Temporal Variability of Asymptomatic Embolization in Carotid Artery Stenosis and Optimal Recording Protocols

Jane Molloy, MRCP; Naheed Khan; Hugh S. Markus, DM

Background and Purpose—Although asymptomatic embolization can be detected in patients with carotid artery stenosis, its temporal variability is unclear. An understanding of this is important in designing optimal recording protocols for future prospective studies of the predictive value of embolic signals (ES). We determined the effect of repeating and extending recording times in patients with symptomatic and asymptomatic carotid stenosis.

Methods—In 20 asymptomatic and 20 symptomatic subjects with >60% carotid stenosis, we used transcranial Doppler ultrasound to record for ES in the ipsilateral middle cerebral artery. Three 1-hour recordings were performed on three separate days, and on one occasion (not necessarily the first) the recording was extended to 2 hours. The recordings were saved onto digital tape for subsequent blinded analysis.

Results—Marked temporal variability was seen in symptomatic patients in whom the cumulative proportion of subjects with ES increased from 10 (50%) after a single hour of recording to 12 (60%) and 15 (75%) after two and three recordings, respectively. Extending the recording to 2 hours increased the yield of ES-positive patients from 6 (30%) to 8 (40%). In symptomatic patients there was excellent agreement between whether patients were positive for ES during each of two consecutive 1-hour recordings (κ=0.78, P=0.0003) but poor agreement between the results of two single-hour recordings performed on different days (κ=0.22, P=0.27). In asymptomatic patients, 4 (20%) were ES positive during the first hour; this increased to 5 (25%) after the recording was repeated once, with no further increase after the third recording. Extending the recording to 2 hours increased the yield from 3 (15%) to 7 (35%). In contrast to symptomatic stenoses, in patients with asymptomatic stenoses there was fair agreement between whether patients were ES positive on two consecutive 1-hour recordings (κ=0.49, P=0.01) or two single-hour recordings performed on different days (κ=0.48, P=0.02). Symptomatic subjects were more likely to have ES (when all 1-hour recordings were considered, 24/60 versus 10/60; P=0.0046). ES in asymptomatic subjects had a higher relative intensity increase than in asymptomatic subjects (P=0.01).

Conclusions—The temporal variability of ES needs to be taken into account in the design of optimal recording protocols and comparisons of results from different studies. Extending the duration of recording beyond an hour in symptomatic stenoses is of less value, but repeating the recording on a different day will often identify additional subjects with ES. In intervention studies in symptomatic patients, the time since last symptoms must be considered. In asymptomatic stenosis, extending the duration of recording beyond an hour will increase the proportion of patients positive for ES. (Stroke. 1998;29:1129-1132.)

Key Words: carotid artery diseases ■ cerebral embolism ■ ultrasonography, Doppler

With the use of transcranial Doppler ultrasound (TCD), embolic signals (ES) can be detected in patients with carotid artery stenosis (CAS). Although in this group of patients the value of ES as a predictive factor in stroke is not established, their presence correlates with a number of indirect markers of stroke risk. They are more frequent in symptomatic than in asymptomatic subjects, and in symptomatic patients they are more frequently detected soon after the appearance of symptoms. They are more frequent in patients with histologically proven plaque ulceration and thrombosis determined on carotid endarterectomy specimens and in patients with plaque ulceration demonstrated angiographically.

Previous studies have reported very different proportions of patients with CAS in whom ES can be detected. One reason for this may be the differing recording times used, which have ranged from 20 minutes to 2 hours. Furthermore, pilot studies have suggested a marked variability in the frequency of ES over time. Before larger prospective studies are performed, it is important to determine an optimum recording protocol. Both recording and subsequent data analysis are time consuming, increasing the importance of using a protocol that will maximize the possibility of ES detection without prolonging recording times unnecessarily.

Therefore, in this study we examined the incidence of ES in asymptomatic and symptomatic patients with CAS. We determined the effect on the proportion of patients in whom ES were detected by both repeating a recording and extending the recording time.
TABLE 1. Characteristics of the Two Study Groups

<table>
<thead>
<tr>
<th>Factor</th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Mean age (SD, range), y</td>
<td>66.75 (9.73, 42–82)</td>
<td>70.4 (8.41, 43–79)</td>
</tr>
<tr>
<td>Male sex</td>
<td>75%</td>
<td>65%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>55%</td>
<td>70%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>20%</td>
<td>40%</td>
</tr>
<tr>
<td>Smoker</td>
<td>85%</td>
<td>70%</td>
</tr>
<tr>
<td>Positive family history</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>Aspirin treatment*</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>Warfarin treatment</td>
<td>. . .</td>
<td>5%</td>
</tr>
</tbody>
</table>

*For symptomatic group on aspirin, doses are as follows: 75 mg, n=9; 150 mg, n=4; 300 mg, n=6. For asymptomatic group: 75 mg, n=13; 150 mg, n=3; 300 mg, n=3.

Subjects and Methods

Twenty symptomatic and 20 asymptomatic patients with >60% CAS as determined by TCD criteria were recruited and completed the study. Symptomatic patients were defined as having symptoms (amaurosis fugax, transient ischemic attack, or stroke) in the territory of the stenosed carotid artery within the last year. Patients with potential cardiogenic sources of emboli were excluded. Seven patients were considered but not recruited for the following reasons: 5 had no acoustic window, 1 underwent carotid endarterectomy before completion of the protocol, and 1 had a major stroke while awaiting surgery.

The demographic characteristics and treatment of the 40 patients are summarized in Table 1. For 39 of the 40 patients, antiplatelet and anticoagulant medication was left unaltered. The 40th patient suffered a gastrointestinal bleed, and aspirin was stopped between the first and second recordings. There was no difference in the degree of carotid stenosis between the two groups of patients: symptomatic, 60% to 79%, 5; symptomatic, 80% to 99%, 15; asymptomatic, 60% to 79%, 3; asymptomatic, 80% to 99%, 17 ($\chi^2=0.63$, $P=0.43$).

TCD recordings were made from the middle cerebral artery ipsilateral to the carotid stenosis by the transtemporal route. A commercially available TCD machine (EME Pioneer 4040) was used with a 2-MHz probe held in place with an external fixation device. Each patient was present on three separate occasions for a 1-hour recording, and on one occasion (but not always the first occasion) this was extended to a 2-hour recording. Mean (SD) time between recordings was 11.48 (10.09) days in the symptomatic group and 18.78 (10.09) days in the asymptomatic group. Mean (range) depth of insonation was 52.6 (48 to 56) mm. We aimed for an axial sample volume of 4 mm; when this delivered insufficient power for adequate recording, the sample volume was increased. Median (mean, range) sample volume was 5 mm (5.38, 4 to 12). Sample volume was kept constant for each patient for all three recordings. The Doppler audio signal was recorded onto digital audiotape. It was subsequently played back through the signal processor of the same TCD machine with the use of a 128-point fast Fourier transform and a fast Fourier transform overlap of >50%. All analyses were performed blinded to the clinical information or patient group. ES were identified by their characteristic sound. In addition, an intensity threshold of $\pm 7$ dB was used. The intensity was calculated from the color-coded intensity scale on the screen. This can be adjusted so that its intensity can be measured to the nearest decibel. The gain was reduced until the color of the adjacent cardiac cycle reached 0, and the peak intensity of the embolic signal was then determined. Interobserver reproducibility studies were performed for the two observers analyzing the tapes.

Statistical Analysis

All statistical analyses were performed on a PC with the use of SPSS for Windows and Genstat. The number of ES per tape was recorded, with a positive recording defined as one containing one or more ES. We evaluated the effects of repeating or prolonging recordings in two ways. First, we determined the cumulative yield resulting from extending and repeating the recordings. Second, we determined which recording protocol resulted in the greatest agreement between different recordings. For this analysis we treated the data as if they were two reproducibility studies: one with two consecutive 1-hour recordings (the 2-hour recording) and one with two nonconsecutive recordings (two 1-hour recordings repeated on different days). Kappa statistics were calculated, and their 95% confidence intervals were derived with the use of the approximate standard error of the kappa statistic provided by SPSS. The agreement was considered excellent for $k>0.75$, fair for $0.4<k<0.75$, and poor for $k<0.4$.

The distribution of the number of ES or their intensity was not normally distributed, and therefore differences were analyzed with the use of nonparametric statistics. In the symptomatic group, the relationship between time from last symptoms and the number of ES per hour was determined with Spearman’s correlation coefficient. To compare the number of ES per hour in the symptomatic and asymptomatic subjects, we attempted to fit a Poisson distribution, but because the variance was much greater than the mean, it was more appropriately fitted by a super Poisson distribution to allow for a dispersion parameter. We therefore applied the Wald test with the addition of a heterogeneity factor into the model to compensate for the variance.

Results

Effect of Repeating and Extending the Recording on the Cumulative Yield

For the purpose of this analysis, the first hour section of the 2-hour recording is treated as an individual 1-hour record. In this way, each patient effectively attended three separate occasions for 1-hour recordings. In symptomatic subjects, 10 (50%) were ES positive at the first examination. After two and three recordings, the cumulative proportion of ES-positive patients increased to 12 (60%) and 15 (75%), respectively. In asymptomatic subjects, 4 (20%) had a positive first recording. Single repetition of the recording gave a cumulative yield of 5 ES-positive patients (25%). A third recording provided no further increase in yield. As for symptomatic subjects, some subjects

TABLE 2. Increase in Proportion of ES-positive Patients Resulting From Increasing the Recording Time From 15 Minutes to 2 Hours for Both Symptomatic and Asymptomatic Patients

<table>
<thead>
<tr>
<th>Time From Start of Recording, min</th>
<th>No. of Positive Recordings (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Symptomatic</td>
</tr>
<tr>
<td>15</td>
<td>3 (15)</td>
</tr>
<tr>
<td>30</td>
<td>5 (25)</td>
</tr>
<tr>
<td>45</td>
<td>5 (25)</td>
</tr>
<tr>
<td>60</td>
<td>6 (30)</td>
</tr>
<tr>
<td>75</td>
<td>7 (33)</td>
</tr>
<tr>
<td>90</td>
<td>7 (33)</td>
</tr>
<tr>
<td>105</td>
<td>8 (40)</td>
</tr>
<tr>
<td>120</td>
<td>8 (40)</td>
</tr>
</tbody>
</table>

This was performed on a 2-hour recording comprising six 20-minute recordings from the ipsilateral middle cerebral artery in six patients with symptomatic carotid stenosis. The probability of agreement of observer 2 compared with observer 1 was 0.93.
who were ES positive on one recording were ES negative on the next recording.

The effect of extending the recording time (by 15-minute increments up to 2 hours) on the yield of ES-positive patients is shown in Table 2. In symptomatic patients during the 2-hour recording, 6 patients (30%) were ES positive by 1 hour; extending the recording for a further hour increased the yield to 8 (40%). In asymptomatic patients during the 2-hour recording, 3 patients (15%) were ES positive by 1 hour; extending the recording for an additional hour increased the yield to 7 (35%). The values for the yield in the first hour of the 2-hour recording are not necessarily the same as those for the first single-hour recording because the 2-hour recording was not always performed on the first occasion (see “Subjects and Methods”).

Comparison Between the Different Recording Strategies

This analysis was performed by treating the data as a “reproducibility” study. The comparison between different recording strategies is presented in Figure 1 and assessed by the kappa statistic. The greater the k value, the greater is the agreement between the two recordings, and therefore the less informative is the second recording. There was an excellent level of agreement between 2 consecutive hours of recording in symptomatic subjects (k = 0.78, P = 0.0003). In contrast, there was no significant agreement between two-hour-long recordings performed on different days in symptomatic patients (k = 0.22, P = 0.27). In contrast, in asymptomatic patients there was a fair level of agreement between two consecutive 1-hour recordings (k = 0.49, P = 0.01) and between two-hour-long recordings performed on different days (k = 0.48, P = 0.02).

Using a similar method of analysis, we determined whether it is more useful to perform a single 2-hour recording or two 1-hour recordings on separate days. We compared which patients were ES positive during the consecutive 2-hour recording with those detected during the summed 2-hour recording made up of two single-hour recordings performed on different days (Figure 1). For asymptomatic stenosis there was a fair level of agreement between the two methods of recording (k = 0.53, P = 0.01), whereas for symptomatic recording there was poor agreement (k = 0.15, P = 0.44).

Comparison Between Symptomatic and Asymptomatic Patients

When we considered all 1-hour recordings, a higher proportion of recordings with ES was found among symptomatic patients (24/60 versus 10/60; χ² = 8.04, P = 0.0046). However, when we considered only those recordings in which ES were detected, there was no difference in the mean (variance) of the total number of ES in the two groups: symptomatic, 7.1 (136.3); asymptomatic, 3.6 (93.8) (b = 0 to 0.09, P < 0.1). However, there was a significant difference in the intensity of ES between the two groups, with median (mean, range) values as follows: symptomatic, 12 (13.73, 7 to 30) dB; asymptomatic, 11 (11.86, 7 to 30) dB (P = 0.01, Mann-Whitney U test).

The relationship between the time since last symptoms and the number of ES per hour is shown in Figure 2. Recordings made on each of the first, second, and third occasions are shown separately. For the 2-hour recording, only the results from the first hour are shown. There was a negative relationship between time since symptoms and the number of ES per hour, which reached significance for two of the three recording periods: first recording, ρ = -0.25, P = 0.1; second recording, ρ = -0.42, P = 0.03; third recording, ρ = -0.37, P = 0.05.
Discussion

This study demonstrates that the recording protocol is crucial in determining the proportion of patients in whom ES can be detected. In common with previous pilot studies, our results confirm the variability of asymptomatic embolization over time. By repeating recordings on three separate occasions, the proportion of ES-positive patients increased from 50% to 75% in symptomatic patients and 20% to 25% in asymptomatic patients.

If ES were detected in symptomatic stenosis patients during a 1-hour period, they were usually detectable in the same subjects during a second consecutive 1-hour recording, as reflected by excellent agreement between the two recordings ($\kappa=0.78$). Therefore, extending the recording from 1 to 2 hours in symptomatic patients is of limited benefit. In contrast, there was no significant agreement between which patients were positive for ES on 1 hour of recording compared with a nonconsecutive second hour separated by a number of days; the mean time between recordings was 11 days in the symptomatic group. These results demonstrate the variability of asymptomatic embolization in patients with symptomatic stenosis; they also demonstrate that although within a 2-hour period the process may be relatively constant, a few days later embolization status may well have changed.

In asymptomatic patients there was fair agreement between which patients were positive for ES during 1-hour recordings compared with those positive during a second consecutive hour ($\kappa=0.49$ versus $\kappa=0.78$ for symptomatic stenosis). This was a level of agreement similar to that seen between two nonconsecutive hours of recording separated by a few days ($\kappa=0.48$). This reflects in part the lower frequency of patients with asymptomatic stenosis in whom ES can be detected and demonstrates the usefulness of either increasing the recording time or repeating recordings in patients with asymptomatic stenosis.

We found a significantly higher proportion of recordings with ES in symptomatic than in asymptomatic patients, as reported previously. When we considered only those recordings in which ES were detected, there was no difference in the frequency of ES between asymptomatic and symptomatic patients. However, there was a highly significant difference between the intensity increase of ES in the two groups, with those in symptomatic recordings having a higher relative intensity. Although there are many technical difficulties in deriving information on embolus size from the intensity of the ES, this difference is consistent with emboli in symptomatic patients being larger or possibly of more echogenic material. In addition, our results confirm a significant inverse relationship between the number of ES per hour and time since last symptoms. It is important that this relationship be taken into account in any studies determining the predictive value of ES in patients with asymptomatic stenosis or the effect of any therapeutic intervention in this group of patients. Patients would need to be matched for time since last symptom.

Substantial indirect evidence suggests that ES in patients with carotid stenosis may be an important predictor of disease risk. They correlate with clinical parameters, as described in our study, and are also associated with plaque ulceration and degree of stenosis, which are both markers of increased stroke risk. In individual case reports they have responded to treatment with antiplatelet or anticoagulant therapy, while in a small prospective study in asymptomatic CAS, the presence of two or more ES per hour was a highly significant independent predictor of stroke risk. However, before the routine clinical use of this technique in predicting stroke risk, further large prospective studies are required to determine this association. Our results will be useful in determining optimal recording protocols for such studies. In patients with asymptomatic carotid stenosis, recording for 1 hour appears to be the minimum reasonable period, and detection of ES-positive patients will be increased to a similar extent by prolonging recording to 2 hours or repeating the recording. In contrast, in patients with symptomatic disease a single hour of recording at one time is probably sufficient, but repeating the recording on a second occasion will identify additional subjects in whom embolization is occurring.

Acknowledgments

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References

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