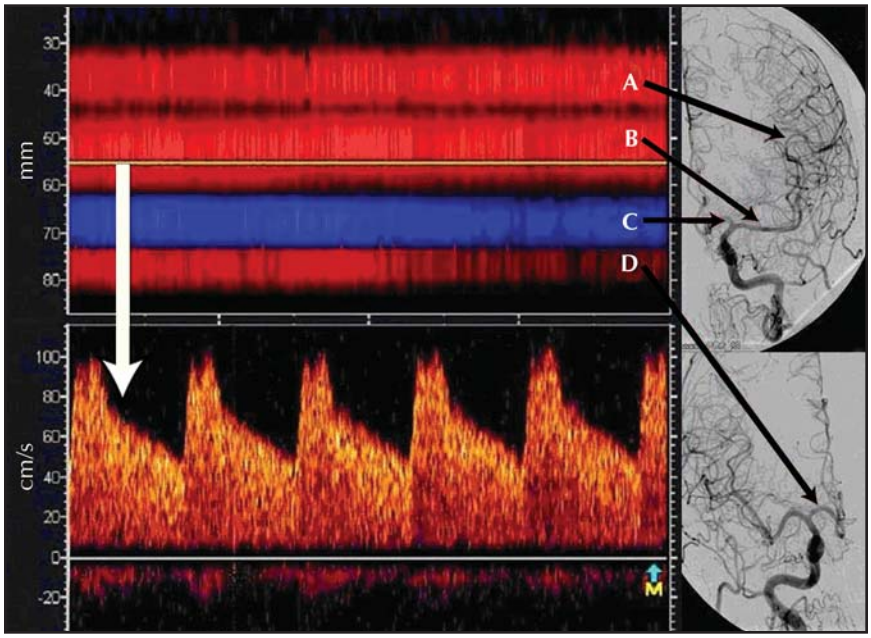

Figure 1. Examination of normal anterior circulation vessels with power motion-mode Doppler during left transtemporal insonation. **A,** left M2 middle cerebral artery (MCA); **B,** left M1 MCA; **C,** left anterior cerebral artery; **D,** right anterior cerebral artery. Sample volume interrogation is set at a depth of 55 mm (M1 MCA).

with and without disease, performance goals of diagnostic TCD should detect and optimize arterial segment-specific spectral waveforms, determine flow direction, and measure cerebral blood flow velocities and flow pulsatility. These practice standards will assist laboratory accreditation processes by providing a standard scanning protocol with transducer positioning and orientation, depth selection, and vessel identification for ultrasound devices equipped with spectral Doppler and PMD/TCD. Future guidelines are expected to address the issues of TCD interpretation and competencies.

Detection of Intracranial Arterial Steno-occlusive Disease

Acute occlusion

A fast-track insonation protocol has been developed for rapid TCD performance and interpretation in the emergency setting of acute cerebral ischemia [11]. Using this protocol (Table 1 in the article by Chernyshev et al. [11]), urgent TCD studies can be completed and interpreted within minutes at the bedside by the treating clinician, nurse, or technologist. The choice of fast-track insonation steps is determined by clinical localization of the infarct-related artery. Most studies can be accomplished within minutes and in parallel with the neurologic examination and other necessary testing. If performed by experienced sonographers, this fast-track ultrasound examination at bedside does not delay treatment.

Although angiographic tests and TCD yield similar results when performed by experienced users [12,13], the scanning protocols and diagnostic criteria used to interpret TCD vary between centers. Some studies limit TCD assessment to the M1 middle cerebral artery (MCA) segments, perform data analysis by calculating only the velocity asymmetry, and do not provide sufficient details on specific TCD scanning procedures. The yield of an urgent ultrasound examination depends on definition of an acute arterial occlusion, the time delay between symptom onset and ultrasound testing, and stroke severity at the time of ultrasound examination.

Unlike coronary arteries, which are small and move considerably with heart contractions, the proximal branches of the circle of Willis are more steadily positioned and can be easily targeted with ultrasound. The thrombolysis in brain ischemia (TIBI) flow grading system was developed to evaluate residual flow noninvasively and to monitor thrombus dissolution in real time (Fig. 2; Table 1) [14]. The TIBI system expands previous definitions of acute arterial occlusion by focusing the examiner's attention on relatively weak signals with abnormal flow waveforms that can be found along arterial stems filled with thrombi. TIBI flow grades correlate strongly with stroke severity and mortality as well as likelihood of recanalization and clinical improvement [15].

Chernyshev et al. [11] reported scanning protocols and interpretation criteria for the neurovascular ultrasound examination (NVUE) that consist of emergent TCD coupled with carotid duplex ultrasound. NVUE had a high yield and accuracy in diagnosing lesions amenable to interventional treatment (LAIT) in patients both eligible and ineligible for thrombolysis. LAIT was defined as an occlusion or near-occlusion, or at least 50% stenosis or thrombi in an artery supplying brain areas affected by ischemia. Compared with DSA, NVUE screening criteria (Table 2 in the article by Chernyshev et al. [11]) predicted the presence of LAIT with 100% sensitivity and 100% specificity despite a 10% rate of no temporal windows and even though individual accuracy parameters for TCD and carotid duplex specific to occlusion location ranged from 75% to 96% because

Table 1. Thrombolysis in brain ischemia (TIBI) flow grading system

TIBI 0: Absent	No flow signals or lack of regular pulsatile flow signals despite varying degrees of background noise
TIBI I: Minimal	Systolic spikes of variable velocity and duration
	Absent diastolic flow during all cardiac cycles; reverberating flow is a type of minimal flow
TIBI II: Blunted	Flattened or delayed systolic flow acceleration compared with control side
	Positive ED velocity
	PI < 1.2
TIBI III: Dampened	Normal systolic flow acceleration
	Positive ED velocity
	≥ 30% decrease in MFV compared with control side
TIBI IV: Stenotic	MFV ≥ 80 cm/s and velocity difference > 30% compared with control side; if velocity difference is < 30%, look for additional signs of stenosis (ie, turbulence, spectral narrowing)
	Affected and comparison sides have MFVs < 80 cm/s due to low ED velocities; MFV > 30% compared with control side; signs of turbulence
TIBI V: Normal	< 30% MFV difference compared with control side
	Similar waveform shapes compared with control side

ED—end-diastolic; MFV—mean flow velocity; PI—pulsatility index.

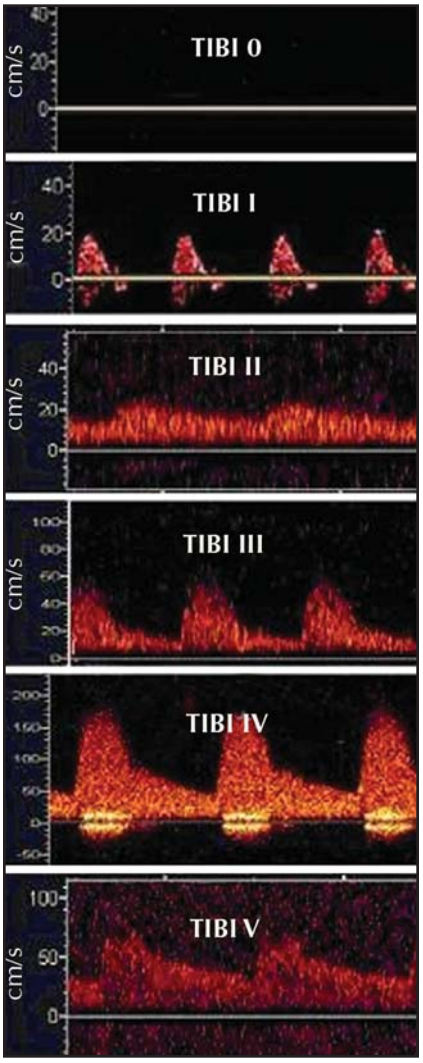

Figure 2. Thrombolysis in brain ischemia (TIBI) residual flow grades. Doppler flow spetra are shown for each TIBI flow grade. See Table 1.

of the presence of tandem lesions. Finally, Tsivgoulis et al. [15] recently reported that PMD/TCD real-time flow signatures can provide information that is complementary to the findings of other imaging modalities, such as CTA (eg, embolization, collateralization of flow with extracranial internal carotid artery [ICA] disease, and alternating flow signals during suboccipital insonation indicative of subclavian steal phenomenon).

Intracranial stenosis

The Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial aimed to define the positive and negative predictive value of TCD/MRA for the identification of 50% to 99% intracranial stenosis in the intracranial ICA, MCA, vertebral artery, and basilar artery (BA) [7••]. SONIA standardized the performance and interpretation of TCD, MRA, CTA (when available), and catheter-based angiography. Studywide cut points defining positive TCD/MRA were used. Hard-copy TCD/MRA studies were centrally read by investigators who were blinded to the results of catheter-based angiography. The trial showed that TCD and MRA can reliably exclude the presence of intracranial stenosis (negative predictive value > 80%). However, abnormal findings on TCD or MRA require a confirmatory test such as angiography to reliably identify stenosis.

Evaluation of Collateral Circulation

Collateral flow helps to maintain cerebral perfusion in the setting of arterial occlusion [16]. Several studies have established the importance of collateral flow in predicting stroke outcome by correlating the degree of collateral circulation with infarct volume and functional status [17,18]. TCD can detect some of these collateral pathways by providing real-time information regarding the direction and the velocity of blood flow.

The intracranial collateral channels are dormant under normal circulatory conditions. A collateral channel opens when a pressure gradient develops between the two arterial systems that have anastomoses. Flow direction will depend on the direction of collateralization and will determine which arterial system is the donor (the source of flow) and which is the recipient (the collateral flow destination). When present, a collateral flow pattern typically implies the presence of a flow-limiting lesion proximal to the site of insonation, which involves the recipient arterial system and the origin of the collateral channel [19,20].

Evaluation of Recanalization

Arterial recanalization indicates successful thrombolysis and often precedes early clinical improvement in ischemic stroke. A recent meta-analysis confirmed the open-artery hypothesis by showing that the occurrence of recanalization is associated with a fourfold to fivefold increase in the odds of a good final functional outcome and a similar reduction in the odds of death. These results lend strong support to the use of recanalization as a surrogate end point in phase 2b trials of neurovascular reperfusion agents and in trials comparing novel and existing predicate recanalization devices in acute ischemic stroke [21].

TCD provides a noninvasive bedside tool for real-time monitoring of the initiation, speed, timing, and amount of arterial recanalization. When recanalization begins, the clot softens and partially dissolves to allow improved residual flow and deliver more tissue plasminogen activator (tPA) to bind with fibrinogen sites. This continuous process facilitates clot lysis under the pressure of arterial blood pulsations. Therefore, the speed of clot lysis can be measured through the temporal profile of flow improvement with real-time ultrasound monitoring of the presence and intensity of TIBI residual flow signals, appearance of microembolic signals, velocity, and pulsatility changes [22]. The initiation, speed, timing, and amount of recanalization represent important monitoring parameters of thrombolytic therapy for acute ischemic stroke and are measured as follows:

1. Waveform change by ≥ 1 TIBI residual flow grade (eg, absent to minimal, minimal to blunted, and minimal to normal signal improvement);
2. Appearance of embolic signals (transient high-intensity signals of variable duration);
3. Flow velocity improvement by ≥ 30% at a constant angle of insonation;
4. Signal intensity and velocity improvement of variable duration at constant skull–probe interface and gain/sample volume/scale settings;
5. Appearance of flow signals with variable (≥ 30%) pulsatility indexes (PIs) and amplitude of systolic peaks.

Once the recanalization process begins, TCD can identify the timing of the highest TIBI flow grade that will indicate completion of recanalization. In patients who experience partial or complete thrombus dissolution, arterial recanalization can be classified as 1) sudden (abrupt appearance of a normal or stenotic low-resistance signal); 2) stepwise (flow improvement over 1 to 29 minutes); or 3) slow (≥ 30 minutes) [22]. Rapid arterial recanalization is associated with better short-term improvement, most likely because of faster and more complete clot breakup with low resistance of the distal circulatory bed [23]. Slow flow improvement and dampened TIBI flow signals are less favorable prognostic signs. Christou et al. [24] noted that among patients who had no change in the severity of neurologic deficit or who worsened by four or more points on the National Institutes of Health Stroke Scale (NIHSS), none had complete recanalization within 300 minutes, implying that a persisting occlusion on TCD may represent severe ischemia [24]. These patients may constitute a target group for further reperfusion therapies such as combined intravenous and intra-arterial thrombolysis or mechanical thrombectomy.

Assessment of Vasomotor Reactivity

Data from randomized controlled trials indicate that hemodynamic and thromboembolic mechanisms of stroke are important in patients with carotid atherosclerosis [25], and interest has recently focused on identifying patients with asymptomatic or symptomatic severe carotid stenosis at the highest risk for stroke [26]. Therefore, vasomotor reactivity (VMR) testing as an index of intracranial collateral capacity may have value in predicting the natural history of asymptomatic carotid occlusive disease and stroke occurrence [26].

VMR assessed by TCD using vasodilating or vasoconstricting stimuli is not a measure of autoregulation. Cerebral autoregulation maintains constant cerebral blood flow with physiologic variations in blood pressure. Changes in the concentration of CO_2 induce a vasomotor response that changes cerebral blood flow parallel with the blood flow velocity changes [27]. Thus, flow velocity changes on TCD during normocapnia, hypercapnia, and hypocapnia may prove to be a useful index of VMR and the capacity of smaller cerebral arteries to adapt to various stimuli. Although decreased VMR was observed in patients with ICA occlusions and symptomatic carotid artery disease in many studies, normal VMR also could be seen in these patients [28,29]. Ringelstein and colleagues [28,29] reported that VMR on the occluded or affected side was decreased by an average of 20% to 25% in comparison with the nonoccluded side or normal controls. Patients with low-flow infarctions, ischemic retinopathy, and recurrent transient ischemic attacks had VMR of less than 38%, which is less than 3 SDs below the normal

controls. VMR also decreases with the severity of carotid stenosis and increases after carotid endarterectomy by an average of 20% to 25% [28,29]. Silvestrini and colleagues [30] prospectively tested the hypothesis that patients with ICA stenosis may be at an increased risk for stroke due to decreased or exhausted vasomotor reserve capacity shown by TCD. In that study, impaired VMR was an independent predictor of recurrent stroke in patients with asymptomatic ICA stenosis or occlusion.

Detection of Cerebral Embolization

TCD can detect spontaneous microembolization of cerebral vessels in real time, and this finding may suggest a vascular origin of focal neurologic symptoms and allow clinicians to investigate potential proximal sources of embolism (heart chambers and septum, aortic arch, arterial stenosis, or dissection) [8]. Moreover, detection of microembolic signals with TCD during intravenous injection of agitated normal saline ("TCD bubble study") may identify paradoxic embolization through a cardiac right-to-left shunt, which is a common cause of ischemic stroke in young stroke patients [8].

In 2004, Rune Aaslid's first ambulatory TCD system (like a Holter monitor for MCA flow velocity) was tested in a clinical setting and showed good-quality digital recordings for more than 5 hours. In view of temporal variability in embolization rates, the authors postulated that this technique would be likely to improve the predictive value of recording for asymptomatic microembolic signals and could be particularly useful in patients in whom embolic signals are relatively infrequent, such as those with asymptomatic carotid stenosis and atrial fibrillation [31]. The same group used 1-hour continuous TCD monitoring of the ipsilateral MCA in 200 patients with more than 50% ICA stenosis. After noting that asymptomatic embolization in carotid stenosis predicted short-term ipsilateral stroke risk, the authors concluded that their findings support the use of TCD to identify patients at high risk for recurrent stroke for therapeutic interventions and as a surrogate marker to evaluate antithrombotic medication [32]. The latter hypothesis was tested in the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial, a randomized, double-blind study in subjects with recently symptomatic carotid stenosis of at least 50%. Patients were screened with TCD and, if microembolic signals were detected, randomized to clopidogrel and aspirin or aspirin monotherapy. Repeated TCD recordings were made on days 2 and 7. CARESS showed that combination therapy with clopidogrel and aspirin was more effective than aspirin alone in reducing asymptomatic embolization in patients with recently symptomatic carotid stenosis [33].

In their pivotal paper describing the development of PMD/TCD, Moehring and Spencer [9] highlighted its potential superiority over single-channel TCD in the detection of microembolic flow signatures. Independent prospective studies conducted in neurosonology laboratories of academic centers provided further evidence for this hypothesis. Saqqur and colleagues [34] have developed stringent criteria for tracking embolic flow signatures on a PMD/TCD track. They showed that, compared with spectral TCD, transcranial PMD/TCD detected more microbubbles, thereby improving the diagnostic accuracy of PMD/TCD in detecting cardiac right-to-left shunts. The reason for the increased yield of microbubble counts with PMD/TCD is greater spatial sampling with simultaneous insonation of MCAs and anterior cerebral arteries (ACAs), allowing detection of emboli traveling in either artery before and after the Valsalva maneuver. Interestingly, in a post hoc analysis, transcranial PMD/TCD continued to show improved microbubble detection when only the MCA counts were assessed.

Detection of Increased ICP

Several approaches have been used to describe the relationship between TCD variables, cerebral perfusion pressure (CPP) and intracranial pressure (ICP). After evaluating patients with severe traumatic brain injury, Chan et al. [35] reported that flow velocities (especially diastolic) decreased as ICP increased and CPP decreased. Below a CPP threshold of 70 mm Hg, a progressive increase was documented in the TCD PI (peak systolic velocity - end-diastolic velocity/mean flow velocity). Homburg et al. [36] found that the PI changes by 2.4% per 1 mm Hg of ICP.

We are currently using the following algorithm to differentiate the mechanisms of increased resistance to flow [37]. If the PI is ≥ 1.2 and a positive end-diastolic flow is present in all arteries, this could be due to hyperventilation, hypertension, or increased ICP; if present in unilateral vessels, this could be due to a compartmental ICP increase, high-grade stenosis or occlusion distal to the site of insonation, intracranial hemorrhage with mass effect, or hydrocephalus; or, if present in one artery, the likely causes are distal obstruction (spasm, stenosis, edema) or hypoplasia. If the PI is ≥ 2.0 and end-diastolic flow is absent in all arteries, extremely high ICP or arrest of cerebral circulation is possible; if present in unilateral vessels, a compartmental ICP increase or occlusion distal to insonation site is possible; or, if present in one artery, distal obstruction (occlusion, severe spasm, edema) is possible.

Detection of Cerebral Circulatory Arrest

A progressive elevation of ICP to extreme levels due to brain edema and mass effect can lead to stepwise compression of small to large intracranial arteries causing cerebral circulatory arrest. A prolonged absence of brain perfusion will eventually lead to brain death. If cerebral

circulatory arrest is suspected, the following diagnostic algorithm is used [37]:

- Positive MCA or BA end-diastolic flow = no cerebral circulatory arrest.
- Absent end-diastolic flow = uncertain cerebral circulatory arrest (too early or too late).
- Reversed minimal end-diastolic flow = possible cerebral circulatory arrest (continue monitoring).
- Reverberating flow = probable cerebral circulatory arrest (confirm in both MCAs at the depths of 50–58 mm and BA at 80–90 mm; then monitor arrest for 30 minutes).

Recently, de Freitas and Andre [38•] performed a systematic review of studies evaluating the use of TCD in patients with the clinical diagnosis of brain death. The overall sensitivity was 88%, and the overall specificity was 98%. The cause of false negatives was a lack of signal in 7% of cases and persistence of flow in the remaining 5%. However, the criteria for brain death were variable, with only seven groups assessing the vertebrobasilar artery and some authors accepting the absence of flow in only one artery.

Detection of Vasospasm

Arterial vasospasm is a complication of subarachnoid hemorrhage (SAH) that becomes symptomatic in more than 25% of patients by producing ischemic brain damage and a delayed ischemic deficit [37]. Delayed ischemic deficit usually occurs when vasospasm results in severe (≤ 1 mm) intracranial arterial narrowing producing flow depletion with extremely high velocities. It may affect the proximal stem and distal branches of intracranial arteries. Vasospasm may coexist with hydrocephalus, edema, and infarction. The differential diagnosis with TCD should always include hyperemia, and it is possible that spasm and hyperemia may coexist because most patients with SAH routinely receive hypertension-hemodilution-hypervolemia therapy.

Although quantitative criteria have been studied extensively [39,40], grading vasospasm severity is difficult, and the interpretation of TCD findings should be individualized. Daily TCDs may detect considerable changes in velocity or pulsatility, which should be related to factors such as the patient's condition, medications, blood pressure, and time after onset.

Proximal vasospasm in any intracranial artery results in a focal or diffuse elevation of mean flow velocities (MFVs) without a parallel FV increase in the feeding extracranial arteries (intracranial–extracranial vessel ratio > 3).

Distal vasospasm in any intracranial artery may produce a focal pulsatile flow (PI ≥ 1.2), indicating increased resistance distal to the site of insonation. No MFV increase may be found.

Additional findings may include daily changes in velocity, ratio, and PIs at any time during the first 2 weeks but particularly pronounced during the critical days 3 to 7 after the onset of SAH.

The differential diagnosis of vasospasm includes hyperemia, a combination of vasospasm and hyperemia in the same vessel, residual vasospasm, and hyperemia. Prognostically unfavorable signs include early appearance of MCA MFV ≥ 180 cm/s, rapid (> 20% or > 65 cm/s) daily MFV rise during critical days 3 to 7, MCA/ICA ratio ≥ 6, and abrupt appearance of high pulsatility (PI > 1.5) of flow in two or more arteries indicating increased ICP and/or distal vasospasm [40,41]. Based on the available evidence, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology has stated that TCD is useful for detecting vasospasm following spontaneous SAH (type A recommendation, class II evidence) [41].

Screening of Sickle Cell Disease

TCD has a pivotal role in predicting the risk of ischemic stroke in children with sickle cell disease. In a prospective study by Adams et al. [42], mean velocities greater than 170 to 200 cm/s were associated with a 44% increase in relative risk of ischemic stroke over 5 years. A subsequent randomized trial showed a 92% reduction in relative stroke risk when blood transfusion was administered in children with TCD findings of MFV ≥ 200 cm/s [43]. Moreover, a recent randomized controlled trial showed that discontinuation of transfusion for the prevention of stroke in children with sickle cell disease results in a high rate of reversion to abnormal blood flow velocities on Doppler studies and stroke [44]. Based on the available evidence, the Therapeutics and Technology Assessment Subcommittee has stated that TCD screening of children with SCD between the ages of 2 and 16 years is effective (type A recommendation, class I evidence) [41].

Therapeutic TCD

Clinical benefit from thrombolysis is directly related to achieving early recanalization. Experimental evidence suggests that ultrasound substantially increases the thrombolytic effect of tPA, particularly if used in the low megahertz to kilohertz frequencies. Ultrasound exposure causes various changes, such as reversible disaggregation of uncrosslinked fibrin fibers, microcavity formation in the shallow layers of thrombus, increased enzymatic transport improving tPA's uptake and penetration into clots, and residual flow enhancement with microstreaming and vessel dilation [45].

A pilot clinical study assessed whether such a therapeutic effect is possible in stroke patients [46]. Stroke patients receiving intravenous tPA were monitored with

portable TCD starting at the time of tPA bolus. Residual flow signals were obtained from the clot location identified by TCD. Among the 40 patients studied, the mean baseline NIHSS score was 19. Recanalization on TCD was found 45 ± 20 minutes after tPA bolus. Recanalization was complete in 12 (30%) patients and partial in 16 (40%) patients. Dramatic recovery during tPA infusion (NIHSS score ≤ 3 points) occurred in eight (20%) patients, all with complete recanalization. Lack of improvement or worsening was associated with no recanalization, late recanalization, or reocclusion on TCD. Improvement by at least 10 NIHSS points or complete recovery was found in 30% of all patients at the end of tPA infusion and in 40% at 24 hours. These preliminary data provided enthusiasm to initiate CLOTBUST (Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA), a phase 2 randomized controlled trial assessing whether such therapeutic monitoring can be safely applied to acute stroke patients. In this trial, 126 patients were randomly assigned to receive continuous TCD monitoring or placebo (63 patients in each group) in addition to intravenous tPA [47]. Complete recanalization or dramatic clinical recovery within 2 hours after the administration of a tPA bolus occurred in 49% of the target group and 30% of the control group ($P = 0.03$). Only 4.8% of patients developed symptomatic intracerebral hemorrhage (sICH). These results showed that 2-MHz continuous TCD monitoring had positive effects in acute stroke and did not increase the rate of sICH.

Various attempts have been made using low-frequency ultrasound to the occluded cerebral arteries. Although kilohertz frequencies penetrate better, a combination of tPA and an experimental kilohertz-delivery system resulted in an excessive risk of ICH in patients with ischemic stroke. The TRUMBI (Transcranial Low-Frequency Ultrasound-Mediated Thrombolysis in Brain Ischemia) multicenter clinical trial included 26 patients who experienced stoke within the preceding 6 hours; 12 of the patients received tPA, and 14 received tPA plus 90 minutes of low-frequency (300 kHz) ultrasound exposure [48]. The study was stopped prematurely due to an increased incidence of sICH (5 of 12 in tPA-only group vs 13 of 14 in the group with ultrasound). Parenchymal hemorrhages with subarachnoid extension or affecting normal brain tissue occurred in the combined treatment group. Potentially, reverberations of the long-wavelength ultrasound occurred inside the head, leading to "hot spots" in addition to the mechanical distortion of the brain microvessels with kilohertz frequencies.

In one study, combining tPA, ultrasound, and gaseous microbubbles showed a signal of further enhancing arterial recanalization [49]. Although these microbubbles, otherwise previously known as diagnostic microbubbles or gaseous microspheres, were originally designed to improve conventional ultrasound images, facilitating thrombolysis is now emerging as a treatment application for this technology. Newer-generation bubbles use specific phospholipid molecules that arrange themselves in nanobubbles with a consistent diameter of 1 to 2 μm or smaller when exposed to mechanical agitation. When injected intravenously, nanobubbles carry gas through the circulation. As the bubbles approach and permeate the thrombus, they can be detected and activated by the ultrasound energy. Upon encountering an ultrasound pressure wave, the phospholipid shell breaks up and releases gas. The result is bubble-induced cavitation with fluid jets that erode the thrombus surface. In the presence of tPA, this erosion increases the surface area for thrombolytic action and accelerates lysis of clots [49].

Molina et al. [50] first tested galactose-based air microbubbles (Levovist; Schering, Berlin, Germany) using 2-MHz TCD and intravenous tPA in humans with acute ischemic stroke. This first-generation microbubble technology is not approved by the US Food and Drug Administration for diagnostic use. The next-generation nanobubbles—the perflutren lipid nano-platform (MRX-815; ImaRx Therapeutics, Tucson, AZ)—are consistent and smaller in size. A multicenter dose-escalation controlled randomized trial using perflutren microspheres is being launched to address this issue.

Conclusions

TCD has clear clinical value in the diagnostic workup of acute stroke patients and is considered an essential tool of a comprehensive stroke center. TCD applications in the setting of acute cerebral ischemia are the detection of intracranial arterial steno-occlusive disease, collateral flow patterns, and asymptomatic microembolic flow signatures; real-time monitoring of recanalization; quantification of impaired VMR and increased ICP; and confirmation of cerebral circulatory arrest. Given the widespread availability of the equipment, increased use of TCD in acute stroke is expected. Advances in technology will focus on simplifying bone window determination and limiting the technique's operator dependency.

As the vascular neurology and neurocritical care communities grow, several factors must be considered when new neurologic intensive care units are created. Because TCD is highly operator dependent, in-depth specialized training is required. The use of TCD should be based on standardized scanning protocols and internally validated interpretation criteria. A professional society endorsing TCD practice should consider active participation in an accreditation process for vascular ultrasound laboratories (perhaps through the Intersocietal Commission for the Accreditation of Vascular Laboratories [www.icavl.org]). Accreditation could enhance the voluntary process of setting a practice standard by promoting competence, self-assessment, and continuing medical education in clinical applications of TCD.

Disclosures

No potential conflicts of interest relevant to this article were reported.

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- •• Of major importance

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Based on literature analysis and extensive personal experience, an international expert panel developed guidelines for TCD performance, interpretation, and competence. These practice standards will assist laboratory accreditation processes by providing a standard scanning protocol with transducer positioning and orientation, depth selection, and vessel identification for ultrasound devices equipped with spectral Doppler and PMD/TCD.

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The aims of the SONIA trial were to define abnormalities on TCD/MRA to see how well they identify 50% to 99% intracranial stenosis of large proximal arteries on catheter angiography. The findings show that TCD and MRA can reliably exclude the presence of intracranial stenosis. Abnormal findings on TCD ultrasound or MRA require a confirmatory test such as angiography to reliably identify stenosis.

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