Views and Reviews

Practice Standards for Transcranial Doppler (TCD) Ultrasound. Part II. Clinical Indications and Expected Outcomes

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ABSTRACT

INTRODUCTION

Transcranial Doppler (TCD) is a physiological ultrasound test with established safety and efficacy. Although imaging devices may be used to depict intracranial flow superimposed on structural visualization, the end-result provided by imaging duplex or nonimaging TCD is sampling physiological flow variables through the spectral waveform assessment.

SUMMARY OF RESULTS

Clinical indications considered by this multidisciplinary panel of experts as established are: sickle cell disease, cerebral ischemia, detection of right-to-left shunts (RLS), subarachnoid hemorrhage, brain death, and periprocedural or surgical monitoring. The following TCD-procedures are performed in routine in- and outpatient clinical practice: complete or partial TCD-examination to detect normal, stenosed, or occluded intracranial vessels, collaterals to locate an arterial obstruction and refine carotid-duplex or noninvasive angiographic findings; vasomotor reactivity testing to identify high-risk patients for first-ever or recurrent stroke; emboli detection to detect, localize, and quantify cerebral embolization in real time; RLS-detection in patients with suspected paradoxical embolism or those considered for shunt closure; monitoring of thrombolysis to facilitate recanalization and detect reocclusion; monitoring of endovascular stenting, carotid endarterectomy, and cardiac surgery to detect perioperative embolism, thrombosis, hypo- and hyperperfusion.

CONCLUSION

By defining the scope of practice, these standards will assist referring and reporting physicians and third parties involved in the process of requesting, evaluating, and acting upon TCD results.

Keywords: TCD, indications, applications and outcomes.

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Introduction

From the stand-point of ultrasound physics, transcranial Doppler (TCD) was invented[1] as one of the simplest tests based on a single-element transducer technology. Clinically, however, TCD is perhaps the most complex physiological test in vascular medicine requiring in-depth skill training and understanding of cerebrovascular anatomy, physiology, and a variety of clinically diverse pathological conditions. Regardless of whether imaging duplex ultrasound or nonimaging TCD system is used for intracranial flow assessment, the end-product is the spectral waveform analysis and determination of physiological flow variables. Hemodynamic changes within normal and abnormal states present a complex task of correct sampling, monitoring, and interpretation even for experienced users across multiple clinical conditions. These are some of the reasons why so few people mastered this technique over the past quarter of a century and so many still remain skeptical. Nevertheless, tremendous progress has been made to establish certain areas where TCD is beyond doubt a valid and reliable diagnostic test that provides unique information, complimentary and often unobtainable from other modalities, with its own prognostic and therapeutic significance. This multispecialty panel of experts convened by the Clinical Practice Committee of the American Society of Neuroimaging set the goal to define clinical indications for and expected outcomes of TCD testing in routine clinical practice.

With advances in stroke diagnosis, treatment, and prevention, TCD became the standard of care at comprehensive stroke centers being one of the essential diagnostic tests and services that a modern stroke team should have at their

Table 1. Diagnostic Test Performance Parameters Documented for TCD

Parameter	Areas covered by published studies
Applicability	Feasibility, tolerability, and success in consecutive patients: TCD is successfully applied to 90% of patients with cerebrovascular diseases with no reports of adverse outcomes in 26 years of research and practice worldwide.
Accuracy	Comparison with DSA/MRA/CTA as well as other clinically relevant studies or outcomes: TCD has good-to-excellent agreement with angiography for the detection of stenoses and occlusions; equal to superior accuracy in the detection of RLS versus TEE; and excellent agreement with nuclear flow studies in determining cerebral circulatory arrest.
Yield	Disease states which diagnosis with TCD was documented in research studies involving the gold standard imaging or clinical assessment range from intracranial stenoocclusive disease, collaterals to cerebral embolization, shunting, vasomotor reactivity, vasospasm after SAH, periprocedural and surgical monitoring, and cerebral circulatory arrest.
Prognosis	TCD has the ability to select children with sickle cell disease in need of blood transfusion and who should stay on blood transfusion to sustain the benefit for primary stroke prevention; to predict outcomes of thrombolytic therapy for acute stroke; to identify high-risk patients that will require interventions to reverse or prevent stroke and to provide less expensive follow-up assessments.

TCD = Transcranial Doppler, DSA = digital subtraction angiography; CTA = CT angiography; MRA = MR angiography; TEE = transesophageal echocardiography; RLS = right-to-left shunt; SAH = subarachnoid hemorrhage.

disposal.[2] Whether one's practice is hospital or office-based, TCD offers a low-cost diagnostic method to find high-risk patients for first-ever, recurrent stroke or stroke progression caused by intracranial steal phenomenon (reversed Robin Hood syndrome), identify stroke pathogenic mechanism, refine results of widely used imaging tests such as carotid duplex or noninvasive angiography, detect right-to-left shunts (RLS), and perform limited follow-up studies to avoid repetition of more expensive or invasive tests.[3-5] Furthermore, with advances in vascular interventions and cardiac surgery, TCD monitoring is now recognized as a practical tool to detect intra- and periprocedural events and prevent untoward outcomes.[3-5]

Specific Clinical Indications

Our multidisciplinary panel of experts reviewed the published literature on TCD from 1982 through December 2009 in their respective fields, including previous updates[6-9] and considered reported clinical indications as established if TCD performance has been tested in terms of applicability, yield, accuracy, and prognosis including outcomes (broadly defined as proven diagnostic value in a specific clinical situation, therapeutic implications of test results, identification of high-risk patients, detection of periprocedural complication mechanism, ie, when information derived from TCD impacted clinical decision making and the choice of management options). These criteria and review of areas that were evaluated in research studies are presented in Table 1.

Specific established clinical indications for TCD in routine clinical practice that met our criteria include: sickle cell disease, cerebral ischemia (stroke, transient ischemic attack; TIA), carotid artery stenosis and occlusions, vasospasm after subarachnoid hemorrhage (SAH), brain death, and periprocedural or surgical monitoring. For evaluating the quality of evidence and strength of recommendations for these specific clinical indications we used the "Format for an Assessment" (Table 2) developed by the American Academy of Neurology (for example, the assessment of clinical indications of single-photon emission computed tomography)[10] and used in a previous update of the American Society of Neuroimaging on TCD indications.[8] Details of these clinical indications and expected outcomes derived from published studies are presented in Table 3.

Sickle Cell Disease

TCD can identify children with the highest risk of first-ever stroke[10] and those in need of blood transfusion [Quality of evidence: class I; Strength of recommendation: type A].[11] In a pivotal trial,[11] TCD detection of time averaged maximum mean flow velocity of 200 cm/s on 2 separate examinations was used to determine the need for blood transfusion that resulted in 90% relative risk reduction of first-ever stroke. This

Table 2. Quality of Evidence and Strength of Recommendation Ratings According to the "Format for an Assessment" Developed by the American Academy of Neurology[4] and Adopted by the American Society of Neuroimaging[10]

Ratings	
Quality of Evidence	
Class I	Evidence provided by one or more well-designed, randomized controlled clinical trial
Class II	Evidence provided by one or more well-designed, clinical studies (eg, case control, cohort studies)
Class III	Evidence provided by one or more expert opinions, nonrandomized historic controls, or case reports
Strength of Recommendation	
Type A	Strong positive recommendation, based on class I evidence or overwhelming class II evidence when circumstances preclude randomized clinical trials
Type B	Positive recommendation, based on class II evidence
Type C	Positive recommendation, based on strong consensus of class III evidence
Type D	Negative recommendation, based on inconclusive or conflicting class II evidence
Type E	Negative recommendation, based on evidence of ineffectiveness or lack of efficacy, based on class II or class I evidence

Table 3. Established Clinical Indications for and Expected Outcomes of TCD Testing

Broad Indication	Specific Indications	Expected Outcomes
Sickle cell anemia	Children	Robust first-ever stroke risk reduction based on TCD criteria for the need of blood transfusion and continuing use of blood transfusions.
Ischemic Stroke or TIA	Patients with acute ischemic symptoms in anterior or posterior circulation who had cranial CT or MRI	TCD can identify patients with proximal arterial occlusions both in anterior and posterior circulation who have the worst prognosis and can benefit the most from intravenous thrombolysis or rescue intraarterial therapies.
Ischemic stroke or TIA	Patients with subacute ischemic symptoms in anterior or posterior circulation who had cranial CT or MRI	TCD helps determine stroke pathogenic mechanism that in turn determines secondary stroke prevention treatment, ie, antiplatelets versus anticoagulation versus stenting versus carotid endarterectomy or systemic hemodynamics manipulation in cases of stenoocclusive disease with hemodynamic compromise. TCD also helps to localize and grade intracranial atheromatous disease process, (anterior vs. posterior vessels, diffuse vs. local disease, $\geq$ 70% stenoses that indicate high risk of stroke recurrence).
Ischemic stroke or TIA	Symptomatic patient at any time window who underwent carotid duplex scanning	Carotid duplex ultrasound may explain only 15-25% of all ischemic events since the prevalence of $\geq$50% proximal ICA stenosis is low. TCD has the ability to further refine stroke mechanism detection by determining the presence of intracranial stenoocclusive disease, embolization, shunting, and impaired vasomotor reactivity (VMR).
Ischemic stroke or TIA	Patients with undetermined stroke mechanism, recurrent TIAs, artery-to-artery versus cardiac source of embolism, suspected arterial dissections	TCD is the gold standard test to detect, localize, and quantify cerebral embolism in real time. No other modality offers spatial and time resolution to detect microembolic activity, localize its source (artery vs. heart), and confirm vascular etiology of patient symptoms.
Ischemic stroke or TIA	Patients with suspected paradoxical embolism with negative echocardiography	TCD is equal or superior in its sensitivity to the presence of any right-to-left shunt compared to echocardiography (Valsavla maneuver is best accomplished during TCD, extracardiac shunting can be indirectly detected with TCD).
Ischemic stroke or TIA	Follow-up	TCD is an inexpensive noninvasive follow-up tool that can detect progression or regression in the severity of extra- and intracranial stenoses through direct velocity measurements, collaterals, and VMR assessment.
Asymptomatic or symptomatic carotid artery stenosis or occlusion	Patients who have the internal carotid artery (ICA) stenosis or occlusion on carotid duplex or angiography	TCD can help identify patients at highest risk of first-ever or recurrent stroke in the setting of an ICA stenosis of variable degree or complete occlusion. TCD findings of artery-to-artery embolization and impaired vasomotor reactivity indicate 3-4-fold higher risk of stroke compared to patients with similar degree of ICA stenosis and normal TCD findings.
Subarachnoid hemorrhage	Days 2-5	TCD can detect the development of vasospasm days before it can become clinically apparent, and this information can be used by intensivists to step up with hemodynamic management of these patients.
	Days 5-12	TCD can detect progression to the severe phase of spasm when development of the delayed ischemic deficit due to perfusion failure through the residual lumen is the greatest. This information can help planning interventions (angioplasty, nicardipine infusions).
	Days 12-end of ICU stay	TCD can document spasm resolution after treatment or intervention, sustainability of vessel patency, and infrequent cases of late or rebound vasospasm development at the end of the second or into the third week after subarachnoid hemorrhage.
Suspected brain death	Increased intracranial pressure, mass effect, herniation	TCD can rule out cerebral circulatory arrest if positive diastolic flow is detected at any ICP values. TCD can confirm clinical diagnosis of brain death by demonstrating complete cerebral circulatory arrest in anterior and posterior circulation. TCD offers serial noninvasive assessments and can minimize the number of nuclear flow studies needed to confirm the arrest of cerebral circulation.
Periprocedural or surgical monitoring	Carotid endarterectomy or stenting	TCD can detect all major causes of perioperative complications, ie, embolism, thrombosis, hypoperfusion, and hyperperfusion. TCD detects real-time flow changes that precede the development of neurological deficits or changes on electroencephalography.
Cardiovascular surgical monitoring	CABG, repairs of ascending aorta	TCD can detect cerebral embolization and hypoperfusion. TCD can help guide perfusion pump settings as well as cannulation and body positioning TCD can identify unsuspected causes of massive air embolization and guide surgeons to explore sites of possible arterial puncture.

trial demonstrated that TCD can select patients for the most effective primary stroke prevention intervention to date that had profound implications on management of children with sickle cell disease. Further observations confirmed that children initially selected by TCD for blood transfusion should stay on transfusion schedule to sustain the benefit in stroke risk reduction.[12] Moreover, recent data including long-term follow-up and final results from the Stroke Prevention Trial in Sickle Cell Anemia (STOP) indicated that persistent elevation in TCD velocities indicates ongoing stroke risk.[13] The skill of TCD testing in children with sickle cell anemia is taught through standard tutorials with sonographers receiving specialized certificates, and diagnostic criteria for interpreting physicians are well defined.[14,15]

Subarachnoid Hemorrhage

Numerous studies have shown the effectiveness of TCD in diagnosing cerebral vasospam both in anterior and posterior circulation following SAH [Quality of evidence: class II; Strength of recommendation: type B].[16-24] More specifically, TCD can detect the development of vasospasm days before it can become clinically apparent (days 2–5 following SAH onset), and this information can be used by intensivists to step up with hemodynamic management of these patients.[8,25] In addition, TCD can detect progression to the severe phase of spasm when development of the delayed ischemic deficit due to perfusion failure through the residual lumen is the greatest. The maximal sensitivity of TCD for detecting cerebral vasospasm is at 8 days after SAH onset, while its sensitivity for diagnosing delayed cerebral ischemia is lower (63%).[25] Also, a recent study has demonstrated the predictive superiority of TCD over single-photon emission computer tomography for the diagnosis of angiographically demonstrated cerebral vasospasm.[23] Moreover, Sloan and colleagues showed that TCD is highly specific (100%) for vertebral and basilar artery vasospasm when mean flow velocities are $\geq$80 and $\geq$95 cm/s, respectively.[24] Another independent study showed that patients with very high basilar artery mean flow velocities (>115 cm/s) had a 50% chance of developing delayed brainstem ischemia, which in turn was associated with adverse functional outcome.[21] Therefore, TCD information can help planning interventions including angioplasty and nicardipine infusions. Based upon the available evidence, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology has recently stated that TCD is useful for the detection of vasospasm following spontaneous SAH.[25]

Cerebral Ischemia

Acute Cerebral Ischemia

With over 1,700 papers published as of December 2009, this subject is one of the most studied among TCD applications. An indication "ischemic stroke" or "transient ischemic attack" may necessitate not only a complete diagnostic examination in order to detect the presence of stenoocclusive disease [Quality of evidence: class II; Strength of recommendation: type B], as outlined in our previous standards,[8,26] but also include vasomotor reactivity assessment, emboli detection, RLS testing as well as continuous real-time intracranial vessel monitoring. We in turn examine specific indications for these TCD tests.

The reasons to perform TCD in patients with suspected or confirmed cerebral ischemia are multiple. Complete or partial TCD examination evaluates up to 16 proximal intracranial arterial segments[26,27] with the goal of detecting normal, stenosed, or occluded intracranial vessels. Vessel patency has prognostic significance as patients with persisting occlusions have worse outcomes if reperfusion therapy is not instituted timely or is ineffective.[26-28] This information is also helpful to select patients for catheter angiography, intraarterial rescue (interventional devices for clot removal),[29] and potentially hemicraniectomy (surgical decompression to save lives after severe ischemic stroke).

TCD evaluation also has diagnostic significance to identify stroke pathogenic mechanism, ie, large-vessel stenosis of $\geq$50%, or artery-to-artery embolism as opposed to a cardiac or paradoxical embolism source. Patients with intracranial disease are at high (10–15% annually) risk of stroke recurrence if only aspirin for secondary prevention is considered.[30] New treatment strategies including statins, selective anticoagulation, and stenting are being used in patients with high-grade stenoses refractory to standard antiplatelet therapy.[31,32]

The same TCD examination can detect collateral flow and the hemodynamic significance of extracranial or intracranial stenoocclusive lesions [Quality of evidence: class II; Strength of recommendation: type B].[33-41] This information is helpful to identify a proximal arterial obstruction and to clarify carotid duplex or noninvasive angiographic findings including MR-angiography (MRA) and CT-angiography (CTA). Carotid duplex and MRA are known to produce falsely elevated estimates of the degree of carotid stenosis and TCD, via collateral and downstream hemodynamic effects, can help clarify false-negative and false-positive diagnosis of severe ICA stenosis. A severe ICA stenosis should produce downstream flow changes directly detectable by TCD, and if no delay in systolic flow acceleration is seen or no collaterals are detected, these TCD findings likely indicate moderate proximal ICA stenosis.[27,33,38] On the other hand, if extracranial duplex scanning could not reveal a severe ICA lesion (eg, high carotid bifurcation), the presence of unilaterally delayed systolic flow acceleration or intracranial collaterals would suggest the presence of a severe proximal ICA lesion.[27,33,38] For intracranial stenoocclusive lesions, intracranial MRA often shows flow gaps due to turbulence or reversal of flow direction, thus overestimating the degree of stenosis. TCD findings of focal elevated velocities confirm the presence of an intracranial stenosis or collaterals when applicable, and validated diagnostic criteria are available.[27,42] More specifically, 2 recent studies have validated the diagnostic accuracy of TCD against CTA for evaluating arterial stenoocclusive disease in the setting of acute (24 hours) cerebral ischemia.[38,39] In both studies, bedside TCD examination yielded satisfactory agreement (sensitivity >75%, specificity >90%) with urgent brain CTA, while it should be noted that in both studies sonographers were blinded to the results of CTA, which in the majority of cases was performed following TCD evaluation.

The yield of standard TCD vessel surveillance (stenoses, occlusions, collaterals, and lesions amenable to intervention) is

substantial if performed alone[40] or in combination with carotid duplex ultrasound[41] particularly in patients with acute cerebral ischemia or TIAs. Identification of patients with proximal arterial occlusions has prognostic information, helps determine stroke pathogenic mechanism, and individualize early management of a stroke or TIA patient in addition to information provided by brain CT or MRI.[40,41] It is therefore recommended to perform TCD studies always in conjunction with ultrasound examination of the extracranial brain supplying arteries. Furthermore, residual flow at the site of acute intracranial occlusion predicts response to intravenous thrombolysis according to findings of 2 independent multicenter studies.[43,44] More specifically, the finding of no detectable residual flow indicates the least chance to achieve recanalization and recovery with systemic thrombolysis and may support an early decision for combined endovascular rescue.[43]

The yield of TCD is greatest the closer in time it is performed to stroke symptom onset[40] and is higher in anterior than in posterior circulation.[26,27,42] More specifically, the recently published recommendations of the American Heart Association for imaging of acute stroke underline that the sensitivity and specificity of TCD for the anterior circulation range from 70% to 90% and 90-95% compared to DSA, while the same accuracy parameters for the posterior circulation are lower (sensitivity: 50-80%, specificity: 80-96%).[42] Notably, the use of power-motion mode TCD (PMD-TCD) or transcranial color-coded duplex (TCCD) increases the diagnostic accuracy of neurosonology for the assessment of vertebrobasilar circulation.[35,45] PMD, B-Mode or color-flow display can depict Doppler signatures that are complimentary to and can increase confidence in standard single-gate spectral findings. More specifically, in a recent study evaluating the diagnostic yield of TCD against CTA in the acute setting of cerebral ischemia (<48 hours) the investigators reported that PMD-TCD contributed information complementary to CTA (real-time embolization, collateralization of flow with extracranial internal carotid artery disease, alternating flow signals indicative of steal phenomenon) in 7% of the studied patients.[38] Similar findings have been reproduced during the separate evaluation of the posterior circulation with PMD-TCD.[35] Recommendations regarding the potential applicability of TCCD in the setting of acute arterial ischemia have recently been introduced by an international consensus panel of 35 experts.[46]

Intracranial Arterial Disease (IAD)

TCD can reliably rule out intracranial stenosis according to the findings of the recently published Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial, which aimed to define the positive and negative predictive value (PPV and NPV) of TCD/MRA for the identification of 50% to 99% intracranial stenosis in the intracranial ICA, MCA (middle cerebral artery), VA (vertebral artery), and BA (basilar artery).[47] SONIA standardized the performance and interpretation of TCD, MRA, CTA (when available) and catheter-based angiography using study-wide cutpoints defining positive findings. Hard copy TCD/MRA studies were centrally read, blinded to the results of catheter-based angiography (gold standard). The trial showed that TCD and MRA can reliably exclude the presence of intracranial stenosis (NPV = 86%, 95%CI 81-89%). However, abnormal findings on TCD or MRA require a confirmatory test such as angiography to reliably identify stenosis (PPV = 36%, 95%CI 27-46%). However, it should be noted that SONIA findings were based on a limited number of vessels evaluated by TCD (n = 451) compared to MRA (n = 1310), while TCD abnormalities associated with occlusion on angiography (despite the fact that they represented severe intracranial disease) were considered false positives because an occlusion was not treated with a stent. This approach resulted in SONIA increasing NPV but decreasing PPV.

A multicenter prospective study[48] was recently performed to determine if SONIA criteria, and TCD can be reliably used between different laboratories that have standardized scanning protocols according to our criteria.[26] Consecutive patients with symptoms of cerebral ischemia evaluated by TCD and catheter angiography at 3 tertiary care centers were prospectively studied. Baseline stroke severity (NIHSS) was documented. TCD measurements of peak systolic (PSV), end-diastolic (EDV), and mean flow (MFV) velocities were performed. The following MFV cut-offs were used for the identification of ≥50% stenosis using published SONIA criteria: MFV MCA >100 cm/s, TICA/ACA >90 cm/s, VA/BA/PCA >80 cm/s, and determined velocity cut-offs for the ≥70% stenosis on angiography. The study also evaluated whether the addition of stenotic to prestenotic ratio (SPR) would increase the accuracy of velocity prediction of IAD with ≥70% stenosis.

Among a total of 172 patients with DSA/TCD data, 33 had confirmed IAD (age 54 ± 13 yrs; 70% men; 50% Caucasian, 18% African-American, 32% Asian; median NIHSS 3, interquartile range 6) providing 375 TCD/DSA measurement pairs for comparison. On DSA, ≥50% stenoses were located in 56 vessels: M1MCA (48%), M2 (4%), TICA (16%), ACA (7%), VA (14%), BA (9%), PCA (2%). IAD >70% on DSA was found in 21 arteries (anterior circulation 18, posterior circulation 3). The accuracy parameters of TCD (SONIA MFV cutoffs) against DSA for ≥50% stenosis were as follows: sensitivity (89%), specificity (99%), PPV (93%), NPV (98%), overall accuracy (97%) [54 true positive, 310 true negative, 4 false positive, and 7 false negatives]. The predictive ability of PSV and MFV for the detection of IAD on DSA did not differ ($P > .9$) both in anterior (middle cerebral artery, anterior cerebral artery, and terminal internal carotid artery) and posterior circulation (vertebral artery, basilar artery, and posterior circulation artery). The optimal PSV cut-off for the detection of ≥70% IAD was >196 cm/s (sensitivity 78%, specificity 95%) and >166 cm/s (sensitivity 100% and specificity 97%) in anterior and posterior circulation, respectively. The optimal MFV cut-off for the detection of ≥70% IAD was >128 cm/s (sensitivity 78%, specificity 96%) and >119 cm/s (sensitivity 100% and specificity 99%) in anterior and posterior circulation, respectively. The addition of an MFV SPR >3 in the MFV criteria (>128 cm/s in anterior and >119 cm/s in posterior circulation increased the TCD accuracy for detecting >70% IAD (sensitivity 90%, specificity 95%).[48]

Investigators concluded that at laboratories with a standardized scanning protocol, SONIA MFV criteria remain reliably predictive of ≥50% stenosis. The new velocity/ratio criteria for

the detection of ≥70% intracranial stenosis show good agreement with invasive angiography.[48]

Finally, a recent single-center study introducing novel criteria for the detection of focal (increased mean flow velocity) and diffuse (low mean flow velocity and high pulsatility index) intracranial disease demonstrated higher yield of TCD for the detection of intracranial stenoses (PPV 75%, NPV = 94%).[49] In addition, a study in Chinese population showed that TCD ultrasound is an important and reliable test for the prediction of recurrent stroke in patients with intracranial atherosclerotic disease.[50] In conclusion, TCD provides important information and may serve a screening tool for the detection of ICAD [Quality of evidence: class II; Strength of recommendation: type B].

Vasomotor Reactivity

In addition to vessel surveillance, TCD testing can include assessment of vasomotor reactivity [Quality of evidence: class II; Strength of recommendation: type B]. During this noninvasive test, voluntary breath-holding for 30 seconds induces hypercapnia and TCD is used to measure velocity response to a natural vasodilatory stimulus.[51] The breath-holding index (BHI) has been validated against MRI and studied in patients with symptomatic and asymptomatic carotid artery stenoses and occlusions.[52–56] No complications were reported for this test since its inception in 1992.[51-57] TCD vasomotor study can identify high-risk patients for first-ever or recurrent stroke in the setting of extracranial internal carotid artery stenoses or occlusions.[52–56] Interestingly, in patients with asymptomatic or symptomatic carotid artery occlusion (CAO) and impaired vasomotor reactivity in the absence of collateral pathways, the annual risk of ipsilateral stroke was shown to be 32.7% compared to 0% in CAO patients with normal vasomotor reactivity and normal collaterals.[53] In addition, Silvestrini et al reported that in patients with asymptomatic carotid artery stenosis (>70%), the annual ipsilateral ischemic event risk was 4.1% in patients with normal and 13.9% in those with impaired vasomotor reactivity (defined as a breath-holding index of <0.69).[52]

This information is not available from carotid duplex ultrasound examination and may require additional contrast studies with MR perfusion or diamox-SPECT, or perfusion CT that are costly, and may lead to complications related to vasoactive diamox effects that last longer than a brief hypercapnia with breath-holding. TCD has an advantage of safe, inexpensive bedside examination of vasomotor reactivity with set diagnostic criteria that have been prospectively validated.[51-56] Findings of a diminished or exhausted vasomotor reactivity were established as a risk factor for stroke[57] and can prompt the consideration of carotid endarterectomy or stenting in patients with asymptomatic carotid stenosis or consideration of extraintracranial bypass surgery in patients with recurrent hemodynamic strokes or TIAs that fail medical therapy. In addition, a recent study showed that a decrease in cerebrovascular reactivity may be responsible for reduction in some cognitive abilities involving the function of the hemisphere ipsilateral to carotid stenosis.[58] Such findings may be of interest for providing a more comprehensive indication to surgical treatment in subgroups of subjects with asymptomatic carotid stenosis.

Cerebral Embolization

Patients with ischemic strokes, TIAs, or asymptomatic high-grade ICA stenosis can also undergo TCD monitoring for emboli to detect, localize, and quantify cerebral embolization[59-62] [Quality of evidence: class II; Strength of recommendation: type B]. This information is helpful to establish the diagnosis and change management strategy, if emboli are found pointing to artery-to-artery embolization or continuing embolization despite treatment both in patients with symptomatic and asymptomatic extracranial or intracranial large artery disease.[63] Of note, the presence of emboli on TCD distal to a high-grade asymptomatic ICA stenosis identifies patients at higher risk of first-ever stroke.[62,63] Sometimes the presence of emboli can be the only sign of a proximal arterial dissection, partially occlusive thrombus, or unrecognized cardiac source of embolism.[64]

In addition, the first ambulatory TCD system (like a "Holter" monitor for MCA flow velocity) was introduced and tested in a clinical setting in 2004 showing good-quality digital recordings for over 5 hours.[65] In view of temporal variability in embolization rates, the authors concluded that this technique would be likely to improve the predictive value of recording for asymptomatic microembolic signals (MES) and may be particularly useful in patients in whom embolic signals are relatively infrequent, such as those with asymptomatic carotid stenosis and atrial fibrillation.[65] The same group used 1-hour continuous TCD-monitoring of the ipsilateral MCA in 200 patients with >50% extracranial ICA stenosis. Interestingly, they noted that asymptomatic embolization in carotid stenosis predicted short-term ipsilateral stroke risk and postulated 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.[66]

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 (≥50%). Patients were screened with TCD, and if MES were detected, they were randomized to clopidogrel and aspirin or aspirin monotherapy. Repeated TCD recordings were made on days 2 and 7. All TCD recordings were centrally read and analyzed. The findings of CARESS indicated that in patients with recently symptomatic carotid stenosis, combination therapy with clopidogrel and aspirin was more effective than aspirin alone in reducing asymptomatic embolization by 61.6% at day 2 ($P = .0005$).[67] This finding has been reproduced in the recently published CLAIR study (Clopidogrel plus aspirin versus aspirin alone for reducing embolization in patients with acute symptomatic cerebral or carotid artery stenosis).[68] This randomized open-labeled, blinded endpoint trial documented a 42.4% ($P = .025$) relative risk reduction of asymptomatic embolization with dual antiplatelet therapy. Neither CARESS nor CLAIR showed a beneficial effect of dual antiplatelet therapy in reducing the risk of recurrent stroke, but when both studies were combined there was a reduction in the risk of 6% (95% CI 1-11) with the use of combination therapy compared with monotherapy.[68]

The prognostic value of TCD detection of MES in patients with asymptomatic carotid stenosis was recently shown in the

Asymptomatic Carotid Emboli Study (ACES), a prospective, multicenter observational study.[69] The investigators evaluated patients with asymptomatic carotid stenosis of at least 70% for the presence of MES with consecutive 1-hour TCD recordings of the ipsilateral middle cerebral artery (2 at baseline; 1 at 6, 12, and 18 months). All patients were followed prospectively for a 2-year period, while all TCD recordings were analyzed centrally by investigators who were blinded to the clinical information. The hazard ratio for the risk of ipsilateral stroke and transient ischemic attack from baseline to 2 years in patients with embolic signals compared with those without was 2·54 (95% CI 1·20-5·36; $P = ·015$). For ipsilateral stroke alone, the hazard ratio was 5·57 (1·61-19·32; $P = ·007$). The absolute annual risk of ipsilateral stroke between baseline and 2 years was 3·62% in patients with embolic signals and 0·70% in those without. Controlling for antiplatelet therapy, degree of stenosis, and other risk factors did not alter the results. The investigators concluded that the detection of MES by TCD can identify groups of patients with asymptomatic carotid stenosis who are at low [MES (−)] or high [MES (+)] risk of future stroke. Consequently, TCD may be a useful risk predictor for identifying those asymptomatic carotid stenosis patients who might benefit from intervention with carotid endarterectomy.[69]

Another recent randomized trial demonstrated the efficacy of TCD in detecting gaseous microembolization during coronary artery bypass grafting (CABG) contributing to neuropsychological decline at 3 months postoperatively. Moreover, the investigators were able to exhibit the superiority of dynamic bubble trap compared to filter devices in reducing cerebral microembolization (median number of microembolic signals with dynamic bubble trap: 99; median number of microembolic signals with filter devices: 162.5) on the basis of TCD findings.[70]

Detection of RLS

Patients with ischemic stroke and TIAs thought to be due to paradoxical embolism can undergo TCD "bubble" test to detect RLS in patients [Quality of evidence: class II; Strength of recommendation: type B].[8,26] TCD has been shown equivalent or even superior to both transthoracic (TTE) and transesophageal (TEE) echocardiography in the detection of RLS.[71-77] Criteria have been developed and validated to quantify the degree of RLS using MES counts on spectral[74] or PMD[75] display. Spencer et al compared the diagnostic yield of single-channel TCD (sgTCD) to PMD for the detection of RLS. They documented significantly more microemboli detectable on PMD (322 ± 166; 95%CI: 388-257) than on sgTCD (186 ± 109; 95%CI:229-143; $P < .001$).[75] Moreover, the diagnostic capabilities of PMD and TEE for detecting PFO were comparable and corresponded to the anatomical findings determined during cardiac catheterization.[75]

The key advantage that TCD offers is that patients can do calibrated Valsalva maneuver, and the test can be repeated with different body positions.[77] TCD has particular value to be performed in younger stroke/TIA patients with suspected paradoxical embolism and negative echocardiographic studies, including negative TTE.[26,78] Moreover, a recent report demonstrated the utility of TCD in diagnosing residual or secondary RLS following balloon occlusion of patent foramen ovale (prevalence 20%, 95%CI 12-29%).[79] PMD TCD detection of RLS is less expensive than echocardiography and has been shown at least equivalent or even superior to both transthoracic and transesophageal echocardiography.[74,75]

Cerebral Circulatory Arrest

The efficacy of TCD for the detection of cerebral circulatory arrest for confirmation of a clinical diagnosis of brain death has been documented by various independent investigators [Quality of evidence: class II; Strength of recommendation: type B].[80-85] A recent systematic review of all available studies evaluating the use of TCD in patients with the clinical diagnosis of brain death showed that TCD had a sensitivity of 88% and specificity of 98% in diagnosing brain death.[86] The cause of false negatives was a lack of signal in 7% of cases and persistence of flow in the remaining 5%. However, it should be noted that the criteria for the diagnosis of brain death in these studies were variable, with only 7 groups assessing the vertebrobasilar artery and some authors accepting the absence of flow in only 1 artery. A latter meta-analysis assessed all available clinical studies evaluating the accuracy parameters of TCD in the diagnosis of brain and rated the quality of each study using standardized methodological criteria. In total, 2 high-quality and 8 low-quality studies were identified and included.[87] Meta-analysis of the 2 high-quality studies showed a sensitivity of 95% (95%CI: 92-97%) and a specificity of 99% (95%CI: 97-100%) to detect brain death. Meta-analysis of all 10 studies showed a sensitivity of 89% and a specificity of 99%.[88]

On the basis of these findings, it can be argued that TCD can rule out cerebral circulatory arrest if a positive diastolic flow is detected at any intracranial pressure (ICP) values.[8,26] TCD can confirm the clinical diagnosis of brain death by demonstrating complete cerebral circulatory arrest in both MCAs and BA. Finally, TCD offers serial bedside noninvasive assessments to detect the timing of cerebral circulatory arrest and ensure proper utilization of confirmatory nuclear flow studies.

Clinical Indications for TCD Monitoring

TCD offers noninvasive real-time monitoring at bedside using standard headframes with no complications reported from these procedures that can be extended up to several hours, if necessary. Continuous monitoring can be deployed in several clinical situations such as:

1. emboli detection in patients with symptomatic or asymptomatic extracranial or intracranial carotid artery disease [Quality of evidence: class II; Strength of recommendation: type B] (as described above);
2. monitoring thrombolytic therapy to increase the chance of tissue plasminogen activator (t-PA)-induced recanalization, to detect reocclusion, or persisting occlusion with no recanalization [Quality of evidence: class II; Strength of recommendation: type B].[25,26,29,43,88-93] More specifically, the presence of persisting occlusion has been linked with adverse functional outcomes at 3 months and increased likelihood of symptomatic intracranial hemorrhage following intravenous thrombolysis, while persisting occlusion has been associated with deterioration following improvement in patients treated with intravenous tissue plasminogen activator.[29,43,88-93] Interestingly, a recent study has shown that a modest increase in the end-diastolic velocity as opposed to peak systolic velocity is associated with complete recanalization/reperfusion, early neurological improvement, and

favorable functional outcome.[93] Thus, it may be postulated that diastolic flow augmentation may represent a novel target for the development of reperfusion therapies.

3. perioperative monitoring during stenting, carotid endarterectomy, and cardiovascular surgery (CABG) to detect embolism, thrombosis, hypo and hyperperfusion as the main causes of perioperative strokes [Quality of evidence: class III; Strength of recommendation: type C] (see above).
4. functional TCD monitoring including vasomotor-reactivity (see below) and specific task testing [Quality of evidence: class III; Strength of recommendation: type D].

Functional transcranial Doppler sonography (fTCD) constitutes a complementary neuroimaging tool measuring cerebral perfusion changes due to neural activation.[94-97] When compared to other perfusion-sensitive neuroimaging techniques like functional magnetic resonance imaging or positron emission tomography, fTCD showed significant correlations with PET and Wada tests in the assessment of neuropsychological task performance including hemispheric language lateralization.[94-97] Due to a continuous registration of blood flow, TCD offers an excellent temporal resolution in comparison to other neuroimaging techniques.[98] The technique is noninvasive and easy to apply, while blood flow measurements are robust against movement artifacts.[99] In conclusion, since its introduction fTCD has contributed substantially to the elucidation of the hemispheric organization of cognitive, motor, and sensory functions in adults and children.[99]

In summary, TCD provides a noninvasive and inexpensive (relative to angiography) monitoring modality that can be used in a variety clinical situations (points 1–4 above) to provide real-time physiological information that is often unobtainable with other testing without increasing patient risks (repeated radiation doses, contrast injections) and associated costs.

Expected Outcomes

Our interdisciplinary panel of experts considered existing clinical conditions for which a variety of TCD tests and monitoring are performed in clinical practice. In Table 2, we summarize established clinical indications, frequency of testing, and expected outcomes. In short, TCD has been shown to provide diagnostic and prognostic information that determines patient management decisions across multiple cerebrovascular conditions and periprocedural/surgical monitoring.

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