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TRANSCRANIAL DOPPLER ULTRASONOGRAPHY IN 2004:
A COMPREHENSIVE EVIDENCE-BASED UPDATE

Therapeutics and Technology Assessment Subcommittee of the American
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ABSTRACT

Objective: To review the use of transcranial Doppler ultrasonography (TCD) and transcranial color-coded sonography (TCCS) for diagnosis. *Methods:* The authors searched the literature for evidence of: 1) if TCD provides useful clinical information in specific clinical settings; 2) if using this information improves clinical decision making, as reflected by improved patient outcomes; and 3) if TCD is preferable to other diagnostic tests in these settings. *Results:* TCD is of established value in the screening of children aged 2-16 years with sickle cell disease for stroke risk (Type A, Class I) and the detection and monitoring of angiographic vasospasm after spontaneous subarachnoid hemorrhage (Type A, Class I-II). TCD and TCCS provide important information and may have value detection of intracranial steno-occlusive disease (Type B, Class II-III), vasomotor reactivity testing (Type B, Class II-III), detection of cerebral circulatory arrest and brain death (Type A, Class II), monitoring carotid endarterectomy (Type B, Class II-III), monitoring cerebral thrombolysis (Type B, Class II-III) and monitoring coronary artery bypass graft operations (Type B-C, Class II-III). Contrast enhanced TCD/TCCS can also provide useful information in right-to-left cardiac/extracardiac shunts (Type A, Class II), intracranial occlusive disease (Type B, Class II-IV) and hemorrhagic cerebrovascular disease (Type B, Class II-IV), although other techniques may be preferable in these settings. Development of power-based or M-Mode TCD and contrast-enhanced TCCS perfusion techniques may revolutionize the bedside evaluation of interventions for acute stroke.

INTRODUCTION

Transcranial Doppler ultrasonography (TCD) is a non-invasive ultrasonic technique that uniquely measures local blood flow velocity (speed and direction) in the proximal portions of large intracranial arteries (1, 2). Flow velocity values using conventional (first generation, non-imaging) or 'blind' TCD are based upon the assumption that the angle of insonation between the ultrasound beam and the direction of arterial flow is 0-30 degrees; approximately 25% of vessels have insonation angles greater than 30 degrees, which results in an increase in the error in measurement. Inadequate temporal bone windows (such as due to bone thickening) limit transcranial insonation in 5-20% of patients. TCD, like many other diagnostic techniques, is operator-dependent and requires training and experience to perform and interpret results correctly. In general, mean flow velocities are felt to be proportional to blood flow in the insonated vessel (2, 3), and have been used for the development of diagnostic criteria, although peak systolic velocities and direction of flow are used for the ophthalmic artery. In addition, indirect Doppler findings, such as waveform characteristics, may be helpful for diagnosis in specific settings. TCD is performed by technologists, sonographers and physicians and is interpreted by neurologists and other specialists.

The utility of TCD was last evaluated by the TTA in 1990 (1). Since then, there have been technical advances and more widespread application of TCD (4-6). As a result, additional data have been generated, which bear upon its clinical utility. An update of the assessment of conventional or non-imaging TCD and imaging or transcranial color-coded sonography (TCCS) by the TTA is thus in order.

TCD is used principally in the evaluation and management of patients with diverse forms of cerebrovascular disease. Conventional or digital subtraction angiography, where available, are considered to be the 'reference standard' test (s) for evaluating vascular patency and degree of stenosis in intracranial vessels. Direct comparisons of TCD with techniques that image the intracranial circulation [conventional angiography, digital subtraction angiography (DSA), computerized tomographic angiography (CTA), and magnetic resonance angiography (MRA)] are variable depending upon the indication (7) and the diagnostic criteria used for correlation purposes in specific disease states. As expected, all non-invasive techniques are less than 100% sensitive and specific when compared to conventional angiography. However, even where comparative data are available from particular centers, concerns regarding the ability to generalize results, which may be due to operator-dependent factors (which apply to all 5 techniques) and comparability of relevant pathology in the tested populations, would limit inferring from published reports how these techniques would perform in settings other than those in which they were directly tested. The chief advantages of the non-invasive techniques over conventional or digital subtraction angiography are that they are often faster to perform, are not associated with the morbidity and rare mortality of conventional angiography, and are often less expensive. However, contrast (with its attendant risks) is used with CTA. For certain clinical settings or types of correlations, the most appropriate gold standard may be computed tomographic (CT) scan, magnetic resonance imaging (MRI), diffusion-weighted MRI (DWI), perfusion-weighted MRI (PWI), transesophageal echocardiography, single photon emission computed tomography, positron emission tomography, electroencephalography (EEG), hemodynamic measurements (such as stump pressure), experimental models, pathology, neuropsychological tests or clinical outcomes, such as transient ischemic attack, stroke, mortality, disabling stroke, or hemorrhagic complications. As such, the

reference standard against which TCD should be evaluated should be selected according to the clinical setting.

The chief advantages of TCD are the following. First, it can be performed at the bedside and consequently be repeated as needed, or applied for continuous monitoring which no other current method can do. Second, TCD is frequently less expensive than other vascular imaging techniques. Finally, dye contrast agents are not used, as they are with conventional angiography, DSA and computed tomographic angiography (CTA). Its chief limitation is that it can demonstrate cerebral blood flow velocities only in a limited portion of large intracranial vessels, although large vessel intracranial arterial disease commonly occurs at these locations. In general, TCD is most useful when the clinical question pertains to those vessel segments. However, in some settings, TCD can detect indirect effects, such as abnormal waveform characteristics suggestive of proximal hemodynamic or distal obstructive lesions, that may be clinically informative (4). The aforementioned limitation also applies to MRA and CTA, depending upon the areas imaged, the algorithms used, and the diligence of the technologist. In addition, DSA and conventional angiography may be inconclusive if all relevant vessels or vessel portions are not imaged, if a critical imaging view is omitted, or if image quality is suboptimal. These caveats and considerations pertaining to the various comparative imaging technologies merit repetition, even though they have not changed since 1990.

The present update will identify indications for which current data support the use of TCD and TCCS. However, when more than one technique may provide clinically relevant information, clinical judgment (including issues of local access, risk, cost, availability and competence) should guide the choice of the

appropriate technique or combination of techniques in particular situations. In addition, recommendations for future research on TCD/TCCS are provided.

METHODS

Assessment of the clinical utility of TCD by the TTA was prompted by the recent publication of a review article on TCD by a panel of experts (5). This review (5) was based upon a Medline search of all articles reporting on the use of TCD through 1999. Articles were classified, by indication, according to a rating system of the quality of evidence utilized in prior TTA work evaluating single photon emission computed tomography (SPECT) (8). At this time, a new rating system was developed by the AAN (9). We reviewed the previously cited papers (5), as well as other or more recent articles, based upon selection of relevant publications cited in these new articles and additional Medline search through June, 2003 using the new rating system (Table 1) (9). Articles cited herein reflect a mixture of diagnostic, therapeutic or prognostic information used as the reference standard in individual studies. When data are inconclusive, a U rating was given.

The present report reflects a summary of the accuracy and clinical utility of TCD. Sensitivity and specificity reflect the ability of a diagnostic test to detect disease. For the purposes of this review, ratings of sensitivity and specificity were operationally defined as excellent ($\geq 90\%$), good (80 to 89%), fair (60 to 79%) and poor ($< 60\%$). Data on sensitivity and specificity of TCD/TCCS according to indication are summarized in Tables 2 and 3. The clinical utility of a diagnostic test may be operationally defined as the value of the test result to the clinician caring for the patient. In this sense,

value to the clinician refers to the ability of a diagnostic test to detect the disease process of interest, influence patient care, or provide prognostic information when compared with an appropriate reference standard or in a well-designed clinical trial. We summarize the clinical utility (Table 4) of TCD/TCCS for each indication and focus on the clinical indications for which conclusions can be drawn.

RESULTS

A. Conventional or Non-imaging TCD

1. Ischemic Cerebrovascular Disease

a. Sickle Cell Disease (SCD): In children with SCD, ischemic cerebral infarction is associated with an occlusive vasculopathy involving the distal intracranial internal carotid artery (ICA) and the proximal portions of the middle (MCA) and anterior (ACA) cerebral arteries. One large cohort study showed that TCD can identify patients at high risk of cerebral infarction, with optimal sensitivity and specificity achieved at a time-averaged mean maximum blood flow velocity of 170 cm/sec (10). A later analysis with a larger cohort with longer follow-up showed that elevated time-averaged mean maximum blood flow velocity of greater than or equal to 200 cm/sec in the ICA or MCA is strongly associated with stroke risk (11). Using the latter flow velocity criterion, the Stroke Prevention Trial in Sickle Cell Anemia (STOP) showed that periodic blood transfusion therapy to lower the hemoglobin S concentration to less than 30% of total hemoglobin concentration in children between the ages of 2 and 16 years with greater than 200 cm/sec in the ICA or MCA on TCD resulted in a 92% reduction in stroke risk (12-14).

TCD screening of children with SCD between the ages of 2 and 16 years is effective for assessing stroke risk (Type A, Class I evidence), although the optimal frequency of testing is unknown (Type U).

b. Right to Left Cardiac Shunts: Paradoxical embolism via a patent foramen ovale (PFO) is a recognized cause of stroke in young adults (15, 16). The presence of an atrial septal aneurysm (ASA) increases the stroke risk of a PFO with right to left shunting (17-19). However, the occurrence of stroke in patients with PFO may not always be due to paradoxical embolism. Data show a high correlation between contrast-enhanced TCD and contrast-enhanced transesophageal echocardiography (TEE), with essentially 100% overlap for the “clinically significant” high number of particles shunted. For example, shorter latency to the appearance of, and a larger number of particles, are more likely to result in the occurrence of cryptogenic infarcts (20, 21). When compared to contrast TEE using intravenous saline containing air bubbles or echo-contrast enhancing agents, the sensitivity and specificity of contrast TCD for detecting right to left cardiac or extracardiac (pulmonary arteriovenous) shunts, which vary by center, protocol, and diagnostic criteria used, is generally high (16-34). The routine performance of the Valsalva maneuver during testing can improve sensitivity and specificity (27), although this has not always been observed (30). The sensitivity of contrast TCD can be improved by using a higher volume of agitated saline (10cc instead of 5cc), use of Echovist (especially Echovist-300) instead of agitated saline, or repeating the Valsalva maneuver if the initial result is negative (34). While extracardiac right-to-left shunts may also be demonstrated by this technique, differentiation from cardiac right-to-left shunt may be difficult in the absence of anatomic information (34).

Contrast TCD has efficacy comparable to contrast TEE for detecting PFO with right to left shunts (Type A, Class II evidence). However, TEE is diagnostically superior in comparison to contrast TCD in light of its ability to provide direct anatomic information regarding the site and nature of the shunt due to the PFO, presence of an ASA, and so on. While the number of microbubbles can be quantified by TCD, the therapeutic impact of this additional information is unknown (Type U).

c. Intracranial Steno-Occlusive Disease: Intracranial atherosclerosis is responsible for up to 10% of transient ischemic attacks (TIAs) and strokes. If extracranial internal carotid disease and cardiac disease have been excluded as the mechanism of symptoms, then identification of intracranial arterial stenosis or occlusion may influence further evaluation and management of the patient. Stenosis and occlusion of the ICA siphon, proximal (M1) segment of the MCA, intracranial vertebral artery (VA), proximal basilar artery (BA), and proximal (P1) segment of the posterior cerebral artery (PCA) can be reliably detected by TCD (5, 35-60). The performance of TCD against MRA, conventional angiography or DSA varies by center, characteristics of and prevalence of disease in the study population, diagnostic criteria and technical expertise. Sensitivity, specificity, positive predictive value and negative predictive value are higher in the anterior circulation than in the vertebrobasilar circulation due to more variable anatomy and technical difficulties in insonation of the vertebrobasilar circulation.

Data are accumulating to define criteria for greater than 50% stenosis of large intracranial arteries (37, 38, 53, 54). Intracranial arterial stenotic lesions in the internal carotid distribution are dynamic. They can evolve over time, with increasing or decreasing flow velocities and appearance of new collateral patterns, the latter suggesting further hemodynamic compromise distal to the stenotic lesion (55-57). In

two recent studies in small, highly selected populations (56, 57) using peak systolic (57) or mean flow (56) velocities and variable noninvasive criteria for change in degree of stenosis, progression of MCA stenosis was associated with new ipsilateral cerebral ischemic symptoms (stroke, TIA) (56) or major vascular events (56, 57) at six months (57) and (median) 26.55 months (56), respectively.

Data are insufficient to establish TCD criteria for greater than 50% stenosis or for progression of stenosis in intracranial arteries (Type U).

d. Acute cerebral infarction: Cerebral angiography shows acute occlusion in 76% of acute MCA territory infarcts (58). TCD can detect these angiographic occlusions with high (>90%) sensitivity, specificity, positive predictive value and negative predictive value (43, 44, 53, 58). In addition, TCD can detect ICA siphon, VA and BA occlusions with fair to good (70-90%) sensitivity and positive predictive value and excellent specificity and negative predictive value, with lower values for vertebrobasilar occlusions (59).

TCD can detect significant cerebral hemodynamic changes in the setting of acute cerebral ischemia (60-62). One prospective study of patients studied within 48 hours of stroke onset (60) found a significant inverse correlation between MCA flow velocities and absolute mean cerebral transit time by radioisotope study in the symptomatic hemisphere. One retrospective study comparing TCD and diffusion- and perfusion-weighted MRI, performed typically within 24 hours of each other (62), found that an MCA flow velocity asymmetry of $\geq 30\%$ and ipsilateral intracranial ICA-to-MCA flow velocity gradient of $\geq 20\text{cm/sec}$ were associated with diffusion/perfusion mismatch, with a positive

predictive value of 82% and negative predictive value of 73%. In another study (61), serial TCD detected dynamic changes in the cerebral circulation, consistent with spontaneous recanalization or deterioration, within the first week after ischemic stroke that were not apparent on a single MRA examination.

Intracranial arterial occlusions detected by TCD are associated with poor neurological recovery, disability or death at 90 days (45-48), whereas normal results are a predictor of early improvement (50, 63). In patients with ICA territory stroke, TCD findings, stroke severity at 24 hours and CT lesion size were independent predictors of outcome at 30 days (47). When combined with carotid duplex sonography, the presence and total number of arteries with suspected steno-occlusive lesions (especially intracranial) by TCD in patients with TIA or ischemic stroke was associated with an increased risk of further vascular events (usually stroke) and death within six months (49). In the Oxfordshire Community Stroke Project (OCSP) (64), data suggest that the pattern of intracranial arterial flow velocity abnormalities may be related to OCSP stroke subtype. TCD-detected M1-MCA occlusions within 6 hours of stroke onset may be an independent predictor of spontaneous hemorrhagic transformation, with a positive predictive value of 72% (65). A recent study (66) showed that delayed (> 6 hours) spontaneous recanalization was independently associated (OR=8.9, 95%CI=2.1-33.3) with hemorrhagic transformation.

TCD is probably useful for the evaluation of patients with suspected intracranial steno-occlusive disease, particularly in the ICA siphon and MCA (Type B, Class II-III evidence). The relative value of TCD

compared with MRA or CTA remains to be determined (Type U). Data are insufficient to give a recommendation regarding replacing conventional angiography with TCD (Type U).

e. Extracranial ICA Stenosis: TCD can detect the hemodynamic consequences of severe extracranial ICA stenosis, such as reversal of the direction of ophthalmic artery flow, presence of collateral flow patterns, absence of ophthalmic or carotid siphon flow, and reduced MCA flow velocity and pulsatility (67-70). Early work suggested that the absence of ophthalmic artery and carotid siphon signals are highly specific for the presence of severe extracranial ICA stenosis and, especially, ICA occlusion (68). Major and minor diagnostic criteria for evaluation of the hemodynamic effects of severe extracranial ICA steno-occlusive disease have been identified (71). There is good agreement between TCD and direction-sensitive MRA concerning flow direction in the posterior communicating artery (72). For patients with angiographically or pathologically confirmed stenosis greater than 70%, accuracy varies according to diagnostic criteria. Use of single TCD measurements or a battery of TCD measurements has widely variable sensitivity and specificity. However, when highly specific carotid duplex criteria are added, sensitivity and specificity are considerably improved (69-71), suggesting that the role of TCD in this setting may be limited.

TCD is possibly useful for the evaluation of severe extracranial ICA stenosis or occlusion (Type C, Class II-III evidence). These observations suggest that more data are needed to determine the incremental value of TCD in this setting.

f. Vasomotor Reactivity (VMR) Testing: TCD evaluation of large basal conducting vessels, which remain relatively constant in diameter during moderate pressure fluctuations or changes in microcirculatory function, can provide an index of relative flow changes in response to small blood pressure changes and physiologic stimuli in order to assess autoregulation and vasomotor reactivity of the distal cerebral arteriolar bed (73-76). TCD VMR testing techniques of static or dynamic cerebral autoregulation include measuring changes in flow velocities in response to hemodynamic stimuli (77-85) (rapid leg cuff deflation, Valsalva maneuver, deep breathing, ergometric exercise, head-down tilting, orthostasis and lower body negative pressure), beat-to-beat spontaneous transient pressor and depressor changes in mean arterial pressure (86), CO₂ inhalation (hypercapnia)/hyperventilation (hypocapnia) (87-105), the breath-holding index (BHI) (106-117), acetazolamide injection (87, 88, 118-124) and the transient hyperemia response and its variants (125-135). Recently, the TCD findings with hypercapnia have been correlated with near-infrared spectroscopy (105).

VMR testing techniques with TCD have been used to evaluate patients with symptomatic or asymptomatic extracranial ICA stenosis or occlusion (87-90, 94-102, 107, 113, 114, 118, 120, 122, 124), cerebral small artery disease (89, 95, 96, 105, 110, 123, 136-139), head injury (131-133) and aneurysmal subarachnoid hemorrhage (134, 135). Acetazolamide may have a slight practical advantage over CO₂ inhalation techniques for evaluation of large artery occlusive disease since its effects are independent of patient cooperation, although it does not permit evaluation of vasoconstrictor responses, may have side effects such as lightheadedness and headache, and increase intracranial pressure (87, 117). Optimal breath-holding index and hyperventilation techniques may be better tolerated and thus more practical alternatives to acetazolamide and CO₂ inhalation techniques (117). While TCD may

detect abnormalities of cerebral hemodynamics (increased or decreased pulsatility) in patients with risk factors for or symptoms of cerebrovascular disease (94, 137-139), the value of TCD evaluation of cerebral hemodynamic impairment and stroke risk has recently been questioned (124, 140).

In patients with severe (>70%) symptomatic ICA extracranial stenosis, vasomotor reactivity in the ipsilateral MCA is significantly reduced (88, 90, 97, 98, 113, 118). Patients with impaired collateral blood flow patterns may have the greatest reduction in VMR (99). One preliminary study (122) of patients with asymptomatic >70% extracranial ICA stenosis suggested that there was a statistically significant relationship between impaired cerebral VMR and the occurrence of ipsilateral ischemic events. In a recent study (112) of patients with asymptomatic 70% extracranial ICA stenosis, the annual ipsilateral ischemic event risk was 4.1% with normal and 13.9% with impaired BHI.

Patients with extracranial ICA occlusion typically have impaired VMR in the ipsilateral MCA (90, 99-102, 104, 115, 116, 120). Vasomotor reactivity may be as low as 30% of normal distal to occluded, symptomatic extracranial ICAs, and it may approach 60% of normal distal to asymptomatic extracranial ICA occlusions (103, 104, 111). One recent study (94) showed that exhausted vasoreactivity in the ipsilateral MCA was an independent predictor of the occurrence of ipsilateral transient ischemic attack and stroke (OR=14.4, 95%CI=2.63-78.74). Another recent study (114) suggests that the prognosis of a patient with extracranial ICA occlusion is significantly influenced by the number and effectiveness, but not the type, of intracranial collateral vessels. Annual stroke risk was 0% with three collaterals, 2.7% with two collaterals, 17.5% with one collateral and 32.7% with no collateral pathways. One study comparing TCD systolic velocity VMR testing with acetazolamide with stable xenon-enhanced

CT cerebral blood flow (124) found that TCD was less sensitive than xenon CT in detecting compromised cerebrovascular reserve. However, this finding may reflect the inability of TCD to detect MCA blood flow originating from collateral sources and use of peak systolic velocities instead of mean flow velocities. In patients with asymptomatic extracranial ICA occlusion, a BHI less than 0.69 reliably distinguishes pathologically reduced from normal cerebral vasomotor reactivity and identifies patients at risk for stroke and transient ischemic attack (111). However, the aforementioned relationship between reduced VMR and clinical outcome in this setting has not always been found (141).

TCD vasomotor reactivity testing is considered probably useful (Type B, Class II-III evidence) for the detection of impaired cerebral hemodynamics in patients with asymptomatic severe (>70%) stenosis of the extracranial ICA, patients with symptomatic or asymptomatic extracranial ICA occlusion and patients with cerebral small artery disease. How the results from these techniques should be used to influence therapy and affect patient outcomes remains to be determined (Type U).

g. Detection of Cerebral Microembolic Signals: In 1990, Spencer, et al. (142) first described to the neurovascular community the occurrence of Doppler signals felt to represent solid material emboli released from carotid plaques during the dissection phase of carotid endarterectomy. Since then, experimental (143-150) and clinical (142, 151-240) studies using this TCD technique have evaluated the presence and characteristics of microembolic signals in a number of cardiovascular and cerebrovascular disorders and procedures.

The physics and technical aspects of ultrasonic detection of microembolic signals or “high intensity transient signals” (“HITS”) by TCD have recently been reviewed (5, 241-244). Random fluctuations in the background physiologic Doppler flow signal, or “Doppler speckle”, occur in normal individuals and must be distinguished from embolic signals and artifacts. Particulate (solid, fat) or gaseous material in flowing blood are larger and of different composition and thus have different acoustic impedance than surrounding red blood cells (RBCs). The Doppler ultrasound beam is thus both reflected and scattered at the interface between the embolus and blood, resulting in an increased intensity of the received Doppler signal. The hierarchy of backscatter of the ultrasound, in descending order, is gaseous emboli, solid emboli and normal flowing blood (including transient RBC aggregates). The most important (and, at times, interacting) technical parameters affecting the detectability of microembolic signals include: a) relative power increase; b) detection threshold; c) sample volume size; d) fast Fourier transform (FFT) frequency resolution; e) FFT temporal resolution; f) FFT temporal overlap; g) instrument dynamic range; h) transmitted ultrasound probe carrier frequency; i) filter settings; and j) recording time. Features of Doppler microembolic signals include: a) short duration (usually < 300 msec); b) amplitude higher than the background blood flow signal; c) unidirectional in the Doppler velocity spectrum; and d) a ‘snap’, ‘chirp’ or ‘moan’ corresponding to the Doppler signal on the audible output of the instrument. Artifacts tend to be of: a) higher intensity (at times overloading the spectral display) with maximal intensities at lower frequencies; and b) bi-directional in the Doppler velocity spectrum. While particle size and echogenicity determine the intensity, velocity, duration and frequency detected by the transducer, there is often considerable overlap of intensities and velocities corresponding to particles of different compositions and sizes (5, 243-246).

Microembolic signals have been detected in patients with asymptomatic (163, 169, 175, 179, 180, 208-211) and symptomatic (152, 163, 169, 175, 178, 179, 181, 208-212, 216) high-grade internal carotid stenosis, prosthetic cardiac valves (159, 170, 172-174, 176, 184-192, 202), myocardial infarction (213), atrial fibrillation (165-168), aortic arch atheroma (214), fat embolization syndrome (215), and retinal (195) or general cerebral vascular (151, 161, 162, 164, 165, 195-206) disease. In addition, these signals have been observed temporally associated with diverse procedures such as coronary catheterization (155, 157), coronary angioplasty (159), direct current cardioversion (157), cerebral angiography (153-156, 160), carotid endarterectomy (142), carotid angioplasty (171), and cardiopulmonary bypass (217-240).

Plaque ulceration is independently associated with ischemic stroke risk in patients with high-grade carotid stenosis (212). TCD can be used to localize the embolic source or monitor the effects of antithrombotic treatment in patients with atherosclerotic cerebrovascular disease (197, 203-207). In patients with high-grade carotid stenosis, sources of asymptomatic microembolic signals may include ulcerated plaques (209, 211) and microscopic platelet aggregates and fibrin clots (210). Asymptomatic cerebral microembolization has been reported to be associated with an increased risk of further cerebral ischemia (OR=8.10, 95%CI=1.58-41.57) in this setting (209). Recently, cessation of microembolic signal detection following institution or modification of antiplatelet but not anticoagulant therapy has been reported in patients with arterioembolic cerebrovascular disease (207).

Comparison between all studies or studies of specific clinical settings is difficult because of differences in diagnostic criteria and detection threshold, different instruments, different instrument settings, nature and

severity of disease, variability in occurrence of microembolic signals, time span between last symptom and detection of microembolic signals, and type of treatment (5, 174, 182, 197, 244). Interobserver agreement for microembolic signal detection and determination of signal type has been variable; a higher detection threshold results in higher specificity and intercenter agreement (194, 200, 201). New hardware and software technical capabilities, such as the coincidence method (183), multigate monitoring (149, 185), multifrequency instrumentation (47, 248), filtering (208), automatic embolus detection (198, 199) by a trained neural network (198) and use of O₂ inhalation (187, 188) may help detection of microembolic signal type and discrimination from artifact (198, 199, 247, 248). However, a completely accurate and reliable characterization of embolus size and composition is not yet possible with current technology. In addition, data are insufficient to ascertain whether detection of microembolic signals leads to improved patient outcomes.

TCD can detect cerebral microembolic signals in a wide variety of cardiovascular/cerebrovascular disorders/procedures (Type B recommendation, Class II-IV evidence). However, data at present are insufficient to support a recommendation regarding the utility of this TCD technique for diagnosis or for monitoring response to antithrombotic therapy in ischemic cerebrovascular disease (Type U).

2. Perioperative and Periprocedural Monitoring

a. Carotid Endarterectomy (CEA): The causes of stroke complicating CEA, both hemodynamic and embolic, have recently been reviewed (249, 250). The principal cause of stroke following CEA, particularly in the postoperative phase, is embolism from the operative site (250). TCD monitoring of the ipsilateral MCA during CEA allows real-time readout of velocity changes in the basal cerebral

arteries. As long as fluctuations in arterial blood pressure and arterial CO₂ content are small, changes in flow velocity reflect changes in cerebral blood flow (251, 252).

Although a precise percent decrease in flow velocity from baseline or a velocity threshold that predisposes to cerebral ischemia has not been established, a large decrease in velocities intraoperatively is considered an indication for pharmacologic blood pressure augmentation, shunt placement, or repair of shunt kinking or thrombosis in the appropriate setting (253-255). In addition, flow velocity changes during cross-clamping correlate with stump pressure measurements (253-255). Reports of intraoperative TCD monitoring in conjunction with EEG monitoring show that while there is high overlap between low MCA flow velocities and ipsilateral EEG slowing, neither technique may identify all candidates for shunting or prevent all strokes (256-259). TCD also has the unique ability to detect microembolic signals that correspond to particulate matter or microbubbles. Hemodynamic changes following CEA include an improvement in MCA, ACA and ophthalmic flow velocities, resolution of side-to-side MCA flow velocity asymmetries, and restoration of cerebrovascular vasoreactivity to CO₂ or acetazolamide challenge (97, 98, 113, 260-263). Finally, increases in MCA flow velocities postoperatively to more than 150% of the preclamp values may identify the hyperperfusion syndrome and the risk of encephalopathy and intracerebral hemorrhage (264).

Not all ischemic events complicating CEA are accompanied by MCA velocity changes. The role of microembolic signals in the production of cerebral ischemia associated with CEA has been actively studied (250, 265-277). Microembolic signals most commonly occur during the dissection phase intraoperatively, during shunting and unclamping, during wound closure, and in the first few hours postoperatively (265-267, 270, 273, 277). The number of microembolic signals during dissection

correlates best with new ischemic lesions seen on MRI (270) and postoperative cognitive deterioration (266). The presence of more than 50 microembolic signals/hr during the early postoperative phase is reported to be predictive for the development of ipsilateral focal cerebral ischemia (268). TCD-detected microembolic signals during dissection and wound closure, greater than 90% MCA velocity decrease at cross clamping, and greater than 100% pulsatility index increase at clamp release have been associated with intraoperative stroke (273). In one study of 500 CEA operations monitored with TCD (250), the occurrence of stroke decreased from 7% during the first 100 TCD-monitored operations to 2% during the last 400 TCD-monitored operations. In another report, a policy of quality control assessment (TCD monitoring and completion angiography) substantially reduced the occurrence of intraoperative stroke (274). In another study (275), post-operative microembolic signals were significantly more common in women, patients not receiving antiplatelet therapy, and following left CEA. Postoperative TCD monitoring may identify patients at risk for carotid thrombosis (266, 268, 272) or ipsilateral hemispheric ischemia who may benefit from variable dose intravenous Dextran-40 therapy (269, 277). TCD may also be used to noninvasively monitor the effect of novel antiplatelet agents on the frequency of microembolic signals following CEA (278). Although microembolic signals are more common following percutaneous transluminal angioplasty of the carotid artery than after CEA, the two groups may show a similar decline in neuropsychological performance (279, 280).

CEA monitoring with TCD can provide important feedback pertaining to hemodynamic and embolic events during and after surgery that may help the surgeon take appropriate measures at all stages of the operation to reduce the risk of perioperative stroke. TCD monitoring is probably useful during and after CEA in circumstances where monitoring is felt to be necessary (Type B, Class II-III evidence).

b. Coronary Artery Bypass Graft (CABG) Surgery: Post-operative neurological complications, including cerebral infarction and encephalopathy, occur in up to 15% of patients who undergo CABG surgery. In addition, neuropsychological testing can document behavioral abnormalities in up to 70% of patients (281-289). The risk of stroke after CABG can be predicted based upon characteristics known before surgery (286, 288, 289-293). Protection of the brain, either by pharmacologic agents (e.g., remacemide) (294) or newer off-pump surgical techniques (295), are areas of active research.

TCD monitoring can show flow velocity changes in all phases of the operation. Flow velocities decrease after induction of anesthesia and during initiation of cardiopulmonary bypass and increase during rewarming; changes correlate best with temperature and arterial CO₂ content (220, 221). Flow velocity changes typically remain within a relatively narrow range and do not correlate with neurological complications (219). During moderately hypothermic cardiopulmonary bypass, CO₂ reactivity is generally preserved, although impaired autoregulation can lead to dependence of MCA flow velocities upon cerebral perfusion pressure (217). There have been no reports of correlations between changes in flow velocities or CO₂ reactivity and neurologic outcome.

Macroemboli and microemboli may occur during cardiopulmonary bypass (230, 231). Cerebral microembolic signals of all types may be detected at all phases of the operation, especially during aortic cannulation, aortic cross-clamping and clamp removal (223, 225). There is a significant correlation between the number of emboli detected by TCD and TEE (225). Recent data suggest that distal aortic arch cannulation (226) or off-pump technique (227, 228) may be associated with lower numbers of

cerebral microemboli. TCD demonstration of the presence of microembolic signals led to the acceptance of membrane over bubble oxygenators during cardiopulmonary bypass (218, 222). More recent studies have suggested that microemboli may occur most often during cardiopulmonary bypass (232), with greater numbers of microemboli associated with longer duration of cardiopulmonary bypass (233, 234). In this latter setting, neuropsychologic impairment may be associated with >10 injections of air into the venous side of the cardiopulmonary bypass circuit by perfusionists (234, 235). Four other studies (222-224, 229) suggested that high numbers of microembolic signals may be associated with post-operative neuropsychological abnormalities. The level of the glial protein S100B, a marker of cerebral injury (236), has been correlated with the number of microembolic signals during aortic cannulation and duration of cardiopulmonary bypass (237). In addition, higher numbers of microembolic signals have been observed in small numbers of patients with stroke or who have longer lengths of hospital stay (238). However, other data indicate that the number of cerebral microemboli and changes in neuropsychological function are not necessarily interrelated, suggesting that location of microemboli, systemic parameters and other factors may be important (239). Finally, patients undergoing cardiac valve replacement surgery may be more likely to have postoperative neuropsychological deficits (240).

TCD is possibly effective in documenting changes in flow velocities and CO₂ reactivity in patients who undergo CABG (Type C, Class III evidence). TCD is probably useful for the detection and monitoring of cerebral microemboli in patients undergoing CABG (Type B, Class II-III evidence). Data are presently insufficient regarding the clinical utility of this information, particularly in patients at various levels of predicted risk for stroke or encephalopathy (Type U).

c. Prosthetic Heart Valves: Microembolic signals, or “HITS”, are common in patients who have received prosthetic heart valves. Most HITS are thought to be gaseous microbubbles and are produced by local high pressure gradients that occur during valve closure. The pressure gradients cause “cavitation”, where the dissolved blood gas is released as microbubbles that enter the circulation. The frequency of these microbubbles is not reduced by antithrombotic therapy (170, 184, 190). The rate of gaseous HITS depends upon the arterial partial pressure of oxygen, as oxygen dissolves more readily in blood, displaces nitrogen, has a shorter lifespan and fewer gaseous microemboli enter the circulation. Thus, inhalation of 100% O₂ significantly reduces the number of microembolic signals (187, 188, 192).

The incidence of symptomatic cerebral thromboembolism in patients with prosthetic heart valves depends upon the site of valve insertion (dual > mitral > aortic) and is about 1% per year despite anticoagulation therapy (193). Microembolic signals have been observed in symptomatic and asymptomatic patients with prosthetic heart valves (186, 189, 190, 192). The occurrence of microembolic signals is generally felt to be innocuous (186, 192), although alterations in attention and memory (189) and other cognitive deficits (240) have been reported. The relation between solid microembolic signals, ischemic cerebrovascular symptoms and neurocognitive deficits in patients with prosthetic heart valves remains to be established.

TCD can detect gaseous and solid microembolic signals in patients who have prosthetic valves (Type C, Class III evidence). Data are insufficient regarding the clinical utility of this information (Type U).

d. Cerebral Thrombolysis: Acute occlusions of intracerebral vessels may undergo recanalization, either spontaneously (296-299) or induced by intravenous or intra-arterial thrombolytic therapy (296, 300-317). Occlusions of the MCA may recanalize according to TCD criteria in 65-89% of patients within 1-3 weeks after stroke onset (58, 65, 296, 297). Sonographic findings that may be observed during spontaneous or induced recanalization of acute MCA occlusions vary according to the pattern and extent of occlusive lesion(s), extent of collateral circulation, rapidity of recanalization, occurrence of re-occlusion and intensity of TCD monitoring (296-298, 300, 301, 303, 305, 308). For example, TCD can differentiate between tandem extracranial ICA/MCA lesions and isolated MCA occlusions; the former may have collateral flow patterns and stenotic terminal ICA signals (311). Most patients with ischemic stroke due to ICA occlusion and treated with thrombolysis do not experience recanalization of the ICA occlusion, although recanalization of associated MCA clot or improvement in MCA collaterals may result in a good outcome (315). In some cases, the dosage and duration of thrombolytic therapy can be tailored by TCD monitoring of vascular patency (308).

Specific sonographic patterns have been associated with clinical severity, early recovery, and mortality in patients treated with intravenous thrombolysis (306). For example, patients with a higher number of TCD collateral channels and higher flow grades at the MCA origin may have lower NIHSS scores (311). Sensitivity and specificity of TCD for detection of angiographic recanalization are generally good to excellent for complete occlusion, partial occlusion and recanalization, although the sensitivity for complete occlusion is low (300). Recanalization within 5-8 hours, especially when accompanied by good collaterals, has been associated with more rapid and improved outcomes (296, 301, 304, 305). The presence of residual flow signals, such as systolic spikes, blunted or dampened waveforms,

thrombus vibration, microembolic signals or transient flow changes, before thrombolysis is associated with an increased likelihood of complete recanalization (317).

Recent data suggest that better short-term clinical improvement may be observed with rapid (within less than 30 minutes) recanalization following thrombolytic treatment (311). A recent study of patients with MCA occlusion treated with thrombolysis (313) showed that normal restoration of flow occurred in 58% of patients with dramatic recovery and 14% of patients without dramatic recovery, suggesting that dramatic recovery is associated with early restoration of MCA flow. One recent 1:2 case-control study of cardioembolic stroke (310) showed that use of intravenous recombinant tissue plasminogen activator therapy was associated with significantly higher 6-hour recanalization rate (66% vs. 15%) and significantly reduced infarct volume ($50.2 \pm 40.3 \text{ cm}^3$ vs. $124.8 \pm 81.6 \text{ cm}^3$) compared with controls (15%). National Institutes of Health Stroke Scale (NIHSS) Score less than 17 (OR=12.1, 95% CI=2.8-68, $p=.001$) and early (less than 6 hours) recanalization (OR=23.4, 95% CI=5.4-96, $p=.001$) were independent predictors of functional independence (modified Rankin Scale Score less than or equal to 2) at three months after stroke. Thrombolysis-related hemorrhagic transformation may be a marker of early successful recanalization, reduced infarct size and improved clinical outcome (314). Findings suggestive of lack of improvement or re-occlusion might influence further interventions, such as intra-arterial thrombolysis (301, 303). Reocclusion is suggested by deterioration in TCD flow signals, with or without clinical change, and absence of hemorrhage on repeat CT scan (316). In patients with M1- or M2-MCA occlusion, arterial reocclusion may occur in up to 34% of patients with any initial recanalization and account for two thirds of deteriorations following improvement. Despite the

occurrence of reocclusion, patients appear to have a better long-term outcome than if there was no recanalization (316).

A recent small randomized trial (318) comparing IV thrombolysis (n=14) and IV thrombolysis with continuous ultrasonic monitoring (n=11) in acute MCA occlusion suggested a higher grade of recanalization at 1 hour and improved clinical outcome at 90 days in patients receiving continuous ultrasonic monitoring. Issues of the use of TCD for hyperacute ischemic stroke patient selection for, as well as efficacy and safety of ultrasonic monitoring of, cerebral thrombolysis are currently being explored in the Combined Lysis of Thrombus in Brain Ischemia with Transcranial Ultrasound and Systemic TPA (CLOTBUST) trial.

TCD is probably useful for monitoring thrombolysis of acute MCA occlusions (Type B, Class II-III evidence). Finally, it has been hypothesized that TCD monitoring may enhance clot dissolution (301, 302) and improve recanalization from thrombolysis (301). Present data are insufficient to define the optimal probe frequency of TCD monitoring to enhance clot dissolution and enhanced recanalization or to influence therapy (Type U).

3. Monitoring in the Neurology/Neurosurgery Intensive Care Unit

a. Subarachnoid Hemorrhage (SAH): Delayed narrowing or vasoconstriction of intracerebral arteries, or vasospasm (VSP), is angiographically detectable in 21-70% of patients with SAH due to a ruptured berry aneurysm. VSP-related ischemic neurological deficits are the major cause of mortality (7.2%) and morbidity (6.3%) in survivors of aneurysmal SAH (319, 320). VSP can occur in patients with

closed or penetrating head trauma and associated SAH (321-347). VSP can also follow other forms of non-aneurysmal SAH, such as intracerebral hemorrhage (ICH) with subarachnoid extension (348), brain tumors (349, 350) and in eclampsia (even without SAH) (351, 352), at times associated with clinical deterioration attributable to VSP (331-350). The temporal profile of TCD-detectable hemodynamic changes attributable to VSP following closed head injury without CT-detectable SAH appears to differ from TCD findings in spontaneous SAH and traumatic SAH (331, 335).

Angiographic VSP can occur in all intracranial arteries, either proximally or distally (319, 353-365). Neurologic deterioration in this setting may be associated with a number of disorders, and the presence of large vessel angiographic vasospasm does not always lead to neurologic deterioration. Clinical syndromes believed to be attributable to severe, flow-reducing VSP in each intracranial vessel have been described (319, 366). The mortality and morbidity from SAH are significantly greater in older patients (367-370). Angiographic vasospasm is believed to be less common in older patients, but may not be less severe or clinically significant (371). An inverse relation between cerebral blood flow, cerebral blood flow velocities and age in this setting has been observed (372-375).

1). Spontaneous SAH (sSAH): In general, TCD flow velocity findings in the MCA correlate well with clinical grade, CT localization of SAH clot, and the time course of angiographic VSP. However, these correlations are somewhat imperfect. There is a significant direct correlation between VSP severity after spontaneous SAH and flow velocities in cerebral arteries, although anatomic and technical factors weaken the association for the intracranial ICA and ACA (319, 320). For the MCA, flow velocities of less than 120 cm/sec or greater than 200 cm/sec, a rapid rise in flow velocities, or a higher Lindegaard (V_{mca}/V_{ica}) ratio (6 ± 0.3) may predict the absence or presence of clinically significant angiographic

MCA-VSP (378-381), although prediction of neurologic deterioration can be problematic (364, 379). A BA/ECVA ratio > 2 may be highly sensitive and specific for the presence of BA-VSP (365). Data for the other intracranial vessels is lacking. A variety of factors, such as technical issues, vessel anatomy, age, intracranial pressure, mean arterial blood pressure, hematocrit, arterial CO₂ content, collateral flow patterns and response to therapeutic interventions influence flow velocities and must be taken into account when interpreting TCD results in this setting (319). For example, there is a 20%-30% reduction in cerebral blood flow (74, 372, 373) and cerebral blood flow velocities (4, 374, 375) in healthy individuals from age 20 to 80 years. Recent data suggest a negative linear correlation between maximum mean flow velocity in the MCA and age (376) and that vasospasm may be present at lower cerebral blood flow velocities than in younger SAH patients (377). In addition, a change of $> 15\%$ from resting MCA flow velocities with institution of induced hypertension may indicate the presence of impaired autoregulation (362). Flow velocity ratios, such as V_{mca}/V_{ica} (for the MCA) and the posterior circulation flow index (V_{ba}/V_{va}) (361) or the BA/ECVA ratio (365) (for the BA), may improve test accuracy.

TCD has also been used to evaluate the vasomotor reactivity of the vasospastic cerebral circulation following SAH; there is an inverse relationship between the severity of VSP and the response to hypercapnia while the response to hypocapnia is normal (382). As a result, patients with severe VSP may experience a further reduction in cerebral blood flow with hypocapnia. In addition, use of the transient hyperemic response test may be helpful in the prediction of delayed cerebral ischemia and outcome following SAH (134, 135).

The sensitivity and specificity of TCD compared with cerebral angiography for the detection of VSP after sSAH in the proximal portions of each intracranial artery have been reported (353-356, 358-360, 378, 383-385). In a recent meta-analysis (364), only 5/26 evaluable TCD studies (354, 356, 358, 359, 378) met at least 7/10 criteria for methodologically high quality studies. Recently, one group of investigators (356, 358, 359) has externally validated criteria for the diagnosis of VSP in each intracranial artery after sSAH in an independent data set using the same methodology and diagnostic criteria but different technologists and neuroradiologists (361). In general, data vary by vessel and are somewhat dependent upon variable diagnostic criteria, variable disease prevalence or the timing of correlative angiography. Specific causes of false positive and false negative TCD examinations have been identified for each intracranial vessel (353, 356-359) and their impact upon the approach to test performance and interpretation have been described (319). TCD flow velocity criteria appear most reliable for detecting MCA VSP and BA VSP. The specificity of TCD can be optimized by increasing the flow velocity criteria and sensitivity by the timing of the angiographic correlation for the diagnosis of VSP (319, 356, 358, 359). $V_{mca}/V_{ica} > 3.00$ improves sensitivity for MCA VSP and $V_{ba}/V_{va} \geq 2.50$ improves specificity for BA VSP (361).

TCD is useful in monitoring the temporal course of VSP after sSAH. Although hypothesis-driven randomized trials have not been conducted, TCD is thought to be valuable in the day-to-day evaluation of SAH patients in VSP and to assess the effect and durability of neuroradiologic interventions (386-390). For example, TCD has been used to support a diagnosis of symptomatic VSP following endovascular coil treatment of acutely ruptured aneurysms (391) and detect VSP following prophylactic transluminal balloon angioplasty in sSAH patients at high risk of developing VSP (392). In addition,

TCD findings have been used as noninvasive surrogate endpoints or to demonstrate biological effects of treatments for vasoconstriction or VSP in clinical trials of pharmacological therapies for eclampsia and sSAH (352, 393-395). Data are insufficient to make a recommendation regarding the use and method(s) of autoregulation testing for prediction of the risk of delayed cerebral ischemia. In general, TCD is not useful for the detection of VSP directly affecting the convexity or vertically oriented branches of the intracranial arteries distal to the basal cisterns (353, 357), although the presence of VSP at these sites may be inferred by indirect Doppler waveform observations (decreased diastolic flow, increased pulsatility, side-to-side differences in pulsatility indices, etc.).

Based upon the available evidence, TCD is useful for the detection of angiographic VSP in the basal segments of the intracranial arteries, especially the MCA and BA, following sSAH (Type A, Class I-II evidence). More data are needed to show how its use affects clinical outcomes in this setting (Type U).

2). Traumatic SAH (tSAH): CT evidence of SAH following closed head injury occurs in 4-63% of patients (324, 338, 339, 343). Patients with tSAH may develop delayed arterial narrowing consistent with VSP (321-326, 331, 335, 337, 339, 343-345), with the site of severe VSP correlating with the site of tSAH (328, 341, 343). The VSP associated with tSAH is more common with massive tSAH (343) and may lead to focal neurological deficits in any vascular distribution (322-325, 328). Closed head injury patients with tSAH or hemodynamically significant VSP with reduced cerebral blood flow (CBF) have a significantly worse prognosis (death, persistent vegetative state, severe disability) than patients without tSAH or VSP (339, 341, 346). Clinical trials suggest that the use of nimodipine in

patients with severe closed head injury (340) or tSAH (344) leads to improved outcomes, similar to sSAH.

The cerebral hemodynamic changes following severe head injury and tSAH are complex (329, 332, 333, 336, 342, 346). TCD has been used in association with ¹³³Xenon CBF or SPECT studies (331, 342, 345, 346), jugular bulb oximetry (330, 332, 333, 346) and intracranial pressure (ICP) measurements (329, 331, 333, 336, 346) to assess these changes. Hyperemia may be defined as a global arterio-venous O₂ difference (AVDO₂) < 4 ml/dl and normal jugular bulb venous O₂ saturation (SJO₂), while ischemia may be defined as an AVDO₂ ≥ 9 ml/dl and reduced SJO₂ (332, 333).

Phase I (hypoperfusion) occurs on the day of injury (Day 0) and is defined by low CBF (mean CBF-15 min = 32.3 ± 2 ml/100gm/min), normal MCA flow velocities (mean MCA velocities = 56.7 ± 2.9 cm/sec), normal hemisphere index (HI) (mean HI = 1.67 ± 0.11), normal global arterio-venous O₂ difference (AVDO₂) (mean AVDO₂ = 5.4 ± 0.5 vol%), and reduced cerebral metabolic rate for oxygen (CMRO₂) (mean CMRO₂ = 1.77 ± 0.18 ml/100gm/min). In Phase II (hyperemia, Days 1-3), CBF increases (46.8 ± 3 ml/100gm/min), AVDO₂ falls (3.8 ± 0.1 vol%), MCA velocities rise (86 ± 3.7 cm/sec), and HI remains < 3 (2.41 ± 0.1) (346). Hyperemia is felt to be due to cerebral vasodilation (347). TCD waveforms in hyperemic patients may show an absent diastolic notch (332).

In some patients, increased flow velocities in the MCA and extracranial ICA and reduced pulsatility (an index of cerebrovascular resistance) may be observed, followed by increased ICP and acute brain swelling on CT scans. The brain swelling may exacerbate the severity of the brain injury and lead to a secondary brain insult. In these cases, as ICP rises, cerebral perfusion pressure (CPP) falls. If CPP is < 70 mm Hg, a progressive and significant increase in pulsatility ($r = -0.942$, $p < .0001$) with reduced

diastolic flow velocities and significant fall in SJO2 ($r = 0.78$, $p < .0001$) may occur (333). In Phase III (vasospasm phase, Days 4-15), there is a fall in CBF (35.7 ± 3.8 ml/100gm/min), a further increase in MCA velocities (96.7 ± 6.3 cm/sec), and a significant rise in HI (2.87 ± 0.22) (346). During Phase IV (after Day 14), the CBF and TCD abnormalities resolve. Less commonly, one may observe persistence of hypoperfusion throughout Phases I-III or persistence of hyperemia through Phases II and III (346).

A number of studies of TCD monitoring of severe head injury patients have been published (328-334, 336, 341-346). When compared with normal controls, patients with increasing severity of head injury will have significantly lower MCA velocities at hospital admission (339). VSP has variably been defined by MCA velocities ≥ 100 cm/sec (328, 330, 332, 342), a $V_{mca}/V_{ica} \geq 3.00$ (328, 341), MCA velocities ≥ 120 cm/sec and $V_{mca}/V_{ica} \geq 3.00$ (345), MCA 'spasm index' (MCA velocities/CBF-15) and BA 'spasm index' (BA velocities/CBF-15) (345). However, the sensitivity and specificity of TCD compared with angiography for the detection of VSP in intracranial arteries following closed head injury have not been reported. As many as 40% of patients will have MCA velocities ≥ 100 cm/sec (328, 330, 342, 345), while as many as 66% of patients will have $V_{mca}/V_{ica} \geq 3.00$ (328, 345). Hemodynamically significant vasospasm, as defined by abnormal MCA velocities (≥ 120 cm/sec), $V_{mca}/V_{ica} > 3.00$, MCA spasm index (> 3.4), BA velocities ≥ 90 cm/sec) or BA spasm index (> 2.5), has been associated with a significantly worse outcome (especially for the spasm indices) (345). Elevated MCA velocities have been associated with noncontusion-related cerebral infarction (330). TCD can also detect changes suggestive of reduced CPP (333). In the German tSAH Study (344), patients receiving nimodipine tended to have lower MCA velocities. Monitoring with TCD and

jugular bulb oxygen saturation (SJO₂) may be used to optimize ventilatory (333) and pharmacologic (342, 344, 345) management of patients with severe closed head injury. Persistently low MCA velocities has been associated with early (<72 hours) death (334). Early (first few days) disturbances in CO₂ vasomotor reactivity has not been associated with an unfavorable outcome (341).

TCD is probably useful for the detection of VSP and cerebral hemodynamic impairment following tSAH (Type B, Class I-III evidence). Data on sensitivity, specificity and predictive value of TCD for VSP after tSAH are needed. Data are insufficient regarding how use of TCD affects clinical outcomes after tSAH (Type U).

b. Increased Intracranial Pressure (ICP) and Cerebral Circulatory Arrest: There is a qualitative relationship between progressive increases in ICP and the evolution of abnormal TCD waveforms, assuming a constant arterial CO₂ content and a constant degree of distal vasoconstriction. Pulsatility changes occur when cerebral perfusion pressure (CPP) is less than 70 mm Hg. The earliest sign of increased ICP is increased pulsatility, followed by progressive reduction in diastolic flow velocities and reduction in mean flow velocities. Compartmental differences in flow velocities and pulsatility indices (PI) may occur with unilateral mass lesions, such as parenchymal intracerebral hemorrhage (ICH) and subdural hematomas (SDH) (396-398). Asymmetry in PI may occur with ICH volumes \geq 25 cc (398). Flow velocity and PI asymmetries may normalize following surgery (397). As regional or generalized ICP elevation becomes increasingly extreme, diastolic flow reaches zero, followed by an alternating flow pattern with retrograde diastolic flow, disappearance of diastolic flow, appearance of small systolic spikes, and eventually no flow. Once the reverberating flow pattern appears, cerebral

blood flow disappears on angiography. Evolutionary changes may occur over a period of minutes to hours (5, 399-403).

Brain death is a clinical diagnosis that can be supported by TCD evidence of absent cerebral blood flow (zero net flow velocity) at all insonation sites. Diagnostic criteria for cerebral circulatory arrest by ultrasonography have been published (399-403). The sensitivity and specificity of TCD for brain death are 91-100% and 97-100%, respectively (399-402). The specificity is imperfect since absence of MCA flow may be transient or basilar artery flow may still be present (396, 397); when systolic spikes are present in multiple intracranial compartments, recovery is unlikely (401). The most stringent criteria require similar waveform patterns to be present in the extracranial common carotid artery (CCA), ICA and VA (403). TCD is especially helpful in patients with suspected brain death who have loss of brainstem function due to isolated brainstem lesions or who received sedative, paralytic or vestibulotoxic agents that render clinical examination difficult. It can also shorten the observation period before organ harvest. TCD can be used as a confirmatory laboratory test to the clinical diagnosis of brain death (404).

TCD is a useful adjunct test for the evaluation of cerebral circulatory arrest associated with brain death (Type A, Class II evidence).

c. Arteriovenous Malformations (AVMs): AVMs are developmental anomalies of the cerebral circulation which are characterized by a direct communication between arteries and veins without an intervening capillary bed with vasomotor capacity. TCD can detect these lesions (405-416). Data on

sensitivity and specificity of TCD for detection of medium and large size AVMs are controversial in view of the lack of blinded comparison of TCD findings with cerebral angiography. However, TCD can obtain information about the physiologic and hemodynamic characteristics of AVMs that is not available by other noninvasive means. AVMs are supplied by arterial feeders serving as high flow shunts with diminished or absent vasomotor reactivity. This permits the differentiation between normal and medium to large sized feeder vessels by TCD vasomotor reactivity testing (415-417). The ability of TCD to detect AVMs decreases with small (<2.5 cm) lesion size (415-417).

TCD can evaluate the short- and long-term hemodynamic responses of AVMs to staged endovascular embolization and/or surgical resection (417-421). The risk of cerebral hemorrhage from an AVM may be evaluated by TCD (412, 415). These comments are tempered by the fact that many of these results are derived from uncontrolled clinical studies with non-representative populations.

TCD is possibly effective for the identification of feeding arteries of medium to large size AVMs and in assessing the hemodynamic effects of staged embolization and/or surgical resection of AVMs (Type C, Class III evidence). TCD is an unacceptable screening test for the detection of AVMs (Type B, Class III Evidence).

B. Transcranial Color-Coded Sonography (TCCS) or Imaging TCD

TCCS is a relatively new, bedside noninvasive technique that shows a real-time two-dimensional depiction of cerebral parenchymal and intracranial vascular structures (422-434). Compared with

conventional TCD, there is more accurate demonstration of vascular anatomy, since imaging of smaller arterial branches and venous structures is feasible (422-425, 433). Depending upon the vessel, the uncorrected insonation angle may be as high as 73 degrees (423-427, 429, 432). As a result, angle-corrected flow velocities may be as much as 25-30% higher than non-angle corrected flow velocities (423-427, 429, 430, 432). Age-specific normative data have been published (432, 435, 436). In Caucasian atherosclerotic patients over age 60, vessel detection rates are lower and blood flow velocities are higher in women (435). Flow velocity measurements are highly reproducible (423, 424, 426). However, errors in flow velocity measurement in two dimensions may still occur because of the three-dimensional course of intracranial arteries and the possibility of large insonation angles (429). Use of the lateral frontal bone window may help with detection of posterior communicating artery flow and flow direction (437, 438). Power-based TCCS does not yet offer any important advantages when compared with frequency-based TCCS (439, 440). Limited data suggest that TCCS and MRA have similar ability to detect stem and branch MCA occlusions (441).

As with conventional TCD, a major limitation of TCCS is insufficient transtemporal ultrasound beam penetration due to hyperostosis of the skull (422-427, 429-435). Transpulmonary echocontrast agents (ECA) increase the Doppler signal intensity and improve the signal-to-noise ratio for transcranial insonation (442-448). The use of an ECA enhances the ability of TCCS to visualize the number and length of basal cerebral arteries and second- or third-order branches of major cerebral arteries (435-447), particularly in patients with poor transtemporal windows (440, 449-458). The use of ECAs may increase the peak systolic velocities in a cerebral artery segment by as much as 26 +/- 10% (453, 457) and produce "bubble-noise" (459). However, if non-contrast enhanced TCCS does not reveal any

intracranial structures, such as the midbrain, or any cerebral artery, then contrast-enhanced (CE)-TCCS will not be diagnostically conclusive (450, 454). A recent power-based TCCS study of 687 consecutive patients (460) showed that an indication for use of an ECA was present in 8.8% of cases. There was a diagnostic result in 75% of cases during transtemporal insonation and 81% of cases during transforaminal insonation. Compared with MRA, sensitivity and specificity of power-based CE-TCCS for intracranial stenosis were 83% and 82%, respectively. ECAs are currently used in clinical practice in Germany but have not yet been approved by the U.S. Food and Drug Administration.

1. Ischemic Cerebrovascular Disease

In patients with ischemic cerebrovascular disease, CE-TCCS may be useful in several ways.

Morphologic data suggest that the threshold arterial diameter allowing for functional collateral flow in the circle of Willis is between 0.4-0.6 mm, which can be detected by TCCS (461). TCCS can detect presence and direction of collateral flow in the anterior (ACoA) and posterior (PCoA) communicating arteries in patients with hemodynamically significant (typically greater than or equal to 80%) ICA stenosis or occlusion, with improvement to as much as 96% diagnostic confidence following use of ECAs (454-467). Sensitivity and specificity for the detection of ACoA and PCoA collateral flow is good to excellent (465). Compared with the temporal bone window, use of the lateral frontal bone window appears to increase the detection of intracranial crossflow patterns via the posterior communicating artery (438).

Limited data suggest that intracranial steno-occlusive disease (53, 450-453), including greater than 50% diameter reduction stenosis (53) or distinction between vessel patency or occlusion with reduced flow

velocity (452, 453), can be detected more reliably with CE-TCCS than with TCD. TCCS can demonstrate areas of parenchymal hypoechogenicity in the MCA distribution suggestive of ischemic cerebral infarction shown on brain CT scan, accompanied by abnormal blood flow velocity pattern, with fair to good sensitivity and specificity (468, 469). Spontaneous (451, 457, 468) and thrombolytic therapy-induced (307, 308, 457) recanalization can be monitored by serial TCCS examinations, with recanalization being more common in patients treated with thrombolytic therapy (457). In addition, hemorrhagic transformation of ischemic infarcts in these settings can be detected (307). TCCS via the suboccipital window can also identify major intracranial veins (70%-90%) and venous sinuses (55%-70%) (470, 471). Venous hemodynamics can be evaluated (471, 472) and a few cases of cerebral venous sinus thrombosis have been diagnosed and monitored (470, 472). Preliminary data suggest that CE-TCCS and power-based TCCS may improve the diagnostic yield (473, 474).

Severe neurologic deficits and large MCA territory ischemic infarctions have been associated with sonographic signs of MCA occlusion or decreased MCA flow velocities within 12 hours of stroke onset (453), while a patent MCA without reduced MCA flow velocities may be predictive of early clinical improvement (452). In patients with severe, space-occupying MCA territory ischemic stroke, serial monitoring of midline shift may identify patients at risk of cerebral herniation and death (475, 476). TCCS is able to facilitate highly reproducible measurement of the oblique diameters of the third and mid-portion of lateral ventricles (477), identify ventricular enlargement and displacement (478, 479) and suggest the presence of increased intracranial pressure (478). Irrespective of stroke subtype (ischemic or parenchymal hemorrhage), TCCS measurements of midline shift are highly reproducible and strongly

correlated ($r=0.93$) with CT measurements (480). Preliminary data suggest that specificity for death caused by specific degrees of MLS-associated cerebral herniation is excellent (476).

(CE)-TCCS is probably useful in the evaluation and monitoring of patients with ischemic cerebrovascular disease (Type B, Class II-IV evidence). Data are insufficient regarding whether (CE)-TCCS can replace conventional angiography, DSA, MRA or CTA (Type U).

2. Hemorrhagic Cerebrovascular Disease

Most of the experience with (CE-) TCCS in hemorrhagic cerebrovascular disease is in aneurysmal SAH (481-490). A marked increase in the echodensity of the basal cisterns or ventricular system indicates the presence of blood in the subarachnoid or intraventricular space, respectively (481). TCCS can detect 76-91% of non-thrombosed intracranial aneurysms greater than or equal to 6mm in size (481-486); use of ECAs or power Doppler may increase the rate of detection, including aneurysms less than 5mm in size (483-486). Transcranial power Doppler imaging can show that aneurysms are larger and less pulsatile at low ICPs and smaller but more pulsatile at higher ICPs (487). TCCS may be used as a noninvasive intraoperative method to visualize and characterize the status of cerebral aneurysms and adjacent basal cerebral arteries before and after aneurysm clipping (488, 489) or coiling (485). Limited data suggest that sensitivity and specificity of TCCS for detection of intracranial ICA and MCA vasospasm are excellent (489). TCCS may also detect VSP in major branches of the circle of Willis following SAH (481, 490); however, limited data exist comparing the utility of (CE-) TCCS with conventional TCD in this setting (490).

Parenchymal hematomas larger than 1 cc in size may be detected by TCCS, although smaller or cortical lesions may be missed (491). Acute (less than 5 days old) hematomas may appear as an echodense lesion when compared with surrounding tissues; evolutionary changes in ICH characteristics can be documented on serial scans. Complications of ICH, such as intraventricular extension, hydrocephalus and increased ICP, can also be demonstrated. Limited data suggest that for ICH, TCCS has excellent sensitivity, specificity, positive predictive value and negative predictive value in patients with adequate transtemporal windows (491).

(CE-) TCCS is probably useful in the evaluation and monitoring of patients with aneurysmal SAH or VSP following SAH (Type B, Class II-IV evidence). Present data are insufficient regarding the use of TCCS to replace CT for diagnosis of ICH (Type U).

C. New Technological Developments

1. Three Dimensional (3D) Contrast-Enhanced Transcranial Color-Coded Sonography (3D CE-TCCS)

3D CE-TCCS is a new technique that permits the reconstruction of serial 2D CE-TCCS images into a three dimensional image of the cerebral circulation (492-496). Ultrasound data are obtained in a standard fashion via the transtemporal window using a TCCS device before and after injection of an ultrasound contrast agent. A magnetic sensor system for spatial localization of the ultrasonic information is used to acquire the 3D data set. The magnetic system induces a low-intensity 3D magnetic field by an array of three coils at 90 degrees to each other near the patient's head. The magnetic position sensor attached to the ultrasound probe sends the spatial orientation (in x, y, z planes) of the probe to a

workstation which also receives the 2D images from the TCCS machine. The probe is moved in a fan-like manner to facilitate the 3D image reconstruction of the intracranial vessels. An off-line Windows NT 4.0 – based software program then produces a realistic surface rendering of the insonated vessels.

The 3D CE-TCCS technique significantly improves the ability of TCCS to identify the basal cerebral arteries and their major branches in normal individuals (492, 493). Preliminary data suggest that 3D CE-TCCS is highly correlated with digital subtraction angiography and can better distinguish between true lesions and artifacts (494). In addition, the technique may be used intra-operatively to monitor the course of surgery for arteriovenous malformations and brain tumors by delineating regions of perfused tissue, vessels, and tumor (495, 496).

2. Second Harmonic Imaging (sHI)

sHI is a new imaging technique that takes advantage of the physical properties of contrast agents by transmitting at the fundamental frequency and receiving at multiples of this frequency (497-502). The non-linearity of the ECA allows capillary blood flow to be separated from tissue echoes. When a gas bubble vibrates at or near its resonating frequency, it produces harmonics, or multiples of the transmitted frequency. The first multiple of the fundamental frequency (second harmonic imaging or sHI) is generally the strongest of all possible harmonic frequencies. The magnitude of the backscattered contrast-enhanced signal at the second harmonic frequency is greater than that of tissue, which leads to a significant increase of the signal to noise ratio. The ultrasound system removes the unwanted fundamental frequency (noise), leaving the second harmonic frequency from the ECA. As a result, sHI

can enhance the ability of TCCS to separate gas bubbles in the microvasculature from the surrounding avascular tissue and qualitatively assess cerebral perfusion in normal subjects (498, 500-502).

sHI can be used to evaluate most patients with hemispheric ischemic stroke (503, 504). It can identify areas of normal from pathologic cerebral parenchymal echo contrast enhancement, such as large areas of ischemia in the distribution of the lenticulostriate arteries, superficial MCA branches, and MCA stem. At this time sHI cannot distinguish between low flow and no flow in the ischemic area. Small infarctions may be suggested by a restricted area of missing contrast enhancement, while missing contrast enhancement in the entire MCA territory is associated with extensive infarction and fatal brain edema. Ongoing experimental studies are evaluating newer ECAs (505, 506).

3. Contrast Burst Imaging (CBI), Time Variance Imaging (TVI) and Contrast Burst Depletion Imaging (CODIM)

CBI, TVI and CODIM are based upon the fact that microbubbles in ECAs undergo partial or complete destruction or splitting when exposed to a high-energy ultrasound field (507). Destructive imaging techniques are the most sensitive flow-independent contrast agent-specific imaging modes for assessing parenchymal perfusion (508). The techniques require that the transtemporal window is adequate and that patients are cooperative.

For CBI and TVI, a bolus application of the ECA results in qualitative/semi-quantitative data pertaining to peak intensity (PI), absolute time to peak intensity (TPI), and peak width (PW). After a bolus injection of the contrast agent, characteristic wash-in/wash-out curves can be observed in a given region

of interest (ROI). CBI, which is derived from power Doppler, uses short sequences of typically 6 broadband pulses with an elevated output power level to minimize acquisition time, improve axial resolution, and optimize microbubble destruction. The destruction of microbubbles leads to processes that produce broadband noise in the Doppler spectrum that partially passes the wall filter and can be displayed color coded as in conventional power Doppler. These signals can be obtained even from nonmoving or very slow moving microbubbles and are consequently associated with perfusion. TVI extracts the amplitude and spectral slope from 10 echoes acquired per beam line. The spectral slope is a parameter describing the symmetry of the power spectrum with respect to the center frequency. Both amplitude and spectral slope will vary over time if the multiple insonifications alter the structure of the microbubbles. TVI identifies and quantifies these variations using a stochastic model for bubble destruction. There are two practical limitations to these techniques. First, time to peak intensity is related to the perfusion rate and vessel topology. Second, the “bolus approach” limits the examination to one image plane per injection, thus making comparisons between brain hemispheres time consuming to perform (509, 510).

An alternate imaging approach that might overcome these drawbacks assumes a constant microbubble concentration in the blood pool during data acquisition. CODIM uses the “replenishment approach” (511), which intends to destroy all microbubbles in the imaging plane with a high-intensity, low-frequency and low-bandwidth insonation and then to image the refilling at a low-power level, i.e., without destroying more bubbles. Briefly, the number of microbubbles in a sample volume depends on the percentage of blood in the sample volume and on the microbubble concentration in the blood. Insonation of the sample volume by an ultrasound pulse will cause microbubble destruction so that the

microbubble concentration decreases instantaneously. Perfusion of the sample volume washes out blood with destroyed microbubbles and washes in new microbubbles, thus repeatedly increasing the concentration between subsequent insonations. Once the insonation of the sample volume at a constant pulsing interval, i.e., the frame rate, has started, the observable microbubble concentration, i.e., the concentration at the time of the insonation, in the sample volume drops until it reaches equilibrium. Since both effects, destruction and perfusion, influence the time-concentration curve in different ways, the effects can be quantified by analyzing the curve. For any given sample volume it is assumed that the blood supply does not originate primarily from regions within the same imaging plane. A fairly constant microbubble concentration can be assumed after a bolus injection of contrast agent some time after the maximum concentration has been reached because the life span of microbubbles in the blood pool is far longer than the time of data acquisition. Two ECAs, Levovist and Optison, are used. The main parameter, perfusion coefficient (PC), is a monotonic nonlinear function of flow velocity (510).

These techniques have been used to describe perfusion in the dog brain (512), calculate CBF values in dogs with craniotomies by means of radiolabelled microspheres (513), and evaluate perfusion in normal human volunteers (514). In normal humans, these techniques have been compared with perfusion-weighted MRI scans (509, 510). In one study (509), there was a characteristic time delay between a branch of a major cerebral artery and brain parenchyma. In addition, there was a marked depth-dependent decrease in PI in both CBI and TVI examinations, whereas TPI was not influenced by the insonation depth. With CODIM, similar PC values were found in multiple gray matter regions independent of depth of examination, while the PC of ipsilateral white matter was significantly lower than

in other ROIs (510). There were no significant differences in regional TPI (CBI, TVI) or PC (CODIM) compared with perfusion-weighted MRI (509, 510).

4. Portable TCD Devices

The NeuroDop (Medasonics, Newark, CA, USA) is one example of a pocket-sized continuous wave ultrasound probe attached to a stethoscope earpiece that may be taken to the emergency room, angiography suite, bedside, etc. to rapidly assess vascular patency during interventions or otherwise assist with therapeutic decision making for stroke patients (515). In a preliminary study (515), the auditory characteristics of the MCA signal by NeuroDop correlated with MCA velocities by TCD. Portable imaging devices have already been marketed for extracranial carotid, echocardiography and general ultrasound indications, but a portable intracranial duplex scanner has not yet been developed.

5. Power M-Mode Doppler (PMD)

The PMD device uses a new means of processing Doppler information to create an M-mode representation of the flow of blood and its constituents (516). A spectrogram and PMD display are generated as follows. The device first digitizes returning echoes after amplification and then processes all Doppler information digitally. Extended dynamic range and filtering operations are used to enhance the signal-to-noise ratio. The PMD image is constructed from a total of 33 sample gates, while the spectrogram and stereo audio output are obtained from the 34th sample gate. The PMD spectral displays are log compressed so the observed color range is proportional to a user-selected dynamic range of the input signal. The color (direction) and intensity assigned to each gate is done as a function of power and independent of velocity; zero or near-zero flow is assigned the color black. This permits

the sonographer to locate an ultrasonic window without limiting insonation to a single insonation depth. As a result, the direction and intensity of flow in the ipsilateral and contralateral vessels may be located in one imaging plane. Artifacts are identified as signals appearing across depths and may be suppressed from the PMD image.

This technique has several potential uses (516, 517). First, the technique may serve as a “window-finding” or “road map” tool. Second, simultaneous display of flow signals over long or tortuous vessel segments in the same imaging plane can demonstrate substantial variation in flow velocities due to changes in vessel trajectory and insonation angles. Third, the identification of velocity aliasing, turbulence and resistance patterns may help demonstrate or infer the location of arterial stenoses in various disease states. Fourth, collateral flow via basal cerebral arteries and leptomeningeal vessels can be seen. Fifth, the detection of microembolic signals may be inferred by the characteristic ‘track’ or signature in the PMD image. Sixth, the time course and accompaniments of spontaneous or induced thrombolysis can be monitored. Finally, the technique can be used to monitor cardiac and other neurovascular procedures.

D. Other Indications

There are insufficient data to support the routine clinical use of TCD/TCCS for other indications including: migraine, cerebral venous thrombosis, monitoring during cerebral angiography, evaluation of arteriovenous malformations, evaluation of cerebral autoregulation in other settings (Type U recommendation). For discussion of these and other possible indications for the use of TCD, the interested reader is referred to other sources (4-6).

SUMMARY AND CONCLUSIONS

In summarizing the role of TCD in the evaluation and management of patients with neurologic disease in specific clinical settings and relating it to other available imaging modalities, we have attempted to consider, for each indication, the following questions:

1. Is there evidence that TCD is able to provide information in the specific clinical setting considered?
2. Is there evidence that using this information in this specific clinical setting leads to improved clinical decision making, as reflected by improved patient outcomes (Clinical Utility)?
3. Are other, previously established, diagnostic tests preferable to TCD in this specific setting?

Since settings in which TCD does not provide information, as defined above, were excluded during the review process, this approach has resulted in four classes of settings:

1. Settings in which TCD is able to provide information and in which its clinical utility is established.
 - a. Screening of children aged 2-16 years with sickle cell disease for assessing stroke risk
(Type A, Class I).

- b. Detection and monitoring of angiographic vasospasm after spontaneous subarachnoid hemorrhage (Type A, Class I-II). More data are needed to show how its use affects clinical outcomes (Type U).
2. Settings in which TCD is able to provide information, but in which its clinical utility, compared to other diagnostic tools, remains to be determined.
 - a. Intracranial Steno-Occlusive disease: TCD is probably useful (Type B, Class II-III) for the evaluation of occlusive lesions of intracranial arteries in the basal cisterns (especially the ICA siphon and MCA). The relative value of TCD compared with MRA or CTA remains to be determined (Type U). Data are insufficient to give a recommendation to replace conventional angiography with TCD (Type U).
 - b. Cerebral Circulatory Arrest (Adjunctive test in the determination of brain death): If needed, TCD can be used as a confirmatory test, in support of a clinical diagnosis of brain death (Type A, Class II).
3. TCD is able to provide important information in this setting, but its clinical utility remains to be determined.
 - a. Cerebral Thrombolysis: TCD is probably useful for monitoring thrombolysis of acute MCA occlusions (Type B, Class II-III). More data are needed to optimize the frequency of monitoring for clot dissolution and enhanced recanalization and effects on clinical outcomes (Type U).
 - b. Cerebral Microembolism Detection: TCD monitoring is probably useful for the detection of cerebral microembolic signals in a variety of cardiovascular/cerebrovascular disorders/

procedures (Type B, Class II-IV). Data do not support the use of this TCD technique for diagnosis and monitoring response to antithrombotic therapy in ischemic cerebrovascular disease (Type U).

- c. Carotid Endarterectomy: TCD monitoring is probably useful during and after CEA in settings where monitoring is felt to be necessary (Type B, Class II-III).
- d. Coronary Artery Bypass Graft (CABG) Surgery: TCD monitoring is probably useful (Type B, Class II-III) during CABG for detection of cerebral microemboli. TCD is possibly useful to document changes in flow velocities and CO₂ reactivity during CABG surgery (Type C, Class III). Data are insufficient regarding the clinical utility of this information (Type U).
- e. Vasomotor Reactivity Testing: TCD is probably useful (Type B, Class II-III) for the detection of impaired cerebral hemodynamics in patients with severe (>70%) asymptomatic extracranial ICA stenosis, symptomatic or asymptomatic extracranial ICA occlusion and cerebral small artery disease. Whether these techniques should be used to influence therapy and improve patient outcomes remains to be determined (Type U).
- f. Vasospasm After Traumatic Subarachnoid Hemorrhage: TCD is probably useful for the detection of VSP following traumatic SAH (Type B, Class I-III), but data are needed to show its accuracy and clinical utility in this setting (Type U).
- g. Transcranial Color-Coded Sonography: TCCS is possibly useful (Type C, Class III) for the evaluation and monitoring of space-occupying ischemic MCA infarctions. More data are needed to show its relative value compared with CT and MRI scanning and how its use affects clinical outcomes (Type U).

4. TCD is able to provide information, but other diagnostic tests are preferable in most instances.
 - a. Right-to-left cardiac shunts: TCD is useful for detection of right-to-left cardiac and extracardiac shunts (Type A, Class II). TEE is diagnostically superior, as it can provide direct information regarding the anatomic site and nature of the shunt.
 - b. Extracranial ICA Stenosis: TCD is possibly useful as an adjunct test for the evaluation of severe extracranial ICA stenosis or occlusion (Type C, Class II-III). In general, carotid duplex or MRA are the diagnostic tests of choice.
 - c. Contrast-Enhanced Transcranial Color-Coded Sonography: (CE)-TCCS may provide information in patients with ischemic cerebrovascular disease and aneurysmal SAH (Type B, Class II-IV). Its clinical utility, compared with CT scanning, conventional angiography or non-imaging TCD, is unclear (Type U).
 - d. Prosthetic Heart Valves: TCD can detect gaseous and solid microembolic signals in patients who have prosthetic heart valves (Type C, Class III), although it is unclear how this information affects clinical outcomes (Type U).

RECOMMENDATIONS FOR FUTURE RESEARCH

1. Ischemic Cerebrovascular Disease
 - a. Sickle Cell Disease: The optimal frequency for screening children between the ages of 2 and 16 years needs to be determined. Data are needed to assess the value of TCD in the evaluation of adults with sickle cell disease and its impact, if any, on selection of treatment and prognosis.

- b. Intracranial Steno-Occlusive Disease: More data are needed to define the ability of TCD to detect $\geq 50\%$ stenosis of major basal intracranial arteries. This will facilitate comparison with MRA and CTA and the determination of the relative value of each technique for specific vascular lesions which may influence patient management. The ability of TCD to predict outcome in vertebrobasilar distribution stroke, if any, requires study. The value of TCD in the prediction of hemorrhagic transformation of ischemic infarction needs confirmation in well designed studies of patients who do and do not receive anticoagulation or thrombolysis.
- c. Extracranial ICA Stenosis: The clinical utility of TCD's ability to detect impaired cerebral hemodynamics distal to high grade extracranial ICA stenosis or occlusion and assist with stroke risk assessment needs confirmation and evaluation in randomized clinical trials. In patients with symptomatic ICA occlusion, it would be useful to directly compare TCD/vasomotor reactivity testing with positron emission tomography to see if TCD would be valuable to select and serially monitor patients for extracranial to intracranial bypass surgery. In patients with asymptomatic high grade ICA stenosis, it would be useful to learn if TCD assessment of vasomotor reactivity or microembolic signal detection can help clinicians appropriately select patients for CEA or angioplasty.

2. Perioperative and Periprocedural Monitoring

- a. Cerebral Microembolization: The ability of TCD to better distinguish between the various types of microembolic signals needs to be enhanced. Clinical utility in specific disease states should be defined.

- b. Carotid Endarterectomy: The incremental value of TCD monitoring compared with other intraoperative monitoring procedures (electroencephalography, evoked potentials, stump pressures, cerebral blood flow, etc.) needs further study.
 - c. Coronary Artery Bypass Graft (CABG) Surgery: More data from well designed studies are needed to show if TCD is able to reliably predict the occurrence of stroke or neurocognitive impairment following CABG. TCD may also be used as a surrogate endpoint for clinical trials of neuroprotective agents or new surgical techniques.
 - d. Cerebral Thrombolysis: The value of TCD in monitoring thrombolytic therapy (intravenous and intra-arterial) and other recanalizing techniques needs to be shown in clinical trials. Data from such studies might help in determining the need for further interventions and predicting the outcome of treated and non-treated patients. In addition, studies should be done to determine if thrombolysis can be enhanced with specific frequency (ies) of transcranial ultrasound.
 - e. Prosthetic Heart Valves: Studies using O₂ inhalation may be useful in determining the value of TCD testing or monitoring with respect to clinical outcomes in this setting.
3. Monitoring in the Neurology/Neurosurgery Intensive Care Unit
- a. Spontaneous Subarachnoid Hemorrhage: More data are needed on the sensitivity and specificity of TCD in the detection of VSP in different age groups, since diagnostic criteria (like normative data) may vary with age. It remains to be shown how TCD findings affect short- and long-term clinical outcomes. The ability of specific TCD measurements to predict long term outcome from SAH requires study.

- b. Traumatic Subarachnoid Hemorrhage: Data on the sensitivity and specificity of TCD in this setting are needed. More data are needed to show the clinical utility and predictive power of TCD in this setting.
- c. Contrast-Enhanced Transcranial Color-Coded Sonography: The incremental value of (CE)-TCCS in diverse settings of ischemic and hemorrhagic cerebrovascular disease, in comparison to TCD, CT, CTA, MRI, MRA and conventional angiography, needs to be confirmed. Whether (CE)-TCCS can assist stroke and NeuroICU clinicians in the monitoring of reperfusion techniques or selection of patients with severe MCA territory infarction for clinical trials of aggressive, putative beneficial or life-saving therapies remains to be determined.

4. New Technological Developments

- a. Three Dimensional Contrast Enhanced Transcranial Duplex Sonography: Data on the sensitivity and specificity of 3D CE-TCCS to detect various disease states and lesions are needed.
- b. Ultrasonic Perfusion Imaging: The value of these techniques to qualitatively and semi-quantitatively assess cerebral perfusion at the bedside in patients with anterior and posterior circulation stroke requires further study. Probes specifically designed for transcranial use, such as 1 MHz emitting and 2 MHz receiving frequency, should be developed and evaluated in patients who do and do not receive thrombolysis or other recanalizing techniques. Data are needed to determine the utility of sHI, CBI, CVI and CODIM in evaluating cerebral perfusion and stroke outcome compared with other techniques, such as single photon emission computed tomography (SPECT), diffusion-/perfusion-weighted magnetic resonance imaging (DWI/PWI) and computed tomographic perfusion (CT Perfusion) imaging. Development and refinement of

these ultrasonic techniques, if shown to provide information similar to PWI, could revolutionize the evaluation of interventions for acute ischemic stroke.

- c. Portable TCD/TCCS Devices: Such devices need to be developed and tested in various disease states.
- d. Power M-Mode Doppler: Data on the sensitivity and specificity of PMD for the detection and monitoring of various disease states, lesions and monitoring of various therapeutic procedures are needed.

5. Other Indications

- a. Further study is needed to define the role of TCD in the aforementioned settings.

DISCLAIMER

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurology problem or all legitimate criteria for choosing a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

APPENDIX

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TABLE 1 - DEFINITIONS FOR CLASSIFICATION OF EVIDENCE

Rating of Recommendations	Translation of Evidence to Recommendation	Rating of Diagnostic Article	Rating of Prognostic Article
A = Established as useful/ predictive or not useful/ predictive for the given condition in the specified population.	>= 1 convincing Class I or >=2 consistent, convincing Class II studies.	Class I: Evidence provided by prospective study in broad spectrum of persons with suspected condition, using a "gold standard" to define cases, where test is applied in blinded evaluation, and enabling assessment of appropriate tests of diagnostic accuracy.	Class I: Evidence provided by prospective study in broad spectrum of persons who may be at risk of outcome (target disease, work status). Study measures predictive ability using independent gold standard to define cases. Predictor is measured in evaluation masked to clinical presentation. Outcome is measured in evaluation masked to presence of predictor.
B = Probably useful/ predictive or not useful/ predictive for the given condition in the specified populations	>= 1 convincing Class II or >=3 consistent Class III studies.	Class II: Evidence provided by prospective study in narrow spectrum of persons with suspected condition or well designed retrospective study of broad spectrum of persons with suspected condition (by "gold standard") compared to broad spectrum of controls where test is applied in blinded evaluation and enabling assessment of appropriate tests of diagnostic accuracy.	Class II: Evidence provided by prospective study of narrow spectrum of persons who may be at risk for having the condition, retrospective study of broad spectrum of persons with condition compared to broad spectrum of controls. Study measures prognostic accuracy of risk factor using acceptable independent gold standard to define cases. Risk factor is measured in evaluation masked to the outcome.
C = possibly useful/ predictive or not useful/ predictive for the given condition in the specified population.	>=2 convincing and consistent Class III studies	Class III: Evidence provided by retrospective study where either persons with established condition or controls are of narrow spectrum, and where test is applied in blinded evaluation.	Class III: Evidence provided by retrospective study where persons with condition or controls are of narrow spectrum. Study measures predictive ability using independent gold standard to define cases. Risk factor measured in evaluation masked to outcome.
D = Data inadequate or conflicting. Given current knowledge, test/predictor unproven.		Class IV: Any design where test is not applied in blinded fashion OR evidence provided by expert opinion or descriptive case series.	Class IV: Any design where predictor is not applied in masked evaluation OR evidence by expert opinion, case series.

TABLE 2: ACCURACY OF TRANSCRANIAL DOPPLER ULTRASONOGRAPHY BY INDICATION

INDICATION	SENSITIVITY (%)	SPECIFICITY (%)	REFERENCE STANDARD	EVIDENCE/ CLASS
Sickle Cell Disease	86	91	Conventional angiography	A/I
Right to Left Cardiac Shunts	70-100	>95	Transesophageal echocardiography	A/II
Intracranial Steno-Occlusive Disease:			Conventional angiography	
Anterior Circulation	70-90	90-95		B/II-III
Posterior Circulation Occlusion -	50-80	80-96		B/II-III
MCA	85-95	90-98		B/II-III
ICA, VA, BA	55-81	96		B/II-III
Extracranial ICA Stenosis:			Conventional angiography	
Single TCD variable -	3-78	60-100		C/II-III
TCD Battery -	49-95	42-100		C/II-III
TCD Battery and Carotid Duplex -	89	100		C/II-III
Vasomotor Reactivity Testing: >= 70% extracranial ICA stenosis/ occlusion			Conventional angiography, clinical outcomes	B/II-III
Carotid Endarterectomy			EEG, magnetic resonance imaging, clinical outcomes	B/II
Cerebral Microembolization			Experimental model, pathology, magnetic resonance imaging, neuropsychological tests	
General				B/II-IV
Coronary Artery Bypass Graft Surgery - microembolization				B/II-III
Prosthetic Heart Valves				C/III
Cerebral Thrombolysis			Conventional angiography, magnetic resonance angiography, clinical outcome	B/II-III
Complete Occlusion	50	100		
Partial Occlusion	100	76		
Recanalization	91	93		

Need the rest of Table 2 and Table 3 and Table 4!

TABLE 3: DEFINITIONS FOR CLINICAL UTILITY

1. Able to provide information and clinical utility established
2. Able to provide information and clinical utility, compared to other diagnostic tools, remains to be determined
3. Able to provide information, but clinical utility remains to be determined
4. Able to provide information, but other diagnostic tests are preferable in most cases