REVIEW ARTICLES

Applications of transcranical Doppler ultrasound in atherosclerotic ischaemic stroke: An Asian perspective

KS Tan, CT Tan, *KS Wong

Division of Neurology, Department of Medicine, University of Malaya, Malaysia
**Department of Medicine & Therapeutics, Chinese University of Hong Kong, Hong Kong SAR, China*

Abstract

TCD (transcranial Doppler) technology has improved considerably in the last decade with a corresponding increase in research interest and clinical applications by neurologists in Asia and the rest of the world. This review was written to assess the current use of TCD in atherosclerotic ischaemic stroke particularly in the areas of diagnosis and prognostication of intracranial cerebral artery disease, acute stroke, cerebral vasomotor reactivity and microembolic signal detection.

INTRODUCTION

Transcranial Doppler (TCD) is a safe and clinically useful technique to evaluate cerebral hemodynamics. TCD examination of the intracranial arteries was first performed in 1982 by Rune Aaslid and his co-workers.[1] TCD uses a low frequency, pulsed wave Doppler transducer to penetrate the thin portions of the skull in order to measure blood flow velocity through Doppler frequency shifts. A composite picture of the different segments of the major cerebral vessels in the anterior and posterior circulations with transorbital, transoccipital and transtemporal insonations allow the sonologist to interpret the overall intracranial haemodynamics. TCD is primarily a technique for measuring relative changes in flow, based on the insonated velocities. When the diameter of the relevant vessel is established by some other method, absolute values of flow can be calculated. Overall, the advantages of TCD lie in its repeatability, portability, non-invasiveness and its real-time applications. In this article, the main clinical applications of transcranial Doppler ultrasound in ischaemic stroke were assessed with emphasis on recent developments.

APPLICATIONS

Diagnosis and prognostication of intracranial cerebral artery disease

Current evidence have shown that TCD is indicated in patients with ischemic cerebrovascular diseases including ischemic stroke, transient ischemic attack (TIA) and may be routinely indicated in asymptomatic patients at high risk of stroke. TCD can detect intracranial haemodynamic derangements such as arterial stenosis, arterial occlusion, collaterals and microembolization.

Arteries where stenoses and occlusion can be reliably insonated by TCD include middle cerebral artery (MCA) M1 segment, internal carotid siphon, intracranial vertebral, proximal basilar and proximal posterior cerebral arteries.[2] Performance of TCD against angiography in the anterior circulation varies by centre. Published literature revealed a sensitivity of 80-90%, specificity of 90-95%, positive predictive value of 85% and negative predictive value of 98%.[3] Sensitivity in the posterior circulation was lower with limitations from variable anatomy and technical factors.[4]

In Asia, atherosclerosis of the large intracranial cerebral arteries is an important cause of cerebrovascular disease. It is reported to account for 17% to 50% of all ischemic strokes.[5-8] Digital subtraction angiography[9-11], pathology,[12] and MR angiographic[13] studies have shown that Caucasians tend to have more severe disease of the extracranial arteries whereas intracranial cerebral atherosclerosis were more common among Orientals and patients of Afro-Carribean origin.[14-15]

Address correspondence to: Dr. Kay-Sin Tan, Division of Neurology, Department of Medicine, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia. Phone: 603 7950 2585 Fax: 603 7950-2968, Email: tanks@ummc.edu.my

In the past, evaluation of these vascular lesions has relied heavily on the availability of digital subtraction angiography. However, due to the potential risk of perioperative thromboembolism from the procedure, the intracranial circulation has not been routinely studied in Asian patients. TCD has some inherent advantages as it is repeatable, non-invasive, sensitive, specific and relatively inexpensive. This has allowed clinicians to study the intracranial circulation alongside other non-invasive techniques such as MR angiography and CT angiography.[16]

TCD is also helpful in determining the prognosis of ischaemic strokes. A 6 month follow up study from Hong Kong showed that the number of abnormal arteries was linearly related to subsequent vascular events.[17] In longer term follow up study from the same cohort, 49% of the 745 study subjects had cerebral artery lesions documented ultrasonographically. With a mean follow up of 28±5 months (up to 42 months), 199 (28%) suffered further cerebrovascular or cardiac events. The 3.5-year cumulative mortality rate was 20.8% and for cerebrovascular event, 29.5%. The annual recurrent stroke rate during the first year was 10.9% for patients without vascular lesion, 17.1% for intracranial atherosclerosis only and 24.3% for both intra-and extra-cranial atherosclerosis. In the second year, the rates were considerably lower. More deaths (p=0.02) and cerebrovascular events (p=0.002) were found among patients with vascular lesions than those without.[18]

Acute stroke

In acute strokes, TCD can detect arterial occlusion and recanalisation as it is the only diagnostic modality that offers real time monitoring capability. TCD evidence of occlusion was present in 69% of thrombolysis-eligible patients during the first six hours of ischaemia. Recanalization occurs rapidly and only 24% of patients have occlusions on TCD within 6-24 hours after stroke onset. In addition, the timing of total recanalisation is often seen before clinical improvement and correlated with clinical recovery.[19-20] The use of TCD to enhance clot lysis as an adjunct to thrombolysis has been observed to produce promising results but will need further evaluation.[21-22]

TCD can also provide complementary information to other modalities of imaging. In the presence of bilateral carotid stenosis, TCD can detect the presence of collaterals, delayed flow acceleration on MCA waveforms as well as anterior and posterior communicating artery cross-over flow. These TCD signs indicate a hemodynamically significant lesion from between 70% internal carotid artery (ICA) stenosis to total occlusion. TCD can also unmask hemodynamically significant distal ICA obstructions and tandem ICA lesions.[23] In one series, TCD was reported to have 94% sensitivity and 97% specificity for hemodynamically significant proximal ICA lesions and 81% sensitivity and 96% specificity for distal ICA lesions.[24] In short, TCD was able to offer relatively sensitive indirect evidence of significant carotid stenosis through the intracranial haemodynamics.

Serial TCDs were also able to offer information on prognosis. A recent study observed that the progression of middle cerebral artery (MCA) occlusive disease recorded serially on TCD was associated with an increase in vascular events.[25]

Vasomotor reactivity

TCD is also invaluable in the assessment of vasomotor reactivity (VMR) of the intracranial vessels. Physiologically, MCA flow velocity decreases during hypocapnia since constriction of distal arterioles increases resistance to flow, increases the pulsatility index (PI) and dampens proximal flow velocity. On the other hand, hypercapnia produces arteriolar vasodilation, decreases resistance and results in increased flow velocities and low PI. VMR can also be assessed by measuring changes in flow velocities in response to hyperventilation, acetazolamide injections and to CO_2 inhalation. In healthy patients, flow velocities may drop by 35% with hypocapnia and increase by up to 50% with hypercapnia. In order to avoid velocity variations during breathing cycles, Doppler spectra from up to 20 cardiac cycles should be averaged.[4,26]

This mean flow velocity change from hyper to hypocapnic state compared to the normocapnic state is referred to as vasomotor reserve capacity (VMRC). The normal VMR value is 86±16%. This response decreases with the progression of carotid artery stenosis until total occlusion. A decrease of up to 30% or less indicates exhausted VMR. Diminished vasoreactivity is predictive of further vascular events in the setting of severe carotid stenosis and therefore has a role in prognostication.[27] Larger studies using this technique may help select at risk patients and possibly select candidates for revascularization therapy. As TCD is a relatively inexpensive method compared to the use of positron emission tomography (PET) or single photon emission computed tomography (SPECT) scans in the evaluation of cerebrovascular reserve, it can be utilised if the more advanced resources are not available particularly in parts of Asia.

Microembolic signal detection

Microembolic signals (MES) detected by TCD correspond to embolic particles as they pass through the cerebral circulation. Particulate emboli (atheroma, thrombus and platelet fibrin aggregates) and gaseous material are believed to produce ultrasound signals of short duration and increased intensity derived from the reflected and scattered ultrasound beam at the interface between embolus and blood. These signals were initially called "high intensity transient signals" or HITS and were produced because of the different acoustic impedance properties. MES moves within the spectral envelope, with the direction of flow, is of short duration and characterized by a time delay between 2 channels as seen with a bigate transducer.[28,29]

In patients with asymptomatic internal carotid artery stenosis, the presence of MES was associated with increasing severity of stenosis.[30] The presence of MES was also associated with an increased risk of future symptoms of cerebral ischaemia[31] and also correlated positively with irregularities of the plaques surface in symptomatic patients.[32]

The presence of MES appeared to be lower in asymptomatic patients with high grade large vessel stenosis. This was supported with studies by Siebler *et al*[33] and Markus *et al*.[34] A recent study by Abbott *et al*[35] also reported the low prevalence of MES in asymptomatic patients with 60-99% ultrasonographically diagnosed extracranial carotid stenosis. MES was found at least once in 60 of 231 (26%) of monitored arteries. This study also observed that 6 of 60 (10.0%) of patients with MES-positive arteries had an ipsilateral carotid stroke/TIA compared with 12 of 171 (7.0%) MES-negative. This finding was not statistically significant.

MES detection has recognized limitations due to several factors. Firstly, an accurate and reliable characterization of the emboli size and composition has been hampered by the lack of a standardized approach to monitoring in previous publications. Secondly, previous studies have included MES from populations with prosthetic valves (gaseous composition) which may have confounded the early data.[36] Thirdly, technical reasons related to the TCD equipment used including probe frequency, duration of recording sessions, computer processing speed and the degree of overlap of the fast Fourier transformed spectral display influence the accurate detection of MES.[2,37,38] The standardization and the unification of the requisite technical specifications for TCD monitoring equipment and greater use of pre-defined embolic signals based on the consensus of published MES criteria will lead to more reliable and reproducible results.[38]

TCD monitoring also requires trained personnel to perform the procedure and interpret the results. This is an extremely labour-intensive method which can be improved by new, ambulatory TCD-equipment as described by Mackinnon *et al*.[39] The interpretation of microembolic signals can also be further enhanced by new automated on-line software based on artificial intelligence techniques.[40]

Embolic signals arising from MCA stenosis and following clot dissolution of acute emboli can be further characterized. These have been described as low frequency MES.[41-42] A more recent description of MCA origin thrombo-embolism documented on TCD monitoring was noted to have characteristic multiple frequencies on both post-FFT and pre-FFT time domain signals.[43] There was also a good relationship between MES found in transcranial Doppler ultrasound and multiple acute lesions on diffusion weighted MR imaging (DWI).[44] As such, MES may possibly be used as a surrogate marker for strokes and for the efficacy of anti-platelet regimens. A previous study showed that MES of arterial origin decreased with the infusion of acetylsalicylic acid.[45] Accordingly, a multi-centre Asian study, *CLAIR* (Clopidogrel plus aspirin for infarct reduction in acute stroke/ TIA patients with large artery stenosis and microembolic signal; personal communication, KS Wong, Prince of Wales Hospital, Hong Kong) is at present actively recruiting patients in order to assess the therapeutic implications of clopidogrel in addition to aspirin on MES and acute infarctions on DWI.

TECHNICAL CONSIDERATIONS

The information provided by TCD is clearly useful in the management of patients with ischaemic stroke. TCD like any other ultrasound-based technique is operator dependent. For this reason, it should be performed and interpreted by individuals with adequate background, training and practical experience.

CONCLUSION

Transcranial Doppler ultrasound is a firmly established investigation of the cerebral circulation. There is a growing body of evidence that TCD will have an increasing impact in the care of patients with cerebrovascular diseases particularly ischaemic strokes in Asia.

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