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

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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 ≥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: 0.58 ± 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 (κ = 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.
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 vertebrobasilar 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 χ2 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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Symptomatic position</th>
<th>Treatment at the time of TCD</th>
<th>Vascular imaging (DSA, MRA or CTA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>M</td>
<td>Broca’s aphasia, right-arm weakness</td>
<td>standing</td>
<td>heparin+ASA</td>
<td>left terminal ICA MCA critical stenosis</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>M</td>
<td>vertigo, ataxia</td>
<td>neck extension</td>
<td>ASA</td>
<td>normal¹</td>
</tr>
<tr>
<td>3</td>
<td>74</td>
<td>F</td>
<td>Broca’s aphasia, right-arm weakness</td>
<td>standing</td>
<td>ASA+plavix</td>
<td>left MCA severe stenosis</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>M</td>
<td>Broca’s aphasia, right-arm weakness</td>
<td>sanding</td>
<td>ASA</td>
<td>left ICA occlusion, right terminal ICA severe stenosis</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>F</td>
<td>arm weakness, dysarthria, vertigo</td>
<td>standing</td>
<td>none</td>
<td>severe right VA and proximal BA stenosis</td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>M</td>
<td>Broca’s aphasia</td>
<td>sitting+VM</td>
<td>none</td>
<td>left MCA severe stenosis</td>
</tr>
<tr>
<td>7</td>
<td>74</td>
<td>M</td>
<td>Broca’s aphasia</td>
<td>sitting</td>
<td>ASA</td>
<td>left MCA severe stenosis</td>
</tr>
<tr>
<td>8</td>
<td>18</td>
<td>M</td>
<td>right vision field cut, double vision, vertigo</td>
<td>standing</td>
<td>none</td>
<td>normal²</td>
</tr>
<tr>
<td>9</td>
<td>79</td>
<td>M</td>
<td>arm and leg weakness, dysarthria, vertigo</td>
<td>sitting</td>
<td>ASA+plavix</td>
<td>severe BA stenosis</td>
</tr>
<tr>
<td>10</td>
<td>77</td>
<td>M</td>
<td>arm and leg weakness, dysarthria, vertigo</td>
<td>standing</td>
<td>ASA+plavix</td>
<td>severe BA stenosis</td>
</tr>
<tr>
<td>11</td>
<td>76</td>
<td>F</td>
<td>dysarthria, left-arm weakness</td>
<td>sitting</td>
<td>plavix</td>
<td>right MCA severe stenosis</td>
</tr>
<tr>
<td>12</td>
<td>64</td>
<td>F</td>
<td>dysarthria, dysphagia, ataxia</td>
<td>walking</td>
<td>aggrenox+ASA</td>
<td>left VA occlusion and right VA moderate stenosis</td>
</tr>
<tr>
<td>13</td>
<td>22</td>
<td>F</td>
<td>dysarthria, double vision, vision field cut</td>
<td>sitting</td>
<td>none</td>
<td>BA occlusion</td>
</tr>
<tr>
<td>14</td>
<td>64</td>
<td>M</td>
<td>double vision, weakness</td>
<td>standing</td>
<td>ASA</td>
<td>right VA severe stenosis</td>
</tr>
<tr>
<td>15</td>
<td>56</td>
<td>M</td>
<td>vision field cut, face and arm weakness</td>
<td>walking</td>
<td>plavix</td>
<td>BA occlusion</td>
</tr>
<tr>
<td>16</td>
<td>71</td>
<td>F</td>
<td>double vision, vertigo</td>
<td>sitting</td>
<td>ASA</td>
<td>BA severe stenosis</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Affected artery</th>
<th>MFV1</th>
<th>MFV2</th>
<th>Affected artery relative ratio</th>
<th>Unaffected artery</th>
<th>MFV1</th>
<th>MFV2</th>
<th>Unaffected artery relative ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>left MCA</td>
<td>110</td>
<td>78</td>
<td>0.29</td>
<td>right MCA</td>
<td>46</td>
<td>40</td>
<td>0.13</td>
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<tr>
<td>2</td>
<td>bilateral PCA</td>
<td>19</td>
<td>0</td>
<td>1.00</td>
<td>left MCA</td>
<td>48</td>
<td>48</td>
<td>0.00</td>
</tr>
<tr>
<td>3</td>
<td>left MCA</td>
<td>68</td>
<td>42</td>
<td>0.38</td>
<td>right MCA</td>
<td>74</td>
<td>70</td>
<td>0.05</td>
</tr>
<tr>
<td>4</td>
<td>left MCA</td>
<td>36</td>
<td>22</td>
<td>0.39</td>
<td>right MCA</td>
<td>66</td>
<td>71</td>
<td>-0.08</td>
</tr>
<tr>
<td>5</td>
<td>BA</td>
<td>42</td>
<td>19</td>
<td>0.55</td>
<td>right MCA</td>
<td>56</td>
<td>38</td>
<td>-0.32</td>
</tr>
<tr>
<td>6</td>
<td>left MCA</td>
<td>56</td>
<td>38</td>
<td>0.32</td>
<td>right MCA</td>
<td>62</td>
<td>76</td>
<td>-0.26</td>
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<tr>
<td>7</td>
<td>left MCA</td>
<td>36</td>
<td>20</td>
<td>0.44</td>
<td>right MCA</td>
<td>56</td>
<td>56</td>
<td>0.00</td>
</tr>
<tr>
<td>8</td>
<td>left PCA</td>
<td>46</td>
<td>30</td>
<td>0.35</td>
<td>right PCA</td>
<td>48</td>
<td>50</td>
<td>-0.04</td>
</tr>
<tr>
<td>9</td>
<td>BA</td>
<td>25</td>
<td>0</td>
<td>1.00</td>
<td>left MCA</td>
<td>66</td>
<td>66</td>
<td>-0.03</td>
</tr>
<tr>
<td>10</td>
<td>BA</td>
<td>150</td>
<td>0</td>
<td>1.00</td>
<td>left MCA</td>
<td>67</td>
<td>67</td>
<td>0.00</td>
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<tr>
<td>11</td>
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<td>46</td>
<td>38</td>
<td>0.17</td>
<td>left MCA</td>
<td>46</td>
<td>39</td>
<td>0.15</td>
</tr>
<tr>
<td>12</td>
<td>right PCA</td>
<td>17</td>
<td>0</td>
<td>1.00</td>
<td>right MCA</td>
<td>47</td>
<td>49</td>
<td>-0.04</td>
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<tr>
<td>13</td>
<td>BA</td>
<td>40</td>
<td>15</td>
<td>0.63</td>
<td>right MCA</td>
<td>53</td>
<td>55</td>
<td>-0.04</td>
</tr>
<tr>
<td>14</td>
<td>right VA</td>
<td>44</td>
<td>27</td>
<td>0.39</td>
<td>right MCA</td>
<td>61</td>
<td>69</td>
<td>-0.13</td>
</tr>
</tbody>
</table>

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.
Standing position

Lying flat position

Affected left MCA

Contralateral MCA (control)

Cerebral angiography:
left supraclinoid ICA
critical stenosis

Sitting position

Lying down position

Right PCA:
MFV 16 cm/s

Left PCA:
MFV 17 cm/s

Cerebral angiography: left VA
occlusion and right VA severe
stenosis

Color version available online
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 ≥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 stud-
ies 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 in-
terventional 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 un-
known. The most accepted hypothesis is that transient
cerebral ischemia results from a low-perfusion hemody-
namic state due to severe extracranial and/or intracra-
nial carotid or MCA or vertebrobasilar arterial disease
[12–14]. In general orthostatic position changes, the long-
standing position, neck extension or hypotension in-
duced by antihypertensive medication have been report-
ed to trigger hypoperfusion TIA, thus suggesting the low-
perfusion hemodynamic mechanism [15, 16]. Any tem-
poral 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 va-
sodilatation in order to maintain CBF in the hypoperfu-
sion tissue. Note that the low PI values documented at rest
are due to reducing inflow because of the intracranial ar-
terial 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 symptom-
atic position [19]. Further studies are needed to better un-
derstand 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 ad-
ditional 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 scan-
ing, single photon emission computed tomography scan
and positron emission tomography withfluorodeoxyglu-
cose 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 hemo-
dynamic status of cerebral arteries in different body posi-
tions 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 pro-
spectively.

One of the main limitation of TCD is that it measures
blood flow velocities and not the actual cerebral perfu-
sion 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 con-
stant, 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 re-
lated 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 sonogra-
phers 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. Fi-
ally, we could not find a correlation between TCD pa-
rameters 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 priori hypothesis.

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

Disclosure Statement

A.V. Alexandrov received research grant (USD >10,000)
NINDS K 23-02229. Speaker bureau for Genentech, Honoraria
(USD <10,000) from Genentech.
References


