Review Article

Monitoring cerebral vasospasm: How much can we rely on transcranial Doppler

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Abstract

Cerebral vasospasm leading to delayed cerebral ischaemia is one of the major concerns following subarachnoid haemorrhage (SAH). Various modalities are present for evaluation and detection of cerebral vasospasm that occurs following SAH. They include transcranial Doppler (TCD), computed tomographic angiography (CTA), computed tomographic (CT) perfusion and digital subtraction angiography (DSA). The recent guidelines have advocated the use of TCD and have described it as a reasonable technique for monitoring the development of vasospasm. This review describes the functioning of TCD, the cerebral haemodynamic changes during vasospasm and TCD-based detection of vasospasm. The review shall highlight as to how the TCD derived values are relevant in the settings of neurocritical care. The data in the review have been consolidated based on our search of literature from year 1981 till 2016 using various data base.

Keywords: Cerebral vasospasm, subarachnoid haemorrhage, transcranial Doppler

Introduction

Cerebral vasospasm is one of the dreaded complications following subarachnoid haemorrhage (SAH). The progressive arterial narrowing may result in reversible delayed ischaemic deficits (DIDs), permanent neurological deficits and lastly in death of the patient. Transcranial Doppler (TCD) sonography is being used as a primary tool for the non-invasive diagnosis of cerebral vasospasm.[1] The AHA/ASA guidelines on the management of aneurysmal subarachnoid hemorrhage (2012) recommends the use of transcranial Doppler (TCD) as a reasonable technique for monitoring the development of cerebral vasospasm (Class II a, Level).[2]

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Methods

The literature was scanned using various search engines like the PubMed, Google Scholar and Medline for the articles published in the various international and national journals from 1981 till 2016. The articles were retrieved using keywords like transcranial Doppler, transcranial Doppler ultrasonography, cerebral vasospasm, role of transcranial Doppler in cerebral vasospasm, transcranial Doppler versus digital subtraction angiography (DSA). Manual search was carried out in the text books of anaesthesia, neuroanaesthesia, neurosurgery and radiology.

Principle

TCD works on the principle of Doppler effect, which states that when a sound wave of a particular frequency (incident wave) strikes a moving object, for example, an

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erythrocyte, the frequency of the reflected wave changes proportionally to the velocity of the reflector (V). This change in frequency of the reflected wave from that of the incident wave is called as the Doppler shift (ΔF). This can be represented by the following equation which forms the basis of calculation of cerebral blood flow velocity (CBFV) using TCD. It works on the principle that with arterial narrowing there is an increase in the blood flow velocity (BFV) within the vessel. BFV is calculated using the Doppler formula: $V = \Delta F \times C/2\ Fi \times \cos\theta$, where V = velocity of the moving target, ΔF = Doppler shift, C = frequency of sound in tissues, Fi = transducer frequency and Cos θ = cosine of angle of insonation of ultrasound waves [Figure 1]. The reflected waves received by the TCD probe generates electrical impulses which are then processed to calculate ΔF, V as well as in the production of a spectral waveform consisting of peak systolic velocity (PSV) and end-diastolic velocity (EDV).[3]

Technique

The TCD machine consists of a 2 MHz ultrasound probe. Depending on the duration of procedure, the TCD probe is either fixed in a headset or may be applied manually in the region of acoustic windows. Acoustic windows are regions of skull, either thin bone or foramina from where ultrasound waves can be transmitted to the cerebral circulation. They are four in number namely transtemporal, transorbital, suboccipital and submandibular windows [Figure 2].[4]

In order to identify the intracranial arteries the following factors are generally used [Table 1]:[4,5]

1. Acoustic window through which the vessel is insonated
2. Depth of sample volume
3. Transducer orientation during insonation
4. Direction of blood flow with respect to the transducer
5. Relationship of the vessel to the junction of middle cerebral artery (MCA), anterior cerebral artery (ACA) and the terminal portion of the internal carotid artery (ICA)
6. Response to dynamic manoeuvres (e.g., compression of the common carotid artery resulting in a temporary decrease in ipsilateral MCA velocity).

Physiologic Determinants of Blood Flow Velocity and Indices

The physiologic determinants of BFV when measured by TCD includes age, gender, viscosity, haematocrit, temperature, carbon dioxide, blood pressure, motor and mental activity.[6] Thus during the course of a TCD study, the measured differences in BFV should be interpreted in the context of these variables. BFVs decrease by 0.3 to 0.5%/year between 20 to 70 years of age.[7-9] These are higher in females as compared to males between 20 to 60 years of age. However no difference is observed after the age of 70 years between males and females.[7] Haematocrit and viscosity are inversely related to cerebral BFV. There is an increase in BFVs by ~20% with a decrease in haematocrit from 40 to 30%.[10,11] The BFV increases with increasing PCO_2.[12] BFV can be higher in patients with higher systemic blood pressures in spite of the presence of an intact autoregulatory system.[13] An inverse relationship has been found between temperature and BFV in a study.[14] Another study done in post-cardiac arrest patients undergoing hypothermic therapy, however, does not support a relationship between temperature and flow velocities.[15]

How Does Transcranial Doppler Differ from Conventional Ultrasound

Both the TCD and conventional ultrasonographic (USG) machines are used in the intensive care units for various studies on human body. The TCD machine is specifically designed to study the flow velocities of intracranial arteries. However, the USG machine can be used for structural imaging of the tissues as well as for study of the blood vessels, including the arteries and the veins. One basic

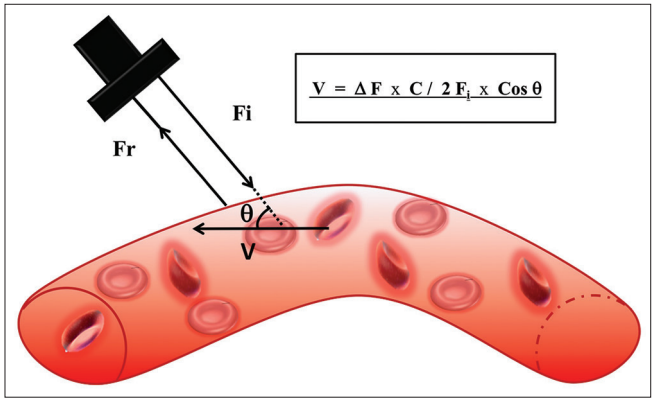

Figure 1: Principle of transcranial Doppler

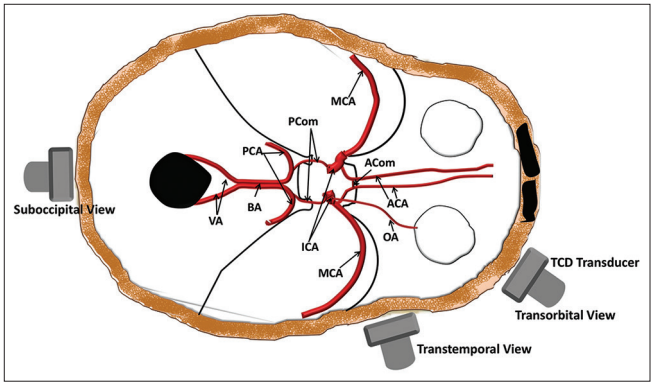

Figure 2: Acoustic windows for insonation of cerebral arteries

Table 1: Insonation characteristics of cerebral vessels using transcranial Doppler ultrasonography

Artery	Depth (mm)	Acoustic window	Flow direction	MFV (adults) (cm/s)	Transducer orientation
MCA	30-65	Transtemporal	Towards	55±12	En face
ACA	60-75	Transtemporal	Away	50±11	Anterior
PCA (Segment 1)	60-70	Transtemporal	Towards	39±10	Posterior
PCA (Segment 2)	60-70	Transtemporal	Away	40±10	Posterior
Ophthalmic artery	45-55	Transorbital	Towards	21±5	Medial
Basilar artery	80-120	Suboccipital	Away	41±10	Superior
Vertebral artery	60-75	Suboccipital	Away	38±10	Superior and oblique
Extracranial ICA	45-50	Retromandibular	Away	30±9	Superior and oblique

MCA=Middle cerebral artery; ACA=Anterior cerebral artery; PCA=Posterior cerebral artery; ICA=Internal carotid artery

difference is in the frequency of the probe used for the Doppler studies. For TCD the frequency of the USG waves used is 2 MHz while it is 4 MHz or more for the Doppler studies of extracranial vessels. Two major advancements since the inception of TCD have been in relation to duplex sonography and the power-motion mode Doppler (PMD). Duplex sonography refers to the use of TCD machine for study of flow velocities along with tissue imaging.[16] PMD on the other hand uses 33 overlapping sample gates that provide information about the complete length of an artery and various bifurcations on a single screen.[16] This system can simultaneously display flow intensity and direction over 6 cm or more of intracranial space. When combined with a single-channel spectral analysis, a particular depth can be selected on the PMD screen to obtain the desired Doppler spectrum.[16] The TCD machine also calculates the pulsatility index (PI) with the help of PSV, EDV as well as the mean flow velocity (MFV). PI has been found to correlate well with intracranial pressure (ICP).[17]

Cerebral Vasospasm: Pathophysiology and Diagnosis

Cerebral vasospasm is defined as a delayed but reversible narrowing of the cerebral blood vessels most commonly involving the proximal arteries that form the Circle of Willis. Clinical vasospasm is narrowing of cerebral artery causing cerebral ischaemia with symptoms and signs such as hemiparesis, apraxia, aphasia, neglect or hemianopia or a decrease of Glasgow Coma Scale by at least two points while angiographic vasospasm is narrowing of arteries as seen on vascular imaging.[18,19] Using DSA and with respect to two-dimensional diameter, vasospasm has been classified as severe if the reduction in vessel calibre is >50%, moderate if it is between 25–50% and mild if the reduction is <25%.[20]

The primary effect of a decrease in the diameter of vessel lumen as seen in cerebral vasospasm is an increase in blood flow resistance. The changes occurring with increase in the degree of vessel spasm can be described as follows:

1. Mild vasospasm: It does not create sufficient change in vessel resistance to influence flow
2. Moderate vasospasm: With this degree of narrowing, the cerebral autoregulation has been seen to compensate for pressure losses in the spastic segment if the arterial blood pressure (ABP) is maintained above the lower limit of autoregulation. Thus in a constant flow regime like this, the flow velocity increases inversely to the change in lumen area. Hence there will be a good correlation between the TCD measurements and the degree of angiographic spasm in these patients[21]
3. Severe vasospasm: When further narrowing occurs, the effects of the vasospasm start to influence flow and a complex situation arises which is similar to the concept of critical stenosis.[22]

This can be explained by the Spencer curves that depict the relationship between the arterial lumen diameter, blood flow volume as well as the flow velocities.[23] The curves have been divided into three zones. Zone 1 (the forward side/upslope) represents the part of Spencer curves where despite the decrease in the lumen diameter, the flow volume remains relatively constant. However there is an increase in flow velocity which is inversely proportional to diameter. In Zone 2 (the plateau phase), further reduction in the lumen diameter results in decrease in blood flow but the velocity remains relatively independent of diameter. Clinical vasospasm and neurological deficits may occur in Zone 2. The Zone 3 (the backside/downslope of the curve) is the stage where the further reduction in diameter results in lower velocities and the flow is reduced to critical values. Clinical vasospasm and neurological deficits are certainly present in Zone 3.[23] This hypothesis which explains the relationship between flow, velocity and diameter becomes increasingly complex as the degree of vasospasm progresses from moderate to severe. Thus flow velocity on TCD alone is a poor criterion for the degree of perfusion. TCD velocities need to be combined with other data to give meaningful assessment of the haemodynamic state of the cerebral circulation. Not understanding the factors involved in the haemodynamics of cerebral vasospasm may

lead to blaming TCD as such for not reliably predicting the incidence of clinical vasospasm.[24]

Advantage of Transcranial Doppler over Other Techniques

TCD is the surveillance tool of choice in patients with SAH for diagnosing vasospasm during the symptomatic phase as well as in the phase when there is no clinical suspicion (pre-symptomatic) or when the clinical suspicion is unreliable as in patients with poor neurological status. Vasospasm is dynamic phenomenon which can improve or worsen over time, a bedside dynamic surveillance tool like TCD would thus be the most appropriate for monitoring as compared to DSA, CT angiography or CT perfusion which gives us only snapshot information about the disease process. Moreover they cannot be used for daily monitoring as they are invasive, require administration of contrast material with nephrotoxic potential as well as transportation of a critically ill patient to the CT or angiography suite[25] [Table 2].

Grading of Severity of Vasospasm Using Transcranial Doppler

Vasospasm can be divided into mild, moderate and severe based on parameters like mean flow velocity, Lindegaard ratio (LR) and Sviri ratio that are derived using TCD. The LR is obtained by dividing the mean flow velocities of the MCA by those of ipsilateral extracranial ICA.[31] The Sviri ratio is obtained by dividing the mean flow velocities of basilar artery (BA) by those of extracranial vertebral artery (VA)[32] [Table 3].

Importance and Reliability of Transcranial Doppler for Indicating Vasospasm

Middle cerebral artery

Lysakowski *et al.* conducted a meta-analysis using data from five trials and 317 tests involving MCA to evaluate the accuracy of TCD as compared to angiography to ascertain the use of TCD as a screening tool for vasospasm.[27] The study observed a sensitivity of 67%, specificity of 99%, positive predictive value (PPV) of 97%, negative predictive value (NPV) of 78%, likelihood ratio (positive) of 17 and likelihood ratio (negative) of 0.4 for indicating vasospasm with the use of TCD. This implies that when there was no MCA spasm on angiography, TCD was not likely to refute it owing to its high specificity. Whereas if MCA spasm was seen on angiography, then the TCD was of no use to confirm it due to its low sensitivity. A high PPV meant that in most patients in whom TCD predicted a spasm did have an angiographic spasm, and a positive likelihood ratio of 17 meant that TCD was 17 times more likely to predict the presence of vasospasm in a patient who had vasospasm than in patients who did not have one. They also concluded that in patients in whom TCD did not indicate the presence of MCA spasm, one could not be sure that there is none (low NPV and low negative likelihood ratio).[27] Based on the observations of the above study it appears that TCD has moderate ability to indicate the presence or absence of cerebral vasospasm. However, in the patients who have a suspicion of vasospasm, the predictibility is high.

Low or very high middle cerebral artery flow velocities versus intermediate velocities

Vora *et al.* in 1999 conducted a landmark study in patients of aneurysmal subarachnoid haemorrhage to determine

Table 2: Comparison between transcranial Doppler and digital substraction angiography/computed tomographic angiography/computed tomographic perfusion

Transcranial Doppler	DSA/CTA/CT perfusion
Bedside	Cannot be done bedside
Non-invasive	Invasive
Dynamic monitor	Not a dynamic monitor
Does not require any contrast medium	Requires administration of contrast medium
Can be repeated multiple times in a day	Cannot be repeated so frequently
No radiation exposure	Radiation exposure present
Indirect method of calibre assessment	Direct methods of calibre assessment [26]
TCD cannot be used to calculate the transit time as well as the interval between the various phases of the blood circulation	DSA can be used to calculate the transit time as well as the interval between the various phases of the blood circulation [20]
Sensitivity and specificity for detecting cerebral vasospasm is dependent on the vessel insonated MCA: Sensitivity of 67% and specificity of 99%[27] ACA: Sensitivity of 42% and specificity of 76% [27] PCA: Sensitivity of 48% and specificity of 69% [28] Basilar artery: Sensitivity of 76.9% and specificity of 79% [29] Vertebral artery: Sensitivity of 43.8% and specificity of 88% [29]	DSA has a sensitivity and specificity for detection of cerebral vasospasm of nearly 100% in all vessels by several studies [20] CTA has a sensitivity of 80% and specificity of 93% [30]

DSA=Digital substraction angiography; CTA=Computed tomographic angiography; MCA=Middle cerebral artery; ACA=Anterior cerebral artery; PCA=Posterior cerebral artery; TCD=Transcranial Doppler; CT=Computed tomographic

the correlation between angiographic vasospasm and TCD velocities. In their study, 101 patients were reviewed retrospectively and MCA mean blood flow velocities (MBFVs) were correlated with angiographic vasospasm. However, despite of existence of a significant correlation between the MBFV and degree of angiographic vasospasm, the bedside application of TCD velocities was limited. The highest velocities of 43% of patients fell in the <120 or ≥200 cm/s range while those of 57% of patients fell in the intermediate range i.e., between 120 to 199 cm/s.[33] [Table 4].

Based on the previous studies that had utilized TCD velocities, it had been observed that a PPV of at least 80% and a NPV of at least 90% were desired before undertaking more invasive measures or for refuting the need for further investigation of vasospasm, respectively. The study categorized the velocities into low, intermediate/high and very high velocities. In the study the PPV of velocities ≥200 cm/s representing moderate-to-severe angiographic vasospasm was 87% while that for velocities <200 was around 50%. Similarly the NPV for velocities <120 cm/s was 94% thus eliminating the need to further investigate for vasospasm. The likelihood ratios for both low and very high velocities were also quite influential [Table 4]. However for TCD values >120 cm/s, the NPVs were similar (~75%) to velocities >200 cm/s and hence were not discriminating for the absence of significant vasospasm. They thus concluded that only low velocities (<120 cm/s) could reliably predict the absence or very high MCA flow velocities (>200 cm/s)

Table 3: Grading of severity of vasospasm using transcranial Doppler

Degree of middle cerebral artery vasospasm[32]	Mean flow velocity (cm/s)	Lindegaard ratio
Mild	120-149	3-6
Moderate	150-199	3-6
Severe	>200	>6
Degree of basilar artery vasospasm[33]	**Mean flow velocity (cm/s)**	**Sviri ratio**
Vasospasm	>70	>2
Moderate or severe vasospasm	>85	>2.5
Severe vasospasm	>85	>3

Table 4: The prediction of cerebral vasospasm based on the various range of middle cerebral artery velocities

TCD velocity	Sensitivity	Specificity	LR+	LR−	PPV	NPV
<120	0.88	0.72	3.14	0.17*	0.55	0.94*
120-159	0.40	0.80	2.00	0.75	0.44	0.77
160-199	0.31	0.93	3.98	0.85	0.56	0.75
≥200	0.27	0.98	16.39*	0.74	0.87*	0.77

**Significant values. LR+=Positive likelihood ratio; LR−=Negative likelihood ratio; PPV=Positive predictive value; NPV=Negative predictive value*

the presence of clinically significant angiographic vasospasm. On the other hand the intermediate velocities (120–199 cm/s) were found to be neither reliable nor supportive for the determination of significant angiographic vasospasm.[33] This can be explained with the help of the Spencer curves which indicate that as the arterial lumen diameter reduces and approaches towards 1 mm or less, the TCD velocities reduces from the high-to-intermediate range.[21,23]

Role of Lindegaard ratio

The LR measured using TCD is the ratio between the MCA MFV/extracranial ICA MFV. It plays a very important role in differentiating between hyperaemia and vasospasm. In hyperaemia the MBFVs of both the MCA and ICA increase resulting in a LR <3. On the other hand in patients with vasospasm the increase in MCA mean BFV is much more than that of ICA resulting in a LR >6. LR between 3 and 6 is a sign of mild VSP and values >6 is an indication of severe VSP.[34]

Anterior cerebral artery

Lysakowski *et al.* in their meta-analysis utilized data from three trials and 171 tests involving ACA to evaluate the accuracy of TCD as compared to angiography to ascertain the usefulness of TCD as a screening tool for diagnosis of ACA vasospasm. The sensitivity was found to be 42% (11–72%), specificity 76% (53–100%), PPV 56% (27–84%) and NPV 69% (43–95%). Since both the sensitivity and specificity were low thus when compared with angiography, the diagnostic accuracy of TCD for diagnosis of ACA vasospasm is low.[27]

Posterior cerebral artery

Wozniak *et al.* in their study examined 84 posterior cerebral artery (PCA) in 47 patients with SAH during the period at risk for vasospasm. The patients had TCD performed within 24 h of cerebral angiography. They found that for PCA vasospasm the sensitivity was 48%, specificity was 69%, PPV was 37%, NPV was 78% likelihood ratio (positive) was 1.5 and likelihood ratio (negative) was 0.8. It was concluded that the sensitivity of TCD to detect PCA vasospasm is limited.[28]

Vertebral and basilar artery

There are a few studies which have focussed on vasospasm related to posterior circulation. TCD has been compared with cerebral angiography to determine the sensitivity and specificity for vertebrobasilar vasospasm.[29] They found that the sensitivity for basilar cerebral artery vasospasm was 76.9%, specificity was 79%, PPV was 63%, NPV was 88%, likelihood ratio (positive) was 3.7 and likelihood ratio (negative) was 0.3. For vertebral cerebral artery vasospasm, the sensitivity was 43.8%, specificity was 88%, PPV was 54%, NPV

Table 5: Applications of transcranial Doppler following subarachnoid hemorrhage

Days following SAH	Application of transcranial Doppler
Days 2-5	Detection of the development of vasospasm before it is clinically apparent Information useful for neurocritical care personnel for stepping up the haemodynamic management
Days 5-12	Detection of progression of vasospasm Information useful for planning of interventions (angioplasty, intraarterial drug therapy)
Day 12 till the end of ICU stay	Vasospasm resolution after treatment or intervention Sustainability of patency of vessels Late or rebound vasospasm (onset at the end of second or in the midst of third week following SAH)

SAH=Subarachnoid haemorrhage; ICU=Intensive care unit

was 82%, likelihood ratio (positive) was 3.5 and likelihood ratio (negative) was 0.6. They concluded that TCD has good specificity for the detection of VA vasospasm and good sensitivity and specificity for the detection of BA vasospasm.[29] The MFV must be >115 cm/s before ischaemia can reliably be predicted using TCD.[35,36] However, more studies are required to support the role of TCD for detection of posterior circulation vasospasm.

Temporal Relationship between Cerebral Blood Velocity changes and Vasospasm as Measured by Transcranial Doppler

In a study conducted by Harders and Gilsbach CBFV was measured using the TCD at least every third day in patients with post-aneurysmal SAH. They found that in the first 72 h following SAH, the CBFV's were normal and there were no signs of vasospasm on angiography. The BFVs increased between Days 3 and 10, highest BFV values were recorded between Days 11 and 20 and normalization occurred within the next 4 weeks.[37] Another study identified rapidly increasing TCD velocity (>50 cm/s/24 h) to be the most useful predictive parameter for development of vasospasm. They also concluded that TCD measurements, when frequently performed early after SAH, helped in identification of patients who were at risk of development of delayed neurological deficits and suggested that even in patients where a rapid rise in TCD velocity had occurred without onset of subsequent neurological deficit, a zone of low CBF might be present though insufficient to cause infarction.[38]

An update published on monitoring of the temporal course of cerebral vasospasm using TCD suggested that daily examinations especially from Day 4 to 10 after SAH showing rapid increases in CBFV values, could identify patients at a higher risk for development of delayed ischaemic neurologic deficits.[39]

Thus based on various studies the Practice Standards for Transcranial Doppler (TCD) Ultrasound were published in 2012 and the expected applications of TCD testing for patients with SAH were laid out as in Table 5.[40,41] In our own experience, TCD has been a useful tool for the diagnosis and management of vasospasm.[42]

Summary

Based on the available data we would like to conclude that use of TCD appears to be reasonable for monitoring of vasospasm in MCA. Low or very high MCA flow velocities (<120 or >200 cm/s) reliably predict the absence or presence of clinically significant vasospasm. Intermediate velocities between 120 and 199 cm/s are unreliable and inconclusive for the determination of significant angiographic vasospasm. Routine daily measurement of TCD velocities in SAH patients should be advocated till the expected period of vasospasm. Diagnostic accuracy of TCD for detection of ACA and PCA vasospasm is limited. The use of TCD for detection of posterior circulation vasospasm that comprises BA and VA vasospasm appears promising. However, further data are required to recommend the routine use of TCD for posterior circulation stroke.

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Conflicts of interest
There are no conflicts of interest.

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