Impaired Clearance of Microemboli and Cerebrovascular Symptoms During Carotid Stenting Procedures

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Background: Transcranial Doppler monitoring shows a high prevalence of microemboli during carotid artery stenting (CAS); however, the occurrence of cerebrovascular symptoms (CVSs) does not seem to be related to the microembolic load.

Objective: To evaluate embolic and hemodynamic transcranial Doppler monitoring findings and their relationships with the occurrence of procedural CVSs.

Patients: Fifty-four patients who had carotid stenosis of more than 70% underwent a total of 57 CAS procedures during transcranial Doppler monitoring of mean blood flow velocity and microembolic signals in the middle cerebral artery. The occurrence of transient ischemic attack, transient monocular blindness, and stroke during the CAS procedure was considered CVSs.

Results: Nine (15.8%) of the 57 patients had CVSs during the procedure (i.e., 6 patients with transient ischemic attack, 1 with transient monocular blindness, 1 with a minor stroke, and 1 with a major stroke). The mean blood flow velocity median values were statistically significantly lower ($P<.001$) in the group of 9 patients with CVSs (36 cm/s; interquartile range, 32.3-38.5) compared with the 48 without CVSs (48 cm/s; interquartile range, 41.5-52). The median number of isolated microembolic signals was similar in the 2 groups (72; interquartile range, 66-81 vs 75; interquartile range, 67-83.5). The median number of microembolic signal showers (clusters of too many signals to be counted separately in one cardiac cycle) presented a nonsignificant prevalence in the patients with CVSs (9; interquartile range, 7.5-11.2) compared with the ones without CVSs (8.2; interquartile range, 7-9).

Conclusion: The low flow velocity in the middle cerebral artery may impair the clearance of the microembolic load and should be considered a precursor of CVSs during the CAS procedure.

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The real benefit of carotid artery stenting (CAS) compared with endarterectomy is still debated. In particular, embolism is considered the main cause of cerebrovascular complications during CAS. Transcranial Doppler (TCD) monitoring shows a prevalence of cerebral microemboli more than 8 times higher than that seen during endarterectomy.

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Microembolism is more prevalent during angioplasty-alone procedures compared with CAS methods and occurs more frequently during the stent deployment phase. The use of cerebral protection devices reduces both the frequency of microembolism and the occurrence of peri-procedural stroke. Nevertheless, the procedural cerebrovascular complication rate, as well as the number of new ischemic lesions seen in magnetic resonance images, is low and does not seem related to the high TCD monitoring microembolic load.

These controversial observations suggest that TCD monitoring detection alone of microemboli may overestimate the true clinical effect of cerebral embolization during CAS and this infers that other factors, such as a concomitant hemodynamic impairment, might affect ischemic damage of the brain. In this respect, the influence of cerebral blood flow velocity on the microembolic load has been scarcely considered so far. In this study we have evaluated embolic and hemodynamic TCD monitoring findings and their relationships with the occurrence of procedural cerebrovascular symptoms (CVSs).
Fifty-four patients (37 men and 17 women; mean age, 70.3 years; age range, 54-83 years), recruited between February 1, 2000, and January 31, 2004, underwent a total of 57 unprotected CAS procedures for internal carotid stenoses (bilateral in 3 cases) of 70% or more, as proved by selective digital subtraction angiography according to the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria. The patients were selected based on a suitable transcranial acoustic window allowing TCD monitoring. All of the patients were seen with cardiological and/or pulmonary risk for anesthesia with contraindications for endarterectomy. All gave their written informed consent to receive endovascular treatment. The risk factor profile of the patients included arterial hypertension in 30 cases (55.6%), diabetes mellitus in 24 cases (44.4%), smoking in 13 cases (24.1%), atrial fibrillation in 14 cases (25.9%), and hypercholesterolemia in 23 cases (42.6%).

The stenoses were symptomatic in 54 patients (3 with transient monocular blindness [TMB], 18 with transient ischemic attacks [TIAs], 29 with minor strokes, and 4 with major strokes) and were asymptomatic in 3 cases because of restenoses after endarterectomy. Severe stenosis or occlusion of the contralateral carotid artery was present in 14 symptomatic cases. No patient showed intracranial tandem carotid stenosis. All patients were treated for at least 1 week prior to the procedure with antiplatelet drugs (100 mg of aspirin once a day in 42 patients and 250 mg of ticlopidine hydrochloride twice a day in 12 patients). Mild sedation was achieved with promazine hydrochloride, and 70 IU/kg of intravenous heparin sodium was used during CAS procedure. Moreover, 1 mg of atropine sulfate was administered intravenously to prevent bradycardia due to carotid sinus stimulation during the dilatation phases.

Using the femoral artery approach, an 8F-guiding catheter was inserted in the common carotid artery. After an initial angiogram, the stenosis was crossed by a guidewire (0.014- to 0.020-inch coronary guidewires) using road-mapping images. Predilatation with a 3-mm-diameter balloon catheter (Gazelle; Boston Scientific Corporation, Natick, Mass) was performed in 19 patients who had severe stenosis. A self-expanding stent (Carotid Wallstent monorail alloy 3.2-3.4 mm or Precise Stent Cordis nitinol 5.0 shaft, 7 × 30 or 7 × 40 mm, 9 × 30 mm or 9 × 40 mm; Boston Scientific Corporation, La Garenne Colombes, France) was navigated into the internal carotid artery and then deployed inside the stenosis to cover the entire lesion. Thereafter, a 5.0- to 5.5-mm-diameter balloon dilatation catheter was steered to the residual stenosis inside the stent and then inflated with 7 to 12 atm for 10 seconds. A final angiogram was performed including the treated vessel, the distal internal carotid artery, and the intracranial branches. No cerebral embolic protection device was used in this study. Continuous electrocardiographic and brachial arterial pressure monitoring was performed during the procedure.

A 2-MHz multichannel transcranial Doppler probe (Multidop X-4; DWL, Sipplingen, Germany) was used in all patients for long-term insonation of the middle cerebral artery ipsilateral to the carotid artery undergoing the endovascular treatment. Transcranial Doppler monitoring of mean blood flow velocity (MFV) and microembolic signals (MESs) in the middle cerebral artery was prolonged during the entire CAS procedure. The TCD probe was fixed to the skull with head tape placed on the transtemporal acoustic window. The middle cerebral artery was insonated with 2 sample volumes of 10 mm at a predetermined depth of 46 to 56 mm (4 to 6 mm apart) to obtain optimum insonation of the vessel. A high-pass filter was set at 100 Hz to eliminate low-frequency arterial wall vibrations. The ultrasonic power emitted at the probe surface was 50 to 100 mW/cm². Intensity was defined as the power measured in decibels contained in the Doppler spectrum. The algorithm for signal intensity measurements used the whole screen as a background, and the scale setting was between −100 cm/s and +150 cm/s, corresponding to a pulse repetition frequency of 6500 Hz. A 64-point fast-Fourier transform with a length of 2 milliseconds and an overlap of 60% was used. These data were stored on a hard disk using a coding system and later analyzed offline by one of us (C.S.) who was blind to patient information.

Mean blood flow velocity values were evaluated in centimeters per second as diastolic flow velocity +½ (systolic blood flow velocity minus diastolic blood flow velocity). The MFV was evaluated in each patient at the start of the CAS procedure and the median values were considered for the comparison between groups.

Microembolic signals were identified according to the recommended guidelines. Microembolic signals were quantified as the number of isolated signals and the number of MES showers (clusters of too many signals to be counted separately in one cardiac cycle). During the passage of the angiographic contrast medium, a high and broad intensity increase of the Doppler spectrum was noted and then it was difficult to identify the high intensity transient signals because of microemboli; therefore, this procedural phase was excluded from data analysis.

Continuous neurological observation was performed during CAS procedure, and the occurrence of focal neurological deficits was observed. Subsequently, these deficits were identified as TIA, TMB, minor stroke, or major stroke. All these disorders were considered CVSs, although only minor and major strokes were considered to be cerebrovascular complications because transient symptoms did not affect the clinical outcome. Cranial computed tomographic scanning was performed at the end of the procedure in all patients who had CVSs with the aim to exclude reperfusion damage with hemorrhage.

A nonparametric analysis was selected. Data are expressed as median and interquartile range. The Mann-Whitney test was used to estimate differences between the 2 groups. P<.05 was considered statistically significant.

 Nine (15.8%) of 57 cases showed CVSs during the procedure that in all cases involved the vascular territory of the carotid artery under treatment. Six (10.5%) of these events were TIAS, 1 (1.8%) was a TMB, 1 (1.8%) was a minor stroke, and 1 (1.8%) was a major stroke. Hence, procedural cerebrovascular complications occurred in 2 patients (3.5%), no patient died, and the only other procedural complication (observed in 2 cases) was transient impairment of consciousness due to severe bradycardia during the dilatation phase. No CVSs occurred after the CAS procedure.

The angiographic control performed at the end of the procedure showed good resolution (<40%) of the stenosis in all cases. At the end of the procedure in the patients who had CVSs, the cranial computed tomographic scan showed no hemorrhagic lesion.

Median blood flow velocity values at the start of the procedure were significantly lower (P<.001) in the group of 9 patients who had CVSs (36 cm/s; interquartile range, 32.3-38.5 cm/s) than in the group of 48 patients who did not have CVSs (48 cm/s; interquartile range, 41.5-52 cm/s) (Figure A).
Microembolic signals were detected in all the patients during the different phases of the CAS procedure (guidewire crossing, predilatation, stent release, and postdilatation). The median number of isolated MESs was 72 (interquartile range, 66-81) in the group who had and those who did not have procedural cerebrovascular symptoms (CVSs). Mean blood flow velocity median values (A), isolated MESs median number (B), and showers of MESs median number (C) in patients who had and those who did not have procedural CVSs.

The Table lists the clinical characteristics of the patients with procedural cerebrovascular symptoms (CVSs)

<table>
<thead>
<tr>
<th>Sex/Age, y</th>
<th>Treated Stenosis, %</th>
<th>Contralateral Stenosis, %</th>
<th>CVS</th>
<th>Phase of CVS Onset</th>
<th>MFV, cm/s</th>
<th>No. of MES Showers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>At Start</td>
<td>At CVS Event</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No. of Isolated MESs</td>
<td>At Onset of CVSs</td>
</tr>
<tr>
<td>F/72</td>
<td>85</td>
<td>30</td>
<td>Minor stroke</td>
<td>Guidewire crossing</td>
<td>40</td>
<td>38</td>
</tr>
<tr>
<td>M/64</td>
<td>90</td>
<td>75</td>
<td>TMB</td>
<td>Predilatation</td>
<td>38</td>
<td>24</td>
</tr>
<tr>
<td>M/73</td>
<td>90</td>
<td>30</td>
<td>TIA</td>
<td>Predilatation</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>M/75</td>
<td>90</td>
<td>85</td>
<td>TIA</td>
<td>Predilatation</td>
<td>33</td>
<td>20</td>
</tr>
<tr>
<td>M/76</td>
<td>80</td>
<td>90</td>
<td>Major stroke</td>
<td>Stent release</td>
<td>36</td>
<td>22</td>
</tr>
<tr>
<td>F/78</td>
<td>75</td>
<td>Occlusion</td>
<td>TIA</td>
<td>Stent release</td>
<td>28</td>
<td>16</td>
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<tr>
<td>M/77</td>
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<td>30</td>
<td>TIA</td>
<td>Stent release</td>
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<tr>
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<td>80</td>
<td>TIA</td>
<td>Stent release</td>
<td>36</td>
<td>26</td>
</tr>
<tr>
<td>F/78</td>
<td>80</td>
<td>30</td>
<td>TIA</td>
<td>Postdilatation</td>
<td>42</td>
<td>34</td>
</tr>
</tbody>
</table>

Abbreviations: MES, microembolic signal(s); MFV, mean blood flow velocity; TIA, transient ischemic attack; TMB, transient monocular blindness.

Microembolic signals were detected in all the patients during the different phases of the CAS procedure (guidewire crossing, predilatation, stent release, and postdilatation). The median number of isolated MESs was 72 (interquartile range, 66-81) in the group who had CVSs and 75 (interquartile range, 67-83.5) in the group who did not have CVSs; this difference was not statistically significant ($P = .60$) (Figure B). The median number of MES showers presented a nonsignificant prevalence ($P = .50$) in the patients with CVSs (9; interquartile range, 7.5-11.2) compared with the ones who did not have CVSs (8.2; interquartile range, 7-9) (Figure C).

The Table lists the clinical characteristics of the patients who had CVSs, their MFV values at the start of the CAS procedure and during the phase of symptoms onset, and the embolic load (number of isolated MESs and MES showers) during the symptomatic phase.

**COMMENT**

Cerebral microembolism is a common event during CAS procedures; nevertheless, the embolic load alone does not seem to have clinical relevance because it has no statistically significant difference between patients who have CVSs and those who do not. On the contrary, we saw that procedural CVSs occur when the embolic load is associated with low cerebral MFV in the middle cerebral artery, according to the concept that hemodynamic and embolic mechanisms are strictly linked and may interact to determine cerebral ischemia. Indeed, the low blood flow velocity in the middle cerebral artery may impair clearance of the emboli generated from the mechanical manipulation of the stenosis, and this may facilitate the onset of ischemia in poorly perfused areas of the brain. This suggestion agrees with the findings of a middle cerebral artery stenosis study by Wong et al that shows a relationship between microemboli and small infarcts, especially along the border zone regions owing to an artery-to-artery embolism with impaired wash out of emboli. According to this, small emboli ranging in diameter from 50 to 300 µm have been found occluding the arterioles of the meningeal space and TCD monitoring is able to detect microemboli of such very small size.

We saw procedural CVSs in about 15% of the cases; nevertheless, only minor and major strokes (3.5%) result in cerebrovascular complications with a prevalence lower than that seen in a systematic review of the literature, which reports a rate of 5.5% in unprotected CAS procedures.
procedures. Transient local symptoms are not usually reported among the clinical results of stenting procedures because they do not worsen the clinical outcome of the patients, whereas they may appear as events that undermine the safety of the procedure. Nevertheless, transient symptoms may be useful for a better understanding of the clinical significance of the procedural embolic and hemodynamic events.

The onset of CVSs occurred in almost all of our patients during dilatation or stent-releasing phases that are usually associated with a transient decrease of the MFV in the ipsilateral middle cerebral artery according to the effectiveness of the intracranial arterial supply. Usually these hemodynamic impairment results are enhanced in patients with severe contralateral carotid stenosis or occlusion, and these patients could not benefit from the ante-mortem cerebral compensation. Moreover, these events could not benefit from the ante-mortem cerebral compensation. These hemodynamic impairment results are enhanced in patients with severe contralateral carotid stenosis or occlusion, and these patients could not benefit from the ante-mortem cerebral compensation.

Clinical settings similar to the CAS procedure have shown that the development of cerebral ischemia is often associated with a vast increase in the frequency of microemboli. The Antonius Carotid Endarterectomy, Angioplasty and Stenting Study Group found that there was a relationship between periprocedural cerebrovascular complications and the presence of more than 4 MES showers at postdilatation. Therefore, the transient hemodynamic impairment during dilatation and stent-releasing phases associated with a tremendously increased embolic load may hamper the washout of microemboli in the middle cerebral artery territory triggering CVSs.

The use of protection devices reduces microembolism and the incidences of cerebrovascular complications; however, protected procedures might prove to be useful especially when middle cerebral artery blood flow velocity is low and a reduction of the embolic load is particularly advisable.

CONCLUSIONS

We suggest that TCD monitoring is able to provide insight into the pathogenesis of procedural cerebrovascular events and that the low blood flow velocity in the middle cerebral artery may impair the clearance of the microembolic load triggering CVSs. Therefore, a comprehensive evaluation of hemodynamic factors and microembolism should be carefully considered as harbingers forecasting CVSs during CAS procedures.

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REFERENCES