Symptomatic Carotid Occlusion Is Frequently Associated With Microembolization

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Background and Purpose—Symptomatic carotid artery disease is associated with significant morbidity and mortality. The pathophysiologic mechanisms of cerebral ischemia among patients with carotid occlusion remain underexplored.

Methods—We conducted a prospective observational cohort study of patients hospitalized within 7 days of ischemic stroke or transient ischemic attack because of ≥50% carotid artery stenosis or occlusion. Transcranial Doppler emboli detection was performed in the middle cerebral artery ipsilateral to the symptomatic carotid. We describe the prevalence of microembolic signals (MES), characterize infarct topography, and report clinical outcomes at 90 days.

Results—Forty-seven patients, 19 with carotid occlusion and 28 with carotid stenosis, had complete transcranial Doppler recordings and were included in the final analysis. MES were present in 38%. There was no difference in MES between those with carotid occlusion (7/19, 37%) compared with stenosis (11/28, 39%; P=0.87). In patients with radiographic evidence of infarction (n=39), 38% had a watershed pattern of infarction, 41% had a nonwatershed pattern, and 21% had a combination. MES were present in 40% of patients with a watershed pattern of infarction. Recurrent cerebral ischemia occurred in 9 patients (19%; 6 with transient ischemic attack, 3 with ischemic stroke). There was no difference in the rate of recurrence in those with compared to those without MES.

Conclusions—Cerebral embolization plays an important role in the pathophysiology of ischemia in both carotid occlusion and stenosis, even among patients with watershed infarcts. The role of aggressive antithrombotic and antiplatelet therapy for symptomatic carotid occlusions may warrant further investigation given our findings. (Stroke. 2017;48:394-399. DOI: 10.1161/STROKEAHA.116.015375.)

Key Words: carotid artery diseases ■ carotid stenosis ■ cerebral ischemia ■ embolism ■ ultrasonography, doppler, transcranial

Symptomatic carotid disease is associated with a high risk of recurrent cerebral ischemia.1–4 This risk is higher in the setting of carotid occlusion compared with carotid stenosis, both in terms of early and late ischemic events.5,6 Proposed mechanisms of infarction among patients with large-vessel disease include cerebral hypoperfusion,7,8 artery-to-artery embolization,9,10 and a complementary interaction between the 2 via reduced perfusion, limiting the ability of the bloodstream to wash out emboli lodged in distal vessels.11,12 However, the frequency of cerebral embolization and its association with different radiographic patterns of infarction among patients with recently symptomatic carotid artery occlusion has not been thoroughly explored.13–15 This area of research is of particular importance as emerging evidence suggests that external or cortical border zone (CBZ)—type watershed infarctions, classically thought to be caused by cerebral hypoperfusion, are often embolic in pathogenesis.16–19

Embolization into the cerebral vasculature can be studied using transcranial Doppler (TCD) to detect microembolic signals (MES). Among patients with carotid occlusion, emboli from the distal portion of the occluded vessel,20 the proximal portion of the occlusion through external carotid artery collaterals (the original stump emboli hypothesis),21 or vasculature contralateral to the occlusion have all been reported.22 Detection of MES has been associated with increased risk of future ischemia in both asymptomatic23 and symptomatic24,25 carotid stenosis in some studies, highlighting the clinical importance of embolization and the validity of intracranial MES detection using TCD to identify debris or thrombus coming from more proximal carotid plaque. Clarifying the

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pathophysiology of cerebral ischemia in symptomatic carotid occlusion has the potential to guide treatment decisions. Whereas interventions to improve cerebral perfusion such as liberalizing blood pressure goals may be useful if hypoperfusion is the underlying mechanism of ischemia, aggressive antithrombotic therapy may be of greater benefit if embolization is the primary mechanism. Some studies have indeed suggested improved outcome among symptomatic carotid occlusion patients treated with anticoagulation.

In this study, we compare the clinical characteristics, MES frequency, and index cerebral infarction pattern between patients with symptomatic carotid occlusion and carotid stenosis.

Methods

Subjects

We conducted a prospective single-center observational study at the Hospital of the University of Pennsylvania of patients hospitalized after an ischemic stroke or transient ischemic attack (TIA) attributed to large-vessel atherosclerotic carotid disease by the treating vascular neurologist. Patients admitted to the Vascular Neurology consult and inpatient services were screened from January 12, 2011, to January 10, 2015, for study enrollment. The diagnosis of ischemic stroke required focal symptoms or signs persisting ≥24 hours or radiographic evidence of infarction.27 TIA was defined as a transient episode of neurological dysfunction caused by focal brain or retinal ischemia without radiographic evidence of acute infarction.28 Patients were eligible for enrollment if they were ≥7 days from symptom onset and had ≥50% carotid stenosis or carotid occlusion ipsilateral to cerebral infarct or TIA symptomatology as confirmed on vascular imaging. Patients with a known high-risk source of cardioembolism as defined in the TOAST trial (Trial of Org 10172 in Acute Stroke Treatment)29 or who were treated with therapeutic anticoagulation were excluded. Clinical, laboratory, and relevant radiographic data were collected using a standardized case report form. The presence or absence of ≥50% stenosis in the contralateral carotid artery on vascular imaging studies done at the time of study enrollment was also recorded.

Recruitment of patients with carotid occlusion, including both TIA and ischemic stroke, revascularization procedures, and mortality were recorded during index hospitalization and at 90-day follow-up by staff blinded to TCD results. Events within 48 hours of carotid endarterectomy or carotid artery stenting were considered periprocedural. Institutional review board approval was obtained before study commencement, and written consent was obtained from all participants.

Imaging

All index infarctions were categorized as watershed or nonwatershed in appearance by a single vascular neurologist (A.L.L.) blinded to final TCD results using a previously described methodology.30 Watershed infarcts were defined as 1 lesion >1.5 cm or ≥1 lesion <1.5 cm in either the CBZ or the internal border zone (IBZ). The CBZ was defined as the junction between the anterior, middle, and posterior cerebral artery territories, and the IBZ was defined as the junction of the anterior, middle, and posterior cerebral arteries with the Hubner, lenticulostriate, and anterior choroidal artery territories. Infarcts were classified as nonwatershed if there were ≥2 ischemic lesions in a nonwatershed territory or an isolated single small lesion (<1.5 cm) in a possible watershed territory.18

Data Acquisition

TCD MES detection was performed using 2-MHz pulse-wave digital TCD (DWL Doppler Box; Compumedics, Singen, Germany). Insonation of the middle cerebral artery ipsilateral to the cerebral infarction or TIA symptomatology at a depth of 45 to 65 mm was performed for 60 minutes using a standard head-frame. Offline manual review of the full duration of TCD recording for detection of MES was performed by an experienced reader (B.L.C.) blinded to clinical and radiographic data using standard criteria to identify MES.31

Statistical Analysis

The primary outcome measure was the percentage of patients with ≥1 MES on TCD recording (MES+). Recurrent cerebral ischemia and mortality within 90 days were secondary outcomes. Parametric and nonparametric comparisons of categorical and continuous variables were made using χ², Fisher, Student t test, and Mann–Whitney U tests as appropriate. All significance tests were 2 sided. We considered type-1 errors <5% (P<0.05) to be statistically significant. All calculations were done using SPSS (IBM Corp Released 2014, Version 23.0; IBM Corp, Armonk, NY).

Results

A total of 68 patients consented to participate; 48 had completed TCD recordings. Of the 20 patients without completed TCD recordings, 17 did not have temporal windows. One patient was excluded after enrollment because of identification of a high-risk cardiac source in addition to carotid disease. The study cohort, therefore, consisted of 47 patients, 19 with carotid occlusion and 28 with carotid stenosis (Figure 1).

Patient characteristics are shown in Table 1. Patients with carotid occlusion were younger, less often had a history of diabetes mellitus, and more often had a history of stroke or TIA than those with carotid stenosis. TCD recordings were obtained a median of 4 days after symptom onset. TCD-monitoring characteristics were similar among those with carotid stenosis and occlusion (Table 2).

Overall, 18 out of 47 patients (38%) were MES+ on TCD. There were no differences in MES detection rates between those with carotid occlusion (7/19, 37%) as compared with those with carotid stenosis (11/28, 39%; Table 2). MES+ patients were less likely to have hypertension compared with MES– patients, but otherwise, there were no significant differences between those with and without MES (Table 3).

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**Figure 1.** Study flow diagram. MCA indicates middle cerebral artery; and TCD, transcranial Doppler.
All 47 patients had neuroimaging available for review; 27 (57%) magnetic resonance imaging and 20 (43%) computed tomography. All patients who presented with ischemic stroke (n=39) had evidence of infarction on imaging. An exclusively watershed pattern of infarction was present in 15 out of 39 patients (38%), an exclusively nonwatershed pattern in 16 out of 39 patients (41%), and 8 out of 39 patients (21%) had evidence of both watershed and nonwatershed infarctions (Figure 2). Among those with evidence of any watershed infarction, 9 out of 23 patients (39%) were found to be MES+. In the subgroup of patients with exclusively watershed infarcts, 6 out of 15 patients (40%) were MES+. The percentage of patients with MES was similar in those with exclusively watershed infarctions compared with those with any other pattern of infarction (40% versus 42%; P=0.92). Similarly, no significant difference was found comparing those with an exclusively IBZ pattern of watershed infarction to those with any other infarct pattern (20% versus 44% MES+; P=0.63). Numerically more patients with exclusively CBZ infarcts had MES than those with an exclusively IBZ pattern, but this was not significant (71% versus 20%; P=0.24; Figure 2). Patterns of cerebral infarction were similar among patients with carotid occlusion compared to patients with carotid stenosis (Table 1).

Recurrent cerebral ischemia occurred in 9 patients (19%; 6 with TIA and 3 with stroke) within the 90-day follow-up period. One of the strokes was periprocedural after a carotid occlusion patient was noted to have partial vessel recanalization at 1 mo and then underwent a carotid endarterectomy.
endarterectomy. Most ischemic events occurred early, with 8 out of 9 cerebral ischemic events (89%) occurring during index hospitalization. One patient died from surgical complications of coronary bypass surgery during index hospitalization (Table 1). There were no differences in clinical outcome between patients with MES compared with those without (Table 3).

Table 2. Transcranial Doppler–Monitoring Results

<table>
<thead>
<tr>
<th></th>
<th>Total (N=47)</th>
<th>Carotid Occlusion (n=19)</th>
<th>Carotid Stenosis (n=28)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean time from symptom onset to transcranial Doppler (SD), h</td>
<td>92 (60)</td>
<td>103 (79)</td>
<td>85 (43)</td>
<td>0.89</td>
</tr>
<tr>
<td>Mean recording time (SD), min</td>
<td>54 (14)</td>
<td>55 (12)</td>
<td>51 (16)</td>
<td>0.42</td>
</tr>
<tr>
<td>Any microembolic signal (%)</td>
<td>18 (38)</td>
<td>7 (37)</td>
<td>11 (39)</td>
<td>0.87</td>
</tr>
<tr>
<td>Median number of microembolic signals (IQR)</td>
<td>2 (1–3)</td>
<td>2 (2–3)</td>
<td>1 (1–5)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range.

Table 3. Comparison of Those With Microembolic Signals (MES+) Versus Those Without (MES−)

<table>
<thead>
<tr>
<th></th>
<th>MES− (n=29)</th>
<th>MES+ (n=18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), y</td>
<td>66 (10)</td>
<td>65 (9)</td>
<td>0.84</td>
</tr>
<tr>
<td>Women (%)</td>
<td>12 (41)</td>
<td>7 (37)</td>
<td>0.89</td>
</tr>
<tr>
<td>Black (%)</td>
<td>8 (28)</td>
<td>4 (21)</td>
<td>0.95</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>26 (90)</td>
<td>11 (61)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>20 (69)</td>
<td>14 (78)</td>
<td>0.51</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>5 (17)</td>
<td>2 (11)</td>
<td>0.57</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>11 (38)</td>
<td>5 (28)</td>
<td>0.48</td>
</tr>
<tr>
<td>Current or former smoker (%)</td>
<td>22 (76)</td>
<td>12 (63)</td>
<td>0.73</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack (%)</td>
<td>8 (28)</td>
<td>5 (28)</td>
<td>0.99</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>3 (10)</td>
<td>0</td>
<td>0.16</td>
</tr>
<tr>
<td>Ischemic stroke (%)</td>
<td>23 (79)</td>
<td>16 (89)</td>
<td>0.65</td>
</tr>
<tr>
<td>Contralateral carotid stenosis (%)</td>
<td>6 (21)</td>
<td>4 (22)</td>
<td>0.90</td>
</tr>
<tr>
<td>Medications before admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No antplatelet (%)</td>
<td>15 (52)</td>
<td>8 (44)</td>
<td>0.63</td>
</tr>
<tr>
<td>Single antplatelet (%)</td>
<td>11 (38)</td>
<td>10 (56)</td>
<td>0.24</td>
</tr>
<tr>
<td>Dual antplatelet (%)</td>
<td>3 (10)</td>
<td>0</td>
<td>0.16</td>
</tr>
<tr>
<td>Statin therapy (%)</td>
<td>16 (55)</td>
<td>10 (56)</td>
<td>0.98</td>
</tr>
<tr>
<td>Medications at the time of transcranial Doppler</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single antplatelet (%)</td>
<td>24 (63)</td>
<td>13 (72)</td>
<td>0.39</td>
</tr>
<tr>
<td>Dual antplatelet (%)</td>
<td>3 (10)</td>
<td>3 (17)</td>
<td>0.53</td>
</tr>
<tr>
<td>Statin therapy (%)</td>
<td>27 (93)</td>
<td>16 (89)</td>
<td>0.62</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent cerebral ischemia at 90 d (%)</td>
<td>6 (21)</td>
<td>3 (17)</td>
<td>0.73</td>
</tr>
<tr>
<td>Death at 90 d (%)</td>
<td>0</td>
<td>1 (6)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Figure 2. Presence of microembolic signals (MES+) by infarct topography.

Discussion

We found that nearly one third of recently symptomatic carotid occlusion patients had MES on TCD monitoring, with a similar MES+ rate between those with carotid stenosis and carotid occlusion. A significant portion of patients with watershed (IBZ and CBZ) infarctions on imaging were MES+, suggesting that embolization may play an important role even in this subgroup.

Our results are concordant with some earlier studies that have compared subjects with carotid occlusion to those with stenosis and noted similar rates of MES detection between the 2 groups (Table 4).32–35 We are aware of 3 previous studies that describe MES frequency and neuroimaging results among stroke/TIA patients.13–15 Only one of these studies contains detailed data on index cerebral infarction patterns. In this study, which examined 30 patients with middle cerebral artery stenosis, MES were more frequently seen in those with watershed infarction than in those without watershed infarction (50% versus 14%); differentiation between CBZ and IBZ was not reported.15 Our finding that MES are common among those with watershed infarcts is in agreement with this previous study and extends their observation to patients with extracranial carotid disease. We, thus, provide further support for the concept that even watershed infarcts may be linked to impaired embolic washout in patients with large-vessel stenosis or occlusion.12

The rate of recurrent cerebral ischemia seen in our cohort overall is consistent with that of previous data.5,6,36 However, unlike some previous studies, we did not see a difference in clinical outcome between MES+ and MES− patients.23–25 Currently, there are no surgical and few targeted therapeutic options for those with symptomatic carotid occlusion in contrast to carotid stenosis.37 Given the frequency of
microembolization we observed, previous trial results demonstrating MES reduction with dual antiplatelet therapy, and possible clinical benefit of anticoagulation in patients with stroke caused by large-vessel disease, further investigation of aggressive antithrombotic regimens among patients with symptomatic carotid occlusions may be warranted.25,26,29,38,39

Our study has many important limitations. First, we likely significantly underestimated the true rate of microembolization in our patients. TCD recordings were done for only 1 hour; more prolonged monitoring would probably have increased the detection rate of MES. Our MES detection rate may also have been higher had we performed TCDs earlier after symptoms onset as MES detection rates vary inversely with time from symptom onset.10 In addition, as is typical with TCD, a minority of our patients did not have temporal bone windows and were not included; often, these patients are older and may have been more likely to show emboli. We also excluded patients treated with therapeutic anticoagulation. It is possible that patients at highest risk for early ischemic recurrence may have been more likely than others to be treated with anticoagulation and, therefore, also potentially more likely to have MES.25,33,40 Second, we are limited in the generalizability of our findings by our relatively small sample size, single-center design, and our selective inclusion and exclusion criteria. Our institutional practices may be unique. For example, all of our included patients received aggressive stroke unit care and more than half of our patients reported preadmission statin use that may significantly lower the risk of early stroke recurrence in patients with carotid disease.41 Some patients in our study were treated with dual antiplatelet therapy that may also reduce both the rate of microembolization and recurrent ischemic events.25,35 Third, we did not capture data on systemic or cerebral hemodynamics in our patients that limits our ability to assess the relative interaction between cerebral hypoperfusion and embolization. We also lack data on the patterns of collateral cerebral blood flow in our patients; this may have prevented us from detecting MES in subjects with atypical collateral flow patterns because we performed TCD only at the middle cerebral artery ipsilateral to the symptomatic carotid.20–22 Finally, although all our patients were acutely symptomatic, we cannot be certain whether our patients had acute or chronic carotid occlusion, which may have different outcomes and mechanisms of ischemia.8

### Conclusions

We found a similarly high rate of microembolization among patients with recently symptomatic carotid occlusion as compared with those with carotid stenosis. MES were found with similar frequency in all infarct patterns, including watershed infarctions. These findings suggest that embolization plays a major role in the mechanism of injury in symptomatic large-vessel carotid disease, including carotid occlusion. Future investigations of aggressive antithrombotic, antiplatelet, or other medical therapy among patients with symptomatic carotid occlusion may be warranted given the current lack of targeted therapeutic options for this high-risk group.

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### Disclosures

None.

### References


23. Liberman et al Symptomatic Carotid Occlusion 399


26. Liberman et al Symptomatic Carotid Occlusion 399


29. The publications committee for the trial of org 10172 in acute treatment (toast) investigators. Low molecular weight heparin, org 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. JAMA. 1998;279:1265–1272.


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