

Asymptomatic Embolization Detected by Doppler Ultrasound Predicts Stroke Risk in Symptomatic Carotid Artery Stenosis

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Background and Purpose—Asymptomatic cerebral emboli can be detected using transcranial Doppler ultrasound (TCD). These embolic signals have potential as a marker of stroke risk and as a surrogate marker to evaluate antiplatelet agents. Small studies have demonstrated that they predict the combined endpoint of stroke and transient ischemic attack (TIA), but no studies have shown that they predict the more important endpoint of stroke alone.

Methods—TCD was used to record for 1 hour from the ipsilateral middle cerebral artery in 200 patients with >50% symptomatic carotid stenosis. The Doppler audio signal was recorded for later analysis blinded to clinical details. Subjects were followed-up prospectively until surgical intervention, stroke, or study end at 90 days.

Results—Embolic signals (ES) were detected in 89 (44.5%). During follow-up, 31 subjects experienced recurrent ipsilateral ischemic events: 7 strokes and 24 TIAs. The presence of ES predicted stroke alone ($P=0.001$) and the combined endpoint of stroke and TIA ($P=0.00001$). This remained significant, with an odds ratio of 4.67 (95% CI, 1.99 to 11.01; $P<0.0001$) after Cox regression to control for age, sex, smoking, hypertension, time from last symptoms, and degree of stenosis. The absence of ES identified a group at low risk for stroke alone and stroke and TIA during follow-up: 0% and 7.5%, respectively, versus 3.5% and 15.5% in all 200 subjects.

Conclusions—Asymptomatic embolization in carotid stenosis predicts short-term ipsilateral stroke risk. This supports use of the technique to identify patients at high-risk for recurrent stroke for therapeutic interventions and as a surrogate marker to evaluate antithrombotic medication. (*Stroke*. 2005;36:971-975.)

Key Words: carotid arteries ■ embolism ■ risk factors ■ stroke ■ ultrasonography

Improved methods of identifying patients at high risk for recurrent embolic events from large-artery atherosclerotic disease are required. This would allow more effective targeting of therapy and improve risk-benefit therapeutic ratios. One such situation is carotid stenosis. Carotid endarterectomy reduces stroke risk in recently symptomatic patients with >70% stenosis.^{1,2} In moderate symptomatic stenosis, the stroke risk is lower and operating has only moderate benefit, although certain high-risk subgroups may benefit more.^{3,4} Similarly, operating on an unselected group of patients with tight asymptomatic carotid stenosis has modest benefit.^{5,6}

A clear implication of these results is that better methods are required to identify those patients with carotid stenosis at high risk for stroke, particularly among those with tight asymptomatic carotid stenosis and moderate symptomatic carotid stenosis.⁷ A number of markers of increased risk have been suggested, including degree of stenosis, plaque ulceration and morphology, brain infarction, and impaired intracerebral hemodynamics.⁷ Although these may allow some risk stratification, most have not been shown to be reliable independent markers of high risk. In patients with carotid

stenosis, stroke is usually caused by embolism. Furthermore, transient ischemic attack (TIA), which is itself associated with markedly increased risk of subsequent stroke, is also believed to be usually caused by embolization. Therefore, an attractive potential risk marker is the detection of asymptomatic embolization using transcranial Doppler ultrasound (TCD).

Solid cerebral emboli, composed of thrombus and platelet aggregates, can be detected using TCD.^{8,9} Cross-sectional studies have suggested such embolic signals (ES) are clinically important, being more common in patients with symptomatic stenosis,^{9,10} recent symptoms,^{11,12} and plaque ulceration.¹³⁻¹⁵ A number of relatively small studies¹⁶⁻¹⁹ have shown that ES are predictors of combined TIA and stroke risk in symptomatic carotid stenosis, but the risk estimates have wide confidence intervals because of the small sample sizes. Furthermore, no studies have demonstrated prediction of the more important clinical endpoint of stroke alone. Therefore, in a single-center study, we recruited consecutive patients with recently symptomatic carotid stenosis, recorded for ES, and prospectively followed-up all patients to determine

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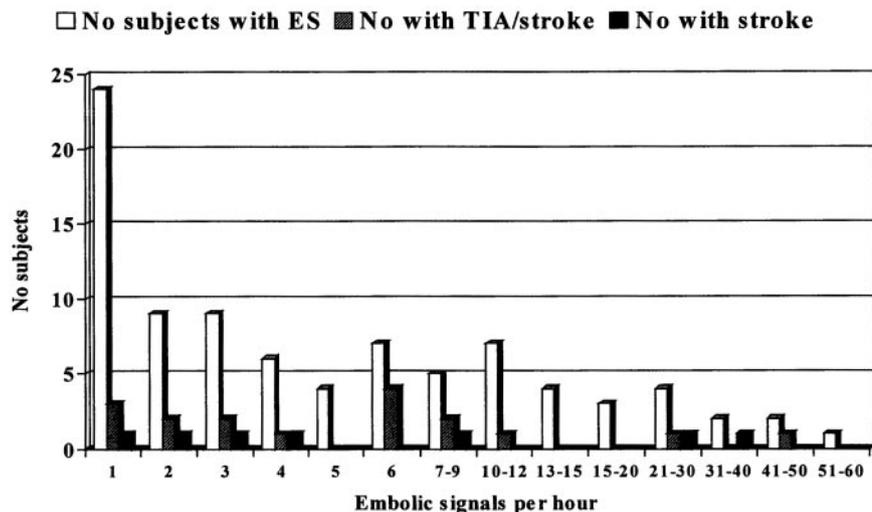


Figure 1. The distribution of ES frequency in the 89 subjects in whom ESs were detected. Also shown is the number in each group who experienced TIA or stroke, and stroke alone, during the follow-up period.

whether the presence of ES during a single 1-hour recording predicted subsequent short-term stroke risk.

Materials and Methods

Two hundred twenty-six consecutive patients presenting with $\geq 50\%$ symptomatic carotid stenosis, as determined using duplex ultrasound, and no obvious cardiac embolic source were prospectively recruited. Of these, successful insonation of the ipsilateral middle cerebral artery (MCA) was possible in 200. Symptomatic status was defined as ipsilateral stroke, TIA, or amaurosis fugax within the past 3 months. The first consecutive 54 subjects have been reported previously.¹⁶ There were no differences in demographics between these 54 subjects and the remaining 146 subjects (mean age, 66.1 [9.7] versus 68.2 [10.7], $P=0.188$; male gender, 35 [64.8%] versus 88 [60.3%], $P=0.558$; hypertension, 34 [63.0%] versus 109 [74.7%], $P=0.104$; current smoking, 18 [33.3%] versus 45 [30.8%], $P=0.734$; time since last event, 36.1 [30.9] versus 29.2 [39.3] days, $P=0.249$; proportion with embolic signals, 28 [51.9%] versus 61 [41.8%], $P=0.203$; or the presence of ipsilateral brain infarction, 27 [50.0%] versus 90 [62.5%], $P=0.220$).

TCD recordings were made from the MCA ipsilateral to the stenosis via the transtemporal route. All recordings were made using a commercially available TCD machine (EME Pioneer 4040; EME) with a 2-MHz probe held in position with an external fixation device. Standard settings were used with a sample volume of 5 mm. Median (range) depth of insonation was 52 (46–56) mm. Each patient underwent recording for 1 hour.

The Doppler audio signal was recorded onto digital audio tape. Tapes were analyzed at a later date by an experienced investigator blinded to the patient identity, and all candidate signals were reviewed by a second observer who remained the same throughout the study. At this time, the recorded Doppler signal was replayed into the same TCD machine, at the same sweep speed of 5.1 seconds, and 128-point fast-Fourier transform spectral analysis was performed with an overlap of $>50\%$. ES were identified by their typical visual appearance on the spectral display and their characteristic sound, according to standard consensus criteria,²⁰ with the addition of an intensity threshold of >7 dB, with intensity measured by a standard method.²¹

All study subjects were prospectively followed-up until stroke, carotid endarterectomy or carotid angioplasty/stenting, death, or study completion at 90 days after recruitment. No patients had treatment delayed in any way for the purposes of study, and the project was approved by the Local Hospital Ethics Committee, and all patients gave signed informed consent. Recurrent stroke was confirmed by CT or MRI. All endpoints were reviewed by an experienced clinician blinded to the results of ES detection.

Statistical Analysis

The relationship between ES and subsequent ipsilateral events was determined using Kaplan–Meier analysis. Censor points were ipsilateral TIA or stroke, carotid endarterectomy, carotid angioplasty/stenting, and nonstroke death. Separate analysis was performed for ipsilateral stroke alone, and for the combined endpoint of ipsilateral stroke and TIA. Data were also analyzed using a Cox regression model to allow controlling for other risk factors. This is only valid when there is a sufficient number of endpoints (recurrent events) and therefore was only performed for the combined endpoint of stroke and TIA, and not for stroke alone. The number of ES per hour in subjects with ES was not normally distributed; therefore, a logarithmic transform was necessary to obtain a normal distribution for analysis of relationships between ES frequency and recurrence. Data from the more recent 146 subjects and the previously reported initial 54 subjects were initially analyzed separately. Only when similar relationships between ES and recurrent events in the 2 data sets were demonstrated were the 2 data sets combined to increase the power to examine associations with ES and their independence from other risk markers.

Results

ES were detected in 89 (44.5%) subjects. In those subjects with ES present, most subjects had ≤ 5 per hour (median, 4.0; range, 1 to 57). The distribution of ES frequencies is shown in Figure 1. Demographic details in subjects with and without ES are shown in Table 1. There were no differences in age, gender, current smoking, or hypertension. There was a negative correlation between time since last symptoms and the number of ES per hour (Spearman $\rho = -0.164$; $P=0.02$) and the mean (SD) time since last symptoms was shorter in patients with ES (22.5 [25.2] versus 38.2 [23.5] days; $P=0.002$). There was no relationship between antiplatelet therapy at time of recording and the presence of ES (Table 1), although there was a trend toward fewer ES in subjects on the combination of clopidogrel and aspirin versus other combinations (1 of 9 versus 88 of 191; χ^2 with Yates correction $P=0.085$).

In the new 146 patients, there were 21 recurrent ipsilateral events: 5 strokes and 16 TIAs. There was a significant relationship between ES and both stroke alone (Kaplan–Meier log rank 8.87; $P=0.0029$) and TIA and stroke (log rank 13.75; $P=0.0002$). Associations with future events were consistent between the new 146 patients and the initial 54

TABLE 1. Details of Risk Factors and Other Potential Risk Markers in Subjects With or Without Embolic Signals

	ES Positive (n=89)	ES Negative (n=111)	P
Age	67.79 (10.96)	68.57 (10.16)	0.605
Male	52	71	0.424
Hypertension	26	31	0.841
Current smoker	31	32	0.141
Symptomatic event			0.633
Stroke	49	58	
TIA/amaurosis fugax	40	52	
Ipsilateral CT infarct	54	63	0.697
Antiplatelet therapy			0.228
None	10	13	
Aspirin	65	75	
Aspirin and dipyridamole	13	15	
Aspirin and clopidogrel	1	8	
Carotid stenosis (%)	85.0 (11.9)	82.4 (15.0)	0.175
Days since last event	22.5 (25.17)	38.2 (23.52)	0.002

subjects. In the first 54 subjects, 8 of 28 (28.57%) with ES had recurrent events, and in the second 146, 16 of 61 (26.23%) with ES had recurrent events ($\chi^2 P=0.817$). Therefore, to explore associations further, the full data set was explored. In the 200 subjects during follow-up, 31 subjects experienced recurrent ipsilateral ischemic events: 7 strokes and 24 TIAs. A significant association was found between ES and both stroke alone (Kaplan–Meier log rank statistic 10.85; $P=0.001$) and the combined endpoint of stroke and TIA (log rank statistic 18.52; $P=0.00001$), shown graphically in Figure 2. This remained significant after Cox regression was used to control for age, sex, current smoking, hypertension, degree of stenosis, and time since last symptoms, with an adjusted odds ratio of 4.67 (95% CI, 1.99 to 11.01; $P<0.0001$). Also, entering antiplatelet therapy during follow-up as aspirin alone (N=138), aspirin and dipyridamole (N=43), or clopidogrel with or without aspirin (N=19) did not alter the relationship between ES and recurrent events (odds ratio, 4.72; 95% CI, 1.99 to 11.19; $P<0.0001$). There was no significant independent association between any of the other variables and risk of stroke and TIA. (Table 2).

The predictive value of a recording negative for ES at baseline was determined. A negative recording, present in 111 subjects, was associated with an ipsilateral stroke risk during follow-up of 0% (compared with an event rate in all 200 subjects of 3.5%) and a combined ipsilateral stroke and TIA rate of 7.4% (compared with an event rate in all 200 subjects of 15.5%).

The possibility of a threshold of ES frequency above which risk was higher was explored in those 89 subjects with ES at baseline. The distribution of recurrent events related to the ES frequency is shown in Figure 1. There was a weak trend to higher ES counts per hour in subjects with stroke alone, compared with TIA, compared with no events, during follow-up, but this was not significant (log [SD] mean ES per hour: stroke alone, 0.743 [0.562]; TIA, 0.655 [0.462]; no recurrent

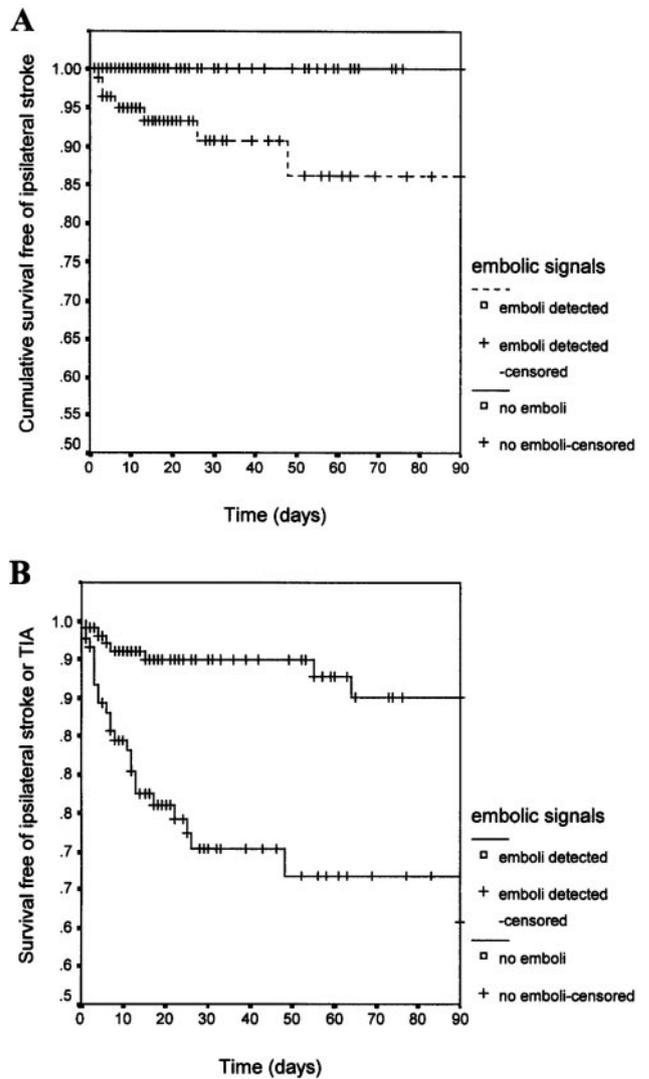


Figure 2. Kaplan–Meier survival plots showing the relationship between the presence of embolic signals and recurrent ipsilateral stroke (A), and recurrent ipsilateral TIA and stroke (B). Censored events include carotid endarterectomy, carotid angioplasty, and nonstroke death.

event, 0.580 [0.504]; ANOVA $P=0.651$.) Using a threshold of an ES count above the median (>4 ES per hour) did not improve prediction of future stroke and TIA compared with a threshold of 1 or more ES per hour, for stroke alone (log rank

TABLE 2. Relationship Between Risk Factors and Subsequent Risk of Stroke and TIA During Follow-up, Determined Using Cox Regression

Risk Factor	Odds Ratio	95% CI	P
Age, y	0.982	0.945–1.020	0.349
Male	1.836	0.896–3.762	0.097
Hypertension	0.719	0.317–1.628	0.428
Current smoker	0.813	0.340–1.941	0.641
Degree of stenosis, %	1.006	0.979–1.033	0.675
Ipsilateral CT/MRI infarct	1.540	0.861–2.755	0.146
Time since symptoms, d	0.983	0.964–1.002	0.072
Embolic signals detected	4.674	1.985–11.007	0.000

statistic 3.19 [$P=0.0739$] versus 10.85 [$P=0.001$], respectively), and for TIA and stroke log rank statistic (9.95 [$P=0.0016$] versus 18.52 [$P=0.00001$], respectively).

Discussion

This study provides the first evidence to our knowledge that asymptomatic ES predict stroke risk in patients with symptomatic carotid stenosis. The larger sample size also allows the predictive value of ES to be estimated with greater confidence. Previous studies have found an association with the combined end point of TIA and stroke but not with stroke alone. Stroke is the clinically relevant end point; therefore, it is important that any association is proven with stroke alone. The presence of ES was a much stronger predictor of future ischemic events than conventional risk factors or other suggested markers, including degree of stenosis and presence of ipsilateral CT infarction. Consistent with previous epidemiological data,²¹ more recent symptoms were associated with increased risk of recurrent events, and in line with this patients with ES had had symptoms more recently. However, multivariate analysis demonstrated that the association with ES was independent of time since last symptoms, and after controlling for the presence of ES the association between recurrent event risk and time from last symptoms was no longer significant. This is consistent with embolization being the pathogenic mechanism in patients with carotid artery stenosis. Our results therefore provide further evidence that Doppler ES detection allows detection of a high-risk group. The absence of ES also identifies a group at low risk for recurrent stroke and TIA.

Doppler ES detection has a number of potential applications in patients with carotid stenosis. For >70% symptomatic stenosis, carotid endarterectomy is of proven benefit, and operating very soon after the event has been associated with a markedly improved outcome.^{1,2} Therefore, urgent endarterectomy is indicated if the patient is fit. However, in patients with completed stroke, many surgeons wait up to 1 month before operating. In addition, in a number of countries, because of resource issues, patients wait a few weeks for carotid endarterectomy. In such cases, ES detection may allow identification of a particularly high-risk group of patients who merit expedited endarterectomy or, if this is not possible, more aggressive antiplatelet therapy. In the recent Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic carotid Stenosis (CARESS) study, combination therapy with clopidogrel and aspirin was associated with a marked reduction in ES, compared with aspirin alone.²²

In patients with 50% to 70% carotid stenosis, the benefit of surgery is less clear, particularly if patients do not undergo operation within the first month.⁴ In this group, ES may allow a high-risk subset to be identified who particularly benefit from endarterectomy. The benefit of surgery in asymptomatic carotid stenosis is even less marked. The recent ACST demonstrated that 32 patients need to undergo operation to prevent one disabling stroke or death over a 5-year period.⁶ Studies are required to determine whether the presence of ES has a similar predictive value in this group; the ongoing Asymptomatic Carotid Emboli Study (ACES) is addressing this issue.²³ Doppler ES detection is also being increasingly

used as a surrogate marker to evaluate the efficacy of antiplatelet agents. Therapeutic efficacy for different agents has been demonstrated in a number of single-center studies,^{24–28} and more recently in the multicenter CARESS trial.²² All of these studies have been in patients with carotid artery disease. The demonstration that ES predict stroke alone, rather than the combined endpoint of TIA and stroke, strengthens their validity as a clinically relevant surrogate end point.

Our study design has a number of strengths. Investigators were blinded to the results of ES recordings reducing bias, which is particularly an issue with diagnosis of TIA. Our sample size is significantly larger than previous studies looking at the predictive value of ES. However, even with a sample size of 200, the number of strokes was small. Therefore, we were unable to perform multivariate analysis with the endpoint of stroke alone. However, Cox regression with the combined endpoint of TIA and stroke demonstrated the independent predictive value of ES. A larger sample size would require a multicenter collaboration. Furthermore, with the increasingly aggressive approach toward treating patients with symptomatic carotid stenosis such a study would be difficult to perform.

Our study recruited subjects over an 8-year period during which the use of antiplatelet agents treatment changed significantly. We examined this in 2 ways. First, we correlated the presence of ES with therapy at the baseline recording. Particularly early in the study, some patients were recruited before any agent was started. There was a trend to less ES with clopidogrel compared with other agents. Real effects of different agents can only be examined by randomized trials, but this trend was consistent with the results of the recent CARESS study. Second, we determined whether different treatments during follow-up could confound the relationship between ES and recurrent events; however, the relationship remained of similar magnitude after this was controlled for.

In this study, we classified patients according to whether any ES were present. In those subjects with ES, we found no clear relationship between the rate of ES per hour and the risk of recurrent stroke and TIA. Using a higher threshold to identify frequent embolizers did not increase the predictive power of the technique. Therefore, with current technology we would advise classifying patients according to whether any ES can be detected. However, the hour duration of recording we used is short for a dynamic process such as embolization. It is now possible to perform prolonged recordings of up to 8 hours using ambulatory transcranial Doppler systems.²⁹ This gives a better estimate of ES load, and it may be possible to more accurately predict recurrent events using this technology and classifying patients according to the rate of embolization.

In patients with symptomatic stenosis who had ES, the early risk of recurrent stroke was $\approx 8\%$. This is consistent with recent data that suggests that the risk of recurrent stroke after TIA is much higher than previously recognized,^{30,31} and that this increased risk is largely accounted for by patients with large-artery disease.³¹ This emphasizes the need for urgent treatment of TIA and minor stroke. In cases suitable and fit for carotid endarterectomy, the benefit of rapid surgery

has been demonstrated;⁴ however, in patients not fit for urgent operation, more aggressive antiplatelet therapy may be appropriate. Although combination antiplatelet therapy has not been proven to be of major benefit in the long-term secondary prevention of stroke, it may be of benefit in the acute phase. This is supported by the results of the CARESS trial and is being evaluated in current studies such as the FASTER study.²²

In conclusion, our study provides a first evidence to our knowledge that asymptomatic ES predict stroke risk in patients with carotid artery stenosis. This technique may have use in risk stratification and also as a surrogate marker for evaluating antithrombotic therapy.

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