Role of transcranial Doppler ultrasonography in acute stroke

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Abstract

Background: Transcranial Doppler (TCD) ultrasonography is the only noninvasive examination that provides a reliable evaluation of intracranial blood flow patterns in real-time, adding physiological information to the anatomical information obtained from other neuroimaging modalities. TCD is relatively cheap, can be performed bedside, and allows monitoring both in acute emergency settings as well as over prolonged periods; it has a high temporal resolution, making it ideal for studying dynamic cerebrovascular responses.

Objective: To define the role of TCD in the evaluation of patients with acute ischemic stroke.

Material and methods: We have analyzed the existing literature on the protocols for performing TCD in the evaluation of patients with acute cerebral ischemia. Extended applications of TCD in enhancing intravenous thrombolysis in acute stroke, emboli monitoring, right-to-left shunt detection, and vasomotor reactivity have also been described.

Results: In acute cerebral ischemia, TCD is capable of providing rapid information about the hemodynamic status of the cerebral circulation, monitoring recanalization in real-time and, additionally, has a potential for enhancing tissue plasminogen activator (TPA)-induced thrombolysis. Extended applications of TCD make it an important and valuable tool for evaluating stroke mechanisms, for planning and monitoring treatment, and for determining prognosis.

Discussion and conclusion: TCD has an established clinical value in the diagnostic workup of stroke patients and is suggested as one of the essential components of a comprehensive stroke center. TCD is also an evolving ultrasound method with increasing diagnostic value and a therapeutic potential in cerebral ischemia.

Keywords

Cerebrovascular disease, ischemic stroke, thrombolysis, transcranial Doppler

Acute ischemic stroke results in focal neurological deficits referable to a particular cerebral arterial territory and usually manifests with weakness affecting one side of the body, speech impairment, visual disturbances, and a variety of other neurological symptoms. Most patients presenting with an acute ischemic stroke have arterial thrombi occluding extracranial and/or intracranial arteries. Intravenously administered tissue plasminogen activator (TPA) induces thrombolysis and remains the only FDA-approved thrombolytic agent for use in ischemic stroke within 3 h from symptom onset.[1] Fast dissolution of the thrombi, and arterial recanalization in acute stroke, often leads to dramatic clinical recovery.[1]

In addition to a rapid clinical examination, several diagnostic tests are employed in the evaluation of ischemic stroke. A non-contrast-enhanced computed tomography (CT) of brain remains the current standard imaging study in acute stroke to differentiate a hemorrhagic from an ischemic event. CT scan can also provide some information regarding the extent and severity of ischemic injury by enabling visualization of early ischemic changes that can be apparent “very early” after the onset of an acute stroke.[3] The non-contrast CT scan may also show the “hyperdense” artery sign that provides some clues to the location of occlusion and clot burden. The Alberta Stroke Program Early CT Score (ASPECTS) may help in a semiquantitative assessment of acute ischemia.[1] An intravenous injection of contrast bolus can then be administered to obtain a rapid sequence CT-angiography (CTA) of the extra- and intracranial arterial tree. This test can be performed rapidly and has an accuracy similar to invasive digital subtraction angiography.[4] Suitable patients presenting within 3 h of symptom onset, with disabling neurological deficits and a CT scan that shows no intracerebral hemorrhage, may be treated with intravenous TPA.[1] Recently Schellinger et al.[5] reported their results, showing MRI-based thrombolysis as being safer and potentially more efficacious than standard CT-based thrombolysis, even in severe acute ischemic strokes with significantly longer time windows.

Assessment of the cerebral vasculature can be performed by employing transcranial Doppler (TCD) ultrasound.
TCD is the most convenient method for this assessment as well for monitoring recanalization in real-time. After occlusion is documented with CTA or any other form of angiography, TCD can be used to monitor recanalization during thrombolytic therapy and can help in selecting patients for further interventions. When performed and interpreted by an experienced neurosonologist, TCD can also be used without CTA as a screening tool for rapid identification of an occlusion, to determine the stroke pathogenic mechanism, and to select the next and most appropriate step in patient management. Bedside TCD examination yields a satisfactory agreement with urgent brain CTA in the evaluation of patients with acute cerebral ischemia, especially when performed in the emergency room and within a short period of each other. TCD can provide real-time flow findings that are complementary to information provided by CTA. Furthermore, ultrasound can be used as an adjunctive therapy for clot dissolution in acute ischemic stroke.

Fast-track ultrasound in acute cerebral ischemia

A fast-track insonation protocol was developed for rapid TCD performance and interpretation in emergency situations for patients presenting with an acute ischemic stroke and being considered for thrombolysis. Using such a protocol, urgent TCD studies can be completed and interpreted within minutes at the bedside by the treating clinician, nurse, or technologist. The information provided by an urgent ‘fast-track’ TCD is further improved by combining it with a rapid cervical duplex examination as described by Chernyshev et al. The expanded fast-track protocol for combined carotid and transcranial ultrasound testing in acute cerebral ischemia is shown in Table 1.

The choice of fast-track insonation steps is determined by the clinical localization of ischemic arterial territory. For example, in patients presenting with middle cerebral artery (MCA) symptoms, if the time permits, insonation begins with locating the MCA on the nonaffect ed side. This determines the presence and the quality of the temporal window, pattern of the normal waveforms, and velocity range for M1, M2 MCA segments and the internal carotid (ICA) bifurcation. This is followed by locating the MCA on the affected side, with insonation starting at the mid-M1-MCA depth range, usually 50-58 mm. The waveforms and systolic flow acceleration are compared to the nonaffect ed side. If a normal MCA flow is found, the distal MCA segments are insonated (range 40-50 mm); this is followed by proximal MCA and ICA bifurcation assessment (range 60-70 mm). The absence of MCA flow signals can also be confirmed by insonation across the midline from the contralateral window (depths of 80-100 mm). This approach may be particularly helpful in patients with insufficient temporal acoustic windows on the affected side. The ophthalmic artery (OA) flow direction and pulsatility is determined next on the affected side at depths of 50-58 mm, followed by the assessment of the ICA siphon via the transorbital window at depths of 60-64 mm. The basilar artery (BA) is insonated next to determine if there is compensatory flow velocity increase or if a stenosis is present. Insonation of the vertebral arteries (VA), OA, and ICA on the nonaffect ed side, as well as the posterior cerebral arteries, is performed whenever time permits. Most studies can be accomplished within minutes and in parallel with the neurological examination and blood draws. When performed by experienced sonographers, this fast-track ultrasound examination at the bedside does not result in any delays in initiation of the definitive treatment. The screen appearance of TCD traces (power-motion Doppler; PMD 100, Spencer Technologies Inc) in a patient with normal findings through the transtemporal acoustic window is shown in Figure 1.

The noninvasive vascular ultrasound evaluation (NVUE) in patients with acute ischemic stroke has a high yield and accuracy in diagnosing lesions amenable to interventional treatment (LAIT), both in patients eligible as well as ineligible for thrombolysis. LAIT is defined as an occlusion or near-occlusion or ≥50% stenosis or thrombi in an artery (or arteries) supplying brain area(s) affected by ischemia. The ultrasound screening criteria for LAIT are shown in Table 2.

The yield of urgent ultrasound examination depends upon the definition of an acute arterial occlusion, time delay of ultrasound testing after symptom onset, and stroke severity at the time of ultrasound examination. TCD performed by experienced sonographers shows reliable results comparable to various angiographic tests, especially when similar diagnostic criteria are used for their interpretation and the TCD and angiography are performed within a short period of each other. This has been validated recently in our local Asian population.

The diagnostic yield of TCD in acute ischemic stroke is particularly high when performed early after the symptom onset. More than 70% of patients who have significant and fixed neurological deficits and are being considered as candidates for thrombolysis may show an arterial occlusion, if examined within the first 6 h of symptom onset. Up to 90% of patients who receive intravenous TPA within the first 3 h after stroke onset demonstrate an acute occlusion on TCD, particularly if the pretreatment National Institute of Health Stroke Scale (NIHSS) is >10 points.
Table 1: Fast-track neurovascular ultrasound examination

Use portable devices with bright display overcoming room light. Stand behind patient’s headrest. Start with TCD because acute occlusion responsible for the neurological deficit is likely located intracranially. Extracranial carotid/vertebral duplex may reveal an additional lesion often responsible for intracranial flow disturbance. Fast-track insonation steps follow clinical localization of patient symptoms.

A. Clinical diagnosis of cerebral ischemia in the anterior circulation

**STEP 1: Transcranial Doppler**
1. If time permits, begin insonation on the nonaffected side to establish the temporal window, normal MCA waveform (M1 depth 45-65 mm, M2 30-45 mm), and velocity for comparison to the affected side.
2. If short on time, start on the affected side: first assess MCA at 50 mm. If no signals detected, increase the depth to 62 mm. If an antegrade flow signal is found, reduce the depth to trace the MCA stem or identify the worst residual flow signal. Search for possible flow diversion to the ACA, PCA, or M2 MCA. Evaluate and compare waveform shapes and systolic flow acceleration.
3. Continue on the affected side (transorbital window). Check flow direction and pulsatility in the OA at depths of 40-50 mm followed by ICA siphon at depths of 55-65 mm.
4. If time permits, or in patients with pure motor or sensory deficits, evaluate BA (depth 80-100+ mm) and terminal VA (40-80 mm).

**STEP 2: Carotid/vertebral duplex**
1. Start on the affected side in transverse B-mode planes followed by color or power-mode sweep from proximal to distal carotid segments. Identify CCA and its bifurcation on B-mode and flow-carrying lumens.
2. Document if ICA (or CCA) has a lesion on B-mode and corresponding disturbances on flow images. In patients with concomitant chest pain, evaluate CCA as close to the origin as possible.
3. Perform angle-corrected spectral velocity measurements in the mid-to-distal CCA, ICA, and external carotid artery.
4. If time permits or in patients with pure motor or sensory deficits, examine the cervical portion of the vertebral arteries (longitudinal B-mode, color or power mode, spectral Doppler) on the affected side.
5. If time permits, perform transverse and longitudinal scanning of the arteries on the nonaffected side.

B. Clinical diagnosis of cerebral ischemia in the posterior circulation

**STEP 1: Transcranial Doppler**
1. Start suboccipital insonation at 75 mm (VA junction) and identify BA flow at 80-100+ mm.
2. If abnormal signals present at 75-100 mm, find the terminal VA (40-80 mm) on the nonaffected side for comparison and evaluate the terminal VA on the affected side at similar depths.
3. Continue with transtemporal examination to identify PCA (55-75 mm) and possible collateral flow through the posterior communicating artery (check both sides).
4. If time permits, evaluate both MCAs and ACAs (60-75 mm) for possible compensatory velocity increase as an indirect sign of basilar artery obstruction.

**STEP 2: Vertebral/carotid duplex ultrasound**
1. Start on the affected side by locating CCA using longitudinal B-mode plane, and turn transducer downward to visualize shadows from transverse processes of midcervical vertebrae.
2. If abnormal signals present at 75-100 mm, find the terminal VA (40-80 mm) on the nonaffected side for comparison and evaluate the terminal VA on the affected side at similar depths.
3. Follow VA course to its origin and obtain Doppler spectra. Perform similar examination on the other side.
4. If time permits, perform bilateral duplex examination of the CCA, ICA, and external carotid artery as described above.

ACA - anterior cerebral artery; CCA - common carotid artery; ECA - external carotid artery; OA - ophthalmic artery; PCA - posterior cerebral artery; BA - basilar artery; and VA - vertebral artery.

Reproduced with permission from Chernyshev et al[8]

In addition to the detection of an arterial occlusion, the yield of urgent ultrasound examination in acute ischemic stroke is further enhanced by the valuable dynamic information regarding the intracranial collaterals, stenotic lesions, spontaneous clot dissolution[14] with recanalization, and arterial re-occlusion, in addition to the detection of acute thrombi in the extracranial carotid arteries.[13,15,16]

Demchuk et al. developed detailed diagnostic criteria and determined their accuracy parameters for the presence and location of a proximal intracranial arterial occlusion on TCD [17] and described specific flow findings associated with intracranial occlusions.[14] In agreement with previous observations, TCD has the highest sensitivity (> 90%) for acute arterial obstructions located in the proximal MCA and ICAs. Spectral TCD has modest sensitivity (55-60%) for posterior circulation.
| Lesion location           | TCD criteria (at least one present)                                                                 | CD criteria                                                                 |
|--------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| **M1/ M2 MCA**           | **Primary:** TIBI grades 0-4 (absent, minimal, blunted, dampened, or stenotic) at depths <45 mm (M2) and 45-65 mm (M1)  | Extracranial findings may be normal or may show decreased ICA velocity on the side of the lesion |
|                          | **Secondary:** Flow diversion to ACA, PCA, or M2 Increased resistance in ipsilateral TICA Embolic signals in MCA Turbulence, disturbed flow at stenosis Nonharmonic and harmonic co Vibrations (bruit or pure musical tones) |                                                                           |
| **TICA**                 | **Primary:** TIBI grades 0-4 at 60-70 mm Increased velocities suggest anterior cross-filling or collateral flow in posterior communicating artery | Decreased ICA velocity unilateral to lesion or normal extracranial findings |
|                          | **Secondary:** Embolic signals in unilateral MCA Blunted unilateral MCA, MFV > 20 cm/s |                                                                           |
| **Proximal ICA**         | **Primary:** Increased flow velocities suggest anterior cross-filling through ACommA or collateral flow through PCommA Reversed OA Delayed systolic flow acceleration in or blunted ipsilateral MCA, MFV > 20 cm/s | B-mode evidence of a lesion in ICA ± CCA; Flow imaging evidence of no flow or residual lumen; |
|                          | **Secondary:** Embolic signals in unilateral MCA Normal OA direction due to retrograde filling of siphon |                                                                           |
| **Tandem ICA/MCA**       | **Primary:** TIBI grades 0-4 and: Increased velocities in contralateral ACA, MCA, or unilateral PCommA or: Reversed unilateral OA | B-mode evidence of a lesion in ICA ± CCA; or: Flow imaging evidence of residual lumen or no flow; |
| **stenosis/occlusion**   | **Secondary:** Delayed systolic flow acceleration in proximal MCA or TICA Embolic signals in proximal MCA or TICA |                                                                           |
|                          | **Basilar artery** | **Primary:** TIBI flow grades 0-4 at 75-100 mm | ICA > 50% stenosis: PSV > 125 cm/s; EDV > 40 cm/s; ICA/CCA PSV ratio >2 | Extracranial findings may be normal or showing decreased VA velocities or VA occlusion |
|                          | **Secondary:** Flow velocity increase in terminal VA and branches, MCAs, or PCommAs High resistance flow signals in VA(s) Reversed flow direction in distal basilar artery (85 mm) | ICA near-occlusion or occlusion: Blunted, minimal, reverberating, or absent spectral Doppler waveforms in ICA |
| **Vertebral artery**     | **Primary** (intracranial VA occlusion): TIBI flow grades 0-4 at 40-75 mm | Extracranial findings may be normal (intracranial VA lesion) or showing decreased VA velocities or VA occlusion |
|                          | **Primary (extracranial VA occlusion): Absent, minimal, or reversed high resistance flow signals in unilateral terminal VA** |                                                                           |
|                          | **Secondary:** Embolic signals Increased velocities or low pulsatility in contralateral VA |                                                                           |

TICA - terminal internal carotid artery; TIBI - thrombolysis in brain infarction; ACommA - anterior communicating artery; PCommA - posterior communicating artery; CD - cervical duplex. Reproduced with permission from Chernyshev et al. [8]
lesions if performed without transcranial color-coded duplex imaging or contrast enhancement. However, with a completely normal spectral TCD, there is less than 5% chance that an urgent angiogram will show any acute obstruction.

Continuous monitoring with TCD during thrombolysis can determine the beginning, duration, timing, and amount of arterial recanalization. Burgin et al. showed a high sensitivity (91%) and specificity (93%) for the single-channel TCD when compared to angiography for MCA occlusion vs complete recanalization in patients receiving thrombolysis for ischemic stroke. While TCD demonstration of an arterial occlusion helps to determine the ischemic nature of acute focal neurological deficits, a normal TCD results would support a lacunar mechanism or prompt the treating physician to suspect non-stroke events such as functional deficits or complicated migraine. The information provided by TCD is complementary to CTA since the former can show flow direction with collateralization, various hemodynamic patterns of recanalization, and re-occlusion, in addition to the observation of spontaneous emboli in real-time, in some cases.

In emergency situations, a fast TCD localization of arterial occlusion can help in explaining the vascular origin of the neurological deficit and indirectly judge whether collateral blood supply can compensate for an occlusion. This information helps to identify patients with large proximal vessel occlusion and select the next most efficient management steps, such as further diagnostic or interventional procedures. A persistent large vessel occlusion or stenosis in patients with acute and spontaneously resolving deficits may also point to a greater likelihood for clinical deterioration within the next 24 h. These TCD findings are also helpful to identify patients with persisting arterial obstructions that will be particularly sensitive to blood pressure changes, head positioning, and inadequate hydration.

Previously, absence of flow signals at and distal to the presumed thrombus location, along with the velocity asymmetry between homologous segments, were considered to define an intracranial arterial occlusion. Theoretically, a complete occlusion should not demonstrate any detectable flow signals. However, in reality, some residual flow around the thrombus are often noted due to its irregular shape, relatively soft composition, and systolic pressures that cause additional distension of arterial walls, thus resulting in a variety of waveforms representing this residual flow. The proximal branches of the circle of Willis are more steadily positioned and can be easily targeted with ultrasound. The Thrombolysis in Brain Ischemia (TIBI) flow-grading system was developed to evaluate residual flow noninvasively and monitor thrombus dissolution in real-time [Figure 2]. The TIBI system expands previous definitions of acute arterial occlusion by focusing the examiner’s attention on relatively weak signals with abnormal flow waveforms that can be found along arterial stems filled with thrombi. TIBI flow grades correlate with stroke severity and mortality as well as the likelihood of recanalization and clinical improvement.

Acute arterial occlusion is a dynamic process since thrombus can propagate, break up, or re-build within seconds or minutes, thereby changing the degree of arterial obstruction and affecting correlation between TCD and angiography. When the term acute occlusion is applied, it means that there is a hemodynamically significant obstruction to flow and these ultrasound findings suggest that if an urgent angiography is performed, it will likely show an arterial lesion that may be amendable to intervention. Furthermore, ultrasound may suggest that more than one occlusion are present in the same patient, i.e., tandem lesions in the ICA and MCA or VA and BA. These tandem lesions are detected by combining TIBI flow grading and criteria for collateral flow signals. In other words, if a distal M1 MCA occlusion is present, it should produce antegrade flow diversion to anterior (ACA) or posterior cerebral artery (PCA). If an additional obstruction exists in the proximal ICA, TCD will show either anterior cross-filling via the anterior communicating artery, stenotic terminal ICA velocities, or...
and/or reversed ophthalmic artery flow.

In summary, bedside ultrasound examination in acute cerebral ischemia can help to a) identify thrombus presence, b) determine thrombus location(s), c) assess collateral supply, d) find the worst residual flow signal, and f) monitor recanalization and reocclusion.

**TCD Monitoring**

Prolonged TCD monitoring for emboli detection and vasomotor reactivity assessment has been performed for years without any evidence of harmful effects. No adverse biological effects have been documented for the frequencies and power ranges used in diagnostic ultrasound. Previous works with TCD monitoring have shown that evolution of the MCA occlusion can be followed in real-time with the recanalization process measured.\(^{24,25}\)

Arterial recanalization indicates successful thrombolysis and the timing of maximum completeness of recanalization on TCD correlates with clinical recovery as predicted from animal models.\(^{26}\) However, recanalization is a process that often begins many minutes before restoration of cerebral blood flow, because TPA binding and activity on the clot surface are proportionate to the area exposed to blood flow. Once recanalization starts, clot softens and partially dissolves to allow some residual flow improvement, thus bringing more TPA to bind with fibrinogen sites. This continuous process facilitates clot lysis under the pressure of arterial blood pulsations. The speed of clot lysis can be measured with real-time TCD monitoring with TIBI residual flow signals and other parameters such as intensity of flow signals, appearance of microembolic signals, and velocity and pulsatility changes.\(^{19}\) The beginning, speed, timing, and amount of recanalization represent important parameters of thrombolytic therapy for stroke and these are measured using the following five parameters:

1. Waveform change by > 1 TIBI residual flow grade (eg, absent to minimal, minimal to blunted, and minimal to normal signal improvement)
2. Appearance of embolic signals (transient high-intensity signals of variable duration)
3. Flow velocity improvement by > 30% at a constant angle of insonation
4. Signal intensity and velocity improvement of variable duration at constant skull/probe interface and gain/sample volume/scale settings
5. Appearance of flow signals with variable (> 30%) pulsatility indexes and amplitude of systolic peaks

Once the recanalization process starts, TCD can detect the arrival of the highest TIBI flow grade that will indicate the completion of recanalization. Arterial recanalization can be classified as: 1) sudden (abrupt appearance of a normal or stenotic low-resistance signal), 2) stepwise (flow improvement over 1 to 29 min), and 3) slow (> 30 min).\(^{19}\) Rapid arterial recanalization is associated with better short-term improvement, most likely because of faster and more complete clot breakup to restore the blood supply to the affected territory. Slow flow improvement and dampened TIBI flow signals are less favorable prognostic signs. Early recanalization and reperfusion of the ischemic penumbra are associated with early and dramatic recovery as well as good long-term outcome.\(^{13}\) Labiche et al.\(^{27}\) showed that most patients who experience early clinical improvement within 2 h of TPA bolus sustain this clinical benefit 3 months after stroke. On the other hand, Christou et al.\(^{26}\) noted that among patients who had no change in the severity of neurological deficit or who worsened by 4 or more NIHSS points, none had complete recanalization within 300 min, implying that a persisting occlusion on TCD may represent severe ischemia. These patients may represent a target group for combined intravenous and intraarterial thrombolysis.

Arterial reocclusion following a partial or complete recanalization was not studied systematically in the NINDS rt-PA Stroke Study\(^{23}\) as no consistent vascular imaging protocol was implemented in this trial. However, deterioration following improvement (DFI) may represent a clinical surrogate of reocclusion; DFI was observed in 13% of patients in this trial. We found that one-third of our patients with early recanalization experienced reocclusion within 2 h of TPA bolus. Also, two-thirds of patients with DFI experienced early reocclusion and we believe that this is the main underlying mechanism of this phenomenon.\(^{26}\) It was further observed that patients with early reocclusion had better long-term outcomes than patients with no early recanalization on TCD. One likely explanation may be that prior to reocclusion, these patients may have had some degree of early recanalization and reperfusion of the penumbral areas, which gave them the ability to tolerate further ischemia for a little more time. A similar phenomenon was observed by Rubiera et al.\(^{29}\) who demonstrated a reocclusion rate of 12% from all TPA-treated patients and of 17% of those who achieved recanalization. They found that at 3 months, patients with reocclusion and patients with persistent occlusion had significantly worse long-term outcomes as compared to patients with a stable recanalization.

**Therapeutic TCD**

A significant portion of patients with acute coronary artery occlusions could not achieve arterial recanalization with systemic thrombolysis alone, and even lower recanalization rates have been demonstrated...
with intravenous thrombolysis in ischemic stroke. del Zoppo et al.\cite{39} showed that only 26% of intracranial occlusions lyse partially or completely after 1 h of intravenous thrombolysis. In the PROACT II trial, only 4% of MCA clots showed complete TIMI grade 3 recanalization after 1 h of infusion of recombinant pro-urokinase at the clot surface.\cite{51}

Clinical benefit from thrombolysis is directly related to achieving early recanalization. Experimental evidence suggests that ultrasound substantially increases the thrombolytic effect of TPA, particularly if used in the low MHz-kHz frequency range. Ultrasound exposure causes various changes, such as reversible disaggregation of uncrosslinked fibrin fibers; microcavity formation in the shallow layers of thrombus; increase in the enzymatic transport of TPA, improving its uptake and penetration of TPA into clots; as well as residual flow enhancement with microstreaming and vessel dilation.\cite{32,34}

Two major limitations exist with TCD that impede its widespread use. Firstly, it is a true operator-dependent technique requiring detailed three-dimensional knowledge of the intracranial arterial anatomy. Secondly, TCD is hampered by the 10-15% rate of inadequate temporal windows most commonly seen in Blacks, Asians, and elderly female patients. This is related to thickness and porosity of the temporal bone attenuating ultrasound energy transmission. Temporal bone squama produces marked attenuation of the signal.\cite{39} A newer technology called power motion-mode TCD (PMD/TCD) appears to improve window detection and simplifies operator dependence of TCD by providing multi-gate flow information simultaneously in the power motion-mode display.\cite{36} PMD/TCD facilitates temporal window location and alignment of the US beam to view blood flow from multiple vessels simultaneously, without sound or spectral clues.\cite{37}

Despite a significant attenuation by the skull bone, the routine diagnostic TCD using 2-MHz frequency with a power output less than 750 mW, transmits some amount of ultrasound energy to the intracranial vessels and could contribute to enhance the activity of TPA. In vitro experiments using cadaver skull have showed that 1 h of 1-MHz TCD helps TPA to recanalize 90% of clots as compared to the 30% rate when TCD exposure was limited to 30 min.\cite{38} Critics may point out that TCD delivers insufficient energy to the clot due to the tremendous attenuation of ultrasound by the skull bone and that lower-frequency/low-power insonation better accelerates TPA-mediated thrombolysis. However, at least 10% of emitted energy is delivered through the skull to the clot-residual flow interface since TCD is able to detect returned signals and display tenuous residual flow and the recanalization process. In their experiments, Spengos et al. showed a three-fold increase in clot lysis when 1-MHz TCD was applied through the intact skull in an in vitro model.\cite{59}

Diagnostic 2-MHz TCD is routinely used in patients with stroke to obtain spectral velocity measurements in intracranial arteries.\cite{23,39} Continuous 2-MHz TCD energy transmission may promote thrombolysis by simply exposing more clot surface to residual flow.\cite{21} When the worst residual flow signal is identified using TIBI grades, the ultrasound beam is usually focused at the intracranial clot location and its interface with surrounding, often minimal, blood flow. The ability of TCD to detect these signals indicates that ultrasonic energy was delivered to the clot and that this energy was scattered, absorbed, and partially reflected at the interface since clot and moving blood have different impedances. A small pressure gradient created by ultrasound waves gives an opportunity for more TPA molecules to bind with clot fibrinogen sites, stream plasma along and possibly through clot structures, and therefore to achieve faster recanalization without the stronger mechanical vibrations and disruptions possible with kHz frequencies. We observed high rate of complete recanalization and dramatic clinical recovery during TPA infusion when continuously monitored by 2-MHz TCD monitoring.\cite{13}

Our pilot clinical study assessed whether such a therapeutic effect is possible in stroke patients.\cite{21} Stroke patients receiving intravenous TPA were monitored with portable TCD, starting at the time of TPA bolus. Residual flow signals were obtained from the clot location identified by TCD. Forty patients with a mean baseline NIHSS score of 19 were studied. Recanalization on TCD was found at 45 ± 20 min after TPA bolus. Recanalization was complete in 12 (30%) and partial in 16 (40%) patients. Dramatic recovery during TPA infusion (NIHSS score <3 points) occurred in 8 (20%) patients, all with complete recanalization. Lack of improvement or worsening was associated with no recanalization, late recanalization, or reocclusion on TCD. Improvement by > 10 NIHSS points or complete recovery was found in 30% of all patients at the end of TPA infusion and in 40% at 24 h. This preliminary data provided the enthusiasm to initiate a proper phase II randomized controlled trial, called CLOTBUST, to assess whether such therapeutic monitoring can be safely applied to acute stroke patients. In this trial, 126 patients were randomly assigned to receive continuous TCD monitoring or placebo (63 patients in each group) in addition to intravenous t-PA.\cite{40} Complete recanalization or dramatic clinical recovery within 2 h after the administration of a TPA bolus occurred in 49% in the target group as compared to 30% in the control group (P = 0.03). Only 4.8% patients
developed symptomatic intracerebral hemorrhage. These results showed the positive effects of 2-MHz continuous TCD monitoring in acute stroke, with no increase in the rate of intracerebral hemorrhage.

Eggers et al.\textsuperscript{41} evaluated the potential of transcranial color-coded sonography (TCCS)-guided, 2-MHz transcranial ultrasound in accelerating thrombolysis in acute stroke patients with occlusion of the MCA-M1 and with contraindications for thrombolytic therapy. They observed more frequent recanalization in the ultrasound group as compared to the control group.

Various attempts have been made using low-frequency ultrasound exposure to the occluded cerebral arteries. Although kilohertz frequencies penetrate better, a combination of tPA and an experimental kilohertz-delivery system resulted in an excessive risk of intracerebral hemorrhage in patients with ischemic stroke. In the TRUMBI trial, Daffertshofer et al.\textsuperscript{42} included 26 patients within the 6-h time window in a multicenter clinical trial, with 12 patients receiving TPA and 14 patients receiving TPA plus 90 min of low-frequency (300 kHz) ultrasound exposure. The study had to be stopped prematurely due to an increased incidence of intracranial hemorrhages (5 of 12 in the TPA group vs 13 of 14 in the TPA plus ultrasound group). Parenchymal hemmorhages with subarachnoid extension or affecting normal brain tissue occurred in the combined treatment group. Potentially, reverberations of the long-wavelength ultrasound occurred inside the head, leading to ‘hot-spots’ in addition to the mechanical distortion of the brain microvessels with kHz frequencies. We have recently demonstrated the feasibility and efficacy of ultrasound-assisted thrombolysis in our local Asian patients.\textsuperscript{43} During our preliminary experience in Singapore, we could identify and localize the vascular occlusions in acute ischemic stroke and observed IV TPA-induced recanalization in real-time. TCD findings of one such case are demonstrated in Figure 3.

The CLOTBUST trial demonstrated that early augmentation of reperfusion resulted in a trend towards favorable clinical recovery.\textsuperscript{40} Based on this trend, a pivotal trial to confirm the efficacy of sonothrombolysis would require an estimated 600 patients.\textsuperscript{40} Considering this as too large a sample for an acute stroke trial, CLOTBUST investigators started to explore further ways to augment early reperfusion that could reduce the sample size of the pivotal trial.

Recently, combining tPA, ultrasound, and gaseous microbubbles showed a signal of further enhancing arterial recanalization.\textsuperscript{14} Although these microbubbles, previously known as diagnostic microbubbles or gaseous microspheres, were originally designed to improve conventional ultrasound images, facilitation of thrombolysis is now emerging as a new treatment application for this technology. Newer generation bubbles use specific phospholipids molecules that, when exposed to mechanical agitation, arrange themselves in nanobubbles of consistent 1-2 µm (or even lesser) diameter. When injected intravenously, nanobubbles carry gas through the circulation. As the bubbles approach and permeate through the thrombus, they can be detected and activated by the ultrasound energy. Upon encountering an ultrasound pressure wave, the phospholipid shell breaks up and releases gas. The result is the bubble-induced cavitation with fluid jets that erode the thrombus surface. In the presence of tPA, this erosion increases the surface area for thrombolytic action and accelerates lysis of clots.\textsuperscript{44,45}

Molina et al. first tested galactose-based air microbubbles (Leovist\textsuperscript{8}, Schering, Berlin, Germany), 2-MHz TCD, and IV-tPA in humans with acute ischemic stroke.\textsuperscript{46} This first-generation microbubble technology is not FDA approved for diagnostic use in USA. Perflutren lipid nanoparticle (MRX 815, ImaRx Therapeutics, Tucson, AZ) is the next-generation nanobubbles that are consistent and smaller in size. The size and biochemical properties of the lipid shell lead to greater transpulmonary passage and, thus, higher concentrations within an arterial thrombus after an intravenous injection.\textsuperscript{47} MRX nanoparticle activated by ultrasound could induce thrombolysis even in the absence of thrombolytics in canine dialysis grafts and in a stroke swine model.\textsuperscript{48-51} In a recently conducted pilot trial, we have reported higher recanalization rates with these third-generation perflutren-lipid microspheres. We observed that perflutren microspheres (µS) reached
and permeated beyond intracranial occlusions, with no increase in sICH after systemic thrombolysis.[52] We also demonstrated that these perfusate-containing µS reached and permeated beyond intracranial occlusions[33] and power motion Doppler gate can quantify the dose of delivered µS and determine a minimum number of µS needed to achieve constant flow enhancement and targeted drug delivery. Although our study shows the feasibility of administering a new generation of µS in acute stroke patients, a further dose-escalation study is needed since it is unclear if more µS delivered to thrombus during tPA infusion will safely facilitate thrombolysis in a dose-dependent manner. A multicenter dose-escalation controlled randomized trial is being launched to address this issue.

Emboli detection

Microembolic signals (MES) appear as signals of high intensity and short duration within the Doppler spectrum as a result of their different acoustic properties compared to the circulating blood.[54] MES have been proven to represent solid or gaseous particles within the blood flow. They occur at random within the cardiac cycle and they can be acoustically identified by a characteristic ‘chirp,’ ‘click,’ or ‘whistle’ sound. Detection of MES can identify patients with stroke or TIA likely due to embolism. Various cross-sectional studies have suggested that these embolic signals are clinically important; they are seen more commonly with carotid stenosis, recent symptoms, and plaque ulceration.[55-57]

Doppler emboli detection is especially important in carotid stenosis. For >70% symptomatic stenosis, carotid endarterectomy is of proven benefit and early intervention after the event has been associated with better stroke risk reduction. However, in many patients with completed stroke, some surgeons wait up to 4-6 weeks before operating. In addition, in a number of countries, because of limited resources, patients wait for longer periods for surgery. In these cases, MES detection by TCD may allow identification of a particularly high-risk group of patients who merit an early intervention or, if this is not possible, more aggressive antithrombotic therapy. Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis Study (CARESS) also revealed that the combination of clopidogrel and aspirin was associated with a marked reduction in MES, compared with aspirin alone.[58] Similar benefits of the combined treatment with aspirin and clopidogrel have been reported in the recently conducted FASTER trial.[59] Similarly, in asymptomatic carotid stenosis, Spence et al.[60] demonstrated that cases that do not show MES on TCD will not benefit from carotid endarterectomy or stenting unless the perioperative or periprocedural risk is <1%. These findings support the notion that asymptomatic carotid stenosis should be managed medically, delaying surgical intervention until the occurrence of emboli, impaired vasomotor reactivity, or symptoms.

Intracranial stenosis

Intracranial arterial steno-occlusive lesions cause characteristic alterations in the Doppler signals, including focal increases in velocity, local turbulence, a poststenotic drop in velocity, and various collateral flow patterns. Intracranial atherosclerosis is responsible for up to 10% of TIA and strokes.[61] Stenosis and/ or occlusion of the ICA siphon, proximal (M1) segment of middle cerebral artery, intracranial vertebral artery, proximal basilar artery, and proximal (P1) segment of the posterior cerebral artery can be reliably detected by TCD. Sensitivity, specificity, positive predictive value, and negative predictive values of TCD are generally higher in the anterior circulation than in the vertebrobasilar circulation owing to the more reliable anatomy of the former and the technical problems in studying the latter.[62]

Intracranial arterial stenotic lesions in the internal carotid distribution are dynamic, and can evolve over time, and the progression may be associated with a new ipsilateral stroke or TIA or major vascular events.[63,64] Existing data suggest an association between the degree of stenosis and recurrent stroke, with higher degrees of stenosis and the number of vessels affected predicting worse prognosis.[65,66]

One of the important limitations of TCD is that there is an insufficient temporal acoustic window and this can be a limiting factor in a significant number of cases, depending upon the population being studied.[67] The yield of TCD in cases with suboptimal acoustic windows can be enhanced with the help of various contrast agents. Furthermore, the ability to assess the intracranial arteries by TCD is as much an art as it is science, and the procedure remains operator dependent. However, when TCD is performed and interpreted by experienced neurosonologists, it provides a higher yield, with results comparable to contrast angiography, especially if these two investigations are performed within a short period of each other.[6]

A short arterial stenosis produces focal velocity increases on the upslope of the so-called Spencer’s curve of cerebral hemodynamics. However, the relationship between flow velocity and diameter reduction is also affected by the length of the stenosis or the presence of multiple distal lesions.[68,69] Intracranial arterial stenosis increases flow velocities on the upslope of the Spencer’s curve of cerebral hemodynamics. However, the velocity can decrease with long and severely narrowed vessels, and this pattern of
diffuse intracranial disease could be relatively common. We have recently reported the abnormal TCD findings of low mean flow velocity in the presence of high pulsatility index as being independently associated with the presence of diffuse intracranial disease after adjusting for demographic characteristics and stroke risk factors. The ability of TCD to detect diffuse intracranial disease increased with the number of arteries affected.

**Vasomotor reactivity**

Although velocities in the MCA do not directly correlate with absolute values of cerebral blood flow, changes in velocity correlate with changes in the flow when the MCA has a constant diameter. Vasomotor reactivity describes the ability of the cerebral circulation to respond to vasomotor stimuli; the changes in cerebral blood flow in response to such stimuli can be studied by TCD. The commonest agent used to measure the cerebral vasomotor reactivity is CO₂. Increased levels of CO₂ cause vasodilatation and increased cerebral blood flow, which is reflected by an increased velocity. Measuring vasomotor reactivity requires a proper setup and controlled conditions with regard to the concentration of CO₂. Markus et al.[71] described a simple measurement of the MCA velocity in response 30 s of breath-holding and termed it as the breath-holding index (BHI):

\[
BHI = \left( \frac{MFV_{\text{end}} - MFV_{\text{baseline}}}{MFV_{\text{baseline}}} \right) \times \frac{100}{ \text{seconds of breath holding}}
\]

(where MFV is the mean flow velocity).

Silverstrini et al.[72] prospectively evaluated BHI in case-controlled studies and showed that impaired vasomotor reactivity can help to identify patients at higher risk of stroke because of asymptomatic carotid stenosis or a previously symptomatic carotid occlusion. A decreased vasomotor reactivity suggests failure of collateral flow to adapt to the stenosis progression. Various studies using different provocative measures for assessing the cerebral vasomotor reactivity have demonstrated a remarkable ipsilateral event rate of around 30% (30% risk of stroke/TIA during about 2 years). Exhausted vasomotor reactivity on TCD represents failed vasodilatory reserve and this finding can be confirmed by performing acetazolamide-challenged HMPAO-SPECT imaging. We have presented our observations of multi-modality imaging of intracranial vasodilatory reserve in one such patient [Figure 4].

In patients with persisting proximal arterial occlusions, hypercapnia can paradoxically decrease the residual flow velocity in the affected vessel at the expected time of

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**Figure 4:** Hemodynamic consequences of a right carotid artery occlusive disease. Diffusion-weighted MRI of the brain (A) shows an acute right posterior ‘border-zone’ infarction. Occlusion of the right internal carotid artery (B) is noted just distal to the carotid bulb on CT angiography of the cervical vessels. HMPAO-SPECT performed at baseline (C) shows adequate perfusion in both cerebral hemispheres. SPECT images obtained after challenge with acetazolamide (Diamox) revealed markedly reduced perfusion in the right cerebral hemisphere (D). Transcranial Doppler ultrasonography (E and F) was performed for vasomotor reactivity assessment, with breath-holding and monitoring of flow in both middle cerebral arteries (MCA) simultaneously. A normal response is noted on the left side (mean flow velocity increased from 50 cm/s to 66 cm/s after 30 s of breath-holding, with a breath-holding index of 1.07), while the mean flow velocity showed a paradoxical reduction (from 23 cm/s to 19 cm/s), suggestive of a failed vasodilatory reserve.

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**Right-to-left shunt detection**

Right-to-left shunts, particularly a patent foramen ovale (PFO), are common in the general population, with a prevalence of 10-35% in various echocardiography and autopsy studies for PFO. The prevalence is even higher in certain selected populations, eg, in patients with cryptogenic stroke or TIA and especially in younger patients without an apparent etiology. A contrast-
enhanced transesophageal echocardiography (TEE) is still believed to be the gold standard for the diagnosis of PFO.

Since the early 1990s, contrast-enhanced TCD has been used as an optimal method for detecting the high-intensity transient signals (HITS) passing through the MCA, thus indicating the presence of a right-to-left shunt. The results of contrast-enhanced TCD have been compared with that of contrast-TEE in various studies and found to be convincing with regard to its sensitivity and specificity. The sensitivity and specificity of contrast-enhanced TCD has been reported to be 68-100% and 67-100%, respectively. A recent study with TCD and TEE performed simultaneously, showed an almost perfect concordance in PFO detection and right-to-left (RLS) quantification. To further elucidate the agreement between TCD and TEE, we have recently reported the effect of the body position during the right-to-left shunt detection by TCD.

In conclusion, TCD has an established clinical value in the diagnostic workup of stroke patients and is suggested as essential component of a comprehensive stroke center. TCD is also an evolving ultrasound method with increasing diagnostic value and therapeutic potential. Validated occlusion criteria and the TIBI classification of residual flow are aimed at easing its use in acute stroke, and technology advances can be expected to simplify bone window determination. Given the widespread availability of this equipment, increased use of this modality in acute stroke is expected and local validation of diagnostic criteria and test performance is required by vascular laboratory accreditation guidelines (www.icavl.org).

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