Embolic Signals in Unselected Stroke Patients
Prevalence and Diagnostic Benefit

Holger Poppert, MD; Suwad Sadikovic; Kerstin Sander, MD; Oliver Wolf, MD; Dirk Sander, MD

Background and Purpose—The present study investigated the prevalence of cerebral microemboli detected by transcranial Doppler sonography in unselected stroke and transient ischemic attack (TIA) patients under standard clinical conditions. We aimed to evaluate the feasibility and the value of the method for clinical use.

Methods—The records of 937 consecutive patients who were investigated between October 1995 and August 2004 at our institution were reviewed. Stroke or TIA were subtyped using the TOAST classification criteria.

Results—Two hundred and eighty-four subjects were excluded because there was an interval of >14 days between onset of symptoms and examination, no definite diagnosis of stroke or TIA at discharge, or an artificial heart valve. Embolic signals (ES) were detected in 37 (5.7%) of the remaining 653 patients. In subjects with positive ES detection the mean interval between symptom onset and ES detection was 4.9 (SD 4.0) days compared with 5.4 (SD 3.5) days in the remaining patients (P=0.01). ES were more common in patients with large-artery atherosclerosis compared with other subtype groups (P<0.001). The proportion of detected signals was influenced by the antithemostatic treatment: ES were found more often in anticoagulated patients than in patients receiving antiplatelet medication (P<0.001).

Conclusions—The study shows a high clinical significance of ES in patients with recent stroke attributable to arterio-arterial embolism or of cardiac embolic origin and the high specificity of the technique. Given the low sensitivity shown, ES detection cannot generally be recommended for routine diagnostics in stroke patients. (Stroke. 2006;37:2039-2043.)

Key Words: cerebrovascular accident ■ intracranial embolism ■ ultrasonography ■ Doppler, transcranial

Embolic signals (ES) detected by transcranial Doppler sonography (TCD) have been shown to be an independent predictor of cerebral ischemia.1-5 The method has particularly been advocated to provide an estimate of the risk of recurrent ischemic events after the first stroke or transient ischemic attack (TIA). Until now, TCD monitoring in stroke patients has predominantly been explored using small and highly preselected groups.

This study determined the prevalence of cerebral microemboli detected in unselected stroke and TIA patients under standard clinical conditions, with the aim of evaluating the feasibility and clinical benefit of the method for identifying patients with embolic sources.

Materials and Methods

Subjects

The records of consecutive patients examined between October 1995 and August 2004 at the Neurovascular Laboratory of the Munich University of Technique Hospital were reviewed. Subjects were excluded if the interval between event and ES detection was >2 weeks, or if the diagnosis at discharge was different from stroke or TIA or was uncertain. Patients with artificial heart valves were also excluded.

Complete clinical neurological examination, ECG, Doppler and color-coded duplex ultrasonography of the extracranial arteries and Doppler ultrasonography of the intracranial arteries were carried out in all patients, as well as a cerebral CT or MRI examination, or both. A 4-lead 24-hour ECG was performed routinely. If >1 ES detection was performed, only the first examination was analyzed. Additional diagnostic investigations such as echocardiography or angiography were taken into account if available.

The Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria were used for classification of stroke etiology.6 The TOAST subtyping was performed by a physician (H.P.) who was blinded to knowledge regarding the TCD findings.

TCD Methodology

For microembolic monitoring, a 2-MHz pulse-wave transcranial Doppler device (MULTI-DOP; DWL Elektronische Systeme) was used for simultaneous, long-term insonation of both middle cerebral arteries using simultaneous 64-point fast Fourier transformation and bigate technique. These parameters were chosen according to the recommendations of the International Consensus Group on Microembolus Detection (2 MHz, fast Fourier transformation between 64 and 256 points, multigated technique).7 An embolus detection level of 11 dB was chosen. TCD recording quality was continuously observed by 1 investigator.

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**Results**

A total of 937 consecutive patients were retrospectively included in the study over a period of 9 years (October 1995 to August 2004). Two hundred and eighty-four patients were excluded from the analysis (Figure 1).

The mean interval between symptom onset and ES detection was 5.3 (SD 3.5) days in the remaining 653 patients. Echocardiography was performed in 557 patients (85.3%). At the time of examination, 417 patients (63.9%) were receiving antiplatelet medication: 316 (48.4%) received acetylsalicylic acid (ASA); 85 (13.0%) received clopidogrel; 10 (1.5%) received both ASA and clopidogrel; and 6 (0.9%) received ASA and dipyridamol. Two hundred and thirty-one patients (35.4%) were anticoagulated: 24 (3.7%) with phenprocoumon, 197 (30.2%) with heparin, and 10 (1.5%) with both. Thirty-three (5.1%) of the mentioned patients received antiplatelet and anticoagulation treatment. Thirty-eight patients (5.8%) had neither antiplatelet nor anticoagulant treatment.

**ES Detection**

ES were detected in 37 patients (5.7%). The subject characteristics and associated frequency of detected ES are shown in Table 1. There was no significant association between the presence of ES and age, sex, hypertension, diabetes, smoking status, hyperlipidemia, and previous stroke or TIA. A higher prevalence of ES was seen in patients with history of myocardial infarction (P=0.037).

In patients with positive ES detection, the mean interval between symptom onset and ES detection was 4.9 (SD 4.0) days, compared with 5.4 (SD 3.5) days in the remaining patients (P=0.01). During the first 3 days after symptom onset significantly more patients showed ES compared with patients screened between days 4 and 14 (10.34% versus 4.50%, P=0.021).

**TABLE 2. Prevalence of ES in Different Stroke Subtypes According to TOAST Classification**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>ES-Positive (n=37)</th>
<th>ES-Negative (n=616)</th>
<th>Difference*, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherothrombotic, n (%)</td>
<td>20 (54.1)</td>
<td>83 (13.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardioembolic, n (%)</td>
<td>5 (13.5)</td>
<td>138 (22.4)</td>
<td>0.228</td>
</tr>
<tr>
<td>Lacunar, n (%)</td>
<td>0 (0.0)</td>
<td>147 (23.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>6 (16.2)</td>
<td>29 (4.7)</td>
<td>0.011</td>
</tr>
<tr>
<td>Unknown, n (%)</td>
<td>6 (16.2)</td>
<td>219 (35.6)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

*Difference indicates the difference in the ratio of ES-positive/ES-negative patients in the selected group compared with the rest of the patients.
The distribution of stroke subtypes and associated frequency of detected ES are shown in Table 2 and Figure 2. ES were significantly more common in patients with large-artery atherosclerosis compared with other subtype groups (P < 0.001).

Bilateral ES were detected in only 3 patients with cardioembolic stroke and 4 patients with stroke attributable to arterioarterial embolism. No significant association with stroke subtype was found (P = 0.457).

The proportion of detected signals was significantly influenced by the antithrombotic treatment: ES was found in 24 anticoagulated patients (10.4%) as compared with 13 patients (3.1%) receiving antiplatelet medication (P < 0.001; Table 3). The significant correlation was approved by multivariate analysis including the TOAST classification as a parameter (P < 0.01; odds ratio 2.84, CI [1.3;6.1]).

**Discussion**

To the best of our knowledge, the present study describes ES monitoring in the largest population of unselected stroke and TIA patients to date, thus providing valuable comparative data on ES prevalence in these patient groups.

The first interesting finding was no occurrence of ES in patients with stroke or TIA attributable to small-vessel disease. This demonstrates a very high specificity of the technique in identification of embolism and discrimination from artifacts.

Comparison of the remaining groups showed ES to be significantly more prevalent in patients with stroke or TIA attributable to large-artery atherosclerosis (19.4%) than in those with cardioembolic stroke or TIA (3.5%). Thus, the technique appears to be of use in diagnostic work-up aiming to clarify the etiology of ischemia, because it might demonstrate the existence of an extracranial embolic source. However, definitive differentiation between cardiac and arterial embolism is not possible.

Kaposzta et al suggested the occurrence of bilateral ES to be exclusively associated with a cardioembolic source.8 The results in our series did not support this notion: 3 patients considered to have arterioarterial embolism showed bilateral ES. Two of them had a unilateral carotid occlusion, so that both hemispheres were supplied by 1 carotid artery. No obvious explanation has been found in the third patient. However, differentiation could be improved by simultaneous recording from the middle cerebral artery and the common carotid artery proximal of the stenosis as proposed by Kaposzta et al.8

Further tools for classification are needed, particularly in patients without attributable stroke subtype according to the TOAST criteria, and ES detection seemed to be a promising method in diagnostic work-up. However, only 2.7% of patients with stroke or TIA of undetermined etiology showed ES suggesting an embolic pathogenesis, thus considerably reducing the value of the technique in this subgroup.

The proportion of detected signals was significantly influenced by the antithrombotic treatment, with reduced ES rates in patients receiving antiplatelet medication. A decline of ES with administration of aspirin has been reported in previous studies5,10 and the recently published Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial revealed a combination of clopidogrel and aspirin to reduce the ES rate in patients with symptomatic carotid stenosis more effectively than aspirin alone.10 Consequently, it has been assumed that ES mainly corresponded to platelet-rich emboli.9 The higher ES prevalence particularly in patients receiving anticoagulation as compared with antiplatelet therapy in our study supports this notion.

Also in keeping with earlier work,8,11–14 we found a short time interval between symptom onset and ES recording to be associated with a higher prevalence of ES. Hence, monitoring soon after symptoms would certainly have resulted in a higher proportion of ES-positive patients in our series, thus increasing the diagnostic value of the technique. However, the aim of our study was to evaluate diagnostic benefit in routine use. The mean interval of 5 days in all patients, including those experiencing TIA, reflects the reality of daily clinical practice. Patients often present several days after initial onset of symptoms and primary diagnostic procedures such as MRI or CT of the brain and Doppler examination of the extracranial arteries have absolute priority.

The importance of the interval after symptom onset might be 1 reason for previous studies reporting considerably variable proportions of ES-positive patients after cerebral ischemia,15–18 ranging from 5.3%18 to 71%.19 in single recordings. Furthermore, a number of studies were conducted before international consensus criteria for the identification of ES were established. For example, only online analysis with a high risk of observer bias or automated ES-detection software resulting in a lack of specificity have been used. Different durations of monitoring were also applied and variable fractions of patients received antiplatelet or anticoagulation therapy. Furthermore, the decibel thresholds that were used for discriminating microembolic signals from background noise and spontaneous intensity fluctuations of the physiological Doppler flow signals differed depending on the varying recommendations of different manufacturers and individual calibrations. Lowering the detection threshold results in increased sensitivity but lower specificity and intercenter agreement.7

Most studies included only small patient populations with different selection criteria including stroke subtypes and time from symptom onset. Few studies included at least 100 successfully monitored patients with respect to stroke subtypes. Daffertshofer et al included 280 stroke patients. They observed ES in 9.3% of all patients: in 14.2% of the subgroup with large-vessel disease compared with 6.2% in patients with cardiac sources of embolism and 4.5% with small-vessel disease.17 However, no standardized criteria were used for subtyping of stroke etiology, which complicates the comparison.

Serena et al included 182 patients and observed ES in 9.3% of all patients: in 20.5% of the subgroup with arterial sources of embolism compared with 17.1% in patients with potential

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**TABLE 3. Prevalence of ES in Different Antithrombotic Treatments**

<table>
<thead>
<tr>
<th>Antithrombotic Treatment</th>
<th>ES-Positive (n = 37)</th>
<th>ES-Negative (n = 616)</th>
<th>Difference*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant, n (%)</td>
<td>24 (64.9)</td>
<td>207 (33.6)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Antiplatelet, n (%)</td>
<td>13 (35.1)</td>
<td>404 (65.6)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>No therapy, n (%)</td>
<td>0 (0.0)</td>
<td>38 (6.2)</td>
<td>0.158</td>
<td></td>
</tr>
</tbody>
</table>

*Difference indicates the difference in the ratio of ES-positive/ES-negative patients in the selected group compared to the rest of the patients; 33 patients received anticoagulant and antiplatelet therapy.

The proportion of detected signals was significantly influenced by the antithrombotic treatment: ES was found in 24 anticoagulated patients (10.4%) as compared with 13 patients (3.1%) receiving antiplatelet medication (P < 0.001; Table 3). The significant correlation was approved by multivariate analysis including the TOAST classification as a parameter (P < 0.01; odds ratio 2.84, CI [1.3;6.1]).
sources of cardioembolism and 0 of 64 with small- vessel disease.\textsuperscript{19}

Kaposzta et al performed TCD recordings of 60 minutes in 100 patients experiencing anterior circulation ischemic stroke within 72 hours after symptom onset.\textsuperscript{7} They found ES in 16\% of all patients: in 10 of 20 patients (50.0\%) in the subgroup with large-vessel disease compared with 1 of 21 patients (4.5\%) with cardiac sources of embolism and 0 of 20 patients with small- vessel territory syndrome. The longer recording time, the lack of TIA patients, and the short interval between symptom onset and TCD recording might explain the higher overall ES prevalence. The reported correlation with stroke subtypes is consistent with our results. Smaller studies have also reported a lack of ES in patients with small vessel disease.\textsuperscript{15,18}

The low overall ES-prevalence demonstrated argues against clinical use of this technique as a screening method in unselected stroke patients, at least with the monitoring duration of 30 minutes. Serial examinations, as well as an increased duration of recording, could certainly increase sensitivity.\textsuperscript{20} Lund et al performed 2 consecutive ES recordings in stroke patients.\textsuperscript{21} Of 18 patients who showed emboli in either recording, only 6 did so in both. Mackinon et al demonstrated a clustering of ES when performing long-term insonations in 24 patients.\textsuperscript{22} On prolongation of the recording time from 1 to 8 hours, the proportion of ES-positive patients increased from 9\% to 75\% in patients with symptomatic carotid stenosis and from 4\% to 26.7\% in those with asymptomatic stenosis. Long-term detection in combination with simultaneous recording from the common carotid artery\textsuperscript{8} might permit a more effective stroke classification, offering support for clinical decision making. All this is time-consum- ing and requires a high degree of cooperation from patients. For this reason, it is hardly applicable in daily clinical practice.

Another important limitation of the technique is the arguable degree of reliability, as reflected by the wide range of ES reported in different studies. Markus et al examined the intercenter agreement among 9 centers, each of which had published studies of ES detection in peer-reviewed journals.\textsuperscript{23} The reported ES rates of a 2-hour tape including recordings of 6 patients ranged from 39 to 142 signals. Furthermore, many old patients cannot be examined because of poor acoustic bone windows. For technical reasons, no reliable conclusion about size and composition of the embolus can be drawn from the ES.

The primary goal of our investigation was to analyze the value of ES detection in clinical routine diagnostics. In contrast, several previous studies examined the predictive value of ES for stroke recurrence.\textsuperscript{2,3,10,28,29} Although some authors have reported promising results\textsuperscript{1,3,26–28} to date, this has been a matter of controversy.\textsuperscript{18,21,24} This underlines the need for further prospective investigations on the basis of new standardized detection protocols that take into account the findings of recently performed long-term detection studies.\textsuperscript{22}

\textbf{Conclusions}

Our study confirmed the reported clinical significance of ES in patients with recent stroke attributable to arterio-arterial embolism or a cardiac embolic source and the high specificity of the technique. Because of its low sensitivity, ES detection cannot generally be recommended as a routine examination in a stroke care unit. It therefore remains primarily a research technique for evaluation of specific problems in preselected patients, at least until technological advances allow effective and automated long-term detection monitoring of the middle cerebral artery and common carotid artery.

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\textbf{Disclosures}

None.

\textbf{References}

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