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REVIEW

Transcranial Doppler ultrasound in neurovascular diseases: diagnostic and therapeutic aspects

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Abstract

Albeit no direct anatomical information can be obtained, neurosonological methods provide real-time determination of velocity, and spectral waveform of blood flow in basal intracranial arteries adds significant benefit to the care of the patients with neurovascular diseases. Several features, such as relative simplicity in terms of interpretation and performance, significantly low cost, totally non-invasiveness, portability, and excellent temporal resolution, make neurosonology increasingly popular tool for evaluation, planning, and monitoring of treatment, and for determining prognosis in various neurovascular diseases. Usefulness of transcranial Doppler in diagnosing/monitoring subarachnoid hemorrhage related vasospasm and sickle cell vasculopathy is already well known. Utility in diagnosis of intracranial arterial stenosis, acute occlusion and recanalization, intracranial hemodynamic effect of the cervical arterial pathologies, intracranial pressure increase, and cerebral circulatory arrest are also well established. Neurosonological determination of vasomotor reactivity, cerebral autoregulation, neurovascular coupling, and micro-embolic signals detection are useful in the assessment of stroke risk, diagnosis of right-to-left shunting, and monitoring during surgery and interventional procedures. Transcranial Doppler is also an evolving ultrasound method with a therapeutic potential such as augmentation of clot lysis and cerebral delivery of thrombolytic or neuroprotective agent loaded nanobubbles in neurovascular diseases. The aim of this study is to give an overview of current usage of the different ultrasound modalities in different neurovascular diseases.

Keywords: ischemic stroke, microbubble, neurovascular disease, sonothrombolysis, subarachnoid hemorrhage, transcranial Doppler.

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Transcranial Doppler ultrasound (TCD), the central neurosonological technique, was introduced almost 30 years ago (Aaslid *et al.* 1982). A low frequency, usually 2 megaHertz (MHz) pulsed-wave transducer (probe) being placed on 'acoustic', or 'sonic', windows is used for routine TCD examination. Ultrasonic examination of a vessel is called as 'insonation'. The thin and plain portion of the temporal bone (transtemporal acoustic window) is utilized to insonate M1 and M2 segments of the middle cerebral artery (MCA), A1 segment of the anterior cerebral artery (ACA), P1 and P2

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Abbreviations used: ACA, anterior cerebral artery; AComA, anterior communicating artery; BA, basilar artery; COGIF, Consensus on Grading Intracranial Flow Obstruction; CTA, computerized tomography angiography; ICA, internal carotid artery; ICP, intracranial pressure; MCA, middle cerebral artery; MHz, MegaHertz; MRA, magnetic resonance angiography; NAIS, Neurosonology in Acute Ischemic Stroke study; OA, ophthalmic artery; OR, odds ratio; PCA, posterior cerebral artery; PComA, posterior communicating artery; PICA, posterior inferior cerebellar artery; PI, pulsatility index; PMD, power motion-mode; SAH, subarachnoid hemorrhage; SAMMPRIS, the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis Study; SCA, superior cerebellar artery; SONIA, the Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis trial; STOP, Stroke Prevention Trial in Sickle Cell Anemia trial; SubCA, subclavian artery; TCDI, transcranial color duplex imaging; TCD, Transcranial Doppler; THRUMBI, Transcranial Low-frequency Ultrasound-mediated Thrombolysis in Brain Ischemia trial; TIBI, Thrombolysis in Brain Ischemia; TICA, terminal portion of the internal carotid artery; tPA, tissue plasminogen activator; VA, vertebral artery; VMR, vasomotor reactivity.

segments of the posterior cerebral artery (PCA), and the terminal portion of the internal carotid artery (TICA). Anterior and posterior communicating arteries (AComA and PComA) are also insonated through this window. Furthermore, Rosenthal's basal vein and deep middle cerebral vein can be examined as well. The ophthalmic artery (OA) and carotid siphon are examined through the transorbital window. V4 segment of vertebral arteries (VA) and basilar artery are insonated transforaminally. Caudal portion of the extracranial internal carotid artery (ICA) is examined in the submandibular region (Fig. 1a). Albeit the detailed examination technique and interpretation of the results are beyond the scope of this review, a summary of general principles can be found below.

Advantages and disadvantages of TCD

TCD is a totally non-invasive ultrasound technique used for real-time evaluation of blood flow velocities in the major basal cerebral arteries on a beat-to-beat basis. Portability, non-invasive nature, and significantly lower cost make TCD a preferred tool for diagnosis and monitoring of the cerebral vascular pathologies. Owing to its excellent temporal resolution, TCD is a powerful tool for functional and dynamic studies. The other advantages include its relative simplicity. Albeit the performance cannot be considered as easy, but interpretation is, indeed, quite uncomplicated in terms of learning and masterity. Accomplishment at the bedside by treating physician is the other key advantage of TCD. Actually, TCD is increasingly recognized as an extension of the clinical examination similar to stethoscope (Garami and Alexandrov 2009). This feature is especially important in the management of critically ill patients who are unsafe to be transported outside of the units for radiological tests (Topcuoglu *et al.* 2010).

In the experienced hands, TCD is probably not inferior to computerized tomography and magnetic resonance angiography (CTA and MRA) in the diagnosis of intervention requiring steno-occlusive lesions in the basal cerebral arteries and their main branches (Alexandrov *et al.* 2012). In addition, it provides complementary hemodynamic information over structural ones when used in conjunction with CTA or MRA. In this respect, it provides dependable information for prolonged periods of monitoring and helps the clinician understand the temporal evolution of these cerebrovascular pathologies (Topcuoglu *et al.* 2010).

Against these advantages, TCD has several important limitations. The first is it does not give direct anatomical information about cerebral vasculature. What we record is that depth, flow direction, and peak systolic, end diastolic and mean flow velocities [PSV, EDV, and Vmean, respectively] for each vessel. These recordings are attained on spectral waveform display [sonogram] obtained via a fast Fourier or other type of mathematical transformation of the signal representing flow (Fig. 1b). Normal TCD sonograms are low resistance waveform with sharp systolic upstroke

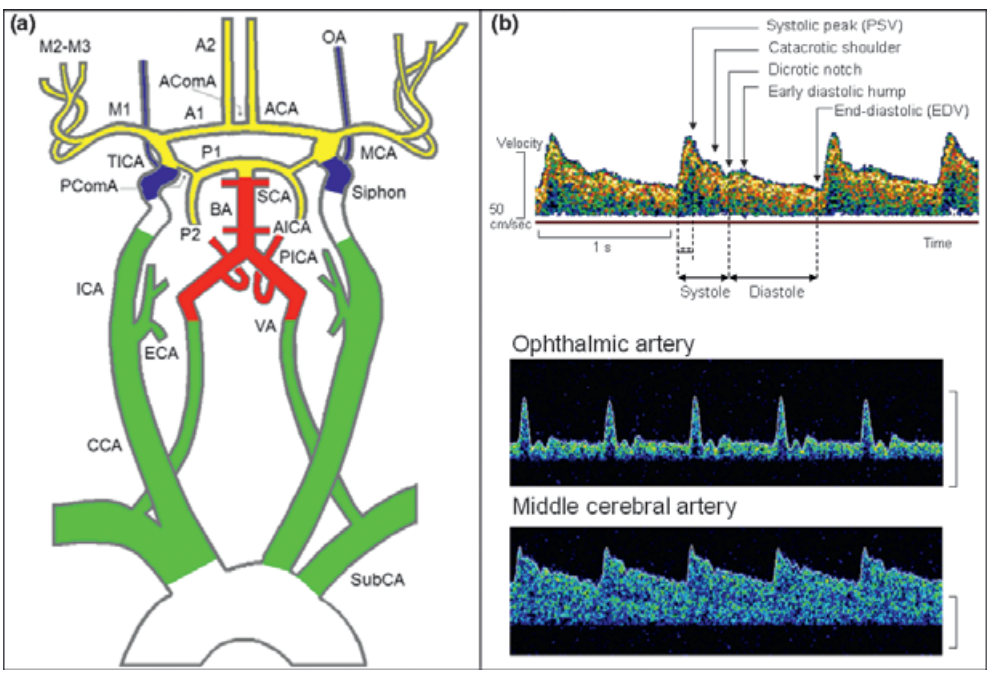

Fig. 1 (a) Insonation area of cervicocerebral vasculature [Yellow with transtemporal transcranial Doppler (TCD); Blue with transorbital Doppler; Red with Transforaminal Doppler and Green with cervical Duplex]. (b) Upper panel shows normal middle cerebral artery (MCA) spectral configuration and points measured on the envelope; Lower panel shows normal OA (high resistance waveform) and MCA (low resistance waveform) flow pattern (bar represents 50 cm/s). **: Systolic upstroke (acceleration) time.

followed by stepwise deceleration. The EDV is usually between 20 and 50% of the PSV, and pulsatility index [PI], calculated as '(PSV-EDV)/Vmean', is below 1.1 in the cerebral arteries. Typical Vmean is normally around 80 cm/s for MCA, 70 for ACA, 60 for PCA, and 40 for TICA, basilar artery (BA) and VA, and 20 for OA (Aaslid *et al.* 1982; Alexandrov *et al.* 2007).

The second, TCD signal is obtained through the bone windows. For anterior circulation, anterior TCD is performed through the temporal bone. The bone is not necessarily permeable to the sound in all patients, especially in the post-menopausal women in whom bone remodeling causes irregularition of the tabular surface and obviates to get transmitted signal back to the probe. Almost 10% of individuals have absolutely no sonic windows (Suri *et al.* 2011). In addition, at least a similar percentage of individuals have low-quality bone windows, resulting in wearisome time expenditures in locating the windows and fixation of the monitoring transducers (Wijnhoud *et al.* 2008). Although usage of sonic contrast agents may be helpful in some of these subjects, they are not practical for repeated examinations (Droste 2008).

The third disadvantage is about highly operator-dependent nature of TCD. The application of this almost 'blind', free hand, and non-imaging technique requires high level of experience and knowledge about the three-dimensional cerebrovascular anatomy. Fortunately, issues with window detection and operator dependence have decreased after advent of the newer neurosonological technologies such as transcranial color duplex imaging (TCDI) and power motion-mode (PMD, M-mode) TCD (Bogdahn *et al.* 1990; Moehring and Spencer 2002). The fourth, and perhaps the most important, disadvantage is variability of TCD signals caused by status of the intracranial distal and extracranial proximal arteries as well as systemic and cardiac physiology and abnormalities. These all are required for correct interpretation of the TCD sonograms.

Transcranial Doppler technologies

TCD was invented by Dr. Rune Aaslid from Bern University in Switzerland in the early eighties (Aaslid *et al.* 1982). He described techniques and the main clinical utilities of TCDs not only for the most prevalent current indications such as intracranial arterial stenosis, vasospasm, and acute occlusion but also for autoregulatory and functional studies (Aaslid *et al.* 1984; Markwalder *et al.* 1984; Lindegaard *et al.* 1986a). Eight years later, TCDI was described by Ulrich Boghdan and his colleagues at Julius Maximilians University in Würzburg (Germany) in 1990 (Bogdahn *et al.* 1990). They unequivocally demonstrated that with low frequency (2–3.5 MHz) phased array transducers, color-coded blood flow, and B-mode parenchymal representation were possible in addition to spectral Doppler (Transcranial triplex ultrasound). TCDI provides color image in both axial and coronal planes, and also B-mode determination of the bony and parenchymal landmarks (Fig. 2a). This anatomical guidance makes identification of the arteries in the circle of Willis as well as navigation of the pulsed Doppler sample volume through these arteries more straightforward compared with TCD (Kern *et al.* 2005). Thereby, TCDI is regarded as easier

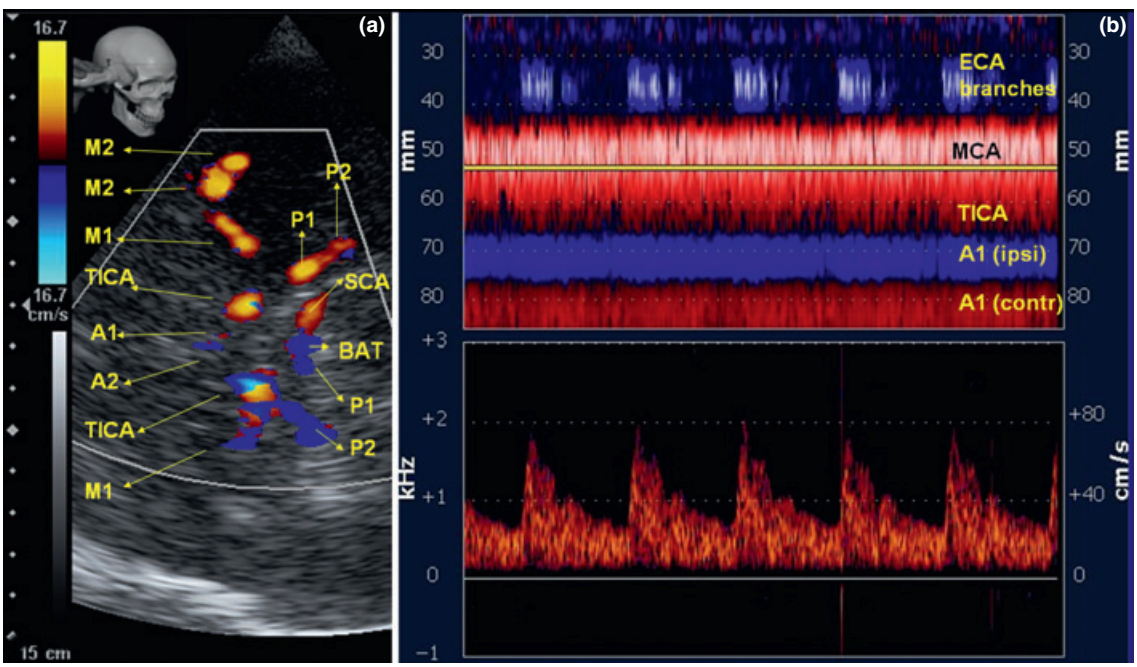

Fig. 2 Normal vessel appearance through transtemporal transcranial color duplex imaging (TCDI) (a) and power motion-mode (PMD) (b). For abbreviations, please refer to the text.

to master in performance and interpretation (McCarville 2008). Detectability of A2 segment of the ACA and V3 segment of the VA is an advantage. Furthermore, unavailability of sufficient bone window can also be detected promptly by the sonic appearance of the contralateral skull band and ipsilateral planum temporale on B-mode imaging (Suzuki *et al.* 2012). TCDI, albeit not considered as the first-line imaging modality, can be used to diagnose and determine of size of intracerebral space occupying lesions including intracerebral hemorrhages and monitor of the midline shift caused by these lesions (Becker *et al.* 1993; Gerriets *et al.* 1999). Ventricular system and its abnormalities such as hydrocephalus can also be pictured with reasonable reliability (Becker *et al.* 1994). Cerebral aneurysms and arteriovenous malformations can also be imaged directly by this modality in addition to documentation of their flow dynamics (Klotzsch and Harrer 2006). The other advantage of TCDI is Doppler angle correction, which provides more accurate measurement of flow velocities (Krejza *et al.* 2001). Newer ultrasound modalities added later to TCDI such as transcranial power and harmonic imaging increased its capability in terms of contrast resolution of vascular and deep parenchymal structures, respectively. Ultrasound of the cervical carotid and vertebral arteries, which can be performed with using 5–13 MHz linear probes usually provided with the TCDI systems, can be performed in the same session. Despite these advantages, it is important to note that the interpretation of TCDI examination is principally based on the analysis of Doppler frequency spectrum like TCD. Vascular wall cannot be imaged by TCDI in contrast to the carotid artery imaging in the neck. Furthermore, the commercially available TCDI devices are not equipped with monitoring capabilities, which obviates its practical use for hemodynamic and functional studies.

Another improvement of neurolsonology is PMD, which was introduced by Merril Spencer and Mark Moehring in 2002 (Moehring and Spencer 2002). In this technique, power and direction of the digital Doppler signal are collected in multiple sample gates placed usually 2 mm apart, together with a single-gate spectrogram from a user-selected depth (Fig. 2b). PMD facilitates bone window location, and alignment of the ultrasound beam to view blood flow from multiple vessels simultaneously. Navigation and vessel location have become easier with this method. Incorporated innovative PMD emboli tracking methodology is also advantageous (Alexandrov *et al.* 2002).

Transcranial Doppler utility in neurovascular disorders

TCD is considered effective in the detection of stenosis, occlusion, and vasospasm of basal cerebral arteries such as MCA, ICA siphon, and vertebrobasilar system. Albeit sensitivity and specificity of TCD are lower in comparison with other non- or semi-invasive imaging modalities (CTA and MRA) in these indications, capability of catching the most of the lesion amenable to the interventional treatment such as stenting, local thrombolysis, angioplasty and local nicardipin application makes TCD a valuable tool for not only detection but also monitoring of the effect of these interventions (Alexandrov *et al.* 2012). TCD is also successfully used for evaluation of intracranial hemodynamic consequences of cervical parent artery steno-occlusive lesions. And also, intracranial pressure (ICP) can reliably be estimated based on TCD spectrogram changes. Another standard indication of TCD is confirmation of brain death by demonstrating cerebral circulatory arrest. Utility of TCD in these standard indications are reviewed below.

Intracranial stenosis

Ultrasonic characteristics of an arterial steno-occlusive lesion are classified into three categories, as first described by Merril Spencer (Fig. 3) (Spencer 1987). The primary change as a result of a stenosis is significant focal increase of the PSV and Vmean seen in, or just after, the stenosis point. Velocity increase thresholds for diameter stenosis exceeding 50% and 70% were validated against catheter angiography in 'the Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA)' and 'Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS)' trial populations, respectively (Feldmann *et al.* 2007; Chimowitz *et al.* 2011). Vmean cut-offs are 100 and 80 cm/s for > 50% stenosis (SONIA criteria) for MCA and VA/BA, respectively. Vmean higher than 120 and 110 cm/s is accepted as indicator 70% stenosis (SAMPRISS criteria) for MCA and VA/BA, respectively. Focal velocity increase can also be determined as 'stenotic/prestenotic ratio' for intracranial arteries just like the peripheral ones, and the ratio higher than three indicates 70% stenosis of MCA and VA/BA (Feldmann *et al.* 2007; Zhao *et al.* 2011). The secondary changes are seen both immediately after (downstream) and before (upstream) the stenosis. Disturbance and dampening of forward flow are the main downstream effects of a hemodynamically important stenosis (hypoperfusion). Usually used cut-offs are < 50 and < 30 cm/s for diminish of PSV and Vmean, respectively; > 20 ms or 290 cm/sn^2 area under spectral envelope for slowness of acceleration or delay of upstroke, and < 0.6 for decrease of PI. Decrease of velocity and increase of PI are main upstream effects of a significant stenosis (distal resistance pattern). The tertiary changes are seen in the collateral circulation and include increase of velocities, decrease of PI and turbulence at the branching points as well as systolic deceleration, and alternating and/or reversed flow in the other territories (Fig. 4) (Spencer 1987; Wilterdink *et al.* 1997; Alexandrov *et al.* 2007).

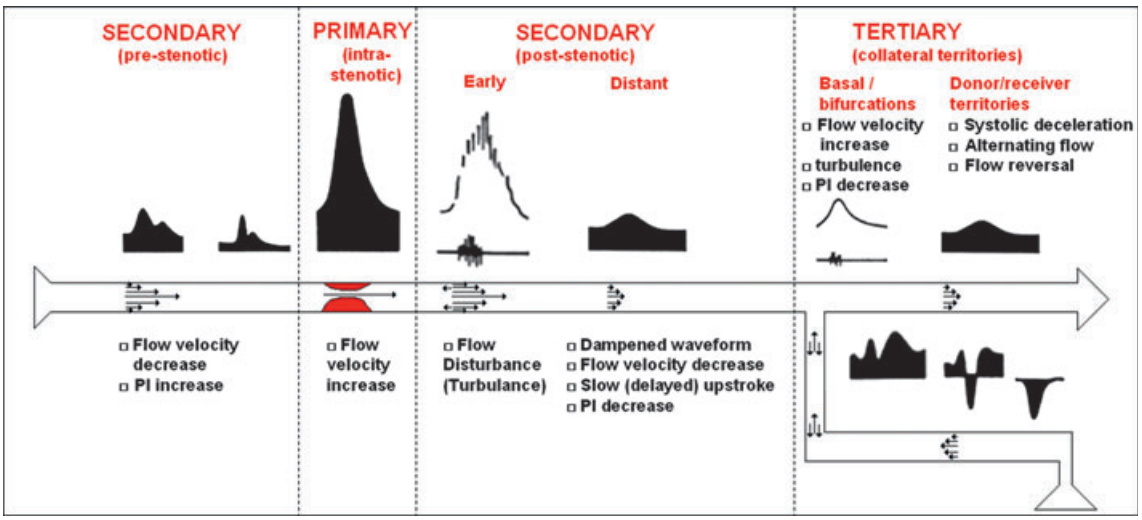

Fig. 3 Spencer's classification of ultrasonic characteristics of an arterial steno-occlusive lesion. Representative examples of waveform changes were also displayed. Some of these spectrums were redrawn from Spencer 1987.

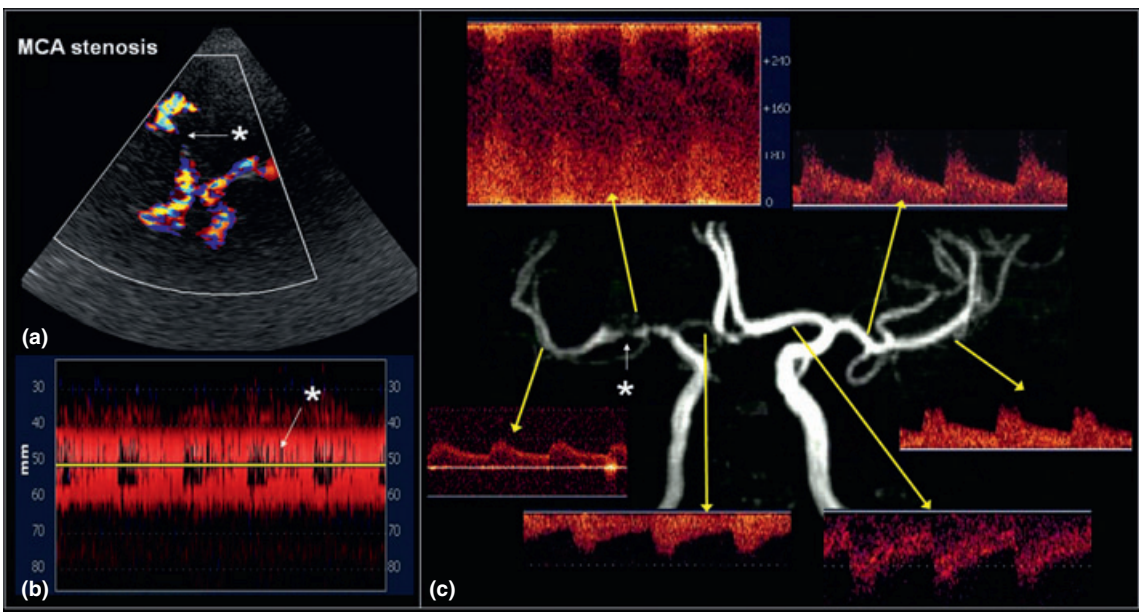

Fig. 4 Appearance of a critical middle cerebral artery (MCA) stem stenosis (white star) on transcranial color duplex imaging (TCDI) (a) and power motion-mode (PMD) (b). Flow disturbance is easily discernible on both TCDI and M-mode. Spectrogram changes are displayed on a corresponding MRA (c). There is significant increase of flow velocities in the stenosis region (PSV 300; Vmean: 220; EDV: 180, cm/s) and decrease in the post-stenosis (PSV: 60, Vmean: 40; EDV: 30, cm/s, and delayed up stroke 0.25 s).

Substantial negative predictive values (86–94% for MCA and 88% for VA/BA) and relatively low positive predictive value (36–73% for MCA and 93% for VA/BA) indicate that TCD as a reliable tool to exclude the presence of intracranial stenosis (Zhao *et al.* 2011). However, it is usually suggested that abnormal findings on TCD might not necessarily have a clinically important implication and require a confirmatory test such as angiography to identify stenosis reliably. Higher thresholds such as 300 cm/s PSV and 200 cm/s Vmean can be used to describe definitely clinically important, in other words high grade (> 80%), stenosis but this will decrease sensitivity of TCD significantly.

Sickle cell vasculopathy

Regular, or whenever required, blood transfusions in children with sickle cell disease and severe stenosis of intracranial basal arteries, defined as Vmean > 200 cm/s, in comparison

with the no transfusion approach, which was associated with an annual stroke risk of 10%, showed a large benefit, approximately 90% relative risk reduction in stroke rate, in STOP (Stroke Prevention Trial in Sickle Cell Anemia) trial (Adams *et al.* 1998). Subsequently, the primary prevention approach consisting of TCD monitoring and regular transfusion in the cases with high TCD velocities has become a standard of care in children with sickle cell anemia (Sloan *et al.* 2004). It is important to note that TCD screening should not be interrupted by advancing age as suggested by the STOP-2 trial, in which interruption of this primary prevention approach was associated with both reversion to abnormal blood flow velocities quickly and an increased rebound stroke risk (Adams and Brambilla 2005).

Vasospasm

Like intracranial stenosis, TCD is also very useful modality for diagnosis and monitoring of vasospasm occurring after subarachnoid hemorrhage (SAH) as a result of berry aneurysm. Abnormal TCD signal characteristics because of SAH-associated vasospasm are similar to those seen in stenosis. Instead of localized of focal increase, vasospasm related velocity increase is usually segmental, that is, affects long segment, and several Doppler characteristics such as harmonic covibration and musical murmurs are relatively frequent (Aaslid and Nornes 1984; Aaslid 2002). Doppler criteria for diagnosis of intracranial arterial vasospasm are summarized in Table 1. Grading criteria for vasospasm were also described, and they are useful for MCA, but not for other arteries according to the authors' experience (Topcuoglu *et al.* 2010).

The main differential diagnosis of increased velocities observed in SAH-related vasospasm is 'hyperemia'. Most commonly, hyperemia is secondary to the therapies applied for vasospasm such as triple-H (hypertension, hemodilution, and hypervolemia) and balloon angioplasty. In SAH cases with increased flow velocities, discrimination of vasospasm and hyperemia can be achieved by normalization of velocities according to the extracranial counterparts. A parallel flow velocity increase in the parent extracranial artery would suggest hyperemia, whereas decreased flow velocity along with increased pulsatility index would be in favor of severe vasospasm (Lindegaard *et al.* 1988; Sloan *et al.* 1997; Soustiel *et al.* 2002). In addition to low intracranial to extracranial Vmean ratios, hyperemia is characterized by absence of spectral characteristics of stenosis, elevated EDV, diffusely increased venous velocities, and fluctuation over hours. Low pulsatile flow in the submandibular ICA along with increased and arterialized flow in the internal jugular veins is also helpful for discrimination (Topcuoglu *et al.* 2010).

It is important to note that bedside TCD can detect vasospasm before the patient develops ischemic neurological deficits or cerebral infarction. Elevated TCD velocities often initiate, and later guide, treatment of vasospasm. As the location and severity of vasospasm can be predicted by the clinical status of the patient and the amount and location of subarachnoid blood on head CT, daily TCD monitoring should – at least – be used for these high-risk patients (Topcuoglu *et al.* 2002).

Table 1 Transcranial Doppler (TCD) criteria for vasospasm

Artery	Main Vmean [cm/s]	Main PSV [cm/s]	Main IC/EC ratio*	Additional
MCA M1 and M2				
Severe	> 200	> 300	> 6.0	Vmean increase > 50% over the baseline (first 3 days) Vmean increase > 80 cm/s through the course of MCA Daily PSV increase > 100 cm/s
Moderate	150–200	250–300	4.5–5.9	
Mild	120–150	200–250	3.0–4.5	
ACA A1				
Concomitant +	–	–	> 4.0	
MCA/ICA – vasospasm	> 130	> 200	–	
VA/BA	> 60	> 120	> 2.5	

*Intracranial (IC) to extracranial (EC) ratios are also called according to who described them firstly. For middle cerebral artery (MCA), Lindegard's ratio is the ratio of Vmean of MCA to the Vmean of submandibular internal carotid artery (ICA); For anterior cerebral artery (ACA) Sloan's hemispheric ratio, which is the ratio of Vmean of the ACA to Vmean of the submandibular ICA, and for basilar artery (BA) Soustiel's posterior circulation index, which is calculated as the ratio of the Vmean of the basilar artery to Vmean of the vertebral artery (just beyond its axis loop) (Lindegaard *et al.* 1986b; Sloan *et al.* 1997; Soustiel *et al.* 2002).

Cervical parent artery steno-occlusive lesions

The primary sonographic feature of cervical ICA stenosis is localized velocity elevation. PSV higher than 125 cm/s indicates presence of a stenosis that can have a hemodynamic significance, whereas PSV and EDV higher than 230 and 100 cm/s, respectively, along with carotid index, calculated as ICA-to-common carotid artery (McCarville) PSV ratio, higher than 4.2 refer to severe ICA stenosis that corresponds a luminal diameter narrowing exceeding 70% (Grant *et al.* 2003; von Reutern *et al.* 2012). This is usually associated with a high

resistance flow configuration in the common carotid artery and hypoperfusion pattern signifying compensatory cerebrovascular dilatation in the carotid siphon and MCA. Reversal of ipsilateral ACA and OA flow, elevation of flow velocity with pseudoturbulence in AComA and PComA, and increase of flow velocity in the contralateral A1 and P1 segments are other findings indicating significance of ICA stenosis (Fig. 5) (Can *et al.* 1997; von Reutern *et al.* 2012). When all of these criteria are used as a battery, they can not only directly document the cervical ICA stenosis but also assess the adequacy of cerebral perfusion status (Wilterdink *et al.* 1997).

TCD is also one of the primary tools to document intracranial hemodynamics of subclavian steal syndrome. Reflecting severity of the steal, systolic deceleration, various types of alternating flow and total retrograde flow are seen in the ipsilateral VA, whereas flow is usually profoundly increased in the donor VA. The basilar artery can show normal, low resistance or alternating flow, or rarely complete flow reversal again depending on the severity of the steal. Flow changes can be further evaluated during hyperemia cuff test (Von Budingen and Staudacher 1992).

Neurosonological methods such as emboli monitoring and vasomotor reactivity can further stratify the risk of parent artery steno-occlusive lesions especially with unstable plaque features, but no hemodynamic significance.

Acute ischemic stroke: occlusion, recanalization, and reperfusion

Cerebrovascular ultrasound is successfully used to determine the vascular patency in the patients with acute stroke. Sonological examination can be accomplished within minutes in emergency or out-of-hospital settings. When performed by a trained person according to a standardized and validated protocol, which should include both TCD and carotid duplex, neurosonological evaluation does not result in any delay in the acute stroke management (Chernyshev *et al.* 2005; Schlachetzki *et al.* 2012). For more rapid interpretation, acute stroke ultrasound is better to be performed by the treating physician at the bedside in parallel with neurological evaluation. It is advantageous that physician can limit the examination to the clinically suspected arteries. Although TCD yield comparable results in the hands of experienced sonographers, other non-invasive imaging modalities (MRA or CTA) are preferred to determine vascular status along with parenchyma imaging

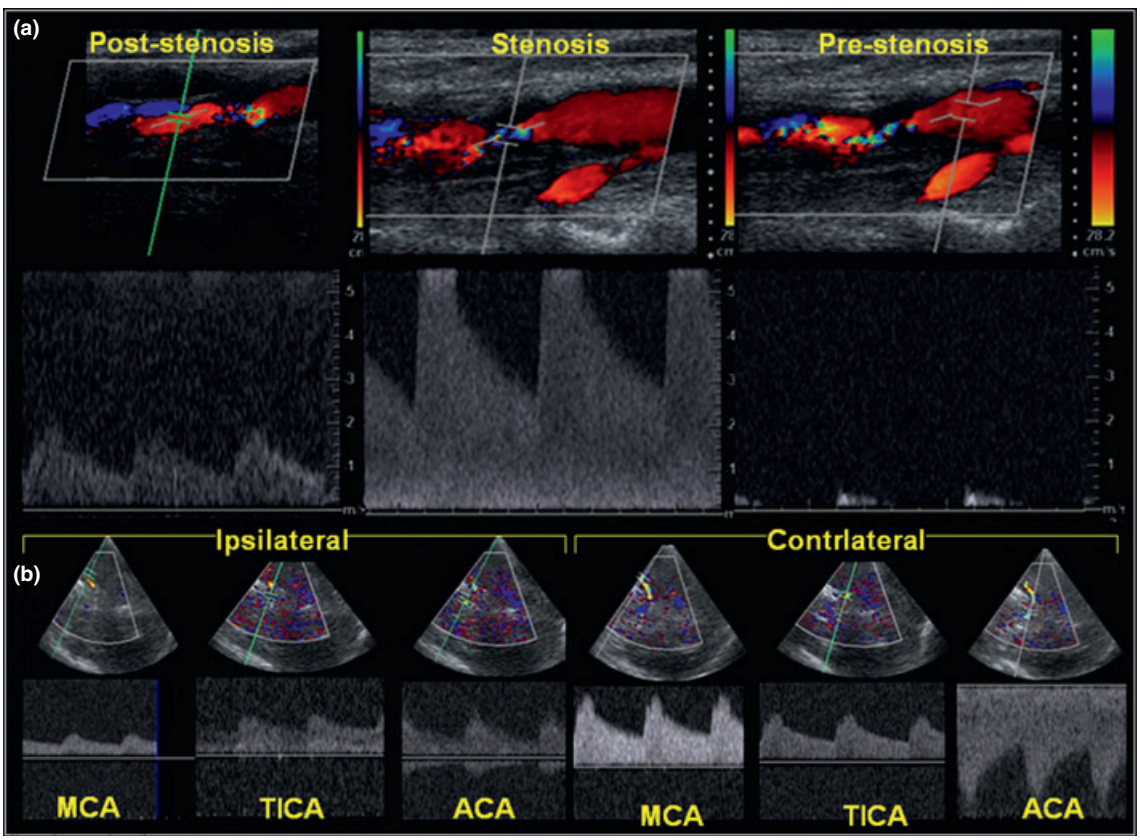

Fig. 5 Critical internal carotid artery (ICA) stenosis: (a) Flow pattern changes in the cervical region; (b) Intracranial hemodynamical changes regarding collateral compensation capacity. In this case, there is significant dampening of ipsilateral middle cerebral artery (MCA) flow; increase of the contralateral A1 flow and reversal of ipsilateral A1 flow indicating transhemispheric flow diversion, which is insufficient.

in most of the centers as an initial imaging choice. In these centers, it is reasonable to correlate TCD with these tests first, and to use it for monitoring later (Topcuoglu *et al.* 2010).

Neurosonological characteristics of flow give information about occlusion, recanalization, and reperfusion following thrombus dissolution, as well as reocclusion. To monitor these critical changes, several grading systems were developed to classify residual flow status in acute stroke patients. As the most widely known system, TIBI (Thrombolysis in Brain Ischemia) (Demchuk *et al.* 2001), and COGIF (Consensus on Grading Intracranial Flow Obstruction) (Nedelmann *et al.* 2009), which is a modification of the TIBI system to TCDI, correlate well with the initial stroke severity, mortality, likelihood of reperfusion, and clinical improvement (Fig. 6). In the multi-center NAIS (Neurosonology in Acute Ischemic Stroke) study, sonographic status of MCA within 6 h after stroke was found to be an independent predictor for outcome. Although 88% of 57 patients with MCA main-stem occlusion were dead or dependent 3 months after stroke, 50% of 176 patients with branch occlusion and 63% of 121 patients with normal MCA flow had good outcome (Allendoerfer *et al.* 2006). Prognostic significance of MCA flow status was confirmed by a recent meta-analysis, performed on 1813 patients from 25 studies. Although a significantly increased mortality (OR: 2.5) is associated with absence of flow in MCA, early clinical improvement was observed in both initially patent (OR: 11.1) or completely recanalized MCA within 6 h after onset (OR: 5.6) (Stolz *et al.* 2008).

TCD is an unique imaging modality to real-time monitor of the efficacy intravenous rtPA treatment for hyperacute stroke. Initiation, speed, timing, and degree of recanalization can reliably be detected by TCD flow configuration changes (Alexandrov *et al.* 2001). A rapid increase of TIBI/COGIF grade indicates fast and more complete clot lysis and high EDV indicates low resistance in the distal circulatory bed. In contrast, slow TIBI/COGIF improvement and dampened waveform are ultrasonic signatures of incomplete recanalization. Persistence of low TIBI/COGIF category after intravenous thrombolysis can streamline to further reperfusion therapies such as intra-arterial thrombolysis or mechanical thrombectomy (Saqqur *et al.* 2005). In addition, abundance of micro-embolic signals on TCD examination can suggest earlier initiation of anticoagulation or antiplatelet agents and hyperemic flow pattern can help the clinician to modify blood pressure limits (Burgin *et al.* 2000).

Intracranial pressure increase and cerebral circulatory arrest

TCD provides an indirect estimation about ICP and cerebral perfusion pressure (CPP). Decrease of EDV and increase of PI are early sonogram changes observed in ICP increase. With further increase of ICP, EDV decreases further, first reaching to zero and ultimately to negative values, called

Category	Appearance	Description
TIBI 0 COGIF 1		**ABSENT FLOW** No flow signal
TIBI 1 COGIF 2		**MINIMAL FLOW** Systolic spikes with variable velocity and duration; zero EDV; reverberating flow
TIBI 2 COGIF 3		**BLUNTED FLOW** Systolic upstroke delayed (duration >0,20 sec); EDV>0; PI<1,2
TIBI 3 COGIF 3		**DAMPENED FLOW** Vmean decrease greater than 30% of contralateral value; upstroke normal; EDV>0
TIBI 4 COGIF 4c		**HYPEREMIC FLOW** Segmentally increased flow velocities (Vmean >80 cm/s and/or >30% compared to the control side, no turbulence; low PI; no harmonics; low degree spectral broadening.
TIBI 4 COGIF 4b		**PSEUDOSTENOTIC FLOW** Focally increased flow velocities (Vmean >30% compared to the control side; EDV>0; Significant turbulence or flow disturbance.
TIBI 5 COGIF 4a		**NORMAL FLOW** Flow velocities normal or in the range of ±%30 of the control side. **[* Bar: 50 cm/sec]**

Fig. 6 Thrombolysis in brain ischemia (TIBI) and Consensus on Grading Intracranial Flow Obstruction (COGIF) criteria: Patients with absent (TIBI grade 0, COGIF grade 1) flow, minimal flow with zero EDV (TIBI grade 1, COGIF grade 2) and low flow that is either a blunted (TIBI grade 2) or dampened (TIBI grade 3, COGIF grade 3) configuration show worse prognosis in comparison with those with flow velocities equal to the contralateral side (TIBI grade 5, COGIF grade 4a), increased segmentally (TIBI grade 4, COGIF grade 4c), or increased focally (COGIF grade 4b).

reversed diastolic (or biphasic) flow. PI increases exponentially after flow reversal, and PSV begins to decrease depending on the residual CPP (Ducrocq *et al.* 1998). It is important to note that absolute values of PI are not useful much for ICP estimation (de Riva *et al.* 2012). However, a temporal pattern of waveform change in a particular patient has utility for prediction of corresponding ICP changes. In patients with raised ICP and/or midline shift, color Doppler/B-mode imaging provides direct structural information such as the position of the third ventricle intracranially and enlargement of the optic nerve sheath transorbitally (Rosenberg *et al.* 2011).

A progressive elevation of ICP to extreme levels can lead to total cessation of flow through cerebral microcirculation, which is called cerebral circulatory arrest. This signifies absence of brain perfusion and, if prolonged, will eventually lead to brain death. Systolo-diastolic to-and-fro or full diastolic flow reversal (net zero forward flow) and systolic spikes comply with the clinical diagnosis of brain death (Fig. 7) (Ducrocq *et al.* 1998). In subjects with no detectable intracranial flow, TCD is not diagnostic owing to the possibility of technical or anatomical causes impeding insonation. Because of this possibility, the sensitivity of TCD examination remains around 95% in confirmation of brain death. However, the specificity, which is considered more important in this specific situation, of TCD is almost 100%. In 12 cases in whom TCD was declared as false positive in germane literature, either TCD examination was incomplete or clinical brain death developed quickly during follow-up. In addition to portability, these very high sensitivity and specificity rates of TCD makes it the confirmatory test of choice in brain death. Utility of TCD can be increased by insonation of the cervical internal carotid artery submandibularly or the carotid siphon transorbitally. Serial examinations can also increase sensitivity further (Conti *et al.* 2009).

Cerebral autoregulation and vasomotor reactivity

Both dynamic and static cerebral pressure autoregulation can be evaluated neurosonologically. Assumption of a proportional change of blood flow velocity in the setting of fixed diameter of parent artery is the theoretical basis of these techniques. It is important to note that TCD measures only flow velocity, not the cerebral blood flow. Therefore, 'the stimulus-response principle' is used in all neurosonological methods, which are modeled to identify relative changes of flow velocity rather than absolute values (Aaslid 2006; Topcuoglu *et al.* 2010). Autoregulatory gain, or static autoregulation index, which is the widely used parameter of static cerebral pressure autoregulation, is calculated as the ratio of Vmeans measured at the baseline and at the specific blood pressure target. Its lower values indicate disturbed autoregulation, where flow and pressure are proportionally related, and higher values indicate intact autoregulation, where flow remains constant in response to changes in blood pressure. With these techniques, both lower and upper limits of the autoregulation plateau can be determined after

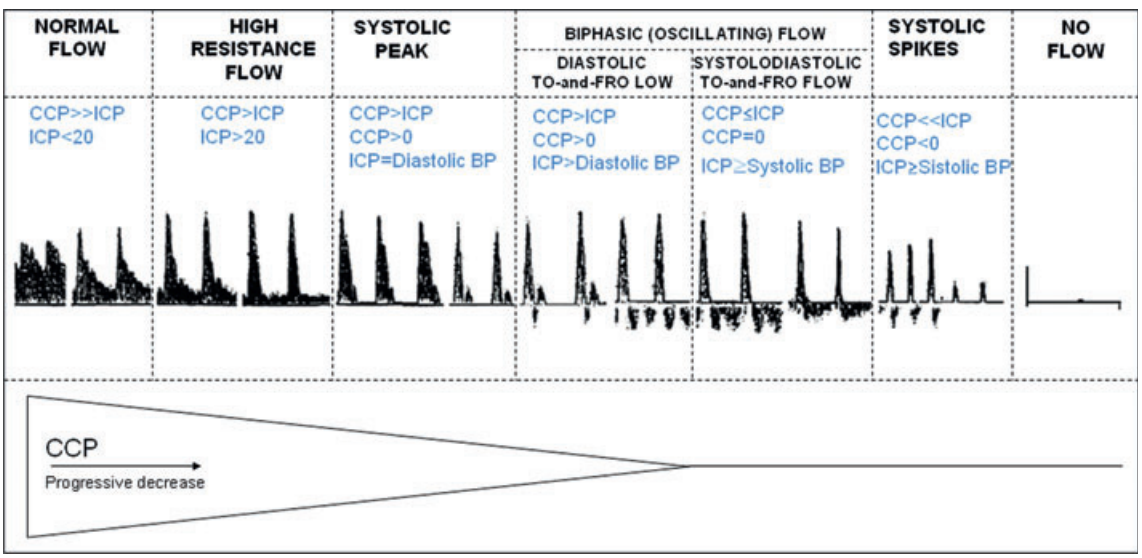

Fig. 7 Progressive waveform changes during intracranial pressure (ICP) increase eventually leading to cerebral circulatory arrest are depicted. Some of the spectrums were adapted from Ducrocq *et al.*, 1998. If ICP increases significantly to the levels obviating spontaneous cerebral circulation, in other words, cerebral circulatory arrest, or brain death, transcranial Doppler (TCD) shows one of the specific flow patterns: The first, alternating flow where there is a systolic forward flow but then complete reversal of the flow during diastole, indicating net zero forward flow; and systolic peaks where there is only a systolic hit to the stagnant blood column but no flow.

lowering and increasing the blood pressure pharmacologically (Larsen *et al.* 1994; Topcuoglu *et al.* 2010).

The beat-to-beat temporal resolution of TCD makes it an ideal tool for measurement of the dynamic pressure autoregulation, where rapid changes of blood pressure are created for determination. The first and still most widely utilized dynamic autoregulation technique is Aaslid's leg-cuff method, where a sudden blood pressure decrease is produced by rapid deflation of specifically designed leg-cuffs (Aaslid *et al.* 1989). During this challenge, relative recovery rates of the flow velocity and blood pressure are measured and mathematically quantified. Other non-pharmacological challenges used for dynamic autoregulation measurement are the common carotid artery compression (transient hyperemic response test) (Giller 1991), tilt-table (Carey *et al.* 2003), Valsalva's maneuver (Tiecks *et al.* 1996), and simply standing up (Sorond *et al.* 2009).

Measurement of the relationship between spontaneous variations of the flow and blood pressure can be used to detect several different aspects of cerebral autoregulation. Although transfer function methods describe its faster components, correlation techniques measure slower dynamic components, which are also known as quasi-static autoregulation. These autoregulation techniques are usually used in brain trauma, SAH, or massive stroke patients who require critical care, where close blood pressure and ICP monitoring are performed (Bellapart and Fraser 2009).

TCD is also used to assess cerebral vasomotor reactivity (VMR), which provides information about capacity of the cerebral autoregulation and collateral circulation together. VMR is defined as a shift between cerebral blood velocity before and after administration of a variety of vasodilatory stimuli. The most broadly used stimuli are carbon dioxide inhalation (carbon dioxide reactivity test) (Ringelstein *et al.* 1988), intravenous acetazolamide injection (Dahl *et al.* 1995), and apnea (the breath-holding test) (Markus and Harrison 1992). All stimuli produce an increase in the arterial carbon dioxide pressure, and therefore cause significant cerebral vasodilatation. The passive position of the subject during the test is an advantage of the acetazolamide test. Carbon dioxide inhalation requires a more sophisticated test set-up such as monitoring of the end-tidal carbon dioxide. The breath-holding test necessitates active cooperation of the subject, who should keep his/her breath for a relatively long duration (at least 30 s). The utility of these VMR tests in evaluating the intracranial hemodynamic status has been studied extensively in patients with ICA occlusive diseases, and shown to be a reliable marker of the future stroke risk in most, but not all, of the studies (Silvestrini *et al.* 2000; King *et al.* 2011). Therefore, it would not be wrong to state that VMR tests could have a role in therapeutic decision of ICA disease, where the benefit-to-harm ratio for revascularization procedures is seemingly low.

Sonothrombolysis

Ultrasound exposure enhances both spontaneous [sonothrombolysis] and thrombolytic agent-mediated lysis of intravascular clot [ultrasound-enhanced thrombolysis].

The underlying mechanism of the tPA enhancing effect of ultrasound exposure is yet to be completely understood. The mechanisms include facilitation of thrombolytic agent permeation into the clot by means of promotion fluid motion around the clot surface (microstreaming), microporous formation or opening of the cross-linked fibrin mesh, direct cleavage of fibrin polymers, and the creation of extra binding sites for tissue plasminogen activator (tPA) on the fibrin network. Also, the stable cavitation phenomenon may be involved in the clot dissolution at this energy level. Residual flow enhancement by means of microstreaming and vessel dilation can also contribute. However, ultrasound exposure associated heating, which is known to increase effectiveness of tPA, remains too few to contribute to sonothrombolysis (Rubiera and Alexandrov 2010; Meairs *et al.* 2012a).

Low-frequency (less than 1 MHz) ultrasound is proposed for sonothrombolysis to overcome high attenuation rate by commercial 2-MHz probes through intact skull. However, this type of ultrasound had been found to be unsafe in acute stroke patients receiving intravenous tPA. THRUMBI (Transcranial Low-frequency Ultrasound-mediated Thrombolysis in Brain Ischemia) trial was terminated prematurely as a result of unacceptably high (36%) symptomatic hemorrhage rate (Daffertshofer *et al.* 2005). In the presence of low rate (22%) of recanalization, high prevalence of SAH and extra-infarct hemorrhages observed in this study is explained, probably in part, by the mechanical effect triggered by intracranial reverberations of this type of long wavelength ultrasound on the small vessels anchored in the subarachnoid space. Reverberations are multiple back and forth runs of ultrasound waves through their trajectory across the brain inside closed skull increase operating ultrasound intensity to unpermitted levels. Actually, it was experimentally shown that sonification associated pressure levels might reach to a level above the inertial cavitation threshold and form standing waves outside the targeted region (Wang *et al.* 2008).

Absence of these type physical adverse effects and observation of higher recanalization rates in sonographically monitored acute MCA territory stroke patients treated with tPA along with well-established safety propfile of diagnostic TCD or TCDI paved a way to test its efficacy in clinical trials. The CLOTBUST (Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA) trial showed significantly more complete recanalization or dramatic clinical recovery within 2 h following tPA bolus (49 and 30%, in TCD plus tPA and only tPA groups, respectively, 63 patients in each group) in patients with TCD monitoring, without any increase in the rate of symptomatic

hemorrhagic transformation (4.8%). Furthermore, this increased rate of recanalization translated into an increased rate of clinical recovery (Alexandrov *et al.* 2004).

Enhancement of tPA-associated clot lysis by ultrasound can significantly be augmented by use of galactose-based diagnostic microbubbles, and even more with perflutren-lipid microspheres without significant increase in symptomatic hemorrhagic transformation. Interaction of artificial and relatively stable microbubbles with ultrasonic pressure waves causes nonlinear cyclic expansion and contraction of the bubbles, which fuel inertial cavitation process and pumping around/in the occluding thrombus resulting in thrombus surface erosion mechanically, microscopic tunnel formation in and microjets around the clot eventually leading to dramatic augmentation thrombolytic delivery into the clot (Meairs *et al.* 2012b). Microbubbles can also increase clot dissolution even in the absence of thrombolytic agents through similar mechanisms. The role of local endogenous fibrinolytic activity is a proposed mechanism. Consequently, uniform demonstration of increase in recanalization rate by ultrasound and tPA with or without use of microbubbles compared with tPA alone given absence of safety issues have led to go through a phase III efficacy trial [CLOTBUSTER] to test this new stroke treatment modality.

Therapeutic ultrasound is a promising stroke treatment paradigm with multiple dimensions. First, pharmacological micro- or nanobubble designs for drug delivery are highly attractive. Preliminary data have already been shown that albumin microbubbles tagged with platelet inhibitor such as eptifibatide or abciximab and liposomes loaded with tPA promoted clot dissolving (Alonso *et al.* 2009; Shaw *et al.* 2009). It is obvious that this kind of local application will, in advance, decrease the systemic dose and exposure, and therefore potentially prevent the systemic adverse effects of the agents. Microbubble technology can be used for gene (transfection) or neuroprotective materials delivery to the tissue of interest locally (Hernot and Klibanov 2008; Meairs *et al.* 2012b). Second, with new transducer design, ultrasound clot lysis with microbubbles can be used to improve microvascular flow or recanalization without reperfusion phenomenon. Even in the absence of parent artery recanalization, microbubbles and ultrasound still improve microcirculation status (Nedelmann *et al.* 2010). Third, ultrasonic opening of blood-brain barrier may also improve intracerebral focal delivery of systemically administered agents (Baseri *et al.* 2010). Fourth, echogenicity provided with these bubbles is advantageous in terms of imaging of the vessel status. Incorporation of perfusion imaging after specific probe designs can also provide a real-time monitoring of tissue perfusion status additionally (Stride 2009). Furthermore, future methods for estimation the intracranial acoustic pressure to detect cavitation energy level can be useful for further titration of ultrasound intensity to improve safety on individual basis (Meairs *et al.* 2012a). Another new avenue of sonothrombolysis is about intracerebral hemorrhage. Actually, a pilot study demonstrated that sonothrombolysis with or without tPA can increase resolution rate of intracerebral hemorrhage through stereotactically placed drainage catheters (Newell *et al.* 2011). Finally, MR-guided focused, short, high-intensity ultrasound for clototripsy through the intact skull may be possible in the near future.

Conflicts of interest

The author has no conflicts of interest.

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