Asymptomatic Embolization in Subjects With Atrial Fibrillation Not Taking Anticoagulants
A Prospective Study

Marisa Cullinane, BSc; Ray Wainwright, MD; Angie Brown, MD; Mark Monaghan, PhD; Hugh S. Markus, DM

Background and Purpose—Embolism is believed to be the major cause of stroke in patients with nonvalvular atrial fibrillation (NVAF). The detection of asymptomatic embolic signals (ES) in individuals with NVAF might allow identification of patients at high risk of stroke and monitoring of therapy in individual subjects. We determined the frequency of asymptomatic ES in patients with NVAF who were not taking warfarin.

Methods—Bilateral transcranial Doppler recordings were made for 1 hour from the middle cerebral arteries of 111 successive patients with NVAF taking aspirin alone or no antithrombotic or anticoagulant therapy. Adequate recordings could be made in 86 patients. In 79 subjects, recordings were performed on a second occasion to study temporal variability. Recordings for a single hour were also made in 30 age-matched control subjects.

Results—ES were detected in 13 (15.1%) of NVAF subjects but in no control subjects ($P = 0.02$). ES were detected both in subjects with symptomatic NVAF (4 of 30 [13.1%], $P = 0.04$ versus controls) and asymptomatic NVAF (9 of 56 [16.1%], $P = 0.02$ versus controls). There was no correlation between the presence of ES and smoking status, diabetes, hypertension, aspirin use, aspirin dose, symptomatic status, left atrial size, left ventricular function, or the presence of left atrial thrombus detected on transthoracic echocardiography. Repeating the recording increased the number of patients with ES to 21 (26.6%). On considering the results of both recordings, again there was no association for either recording between the presence of ES and smoking status, diabetes, hypertension, aspirin use, aspirin dose, age, symptomatic status, left atrial size, or left ventricular function. On repeating the recording, in the symptomatic group only 2 patients (8%) changed status, in contrast to 15 (29%) in the asymptomatic group.

Conclusions—ES can be detected in patients with NVAF at a low frequency. Particularly in asymptomatic patients, ES show marked temporal variability. We found no correlation between the presence of previously reported clinical and echocardiographic markers of increased stroke risk and the presence of ES. This association requires further investigation before the clinical utility of this technique in patients with NVAF is decided. (Stroke. 1998;29:1810-1815.)

Key Words: atrial fibrillation ■ cerebrovascular diseases ■ cerebral embolism ■ ultrasonics
failure can only be determined when stroke has occurred. Recently, it has been demonstrated that circulating cerebral emboli can be detected using Doppler ultrasound. In vitro and in vivo studies have shown the technique to be both sensitive and specific. 1-9 Embolic signals (ES) have been detected in patients with a variety of potential embolic sources, including symptomatic and asymptomatic carotid stenosis10,11 and prosthetic heart valves.12,13 Considering the frequency and importance of emboli as a cause of stroke on a population basis, there have been few studies using this technique in subjects with atrial fibrillation. In the largest study to date, Infeld et al14 performed recordings in 54 patients with atrial fibrillation, half of whom had presented with recent stroke, and in 19 control subjects in sinus rhythm. ES were detected in 22% of symptomatic subjects and in 7% of asymptomatic subjects, but many patients were taking warfarin, which may have reduced the incidence of ES. There have been no large studies in patients not taking warfarin. In this study, we recruited successive patients with NVAF who were not taking warfarin or other anticoagulants and determined the prevalence of asymptomatic ES. We correlated the presence of ES with clinical and echocardiographic markers of increased risk. By repeating the recordings on a second day, we determined the variability in the frequency of ES over time.

Subjects and Methods

Subjects
Successive subjects identified with NVAF who were taking no antplatelet therapy or were taking aspirin were considered for the study. Patients taking warfarin or heparin were excluded. Asymptomatic subjects with NVAF were prospectively identified from clinics providing cardiac and health care for the elderly and from routine screening of electrocardiographs and 24-hour electrocardiograms performed within the cardiology department. Symptomatic subjects were recruited from successive patients presenting to the neurology service and the acute stroke unit. Subjects were classified as symptomatic if they had experienced stroke or TIA within 1 year of the first recording. Spouses and urology outpatients in sinus rhythm and with no history of stroke or TIA were used as age-matched control subjects. Both control and NVAF subjects underwent a carotid duplex ultrasound scan and were excluded if carotid stenosis (>50% diameter) was present. Subjects were defined as smokers if they currently smoked cigarettes, as hypertensive if they were taking hypertensive therapy or if blood pressure was >160 mm Hg systolic or >95 mm Hg diastolic, and as diabetic if they had insulin-dependent or non–insulin-dependent diabetes mellitus.

In all patients with NVAF in whom technically successful transcranial Doppler recordings could be performed, transhoracic echocardiography was planned. All echocardiograms were performed using a Sonos 1500 (Hewlett-Packard Ltd). Left atrial size was measured in the long axis parasternal view using M-mode, and a mean of 3 readings was taken. Left ventricular function was measured using Simpson’s method of discs in the long- and short-axis apical views to estimate the ejection fraction. However, in a number of patients, endocardial border detection was insufficient for ejection fraction estimation. Therefore, a subjective measure of left ventricular function was also recorded for each subject; left ventricular function was placed into 1 of 5 categories (from 1 = normal to 5 = very poor). All echocardiography was performed by an operator blinded to the results of the transcranial Doppler recording. In all patients with NVAF, blood was taken for determination of fibrinogen level, which was derived from the prothrombin time.

Transcranial Doppler Recordings

Transcranial Doppler ultrasonography was performed using a Pioneer TC4040 (Nicolet-EME Ltd) with a 2-MHz transducer. A sample volume of 10 mm and a sweep speed of 5 seconds were used for all patients. A 128-point fast Fourier transform (FFT) was used for spectral analysis. FFT time-window overlap was >66%. The subject was placed in a sitting position, the middle cerebral artery (MCA) was identified via the transtemporal window, and the transducer was fixed in position using a standard headset. Bilateral recordings were performed for 1 hour. Mean ± SD depth of insonation of the MCA was 53.0 ± 4.0 mm on the left and 52.4 ± 3.9 mm on the right. The Doppler signal was stored on digital audiotape using a TCD-D7 recorder (Sony Ltd). In all subjects who consented, the recording was repeated on 1 further occasion approximately 1 week later to determine variability. The results of the first study were not known at the time of the second recording. All subjects gave informed consent, and the study was approved by the local hospital ethics committee.

Analysis was performed off-line by an observer (observer 1) blinded to both subject group and whether subjects were controls or not. An ES was identified as a predominantly unidirectional short-duration intensity increase, accompanied by a characteristic clicking or chirping sound.15 A threshold of >7 decibels was used because this has been shown to increase interobserver agreement without too great a loss of sensitivity.16 Intensity was determined from measurements made using the color scale on the spectral display of the peak intensity of the embolic ES, and the intensity of the background spectra at the same frequency and part of the cardiac cycle, from the preceding or subsequent cardiac cycle. All possible ES detected were saved and then reviewed by a second experienced observer (observer 2); if both observers agreed that the signal was an ES, it was then included in subsequent analysis. Interobserver reproducibility in identifying ES was assessed by the 2 observers independently analyzing a separate recording that was 105 minutes long and had been prepared from MCA recordings from 6 patients. Agreement was calculated using the proportion of specific agreement, which estimates the probability that 1 observer will identify a specific ES if another observer has identified it, with a probability of 1 indicating complete agreement.17 Observer 1 detected 90 ES, and the agreement of observer 1 with observer 2 was 0.88. Observer 2 detected 89 ES, and the agreement of observer 2 with observer 1 was 0.87.

Data Analysis

Not all patients agreed to participate in 2 recordings, and therefore a first analysis was performed using only the results of the first recording for all patients. These analyses were then repeated using combined data from both recordings in those patients for whom 2 recordings had been made. For all calculations, a patient was defined as being ES-positive if ES were detected in either MCA and on either recording in the analysis of data from both occasions. The rate of embolization was expressed as the number of ES per hour of recording from each MCA, ie, a patient with a successful bilateral recording for 1 hour had 2 hours of successful recording. The difference in the proportion of NVAF subjects with ES compared with controls was determined by the χ² test. The association between the presence of ES and clinical characteristics, symptomatic status, or echocardiographic criteria was determined using χ² tests (with Yates’ correction where appropriate) or t tests as indicated. In those patients in whom ES were detected, comparison was made between the number of ES per hour and a number of clinical parameters; as the distribution of ES frequency was skewed, nonparametric statistics were used for this analysis (Mann-Whitney U test and Spearman’s rank correlation coefficient as appropriate).

Results

Subject Characteristics

One hundred eleven successive subjects identified with NVAF were prospectively recruited. Twenty-three had no acoustic window; therefore, recordings were performed in 88.
Two further patients were excluded after echocardiography showed other significant cardiac disease (mixed mitral valve disease in 1, hypertrophic cardiomyopathy in 1). Therefore, recordings were analyzed in 86 patients with NVAF. Of these, 56 were asymptomatic with a mean±SD age of 75.2±9.2 years, and 30 were symptomatic with a mean age of 73.7±9.4 years. Seven had paroxysmal NVAF, and the remainder had chronic continuous NVAF. In symptomatic patients, the mean number of days between symptoms and first recording was 49.6 days (range, 1 to 227 days). In 84 of the 86 subjects, bilateral recordings were performed, but in 2 subjects the MCA could only be identified on 1 side, and therefore unilateral recordings were performed. Seven subjects did not have a further recording because of refusal to return or illness; therefore, 79 subjects had a second 1-hour recording. All 7 patients with paroxysmal NVAF had successful bilateral recordings on 2 occasions. Thirty normal control subjects were prospectively recruited with a mean±SD age of 71.9±7.9 years. In all, a single 1-hour bilateral recording was performed. The clinical characteristics of the 86 NVAF subjects and the 30 controls are shown in Table 1.

### Results for 1-Hour Recording
ES were detected in 13 (15.1%) of NVAF subjects but in no controls (P=0.02). They were detected in subjects with both symptomatic NVAF (4 of 30 [13.3%], P=0.04 versus controls) and asymptomatic NVAF (9 of 56 [16.1%], P=0.02 versus controls).

There was no difference in the proportion of patients with symptomatic or asymptomatic NVAF who had ES (P=0.74). The association of ES with clinical features is shown in Table 2. There was no association between the presence of ES and smoking status, diabetes, hypertension, aspirin use, aspirin dose, or symptomatic status. ES were detected in more female than male patients with NVAF (76.9% versus 23.1%, P=0.04). There was no difference in mean±SD fibrinogen levels between ES-positive and ES-negative subjects (4.68±1.2 versus 4.56±1.2 g/L, P=0.45).

Echocardiography was performed in 81 of 86 subjects with NVAF, of whom 13 were ES-positive and 68 ES-negative. Mean±SD left atrial size was 3.76±0.87 cm in ES-positive patients and 3.97±0.80 cm in ES-negative patients (P=0.45). Left ventricular function was poor or very poor (grades 4 or 5) in 2 (15.4%) ES-positive compared with 3 (4.4%) ES-negative patients (P=0.38). In those subjects in whom it could be determined (n=67), there was no difference in ejection fraction between patients with and without ES (mean±SD: 56.3±16.9% versus 51.5±15.1%; P=0.40).

### Results for Two 1-Hour Recordings
Considering all 79 subjects with NVAF who had 2 recordings, ES were detected in 21 (26.6%). There was no differ-

---

**TABLE 1. Characteristics of NVAF and Control Groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NVAF (n=86)</th>
<th>CONTROL (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD age, y</td>
<td>74.7±9.3</td>
<td>71.9±7.9</td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>51:35</td>
<td>25:5</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>30 (34.9)</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>2 (2.3)</td>
<td>0</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>10 (11.6)</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>17 (19.8)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td>13 (15.1)</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>On aspirin, n (%)</td>
<td>62 (72.1)</td>
<td>0</td>
</tr>
<tr>
<td>Mean±SD aspirin dose</td>
<td>109.0±105.9</td>
<td>0</td>
</tr>
<tr>
<td>Paroxysmal AF, n (%)</td>
<td>7 (8.1)</td>
<td></td>
</tr>
</tbody>
</table>

MI indicates previous myocardial infarction.

---

**TABLE 2. Relationship Between Presence of ES and Cardiovascular Risk Factors, Aspirin Therapy, and Echocardiographic Indices in All Subjects With NVAF**

<table>
<thead>
<tr>
<th></th>
<th>One TCD Recording (n=86)</th>
<th>Two TCD Recordings (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ES-Positive (n=13)</td>
<td>ES-Negative (n=73)</td>
</tr>
<tr>
<td>Age, y</td>
<td>76.1±9.4</td>
<td>74.4±9.3</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>3 (23.1)</td>
<td>48 (65.8)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>2 (15.4)</td>
<td>8 (11.0)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>4 (30.8)</td>
<td>26 (35.6)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>2 (15.4)</td>
<td>8 (11.0)</td>
</tr>
<tr>
<td>Symptomatic status, n (%)</td>
<td>4 (30.8)</td>
<td>26 (35.6)</td>
</tr>
<tr>
<td>Taking aspirin, n (%)</td>
<td>8 (61.5)</td>
<td>54 (74.0)</td>
</tr>
<tr>
<td>Daily aspirin dose, mg</td>
<td>95.5±104.0</td>
<td>113.7±106.9</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>3 (23.1)</td>
<td>14 (19.2)</td>
</tr>
<tr>
<td>LA size, cm</td>
<td>3.76±0.87</td>
<td>3.97±0.80</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>56.3±16.9</td>
<td>51.2±15.1</td>
</tr>
</tbody>
</table>

Data are presented for the first recording and then for the combination of the 2 recordings in those subjects who had 2 recordings. Not all patients had echocardiography; therefore, percentages given are with respect to those who did. Ejection fraction was estimated in 67 patients with 1 recording and 65 patients with 2 recordings.

TCD indicates transcranial Doppler; MI, myocardial infarction; LA, left atrial; and LV, left ventricle. Values are mean±SD unless otherwise indicated.
ence in the proportion of symptomatic and asymptomatic patients with ES detected on either occasion: 5/27 (18.5%) versus 16/52 (30.8%), \( P = 0.24 \). As for the single recording, there was no association between patients who were ES-positive on either recording and smoking status, diabetes, hypertension, aspirin use, aspirin dose, age, symptomatic status, left atrial size, left ventricular function, or ejection fraction (see Table 2).

The results were similar when only those patients with continuous NVAF were considered for the single 1-hour recording and when both 1-hour recordings were considered (Table 3).

**Other Analyses**

Considering all symptomatic NVAF subjects, there was no correlation between the frequency of ES and time from last symptoms to current recording for either the first or second recording period (first recording, \( \rho = 0.16, P = 0.40 \); second recording, \( \rho = -0.02, P = 0.91 \)). There was also no association between the presence of ES and recent symptoms when the data were analyzed using a cutoff of 28 days as indicating recent symptoms (first recording: recent symptoms, 2/16 ES-positive; no recent symptoms, 2/14 ES-positive \( [P = 0.9] \); second recording: recent symptoms, 3/12 ES-positive; no recent symptoms, 2/15 ES-positive \( [P = 0.4] \)).

In subjects who were positive for ES, and when considering only the first recording, the median rate of embolization was greater in symptomatic than asymptomatic subjects: 1 (range, 0.5 to 5.5) versus 0.5 (0.5 to 1.0) per hour, \( (P = 0.02) \). Considering only the second recording, there was no difference between the 2 groups: symptomatic, 0.5 (0.5 to 1.0); asymptomatic, 1.0 (0.5 to 2.0) per hour \( (P = 0.14) \). Considering all ES, there was no difference in the intensity of ES between asymptomatic and symptomatic subjects with NVAF (mean \( \pm \) SD intensity: symptomatic, 10.26 \( \pm \) 3.4 dB; asymptomatic, 11.32 \( \pm \) 4.8 dB; \( P = 0.84 \)).

**Temporal Variability**

In the symptomatic group, only 2 patients changed status between the 2 recordings. Three subjects were ES-positive on both recordings and 22 ES-negative on both recordings. Two subjects were ES-negative on the first recording but positive on the second recording, while no subjects were ES-positive on the first recording and ES-negative on the second recording. In contrast, in asymptomatic patients there was marked variability between the results of recordings performed on the 2 occasions. In this group, only 1 subject remained ES-positive on both recordings, while 36 patients were ES-negative on both recordings. Seven subjects who were ES-negative on the first recording became ES-positive on the second recording, while 8 subjects who were ES-positive on the first recording became ES-negative on the second recording.

**Discussion**

Our results demonstrate that ES can be detected in subjects with NVAF who are not taking anticoagulants and are significantly more common in this group than in age-matched normal control subjects. However, ES were only found in a minority of subjects with NVAF and at a low frequency; in subjects with ES, the median rate was 1 per hour or less. There have been few studies of the prevalence of ES in atrial fibrillation, and in the majority of cases, atrial fibrillation has been only a small subgroup in a larger study of patients with potential embolic sources, but these studies also have reported ES in this group of patients. The largest study to date recorded for 30 minutes in 54 patients with atrial fibrillation and found ES in 2 of 27 asymptomatic patients compared with 6 of 27 symptomatic patients. However, interpretation of these results is complicated because many of the patients, and a larger proportion of symptomatic than asymptomatic patients, were taking anticoagulants. This is known to reduce stroke rate and therefore might reduce the rate of asymptomatic embolization. Our study prospectively
recruited a larger, more homogenous group of patients with NVAF, but despite the fact that none was taking warfarin, the rate of embolization remained low. The rate of embolization is lower than that reported in carotid artery stenosis, the condition in which most studies with Doppler embolic signal detection have been performed.  

In the subjects with NVAF, we found no relationship between the presence of ES and a number of known markers of increased stroke risk. ES were not more common in patients with cerebrovascular symptoms, and in symptomatic patients they were no more common in patients with recent symptoms. There was no reduction in their frequency in patients taking aspirin or in patients with echocardiographic markers of increased risk, such as increased left atrial size and impaired left ventricular function. Part of the lack of correlation with the echocardiographic data may be related to the insensitivity of transthoracic echocardiography, particularly in identifying left atrial thrombus. It was not considered ethical to perform transesophageal echocardiography in our primarily elderly patients solely for the sake of this study. The only association we found with ES was with female gender. There is no obvious pathophysiological explanation for this, and it may merely reflect the large number of statistical comparisons made. In contrast to the lack of association with markers of increased stroke risk, a number of previous studies in similar numbers of patients with carotid artery stenosis have found an association with a variety of markers of increased stroke risk in this group of patients, including symptomatic status, time from last symptoms, and plaque ulceration and thrombus.

The lack of an association in patients with NVAF between clinical and echocardiographic markers of risk may have a number of explanations. First, it may reflect the size of the study population, but we did not find even a trend toward an increased proportion of ES in symptomatic patients or patients with recent symptoms. Second, particularly in patients with asymptomatic NVAF, when recordings were repeated there was marked variability in which subjects were ES-positive, and this variability may weaken any association with markers of clinical risk. Third, it is possible that even if the majority of strokes in patients with NVAF are embolic in origin, the asymptomatic ES we detected are not clinically relevant and are not a good predictor of which patients will have clinically symptomatic emboli in this situation. It is likely that these asymptomatic ES are caused by small emboli, whereas stroke is likely to result from larger, less frequent emboli. Fourth and more controversial, embolism might not represent the primary pathogenic mechanism in many patients with NVAF. It has been suggested that the stroke risk in this group of subjects may partly reflect the high frequency and severity of cardiovascular risk factors in this population, who also have a higher prevalence of atheromatous disease, which itself directly causes stroke. The effect of anticoagulation in reducing stroke risk does not prove a causal association via a mechanism of cardiogenic embolism; anticoagulation could conceivably reduce stroke risk via reducing large artery to artery embolism and in situ thrombosis in these patients, as well as by reducing cardiogenic embolism. However, pathological studies support the concept that at least some strokes in these patients are caused by emboli. Further studies are required to determine the relevance of asymptomatic ES in this population. Initially, this should include determining the effect of warfarin, which is known to reduce stroke risk, on ES frequency; we are currently studying this in another group of patients with NVAF. It is possible that factors other than the mere presence or absence of ES could determine whether individual subjects are symptomatic. These could include the frequency or nature of the emboli. Although ES, in subjects who had ES, occurred at a higher rate in symptomatic compared with asymptomatic patients on the first recording, this difference could not be replicated when the data from the second recording was analyzed separately. The significant difference on the first recording may merely reflect the large number of comparisons made in our analysis. Some limited information on the nature and size of emboli can be derived from the intensity of ES. However, there was no difference in the mean intensity of ES in the symptomatic and asymptomatic groups. To determine variability over time and optimal recording protocols, we repeated the recording in subjects with NVAF wherever possible. In the symptomatic group, only 2 patients (8%) changed status in contrast to 15 (29%) in the asymptomatic group. Only 1 patient in this latter group remained ES-positive on both occasions. This variability makes the technique potentially less useful as a method of monitoring disease activity in individual patients. Further studies are required to determine how many recordings need to be performed before the proportion of ES-positive patients reaches a maximum and to determine optimal recording protocols to be used in studies of the predictive value of ES in predicting stroke risk in this group of patients.

In conclusion, we have demonstrated that asymptomatic ES occur in patients with NVAF who are not being treated with anticoagulants at a significantly greater frequency than in age-matched control subjects. Perhaps surprisingly, we found no correlation between the presence of ES and a number of known clinical and echocardiographic markers of increased stroke risk, although the reasons for this lack of association require further investigation.

Acknowledgments

This work was funded by a project grant from the Stroke Association of the UK. We thank Dr H. Hambley for performing fibrinogen assays. We thank the consultants who allowed us to study patients under their care, especially Professor S. Jackson, Professor C. Swift, Dr A. Blackburn, Dr J. Evans, and Dr P. Bath.

References


Asymptomatic Embolization in Subjects With Atrial Fibrillation Not Taking Anticoagulants: A Prospective Study
Marisa Cullinane, Ray Wainwright, Angie Brown, Mark Monaghan and Hugh S. Markus

Stroke. 1998;29:1810-1815
doi: 10.1161/01.STR.29.9.1810
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/29/9/1810