Perfusion Insufficiency in Limb-Shaking Transient Ischemic Attacks

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We describe a 63-year-old man with severe bilateral internal carotid artery disease who presented with repeated, brief attacks of left limb shaking precipitated by his standing up. Cerebral blood flow measured by xenon-133 inhalation showed reduced resting flows and a focal perfusion deficit in the right dorsofrontal and upper rolandic regions. Blood flow velocity and pulsatility index of the right middle cerebral artery measured by transcranial Doppler ultrasonography were also reduced. With hypercapnic challenge, both hemispheric tissue perfusion and blood flow velocity showed impaired reactivity. With induced hypotension, the focal perfusion deficit in the right dorsofrontal region was accentuated. Following right internal carotid endarterectomy, resting cerebral blood flow and blood flow velocity improved, as did hypercapnic vasoreactivity. These reversible deficits in cerebral blood flow and vasoregulation, which were maximal in the dorsofrontal region, are consistent with low perfusion in the border zone territory or the distal fields and demonstrate that hemodynamic failure is the likely mechanism for limb-shaking transient ischemic attacks from severe carotid artery disease. (Stroke 1990;21:341-347)

Attacks of limb-shaking are an uncommon manifestation of transient cerebral ischemia, characterized by brief, repetitive jerking movements of the arm or leg, resembling simple partial motor seizures. Since the first recognition of this phenomenon by Fisher, subsequent observations have firmly established its association with severe carotid occlusive disease. Attacks appear to cease following carotid endarterectomy, although hemodynamic studies have not been previously reported to support the specific role of perfusion insufficiency in the border zone territory.

We describe an unusual patient with limb-shaking transient ischemic attacks (TIAs) whose symptoms occurred repeatedly upon his standing up. Hemodynamic findings from xenon-133 cerebral blood flow (CBF) and transcranial Doppler ultrasonography (TCD) studies obtained during hypercapnia and induced hypotension support the mechanism of distal-field ischemia in the pathogenesis of these attacks.

Case Report

A 63-year-old right-handed man with hypertension (treated with α-methyldopa) and diet-controlled diabetes mellitus presented with recurrent, brief, stereotypical attacks of left limb shaking precipitated by his standing up. He described “buckling and jerking” of his left leg, without weakness, which interfered with ambulation; he was unable to grasp objects with his left hand because of clumsiness. Each attack occurred reliably on his standing up from either a supine or a sitting position, with a 5-second latency. Each attack usually lasted no longer than 10 seconds; a few attacks lasted as long as 1–2 minutes. He experienced as many as six attacks daily; during each attack he remained fully alert and was capable of normal conversation. He was admitted to another hospital where neurologic examination and computed tomography (CT scan) of the head were normal. Intravenous heparin was begun after Doppler studies showed severe bilateral internal carotid artery (ICA) disease. Despite this therapy, he continued to experience daily attacks of left leg “twitching.”

On admission to our hospital, the neurologic examination was normal. There was no evidence of mental impairment. His blood pressure (BP) was 149/94...
mm Hg, with a regular pulse of 70/min; no BP changes occurred when he moved between the lying, sitting, or standing positions. Routine blood work was normal except for a glucose concentration of 168 mg/dl; his hematocrit was 44.7%. α-Methyldopa had been stopped just before his transfer, and heparin was continued. Electrocardiography (ECG) showed sinus bradycardia and intraventricular conduction delay with left ventricular hypertrophy. Echocardiography showed no valvular disease and normal ventricular function. Routine electroencephalogram was normal.

Cerebral angiography disclosed a >95% stenosis of the right ICA with delayed, anterograde blood flow to the intracranial circulation but no missing branches in the right middle cerebral artery (MCA). The left ICA was completely occluded, with intracranial opacification occurring through retrograde ophthalmic blood flow. No disease was seen in the vertebrobasilar system. A small posterior communicating artery that did not contribute flow to the anterior circulation was present.

During the 6 days that he was under observation before surgery, no cerebrovascular symptoms occurred despite spontaneous fluctuations in BP (ranging from 120/70 to 190/90 mm Hg). The estimated mean arterial blood pressure (MABP) most commonly observed under these conditions ranged from 85 to 100 mm Hg. He underwent right ICA endarterectomy without complication. The examinations postoperatively and at discharge from the hospital were normal.

Methods

Regional CBF was measured using the xenon-133 inhalation technique with a commercial 32-detector system (Novo Cerebrograph 32c, Hadsund, Denmark) according to the method described by Prohovnik. Intra-arterial BP, end-tidal PCO₂ (PeCO₂), and ECG were all monitored continuously during the CBF measurements. The initial CBF studies were undertaken >7 days after the last TIA and 2 days before surgery, under conditions of normocapnia (PeCO₂ = 38.7 mm Hg, BP = 190/80 mm Hg, MABP = 117 mm Hg), hypercapnia (PeCO₂ = 46.1 mm Hg, BP = 198/88 mm Hg, MABP = 125 mm Hg) induced by the patient's inhalation of 4% CO₂, and normocapnic hypotension (PeCO₂ = 37.3 mm Hg, BP = 111/76 mm Hg, MABP = 88 mm Hg) induced by the infusion of 0.2 mg/min i.v. trimethaphan in saline. We used trimethaphan to induce controlled hypotension because of its short duration of action, the absence of an effect on cerebral vascular tone, and its use in previous studies of BP auto-regulation. We aimed to achieve a degree of relative hypotension considered clinically safe for the patient, a BP not below the lowest level recorded before the CBF measurements when he was free of symptoms. BP was reduced smoothly over 20 minutes until an MABP of 88–90 mm Hg was reached, after which the trimethaphan infusion was stopped; BP returned to baseline after 5 minutes. The patient reported no symptoms before, during, or after CBF measurement.

Blood flow velocity in the MCAs was measured with a commercial TCD device (TC2-64B, Carolina Medical Electronics, King, North Carolina). TCD studies were performed before the CBF measurements in both MCAs and concurrently with the CBF measurements in the right MCA only, under conditions of normocapnia, hypercapnia, and normocapnic hypotension. Peak systolic and mean blood velocities were recorded as well as the pulsatility index (PI; peak systolic velocity—end-diastolic velocity+mean velocity). During the concurrent measurements of CBF and blood flow velocity, the sweep speed was reduced to 14 seconds; the blood flow velocity measurements reported are the average of 12 or 13 cardiac cycles. Recordings were obtained every 2 minutes along with BP.

Three days after right ICA endarterectomy, CBF and blood flow velocity were measured again during normocapnia (PeCO₂ = 39.8 mm Hg, BP = 140/70 mm Hg, MABP = 93 mm Hg) and hypercapnia (PeCO₂ = 44.9 mm Hg, BP = 155/80 mm Hg, MABP = 105 mm Hg), using methods identical to those used for the preoperative measurements. Right and left MCA blood flow velocity and PI were also measured immediately after endarterectomy, and 6 and 45 days later.

All CBF data were analyzed using the model with six unknowns. Results are reported as the initial slope index (ISI), defined as the clearance rate per minute; ISI may be expressed as milliliters per 100 g per minute if the mean tissue partition coefficient for xenon is assumed to be 1.0. Because temporal resolution of the xenon-133 regional CBF method is limited by its 11-minute duration, it is not strictly comparable with the more instantaneous TCD values, nor is it optimal for detecting the transient perfusion changes induced by brief-acting trimethaphan. A rapid monoeponential regional CBF index has been developed by Wyper et al. which we have modified and validated. The Wyper index was used here to detect brief changes and is expressed in ISI units as well.

For both CBF and TCD findings, a vascular reactivity index (RI) was calculated to quantify the changes occurring with hypercapnia compared with the normocapnic resting (baseline) state. CBF RI was defined as the percentage change in CBF per unit change in PCO₂. Blood flow velocity RI was defined as the percentage change in peak velocity per unit change in PCO₂ (averages for three 14-second periods).

Results

Before surgery, baseline hemispheric CBF was reduced bilaterally compared to normal values (Table 1), with an abnormal regional CBF pattern (Figure 1, top) indicating a hypofrontal CBF on the right with a focal reduction in the upper Rolandic and dorsofrontal regions. With hypercapnia, CBF RI was...
TABLE 1. Cerebral Blood Flow and Blood Flow Velocity Changes After Right Internal Carotid Endarterectomy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pco2 (mm Hg)</th>
<th>MABP (mm Hg)</th>
<th>Cerebral blood flow</th>
<th>Velocity on right (cm/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right ISI Wyper</td>
<td>Left ISI Wyper</td>
</tr>
<tr>
<td>Preoperative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normocapnia</td>
<td>38.7</td>
<td>116.7</td>
<td>43.3</td>
<td>57.0</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>46.1</td>
<td>124.7</td>
<td>44.1</td>
<td>59.3</td>
</tr>
<tr>
<td>Hypotension</td>
<td>37.3</td>
<td>87.6</td>
<td>42.7</td>
<td>51.5</td>
</tr>
<tr>
<td>Postoperative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normocapnia</td>
<td>39.8</td>
<td>93.3</td>
<td>46.5</td>
<td>61.2</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>44.9</td>
<td>105.0</td>
<td>49.1</td>
<td>67.0</td>
</tr>
</tbody>
</table>

Pco2, end-tidal Pco2; MABP, mean arterial blood pressure; ISI, initial slope index.

low bilaterally (0.3%/mm Hg and 0.4%/mm Hg on the right and left, respectively) and the region of reduced CBF became wider, spreading forward to the upper and anterior frontal convexity (Figure 1, middle), the area corresponding topographically to the border zone between the anterior cerebral artery and the MCA. With hypotension, the dorsofrontal and upper Rolandic blood flow deficits became even more apparent (Figure 1, bottom); absolute CBF (ISI) showed a small decline (Table 1). The Wyper index revealed an even larger blood flow reduction from baseline (9.6% on the right and 7.3% on the left, Table 1).

Following endarterectomy, baseline ISI on the right improved by 7%; no significant change occurred on the left (Table 1). A unilateral hemispheric change of 7% is significant (p<0.001) in our laboratory. The focal blood flow deficit seen preoperatively at baseline and with hypercapnia was no longer evident (Figure 2). Two detectors (F1 and F3) were excluded from the hypercapnic studies due to artifacts and thus do not appear on the flow map. After surgery, hypercapnic vasoreactivity was improved overall, with an RI of 1.2%/mm Hg on the right (Figure 3) and 0.8%/mm Hg on the left.

Before surgery, baseline blood flow velocity waveforms in the MCAs appeared attenuated bilaterally, with a symmetric PI (0.88 on the right and 0.85 on the left); peak velocity was higher on the right (Figure 4). During hypercapnia, blood flow velocity fell slightly (Table 1). An example of changes in the TCD waveform between normocapnia and hypercapnia is shown in Figure 5. Hypercapnic reactivity was -0.92%/mm Hg. During hypotension, mean and peak velocities were recorded simultaneously with MABP and pulse. Figure 6 shows that both peak and mean blood flow velocities varied directly with MABP. The relation between peak velocity (Y) and MABP (X) can be expressed as Y = 0.34X - 11.8 (r²=0.74).

Within hours after surgery (day 0, Figure 4), TCD measurements showed a marked increase in peak blood flow velocity and an increase in PI on the right; by day 6 after surgery, peak blood flow velocity had returned to baseline, although the improvement in PI was sustained (day 45, Figure 4). No significant changes were

FIGURE 1. Map of cerebral blood flow asymmetry (right initial slope index [ISI]+left ISI×100) before carotid endarterectomy under normocapnic (top), hypercapnic (middle), and hypotensive (bottom) conditions. Asymmetry is indicated by intensity of shading, quantified by scale on left, given in percent. Under normocapnic conditions there was hypofrontality and reduced perfusion focaly in right dorsofrontal and upper Rolandic regions (detectors C1, C2, P1, and P2). With hypercapnia, more extensive zone in right dorsofrontal region was apparent, extending to superior and inferior frontal regions (detectors F4, F2, F1, F3, F5 and T2). During hypotension, blood flow deficit in right dorsofrontal and prerolandic regions (detectors C1, P1, F4, F2, P1, and F3) was further accentuated.
FIGURE 2. Map of cerebral blood flow asymmetry (right initial slope index [ISI] + left ISI × 100) after carotid endarterectomy under normocapnic (top) and hypercapnic (bottom) conditions. Asymmetry is indicated by intensity of shading, quantified by scale on left, given in percent. Focal blood flow deficit seen preoperatively (Figure 1) was no longer evident.

observed in either velocity or PI on the left. With the hypercapnic challenge, peak blood flow velocity in the right MCA showed an RI of 1.4%/mm Hg (Figure 3), an improvement from the preoperative state.

Discussion

The hemodynamic changes observed in our patient are consistent with the mechanism of perfusion insufficiency as the probable cause for his limb-shaking TIAs. On the symptomatic side, perfusion was reduced focally in the upper frontal convexity, the region of the distal fields between the anterior cerebral artery and the MCA. These blood flow deficits were accentuated in the challenge studies, showing impairment in hypercapnic vasoreactivity and BP autoregulation, measured by both CBF and TCD. Following right carotid endarterectomy, the focal blood flow deficits and vasoreactivity improved. These focal hemodynamic findings occurred in the absence of a parenchymal lesion on CT or a deficit on neurologic examination.

Despite the asymptomatic occlusion on the left, baseline CBF and especially vasoreactivity were worse on the symptomatic right side, which showed a severe stenosis with no collateral blood flow on angiography. Impairment in hypercapnic vasoreactivity appears to indicate maximal vasodilation with poor hemodynamic reserve, reflecting inefficient or sparse collateral channels. Such patients may be

FIGURE 3. Bar graph. Cerebral vasoreactivity to hypercapnia expressed as reactivity index (RI). Cerebral blood flow RI (filled bars) is percentage change in initial slope index per unit change in PCO₂. Measured by transcranial Doppler ultrasonography, blood flow velocity RI (shaded bars) is percentage change in peak velocity per unit change in PCO₂. RI improved after carotid endarterectomy.

FIGURE 4. Time course of peak blood flow velocity (top) and pulsatility index (bottom) in right (●, upper line) and left (○, lower line) middle cerebral artery (MCA) before and after right carotid endarterectomy. Values at day 0 refer to measurements taken within hours after surgery. Increase in MCA peak velocity after surgery was temporary, while increase in pulsatility index was sustained. No significant changes occurred in left MCA.
especially susceptible to infarction in the distal-field territory. The anterior border zone generally includes the upper frontal convex region, where baseline CBF and vasoreactivity were most deficient in our patient. Among patients with severe carotid artery disease studied by positron emission tomography (PET), Leblanc et al have demonstrated that this zone shows the highest blood volume, implying maximal vasodilation, combined with focally low perfusion.

The blood flow velocity response to hypercapnia measured by TCD before surgery was similarly impaired, with a slight decline rather than the expected increase during the hypercapnic challenge. This negative reactivity may indicate a steal effect, a paradoxical response that has been observed in some patients with severe carotid artery disease. The normal velocity response to hypercapnia in healthy subjects without occlusive disease (2.9–3.5%/mm Hg change in Pco2) appears to be constant over the physiologic range of 20–60 mm Hg. Among patients with unilateral carotid artery occlusions, Ringelstein et al have shown that vasomotor reactivity measured by TCD is severely reduced, especially in patients who have distal-field infarcts, ischemic ophthalmopathy, or orthostatic TIAs.

A focal loss of BP autoregulation was also demonstrated in our patient, as indicated by the accentuation of his blood flow deficit in the right dorsolateral region during hypotension. Perfusion is normally unchanged by mild hypotension. In our patient, the 25% decrease in BP from baseline was accompanied by a small (9%) drop in CBF assessed by the Wyper index and no significant change in the ISI, suggesting that global BP autoregulation in the hemispheres was only marginally impaired. The degree of hypotension achieved was modest (for safety reasons) and would not be expected to cause significant global CBF reductions, even in elderly patients with arteriosclerosis. Nonetheless, our patient showed a well-defined focal CBF deficit consistent with the findings during hypercapnia. The findings during both challenges suggest maximal vasodilation in the border zone territory in the upper frontal convexity, with an inability to dilate further in response to hypercapnia or hypotension.

The interpretation of our patient's TCD response to hypotension is less certain. It is not clear that TCD blood flow velocity under non-steady-state conditions truly reflects perfusion. Furthermore, we cannot exclude the possibility that some of the variance in TCD blood flow velocity in response to hypotension reflects dilatation of the MCA, even though such dilatation is expected to be slight. However, recent studies of BP autoregulation in normal humans using TCD have suggested that the initial decrease in blood flow velocity with hypotension normalizes to baseline within 4 seconds after a step decline in BP. We did not observe this rapid compensatory response during any period of induced hypotension in our patient.

Our patient's clinical profile and response to therapy are consistent with these hemodynamic findings. Brief, repetitive attacks appear to correlate with
hemodynamic carotid artery disease, with perfusion failure rather than embolism being the inferred ischemic mechanism. The TIAs in this patient were only seconds to minutes long, occurring at least once daily over 2 weeks. Moreover, the occurrence of limb-shaking as the main manifestation of a TIA appears well established as a sign of severe carotid artery disease and is presumed to reflect ischemia rather than epilepsy. Our experience with another patient, in whom no epileptiform discharges were recorded during a witnessed attack, argues against a seizure mechanism as the explanation for limb-shaking with carotid artery disease. In addition, motor deficits with a crural emphasis suggest ischemia in the high convex region of the frontal lobe, in the arterial zone most distal to the occluded ICA. Our patient complained mainly of leg symptoms, with his arm less affected. Finally, the provocation of symptoms by orthostatic changes underscores the mechanism of perfusion failure, as proposed by Caplan and Sergay. Thus, we believe that limb-shaking is probably a specific sign of border zone ischemia, a thesis supported by both PET findings in other patients and by the specific clinical-hemodynamic correlations in our patient.

The apparent rarity of orthostatic cerebral ischemia may reflect its underrecognition or the special circumstances under which symptoms from low blood flow alone may occur. Only one of the eight patients reported by Baquis et al experienced limb-shaking related to orthostatic changes; four of the seven patients with angiography had bilateral ICA occlusions. We found no evidence of orthostatic hypotension in our patient while off antihypertensive medication. In the setting of autonomic dysfunction from diabetes mellitus and bilateral severe carotid artery disease, we suspect that α-methyldopa produced some degree of orthostatic hypotension, exacerbating already-marginal cerebral perfusion in the distal-field territory. This combination of conditions probably accounts for our patient's orthostatic symptoms, which ceased when the antihypertensive was stopped.

We believe the combined use of CBF and TCD methods with challenge studies helped to clarify the pathophysiologic mechanism of the TIAs in our patient. CBF studies proved most useful in demonstrating the focal hemispheric disturbance in BP and CO2 autoregulation, while TCD provided unique information about the instantaneous variations in blood flow velocity in response to hypercapnia or hypotension. We and others have shown that the presence of extracranial carotid artery disease alone is not a reliable guide to the state of cerebral perfusion. Thus, these relatively inexpensive noninvasive methods, supplemented by challenge studies, may prove useful as "cerebrovascular stress tests" to identify subgroups of patients with severe carotid artery disease suffering from hemodynamic failure.

References


KEY WORDS • perfusion • carotid artery diseases • cerebral ischemia, transient • hypotension, orthostatic
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