Cerebral Microemboli and Brain Injury During Carotid Artery Endarterectomy and Stenting

Mona Skjelland, MD; Kirsten Krohg-Sørensen, MD, PhD; Bjørn Tennøe, MD; Søren J. Bakke, MD; Rainer Brucher, PhD; David Russell, MD, PhD, FRCPE

Background and Purpose—Cerebral microembolic signals detected by transcranial Doppler are frequent during carotid angioplasty with stenting and carotid endarterectomy (CEA). Their potential harmful effects on the brain are, however, unclear. The aim of this study was to relate the frequency and type of per-procedural microembolic signals to procedure-related ipsilateral ischemic strokes and new ipsilateral ischemic lesions on diffusion-weighted cerebral MRI.

Methods—Eighty-five patients who were prospectively treated with CEA (61) or carotid angioplasty with stenting (30) for high-grade (≥70%) internal carotid artery stenoses were monitored during the procedures using multifrequency transcranial Doppler with embolus detection and differentiation. Pre- and postprocedural cerebral diffusion-weighted cerebral MRIs were performed on a subset of patients.

Results—Solid and gaseous microemboli were independently associated with procedure-related ipsilateral ischemic strokes (solid: P=0.027, gaseous: P=0.037) or new ipsilateral diffusion-weighted cerebral MRI lesions (solid: P=0.043, gaseous: P=0.026). Microembolic signals were detected during all procedures except one (CEA); 17% and 21% of all emboli were solid during carotid angioplasty with stenting and CEA, respectively. Patients undergoing carotid angioplasty with stenting had more solid (P<0.001) and gaseous (P<0.001) emboli and more new ipsilateral ischemic strokes (P=0.033) compared with patients undergoing CEA. Echoluent plaques (P=0.020) and preprocedural diffusion-weighted cerebral MRI ischemic lesions (P=0.002) were associated with increased numbers of solid emboli.

Conclusions—Solid and gaseous microemboli were increased in patients with procedure-related ipsilateral ischemic strokes or new diffusion-weighted cerebral MRI lesions, which suggests that both solid and gaseous emboli may be harmful to the brain during CEA and carotid angioplasty with stenting. (Stroke. 2009;40:230-234.)

Key Words: embolic stroke ■ embolism ■ endarterectomy ■ endovascular treatment ■ TCD ■ transcranial Doppler

Cerebral microembolic signals (MES) are frequent during both carotid endarterectomy (CEA) and carotid angioplasty with stenting (CAS).1–3 Some authors have found that these emboli may predict cerebrovascular symptoms,4–6 whereas this was not confirmed by others.2,3,7,8 Evidence suggesting that per-procedural microemboli may themselves damage the brain has also been inconclusive. One study found an association between MES and new cerebral ischemic lesion demonstrated on diffusion-weighted MRI (DWI),6 whereas others did not.2,8,9 The aim of this study was therefore to assess the frequency and type of per-procedural cerebral microemboli during CEA and CAS and to relate these emboli to ipsilateral ischemic stroke or new ipsilateral cerebral ischemic lesions on DWI.

Subjects and Methods

Patients

Eighty-five consecutive patients with 91 high-grade carotid artery stenoses with diameter reductions ≥70% (median 80%) were prospectively included in the study. Seventy-five patients (82%) were men and the mean age of all patients was 66 years (SD, 8.9; range, 42 to 83). Sixty-one (67%) stenoses were treated with CEA and 30 (33%) with CAS. All patients had a color duplex ultrasound examination of the precerebral vessels, CT angiography of the carotid and intracranial arteries, and a clinical neurological examination (by a neurologist) within 2 days before and after the procedure. One of the goals of the study was to examine patients with DWI within 2 days before and after the procedure. However, this proved to be impossible in all patients due to capacity limitations at the department of neuroradiology at our hospital. All patients who experienced symptoms during or after the procedure were examined with DWI after the procedure. In 73 (80%) of the 91 procedures, cerebral DWI was performed within 2 days before the procedure; DWI was repeated within 2 days after 58 (79%) of these 73 procedures. A stenosis was classified as symptomatic if the patient had experienced ipsilateral cerebrovascular or ocular ischemic symptoms within 180 days before treatment confirmed by cerebral CT or MRI. According to this definition, 51 (56%) of the stenoses were symptomatic. The 40 asymptomatic stenoses were treated for the following reasons: prophylactic operations before coronary artery bypass grafting (9 stenoses [22.5%]), occlusion/high-grade stenoses of the contralateral carotid artery with reduced collateral cerebral

Received January 8, 2008; final revision received May 6, 2008; accepted May 20, 2008.

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Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.107.513341
The 2 treatment groups were similar with regard to baseline characteristics (Table 1). All patients gave informed consent before the procedure.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment Group (n=30)</th>
<th>Control Group (n=61)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>66 (8.7)</td>
<td>66 (8.9)</td>
<td>0.888</td>
</tr>
<tr>
<td>Male sex*</td>
<td>23 (77)</td>
<td>52 (85)</td>
<td>0.312</td>
</tr>
<tr>
<td>Body mass index, kg/m²*</td>
<td>26 (20–31)</td>
<td>26 (20–35)</td>
<td>0.792</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg*</td>
<td>145 (110–193)</td>
<td>150 (111–194)</td>
<td>0.432</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg*</td>
<td>77 (67–100)</td>
<td>81 (32–101)</td>
<td>0.645</td>
</tr>
<tr>
<td>Degree of stenoses*</td>
<td>80 (70–95)</td>
<td>80 (70–95)</td>
<td>0.057</td>
</tr>
<tr>
<td>Symptomatic plaque*</td>
<td>15 (50)</td>
<td>34 (55.7)</td>
<td>0.606</td>
</tr>
<tr>
<td>≥70% contralateral stenoses*</td>
<td>10 (33)</td>
<td>18 (30)</td>
<td>0.269</td>
</tr>
<tr>
<td>Echolucent plaque*</td>
<td>13 (43.3)</td>
<td>15 (24.6)</td>
<td>0.069</td>
</tr>
<tr>
<td>Preprocedural ipsilateral DWI ischemia*†</td>
<td>23 (82)</td>
<td>34 (76)</td>
<td>0.288</td>
</tr>
<tr>
<td>Lipid-lowering drug*</td>
<td>24 (80)</td>
<td>54 (88.5)</td>
<td>0.275</td>
</tr>
<tr>
<td>Smoker within last 6 months*</td>
<td>11 (36.6)</td>
<td>29 (47.5)</td>
<td>0.428</td>
</tr>
<tr>
<td>White blood cell count, 10⁹/L</td>
<td>7.1 (3.8–10.6)</td>
<td>7.5 (3.8–12.1)</td>
<td>0.577</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>3 (–12–28)</td>
<td>4 (1–39)</td>
<td>0.212</td>
</tr>
<tr>
<td>Platelet count, 10⁹/L</td>
<td>246 (121–434)</td>
<td>246 (104–391)</td>
<td>0.660</td>
</tr>
<tr>
<td>HbA1C, %</td>
<td>5.9 (4.6–8.1)</td>
<td>5.8 (4.1–8.8)</td>
<td>0.331</td>
</tr>
<tr>
<td>Cholesterol mmol/L</td>
<td>4.6 (1.0)</td>
<td>4.6 (1.1)</td>
<td>0.713</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.2 (0.6–3)</td>
<td>1.4 (0.4–5.3)</td>
<td>0.527</td>
</tr>
</tbody>
</table>

Numbers are medians (range) or *numbers (percentages). Age is given as unadjusted mean (SD). Symptomatic plaque = cerebrovascular ischemic symptoms ipsilateral to the stenotic internal carotid artery within the last 6 months before the procedure.

*Cerebral DWI was performed before 73 procedures (28 CAS and 45 CEAs).

Carotid Artery Stenting
All 30 patients received dual antiplatelet agents (75 mg clopidogrel and 75 mg aspirin) daily at least 3 days before and 3 months after CAS. Heparin was given (5000 IU intravenously) before stent delivery. Five patients (16.7%) underwent predilatation of the stenoses before stent delivery. One (3.3%) procedure was performed without a protection device; the remainder was performed with distal filter devices. One (3.3%) procedure was performed without a protection device; most (80.6%) procedures were performed with an embolic protection device (EV3, Plymouth, Minn). The procedures were performed under local anesthesia through percutaneous transfemoral access by 2 experienced interventional radiologists. Ipsilateral carotid and intracranial angiography (contrast agent Visipaque 270 mg/mL; Iodixanol; GE Healthcare, AS, Oslo, Norway) was performed to assess technical success.

Ultrasound Examinations
Transcranial Doppler monitoring of the ipsilateral middle cerebral artery was carried out continuously during CEA and CAS using a multifrequency transcranial Doppler (EmboDop; DWL, Singen, Germany). Cerebral MES were automatically identified and differentiated and their time of occurrence was simultaneously registered. The criteria for the automatic detection and differentiation of cerebral MES using multifrequency transcranial Doppler were based on those described previously11,12 but refined as follows: the detection level for MES was a ≥7-dB power increase above background level (dEBR; embolus blood ratio), which lasted ≥4 ms simultaneously in both 2.0- and 2.5-MHz frequency channels and the lower dEBR detection limit for solid emboli was y = 0.1 × 0.12 dB where y = dEBR and x = 2.0 MHz EBR.13 The insonation and reference gate depths were 55 and 45 mm, and the sample volume 12 mm, filter setting 00 Hz, and power 188 mW. The carotid stenoses were classified according to the degree of stenosis by color Duplex ultrasound examinations (HDl 5000; Philips)14 and morphological analysis (echolocancy) of the plaque was performed as described previously.15

Radiological Assessments
The carotid stenoses were classified by CT angiography according to consensus criteria.16 Cerebral MRI with DWI (diffusion-weighted images, T2, and fluid-attenuated inversion recovery) was assessed by experienced neuroradiologists, who were aware of the purpose of the study but blinded for all clinical details and the number of types of per-procedural microemboli.

Clinical Assessment
The clinical outcome measures were ipsilateral (to the procedure) cerebral or retinal ischemic stroke during or within 30 days after the procedure. Any new focal neurological deficit (caused by cerebral or retinal ischemia) that persisted for more than 24 hours was classified as an ischemic stroke or retinal infarct, whereas symptoms lasting <24 hours were classified as transitory ischemic attacks.

Statistical Analysis
The numbers of MES during the monitoring periods are shown as median and range (nonnormal distribution). Statistical analyses included descriptive statistics with mean (± SD) and median (range) for continuous variables and number (percentage) for categorical variables. For comparison of normally distributed data, we used Student t test and nonparametric tests for data with a nonnormal distribution. Pearson χ² or Fisher exact test was used to assess associations between categorical variables. A probability value of <0.05 was considered statistically significant. All probability values were 2-sided. All calculations were carried out using the statistical software SPSS for Windows (Version 14; SPSS Inc, Chicago, Ill).

Results
Cerebral Microembolic Signals and Cerebrovascular Symptoms
Cerebral microemboli were detected in all 30 patients during the CAS procedures and in 60 (99%) of the 61 patients during the monitoring periods. All 30 patients received dual antiplatelet agents (75 mg clopidogrel and 75 mg aspirin) daily at least 3 days before and 3 months after CAS. Heparin was given (5000 IU intravenously) before stent delivery. Five patients (16.7%) underwent predilatation of the stenoses before stent delivery. One (3.3%) procedure was performed without a protection device; the remainder was performed with distal filter devices. The procedures were performed under local anesthesia through percutaneous transfemoral access by 2 experienced interventional radiologists. Ipsilateral carotid and intracranial angiography (contrast agent Visipaque 270 mg/mL; Iodixanol; GE Healthcare, AS, Oslo, Norway) was performed to assess technical success.
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Gaseous microemboli 236 (27–524) 13 (2–106) <0.001

Ipsilateral ischemic stroke* 3 (10) 0 0.033

Ipsilateral ischemic DWI lesions (n=58)*† 6 (21.4) 2 (6.7) 0.103

Numbers are medians (range) or *numbers (percentages).
†Cerebral DWI was performed before and after 58 procedures (28 CAS and 30 CEA).

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†Cerebral DWI was performed before 73 procedures.

Table 3. Baseline and Procedure-Related Variables in Patients According to Ipsilateral Ischemic Stroke During and 30 Days After CAS/CEA (n=85 Patients)

<table>
<thead>
<tr>
<th></th>
<th>Ipsilateral Ischemic Stroke (n=3)</th>
<th>No Ipsilateral Ischemic Stroke (n=82)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of stenoses*</td>
<td>80 (80–80)</td>
<td>80 (70–95)</td>
<td>0.520</td>
</tr>
<tr>
<td>Symptomatic stenoses*</td>
<td>2 (66.7)</td>
<td>26 (29.5)</td>
<td>0.171</td>
</tr>
<tr>
<td>Pre-procedural ipsilateral DWI ischemia† (n=73)*</td>
<td>3 (100)</td>
<td>52 (74.3)</td>
<td>0.312</td>
</tr>
<tr>
<td>MES solid</td>
<td>70 (13–116)</td>
<td>6 (0–128)</td>
<td>0.027</td>
</tr>
<tr>
<td>MES gaseous</td>
<td>235 (85–524)</td>
<td>19 (2–510)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Discussion

In this study, we found that there was an association between solid and gaseous microemboli during CAS and CEA and procedure-related ipsilateral ischemic strokes or new ipsilateral cerebral ischemic DWI lesions. This suggests that both solid and gaseous emboli may cause injury to the brain during these procedures. The median numbers of gaseous and solid emboli were, respectively, 18- and 11-fold higher during CAS compared with patients undergoing CEA and those undergoing CAS had more ipsilateral ischemic strokes. These results should, however, be interpreted with considerable caution because this study was not a randomized study, which was designed to assess the efficacy or safety of CAS compared with CEA.

Studies in patients receiving a mechanical heart valve have suggested that gaseous microemboli may not cause injury to the brain because they are small and do not dissolve in the blood. The theoretical diameter limits for microemboli detected in the middle cerebral artery with the ultrasonic Doppler method used in this study is approximately 3 to 40 μm for gaseous and 80 to 400 μm for solid.

Cerebral Microembolic Signals and Cerebral MRI Lesions

Fifty-five (75%) of the 73 patients who had a preprocedural cerebral DWI had ipsilateral ischemic lesions on DWI. Thirty-one (56%) of these 55 patients had experienced symptoms from the ipsilateral cerebral hemisphere during the 6-month period before the procedure. Patients with preprocedural DWI lesions had higher numbers of solid (P=0.002) but not gaseous (P=0.075) emboli compared with patients without such lesions (Table 4).

Six (21%) of the 28 patients undergoing CAS who had postprocedural DWI and 2 (7%) of the 30 patients undergoing CEA with a postprocedural DWI had new ipsilateral ischemic DWI lesions (P=0.103; Table 2). Three of these 8 patients had relevant clinical symptoms.

Patients with new ipsilateral DWI lesions had higher numbers of solid (44; range, 4 to 116) and gaseous (250; range, 16 to 524) emboli compared with patients without new ischemic lesions (9; range, 0 to 108 and 33; range, 2 to 510). There was an independent association between solid (P=0.043) and gaseous (P=0.026) microemboli and new ipsilateral DWI lesions (Table 5). There was no statistical difference in the total number of new ipsilateral ischemic DWI lesions, which was 9 in the 6 patients undergoing CAS and 11 in the 2 patients undergoing CEA (P=0.301).

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Discussion

In this study, we found that there was an association between solid and gaseous microemboli during CAS and CEA and procedure-related ipsilateral ischemic strokes or new ipsilateral cerebral ischemic DWI lesions. This suggests that both solid and gaseous emboli may cause injury to the brain during these procedures. The median numbers of gaseous and solid emboli were, respectively, 18- and 11-fold higher during CAS compared with patients undergoing CEA and those undergoing CAS had more ipsilateral ischemic strokes. These results should, however, be interpreted with considerable caution because this study was not a randomized study, which was designed to assess the efficacy or safety of CAS compared with CEA.

Studies in patients receiving a mechanical heart valve have suggested that gaseous microemboli may not cause injury to the brain because they are small and do not dissolve in the blood. The theoretical diameter limits for microemboli detected in the middle cerebral artery with the ultrasonic Doppler method used in this study is approximately 3 to 40 μm for gaseous and 80 to 400 μm for solid.
It would seem unlikely that solid microemboli of this size, which may consist of atherosclerotic material, platelet aggregates, blood clots, or soft fat-containing particles, can pass through the brain’s microvasculature (7 to 10 μm), whereas this may be possible for much smaller gas bubbles. During CAS, however, gaseous microemboli often occur in showers within a very short time frame after injections of saline or contrast agent. Clearance of these showers of gaseous microemboli may be impaired if there is a decreased perfusion pressure distal to the stenosis.19,20 Gaseous microemboli may also occur during phases of CEA when there is hemodynamic impairment, but their much smaller numbers may reduce the risk of brain injury due to clearance problems. Previous studies have shown that the passage of gaseous or solid microemboli through the cerebral microvasculature may also cause damage to the endothelium, which causes activation of leukocytes and inflammation. This may induce secondary ischemia and delayed minor cerebrovascular symptoms or increasing neuropsychological symptoms.21,22 The potential harmful effects on the brain due to solid and gaseous microemboli may therefore be more pronounced than detected during the initial clinical examinations after the procedure.

Some authors have reported an association between total MES and stroke,4–6 whereas others have concluded that cerebral microemboli are clinically silent.2,3,7,8 This lack of agreement may be due to the use of different Doppler systems, detection criteria, lack of differentiation between solid and gaseous emboli, or different definitions of clinical outcome. Clinical outcome in some of these studies included both ischemic and hemorrhagic stroke and symptoms from both the ipsilateral and contralateral cerebral hemispheres.

Table 4. Numbers (Median, Range) of Solid and Gaseous Cerebral Microemboli According to Baseline Variables (n=91)

<table>
<thead>
<tr>
<th></th>
<th>Solid Emboli</th>
<th></th>
<th>Gaseous Emboli</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of stenosis</td>
<td>4 (1–128) 8 (0–116)</td>
<td>0.128</td>
<td>16 (2–612) 22 (5–524)</td>
<td>0.231</td>
</tr>
<tr>
<td>Echolucent versus echolucent/heterogenic plaques</td>
<td>14 (1–116) 5 (0–128)</td>
<td>0.020</td>
<td>61 (2–524) 17 (2–612)</td>
<td>0.112</td>
</tr>
<tr>
<td>Symptomatic versus asymptomatic stenoses</td>
<td>7 (0–108) 6 (0–128)</td>
<td>0.762</td>
<td>20 (2–433) 19 (2–612)</td>
<td>0.959</td>
</tr>
<tr>
<td>Preprocedural ipsilateral DWI ischemia versus no ischemia</td>
<td>11 (0–128) 2 (0–45)</td>
<td>0.002</td>
<td>27 (2–612) 10 (2–306)</td>
<td>0.075</td>
</tr>
</tbody>
</table>

*Cerebral DWI was performed before 73 procedures.

Two previous studies have attempted to differentiate between solid and gaseous emboli during CAS using multifrequency Doppler.9,21 However, they did not use the refined automatic differentiation criteria that were used in this study.13 The numbers of patients were also small and no cerebrovascular symptoms were observed. Rosenkranz et al found that 14% of all emboli during CAS in 27 patients were solid and Chen et al found that 39% of the emboli were solid in 10 patients undergoing CAS.

Automatic embolus detection and differentiation in this study was based on refined multifrequency transcranial Doppler criteria.13 This method has 3 potential limitations, ie, sensitivity when detecting small solid emboli (<80 μm, corresponding to an EBR of <7 dB), correctly differentiating small gaseous emboli (<3 μm, corresponding to an EBR of <7 dB), and counting all of the emboli when several enter the sample volume at the same time.12 It is important to stress, however, that the criteria for automatic embolus detection and differentiation using multifrequency Doppler were clearly defined before the study and therefore were exactly the same for all patients.

Finally, we found an increased number of ipsilateral solid, but not gaseous, emboli in patients with echolucent plaques and in patients who had ipsilateral DWI lesions previous to the procedures. This suggests an association between plaque morphology and solid embolization, which supports the results of previous studies in which an association was found between plaque morphology and ischemic stroke.15,24,25

Conclusions

We found that there was an association between ipsilateral solid and gaseous microemboli during carotid revascularization and procedure-related ipsilateral ischemic strokes or new ipsilateral DWI lesions. These results suggest that both solid and gaseous cerebral microemboli may be harmful to the brain during CAS and CEA and that their numbers should be reduced to a minimum during these procedures.

Source of Funding

This work was supported by The Norwegian Foundation for Health and Rehabilitation.

Disclosures

None.

References


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*Stroke*. 2009;40:230-234; originally published online October 16, 2008; doi: 10.1161/STROKEAHA.107.513341

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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