Malignant Emboli on Transcranial Doppler During Carotid Stenting Predict Postprocedure Diffusion-Weighted Imaging Lesions

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Background and Purpose—Carotid angioplasty and stenting (CAS) has a higher incidence of periprocedural stroke compared with endarterectomy. Identifying CAS steps with the highest likelihood of embolization may have important implications. We evaluated CAS safety by correlating the findings of procedural transcranial Doppler with postprocedure diffusion-weighted imaging (DWI) lesions.

Methods—In this prospective study, transcranial Doppler monitoring was performed during CAS procedures, which were divided into 11 steps. Embolic signals on transcranial Doppler were counted and classified based on the relative energy index of microembolic signals into microemboli ≤1 or malignant macroemboli >1. Poststenting MRI was performed in all cases. A negative binomial regression model was used to evaluate the predictive value of transcranial Doppler emboli for new DWI lesions.

Results—Thirty subjects were enrolled. Seven of 30 subjects (23.3%) were asymptomatic. The median embolic signal count was 212.5 (108 microemboli and 80 malignant macroemboli). Stent deployment phase showed the highest median embolic signals count at 58, followed by protection device deployment at 30 (P=0.0006). Twenty-four of 30 (80%) had new DWI lesions on post-CAS MRI. The median DWI count was 4 (interquartile range 7). Two of 30 (6.7%) had new or worsening clinical deficits post-CAS. For every malignant embolus, the expected count of DWI lesions increases by 1% (95% confidence interval, 0%–2%; P=0.032).

Conclusions—We observed a high incidence of embolic signals during CAS procedure, especially, when devices were deployed. Most subjects developed new DWI lesions, but only 6.7% had deficits. Malignant macroemboli predicted new DWI lesions. (Stroke. 2013;44:1317-1322.)

Key Words: antiplatelet therapy ■ carotid angioplasty and stenting ■ clinical trial ■ embolism ■ magnetic resonance imaging ■ stroke ■ transcranial Doppler

Carotid angioplasty and stenting (CAS) procedures have an increased risk of periprocedural stroke compared with endarterectomy.¹ This is associated with a high incidence (up to 50%)² of new ischemic lesions on MRI of the brain performed after the procedure. Although it is imperative to improve the safety of the procedure, investigating the relative safety of each step will be critical to guide future procedure modifications.³

We investigated the relative safety of all CAS steps by performing intraprocedural transcranial Doppler (TCD) monitoring and correlating TCD findings with postprocedure brain MRI.

Methods

This was a prospective, single-arm, cohort study to assess the safety of each step performed during CAS procedure. Eligible subjects were identified from the Foothills Medical Center of the University of Calgary, Alberta, Canada. Subjects with carotid stenosis (any symptom-status) planned for CAS and able to provide an informed consent were included. Subjects unable to have an MRI scan or those with absent bone window for TCD monitoring were excluded. Subjects with carotid stenosis (any symptom-status) planned for CAS and able to provide an informed consent were included. Subjects unable to have an MRI scan or those with absent bone window for TCD monitoring were excluded. Subjects with carotid stenosis (any symptom-status) planned for CAS and able to provide an informed consent were included. Subjects unable to have an MRI scan or those with absent bone window for TCD monitoring were excluded.
artery access was used in all cases. A single bolus of intravenous unfractionated heparin (7000 U) was administered, after access was obtained. After crossing the aortic arch, the target common carotid artery was catheterized. Distal protection device (Filter Wire EZ Embolic Protection System, Boston Scientific, Natick, MA) was advanced across the stenosis and then deployed in the high cervical segment of the internal carotid artery. Distal protection was performed in all patients. A 4-mm diameter angioplasty balloon was then advanced into the narrowest segment of the stenosis, where it was inflated and then deflated. Carotid WALLSTENT (Boston Scientific) stent sized appropriately to the patient anatomy was then advanced and deployed across the stenosis. Poststenting dilatation was then done using a 5-mm balloon. The distal protection device was then retrieved, and angiographic images were obtained for final results. A femoral artery closure device (AngioSeal, St. Jude Medical, St. Paul, MN) was used at the end of the procedure.

Subjects presenting with stroke symptoms remained in the hospital for further rehabilitation before discharge. Otherwise, subjects were monitored overnight and were discharged the next day. All subjects were treated with dual antiplatelet therapy (acetylsalicylic acid, and loading and maintenance doses of clopidogrel) and high-dose statin therapy. Postprocedure, clopidogrel was stopped after 3 months, whereas acetylsalicylic acid and statin therapy were continued indefinitely.

TCD Monitoring and Interpretation
Transcranial power motion (M-mode Doppler machine (100 mL/L; Spencer Technologies, Seattle, WA) was used to acquire 2-MHz TCD information at 45–65 mm depth. The ultrasound probes were fixed using a head frame (Marc 500; Spencer Technologies) for monitoring. The ipsilateral proximal middle cerebral artery segment was sonated at a depth between 45 and 65 mm. When possible, ipsilateral anterior cerebral or internal carotid arteries were imsonated.

During the procedure, the interventionalist communicated to a TCD technologist the progress of the stenting steps. The times of all steps and contrast injections were recorded.

The number and size of TCD emboli for each CAS step were manually recorded offline by a single reader (M.A.A.). Subjects were identified by random serial numbers on the TCD machine. The analysis was performed for groups of ≥5 subjects to further mask subjects’ identity. Emboli were defined on both the spectrogram and the power M-mode to improve reliability.1 Embolic signals on the spectrogram were identified visually as unidirectional, short-lasting (<300 ms) signals with an amplitude of >3 dB above background and typical chirping sound.2 Embolic signals on power M-mode were identified as at least 3 dB higher than the highest spontaneous power M-mode background blood flow, which reflect motion in 1 direction at a minimum spatial extent of 7.5 mm and temporal extent of 30 ms and must traverse a prespecified depth.3 Signals detected during contrast injections were excluded. Emboli were recorded quantitatively for each step, and their sizes were estimated using the relative energy index of micro emboli signals, as described previously.7 Emboli with relative energy index of micro signal >1.0 were considered malignant.

Postprocedure Clinical and MR Brain Assessment
Subjects were assessed for the development of any new or worsening neurological deficits in the first 24 hours poststenting. Assessments were performed by one of the study’s neurologists, and independently by the admitting neurologist or vascular neurosurgeon. MRI brain was performed, including sequences typically required to diagnose acute ischemic brain lesions. All sequences were performed in the axial plane with 3-mm slice thickness and zero gaps.

Pre- and poststenting MRI were analyzed by an independent reader (S.M.) blinded to the subjects’ clinical and TCD data. The number of new diffusion-weighted imaging (DWI) lesions on the poststent MRI was compared with presten MRI. Among asymptomatic subjects where presten MRI was not performed, all DWI lesions on poststen MRI were assumed to be new.4 The volume of DWI lesions was measured using Quantomo software (Cybertrill Inc., Calgary, Canada).8

Analysis
The primary outcome was the number and size of TCD emboli during each step of the CAS procedure. Secondary outcomes were the number of new DWI lesions on postprocedure MR, and the relationship of the number and size of TCD emboli with new DWI lesions count. A sample of 30 subjects was chosen for feasibility. The stenting procedure was divided into 11 steps as follows: crossing the aortic arch, cannulating the common carotid artery, crossing the lesion with the protection device, deploying the protection device, crossing the lesion with the presententing balloon, inflating/deflating the pre-stenting balloon, crossing lesion with the stent, deploying the stent, crossing the lesion with the poststenting balloon, inflating/deflating the poststenting balloon, retrieving the protection device and guide catheter.

Continuous and categorical variables were summarized as appropriate. Mann–Whitney test was used to compare continuous variables. A negative binomial model, adjusting for age and symptomatic status, was fitted to investigate the relationship between the number and size of TCD emboli on the development of DWI lesions. All tests were 2 tailed, and a significance level of 0.05 was used. The Conjoint Health Research Ethics Board of the University of Calgary approved the study.

Results
Baseline Characteristics
Between March 2011 and June 2012, 30 subjects were enrolled. Eight subjects (75% female) were excluded for absent temporal insonation window, and 2 subjects were excluded for the presence of MRI contraindication. The baseline characteristics are shown in Table 1.

Five subjects (16.7%) aged ≥80 years. The median time from onset of neurological symptoms to stenting was 14 days (interquartile range [IQR] 35 days). The degree of carotid stenosis at angiography was severe (>70%) in all, but 1 subject (55% stenosis). The stenosis was atherosclerotic in all subjects.

TCD monitoring was well-tolerated and had adequate quality in all subjects. Physicians performing stenting did not report any delays or interference caused by the TCD monitoring.

Clinical Outcomes
No inprocedural complications were encountered. Two subjects (6.7%) had new strokes within the first 24 hours after the procedure. The first was a 68-year-old man who presented with mild left-sided weakness 2 weeks before stenting. He underwent uneventful stenting procedure. He was noted to have worsening of his deficits on the next morning post-CAS. TCD monitoring showed a median total embolic signals count of 364 (versus 212.5 median counts in subjects with no clinical events post-CAS) and a median malignant emboli count of 154 (versus 80 in subjects with no clinical events post-CAS). MRI of the brain on the day after the procedure showed a total of 25 bihemispheric new DWI lesions (versus median count of 4 DWI lesions in subjects with no clinical events post-CAS, but positive DWI lesions). The total volume of his DWI lesions was 6.1 mL (versus median volume of 0.5 mL in subjects with no clinical events post-CAS, but positive DWI lesions). He required a short period of inpatient rehabilitation and subsequently was discharged home with a walker. The second patient was a 67-year-old woman who presented with a mild slurred speech 6 weeks before stenting.
She underwent stenting for a 75% right carotid stenosis and was neurologically normal on the day of the procedure. Approximately 12 hours post-CAS, she developed sudden mild weakness on the right side (contralateral hemisphere to the CAS side). TCD monitoring showed a median total embolic signals count of 83 (versus 212.5 median counts in subjects with no clinical events post-CAS) and a median malignant emboli count of 33 (versus 80 in subjects with no clinical events post-CAS). Follow-up MRI showed a total of 6 bihemispheric new DWI lesions (versus median count of 4 DWI lesions in subjects with no clinical events post-CAS, but positive DWI lesions). The total volume of the DWI lesions was 2 mL (versus median volume of 0.5 mL in subjects with no clinical events post-CAS, but positive DWI lesions). The weakness resolved quickly, and she was discharged home in a few days neurologically normal.

**MRI Results**

Sixteen subjects (53.3%) with symptomatic carotid stenosis underwent prestenting MRI. The median time from the pre-stenting MRI to CAS procedure was 5 days (IQR 10). There was evidence of DWI lesions on the pre-CAS MRI in 13 of 16 subjects (81.3%). All subjects underwent poststenting MRI within 24 hours of the procedure. Twenty-four subjects (80%) had at least 1 new DWI lesion (Figure 1). The median number of new DWI lesions was 4 (IQR 7). The clinical characteristics of subjects with versus without DWI lesions are shown in Table 1. The median total DWI volume was 0.5 mL (IQR 0.9). Nine of 24 (37.5%) had total DWI lesions volume ≥1 mL. Only 2 subjects had lesion volumes ≥3 mL (Table 2).

**TCD Monitoring Results**

The median number of TCD embolic signals was 212.5 (IQR 94). The distribution of the embolic signals by size in each CAS procedure step is shown in Figure 2. All CAS steps generated embolic signals. The highest number of total emboli was observed during the deployment of devices (balloons, stent, and protection device). The stent deployment had the highest median count (58) followed by distal protection device deployment (30; P=0.0008). There was no significant difference in the median number of total embolic signals in subjects with versus without new DWI lesions poststenting: 201.5 versus 248.5, respectively (P=0.11). The median number of malignant emboli in subjects with versus without new DWI lesions poststenting was also similar (80.5 versus
Similarly, there was no significant difference in the median number of total emboli in subjects with versus without new neurological deficit poststenting: 223.5 versus 224.5 (P = 0.92).

### Relations Between TCD Emboli and Poststenting DWI Lesions

A multivariable negative binomial regression showed no effect of the number of total emboli on expected DWI count.

**Figure 2.** The mean count of all embolic signals on transcranial Doppler according to size and carotid angioplasty and stenting step.
adjusting for age and symptoms’ status \( (P=0.5) \). However, malignant emboli had a significant association with expected DWI lesions count. For every malignant embolus, the expected DWI count would increase by a factor of 1.1\% after adjusting for age and symptoms’ status \( (95\% \text{ confidence interval, } 0\%–2\%; P=0.032) \).

**Symptomatic Versus Asymptomatic Subjects**

The study enrolled 7 asymptomatic subjects \( (23.3\%) \). The median number of DWI lesions on poststenting MRI was not different between asymptomatic and symptomatic subjects \( (4 \text{ in each group}) \). The median number of total emboli was also not different between the asymptomatic versus symptomatic groups \( (169 \text{ and } 217, \text{ respectively; } P=0.6) \). In addition, no difference was noted in the median number of malignant emboli between the asymptomatic and symptomatic groups \( (62 \text{ versus } 84, \text{ respectively; } P=0.3) \).

**Discussion**

We observed a high incidence of embolic signals on TCD during the stenting procedure, especially, when devices (protection device, balloons, or stent) were deployed. Postprocedure new ischemic lesions on MRI were observed in the majority of subjects \( (76.9\%) \), despite the use of protection devices. Most lesions had a very small total volume \( (\text{median } 0.5 \text{ mL}) \). Only 2 subjects \( (6.7\%) \) developed new or worsening neurological deficits. There was no difference in the qualifying events in subjects with versus without ischemic MRI lesions.

We did not identify an association between the TCD emboli total count and the number of DWI lesions, but malignant emboli predicted DWI lesions. This confirms a prior report describing the association of malignant TCD emboli with the presence of ulcerated carotid plaque or luminal thrombi and with poor clinical outcome in patients with carotid stenosis.

The lack of association between total emboli count and DWI lesion could have several explanations. Because the majority of embolic signals were microemboli, experimental studies have shown that smaller emboli tend to migrate to small penetrating arteries. It is possible that such emboli produced tiny infarcts beyond MRI resolution. It is also possible that the observed TCD embolic signals represent a mixture of air and solid emboli. Although it is plausible that solid emboli carry a higher risk of producing DWI lesions, it is unknown whether gaseous malignant emboli are benign. Stroke resulting from air emboli have been reported. In addition, gaseous emboli were shown to be independently associated with clinical stroke or new DWI lesions after carotid stenting.

In this study, TCD monitoring was restricted to the stenting procedure, whereas the MRI brain was done within 24 hours of the procedure. Therefore, any embolization occurring after the procedure might have been missed. The relative magnitude and importance of late embolization is not clear. There is evidence that embolization continues to occur after the stenting procedure. In a study on 59 patients who underwent MRI scans at 3 time points: before CAS, within 3.5 hours, and 18 hours after CAS, 12 patients \( (20.3\%) \) had new DWI lesions on the 3.5-hour MRI. In addition, the 18-hour MRI showed new lesions in 10 patients \( (17\%) \) who had either negative or fewer DWI lesions count on the first MRI. Late embolization might be another potential factor that accounts for the lack of significant associations between total intraprocedural emboli and DWI lesions.

A novel aspect of our study is the breakdown of CAS procedure into defined steps with detailed timing. The findings that stent and protection device deployments were the steps associated with highest embolic signals should help focus future efforts aiming to improve the stenting procedure safety. Most prior studies have not described detailed neurological event timing, and it is unknown whether these events occurred during the CAS procedure or immediately after. In the EV3-S study, all 17 strokes that occurred on the same day of CAS occurred during the procedure itself. Delayed events on the same day of the procedure or in the next few days have also been reported. The timing of these events may have implications for the underlying pathomechanisms. Intraprocedural neurological events could be related to embolization from the catheters and devices. Other mechanisms as hemodynamic instability and thromboemboli from the stent surface may play a role in the delayed events.

Transcranial monitoring during CAS could serve many purposes. The use of embolic signals as a risk marker for developing DWI lesions could help guide and evaluate individual steps in the stenting procedure. Potential applications may include testing the relative safety of new stents designs or whether the use of distal protection devices enhances the procedural safety.

This study has limitations. This is a single-center cohort where subjects were carefully selected to undergo stenting in a nonrandomized fashion for the presence of an absolute or relative contraindication for endarterectomy. This might have accounted for the observed high incidence of DWI lesions \( (76.9\%) \), after the procedure which exceeded the incidence reported in the literature \( (up \text{ to } 50\%) \). Moreover, this study used a 3-mm thickness MRI acquisition protocol detecting small lesions that would have been missed in the standard 5-mm DWI slices. The study reports only short-term results without long-term outcomes. The study recruited only 3 women \( (10\%) \), which could be related to 2 factors. First, there is evidence that women with carotid stenosis have better outcomes after endarterectomy than stenting and, therefore women could have been preferentially referred for endarterectomy. In this study, 1 of the 2 subjects with neurological worsening after stenting was a woman. Second, women are known to have poor or absent temporal acoustic window compared with men. The TCD recordings were interpreted by a single observer. Another limitation is restricting the TCD monitoring period to the CAS procedure itself. While doing extended monitoring, for example, first 6 to 12 hours after CAS may not have been feasible in all subjects; this can be considered in a subset of future recruits.

In this prospective cohort study, we have demonstrated the feasibility of performing TCD monitoring during carotid stenting procedures, a high incidence of emboli detected on TCD during devices deployments, particularly, stent deployment, and a preliminary observation that large emboli size predicts perioperative imaging–defined ischemic stroke.
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Disclosures

None.

References

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