The Role of Transcranial Doppler Ultrasonography in the Diagnosis and Management of Vasospasm After Aneurysmal Subarachnoid Hemorrhage

Scott A. Marshall, MD[a,b,*], Paul Nyquist, MD, MPH[a,c], Wendy C. Ziai, MD, MPH[a,c]

KEYWORDS

• Transcranial Doppler • Vasospasm
• Subarachnoid hemorrhage • Lindegaard Index

Aneurysmal subarachnoid hemorrhage and its accompanying sequelae are management challenges for the neurosurgeon and neurointensivist. Transcranial Doppler ultrasonography (TCD) has emerged as a tool used extensively by many centers for the surveillance and monitoring of vasospasm after aneurysmal subarachnoid hemorrhage (SAH).[1] The overall management of the primary and secondary complications of SAH is complex, and the use of appropriate tools and diagnostic strategies is helpful. TCD has emerged as an inexpensive, noninvasive tool used not only for bedside monitoring of intracerebral hemodynamic changes seen with SAH. TCD can also be used to evaluate other neurologic conditions in the Neurosciences Critical Care Unit such as

The views and opinions herein belong solely to the authors. They do not nor should they be construed as belonging to, representative of, or being endorsed by the Uniformed Services University of the Health Sciences, the US Army, The Department of Defense, or any other branch of the federal government of the United States.

[a] Division of Neurosciences Critical Care, Departments of Anesthesiology Critical Care Medicine, Johns Hopkins University School of Medicine, Meyer 8-140, 600 North Wolfe Street, Baltimore, MD 21287, USA
[b] Department of Neurology, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814, USA
[c] Departments of Neurosurgery and Neurology, Johns Hopkins University School of Medicine, Meyer 8-140, 600 North Wolfe Street, Baltimore, MD 21287, USA
* Corresponding author. Department of Neurology, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814.
E-mail address: scott.marshall@amedd.army.mil

Neurosurg Clin N Am 21 (2010) 291–303
doi:10.1016/j.nec.2009.10.010
1042-3680/10/$ – see front matter

intra- and extracranial vascular stenosis, arteriovenous malformations, intraoperative emboli, venous sinus thrombosis, ischemic stroke, sickle cell disease, and brain death.[2–4] This article provides a brief review of the pathophysiology of vasospasm, and other devices used to detect vasospasm. Also reviewed are the indices and technical aspects of TCD ultrasonography, the interpretation of data obtained from TCD studies, and TCD-based management algorithms for vasospasm.

VASOSPASM AFTER SUBARACHNOID HEMORRHAGE

The diminution of blood flow transiting through the cerebral vasculature seen after aneurysmal SAH due to vasoconstriction is referred to as vasospasm.[5,6] Arterial spasm after SAH was originally described by Ecker, and has since been the subject of decades of laboratory research and clinical investigation.[7] Various definitions of vasospasm are employed, including vasospasm seen on digital subtraction angiography or computed tomography angiography referred to as ''angiographic vasospasm'' and ''clinical vasospasm,'' which includes ''delayed ischemic neurologic deficit'' (DIND) and ''delayed cerebral ischemia.'' (DCI) DIND and DCI refer to clinical signs of transient or permanent neurologic deficits occurring remotely from the initial SAH or surgery, after other complications of SAH potentially causing neurologic deficits have been excluded.[5] The exact cause of vasospasm is not clearly understood, but it is thought that extra-arterial blood products surrounding the arterial wall trigger a cascade of events at the cellular level, that culminate in vasoconstriction.[1,4,5] Other factors involved include decreased vascular autoregulation, reversible vasculopathy, and relative hypovolemia.[8,9] A further review of the current pathophysiology of vasospasm is presented in this edition of *Neurosurgical Clinics*. Vasospasm occurs most intensely adjacent to the subarachnoid clot, but can occur distantly from the majority of the subarachnoid blood, and is predicted by clot volume, age, location, and density of the SAH seen on the initial computed tomography (CT) scan.[10,11] In the past, the most likely cause of mortality after SAH was from aneurysmal rerupture in the early period after SAH. Due to more aggressive early surgical and endovascular treatment of ruptured aneurysms, this has now been replaced by hydrocephalus and vasospasm.[12,13]

The incidence of angiographic vasospasm after aneurysmal subarachnoid hemorrhage has been estimated to occur in 50% to 70% of patients with aneurysmal SAH, with approximately 50% of those exhibiting symptoms of clinical vasospasm.[14] A review of angiography studies of more than 2700 cases of aneurysmal SAH found the average incidence to be approximately 67%, with the highest incidence occurring between days 10 and 17 after SAH.[15] Vasospasm classically is reported to occur from days 4 to 14 after aneurysmal SAH, but variations on this rule abound.[1,5,12–14,16,17] The incidence of *early* angiographic vasospasm, detected within 48 hours of aneurysm rupture, occurs in 10% to 13% of SAH patients and is associated with prior aneurysmal SAH, large aneurysms, intraventricular hemorrhage, and with reduced morbidity at 3 months.[18] The impact of clinical vasospasms on outcome has been established, with both morbidity and mortality estimates ranging from 10% to 20%.[15,19]

MODALITIES USED FOR MONITORING CEREBRAL VASOSPASM

It should be emphasized that vasospasm is a clinical diagnosis, and radiographic studies and other markers of brain perfusion support this diagnosis through evidence of diminished vessel caliber. Left unchecked, patients with vasospasm may progress from diffuse neurologic signs such as confusion, increasing somnolence, and combativeness to focal neurologic deficits suggestive of infarction. Radiographic findings often precede such clinical deficits, and thus offer the opportunity to intervene to prevent neurologic injury. To this effect, in 1982 Aaslid and colleagues[20,21] provided the first descriptions of the use of TCD for such purposes, by monitoring flow in intracranial arteries and later used TCD in the assessment of arterial vasospasm. Much work has been done on the use of this technology in the evaluation of cerebral blood flow, due to its relative inexpensiveness, bedside availability, and noninvasive nature. The gold standard for the diagnosis of cerebral vasospasm has remained digital subtraction angiography. Because of its expense, potential for severe complications, and the need to move the patient to the angiography suite, this test is impractical for use as a frequent monitor of vasospasm.[22] The major advantage of angiography is the potential for both diagnosis and therapeutic intervention, discussed elsewhere in this issue. Computed tomography angiography (CTA) has emerged as a potentially helpful tool in the evaluation of vasospasm, with relatively good sensitivity and specificity for discovery of severe vasospasm in the proximal arteries of the circle of Willis, and with a high negative predictive value.[23] Some have raised concern that sending

a patient who has severe vasospasm to undergo CTA may delay definitive treatment with angioplasty or intra-arterial injection of antispasmodic agents.[5] CTA is relatively insensitive for mild and moderate vasospasm, and ideally requires a baseline study early on in the course of SAH for purposes of comparison.[24] Ionita and colleagues[22] reported that with strongly positive or strongly negative TCD findings and a correlative neurologic examination, obtaining a CTA was not of added value in the management of such patients. These investigators suggested that CTA's best role may be in a patient population with indeterminate TCD findings and an examination suggestive of vasospasm. Magnetic resonance angiography (MRA) has been used by some to assess for vasospasm after SAH, although it is a technology limited by logistics, acquisition time, motion, and hardware artifact.[25–27] Other emerging technologies employ an altogether different approach to the detection of vasospasm. Perfusion imaging such as MR perfusion, CT perfusion (CTP), single photon emission computed tomography (SPECT), positron emission tomography (PET), and diffusion-weighted MR imaging are being studied for use with this indication.[28–32] Of these technologies, a combination of CTA and CTP may be useful as a second-tier diagnostic study in cases where a high index of suspicion exists or TCDs are not reliable.[12] Continuous electroencephalography (EEG) is also under investigation as a means to detect subclinical cortical dysfunction related to inadequate cerebral perfusion from vasospasm. A recent study has shown this to be a beneficial mode of monitoring SAH patients, allowing for detection of subsequent vasospasm days before the detection of abnormalities by TCD.[33,34] Several logistical limitations to continuous EEG monitoring preclude widespread use of this technique currently, although further data correlating this technique to the development of vasospasm may make its use more widespread in the future.

TCD has become the most common screening tool for vasospasm monitoring due to its portability and noninvasive nature, and ease of repeat testing.[35] Many advocate frequent TCD monitoring with schedules ranging from every other day to twice daily, usually starting on the first day after SAH onset, ending with resolution of vasospasm.[1,5,16] TCD is also recommended for following the temporal course of angiographic vasospasm during its peak incidence.[36]

The efficacy of TCD as a monitor for vasospasm is controversial.[37] TCD is operator dependent, and limitations of insonation secondary to adequate acoustic windowing restrict its use in about 8% of patients.[12,38] Other limiting factors include the rate of false-negative studies and variability between technicians performing examinations.[39] These limitations may be overcome with new TCD techniques.[40]

Many studies have established TCD threshold velocities for vasospasm diagnosis. These studies usually incorporate TCD and angiographic comparisons. In such work, a relationship has been demonstrated between intracerebral vessel diameter on angiography and velocities measured with TCDs.[41,42] The underlying principle used for TCD estimations of cerebral blood velocity is based on variations of the Bernoulli equation. The velocity of blood flow in a conduit is inversely related to the diameter of that conduit. As the diameter of a blood vessel decreases, the blood velocity will increase. Although the vessel itself is not directly visualized with TCD ultrasonography, an indirect evaluation of the vessel diameter is achieved using the Doppler effect by calculating the Doppler shift, which is the difference between the frequencies of the transmitted and received ultrasound waves.[43,44] The following equation allows for the calculation of vessel flow velocities and gives an indirect indication of vessel diameter.[5]

$$f = 2 * f_0 * v/c$$

$$v = f * c/(2 * f_0)$$

where f_0 is transmitted ultrasound frequency (1.0–3.0 MHz in TCD)

c is velocity of sound in blood (approximately 1540 m/s)

v is velocity of blood flow.

INDICES AND TECHNICAL ASPECTS TCD ULTRASONOGRAPHY

TCD provides several indices that are useful when making clinical decisions regarding the management of vasospasm in SAH patients. The flow velocity (FV) is the most used metric and is further defined by the mean flow velocity (MFV), the peak systolic flow velocity (V_s), and the end-diastolic flow velocity (V_d). In clinical practice, the mean flow velocity ($MFV = \{V_s - V_d/3\} + V_d$) is typically reported, but additional information is used to calculate the resistance index (RI) and pulsatility index (PI). Both the RI and PI are presumptive measures of downstream vascular resistance, and serve as indicators of extravascular or intracranial pressure (equations 1, 2). Elevated RI and PI occur secondary to vascular stenosis, distal vasospasm, and elevated intracranial compliance.[45]

$$RI = (FVsystolic - FVdiastolic)/FVsystolic \quad (1)$$

$$\text{Gosling Pulsatility Index : } PI = (FVsystolic - FVdiastolic)/MFV \quad (2)$$

The Lindegaard index (LI) is an important method of correcting for increases in hyperdynamic systemic flow velocities, either physiologic or induced, in patients with SAH. To calculate the LI, the MFV of the middle cerebral artery (MCA) is compared with an ipsilateral extracranial vessel, namely the proximal internal carotid artery (ICA). This ratio (equation 3) helps to distinguish global hyperemia from vasospasm, especially in the setting of triple-H therapy.[41]

$$LI = MFV_{mca}/MFV_{ica} \quad (3)$$

An understanding of normal TCD velocities is vital to understanding TCD findings of vasospasm, and it is recognized that each major cerebral artery has its own range of normal values. Data from a large study with normal volunteers has proposed normal values for mean velocity and pulsatility index in the anterior and posterior circulation (**Tables 1–3**).[46] The velocities are reported for men and women separately, as many of these differences were found to be statistically significant. FV may vary between technicians acquiring TCD indices by as much as 7.5% on the same day and 13.5% on different days.[47] A combination of TCD velocities, Lindegaard ratios, clinical characteristics, and a spasm index (TCD velocities/hemispheric blood flow obtained from ^{133}Xe cerebral blood flow studies), called the Vasospasm probability index, has been proposed recently.[11] The combination of Fisher grade, Hunt and Hess grade, and spasm index accurately detected clinical vasospasm in 92.9%. A model that included Fisher grade, Hunt and Hess grade, and Lindegaard ratio had an accuracy of 89.9% for detection of angiographic vasospasm. This study, along with others, suggests that the predictive value of TCD can be improved when used with other indicators. Another proposed "vasospasm risk index" found that a combination of high Fisher grade, early increase in the MCA MFV 110 cm/s or more recorded on or before post-SAH day 5, Glasgow Coma Scale score less than 14, and ruptured aneurysm of the anterior cerebral or internal carotid arteries translated into a high probability of identifying patients who would develop symptomatic vasospasm.[48,50]

An explanation of why TCD measurements alone may not correlate with angiographic or symptomatic vasospasm is likely based on the effect of decreased vessel lumen diameter on flow resistance in different hemodynamic situations. It has been postulated that with moderate vasospasm, cerebral autoregulation compensates for perfusion pressure reduction in the region of spasm (as long as arterial blood pressure [ABP] is above the lower limit of autoregulation), and flow velocity increases as lumen area falls, yielding good correlation between angiographic and TCD measured spasm.[51] This situation is depicted by region I on the Spencer curve (**Fig. 1**). In region II a plateau occurs whereby volume of flow is reduced and velocity remains high independent of diameter. Clinical vasospasm may occur because autoregulation is not effective. If ABP is increased (from A to B) with hypervolemic therapy,

Table 1
Normal reference TCD values for males

	MFV[a]		
Insonated Vessel	**Age 20–39**	**Age 40–59**	**Age >60**
ACA	54–62	51–61	45–55
MCA	66–74	62–69	55–62
PCA (P1)	48–53	41–48	40–45
PCA (P2)	43–49	40–45	39–45
Vertebral	37–43	29–36	30–35
Basilar	39–49	27–39	30–37

Abbreviations: ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; MFV, mean flow velocity.

[a] Range in cm/s.

Data from Martin PJ, Evans DH, Naylor AR. Transcranial color-coded sonography of the basal cerebral circulation. Reference data from 115 volunteers. Stroke 1994;25:390–6.

Table 2
Normal reference TCD values for females

	MFV[a]		
Insonated Vessel	**Age 20–39**	**Age 40–59**	**Age >60**
ACA	57–64	62–71	44–58
MCA	73–80	73–83	53–62
PCA (P1)	52–57	50–56	37–47
PCA (P2)	45–51	50–57	37–47
Vertebral	45–51	44–50	31–37
Basilar	51–58	47–56	29–47

Abbreviations: ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; MFV, mean flow velocity.

[a] Range in cm/s.

Data from Martin PJ, Evans DH, Naylor AR. Transcranial color-coded sonography of the basal cerebral circulation. Reference data from 115 volunteers. Stroke 1994;25:390–6.

volume flow increases and ischemic symptoms may improve, but the patient may paradoxically have much higher TCD velocities than in a normotensive setting. Here the correlation between TCD velocity and the degree of angiographic vasospasm is likely to be poor. Under conditions of critical stenosis (region III), additional reduction in lumen diameter results in lower TCD velocities, and reduction of flow to critical values with resultant neurologic deficits. Here TCD is unable to provide sufficient information to assess the hemodynamic state of the cerebral circulation.[51]

New imaging technology available for clinical use may make TCD more accurate and less subject to operator error. Power M-mode (PMD)/TCD facilitates the location of the acoustic temporal windows and allows viewing blood flow from multiple vessels at the same time.[1] The display that is used in PMD/TCD allows for color-coded information regarding the directionality of blood flow, and this has allowed for PMD/TCD to be the most commonly used form of TCD performed currently at the bedside.[5] Transcranial color-coded duplex sonography (TCCS) allows 2-dimensional representation of the large cerebral arteries in color with outlining of parenchymal structures, in addition to color-coded flow directionality information.[5] In a prospective comparison of the accuracies of TCCS and TCD in the diagnosis of MCA vasospasm using same-day digital subtraction angiography as the reference standard, the accuracy of TCCS and TCD was similar, although improvements in sensitivity of TCCS in detecting MCA vasospasm was noted.[40] TCCS allowed for the detection of vasospasm at an earlier stage and at lower velocities (using a threshold of 120 cm/s), which may allow for more timely interventions to arrest the complications of vasospasm when it occurs. At higher velocities (threshold of 200 cm/s), conventional TCD and TCCS exhibited similar accuracy in the detection of vasospasm. However,

Table 3
Pulsatility index normal values

	Pulsatility Index		
Insonated Vessel	**Age 20–39**	**Age 40–59**	**Age >60**
ACA	0.78–0.85	0.73–0.79	0.87–0.97
MCA	0.82–0.87	0.79–0.83	0.93–1.02
PCA (P1)	0.8–0.88	0.75–0.82	0.91–1.02
PCA (P2)	0.79–0.86	0.75–0.8	0.91–1.03
Vertebral	0.79–0.85	0.74–0.82	0.89–0.99
Basilar	0.76–0.86	0.73–0.83	0.86–1.03

Abbreviations: ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.

Data from Martin PJ, Evans DH, Naylor AR. Transcranial color-coded sonography of the basal cerebral circulation. Reference data from 115 volunteers. Stroke 1994;25:390–6.

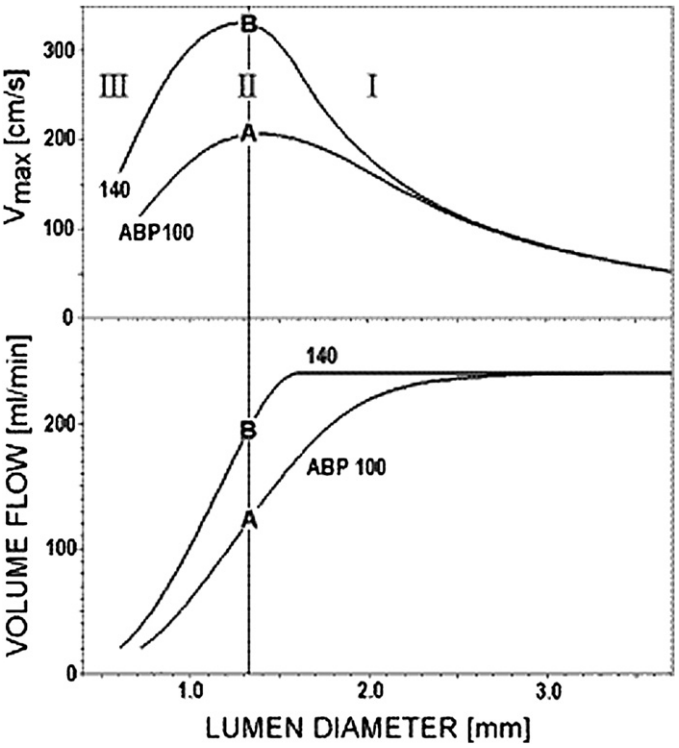

Fig. 1. "Spencer" curves (*above*) and volume flow as a function of lumen diameter (*below*) for 2 levels of arterial blood pressure (ABP). (*From* Aaslid R. Transcranial Doppler assessment of cerebral vasospasm. Eur J Ultrasound 2002;16(1–2):3–10; with permission.)

the investigators were unable to recommend universal additional capital investment of this technology by intensive care units (ICU) to routinely perform TCCS over traditional TCD. This question is currently being investigated.

INTERPRETATION OF DATA FROM TCD ULTRASONOGRAPHY

TCD studies generate a great deal of information, as they are performed daily to every other day in the Neurosciences ICU for patients with SAH.[1,5,16] These data can be interpreted based on absolute criteria for vasospasm, or used to see trends in the tempo of vasospasm over the course of several days.[37] Studies establishing the correlation between TCD mean flow velocities with decreases in vessel diameter on angiography have been most convincing for examinations of the MCA, but it is not acceptable to interpret flow velocity as cerebral blood flow or use TCD indices to estimate cerebral perfusion pressure.[1] Studies attempting to correlate these 2 parameters of perfusion have not been supportive.[52–54] Data comparing results of TCD and vasospasm seen on digital subtraction angiography give estimates for potential cutoff values for considering vasospasm in different cerebral arteries (**Table 4**). One of the most important questions regarding the use of TCD is the proper placement of the reference standard. In the case of TCD, this concerns mostly the MFV.

Vasospasm in the anterior cerebral artery (ACA) may be difficult to detect with TCD, in part due to anatomic factors.[41] In a study by Suarez and colleagues[55] of 199 SAH patients, the correlation between elevated TCD flow velocities and symptomatic vasospasm was better in either the ICA (sensitivity: 80%; specificity: 77%) or MCA (64% and 78%) distributions compared with the ACA (45% and 84%).[56]

To improve the sensitivity of TCD of the ACA, Lindegaard and colleagues[41] had suggested that clinicians use both ACAs to access vasospasm on either side, because the collateralization of the ACAs by the anterior communicating artery (ACom) is so prominent. In any case, sensitivity has been a challenge in TCD studies of this vessel to detect vasospasm, and some investigators have suggested using not absolute velocity values but rather a relative increase in MFVs of greater than 50% change over subsequent examinations or a change of 50 cm/s in MFV over a 24-hour period.[57,58] The issue with accuracy of TCD for

Table 4
A composite of practical MFV and other parameters from TCD ultrasound indicating vasospasm after aneurysmal SAH

Insonated Vessel	Mild Vasospasm MFV, cm/s	Moderate Vasospasm MFV, cm/s	Severe Vasospasm MFV, cm/s	Intracranial MFV/ Extracranial MFV
ACA	φ	MFV >50% increase from baseline in 24 h	MFV >50% increase from baseline in 24 h	φ
ICA (terminal)	>120	>130	φ	φ
MCA	>120	>130	>200	>3 mild[a] >6 severe
PCA	φ	>110	>110	φ
Basilar	>60	>80	>115	>3 severe[b]
Vertebral	>60	>80	>80	φ

Abbreviations: ACA, anterior cerebral artery; MCA, middle cerebral artery; MFV, mean flow velocities; PCA, posterior cerebral artery; φ, limited data to guide recommendations.
[a] Middle cerebral artery/extracranial internal carotid artery.
[b] Basilar artery/extracranial vertebral artery.
Data from Refs.[22,49,51,57,62–65,71–73]

the ACA may be mostly technical and anatomic, as increasing the FV cutoff from 120 to 140 cm/s failed to increase sensitivity for detecting vasospasm in one study.[59] In that article, where TCD ultrasound was performed for 75 ACAs in 41 patients, TCD did have a specificity of nearly 100%, although in patients with postcommunicating ACA (A2 segment) vasospasm on angiography, no abnormal findings were evident on TCD. In this study, TCD insensitivity to angiographic vasospasm was explained by aneurysm location, with all false negatives occurring in patients with ACom aneurysms. This finding has been demonstrated in other studies, and is problematic given the frequency of aneurysms in this region.[60,61] In addition, others have reported a higher rate of cerebral ischemia in the setting of negative TCDs in the ACA vascular territory, although intraoperative ischemia may be confounding.[62]

The best data for correlating increased MFV with angiographic vasospasm exist for the MCA. Lindegaard and colleagues[41] proposed a cutoff of MFVs of 140 cm/s for detecting vasospasm in the MCA, based on their work with 51 patients. Langlois and colleagues[63] showed that a cutoff of 130 cm/s for the MCA had a sensitivity of 73% and a specificity of 100% for detecting vasospasm. In another study of 49 patients using a cutoff of at least 130 cm/s, specificity reached 100% for finding vasospasm in the MCA.[64] In a larger study of more than 100 patients, an MFV of less than 120 cm/s was able to reliably predict absence of vasospasm (negative predictive value of 94%) and MFV of greater than 200 cm/s reliably predicted moderate to severe angiographic vasospasm (87% positive predictive value).[65] This study group recommended caution when interpreting intermediate velocities (ie, 120–200 cm/s). Others have used the Lindegaard ratio (intracranial MCA MFV/extracranial ICA MFV) to overcome issues related to cerebral hyperemia.[41] Lindegaard's original ratios indicating vasospasm were values greater than 10 in severe cases, with normal ranges from 1.1 to 2.3 and a median of 1.7.[41] A recent article used an LI of greater than 6 to reliably predict vasospasm in patients with clinical findings possibly indicating ischemia.[22] The LI is subject to variability because a small decrease in the ICA velocity may greatly overestimate the degree of vasospasm. This variability can be minimized by insonating the distal portion of the extracranial ICA as close as possible to the base of the skull (depth 40–50 mm).[51]

Other helpful corrections may be to standardize MCA MFVs to a patient's age and sex, although this has only been reported to have aided in the identification of mild arterial vasospasm, and has not been largely accepted in clinical practice.[66] It is recognized that a small percentage of patients develop only distal vasospasm (7.5%), which may be outside the range of TCD insonation.[67,68] For this reason the M2 segments should be evaluated for elevated velocities and bruits that may indicate distal spasm.[69]

ICA vasospasm in the terminal aspect of the vessel has been studied by several investigators. In a retrospective study, Creissard and Proust[70] reported sensitivities of 95% for the detection of

vasospasm with an ICA aneurysm, if the MCA (M1) and the ICA are successfully insonated. A prospective study by the same investigators reported lower sensitivities for detection of vasospasm in the ICA.[61] Older work with 49 patients and 90 intracranial ICAs reported a specificity and positive predictive value of 100% when MFV values exceeded 130 cm/s in the intracranial ICA.[64]

Detection of vertebral or basilar artery vasospasm with TCD has different criteria than for the anterior circulation. In an article addressing the question of posterior circulation specifically, a cutoff velocity of 85 cm/s in the basilar artery predicted more frequent progression to cerebral ischemia, indicating that if this degree of vasospasm was diagnosed with TCD, interventions to reduce neurologic injury should be introduced earlier.[62] In a study correlating the relationship between basilar artery (BA) vasospasm and regional cerebral blood flow, the risk for delayed brainstem ischemia increased significantly when TCD BA FVs were greater than 115 cm/s.[71] **Fig. 2** shows an example of BA vasospasm on TCD. As mentioned earlier, a modified version of the LI for the posterior circulation is available. This study calculated normative values for the intracranial/extracranial vertebral artery (VA) FV ratio (IVA/EVA) and BA/extracranial VA FV ratio (BA/EVA), and evaluated 34 SAH patients with TCD and CT angiography (CTA).[72] A BA/EVA ratio of more than 2 was 100% sensitive and 95% specific for detection of BA vasospasm. In addition, the BA/EVA ratio showed close correlation with BA diameter and was greater than 3 in all patients with severe vasospasm.

TCD detection of vasospasm in the posterior cerebral artery (PCA) was studied by Wozniak and colleagues.[73] The difficulty with use of TCD for insonating the ACA and PCA was specifically addressed in this article. In a study of 84 PCAs in 53 patients, they reported sensitivity of 48% and specificity of 69% in technically adequate TCDs with an MFV cutoff value of 90 cm/s. If this value was increased to 110 cm/s, the specificity increased to 93% with sensitivity remaining low. A false-positive rate of 37% was attributed to anatomic factors, including occlusion as well as operator inexperience.[73] The PCA, like the ACA, has proven to be a difficult vessel for which to reliably establish TCD criteria for vasospasm.

Although TCD monitoring of vasospasm is usually started after aneurysm repair has occurred, there may be a role for early monitoring to establish increased risk of DCI. In a study of 199 patients with TCD examinations within 48 hours of SAH onset, 38% of patients had MCA elevation greater than 90 cm/s, which was associated with younger age, angiographic vasospasm on admission, and elevated white blood cell count.[74] DCI occurred in 19% of these patients, which was independently predicted by elevated admission MCA MFV of more than 90cm/s and poor clinical grade. These data suggest that transient vasospasm during the early phase of SAH may predict delayed arterial spasm and DCI.

LIMITATIONS OF TCD

Several factors known to affect TCD velocity measurements that may impact assessment during SAH include hematocrit, arterial carbon dioxide tension, the patient's level of consciousness, and the observer's level of experience.[75] It has been suggested that because vasospasm may be episodic, intermittent measurements may miss episodes of vasospasm.[76] One study of continuous TCD measurement of cerebral blood flow velocities revealed a significant moment-to-moment variability of the MCA MFV in both patients and volunteers, ranging from −38% to 78%, suggesting that either false-negative or false-positive results may occur in the diagnosis of vasospasm.[76] In this study, continuous TCD

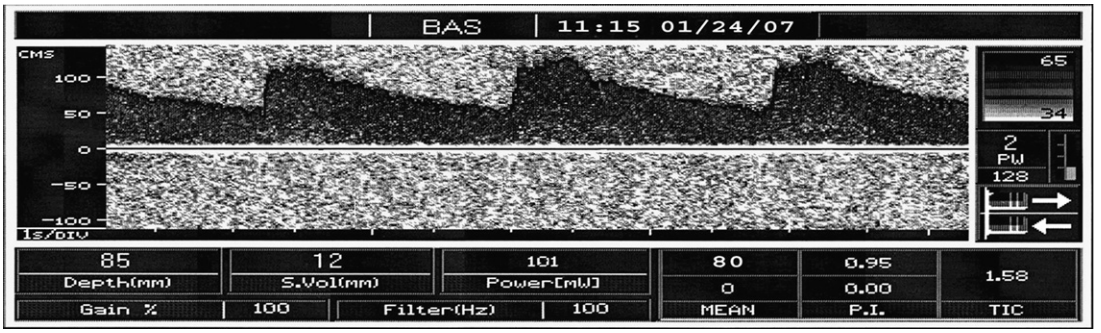

Fig. 2. Basilar artery vasospasm in a SAH patient with good correlation on cerebral angiography.

monitoring did not improve upon the sensitivity of intermittent TCD for detection of velocity evidence of vasospasm that was confirmed by angiography. At this time there seems to be no particular advantage of continuous TCD monitoring, although further study into how moment-to-moment variability affects detection of vasospasm has been suggested.[77]

MANAGEMENT ALGORITHMS

Our practice has evolved to use TCD ultrasonography in all patients with aneurysmal SAH by the performance of daily studies correlated with clinical examinations and physiologic data. Patients admitted with aneurysmal SAH are studied as soon as possible after digital subtraction angiography and securing of the aneurysm. In the setting of clinical stability, TCDs are continued daily while patients are maintained in a state of normovolemia and normonatremia. When a patient without new examination findings enters the window for increased risk of developing vasospasm, if TCD velocities increase to generally accepted levels for vasospasm for that vessel, fluid balance is shifted to maintaining a positive fluid state, and serum sodium is augmented with hypertonic saline if cerebral salt wasting develops. Patients are allowed to autoregulate blood pressure up to systolic pressures (SBP) of 200 mm Hg or mean arterial pressures (MAP) of 120 to 140 mm Hg, depending on the clinical status of the patient and other existing comorbidities. The placement of a pulmonary artery catheter or PiCCO-catheter may also be considered to optimize cardiopulmonary function and fluid management. If clinical suspicion for vasospasm increases with either increasing TCD values or clinical findings of potential ischemia, hypervolemic and hypertensive therapy is begun with either phenylephrine or norepinephrine and placement of a hemodynamic monitor. As an alternative, dobutamine or milrinone may be used in the setting of neurogenic stunned myocardium to augment cardiac output.

Depending on the clinical status of the patient and the reliability of the neurologic examination, other diagnostic imaging protocols may then be considered. The use of a perfusion study such as CT perfusion may be helpful in these cases, but if the suspicion is strong for clinical worsening then titration of MAP or SBP goals is warranted. Cerebral angiography, as both a diagnostic and therapeutic intervention, may be performed at this stage. TCD follow-up then may be vital in assessing the results of therapy and, along with the clinical examination, will aid in the timing of repeat angiography and will guide hemodynamic management.

OTHER USES OF TCD ULTRASONOGRAPHY

Several clinical applications of TCD exist currently in practice. TCD ultrasonography may be helpful in the setting of head trauma, as a marker of increased intracerebral pressure (ICP), assessment of cerebral autoregulation, brain death, ischemic stroke, intraoperative monitoring, and assessment of right to left shunt (ie, patent foramen ovale).[2–4,43,78] The utility of TCD in the Neurosciences ICU is primarily concerned with cerebral vasospasm and occlusive intracranial disease related to stroke, although new uses of TCD ultrasonography as a diagnostic, and even as a therapeutic tool, are increasing.

Evidence has emerged regarding the incidence of vasospasm after traumatic SAH or blast-related head injury.[6,62] This incidence has been reported to be higher in some populations with traumatic SAH than aneurysmal SAH, a concept that is not consistent with prior conventional teaching regarding vasospasm.[79] In a prospective cohort study of 299 patients with traumatic brain injury, hemodynamically significant vasospasm in the anterior circulation was found in 44.6% of the patients, whereas vasospasm in the BA (BA FV >90 cm/s) or hemodynamically significant vasospasm in the posterior circulation was found in 19% and 22.5% of patients, respectively.[80] The most common day of vasospasm onset was post injury day 2. Vasospasm resolved after 5 days in 50% of the patients with anterior circulation spasm and after 3.5 days in 50% of patients with posterior circulation spasm. It was recommended that TCD monitoring be used in the management of patients with traumatic brain injury. The use of TCD in sickle cell disease is widespread, and level IA evidence exists for use as a guide to help decide timing and frequency of transfusion therapy as a means to prevent stroke in this population.[81] Guidelines have been published as to insonation protocols and interpretation for performance of TCD in this setting in accordance with the STOP trial.[82]

The use of TCD in brain death may provide helpful additional information as confirmatory testing for this clinical diagnosis. Several centers use this as a standard practice, and recent work showed improved results with no false positives reported in a study of 184 patients with the inclusion of transcervical and transorbital carotid insonation in the brain death TCD protocol.[83] TCD has not to date been accepted as a formal ancillary test for diagnosis of brain death.

The correlation of TCD PI and intracranial pressure deserves discussion. ICP and PI have been shown in early work to share a direct correlation.[84]

The PI (equation 2) as a ratio is sensitive to changes in ICP, because downstream compression of arterioles due to high ICP will decrease the denominator of this equation (MFV), which is a surrogate measure of flow. This process is a result of the increased downstream vascular resistance created by compression of smaller arterioles, but not of the larger insonated arteries of the circle of Willis. Also, as increased ICP reduces compliance of the entire system, velocity variations due to the rigidity of arteries and reduced diastolic flow velocities will increase the numerator of this relationship. In turn, both of these factors will increase the index, and may indicate increasing ICP.[45] Follow-up prospective studies on this relationship have shown this correlation to be significant in a mixed population of neurosurgical patients who underwent TCD evaluation with an extraventricular drain in place.[45,85] This correlation has not gained acceptance as a surrogate for invasive ICP monitoring, although information provided by TCD ultrasonography may guide decisions to place invasive extraventricular drains, subdural monitors, or intraparenchymal monitors for suspicion of increased ICP in patients with severe neurologic illness or trauma.

The only current use of TCD as a therapeutic entity involves the management of ischemic stroke.[4] Patients enrolled in the Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic rt-PA (CLOTBUST) trial had increased rates of recanalization when treated with recombinant tissue plasminogen activator (rt-PA) and TCD ultrasound monitoring, and showed a trend toward improved outcomes.[86,87] Complete recanalization within 2 h after rt-PA bolus occurred in 25% of patients treated with rtPA + TCD compared with 8% who received rt-PA alone. This result is thought to be due to better penetration of rt-PA into the blood clot due to concomitant ultrasound during clot lysis.[88,89] The administration of intra-arterial (IA) contrast microbubbles together with IA rt-PA and continuous TCD monitoring during bridging IA-rescue therapy for acute ischemic stroke has also shown enhanced thrombolytic effect and increased recanalization rates compared with rt-PA alone.[90] Intra-arterial rt-PA delivery may also be enhanced with delivery of low-intensity ultrasound at the site of the occlusion via the EKOS Micro-Infusion Catheter (1 × 7–2 × 1-MHz pulsed wave ultrasound) (EKOS catheter, IMS trial).[89] The EKOS catheter is also being tested as an intraventricular application for enhancement of thrombolytic treatment of intraventricular hemorrhage (SLEUTH trial).

SUMMARY

The utility of TCD in the Neurosciences ICU has grown substantially since its introduction in 1982. TCD currently maintains an important role in the day-to-day management and triage of more invasive and expensive diagnostic tests and subsequent intervention in the setting of vasospasm due to aneurysmal SAH. Limitations currently exist to the use of TCD as a lone marker of radiographic vasospasm but as the technology continues to advance, these shortcomings may be overcome. At this time issues remain particularly with regard to the diagnosis of vasospasm in ACA and PCA distribution in the presence of ACom aneurysms. Technical advances such as Power-M mode TCD and TCCS may help refine this test in the future. Complete TCD evaluations, including calculation of LI for the anterior circulation and a modified LI for the posterior circulation, may increase the specificity for vasospasm detected by TCD in the setting of cerebral hyperemia. Like many tools used in the ICU, TCD is best employed as part of the multimodality approach that incorporates radiographic, metabolic, and clinical findings to better manage patients with vasospasm from SAH.

REFERENCES

1. Saqqur M, Aygun D, Demchuck A. Role of transcranial Doppler in neurocritical care. Crit Care Med 2007;35(Suppl 5):s216–23.
2. Bassocchi M, Quaia E, Auiani C, et al. Transcranial Doppler: state of the art. Eur J Radiol 1998;27(Suppl 2):S141–8.
3. Lowe LH, Bulas DI. Transcranial Doppler monitoring and clinical decision making after subarachnoid hemorrhage. J Stroke Cerebrovasc Dis 2003;35: 54–65.
4. Kincaid MS. Transcranial Doppler ultrasonography: a diagnostic tool of increasing utility. Curr Opin Anaesthesiol 2008;21:552–9.
5. Rigamonti A, Ackery A, Baker AJ. Transcranial Doppler monitoring in subarachnoid hemorrhage: a critical tool in critical care. Can J Anesth 2008; 55:112–23.
6. Armonda RA, Bell RS, Vo AH, et al. Wartime traumatic cerebral vasospasm: recent review of combat casualties. Neurosurgery 2006;59:1215–25.
7. Ecker A, Riewmanschneider PA. Arteriographic demonstration of spasm of the intracranial arteries. With special reference to saccular arterial aneurisms. J Neurosurg 1951;8:600–67.
8. Sarrafzadeh AS, Haux D, Ludemann L, et al. Cerebral ischemia in aneurysmal subarachnoid

hemorrhage: a correlative microdialysis-PET study. Stroke 2004;35:638–43.
9. Vajkoczy P, Horn P, Thome C, et al. Regional cerebral blood flow monitoring in the diagnosis of delayed ischemia following aneurysmal subarachnoid hemorrhage. J Neurosurg 2003;98:1227–34.
10. Reilly C, Amidei C, Tolentino J, et al. Clot volume and clearance rate as independent predictors of vasospasm after aneurysmal subarachnoid hemorrhage. J Neurosurg 2004;101(2):255–61.
11. Gonzalez NR, Boscardin WJ, Glenn T, et al. Vasospasm probability index: a combination of transcranial Doppler velocities, cerebral blood flow, and clinical risk factors to predict cerebral vasospasm after aneurysmal subarachnoid hemorrhage. J Neurosurg 2007;107:1101–12.
12. Zubkov AY, Rabinstien AA. Medical management of cerebral vasospasm: present and future. Neurol Res 2009;31(6):626–31.
13. Smith M. Intensive care management of patients with subarachnoid hemorrhage. Curr Opin Anaesthesiol 2007;20:400–7.
14. Keyrouz SG, Diringer MN. Prevention and therapy of vasospasm in subarachnoid hemorrhage. Crit Care 2007;11:220.
15. Dorsh NW, King MT. A review of cerebral vasospasm in aneurysmal subarachnoid hemorrhage. Part I: incidence and effects. J Clin Neurosci 1994;1:19–26.
16. Mascia L, Fedorko L, terBrugge K, et al. The accuracy of transcranial Doppler to detect vasospasm in patients with aneurysmal subarachnoid hemorrhage. Intensive Care Med 2003;29:1088–94.
17. Otten ML, Mocco J, Connolly ES, et al. A review of medical treatments of cerebral vasospasm. Neurol Res 2008;30:444–9.
18. Baldwin ME, Macdondald RL, Huo D, et al. Early vasospasm on admission angiography in patients with aneurysmal subarachnoid hemorrhage is a predictor for in hospital complications and poor outcome. Stroke 2004;35(11):2506–11.
19. Bleck TP. Rebleeding and vasospasm after SAH: new strategies for improving outcome. J Crit Illn 1997;12:572–82.
20. Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg 1982;57:769–74.
21. Aaslid R, Huber R, Nornes H. Evaluation of cerebrovascular spasm with transcranial Doppler ultrasound. J Neurosurg 1984;60:37–41.
22. Ionita CC, Graffagnino C, Alexander MJ, et al. The value of CT angiography and transcranial Doppler sonography in triaging suspected cerebral vasospasm in SAH prior to endovascular therapy. Neurocrit Care 2008;9:8–12.
23. Anderson GB, Ashforth R, Steinke DE, et al. CT angiography for the detection of cerebral vasospasm in patients with acute subarachnoid hemorrhage. Am J Neuroradiol 2000;21(6):1011–5.
24. Sanelli PC, Ougorets I, Johnson CE, et al. Using CT in the diagnosis and management of patients with cerebral vasospasm. Semin Ultrasound CT MR 2006;27(3):194–206.
25. Heiserman JE. MR angiography for the diagnosis of vasospasm after subarachnoid hemorrhage. Is it accurate? Is it safe? Am J Neuroradiol 2000;21(9): 1571–2.
26. Grandin CB, Cosnard G, Hammer F, et al. Vasospasm after subarachnoid hemorrhage: diagnosis with MR angiography. Am J Neuroradiol 2000; 21(9):1611–7.
27. Gauvrit JY, Leclerc X, Ferre JC, et al. Imaging of subarachnoid hemorrhage. J Neuroradiol 2009; 36(2):65–73.
28. Novak L, Emri M, Molnar P, et al. Regional cerebral (18)FDG uptake during subarachnoid hemorrhage induced vasospasm. Neurol Res 2006; 28(8):864–70.
29. Sviri GE, Britz GW, Lewis DH, et al. Dynamic perfusion CT in the diagnosis of cerebral vasospasm. Neurosurgery 2006;59:319–25.
30. Yonas H. Cerebral blood measurements in vasospasm. Neurosurg Clin N Am 1990;1:307–18.
31. Condeltte-Auliac S, Bracard S, Anxionnat R, et al. Vasospasm after SAH: interest in diffusion weighted MR imaging. Stroke 2001;32:1818–24.
32. Jabre A, Babikian V, Powsner RA, et al. Role of single photon emission computed tomography and transcranial Doppler ultrasonography in clinical vasospasm. J Clionm Neurosci 2002;9:400–3.
33. Claassen J, Mayer SA. Continuous EEG monitoring in neurocritical care. Curr Neurol Neurosci Rep 2002;2:534–40.
34. Claassen J, Hirsch LJ, Dreiter KT, et al. Quantitative continuous EEG for detecting delayed cerebral ischemia in patients with poor grade subarachnoid hemorrhage. Clin Neurophysiol 2004;115:2699–710.
35. Daffertshofer M, Gass A, Ringleb P, et al. Transcranial low-frequency ultrasound-mediated thrombolysis in brain ischemia: increased risk of hemorrhage with combined ultrasound and tissue plasminogen activator: results of a phase II clinical trial. Stroke 2005; 36(7):1441–6.
36. Sloan MA, Alexandrov AV, Tegeler CH, et al. Assessment: transcranial Doppler ultrasonography: report of the therapeutics and technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2004;62(9):1469–81.
37. Bederson JB, Connolly ES, Batjer HH, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the stroke council, American Heart Association. Stroke 2009;40(3):994–1025.

38. Moppett IK, Majajan RP. Transcranial Doppler ultrasonography in anesthesia and intensive care. BJA 2004;93(5):710–24.
39. Lysakowski C, Walder B, Costanza MC, et al. Transcranial Doppler versus angiography in patients with vasospasm due to a ruptured cerebral aneurysm: a systematic review. Stroke 2001;32:2292–8.
40. Swiat M, Weigele J, Hurst RW, et al. Middle cerebral artery vasospasm: transcranial color-coded duplex sonography versus conventional nonimaging transcranial Doppler sonography. Crit Care Med 2009; 37(3):963–8.
41. Lindegaard KF, Nornes H, Bakke SJ, et al. Cerebral vasospasm after subarachnoid hemorrhage investigated by means of transcranial Doppler ultrasound. Acta Neurochir Suppl (Wien) 1988;42:81–4.
42. Sloan MA, Haley EC Jr, Kassell NF, et al. Sensitivity and specificity of transcranial Doppler ultrasonography in the diagnosis of vasospasm following subarachnoid hemorrhage. Neurology 1989;39: 1514–8.
43. Kassab MY, Majid A, Farooq MU, et al. Transcranial Doppler: an introduction for primary care physicians. J Am Board Fam Med 2007;20(1):65–71.
44. McGirt MJ, Blessing RP, Goldstein LB. Transcranial Doppler monitoring and clinical decision-making after subarachnoid hemorrhage. J Stroke Cerebrovasc Dis 2003;12(2):88–92.
45. Bellner J, Romner B, Reinstrup P, et al. Transcranial Doppler sonography pulsatility index (PI) reflects intracranial pressure (ICP). Surg Neurol 2004;62: 45–51.
46. Martin PJ, Evans DH, Naylor AR. Transcranial color-coded sonography of the basal cerebral circulation. Reference data from 115 volunteers. Stroke 1994; 25:390–6.
47. Maeda H, Etani H, Handa N, et al. A validation study on the reproducibility of transcranial Doppler velocimetry. Ultrasound Med Biol 1990;16:9–14.
48. Qureshi AI, Sung GY, Suri MAK, et al. Prognostic value and determinants of ultraearly angiographic vasospasm after aneurismal subarachnoid hemorrhage. Neurosurgery 1999;44:967–74.
49. Sloan MA, Burch CM, Wozniak MA, et al. Transcranial Doppler detection of vertebrobasilar vasospasm following subarachnoid hemorrhage. Stroke 1994; 25:2187–97.
50. Qureshi AI, Sung GI, Razumovsky AY, et al. Early identification of patients at risk for symptomatic vasospasm after aneurysmal subarachnoid hemorrhage. Crit Care Med 2000;28:984–90.
51. Aaslid R. Transcranial Doppler assessment of cerebral vasospasm. Eur J Ultrasound 2002;16(1–2):3–10.
52. Barwish RS, Ahn E, Amiridze NS. Role of transcranial Doppler in optimizing treatment of cerebral vasospasm in subarachnoid hemorrhage. J Intensive Care Med 2008;23(4):263–7.
53. Clyde BL, Resnick DK, Yonas H, et al. The relationship of blood velocity as measured by transcranial Doppler ultrasonography to cerebral blood flow as determined by stable xenon computed tomographic studies after aneurysmal subarachnoid hemorrhage. Neurosurgery 1996;38(5):896–904.
54. Romner B, Brandt L, Berntman L, et al. Simultaneous transcranial Doppler sonography and cerebral blood flow measurements of cerebrovascular CO_2-reactivity in patients with aneurysmal subarachnoid haemorrhage. Br J Neurosurg 1991;5(1):31–7.
55. Suarez JI, Qureshi AI, Yahia AB. Symptomatic vasospasm diagnosis after subarachnoid hemorrhage: evaluation of transcranial Doppler ultrasound and cerebral angiography as related to compromised vascular distribution. Crit Care Med 2002;30(6): 1348–55.
56. Barwish RS, Ahn E, Amiridze NS. Role of transcranial Doppler in optimizing treatment of cerebral vasospasm in subarachnoid hemorrhage. J Intensive Care Med 2008;23(4):263–7.
57. Grolimund P, Seiler RW, Aaslid R, et al. Evaluation of cerebrovascular disease by combined extracranial and transcranial Doppler sonography: experience in 1,039 patients. Stroke 1987;18:1018–24.
58. Grosset D, Straiton J, McDonald I, et al. Use of a transcranial Doppler to predict development of a delayed ischemic deficit after subarachnoid haemorrhage. J Neurosurg 1993;78:183–7.
59. Lennihan L, Petty GW, Fink ME, et al. Transcranial Doppler detection of anterior cerebral artery vasospasm. J Neurol Neurosurg Psychiatr 1993;56: 906–9.
60. International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet 2002;360:1267–74.
61. Creissard P, Proust F, Langlois O. Vasospasm diagnosis: theoretical and real transcranial Doppler sensitivity. Acta Neurochir (Wien) 1995;136(3–4): 181–5.
62. Soustiel JF, Bruk B, Shik B, et al. Transcranial Doppler in vertebrobasilar vasospasm after subarachnoid hemorrhage. Neurosurgery 1998;43: 282–91.
63. Langlois O, Rabehaniona C, Proust F, et al. Diagnosis of vasospasm: comparison between arteriography and transcranial Doppler. A series of 112 comparative tests. Neurochirurgia 1992;38(3):138–40.
64. Burch CM, Wozniak MA, Sloan MA, et al. Detection of intracranial internal carotid artery and middle cerebral artery vasospasm following subarachnoid hemorrhage. J Neuroimaging 1996;6(1):8–15.
65. Vora YY, Suarez-Almazor M, Steinke DE, et al. Role of transcranial Doppler monitoring in the diagnosis

of cerebral vasospasm after subarachnoid hemorrhage. Neurosurgery 1999;44(6):1237–47.
66. Krejza J, Mariak Z, Lewko J. Standardization of flow velocities with respect to age and sex improves the accuracy of transcranial color Doppler sonography of middle cerebral artery spasm. Am J Roentgenol 2003;181(1):245–52.
67. Newell DW, Grady MS, Eskridge JM, et al. Distribution of angiographic vasospasm after subarachnoid hemorrhage: implications for diagnosis by transcranial Doppler ultrasonography. Neurosurgery 1990; 27:574–7.
68. Oertel M, Boscardin WJ, Obrist WD, et al. Posttraumatic vasospasm: the epidemiology, severity, and time course of an underestimated phenomenon: a prospective study performed in 299 patients. J Neurosurg 2005;103(5):812–24.
69. Mursch K, Bransi A, Vatter H, et al. Blood flow velocities in middle cerebral artery branches after subarachnoid hemorrhage. J Neuroimaging 2000;10:157–61.
70. Creissard P, Proust F. Vasospasm diagnosis: theoretical sensitivity of transcranial Doppler evaluated using 135 angiograms demonstrating vasospasm. Practical consequences. Acta Neurochir (Wien) 1994;131(1–2):12–8.
71. Sviri GE, Lewis DH, Correa R, et al. Basilar artery vasospasm and delayed posterior circulation ischemia after aneurysmal subarachnoid hemorrhage. Stroke 2004;35:1867–72.
72. Soustiel JF, Shik V, Shreiber R, et al. Basilar vasospasm diagnosis: Investigation of a modified "Lindegaard Index" based on imaging studies and blood velocity measurements of the basilar artery. Stroke 2002;33:72–7.
73. Wozniak MA, Sloan MA, Rothman MI, et al. Detection of vasospasm by transcranial Doppler sonography: the challenges of the anterior and posterior cerebral arteries. J Neuroimaging 1996;6:87–93.
74. Carrera E, Schmidt JM, Oddo M, et al. Transcranial Doppler ultrasound in the acute phase of aneurysmal subarachnoid hemorrhage. Cerebrovasc Dis 2009;27(6):579–84.
75. Manno EM. Transcranial Doppler ultrasonography in the neurocritical care unit. Crit Care Clin 1997;13: 79–104.
76. Venkatesh B, Shen Q, Lipman J. Continuous measurement of cerebral blood flow velocity using transcranial Doppler reveals significant moment-to-moment variability of data in healthy volunteers and in patients with subarachnoid hemorrhage. Crit Care Med 2002;30(3):563–9.
77. Bell RD, Benitez RP. Continuous measurement of cerebral blood flow velocity by using transcranial Doppler reveals significant moment-to-moment variability of data in healthy volunteers and in patients. Crit Care Med 2002;30(3):712–3.
78. White H, Venkatesh B. Applications of transcranial Doppler in the ICU: a review. Intensive Care Med 2006;32:981–94.
79. Soustiel JF, Shik V, Feinsod M. Basilar vasospasm following spontaneous and traumatic subarachnoid haemorrhage: clinical implications. Acta Neurochir (Wien) 2002;144:137–44.
80. Alexandrov AV. Ultrasound enhanced thrombolysis for stroke. Int J Stroke 2006;1(1):26–9.
81. Lee MT, Piomelli S, Granger S, et al. Stroke Prevention Trial in Sickle Cell Anemia (STOP): extended follow-up and final results. Blood 2006;108(3): 447–52.
82. Nichols FT, Jones AM, Adams RJ. Stroke prevention in sickle cell disease (STOP) study guidelines for transcranial Doppler testing. J Neuroimaging 2001; 11(4):354–62.
83. Conti A, Iacopino DG, Spada A, et al. Transcranial Doppler ultrasonography in the assessment of cerebral circulation arrest: improving sensitivity by transcervical and transorbital carotid insonation and serial examinations. Neurocrit Care 2009;10(3): 326–35.
84. Klingelhöfer J, Conrad B, Benecke R, et al. Evaluation of intracranial pressure from transcranial Doppler studies in cerebral disease. J Neurol 1988;235(3):159–62.
85. Voulgaris SG, Partheni M, Kaliora H, et al. Early cerebral monitoring using the transcranial Doppler pulsatility index in patients with severe brain trauma. Med Sci Monit 2005;11(2):CR49–52.
86. Alexandrov AV, Molina CA, Grotta JC, et al. CLOTBUST Investigators. Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. N Engl J Med 2004;351:2170–8.
87. Alexandrov VA, Babikian VL, Adams RJ, et al. The evolving role of transcranial Doppler in stroke prevention and treatment. J Stroke Cerebrovasc Dis 1998;7(2):101–4.
88. Francis CW, Blinc A, Lee S, et al. Ultrasound accelerates transport of recombinant tissue plasminogen activator into clots. Ultrasound Med Biol 1995;21: 419–24.
89. Tachibana K, Tachibana S. Albumin microbubble echo-contrast material as an enhancer for ultrasound accelerated thrombolysis. Circulation 1995; 92:1148–50.
90. Ribo M, Molina CA, Alvarez B, et al. Intra-arterial administration of microbubbles in continuous 2-MHz ultrasound insonation to enhance intra-arterial thrombolysis. J Neuroimaging 2009 [Epub ahead of print].