Real-Time Hemodynamic Assessment of Downstream Effects of Intracranial Stenoses in Patients with Orthostatic Hypoperfusion Syndrome

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Key Words

Intracranial arterial stenosis · Arterial flow velocity · Hypoperfusion

Abstract

Background: Arterial flow velocity changes on transcranial Doppler can reflect changes in cerebral flow during position-induced ischemia if obtained during short-term monitoring of positional changes. **Subjects and Methods:** Our multicenter group monitored symptomatic and asymptomatic arteries in patients with recurrent neurological deficits during positional changes and documented intracranial arterial stenosis. Bilateral posterior cerebral and middle cerebral arteries were monitored dependent on clinical symptom localization. The symptomatic artery was monitored distal to the intracranial stenosis, and mean flow velocities (MFV) were recorded at different body positions. The symptomatic artery relative MFV ratio was defined as the ratio of symptomatic artery MFV in the asymptomatic position – MFV in the symptomatic position/MFV in the asymptomatic

position. **Results:** Sixteen patients underwent transcranial Doppler monitoring: mean age 62 ± 19 years, 11 (69%) men, 6 (40%) with transient ischemic attacks. Ten patients (63%) had posterior and 6 anterior circulation symptoms. Patients developed neurological symptoms while standing up (63%) and/or sitting (44%), walking (13%) or during neck extension (6%). Symptomatic artery MFV dropped by $\geq 25\%$ from the resting to the symptomatic position in all patients except for one. The mean symptomatic artery MFV relative ratio was higher compared with the mean asymptomatic artery MFV relative ratio: 0.5 ± 0.28 versus -0.02 ± 0.1 ($p = 0.001$, Wilcoxon test). The symptomatic artery relative ratio of >0.25 had a 94% sensitivity and 100% specificity for predicting neurological symptom development during testing ($\kappa = 0.9$, $p < 0.001$). **Conclusions:** A significant reduction in intracranial flow velocity distal to an intracranial stenosis can identify patients whose symptoms can worsen with positional changes. These patients may prove a target for interventional revascularization techniques.

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Introduction

Intracranial atherosclerotic stenosis is the culprit behind at least 8% of all ischemic stroke subtypes [1, 2]. Subsequent infarctions secondary to intracranial atherosclerotic stenosis result from either flow failure known as hypoperfusion syndrome or artery-to-artery embolism [3].

The hypoperfusion cerebral transient ischemic attack (TIA) is uncommon and rarely reported in the literature. These TIAs typically occur with large artery hemodynamic stenosis in the internal carotid artery or in vertebralbasilar arteries resulting in a distal low-perfusion state and exhausted autoregulation with compromised vasomotor reserve [4–8].

Several conventional techniques have been used to evaluate the presence of stenotic disease in the anterior and posterior circulation like cerebral angiography, carotid ultrasound, CT and magnetic resonance angiography [9, 10].

In contrast to these conventional techniques, transcranial Doppler (TCD) may provide a dynamic real-time tool for quantitative measurements of arterial flow velocity changes that reflect changes in cerebral blood flow (CBF) during orthostatic or position-induced ischemia if obtained at a constant angle of insonation and during short-term monitoring of positional changes [11].

The objective of our study is to derive TCD monitoring criteria for hypoperfusion TIA syndrome in a series of patients with presumptive clinical hypoperfusion TIA caused by intracranial critical arterial stenosis or mechanical vascular compression with positional changes.

Subjects and Methods

We performed a retrospective collection of case series from multiple tertiary care university centers in North America, Europe and Asia of patients with documented intracranial severe or critical arterial stenosis or with mechanical vascular compression and recurrent neurological deficits during body or head positional changes. Verbal consent was taken from patients for potential research publication.

Cases of acute or subacute hypoperfusion TIA or stroke were defined as acute focal neurological symptoms that were induced by positional changing and caused by intracranial hemodynamic arterial stenosis or mechanical extracranial vascular compression confirmed on cerebral angiography or other noninvasive vascular imaging modalities (computed tomographic angiography or magnetic resonance angiography). All patients had neurological symptoms more than once, induced by positional changes (standing up, sitting, walking or during neck extension). Patients with a single neurological event were not included in our study population since the mechanism of their TIA was not clear.

Diagnostic TCD was performed at the bedside to detect an intracranial arterial stenosis or occlusion, and continuous TCD monitoring of the presumptively symptomatic artery was performed. In the presence of posterior circulation symptoms, bilateral posterior cerebral arteries (PCAs) through the temporal window or the basilar artery through the foramen magnum window were monitored. In the presence of hemispheric symptoms, the affected middle cerebral artery (MCA) was monitored distal to the intracranial stenosis/occlusion site dependent on the localization of clinical symptoms. In the presence of an anterior circulation stroke, the unaffected MCA was used for comparison, whereas in patients with posterior circulation symptoms, either the MCA or internal carotid artery was used for comparison. The TCD monitoring of affected and unaffected arteries was performed either simultaneously using a standard bilateral head frame or in sequence with only 1 transducer at a time positioned at a fixed angle. Finally, a 1-hour TCD emboli monitoring of the affected artery distal to the intracranial stenosis was performed to rule out concurrent microembolic activity.

The mean flow velocity (MFV) and pulsatility index (PI) of the affected and unaffected arteries at baseline in the resting position (supine) and in 5–10 min of being in the symptomatic position (sitting, standing or neck extension) were recorded and analyzed. An equilibration period of 5–10 min was instituted between measurements to ensure stability of both heart rate and arterial pressure to avoid a confounding influence on MFV.

The symptomatic artery relative MFV ratio was defined as follows: the ratio of affected artery MFV in the asymptomatic position – MFV in the symptomatic position/MFV in the asymptomatic position.

The unaffected artery relative MFV ratio was defined as follows: the ratio of unaffected (control) artery MFV in the asymptomatic position – MFV in the symptomatic position/MFV in the asymptomatic position.

Statistical analysis was performed using the χ^2 test, Fisher's exact test, the unpaired t test, the paired t test, the Mann-Whitney U test and the Wilcoxon signed-rank test as indicated.

Results

Sixteen patients underwent TCD monitoring for possible acute or subacute positional TIA or stroke. The mean age was 62 ± 19 years, and 11 (69%) were men. Six patients had TIA (40%) and the rest had both TIA and stroke (60%). Ten patients (63%) had posterior and 6 (37%) had anterior circulation symptoms. Patients developed neurological symptoms while standing up (37.5%) and/or sitting (44%), walking (12.5%) or during neck extension (6%) (table 1). Only 3 patients had angioplasty (2 with basilar artery stenosis and 1 with left MCA critical stenosis), 1 was treated with coumadin, 5 were treated with hydration, bed rest and antiplatelet agents (acetylsalicylic acid, plavix, aggrenox or acetylsalicylic acid and plavix) and the rest were treated with only antiplatelet agents.

Table 1. Demographic data

Patient	Age years	Sex	Symptoms	Symptomatic position	Treatment at the time of TCD	Vascular imaging (DSA, MRA or CTA)
1	56	M	Broca's aphasia, right-arm weakness	standing	heparin+ASA	left terminal ICA MCA critical stenosis
2	50	M	vertigo, ataxia	neck extension	ASA	normal ¹
3	74	F	Broca's aphasia, right-arm weakness	standing	ASA+plavix	left MCA severe stenosis
4	60	M	Broca's aphasia, right-arm weakness	sanding	ASA	left ICA occlusion, right terminal ICA severe stenosis
5	80	F	arm weakness, dysarthria, vertigo	standing	none	severe right VA and proximal BA stenosis
6	68	M	Broca's aphasia	sitting+VM	none	left MCA severe stenosis
7	74	M	Broca's aphasia	sitting	ASA	left MCA severe stenosis
8	18	M	right vision field cut, double vision, vertigo	standing	none	normal ²
9	79	M	arm and leg weakness, dysarthria, vertigo	sitting	ASA+plavix	severe BA stenosis
10	77	M	arm and leg weakness, dysarthria, vertigo	standing	ASA+plavix	severe BA stenosis
11	76	F	dysarthria, left-arm weakness	sitting	plavix	right MCA severe stenosis
12	64	M	dysarthria, dysphagia, ataxia	walking	aggrenox+ASA	left VA occlusion and right VA moderate stenosis
13	22	F	dysarthria, double vision, vision field cut	sitting	none	BA occlusion
14	64	M	double vision, weakness	standing	ASA	right VA severe stenosis
15	56	M	vision field cut, face and arm weakness	walking	plavix	BA occlusion
16	71	F	double vision, vertigo	sitting	ASA	BA severe stenosis

ASA = Acetylsalicylic acid; ICA = intracranial atherosclerotic; VA = vertebral artery; BA = basilar artery; VM = Valsalva maneuver.

¹ Patient No. 2 had large cervical anterior and posterior osteophytes that were causing mechanical compression of the left vertebral artery in the neck with the extension position. In addition, his right vertebral artery was hypoplastic on CT angiography.

² Patient No. 8 had meningitis and symptoms suggestive of spontaneous intracranial hypotension, but he developed focal symptoms referable to the left PCA territory while in hospital. Symptoms were reproducible with postural changes that likely induced a dominant vertebral artery obstruction. He received bed rest, hydration and a course of antibiotics, and symptoms could no longer be induced in 1 week.

Table 2. TCD flow findings

Patient	Affected artery	MFV1	MFV2	Affected artery relative ratio	Unaffected artery	MFV1	MFV2	Unaffected artery relative ratio
1	left MCA	110	78	0.29	right MCA	46	40	0.13
2	bilateral PCA	19	0	1.00	left MCA	48	48	0.00
3	left MCA	68	42	0.38	right MCA	74	70	0.05
4	left MCA	36	22	0.39	right MCA	66	71	-0.08
5	BA	42	19	0.55				
6	left MCA	56	38	0.32	right MCA	62	78	-0.26
7	left MCA	36	20	0.44	right MCA	56	56	0.00
8	left PCA	46	30	0.35	right PCA	48	50	-0.04
9	BA	25	0	1.00				
10	BA	150	0	1.00				
11	right MCA	46	38	0.17	left MCA	66	68	-0.03
12	right PCA	17	0	1.00	right MCA	67	67	0.00
13	BA	40	15	0.63	right MCA	46	39	0.15
14	right VA	44	27	0.39	right MCA	47	49	-0.04
15	BA	36	21	0.42	right MCA	53	55	-0.04
16	BA	47	23	0.51	right MCA	61	69	-0.13

MFV1 = Mean flow velocity in the asymptomatic position; MFV2 = mean flow velocity in the symptomatic position; affected artery relative ratio = ratio of affected artery MFV in the asymptomatic position – MFV in the symptomatic position/MFV in the asymptomatic position; unaffected artery relative ratio = ratio of unaffected (control) artery MFV in the asymptomatic position – MFV in the symptomatic position/MFV in the asymptomatic position; BA = basilar artery; VA = vertebral artery.

Cerebral angiography:
left supraclinoid ICA
critical stenosis

Cerebral angiography: left VA
occlusion and right VA severe
stenosis

Fig. 1. An example of 3 patients with anterior and posterior circulation hypoperfusion TIA syndrome. **a** Anterior circulation hypoperfusion TIA: a 55-year-old man with orthostatic episodes of expressive aphasia and right-arm weakness. Digital subtraction angiography showed critical left supraclinoid internal carotid artery (ICA) stenosis. The affected MCA MFV dropped from 110 cm/s in the lying down position to 78 cm/s in the standing position. The affected artery MCA MFV relative ratio was 0.29 (110–78/110) and the unaffected MCA relative MFV ratio was 0.13 (46–40/40). **b** Posterior circulation hypoperfusion TIA: a 64-year-old man with orthostatic episodes of dysarthria, dysphasia and ataxia. Cerebral angiography revealed left vertebral artery (VA) occlusion and right vertebral artery stenosis. The affected PCA MFV

dropped from 17 cm/s in the lying flat position to 0 cm/s in the sitting-up position. The affected artery PCA relative MFV ratio was 1 (17–0/17), and the unaffected (control) right MCA MFV relative ratio was 0 (67–67/67). **c** Posterior circulation hypoperfusion TIA: a 50-year-old man with transient episodes of ataxia and vertigo induced by neck extension. The patient had large cervical anterior and posterior osteophytes that were causing mechanical compression of the left vertebral artery in the neck. In addition, his right vertebral artery was hypoplastic on CT angiography. His TCD monitoring of bilateral PCAs revealed a drop in the MFV from 19 to 0 cm/s with neck extension. The affected artery MFV relative ratio was 1 (19–0/19) and the unaffected (control) left MCA MFV relative ratio was 0 (48–48/48).

TCD flow findings are summarized in table 2. The mean affected artery MFV in the resting position was 52 ± 34 cm/s. It did drop to 24.8 ± 20 cm/s in the symptomatic position ($p < 0.001$, Wilcoxon test). The mean unaffected artery MFV was 57 ± 10 and 59 ± 13 cm/s in the resting and symptomatic positions, respectively ($p = 0.37$). Figure 1 shows 3 cases with MFV changes when symptoms were induced with different body positions.

The affected artery MFV dropped by $\geq 25\%$ from resting to the symptomatic position in all patients except for one (drop by 17%). The mean MFV relative ratio of the affected arteries was higher compared with the mean MFV relative ratio of the unaffected arteries: 0.5 ± 0.28 versus -0.02 ± 0.1 ($p = 0.001$, Wilcoxon test). The affected artery relative MFV ratio of >0.25 had a 94% sensitivity, 100% specificity, 100% positive predictive value and 93% negative predictive value for predicting neurological symptom development during testing (κ test for agreement 0.9; $p < 0.001$).

The mean affected artery PI in the resting and symptomatic positions was 0.8 ± 0.25 and 0.88 ± 0.48 , respectively ($p = 0.29$, Wilcoxon test). The mean unaffected artery PI in the resting and symptomatic positions was 0.88 ± 0.08 and 0.89 ± 0.12 ($p = 0.68$, Wilcoxon test). In addition, the mean drop in PI in the symptomatic artery and the unaffected artery was 0.15 ± 0.49 and 0.008 ± 0.12 , respectively ($p = 0.15$). No microembolic activity was detected during the TCD emboli monitoring.

Discussion

Our study showed that the affected artery relative MFV ratio in the symptomatic position corresponds to the development of clinical symptoms and could be helpful in identifying patients with hypoperfusion TIA syndrome. The orthostasis-induced flow changes and clinical symptoms provide a study population suitable to test

these findings prospectively. If further independent studies validate our newly developed criteria, the dynamic TCD technique may enhance the recognition of patients with imminent hypoperfusion symptoms and triage them to a more definitive therapy. The management of hypoperfusion TIA is still controversial – between an interventional stenting treatment of the stenotic artery and just blood pressure management. Future trials using TCD as an adjunctive diagnostic tool are warranted.

The exact mechanism of hypoperfusion TIA is unknown. The most accepted hypothesis is that transient cerebral ischemia results from a low-perfusion hemodynamic state due to severe extracranial and/or intracranial carotid or MCA or vertebrobasilar arterial disease [12–14]. In general orthostatic position changes, the long-standing position, neck extension or hypotension induced by antihypertensive medication have been reported to trigger hypoperfusion TIA, thus suggesting the low-perfusion hemodynamic mechanism [15, 16]. Any temporal reduction in CBF can result in a cerebral ischemia which could manifest in several ways like limb-shaking TIA or brief stereotyped orthostatic focal neurological symptoms [17, 18].

On a cellular level, the chronic hypoperfusion state produces lactic acidosis that in turn leads to arterial vasodilatation in order to maintain CBF in the hypoperfusion tissue. Note that the low PI values documented at rest are due to reducing inflow because of the intracranial arterial stenosis, and the lack of response in flow pulsatility despite a significant velocity reduction may be attributed to lower impedance of collateral vessels in the symptomatic position [19]. Further studies are needed to better understand this phenomenon where TCD and perfusion brain MRI can be performed in sequence. Finally, the lack of PI changes in the unaffected vessels parallels no change in flow velocities that eliminated the need for additional vasodilation as perfusion conditions were largely unchanged in the patent vessels.

Several neuroimaging modalities have been used to evaluate CBF of the brain in patients with hypoperfusion TIAs. Xenon-133 inhalation, xenon-enhanced CT scanning, single photon emission computed tomography scan and positron emission tomography with fluorodeoxyglucose have been used to determine regional CBF [7, 20]. TCD is a noninvasive and inexpensive monitoring tool that can be performed at the bedside to assess the hemodynamic status of cerebral arteries in different body positions as we demonstrated in our study. It can become a critical part in confirming the etiology of hypoperfusion TIA syndrome by suggesting a drop in blood flow rather

than being an embolic phenomenon in the presence of critical arterial stenosis. In addition, there is a potential role for TCD monitoring in selecting further treatment and follow-up. This issue has not been addressed in the present study and we are planning to investigate this prospectively.

One of the main limitation of TCD is that it measures blood flow velocities and not the actual cerebral perfusion flow in the brain tissues. However, the intracranial flow velocity can reflect CBF and the velocity changes can be proportional to changes in CBF tissue as long as the following factors are taken into consideration during the TCD monitoring: the angle of insonation remains constant, the perfusion territory remains the same, and the effect of only 1 stimulus is observed [21]. In our study, we tried to account for these factors in all cases during the TCD monitoring. Another limitation of this study is related to the fact that TCD is still operator dependent and requires specialized training for application in the stroke setting. This was addressed by ensuring that all sonographers were trained and certified in TCD skills pertinent to the stroke setting. In addition, the head frame may not be deployed in all cases of posterior symptoms, so the hand-held MFV measurements could be suboptimal. Finally, we could not find a correlation between TCD parameters and blood pressure measurements in our study patients. In addition, different types of collateral blood flow on cerebral angiography were not provided since our study was a retrospective one, and this correlation was not put in our a prior hypothesis.

In conclusion, dynamic TCD monitoring may be helpful in identifying TIAs or strokes due to hypoperfusion in patients with steno-occlusive intracranial arterial disease. Further studies are needed to validate our TCD findings in a heterogeneous group of patients with symptomatic and asymptomatic intracranial arterial stenosis.

Disclosure Statement

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