Use of Transcranial Doppler (TCD) Ultrasound in the Neurocritical Care Unit

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KEYWORDS

• Transcranial Doppler • Neurocritical care unit • Vasospasm • Stroke • Intracranial hypertension

KEY POINTS

- Transcranial Doppler (TCD) is a bedside procedure that measures linear cerebral blood flow velocity (CBFV) through the intracranial circulation and pulsatility index (PI).
- Several different disease processes can lead to intracerebral vasospasm, for example after subarachnoid hemorrhage, and traumatic brain injury. Intracerebral vasospasm will be represented by abnormally high CBFV.
- The PI's changes can be used for evaluation of high intracranial pressure (ICP). The PI is the reflection of downstream resistance and will be affected by abnormally high ICP.
- TCD can be used for detection of cerebral vessel occlusion and estimation of cerebrovascular reactivity. Contrast TCD is used for the diagnosis of right to left cardiac shunts, for patients with cryptogenic stroke.
- TCD is the unique standard for the detection of microembolic signals in real-time.
- TCD has high accuracy to confirm total cerebral circulatory arrest and has been used as an ancillary test to support clinical diagnosis of brain death.

INTRODUCTION

Transcranial Doppler ultrasonography (TCD) was introduced into the practice of medicine in 1986 and has been used extensively in a variety of inpatient and outpatient settings. TCD ultrasonography uses a handheld 2-MHz transducer that is placed on the surface of the scalp to measure the cerebral blood flow velocity (CBFV) and pulsatility index (PI) within the intracranial arteries. Because of its noninvasiveness and easy applications, TCD examinations have gained an important role in the very early phase, as well during the repetitive assessment of patients with cerebrovascular diseases (CVDs). This has led to a broad application of TCD in outpatients and inpatients, and emergency and intraoperative settings. This article describes specific clinical applications of TCD to diagnose and monitor vasospasm (VSP) for patients after subarachnoid hemorrhage (SAH) of different etiologies (aneurysm rupture, traumatic brain injury [TBI]) and cerebral hemodynamic changes in patients after stroke (including cryptogenic stroke). Other important clinical applications of TCD discussed are emboli monitoring, management of patients with sickle-cell disease, and so-called functional TCD. Advanced TCD application for

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Neurosurg Clin N Am 24 (2013) 441–456
http://dx.doi.org/10.1016/j.nec.2013.02.005
1042-3680/13/$ – see front matter

diagnosis and monitoring of patients with intracranial hypertension and confirmation of clinical diagnosis of brain death are also presented.

It should be noted that TCD has also been frequently used for the clinical evaluation of cerebral autoregulatory reserve, and to monitor cerebral circulation and emboli during cardiopulmonary bypass, carotid endarterectomies, and carotid artery stenting. Over the past decade, Power M mode, color Doppler imaging, and use of ultrasound contrast agents have extended the scope of TCD clinical applications. In addition, TCD is being increasingly used as a research tool.

Basic Concepts

TCD examination involves placement of the probe of a range-gated ultrasound Doppler instrument, allowing the velocities in the arteries to be determined from the Doppler signals.[1] At 2-MHz frequency, the attenuation in bone and soft tissues is considerably less as compared with higher frequencies and provides satisfactory recordings of intracranial CBFVs.[1] An ultrasonic beam transmitted by the probe crosses the skull at prespecified locations and is reflected back from the flowing erythrocytes in the blood vessels. These erythrocytes move at different speeds and the resultant Doppler signal obtained is a mixture of different frequency components. The Doppler shift is the difference between the transmitted signal and the received signal and the time interval from pulse emission to reception determines the depth from which any Doppler frequency shift is detected.[1,2] Spectral analysis then presents 3-dimensional Doppler data in a 2-dimensional format. The time vector is represented on the horizontal scale while velocity (frequency shift) is displayed on the vertical scale. The brightness of color represents the signal intensity. Mean CBFV is calculated using a spectral envelope (also known as Fast Fourier transformation [FFT]), which corresponds to the time averaged flow velocity throughout a cardiac cycle[3]: Mean CBFV = [PSV + (EDV $\times$ 2)]/3, where PSV is peak systolic CBFV and EDV is end-diastolic CBFV.[4]

The relationship between the velocity and pressure exerted by blood flowing through the cerebral arteries is described by the Bernoulli principle, which states that as the velocity of flow increases, the pressure exerted by that fluid decreases. TCD ultrasonography is based on the principle that the CBFV in a given artery is inversely related to the cross-sectional area of that artery.[5] Thus, TCD ultrasonography provides an indirect evaluation of the vessel diameter by calculating the Doppler shift.[4] TCD also allows measurement of PSV and EDV. Using these values, the mean CBFV, PI, and resistance index (RI) can be calculated.[6]

There are several physiologic factors affecting CBFV, among them age, hematocrit, vessel diameter, gender, fever, metabolic factors, exercise, and brain activity.[6–9] **Table 1** outlines mean CBFV based on different age groups in anterior and posterior circulation. Other variables measured with TCD examination are a PI (Gosling Index) and/or RI (Pourcelot Index): PI = (PSV − EDV)/mean CBFV and RI = (PSV – EDV)/PSV.[4] The physiologic meaning of these indices is the reflection of downstream resistance. **Table 2** outlines Mean CBFVs and associated conditions.[4–6,14,15]

PI It is a calculated index of the TCD waveform. The pulsatility of the waveform reflects the amount of resistance in the more distal cerebral blood vessels.[4,16] With the intracranial pressure (ICP) higher than 20 mm Hg, the PI has been evaluated as an alternative to direct ICP measurement.[15,17,18] There is also a significant correlation between the cerebral perfusion pressure (CPP) and PI.[4,18] Similarly, it has been observed that that RI also has good correlation with elevated ICP in various intracranial processes. However, as compared with the PI, the RI is less sensitive to ICP changes.[17] The PI and RI have been observed to be influenced by factors such as arterial blood pressure, cerebral vascular resistance, partial pressure of carbon

Table 1
Mean cerebral blood flow velocities (cm/s) based on age groups

Artery	Age 20–40 y	Age 40–60 y	Age >60 y
Anterior cerebral artery	56–60	53–61	44–51
Middle cerebral artery	74–81	72–73	58–59
Posterior cerebral artery (PCA) (P1)	48–57	41–56	37–47
PCA (P2)	43–51	40–57	37–47
Vertebral artery	37–51	29–50	30–37
Basilar artery	39–58	27–56	29–47

Data from Refs.[10–13]

Table 2
Clinical scenarios associated with changes in CBFV

Elevated CBFV	Decreased CBFV
Vasospasm/Hyperemia	Elevated intracranial pressure
Elevated $Paco_2$	Hypothermia
Loss of autoregulatory mechanism	Low blood pressure (BP)
Stenosed arterial tree	Reduced cerebral blood flow
Increasing age	Reduced cardiac output (below 35% ejection fraction)
Volatile anesthetic agents	Reduced $Paco_2$
Sickle cell anemia	Pregnancy
AV malformation	Anesthetics except ketamine
Meningitis (especially bacterial)	Fulminant hepatic failure
Preeclampsia	Brain death
Fever	
Sepsis	

Abbreviations: AV, arteriovenous; CBFV, cerebral blood flow velocity.

dioxide, and presence of arteriovenous malformation.[4,19] Agewise distribution of normal PIs are outlined in **Table 3** and variations in PI and RI values with disease states are given in **Table 4**. Insonation of cerebral arteries is done using 4 windows: (1) Temporal, (2) Orbital (3) Foraminal, and (4) Submandibular. Power M-mode (PMD) simplifies operator dependence by simultaneously displaying the power and direction of the blood flow over a wide range of depth, without sound or spectral clues.[20]

Variations

Few studies have discussed side-to-side as well as day-to-day variations in TCD CBFV.[6,11,21] These studies suggest that side-to-side variation of more than 14% should be considered abnormal. Most individuals (95%) should have day-to-day variation less than 10 cm per second. Same day interobserver variability has been reported to be approximately 7.5%, and approximately 13% on different days.[6,21] Variation in middle cerebral artery (MCA) CBFV has also been observed with age, pregnancy, menstruation, and arousal of individuals.[6,11,22,23]

NEUROINTENSIVE CARE UNIT TCD APPLICATIONS

Vasospasm after SAH, TBI, and Tumor Resection

Symptomatic VSP after aneurysm rupture (aSAH) is associated with a high incidence of permanent disability and death.[24,25] TCD ultrasonography is a noninvasive and relatively inexpensive investigative modality and is being used increasingly after aSAH for the surveillance and monitoring of VSP.[2,26,27] VSP detected on TCD may precede neurologic deficits, prompting earlier intervention.[28] Hemodynamic changes seen in intracerebral vasculature after aSAH can be diagnosed and monitored using TCD; therefore, the primary application of TCD in aSAH is in the surveillance of VSP.[10,29]

Symptomatic VSP is a clinical diagnosis and its pathophysiology defined as decrease in blood flow through the regions of the brain after aSAH due to the constriction of cerebral arteries and it contributes to significant morbidity and mortality (up to 20%) after aSAH.[4,10,30,31] Angiographic VSP, as seen on digital subtraction angiography (DSA) and computed tomography angiography (CTA) occurs in up to 50% to 70% of patients of aSAH with about half of them suffering from clinical symptoms.[31,32] The exact reason for the occurrence of delayed cerebral ischemia is not clearly understood, and several theories exist.[33] Clinically, terms of delayed ischemic neurologic deficit

Table 3
Normal pulsatility index (mean ± SD) based on age groups

Artery	Age 20–40 y	Age 40–60 y	Age >60 y
Anterior cerebral artery	0.80 ± 0.14	0.85 ± 0.16	1.02 ± 0.18
Middle cerebral artery	0.83 ± 0.14	0.82 ± 0.13	0.96 ± 0.17
Posterior cerebral artery	0.76 ± 0.12	0.79 ± 0.12	0.94 ± 0.16
Vertebral artery	0.82 ± 0.03	0.78 ± 0.04	0.94 ± 0.05
Basilar artery	0.81 ± 0.05	0.78 ± 0.05	0.95 ± 0.09

Data from Marshall SA, Nyquist P, Ziai WC. The role of transcranial Doppler ultrasonography in the diagnosis and management of vasospasm after aneurysmal subarachnoid hemorrhage. Neurosurg Clin N Am 2010;21(2):291–303; and Martin PJ, Evans DH, Naylor AR. Transcranial color-coded sonography of the basal cerebral circulation. Reference data from 115 volunteers. Stroke 1994;25(2):390–6.

Table 4
PI and RI indices and associated conditions

Elevated PI/RI	Decreased PI/RI
Elevated ICP (due to TBI, ICH, SAH, stroke)	Vasospasm/Hyperemia
Hydrocephalus	AV malformation
Fulminant hepatic failure	
Meningitis (especially bacterial)	
Encephalopathy	
Brain death	

Abbreviations: AV, arteriovenous; ICH, intracranial hemorrhage; ICP, intracranial pressure; PI, pulsatility index; RI, resistance index; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury.

Insonation of cerebral arteries is done using 4 windows: (1) Temporal, (2) Orbital (3) Foraminal, and (4) Submandibular.

Data from Refs.[4–6,14,15]

(DIND) and delayed cerebral ischemia (DCI) have been used to describe symptomatic VSP. Although VSP has been classically reported to occur between days 4 and 14 after aSAH, variations to this do occur and VSP has been reported as early as within 48 hours (in up to 13% of patients), and as late as 17 days[10,34–38] but could be also evident up to day 20 by TCD.[51,52]

Vasospasm on TCD ultrasound

Mild VSP Mean CBFV (cm/s): Terminal internal carotid artery (ICA) 120–130, MCA 120–130, basilar artery (BA) 60–80, vertebral artery (VA) 60–80.[10,39–49]

Moderate VSP Mean CBFV (cm/s): Anterior cerebral artery (ACA) >50% increase in 24 hours, terminal ICA >130, MCA 130–200, posterior cerebral artery (PCA) >110, BA 80–115, VA >80.[10,39–49]

Severe VSP Mean CBFV (cm/s): ACA >50% increase in 24 hours, MCA >200, PCA >110, BA >115, VA >80.[10,39–49]

In the intensive care unit (ICU), patients after aSAH often will be treated with triple-H therapy (hypertension, hypervolemia, hemodilution) that would cause increased cerebral blood flow (CBF) to the brain.[27,50] Therefore, it is very important to compliment full TCD examination with the measurement of so-called Lindegaard Index (LI), defined as the ratio of the mean CBFV of the MCA to that of extracranial portion of the ipsilateral ICA. This ratio increases with the severity of VSP. Normal values for this index ranges from 1.1 to 2.3 (median 1.7 at days 1–2) and in the absence of vasospasm is less than 3.[14] If the CBFV is found to elevated but the ratio is less that 3, then the elevation is thought to be due to hyperemia. Also, a ratio more than 6 is consistent with severe VSP.[3,5,12]

Lindegaard index

Mild to moderate VSP: >3, as measured by MCA CBFV/extracranial ICA CBFV.

Severe VSP: >6, as measured by MCA CBFV/extracranial CBFV.

VSP and its consequences represents significant events in a high proportion of patients after aSAH, therefore by our opinion daily TCD monitoring when a patient is in the ICU is warranted for the management of this subpopulation. Therefore, knowledge of the time course of the development and resolution of VSP after aSAH using TCD may help the clinician predict which patients are at higher risk of developing DCI, thereby guiding medical treatment or endovascular intervention.[52]

TCD has long been used for diagnosis and monitoring of VSP in patients with SAH, but studies of diagnostic accuracy for detection of VSP vary widely with regard to sensitivity and specificity of TCD. The sensitivity and specificity of TCD in prediction of VSP vary according to the vessel, diagnostic criteria, and timing of correlative angiography (**Table 5**).[29] In addition, CBFV's on TCD can be influenced by technical issues (absence of temporal bone windows), vessel anatomy, and skills of neurosonographers. For the MCA, TCD is not likely to indicate a spasm when angiography does not show one (high specificity), and TCD may be used to identify patients with a spasm (high positive predictive value [PPV]).[53] Earlier work indicates relatively low sensitivity of TCD for detecting ACA VSP, therefore caution should be exercised in using negative TCD results to make treatment decisions based on the assumed absence of VSP.[54] TCD appears to be highly predictive of an angiographically demonstrated VSP in the MCA; however, its diagnostic accuracy is lower with regard to VSP in the BA.[55,56] In this regard, the combination of predictive factors (clinical, CT and TCD) to detect VSP after aSAH may be superior in accuracy compared with the single independent tests.[57]

In general, increased mean CBFV on TCD predicts VSP of large intracranial arteries after aSAH. However, Rajajee and colleagues[58] retrospectively studied 81 patients with aSAH who underwent TCD between days 2 and 14 and reported that low PI (mean 0.71 $\pm$ 0.19) was found to be an independent predictor of large vessel VSP (P = .03, odds ratio [OR] 0.04, 95% confidence

Table 5
Ranges of sensitivity, specificity, PPV, and NPV of transcranial Doppler ultrasonography to detect vasospasm in different arteries

Vessels	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Internal carotid artery C1 segment	100	91	73	56
Anterior cerebral artery A1 segment	13–82	65–100	41–100	37–80
Middle cerebral artery M1 segment	38–91	94–100	83–100	29–98
Posterior cerebral artery P1 segment	48	69	37	78
Vertebral artery	43.8	88	54	82
Basilar artery	73–76.9	79	63	88

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.
Data from Refs.[29,37,44,45,48,49,53,55]

interval [CI] 0.001–0.54). In this large study, the investigators analyzed 1877 TCD examinations in 441 patients with aSAH within 14 days of onset.[52] After controlling for variables, all TCD CBFV between 120 and 180 cm/s implied an incremental risk of DCI after SAH, with maximal sensitivity by day 8.

TCD criteria for BA VSP are still poorly defined. However, Sviri and colleagues[55] showed that the CBFV ratio between the BA and the extracranial VAs strongly correlated with the degree of BA narrowing (r^2 = 0.648; P<.0001). A ratio higher than 2.5 with BA velocity greater than 85 cm/s was associated with 86% sensitivity and 97% specificity for BA narrowing of more than 25%. A BA/VA ratio higher than 3.0 with BA velocities higher than 85 cm/s was associated with 92% sensitivity and 97% specificity for BA narrowing of more than 50%. The investigators argued that the BA/VA ratio improves the sensitivity and specificity of TCD detection of BA VSP. Grading criteria for BA VSP still needed to be validated in a prospective trial.

It is clear that quest for "fine tuning" of this TCD application is still not over. By our opinion, trending of the CBFVs and day-to-day comparison of the changes are critical and has good predictive value. In addition, CBFV increase of 50 cm/s or more during a 24-hour period indicates high risk for DCI.[59]

Monitoring Cerebral Vasospasm

Early studies on angiographic VSP revealed maximal spasm at the site of lesion, which extended several centimeters to adjacent arteries to a lesser degree.[60] The time course of VSP as evaluated by TCD ultrasonography has been found to be similar to that reported in angiographic studies.[61] One such review of 26 studies comparing TCD and angiography showed 99% specificity for absence of elevated CBFV by TCD in the MCA when angiography is also negative, and, thus, TCD had a high PPV to identify patients with VSP.[53]

Although digital subtraction angiography is the gold standard for diagnosis of cerebral VSP, TCD ultrasonography is relatively inexpensive and noninvasive, and can be repeatedly done at the bedside.[62] Moreover, a relationship between TCD-measured CBFVs and intracerebral vessel diameter (as observed on DSA) has been demonstrated.[14,40] TCD is typically performed from the day of SAH and can be repeated either twice daily or every other day, until there is absence of elevated CBFVs.[5,25,29]

To examine the predictive value of a rapid rise (>50 cm/s/24 h) in TCD CBFV in diagnosis of progressive VSP, Grosset and colleagues[59] correlated TCD-measured CBFV with increases to regional CBF changes (on single-photon emission computed tomography) and clinical course in 20 patients. Almost all the patients' perfusion patterns were abnormal and correlated with sites of increased CBFV on TCD. The investigators proposed that patients could be selected for prophylactic anti-ischemic therapy using TCD.

To test the predictive reliability of TCD to monitor cerebral VSP after aSAH, Nakae and colleagues[63] retrospectively measured increases in CBFV ratio of the ipsilateral to contralateral MCA and compared that to conventional absolute CBFV in 142 patients with aSAH, who underwent 1262 TCD studies. Their results showed that the receiver operating characteristic curve for delayed cerebral ischemia had an area under the curve of 0.86 (95% CI: 0.76–0.96) when the 2 sides were compared versus 0.80 (95% CI 0.71–0.88) when the absolute CBFV was used. The threshold value that best discriminated between patients with and without DCI was 1.5.

TBI represents the leading cause of morbidity and mortality in individuals younger than 45 years.

Outcome from TBI is determined by 2 substantially different factors: (1) the primary insult occurring at the moment of impact and (2) the secondary insult represents consecutive pathologic processes initiated at the moment of injury with delayed clinical presentation. Cerebral ischemia due to the onset of posttraumatic VSP and intracranial hypertension are major contributing factors for secondary injury. In addition, parenchymal contusions and fever are defined as independent risk factors for development of posttraumatic VSP.[9] The extent and timing of posttraumatic cerebral hemodynamic disturbances have significant implications for the monitoring and treatment of patients with TBI. Martin and colleagues[64] have described a triphasic pattern in CBF after TBI. Immediately after TBI, global CBF is reduced leading to hypoperfusion. This may be ensued by hyperperfusion over the next 24 to 72 hours, following which VSP may be seen.[64,65] After TBI, elevated CBFV not due to hyperemia can be captured on TCD as a waveform notch during diastole, which is absent in patients with hyperemia.[66]

In the past decade, it was also seen that TBI is associated with the severest casualties from Operation Iraqi Freedom and Operation Enduring Freedom. Armonda and colleagues[30] indicated that VSP occurred in a substantial number of patients with war-time TBI and clinical outcomes were worse in such patients. Their recent work indicates that TCD signs of mild, moderate, and severe VSP were observed in 37%, 22%, and 12% of patients, respectively.[67] These findings demonstrate that cerebral arterial VSP is a frequent and significant complication of combat TBI; therefore, daily TCD monitoring is recommended for their recognition and subsequent management (**Fig. 1**).

Post TBI, brain swelling is a frequent cause of intracranial hypertension and herniation syndromes.[68] Recently, decompressive craniectomy has experienced a revival, although its actual benefit on neurologic outcome remains debateable.[68] A better understanding of ICP dynamics, as well as of the metabolic and cerebral hemodynamic processes, may be useful in assessing the effect of this surgery on the pathophysiology of the swollen brain. Few studies have addressed the effect of decompressive craniectomy on intracranial hemodynamics. Nineteen patients with swelling and herniation after TBI had TCD CBFV's measurements of bilateral MCA and distal ICA before and after surgery, in one prospective study.[68] The investigators reported a significant elevation of ipsilateral CBFV and decrease in PI in most patients with swelling and transtentorial herniation syndrome. This elevation in CBFV was also seen on the contralateral side. In patients with posthemicraniectomy, cerebral vessels may shift and the distance from the scalp to the intracranial vessel may be increased. Therefore, this factor must be considered while performing TCD ultrasonography for this group of patients. Further studies will be needed to advocate the routine use of TCD to monitor effect of decompressive craniectomy on cerebral hemodynamics.

The occurrence of VSP and DCI after resection of intracranial tumor has not received extensive attention clinically, and is often misdiagnosed and improperly treated as surgical brain damage or brain swelling. Reports are sparse and mainly as case series.[69] VSP is an infrequent but definite complication of surgery for tumors. Some of the factors that appear to correlate with a higher incidence of postoperative VSP include a larger tumor size, the need for preoperative embolization indicating increased tumor vascularity, vessel encasement, displacement, and narrowing and increased intraoperative blood loss.[70,71] However, DCI from VSP after tumor resection is a complication that is being reported in increasing numbers. It is suggested that accumulation of blood in the basal cisterns may have been responsible for this unusual condition, and it is therefore important to consider VSP as a probable etiologic cause of clinical deterioration in patients undergoing the surgical removal of a cerebral tumor.[70] For this reason, whenever any neurologic deterioration occurs in such patients, it is advisable to perform TCD to verify the presence of any VSP and promptly commence suitable treatment.

One of the limitations of TCD is that it is unknown if TCD has the ability to predict clinical deterioration and infarction after aSAH, TBI, and tumor resection due to DCI. In spite of this, TCD examination is noninvasive, inexpensive, and the pattern of CBFVs observed in patients after aSAH is very distinctive, enabling immediate detection of abnormally high CBFVs and appears to be predictive of VSP and DCI.[11,24,46,48,51,52,55,59,68–74] TCD is useful in monitoring the temporal course of VSP after SAH. Even though repeat angiography is unavoidable in most aSAH patients, TCD can guide the timing of this procedure and the tailoring of aggressive treatment regimens. The key is not to predict compromised perfusion by TCD, but to identify patients going into VSP and to quickly confirm VSP when subtle signs are present, before apparent neurologic deterioration. It is useful to perform TCD test on admission (or as soon as possible after surgery) and perform daily TCD studies when the patient is in the ICU. The frequency with which TCD should be performed may be guided by patient clinical presentation, knowledge of risk factors for VSP, and early clinical course. Infrequently,

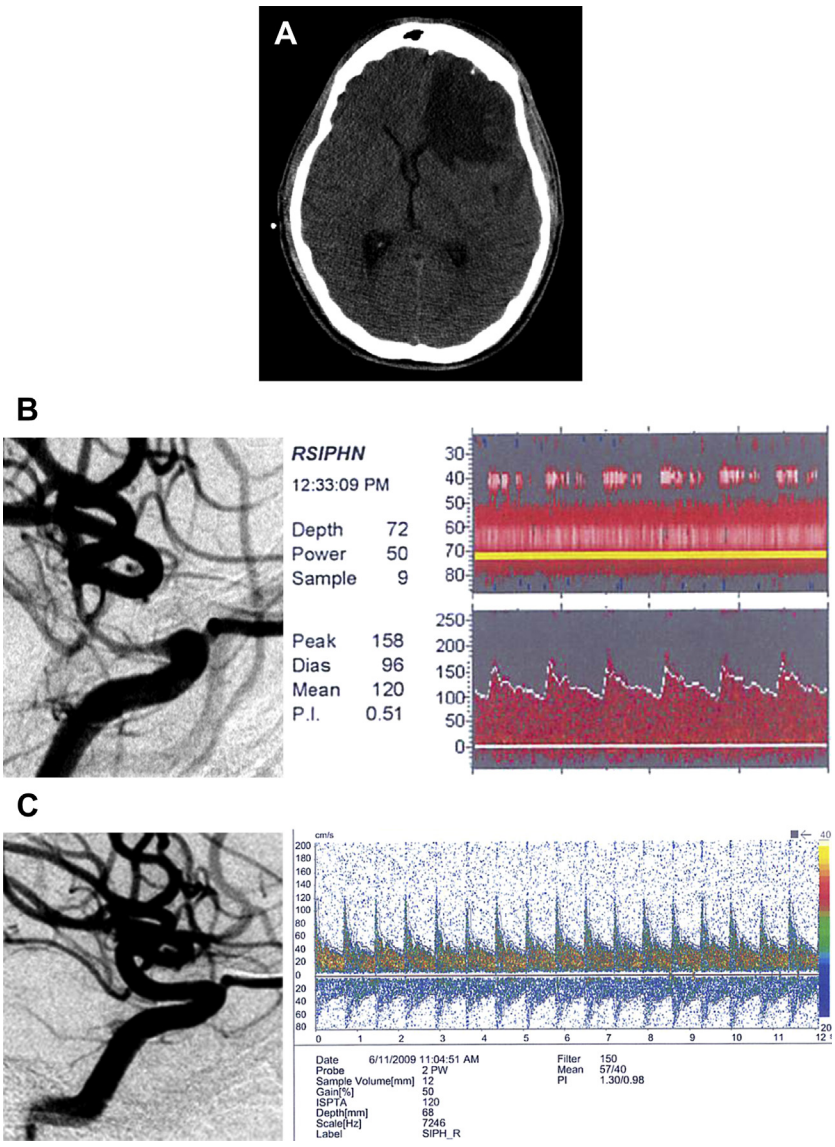

Fig. 1. Patient with right side contusion, base skull Fx, L1-L5–Fx. (*A*) CT scan demonstrating contusion. (*B*) Right common carotid artery injection showing severe vasospasm affecting right carotid siphon before angioplasty and corresponding TCD measured CBFV in the right carotid siphon. (*C*) Resolution of vasospasm after transluminal angioplasty and TCD showed CBFV normalization after angioplasty.

clinical VSP occurs earlier than natural history would suggest; daily TCD can be the least expensive option to identify patients at risk for deterioration. The presence and temporal profile of CBFVs in all available vessels must be detected and serially monitored. TCD studies should be performed after endovascular treatment to identify patients with recurrent VSP. The high sensitivity of TCD to identify abnormally high CBFVs due to the onset of VSP demonstrates that TCD is an excellent first-line examination to identify those patients who may need urgent aggressive treatment. However, prior endovascular treatment presence of VSP must be confirmed by cerebral angiography, which still is the gold standard for cerebral vessel visualization. In addition, a dedicated and experienced team of neurointensivists, neurologists, neurosurgeons, and neuroradiologists are required to provide the best available care and better outcome for those patients suffering SAH and TBI.

To conclude, VSP continues to adversely affect a significant proportion of aSAH and TBI population and remains a challenge for all clinicians

interested in reducing the adverse outcomes associated with aSAH and TBI. Today, if the question were to be asked if TCD can be used for evaluation of the presence or absence of abnormally elevated CBFV that is most likely due to the VSP; the unequivocal answer will be yes. TCD is a noninvasive ultrasound modality capable of identifying patients who are progressing to or suffering VSP. Several features of TCD assessment of VSP are similar to cerebral angiography. High CBFV measured by TCD, like severe angiographic VSP, are associated with DCI and infarction, although some patients can remain asymptomatic despite these changes. Most likely, validation of new TCD criteria for VSP and combination of different physiologic monitoring modalities that includes TCD, electroencephalography, brain tissue oxygen monitoring, cerebral microdialysis, and near-infrared spectroscopy will improve TCD accuracy to predict clinical deterioration and infarction from DCI.

Cerebral Autoregulation

Cerebral autoregulation (CA) is a homeostatic mechanism which reduces changes in CBF due to variations in CPP. It is known that CBF remains relatively constant when CPP is within 50 to 150 mm Hg[3].

In patients with TBI, TCD may be useful as a noninvasive means of calculating CPP. Czosnyka and colleagues[72] studied the reliability of CPP using TCD-measured CBFV in MCA (mean and diastolic) in 96 patients with TBI (Glasgow Coma Scale <13). The CPP measured by TCD and the calculated CPP (MAP minus ICP, measured using an intraparenchymal sensor) were compared. The results showed that in 71% of the studies, the estimation error was less than 10 mm Hg and in 84% of the examinations, the error was less than 15 mm Hg. The TCD method had a high positive predictive power (94%) for detecting low CPP (<60 mm Hg). Day-by-day variability in 41 patients was reasonable (r = 0.71). In addition, continuous waveform analysis of MCA CBFV and CPP correlates with coma score after resuscitation and outcome and hence may be considered reliable for assessment of autoregulation in ventilated TBI patients.[73]

Lang and colleagues[74] recorded CBFV and continuous arterial BP at a controlled ventilatory frequency in 12 patients with severe aSAH and compared it with 40 controls. Cerebral autoregulation was significantly impaired in patients with SAH when compared with normal subjects (P<.01 for days 1–6, and P<.001 for days 7–13). The investigators concluded that autoregulation can be assessed in a graded fashion in patients with SAH and impairment in autoregulation precedes VSP. Also, ongoing VSP worsened autoregulation and in the early phase (days 1–6) after SAH, autoregulation impairment is predictive of outcome.

Stroke Diagnosis and Management

The American Academy of Neurology Report of the Therapeutics and Technology Assessment Subcommittee mentions that TCD can detect acute MCA occlusions with greater than 90% sensitivity, specificity, PPV and NPV.[62] This report also mentions that TCD has 70% to 90% sensitivity and PPV and excellent specificity and NPV for occlusion of ICA siphon, VA, and BA.[62] A few studies have evaluated the prognostic value of TCD in acute ischemic stroke. TCD has been compared with magnetic resonance angiography (MRA) and CTA in acute stroke.[75–77] It can be used to evaluate intracranial steno-occlusive disease, particularly in the terminal ICA, ICA siphon, and MCA. In a prospective study including 30 patients, TCD showed a sensitivity of 96% and specificity of 33% for recognizing abnormal CBFV (anterior and posterior circulation vessels were evaluated together).[76] In the same study, for MCA lesions, specificity was 100% and sensitivity was 93%, whereas MRA showed a sensitivity of 46% and a specificity of 74% for assessing intracranial vascular anatomy. In the emergency room, bedside TCD is in agreement with urgent CT angiogram of the brain in the evaluation of patients with acute cerebral ischemia. TCD may provide real-time flow findings that are complementary to information provided by CTA.[77]

In a study involving 705 patients, Wong and colleagues[78] observed that in patients with predominantly intracranial large-artery occlusive disease, the presence and the total number of occlusive arteries in the cranio-cervical circulation (based on TCD measurements) can predict further vascular events or death within 6 months after stroke (adjusted OR 1.25 per occlusive artery, 95% CI 1.12–1.39). Molina and colleagues[79] studied the effect of delayed spontaneous recanalization on hemorrhagic conversions of MCA strokes in 53 patients. In their study, TCD detected delayed recanalization (>6 hours) after acute cardio-embolic stroke of MCA, and was found to be an independent predictor of hemorrhagic transformation (OR 8.9; 95% CI 2.1–33.3).

TCD detections of complete intracranial arterial occlusions were associated with poor neurologic recovery, disability, or death after 90 days in 2 separate studies.[80,81] Normal TCD results may be predictive of early improvement from

stroke.[62,82] In patients with acute ICA occlusion, TCD finding of arterial occlusion along with stroke severity at 24 hours and CT lesion size were independent predictors of outcome after 30 days.[80] In one study, the investigators determined TCD accuracy for occlusion of intracranial arteries in patients with cerebral ischemia.[75] In this study, sensitivity for occlusion site was as follows: proximal ICA 94%, distal ICA 81%, MCA 93% terminal VA 56%, BA 60%, and specificity ranged from 96% to 98%. This study also demonstrated that TCD had specificity of 94.4 and NPV of 94.4% in the diagnosis of anterior or posterior circulatory occlusion.[75] TCD had the highest accuracy for ICA and MCA occlusions and if the results of TCD were normal, there was a 94% chance that angiographic studies were negative. Another study performed CT scan, DSA and TCD on 48 patients within 4 hours of the onset of acute hemispheric ischemic stroke.[83] In this study, the most significant TCD findings were absence of flow in the occluded carotid siphon or MCA origin (correlated by angiography) and reduced CBFV and asymmetry (symptomatic <asymptomatic) when the occlusion was located in the terminal MCA. TCD was used to assess collateral circulation by demonstrating higher CBFV in ACA and PCA.

To test the utility of TCD in demonstration of arterial occlusion and subsequent recanalization in patients with acute ischemic stroke treated with intravenous tissue plasminogen activator (tPA), Burgin and colleagues[84] compared posttreatment TCD with angiography (DSA or MRA) in 25 patients. TCD was performed at 12 ± 16 hours and angiography at 41 ± 57 hours after stroke onset. Accuracy of TCD to recognize recanalization was as follows: sensitivity 91%, specificity 93%, PPV 91%, and NPV 93%. TCD predicted the presence of complete occlusion on angiography with sensitivity of 50%, specificity of 100%, PPV of 100%, and NPV of 75%. TCD flow signals correlated with angiographic patency ($\chi^2 = 24.2$, $P<.001$).

Emergency TCD findings over the first 48 hours are related to early neurologic changes in patients with acute ischemic stroke. In a study with 93 patients, Toni and colleagues[85] performed serial TCDs at 6, 24, and 48 hours after stroke onset. On logistic regression, normal TCD was found to be an independent predictor of early improvement (OR 0.17; 95% CI 0.06–0.46). Abnormal TCD (asymmetry or no-flow) was an independent predictor of early deterioration (OR 5.02; 95% CI, 1.31–19.3). Abnormal TCD has been found to be predictive of larger chronic CT lesions and more extensive ischemic change within the MCA territory. This was demonstrated by Kushner and colleagues,[82] who compared TCD findings at 6 hours or less after acute proximal MCA occlusion with CT scan findings at 1 to 3 months ($P<.005$). Abnormal TCD was predictive of chronic cortical infarct in MCA territory and correlated with angiographic findings as well ($P<.001$).

Ischemic stroke occurs in an estimated 11% of patients with homozygous sickle cell disease (Hb SS) by the age of 20 years and is a major cause of morbidity.[86] The Stroke Prevention Trial in Sickle Cell Anemia (STOP Trial) demonstrated a significant benefit of chronic red-cell transfusion in reducing the risk of a first stroke by 90% and it used TCD to screen and identify children at greatest risk of ischemic stroke.[86] The STOP study is the most successful stroke prevention trial to date and the data provide the strongest evidence for effective clinical application of TCD to prevent ischemic stroke in children with sickle cell anemia; therefore, TCD screening is recommended as practice standard. Adams and colleagues[87] followed 315 patients with sickle cell disease for more than 5 years and found that elevated maximal CBFV (especially >200 cm/s) in the intracranial ICA and MCA were independently predictive of ischemic stroke ($P<.0001$). In another study including 130 patients, transfusion greatly reduced the risk of a first stroke in children with sickle cell anemia who had abnormal results on TCD examination.[88]

TCD examination performed within 24 hours of stroke symptom onset greatly improves the accuracy of early stroke subtype diagnosis in patients with acute cerebral ischemia.[89] Early and accurate detection of occluded arteries affects therapeutic strategies in patients with acute cerebral ischemia. It is well known that clinical course of stroke may include either spontaneous improvements or deterioration related to dynamic changes in cerebral perfusion. Serial daily TCD examinations may reveal dynamic changes in cerebral circulation that may be missed on a single neuroimaging study.[90] These serial rapid measurements of cerebral hemodynamics in patients with acute cerebral ischemia with TCD offers new insight into the process of diagnosis of acute stroke and provides guidance for and monitoring of therapeutic interventions.[90]

Patent Foramen Ovale Screening for Cryptogenic Stroke and Risk Assessment

Approximately 30% of adults have a patent foramen ovale (PFO) in the heart, but the frequency is even higher (approximately 50%) in patients with cerebral infarct of unknown etiology (cryptogenic infarct), especially in the younger age group.[91–94]

Although transesophageal echocardiogram (TEE) is better than contrast TCD (cTCD) because it provides direct anatomic information on the nature of the shunt or atrial septal aneurysm presence, cTCD is comparable with contrast TEE for detecting right-to-left shunts due to PFO.[62] However, cTCD is noninvasive, provides direct evidence of emboli passage through the cerebral vessels, and an optimal Valsalva maneuver performance because it does not require sedation and is easy to perform at the bedside. Almost perfect concordance between simultaneous contrast TCD and TEE in the quantification of right-to-left shunts was shown by Belvís and colleagues.[95] Recently, in a prospective study with 134 patients, it was shown that among patients diagnosed with PFO, the shunt was detected at baseline by cTCD in 69% of cases, by transthoracic echocardiography (TTE) in 74%, and by TEE in 58%. TTE and cTCD showed higher sensitivity (100% vs 97%; nonsignificant difference) than TEE in the diagnosis of PFO (86%; $P<.001$).[96]

In a study involving 69 patients, Albert and colleagues[97] concluded that observation of more than 10 microbubbles of agitated saline at less than 10 seconds on cTCD (with Valsalva maneuver), is highly sensitive and specific for the diagnosis of right-to-left cardiac shunts. Similarly, Droste,[98] in a study with 81 patients, showed that cTCD performed with Echovist-300 (D-galactose microparticulate) yielded a 100% sensitivity to identify TEE-proven cardiac right-to-left shunts. Also, Schwarze and colleagues[99] described the optimal methodology for performance of cTCD. Their findings suggested that 10 mL of contrast medium should be injected with the patient in the supine position and Valsalva maneuver must be performed 5 seconds after the start of the injection.

Emboli Monitoring

TCD ultrasonography currently represents only one available standard of detecting microembolic material in gaseous and solid state in real-time, within the intracranial cerebral arteries. Various disease states in which microembolic signals can be found are listed in **Table 6**.

These microembolic signals, also called MES or high-intensity transient signals (HITS) have distinct acoustic impedance properties when compared with erythrocytes that flow simultaneously.[62,100] The ultrasound signals reflect off emboli before flowing erythrocytes in blood and because of this phenomenon, the reflected Doppler signal has a higher intensity signal.[62] Asymptomatic embolic signals detected using TCD are frequent in patients with carotid artery disease and detection of embolic signals by TCD can identify groups of patients with asymptomatic carotid stenosis who are at low or high risk of future stroke.[101]

In a study involving 81 patients, Goertler and colleagues[102] used TCD ultrasonography to localize an embolic source and to monitor the effects of antithrombotic treatment in patients with atherosclerotic cerebrovascular disease. Stork[103] hypothesized that smaller platelet aggregates and fibrin clots, which are not detected macroscopically, are the most likely sources of TCD-detected microembolic signals. Molloy and Markus observed that TCD-based identification of asymptomatic embolization in patients with carotid artery stenosis may be an independent predictor of future stroke risk in patients with both symptomatic and asymptomatic carotid stenosis.[104]

Table 6
Microembolic signals

Microembolic signals have been detected in patients with the following:
Asymptomatic high-grade ICA
Symptomatic high-grade ICA
Prosthetic cardiac valves
Myocardial infarction
Atrial fibrillation
Aortic arch atheroma
Fat embolization syndrome
Cerebral vascular disease
Coronary artery catheterization
Coronary angioplasty
Direct current cardioversion
Cerebral angiography
Carotid endarterectomy (CEA)
Carotid angioplasty
Cardiopulmonary bypass
Brain aneurysm
Hughes-Stovin syndrome
Marantic endocarditis
Deep vein thrombosis
Mitral valve prolapse
Polyarteritis nodosa
Pelvic vein thrombosis
Intravenous catheter infection
Renal vein thrombosis
Idiopathic dilated cardiomyopathy
Renal vein thrombosis
Dilated cardiomyopathy
Aortic aneurysm, abdominal
Idiopathic dilated cardiomyopathy
Endocarditis
Atrial myxoma
Ventricular aneurysm
Surgery complication
Cholesterol embolism

Patients with ischemic strokes, transient ischemic attacks, or asymptomatic high-grade ICA stenosis can also undergo TCD monitoring to detect, localize, and quantify cerebral embolization.[105] This information is helpful to establish the diagnosis and change management strategy. Asymptomatic embolic signals on TCD helps predict stroke risk in symptomatic carotid stenosis and postoperatively after carotid endarterectomy.[106] Sometimes the presence of emboli can be the only sign of a proximal arterial dissection, partially occlusive thrombus, or unrecognized cardiac source of embolism.[105,107]

Carotid Endarterectomy/Carotid Artery Stenting Treatment Effect Evaluation

TCD monitoring of the ipsilateral MCA during carotid endarterectomy (CEA) provides surgeons with constant status of flow velocities, which correlate with stump pressure during cross-clamping.[62,108] Large reductions in CBFV on TCD during CEA may be an indication for procedures that maintain blood flow to the brain (including shunt placement and augmentation of blood pressure).[62]

During CEA, microembolic signals are most commonly encountered intraoperatively during dissection and while shunting or unclamping. The presence of microembolic signals during dissection correlates best with new ischemic lesions seen on magnetic resonance imaging.[62] These signals are also noticed on TCD during wound closure and in the immediate postoperative phase.[103,108–113]

Jansen and colleagues[114] used combined electroencephalogram (EEG) and TCD intraoperative monitoring of thromboembolic phenomena to focus on the additional value of TCD to detect ischemia during surgery. They concluded that during CEA, information from intraoperative TCD directly influenced surgical technique and provided information about thromboembolism and hemodynamic changes that are not detected by EEG alone.

In a study involving 65 patients, Levi and colleagues[110] observed TCD signals for microembolisms within 24 hours after CEA. They concluded that more than 50 microembolic signals occurred in about 10% of cases and are predictive of ipsilateral focal cerebral ischemia (PPV = 0.71). Gaunt and colleagues[109] studied 100 consecutive patients undergoing CEA with intraoperative TCD. They found that more than 10 particulate emboli during initial carotid dissection correlated with a significant deterioration in postoperative cognitive function. They concluded that immediate intervention, based on TCD evidence of embolization, has the potential to avert neurologic deficits during CEA. Also, Ackerstaff and colleagues,[112] in their study of 31 patients undergoing CEA, concluded that factors associated with operative stroke were TCD-detected microemboli during dissection and wound closure, 90% or higher MCA velocity decrease at cross-clamping, and 100% or more PI increase at clamp release.

In one study, 500 patients underwent CEA with TCD monitoring of the ipsilateral MCA during various phases of CEA to determine hemodynamic changes and incidence of microembolic signals. This study concluded that embolism (54%) is the primary cause of cerebrovascular complications from CEA. Hypoperfusion (17%) and hyperperfusion (29%) were also identified by TCD. By responding to information provided by TCD, the incidence of permanent deficits in these patients decreased from 7% in the first 100 operations to 2% in the last 400 ($P \leq .01$).[108]

In conclusion, TCD monitoring during CEA and CAS provides information about embolic phenomena and flow patterns in cerebral vasculature that may prompt appropriate measures at several stages of CEA to reduce the risk of perioperative stroke. However, TCD monitoring is still considered an investigational technique for application and clinical use during different cardiovascular surgeries.[62]

Diagnosis and Monitoring of Intracranial Hypertension and Brain Death Evaluation

Brain death is a medical, social, and legal issue and brain death is accepted as a legal and medical criterion for death. Brain death is confirmed with the help of physical examination and ancillary diagnostic modalities, such as EEG, radionuclide scans, and angiography. TCD ultrasonography can also be used for supporting diagnosis of brain death. TCD may be of value in this indication, as it is portable, less time consuming, and can be performed at bedside.

TCD provides information on the flow velocity, direction of flow, shape of the Doppler waveform, and also differences in pulsatility amplitudes between systolic and diastolic CBFV, which can be used to support diagnosis of brain death.[115]

Increased ICP initially leads to increased PIs, followed by progressive reduction in mean and diastolic CBFVs. Changes in PI are also known to occur when CPP is lower than 70 mm Hg. With severe elevation of ICP exceeding end-diastolic BP, diastolic CBFV approaches nil. With further elevations in ICP, there is observation of retrograde diastolic flow, appearance of small

systolic spikes, and finally absence of flow. With prolonged presence of these lethal flow patterns, brain death is likely.[62,116–120]

Classically described waveform patterns in brain death diagnosis are an oscillating "to-and-fro" movement of blood flow (attributed to reversal of flow in diastole), as well as small early systolic spikes.[115,121] These waveform abnormalities represent arrest of intracerebral circulation and occur as a result of elevated ICP.

Zurynski and colleagues[116] studied 111 patients who were brain dead (vs 29 comatose patients in the control group) with TCDs performed before formal clinical brain death testing. They described short, sharp systolic patterns on TCD followed by diastolic reversal of flow or systolic peaks with absence of flow in either direction in all (100%) patients. In comparison, none of the patients in the control group showed reversal of flow. Another study explored the diagnostic accuracy of TCD in 184 patients who were brain dead. The investigators of this study concluded that TCD was able to diagnose brain death with a specificity of 100% and sensitivity (on serial testing) of 95.6%. No false-positives were observed.[122] Hadani and colleagues[123] had similar results when they studied TCD readings in 137 patients.

The consensus opinion on diagnosis of cerebral circulatory arrest using Doppler-sonography Task Force Group confirms that extracranial and intracranial Doppler sonography is useful as a confirmatory test to establish irreversibility of cerebral circulatory arrest. Although optional, TCD is of special value when the therapeutic use of sedative drugs renders EEG unreliable.[124] This statement also mentions that the absence of flow in MCA precedes complete loss of brain stem functions. The AAN Practice Parameters for Determining Brain Death in Adults considers TCD a confirmatory test of brain death along with clinical testing and other allied tests.[125]

SUMMARY

In the contemporary neurointensive care of patients with CVD, SAH, TBI, and other illnesses in which cerebral hemodynamics can be disturbed or impaired, basic neurologic monitoring should be expanded by extended neuromonitoring, including TCD. Growing evidence clearly supports the integration of extended neuromonitoring to unmask otherwise occult alterations and to differentially adapt the type, extent, and duration of therapeutic interventions. By expanding our knowledge and experience, the integration of extended neuromonitoring in daily clinical routine will provide us with the means to improve outcome, which has not been possible by relying only on neurologic examination alone, as practiced in the past.

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