Transcranial Doppler ultrasonography: a diagnostic tool of increasing utility

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Purpose of review

Since its introduction in 1982, transcranial Doppler ultrasonography has become an important diagnostic and monitoring tool in patients with surgical disease. It has applications in the perioperative period, as well as in the intensive care unit. It is therefore appropriate for the anesthesiologist to maintain an understanding of its current utility.

Recent findings

Transcranial Doppler has an established role in diagnosing cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage and for guiding transfusion therapy in children with sickle cell disease. It has application in the preoperative evaluation of patients with cerebrovascular disease, as well as that of an intraoperative monitor in carotid endarterectomy and carotid stenting. It is useful for detecting right-to-left shunts in settings in which transesophageal echocardiography is not desirable. Its value in settings such as traumatic brain injury, hepatic failure, and migraine headache has yet to be fully clarified.

Summary

Although there are several settings in which transcranial Doppler has well established usefulness, there are many more in which it is likely valuable, such as traumatic brain injury, ischemic stroke, and fulminant hepatic failure. Further research is needed in these fields to elucidate the exact role for transcranial Doppler.

Keywords

carotid endarterectomy, cerebral vasospasm, ischemic stroke, migraine, patent foramen ovale, sickle cell, transcranial Doppler ultrasonography, traumatic brain injury

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Introduction

Transcranial Doppler ultrasonography (TCD) was introduced by Aaslid *et al.* [1] to measure blood flow velocity in the cerebral arteries. As a monitor and diagnostic tool, it has application in the perioperative period and in the intensive care unit. It is essential that the anesthesiologist, particularly the neuroanesthesiologist and intensivist, stays abreast of its current uses.

An overview of TCD will provide a basis for understanding its diverse applications. Except in certain circumstances, the diameter of basal cerebral arteries remains fixed. Therefore, the velocity of flow through those vessels is proportional to the volume of flow. Although absolute flow cannot be determined, relative changes in flow can be detected. In addition, TCD yields a flow velocity waveform that provides information regarding the vascular resistance, as well as the presence of turbulence or emboli.

Ischemic stroke and clot lysis

Although digital subtraction angiography (DSA) remains the gold standard for establishing the presence and location of a vascular occlusion when acute ischemic stroke is suspected, a combined approach to this patient using both TCD and carotid duplex has a high sensitivity and specificity for detecting lesions amenable for intervention [2]. In a setting in which appropriately trained personnel are available, such a diagnostic approach could bolster confidence in the diagnosis without the use of DSA, while allowing quick intervention with thrombolytic therapy.

Ischemic stroke is the only setting in which TCD also has a therapeutic function. The Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic tPA (CLOTBUST) trial demonstrated that patients who underwent continuous TCD monitoring of the lesion during thrombolysis had a higher rate of early recanalization, with a trend toward better recovery,

presumably due to better exposure of the thrombus to thrombolytic [3,4]. Concomitant administration of intravenous (i.v.) microbubbles during thrombolysis with TCD monitoring further increases the rate of recanalization [5]. Although standard TCD with 2 mHz ultrasound appears safe when used for this purpose, low frequency ultrasound, which has less energy loss as it penetrates the brain tissue, does not. One trial was stopped early because of an increased incidence of hemorrhage in patients treated with tissue plasminogen activator (tPA) and 300 kHz ultrasound [6]. As continuous monitoring of the occlusion with standard TCD confers benefit, particularly with more distal lesions in the middle cerebral artery (MCA), this therapy should be considered when available [7••].

Preventing stroke

As stroke entails irreversible brain injury, primary prevention is essential to reduce its burden. TCD has an established role in stroke prevention for children with sickle cell disease, and its role in adult stroke prevention is becoming increasingly important.

In children with sickle cell disease, the vascular changes that lead to the stroke occur over time; flow velocity progressively increases prior to stroke [8]. One study demonstrated that a mean flow velocity of at least 200 cm/s in the internal carotid artery (ICA) or MCA was strongly associated with stroke [9]. The incidence of stroke can be reduced through periodic transfusion therapy to lower the hemoglobin S concentration below 30% [10]. Screening of sickle cell children with TCD between years 2 and 16 is now standard practice. Although the ideal frequency for screening has not been established, it appears that a child with abnormal velocities should continue to receive transfusions to sustain stroke reduction [11,12•].

In adults with large vessel cerebrovascular disease (carotid and MCA stenosis), emboli detectable with TCD (MESs or microembolic signals) have an established association with stroke, recurrent stroke, and transient ischemic attack (TIA) [13–15,16•]. As an omen of future stroke, MESs also provide a target for therapeutic intervention. A study evaluating the efficacy of clopidogrel and aspirin in combination versus aspirin alone for prevention of ischemic events in recently symptomatic carotid stenosis found that combination therapy was more effective in decreasing MES [17]. As this study was not powered to detect a clinical difference, that is, a decrease in TIA or stroke, we do not know whether elimination of MES is an appropriate goal for therapy. While the debate over the role of MES-guided therapy in stroke prevention is ongoing, a larger study to clarify this point would be welcome [18].

Perioperative use in carotid artery disease

Carotid endarterectomy (CEA) reduces stroke rate in patients with symptomatic carotid stenosis more than/equal to 70% and, to a lesser extent, in patients with 50–69% stenosis [19,20]. In asymptomatic disease, the benefit of CEA over medical therapy is less apparent and dependent upon the incidence of perioperative stroke [21,22]. Medical therapy has traditionally consisted of aspirin alone, but with advances in medical therapy, including statins, additional antiplatelet agents, and antihypertensive therapy, the margin of benefit of surgery may be even less [23]. It is therefore critical to determine who will benefit from surgery, and TCD has a role in this process.

Stroke from carotid stenosis may be heralded by MES in patients with asymptomatic disease. In asymptomatic patients with microemboli, 1-year stroke rate is 15.6%, while it is 1% for those without [24]. Owing to the risk of surgical morbidity that lies between these two numbers, TCD could be used to direct only those patients with MES to CEA. Such a management technique needs prospective validation.

Although carotid stenosis rarely causes morbidity due to hemodynamic compromise from the stenosis itself, substantive research into risk for stroke has paradoxically focused on vasomotor reactivity of the cerebral vasculature. Evaluating vasomotor reactivity, or CO_2 reactivity of cerebral blood flow, entails a TCD study in which flow velocities are measured as arterial CO_2 tension is allowed to rise. When flow velocities fail to rise significantly with an increase in CO_2, vasomotor reactivity is said to be exhausted.

Interestingly, exhausted vasomotor reactivity is associated with subsequent stroke in patients with asymptomatic stenosis or occlusion [25,26]. Other evidence indicates that the vasomotor reactivity is an indicator of the quality of vascular collaterals [27]. Selecting patients for medical or surgical therapy based on their vasomotor reserve is an attractive management strategy but one that lacks prospective analysis regarding its efficacy and safety.

In the setting of complete carotid occlusion, in which risk of further stroke is substantial, CEA is not an option. Vascular bypass procedures creating an anastamosis between the external and internal carotid arteries (external carotid/internal carotid bypass) have been used in the past. This procedure was shown not to prevent subsequent ischemic stroke, however [28]. Recent criticism of patient selection in this study has renewed interest in external carotid/internal carotid bypass surgery, with the suggestion that surgery may yet benefit those with exhausted vasomotor reactivity [29].

For patients undergoing CEA, TCD has a useful role as a monitor. Although regional anesthesia with ongoing neurological assessment may obviate the need for additional monitoring, CEA is frequently performed under general anesthesia in which further monitoring is desired. Whereas most monitors are used to detect cross-clamp ischemia, TCD is unique in its ability to detect other events known to produce neurological deficit, including postoperative thrombosis, intraoperative and postoperative embolism, intraoperative ischemia, and postoperative hyperperfusion [30].

Halsey [31] attempted to define the role for TCD as a monitor for cross-clamp ischemia. In this study, ischemia developing during occlusion of the carotid artery was considered severe if mean flow velocity in the MCA dropped below 15% of baseline and mild if it dropped within 16–40% of baseline. This study demonstrated the significant risk of stroke with shunting (presumably due to embolic events) and showed that the benefit of the shunt was justified only in severe ischemia. More recent studies have debated the appropriate threshold of flow velocity at which a shunt is appropriate; a drop of 60–70% from baseline appears to be tolerated by many patients, whereas a recent study has advocated a more conservative threshold of approximately 50% [32,33••]. In addition to cross-clamp ischemia, TCD is able to detect shunt malfunction and intraoperative emboli, which may occur during shunt placement, surgical dissection, and wound closure [34].

Stroke that occurs in the early post-CEA period is thought to be due to early carotid thrombosis and may be preceded by MES [35]. Naylor *et al.* [36] demonstrated good results in stroke reduction by titrating dextran therapy to a reduction of TCD-detected MES in the postoperative period.

Approximately 1% of patients may develop hyperperfusion syndrome following CEA, resulting in cerebral hemorrhage [37]. Although it is likely a multifactorial phenomenon, Komoribayashi *et al.* [38] demonstrated that its occurrence correlates with both preoperative exhaustion of cerebrovascular reserve as well as intraoperative ischemia. Whereas most patients experience a temporary increase in flow velocities as measured by TCD following release of the cross-clamp, these patients remain elevated. Flow velocity may be 30–230% over baseline [39]. Symptoms include ipsilateral headache, facial and eye pain, seizures, and focal neurological deficit, due to either cerebral edema or hemorrhage. Judicious blood pressure management may be useful to minimize the risk of hemorrhage in this setting [40••]. Owing to the possibility of hyperperfusion occuring at normal systemic pressures, mild relative hypotension may be necessary, and TCD guidance of therapy is prudent.

Carotid stenting has become a viable alternative to CEA for treatment of carotid stenosis. A discussion of the indication for a stent over surgical intervention is beyond the scope of this review. TCD does serve a role in this percutaneous procedure, which entails many risks similar to CEA, specifically neurologic and cardiac complications. Neurologic deficit following stent deployment has been associated with macroembolism, multiple microemboli, air embolism, as well as angioplasty-induced asystole and prolonged hypotension with MCA flow velocity reduction more than 70% [41]. One study found that, in the presence of microemboli, MCA flow velocity was inversely associated with TIA and stroke [42]. Patients who suffered neurological deficit had an average flow velocity of 36 cm/s as compared with 48 cm/s in the group without deficit. At this point, TCD seems most appropriate as a tool to assess improvement of stenting technique with respect to embolic load.

Race and cerebrovascular disease

Among persons of Asian and African descent, intracranial stenosis is more common than carotid disease as the cause of stroke [43]. Wong *et al.* [44] found that, in Chinese patients presenting with acute cerebral ischemia, the number of intracranial stenoses correlated with the 6-month risk of further vascular events or death. This study highlights the need to perform a detailed TCD examination on patients with stroke, particularly those of Asian and African descent.

Intraoperative monitoring

In addition to CEA, TCD has been applied to other surgical procedures for intraoperative monitoring. In particular, cardiac surgery with cardiopulmonary bypass has been an area of research with TCD. Use of TCD allows guided management of perfusion pressure to maintain appropriate cerebral blood flow velocities. No data exist relating this type of management to outcome, however. TCD does allow detection of cerebral emboli during bypass surgery [45]. The embolic load has been associated with postoperative neuropsychological dysfunction [46]. In addition, renal dysfunction is a known complication of bypass surgery that is also associated with embolic load as detected by TCD [47]. One must interpret such a finding cautiously, as there is likely a positive correlation between emboli to the brain and those to the kidneys, but this assumption is not proven.

Surgical repair of type A aortic dissection has modest outcome data supporting the use of TCD for intraoperative management with retrograde cerebral perfusion [48]. In this study, neurologic outcome was improved by ensuring adequate cerebral perfusion with TCD.

Patent foramen ovale

Right-to-left shunt, typically via a patent foramen ovale (PFO), is a risk factor for stroke [49,50]. Patients who suffer a stroke without obvious causes should undergo an evaluation for a PFO or other shunt. Although the gold standard for detecting a PFO is transesophageal echocardiography (TEE), TCD has been employed for this purpose. Bilateral MCA flow velocity monitoring during an i.v. injection of agitated isotonic saline has good efficacy in the detection of right-to-left shunt. A concomitant Valsalva maneuver improves the sensitivity. A comparison of TCD with TEE found excellent concordance between the two studies in evaluating right-to-left shunt [51]. Although most right-to-left shunts occur via a PFO, one concern with TCD is that it does not provide anatomic imaging of the heart and cannot distinguish an intrapulmonary from an intracardiac shunt. In addition, it does not provide information regarding the presence of an atrial septal aneurysm, which, in combination with a PFO, confers risk for stroke and stroke recurrence [52,53]. TCD remains an appropriate initial screening tool for PFO, as it is noninvasive.

Persons with migraine headaches, particularly those preceded by an aura, commonly have a PFO [54–56,57•]. PFO closure resulted in a dramatic decrease in migraine symptoms in one retrospective cohort study [58]. A large prospective study called the Migraine Intervention with STARFlex Technology (MIST) trial showed no benefit to PFO closure versus sham procedure, however [59••]. TCD screening of migraineurs is therefore not recommended at this point.

Cerebral vasospasm

Although in most situations changes in flow velocity as detected by TCD indicate proportional changes in flow, cerebral vasospasm following subarachnoid hemorrhage (SAH) is the exception to this paradigm. Breakdown of blood in this space damages vessels and causes a decrease in vascular diameter. The correlation between flow velocity and flow is lost. As flow velocities increase, cerebral perfusion may be preserved or compromised. Despite therapy with nimodipine, volume loading, induced hypertension, and angioplasty, many patients develop delayed ischemic neurologic deficit. Cerebral angiography is the gold standard for diagnosing cerebral vasospasm, but TCD has become an important tool to detect its onset, location, severity, and response to therapy. TCD was first used for this purpose by Aaslid *et al.* [60] in 1984.

Numerous studies have evaluated flow velocity criteria for the diagnosis of vasospasm in each of the basal cerebral arteries [61–65]. In addition, the Lindegaard index [66], the ratio of the MCA flow velocity to the extracranial ICA flow velocity, was developed to distinguish true vasospasm from hyperdynamic flow. In vasospasm, the flow velocity should be elevated only in the intracranial vessel, and the index will be high, whereas a hyperdynamic state would be expected to increase velocity in all vessels, with little change in the index. A meta-analysis evaluated the sensitivity and specificity of TCD in the diagnosis of vasospasm and found some variability between the vessels in question [67]. The data on the MCA were most extensive and found high specificity and positive predictive value (99 and 97%, respectively) for the diagnosis of spasm with TCD but a somewhat lower sensitivity and negative predictive value (67 and 78%, respectively). For most of the studies evaluated in this meta-analysis, a cutoff of 120 cm/s was used as the threshold for MCA vasospasm. Detailed criteria have also been developed to diagnose basilar artery vasospasm using a posterior circulation index, in which the ratio of the basilar artery and extracranial vertebral artery is calculated [68]. Although this ratio was originally described by Sloan *et al.* [69] in a nonpeer-reviewed article, and utilized further by Soustiel *et al.* [70], its role in aneurysmal SAH is most clearly defined by Sviri *et al.* [68]. This ratio typically becomes concerning with values in the 2–3 range. In fact, a ratio higher than 3 in combination with a basilar artery velocity greater than 85 cm/s had a 92% sensitivity and 97% specificity for 50% or greater narrowing of the basilar artery.

A recent evidence-based assessment of the literature on the use of TCD supported its application in monitoring for vasospasm following SAH, particularly for vasospasm in the middle cerebral and basilar arteries [71].

Causes of acute neurological deterioration in patients with SAH other than cerebral vasospasm include further hemorrhage, cerebral edema, hydrocephalus, and even cerebrospinal fluid hypovolemia [72]. Although a computed tomography (CT) scan of the head is essential in the diagnosis, TCD may give clues to the diagnosis of subacute changes, however. Elevated intracranial pressure from cerebral edema or hydrocephalus increases the pulsatility index [73,74]. TCD may therefore be useful to guide further workup when the diagnosis is unclear.

Traumatic brain injury

Traumatic brain injury (TBI) is one area in which TCD has many applications. As mentioned earlier, the pulsatility of the TCD waveform correlates well with intracranial pressure (ICP), allowing TCD to be used for an instantaneous look at cerebral hemodynamics when an ICP monitor has not yet been placed or is contraindicated due to coagulopathy [73,74]. Furthermore, TCD can demonstrate cerebral circulatory arrest (discussed later)

and guide therapeutic manipulation of intracranial pressure and mean arterial pressure. In addition, it may provide some prognostic information; low flow velocities in the MCA (<40 cm/s) and high pulsatility indices (>1.5) correlate with poor 6-month outcome [75]. One study advocates TCD evaluation of TBI patients with adjustment of cerebral perfusion pressure based on flow velocity and pulsatility index in order to minimize TBI-associated cerebral hypoperfusion [76•].

Blunt head and neck trauma may cause cervical artery dissection, which confers risk for subsequent stroke [77]. Therapy includes antiplatelet agents to prevent thromboembolic stroke. TCD can be used to detect emboli and their resolution with antiplatelet therapy, with unknown effect on outcome.

Finally, autoregulation testing can be performed in this patient population. Cerebral autoregulation may be impaired by even mild TBI and is associated with worse outcome in both adult and pediatric patients with TBI [78–80]. Testing autoregulation provides information that may be used to guide management of these patients. Although no literature exists to support such practice, it may be reasonable to delay some surgical procedures in these patients while autoregulation is impaired.

Cerebral autoregulation has a dynamic aspect, that is, how quickly cerebral blood flow is corrected once blood pressure changes, and a static aspect, that is, how close to baseline flow returns once a new stable blood pressure has been achieved. The quintessential dynamic autoregulation study is the thigh cuff test popularized by Aaslid *et al.* [81]. This method entails inflating bilateral thigh cuffs to greater than systolic pressure, which, when released, effect a drop in systemic pressure and a fall in TCD-measured flow velocities. The rate of return of cerebral blood flow is then graded in a semi-quantitative fashion. Static autoregulation testing relies on steady-state measurements. The classic example of this method is given by Tiecks *et al.* [82], in which flow velocities at two different blood pressures (or cerebral perfusion pressures) are used to calculate an autoregulatory index (estimated percentage change in cerebral vascular resistance divided by percentage change in cerebral perfusion pressure). Whereas these aforementioned techniques require intervention in the participant's blood pressure, passive methods for assessing autoregulation rely on spontaneous fluctuations in pressure correlated with continuous monitoring of either ICP or some component of flow velocity. This method has been used extensively by Czosnyka *et al.* [83]. In short, this technique is based on the premise that swings in blood pressure should not have concomitant swings in flow velocity or ICP if autoregulation is intact, whereas these parameters would have a positive correlation in the setting of impaired autoregulation.

Other methods of assessing autoregulation using TCD include the tilt test, which uses positional change to effect a drop in pressure at the circle of Willis, as well as carotid compression, which provides a transient hyperemia following release of the compression that correlates with autoregulatory ability. A detailed discussion of these techniques is available elsewhere [84,85].

Recent evidence has suggested that impairment of static autoregulation in TBI is more predictive of poor outcome than that of dynamic autoregulation [86••].

Liver failure

Fulminant hepatic failure is associated with cerebral edema and intracranial hypertension of uncertain causes, though ammonia and oxidative stress likely play a role [87]. Therapeutic options for managing intracranial pressure are limited (an overview is available in Tofteng and Larsen [88]), and orthotopic liver transplant remains the definitive therapy. Although intracranial pressure monitors are commonly placed in these patients, their use does not improve outcome and is associated with complications due to the inevitable coexisting coagulopathy [89]. This clinical setting appears to be well suited to noninvasive estimation of cerebral perfusion pressure with TCD as well as detection of cerebral circulatory arrest in the deeply encephalopathic unexaminable patient. Efforts have been made to characterize the nature of flow velocity patterns in hepatic failure, but as yet there are no clear data defining the utility of TCD in this setting [90].

In addition to intracranial hypertension, these patients often have impaired cerebral autoregulation that normalizes with orthotopic liver transplantion [91]. Although this is a curious phenomenon, the role of autoregulation testing in this patient population is unclear.

Brain death

Although brain death remains a clinical diagnosis, a confirmatory study is desired at times. Cerebral blood flow velocities undergo a well recognized progression in the context of brain death. As intracranial pressure increases, pulsatility increases. Diastolic flow velocity decreases and eventually reverses. At this point, the patient may have no net antegrade cerebral blood flow. The pattern may progress to brief systolic spikes and then to unobtainable signals. A recent study has demonstrated a specificity of 100% and sensitivity of 96.5% for TCD in the diagnosis of brain death [92]. This is currently accepted as a confirmatory test for brain death in many centers. However, care must be taken to consider the context in which these flow velocity patterns are recorded. Certain conditions can create diastolic flow

reversal without brain death. Patent ductus arteriosus, severe aortic insufficiency, and intraaortic balloon pump support may all result in a similar pattern of cerebral blood flow [93,94].

Conclusion

According to the aforementioned evidence-based review of TCD, the best indications for its use are stroke prevention in the setting of pediatric patients with sickle cell disease and monitoring for vasospasm in aneurysmal SAH [71]. Although many of the other applications of TCD currently lack definitive evidence to their effect on patient outcome, clarification of the value of TCD in these situations is certainly to be expected from studies that could be completed in the near future. Furthermore, the lack of evidence for outcome benefit with respect to a noninvasive monitor does not suggest it is without use [95].

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 685).

1 Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg 1982; 57:769–774.

2 Chernyshev OY, Garami Z, Calleja S, *et al.* Yield and accuracy of urgent combined carotid/transcranial ultrasound testing in acute cerebral ischemia. Stroke 2005; 36:32–37.

3 Alexandrov AV, Molina CA, Grotta JC, *et al.,* CLOTBUST Investigators. Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. N Engl J Med 2004; 351:2170–2178.

4 Francis CW, Blinc A, Lee S, Cox C. Ultrasound accelerates transport of recombinant tissue plasminogen activator into clots. Ultrasound Med Biol 1995; 21:419–424.

5 Molina CA, Ribo M, Rubiera M, *et al.* Microbubble administration accelerates clot lysis during continuous 2-MHz ultrasound monitoring in stroke patients treated with intravenous tissue plasminogen activator. Stroke 2006; 37:425–429.

6 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; 36:1441–1446.

7 •• Saqqur M, Uchino K, Demchuk AM, *et al.,* CLOTBUST Investigators. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. Stroke 2007; 38:948–954.

This analysis of the data from the CLOTBUST trial demonstrates how location of vascular occlusion affects the likelihood of recanalization in ischemic stroke, in addition to showing the benefit of continuous sonographic monitoring of the lesion.

8 Adams R, McKie V, Nichols F, *et al.* The use of transcranial ultrasonography to predict stroke in sickle cell disease. N Engl J Med 1992; 326:605–610.

9 Adams RJ, McKie VC, Carl EM, *et al.* Long-term stroke risk in children with sickle cell disease screened with transcranial Doppler. Ann Neurol 1997; 42:699–704.

10 Adams RJ, McKie VC, Hsu L, *et al.* Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 1998; 339:5–11.

11 Adams RJ, Brambilla D, Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP 2) Trial Investigators. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. N Engl J Med 2005; 353:2769–2778.

12 • Mazumdar M, Heeney MM, Sox CM, Lieu TA. Preventing stroke among children with sickle cell anemia: an analysis of strategies that involve transcranial Doppler testing and chronic transfusion. Pediatrics 2007; 120:e1107–e1116.

In an attempt to further define the role of TCD in sickle cell disease, this study used data from existing literature to create a computer-based model evaluating multiple strategies of screening and transfusion. It ultimately concluded that screening children annually with TCD until age 10, with monthly transfusion in high-risk patients until age 18, was most effective.

13 Molloy J, Markus HS. Asymptomatic embolization predicts stroke and TIA risk in patients with carotid artery stenosis. Stroke 1999; 30:1440–1443.

14 Markus HS, MacKinnon A. Asymptomatic embolization detected by Doppler ultrasound predicts stroke risk in symptomatic carotid artery stenosis. Stroke 2005; 36:971–975.

15 Gao S, Wong KS, Hansberg T, *et al.* Microembolic signal predicts recurrent cerebral ischemic events in acute stroke patients with middle cerebral artery stenosis. Stroke 2004; 35:2832–2836.

16 • Iguchi Y, Kimura K, Kobayashi K, *et al.* Microembolic signals at 48 h after stroke onset contribute to new ischaemia within a week. J Neurol Neurosurg Psychiatry 2008; 79:253–259.

This study offers a tangible marker (MES) in stroke patients, which could potentially be targeted with medical therapy in an effort to reduce further ischemic events.

17 Markus HS, Droste DW, Kaps M, *et al.* Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. Circulation 2005; 111:2233–2240.

18 Wong KS. Is the measurement of cerebral microembolic signals a good surrogate marker for evaluating the efficacy of antiplatelet agents in the prevention of stroke? Eur Neurol 2005; 53:132–139.

19 North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991; 325:445–453.

20 Chaturvedi S, Bruno A, Feasby T, *et al.,* Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Carotid endarterectomy – an evidence-based review: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2005; 65:794–801.

21 Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. JAMA 1995; 273:1421–1428.

22 Halliday A, Mansfield A, Marro J, *et al.,* MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004; 363:1491–1502.

23 Ederle J, Brown MM. The evidence for medicine versus surgery for carotid stenosis. Eur J Radiol 2006; 60:3–7.

24 Spence JD, Tamayo A, Lownie SP, *et al.* Absence of microemboli on transcranial Doppler identifies low-risk patients with asymptomatic carotid stenosis. Stroke 2005; 36:2373–2378.

25 Silvestrini M, Vernieri F, Pasqualetti P, *et al.* Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. JAMA 2000; 283:2122–2127.

26 Markus H, Cullinane M. Severely impaired cerebrovascular reactivity predicts stroke and TIA risk in patients with carotid artery stenosis and occlusion. Brain 2001; 124 (Pt 3):457–467.

27 Vernieri F, Pasqualetti P, Matteis M, *et al.* Effect of collateral blood flow and cerebral vasomotor reactivity on the outcome of carotid artery occlusion. Stroke 2001; 32:1552–1558.

28 The EC/IC Bypass Study Group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. N Engl J Med 1985; 313:1191–1200.

29 Herzig R, Hlustik P, Urbanek K, *et al.* Can we identify patients with carotid occlusion who would benefit from EC/IC bypass? Review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2004; 148:119–122.

30 Riles TS, Imparato AM, Jacobowitz GR, *et al.* The cause of perioperative stroke after carotid endarterectomy. J Vasc Surg 1994; 19:206–214.

31 Halsey JH Jr. Risks and benefits of shunting in carotid endarterectomy. The International Transcranial Doppler Collaborators. Stroke 1992; 23:1583–1587.

32 Ackerstaff RG, Moons KG, van de Vlasakker CJ, *et al.* Association of intraoperative transcranial Doppler monitoring variables with stroke from carotid endarterectomy. Stroke 2000; 31:1817–1823.

33 Moritz S, Kasprzak P, Arlt M, *et al.* Accuracy of cerebral monitoring in detecting •• cerebral ischemia during carotid endarterectomy: a comparison of transcranial Doppler sonography, near-infrared spectroscopy, stump pressure, and somatosensory evoked potentials. Anesthesiology 2007; 107:563–569.
Percentage change in TCD-measured flow velocity of the MCA had the highest area under the receiver operating characteristic (ROC) curve (as compared with other modalities studied) for diagnosing cerebral ischemia during carotid cross-clamp.

34 Naylor AR, Wildsmith JA, McClure J, *et al.* Transcranial Doppler monitoring during carotid endarterectomy. Br J Surg 1991; 78:1264–1268.

35 Laman DM, Wieneke GH, van Duijn H, van Huffelen AC. High embolic rate early after carotid endarterectomy is associated with early cerebrovascular complications, especially in women. J Vasc Surg 2002; 36:278–284.

36 Naylor AR, Hayes PD, Allroggen H, *et al.* Reducing the risk of carotid surgery: a 7-year audit of the role of monitoring and quality control assessment. J Vasc Surg 2000; 32:750–759.

37 Piepgras DG, Morgan MK, Sundt TM Jr, *et al.* Intracerebral hemorrhage after carotid endarterectomy. J Neurosurg 1988; 68:532–536.

38 Komoribayashi N, Ogasawara K, Kobayashi M, *et al.* Cerebral hyperperfusion after carotid endarterectomy is associated with preoperative hemodynamic impairment and intraoperative cerebral ischemia. J Cereb Blood Flow Metab 2006; 26:878–884.

39 Jorgensen LG, Schroeder TV. Defective cerebrovascular autoregulation after carotid endarterectomy. Eur J Vasc Surg 1993; 7:370–379.

40 Ogasawara K, Sakai N, Kuroiwa T, *et al.,* Japanese Society for Treatment at •• Neck in Cerebrovascular Disease Study Group. Intracranial hemorrhage associated with cerebral hyperperfusion syndrome following carotid endarterectomy and carotid artery stenting: retrospective review of 4494 patients. J Neurosurg 2007; 107:1130–1136.
This retrospective review is fascinating in that it indicates that cerebral hyperperfusion following carotid artery stenting is a different entity from that occurring after endarterectomy, with a different time course and benefitting less from tight blood pressure control.

41 Ackerstaff RG, Suttorp MJ, van den Berg JC, *et al.,* Antonius Carotid Endarterectomy, Angioplasty, and Stenting Study Group. Prediction of early cerebral outcome by transcranial Doppler monitoring in carotid bifurcation angioplasty and stenting. J Vasc Surg 2005; 41:618–624.

42 Orlandi G, Fanucchi S, Gallerini S, *et al.* Impaired clearance of microemboli and cerebrovascular symptoms during carotid stenting procedures. Arch Neurol 2005; 62:1208–1211.

43 Caplan LR, Gorelick PB, Hier DB. Race, sex and occlusive cerebrovascular disease: a review. Stroke 1986; 17:648–655.

44 Wong KS, Li H, Chan YL, *et al.* Use of transcranial Doppler ultrasound to predict outcome in patients with intracranial large-artery occlusive disease. Stroke 2000; 31:2641–2647.

45 Barbut D, Yao FS, Hager DN, *et al.* Comparison of transcranial Doppler ultrasonography and transesophageal echocardiography to monitor emboli during coronary artery bypass surgery. Stroke 1996; 27:87–90.

46 Pugsley W, Klinger L, Paschalis C, *et al.* The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. Stroke 1994; 25:1393–1399.

47 Sreeram GM, Grocott HP, White WD, *et al.* Transcranial Doppler emboli count predicts rise in creatinine after coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2004; 18:548–551.

48 Estrera AL, Garami Z, Miller CC 3rd, *et al.* Cerebral monitoring with transcranial Doppler ultrasonography improves neurologic outcome during repairs of acute type A aortic dissection. J Thorac Cardiovasc Surg 2005; 129:277–285.

49 Sastry S, Riding G, Morris J, *et al.* Young Adult Myocardial Infarction and Ischemic Stroke: the role of paradoxical embolism and thrombophilia (The YAMIS Study). J Am Coll Cardiol 2006; 48:686–691.

50 Lechat P, Mas JL, Lascault G, *et al.* Prevalence of patent foramen ovale in patients with stroke. N Engl J Med 1988; 318:1148–1152.

51 Belvis R, Leta RG, Marti-Fabregas J, *et al.* Almost perfect concordance between simultaneous transcranial Doppler and transesophageal echocardiography in the quantification of right-to-left shunts. J Neuroimaging 2006; 16:133–138.

52 Cabanes L, Mas JL, Cohen A, *et al.* Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age. A study using transesophageal echocardiography. Stroke 1993; 24:1865–1873.

53 Mas JL, Arquizan C, Lamy C, *et al.,* Patent Foramen Ovale and Atrial Septal Aneurysm Study Group. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. N Engl J Med 2001; 345:1740–1746.

54 Anzola GP, Magoni M, Guindani M, *et al.* Potential source of cerebral embolism in migraine with aura: a transcranial Doppler study. Neurology 1999; 52:1622–1625.

55 Carod-Artal FJ, da Silveira Ribeiro L, Braga H, *et al.* Prevalence of patent foramen ovale in migraine patients with and without aura compared with stroke patients. A transcranial Doppler study. Cephalalgia 2006; 26:934–939.

56 Lamy C, Giannesini C, Zuber M, *et al.* Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: the PFO-ASA Study. Atrial Septal Aneurysm. Stroke 2002; 33:706–711.

57 Domitrz I, Mieszkowski J, Kamińska A. Relationship between migraine and • patent foramen ovale: a study of 121 patients with migraine. Headache 2007; 47:1311–1318.
Another TCD study confirming the association between PFO and migraine with aura.

58 Reisman M, Christofferson RD, Jesurum J, *et al.* Migraine headache relief after transcatheter closure of patent foramen ovale. J Am Coll Cardiol 2005; 45:493–495.

59 Dowson A, Mullen MJ, Peatfield R, *et al.* Migraine Intervention With STARFlex •• Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. Circulation 2008; 117:1397–1404.
This is, to our knowledge, the only prospective randomized controlled trial evaluating PFO closure in the treatment of migraine headache. Closure conferred no benefit over sham procedure.

60 Aaslid R, Huber P, Nornes H. Evaluation of cerebrovascular spasm with transcranial Doppler ultrasound. J Neurosurg 1984; 60:37–41.

61 Aaslid R, Huber P, Nornes H. A transcranial Doppler method in the evaluation of cerebrovascular spasm. Neuroradiology 1986; 28:11–16.

62 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; 39:1514–1518.

63 Sloan MA, Burch CM, Wozniak MA, *et al.* Transcranial Doppler detection of vertebrobasilar vasospasm following subarachnoid hemorrhage. Stroke 1994; 25:2187–2197.

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; 6:8–15.

65 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.

66 Lindegaard KF, Nornes H, Bakke SJ, *et al.* Cerebral vasospasm after subarachnoid haemorrhage investigated by means of transcranial Doppler ultrasound. Acta Neurochir Suppl (Wien) 1988; 42:81–84.

67 Lysakowski C, Walder B, Costanza MC, Tramer MR. Transcranial Doppler versus angiography in patients with vasospasm due to a ruptured cerebral aneurysm: a systematic review. Stroke 2001; 32:2292–2298.

68 Sviri GE, Ghodke B, Britz GW, *et al.* Transcranial Doppler grading criteria for basilar artery vasospasm. Neurosurgery 2006; 59:360–366.

69 Sloan MA, Zagardo MT, Wozniak MA, *et al.* Sensitivity and specificity of flow velocity ratios for the diagnosis of vasospasm after subarachnoid hemorrhage: preliminary report. In: Klingelhöfer J, Bartels E, Ringelstein EB, editors. New trends in cerebral hemodynamics and neurosonology. Amsterdam: Elsevier; 1997. pp. 221–227.

70 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; 33:72–77.

71 Sloan MA, Alexandrov AV, Tegeler CH, *et al.,* Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: transcranial Doppler ultrasonography: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2004; 62:1468–1481.

72 Komotar RJ, Ransom ER, Mocco J, *et al.* Critical postcraniotomy cerebrospinal fluid hypovolemia: risk factors and outcome analysis. Neurosurgery 2006; 59:284–290.

73 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:CR49–CR52.

74 Bellner J, Romner B, Reinstrup P, *et al.* Transcranial Doppler sonography pulsatility index (PI) reflects intracranial pressure (ICP). Surg Neurol 2004; 62:45–51.

75 Tan H, Feng H, Gao L, *et al.* Outcome prediction in severe traumatic brain injury with transcranial Doppler ultrasonography. Chin J Traumatol 2001; 4:156–160.

76 Ract C, Le Moigno S, Bruder N, Vigué B. Transcranial Doppler ultrasound • goal-directed therapy for the early management of severe traumatic brain injury. Intensive Care Med 2007; 33:645–651.
This study suggests a therapy in TBI guided by TCD findings.

77 Arauz A, Hoyos L, Espinoza C, *et al.* Dissection of cervical arteries: long-term follow-up study of 130 consecutive cases. Cerebrovasc Dis 2006; 22:150–154.

78 Junger EC, Newell DW, Grant GA, *et al.* Cerebral autoregulation following minor head injury. J Neurosurg 1997; 86:425–432.

79 Hiler M, Czosnyka M, Hutchinson P, *et al.* Predictive value of initial computerized tomography scan, intracranial pressure, and state of autoregulation in patients with traumatic brain injury. J Neurosurg 2006; 104:731–737.

80 Vavilala MS, Muangman S, Tontisirin N, *et al.* Impaired cerebral autoregulation and 6-month outcome in children with severe traumatic brain injury: preliminary findings. Dev Neurosci 2006; 28:348–353.

81 Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. Stroke 1989; 20:45–52.

82 Tiecks FP, Lam AM, Aaslid R, Newell DW. Comparison of static and dynamic cerebral autoregulation measurements. Stroke 1995; 26:1014–1019.

83 Czosnyka M, Smielewski P, Czosnyka Z, *et al.* Continuous assessment of cerebral autoregulation: clinical and laboratory experience. Acta Neurochir Suppl 2003; 86:581–585.

84 Vavilala MS, Kincaid MS, Muangman SL, *et al.* Gender differences in cerebral blood flow velocity and autoregulation between the anterior and posterior circulations in healthy children. Pediatr Res 2005; 58:574–578.

85 Giller CA. A bedside test for cerebral autoregulation using transcranial Doppler ultrasound. Acta Neurochir (Wien) 1991; 108:7–14.

86 Puppo C, López L, Caragna E, Biestro A. One-minute dynamic cerebral auto•• regulation in severe head injury patients and its comparison with static autoregulation. A transcranial Doppler study. Neurocrit Care 2008; 8:344–352.
This study is interesting because it forces one to consider what the differences are between static and dynamic autoregulation of cerebral blood flow, and why each may be impaired in isolation, and what the implication of that impairment is to the patient.

87 Norenberg MD, Rao KV, Jayakumar AR. Mechanisms of ammonia-induced astrocyte swelling. Metab Brain Dis 2005; 20:303–318.

88 Tofteng F, Larsen FS. Management of patients with fulminant hepatic failure and brain edema. Metab Brain Dis 2004; 19:207–214.

89 Vaquero J, Fontana RJ, Larson AM, *et al.* Complications and use of intracranial pressure monitoring in patients with acute liver failure and severe encephalopathy. Liver Transpl 2005; 11:1581–1589.

90 Abdo A, Lopez O, Fernandez A, *et al.* Transcranial Doppler sonography in fulminant hepatic failure. Transplant Proc 2003; 35:1859–1860.

91 Ardizzone G, Arrigo A, Panaro F, *et al.* Cerebral hemodynamic and metabolic changes in patients with fulminant hepatic failure during liver transplantation. Transplant Proc 2004; 36:3060–3064.

92 Hadani M, Bruk B, Ram Z, *et al.* Application of transcranial Doppler ultrasonography for the diagnosis of brain death. Intensive Care Med 1999; 25:822–828.

93 Wilcox WD, Carrigan TA, Dooley KJ, *et al.* Range-gated pulsed Doppler ultrasonographic evaluation of carotid arterial blood flow in small preterm infants with patent ductus arteriosus. J Pediatr 1983; 102:294–298.

94 Brass LM. Reversed intracranial blood flow in patients with an intra-aortic balloon pump. Stroke 1990; 21:484–487.

95 Moller JT, Johannessen NW, Espersen K, *et al.* Randomized evaluation of pulse oximetry in 20,802 patients: II. Perioperative events and postoperative complications. Anesthesiology 1993; 78:445–453.