Prevalence of Embolic Signals in Acute Coronary Syndromes

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Background and Purpose—The purpose of this study was to assess the prevalence of embolic signals (ES) in acute coronary syndromes (ACS) and their association with stroke.

Methods—From December 2004 to October 2006, 209 consecutive patients with ACS (without prosthetic heart valves or previous stroke) were studied within 72 hours of symptom onset. Patients underwent ES monitoring in both middle cerebral arteries by transcranial Doppler for 30 minutes. Median follow-up was 14 months after discharge.

Results—Patients were treated according to current European Society Cardiology guidelines. Specifically, 92% of patients received heparin(s), 100% aspirin, 92% clopidogrel, 67% intravenous glycoprotein IIb/IIIa inhibitors, 9% fibrinolysis, and 67% underwent angioplasty. ES were detected in 7 patients (prevalence 3.4%; 95% CI, 1.4 to 6.8). Except for a higher prevalence of ES in patients with unstable angina versus other ACS categories (8.5% versus 1.9%, P=0.047), none of the factors among baseline characteristics, clinical features, ACS treatment, and cardiac findings were associated with the presence of ES. During hospitalization, 3 patients without ES had cerebrovascular events (one stroke and 2 transient ischemic attacks), whereas no cerebrovascular events occurred in patients with ES.

Conclusions—The prevalence of ES among hospitalized patients with ACS is currently low, possibly because of improvement in ACS treatment. In this ACS sample, ES did not appear associated with short-term risk of cerebrovascular events. (Stroke. 2010;41:261-266.)

Key Words: acute coronary syndrome ■ cerebrovascular event ■ myocardial infarction ■ stroke ■ unstable angina

In a meta-analysis of stroke incidence after myocardial infarction, the risk of stroke was estimated to be approximately 1.1% during hospitalization, 1.2% at 30 days, and 2.1% at 1 year. Although the risk of stroke after an acute coronary syndrome (ACS) is not very high, its occurrence considerably increases the early morbidity and mortality associated with ACS.

Embolic signals (ES) are high-intensity signals detected by insonation of the middle cerebral artery by transcranial Doppler (TCD) through the temporal bone window. ES are a common finding in patients with carotid artery stenosis, in which they have been found in 13 of 38 patients with a median of 3 per hour in comparison to patients with asymptomatic carotid stenosis in which they have been found in only one of 28 patients (P=0.003). In the first hour after carotid endarterectomy, the average number of ES detected per hour of monitoring was 14.0 and a rate of ES >10 per hour was a marker of a higher 30-day perioperative rate of transient ischemic attack (TIA) or stroke. In asymptomatic carotid stenosis, ES rate per hour was 0.16 and was not correlated to cerebrovascular events ES are also common in patients with prosthetic valves, and their prevalence depends on the type of valve. Their presence is more frequent in St Jude Medical valves (72% of cases, median of 4 ES per hour) and Björk Shiley Monostrut type (92% of cases, median of 133 ES per hour) and only in 9% of cases with Sorin biological (median of 0 ES per hour). However, their presence has no clinical relevance and their nature seems to be gaseous. In patients with atrial fibrillation not anticoagulated, ES can be found in 15% of the cases with a low frequency (median 1 ES per hour). Their presence is not associated with risk factors of cardiac emboli (smoking status, diabetes, hypertension, aspirin use, aspirin dose, left atrial size, left ventricular function, or the presence of left atrial thrombus detected on transthoracic echocardiography). In case of severe left ventricular dysfunction, ES can also be found in 26% of the patients. Only one study published in 1999 reported a prevalence of ES as high as 17% in patients with myocardial infarction with a mean rate of ES of 0.5±1.6 per 30 minutes; the authors found that the presence of ES was related to postmyocardial stroke. Since then, how-
ever, antithrombotic treatment for ACS has changed, which may have modified the prevalence of ES.

In this study, we aimed at re-evaluating the incidence of ES in a consecutive series of patients with ACS and exploring the predictive value of ES on stroke events.

Methods

The ethics committee of Bichat Hospital (Paris) approved the research protocol and all subjects provided signed informed consent before enrollment in the study.

Consecutive adult patients (≥18 years of age) were recruited in the coronary intensive care unit from December 2004 to October 2006 if they had ACS diagnosed by a cardiologist according to standard clinical categorizations: ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina. Patients with prosthetic heart valves were not eligible for inclusion because ES are usually related to microbubbles and have little clinical relevance. To exclude confounding, patients with a history of stroke were also not eligible for inclusion. Patients were enrolled within 72 hours of admission in the intensive care unit. Information on demographics, risk factors, clinical characteristics, pharmacological and nonpharmacological treatments, and clinical events during hospitalization was collected using a structured questionnaire. A neurological examination and extracranial continuous Doppler were performed before TCD monitoring.

All cerebral and cardiac imaging procedures (electrocardiography, coronary angiography, transthoracic echocardiography) were recorded. We appointed a full-time clinical research assistant to ensure completeness of data collection.

TCD Monitoring

TCD was performed by an experienced observer (E.M., >500 TCD examinations per year for 6 years) with a DWL-type MultiDop device with 2 2-MHz transducers. A sample volume of 10 mm was used. The middle cerebral arteries (MCAs) were identified through the transtemporal windows and the probes were fixed onto the temporal skull using a standard headset. MCA insolation deepness was 50 to 61 mm. The study duration was 30 minutes in the presence of the expert ultrasonographer (E.M.). All ES were detected online by the observer and by an expert ultrasonographer (P.-J.T.) blinded to the first offline reading. ES detected by the DWL automated detection software were analyzed offline by the observer; as well, ES detected by the DWL automated detection software were analyzed offline by the observer and by an expert ultrasonographer (P.-J.T.) blinded to the first offline reading and any patient characteristics. Any disagreement was resolved by consensus. ES were defined as a unidirectional high-intensity signal and any patient characteristics. Any disagreement was resolved by consensus. ES were defined as a unidirectional high-intensity signal of short duration with a typical sound (“chirp”) according to the criteria described by the International Consensus Group on Microemboli Detection.

Diagnostic Criteria of Extracranial and Intracranial Stenosis

Extracranial stenosis was assessed by continuous Doppler and defined by localized peak systolic velocity >160 cm/s at the bifurcation or at the internal carotid artery origin.

Intracranial stenosis was assessed by TCD and defined as an elevation in peak systolic velocity >150 cm/s for proximal MCAs; >120 cm/s for vertebral arteries or basilar arteries; or >100 cm/s for carotid siphon or a difference >30% compared with the contralateral artery.

Follow-Up

One-year follow-up was obtained by neurologists in the outpatient clinic consultation during face-to-face interviews or by research nurses through telephone calls with the collection of information on the occurrence of vascular events (including stroke, TIA, ACS requiring hospitalization, and cardiac revascularization) or death after discharge. In case of an event, medical records were obtained whenever possible and reviewed by one neurologist (E.M.).

Statistical Analysis

The sample size for the present study was calculated to determine the prevalence of ES with a 95% CI of 10%. Assuming a prevalence of 17%, based on a previous study, 120 patients were needed. Data are presented as mean±SD for continuous variables and count (percentage) for qualitative variables. For event rate calculations, only the first-time events of interest were considered. ACS groups were compared using the χ² test for qualitative variables (Fisher exact test was used when the expected cell frequency was <5) and analysis of variance for continuous variables. In an exploratory analysis, we compared the prevalence of ES according to baseline characteristics, clinical features, cardiac findings, admission treatments, and outcomes using Fisher exact test. Statistical testing was done at the 2-tailed α level of 0.05. Data were analyzed using SAS software Version 9.1 (SAS Institute, Cary, NC).

Results

During the study period, 391 patients were screened of whom 367 were eligible; 137 patients declined to participate and 21 were excluded because of failure to find an acoustic temporal window. TCD recording was available in 209 patients; both MCAs were recorded in 80% (n=168) of the patients; in the rest, only one side was monitored (n=41; Figure).

Table 1 describes the demographic and clinical characteristics of the study sample both overall and according to ACS category. ACS categories were STEMI (59% [n=123]), unstable angina (22% [n=47]), and NSTEMI (19% [n=39]). Patients with unstable angina had a higher prevalence of hypertension and history of ACS than the other groups. Current smoking was more frequent in patients with STEMI, whereas those with NSTEMI had less frequent left ventricular wall motion abnormalities.

All patients were treated according to the current European Society of Cardiology guidelines.2 Specifically, heparins (either unfractionated or low-molecular-weight) were given before TCD monitoring in 92% of patients, aspirin in 100%, clopidogrel in 92%, intravenous glycoprotein IIb/IIIa inhibitors in 67%, fibrinolysis in 9%, and angioplasty was performed in 67%. Patients with STEMI were more intensively treated than the other groups, especially regarding angioplasty and intravenous glycoprotein IIb/IIIa inhibitor and fibrinolytic therapy (Table 2).

TCD monitoring was performed with a median delay of 32 hours after symptom onset (interquartile range, 20 to 46
hours) with no difference between ACS categories \((P=0.91)\). The median timing between coronary angiography and TCD monitoring was 11 hours (interquartile range, 5 to 32 hours) with a significant difference between ACS categories \((P<0.001)\); patients with STEMI had a longer delay (median, 26.6 hours) than patients with unstable angina (median, 6 hours) and with NSTEMI (median, 6 hours). ES were detected in only 7 patients, giving a prevalence of 3.4% (95% CI, 1.4 to 6.8). Table 3 describes several characteristics of patients with a diagnosis of ES. Three patients had multiple ES with the highest number being 34 in a man aged 46 years with NSTEMI; monitoring was made 15:10 hours after the ACS and 6 hours after the coronary angiography; no clinical event was observed and a brain MRI scan performed 1 month later was normal. Except for a higher incidence of ES in patients with unstable angina (8.5% \([n=4]\)) in comparison with the other ACS categories \((1.9\% \,[n=3]; P=0.047)\), we found no relevant difference in the prevalence of ES across cardiovascular risk factors, cardiac imaging, conventional ACS treatments, and characteristics of ES monitoring (bilateral versus unilateral MCA examination, timing with respect to ACS onset or coronary angiography), but we caution that the power of the analysis was limited by the small number of patients with ES.

During hospitalization, one stroke (0.5%), 2 TIAs (1.0%), 13 recurrent ACSs (6.2%), and 2 sudden deaths (1%) occurred in patients without ES, whereas no vascular events occurred in patients with ES. After discharge, 95% \((n=197)\) of patients were followed-up for a median of 14 months (interquartile range, 12 to 16). A total of 149 patients had face-to-face follow-up visits and 48 had a telephone interview. Twenty-one additional recurrent ACSs \((n=21)\) and 3 deaths (one fatal myocardial infarction, one fatal subdural hemorrhage, and one of unknown cause) occurred during the follow-up period. Three of 7 patients with ES (43%) had recurrent ACS of the same type of qualifying ACS (all occurred after 6 months) in comparison to 31 of 202 patients without ES who had recurrent ACS \((16\%, P=0.10)\).

**Discussion**

The prevalence of ES in consecutive patients with an ACS was 3.4% in our study, which was lower than the unique study in the literature of ES detection in patients with ACS. The in-hospital incidence of stroke events was 0.5% and that of TIA was 1.0%; these data concur with a study showing a reduction over time in the incidence of adverse cardiovascular events in patients hospitalized for an ACS. In our study, none of the patients who had a stroke or a TIA had presented ES. Among the 7 patients with ES, only one had an ipsilateral 70% carotid stenosis as another potential source of emboli. Although ES were more likely to be of a platelet nature, we could not exclude a gaseous origin due to coronary angiography.

In recent years, the incidence of stroke after an ACS has decreased compared with that reported in historical series. The report of a 17% prevalence of ES in patients with ACS was based on 100 patients with myocardial infarction recruited between 1997 and 1999. Since then, treatments for
ACS have improved, and the use of antithrombotic therapies, angioplasty, and stenting has increased (Table 4), which has been associated with a major reduction in the incidence of mortality and adverse cardiovascular events during hospitalization in patients with ACS. In the early 1990s, aspirin was the only antiplatelet agent used after myocardial infarction. After the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial, however, patients with non-ST-elevation acute myocardial infarction were treated with a combination of aspirin and clopidogrel. This dual-antiplatelet therapy has also become standard treatment in patients with ACS.

A post hoc analysis of the Survival And Ventricular Enlargement (SAVE) trial showed that a 5% reduction in ventricular function was associated with an 18% increase in the risk of stroke. In our series, only 2 patients (1%) had left ventricular function lower than 30%. No patients with ES had severe heart failure. In patients with asymptomatic carotid stenosis, Spence et al found that better medical treatment reduced ES prevalence over time. In this study, the patients had a prevalence of ES of 12.6% when monitored before 2003 as compared with 3.7% in those monitored after 2003 (P<0.0001). This reduction was also correlated to a reduction in clinical events with 17.6% stroke, death, and myocardial infarction before 2003 as compared with 5.6% in those studied since 2003 (P<0.0001). This reduction was related to better management of vascular risk factors with systematic use of statins, aggressive blood pressure-lowering and diabetes control, and smoke cessation.

The duration of TCD monitoring in our study was 30 minutes. Longer or more frequent monitoring might have detected more ES as has been described in another clinical situation; anyway, the low prevalence of cerebrovascular events makes ES monitoring not useful in practice in the absence of reliable automated detection. Conversely, 21 patients could not be monitored because of the absence of a transtemporal window related to bone thickness. Moreover, among patients with TCD monitoring, only one MCA artery was monitored in 20% of the cases. However, it is unlikely that these technical limitations explained the difference with the previous study because our ES detection rate was similar in patients with unilateral (2.4% [n=1]) and bilateral TCD monitoring (3.6% [n=6]).

Given the small number of patients with ES in our series, we were unable to identify predictors of the presence of ES due to the lack of adequate statistical power. The presence of ES was not related to in-hospital stroke or TIA. Silent strokes were not excluded by systematic MRI, because some patients had worse ejection fraction and more akinetic segments.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>ES</th>
<th>Intensity, Decibels</th>
<th>Time of Bilateral Examination</th>
<th>Timing, Hours</th>
<th>Demographic Sex, Age</th>
<th>TCD Monitoring</th>
<th>Clinical Characteristic</th>
<th>Treatment Before TCD Monitoring</th>
<th>Follow-Up Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ES</td>
<td></td>
<td>Bilateral</td>
<td>Timing,*</td>
<td>AF</td>
<td>LVEF ≤30%</td>
<td>ICA Stenosis</td>
<td>GP</td>
<td>Fibrolytic Therapy</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>10</td>
<td>Yes</td>
<td>43</td>
<td>Men, 83</td>
<td>STEMI</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>10, 11</td>
<td>Yes</td>
<td>5</td>
<td>Men, 58</td>
<td>Unstable</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>10</td>
<td>Yes</td>
<td>6</td>
<td>Women, 74</td>
<td>STEMI</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>9</td>
<td>Yes</td>
<td>9</td>
<td>Men, 61</td>
<td>Unstable</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>10</td>
<td>No</td>
<td>8</td>
<td>Men, 56</td>
<td>Unstable</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>9</td>
<td>Yes</td>
<td>29</td>
<td>Men, 62</td>
<td>Unstable</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>9 to 16</td>
<td>Yes</td>
<td>6</td>
<td>Men, 46</td>
<td>NSTEMI</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Time between TCD monitoring and coronary angiography.
AF indicates atrial fibrillation; LVEF, left ventricular ejection fraction; ICA, internal carotid artery; GP, glycoprotein; PTCA, percutaneous transluminal coronary angioplasty; MI, myocardial infarction.
who underwent coronary stenting after TCD monitoring could not be re-evaluated in the days after the procedure.

In our series, 3 neurological events occurred in 3 different patients, one involving the posterior cerebral artery territory. Because we only insonated the MCAs, silent microembolism may have been too low in our study, and the decreased incidence of stroke may be related to the use of new treatments for ACS. Thirty minutes of ES detection within 72 hours of ACS symptom onset did not help stratify the short-term stroke risk in patients undergoing intensive, contemporary management.

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Sources of Funding
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Disclosures
None.

References
5. Abbott AL, Chambers BR, Stork JL, Levi CR, Bladin CF, Donnan GA. Glycoprotein IIb/IIIa inhibitor. LV thrombus 2% 4%
6. Clopidogrel 92% 0
7. Glycoprotein IIb/IIIa inhibitor 67% 0
8. ES prevalence 3% 17%
9. Outcomes events
   Median of follow-up 14 months 8 days
   Stroke 1 (0.5%)* 3 (3%)
   TIA 2 (1%)*

*All occurred before discharge.
LV indicates left ventricular; MI, myocardial infarction.

Table 4. Comparison of Method and Results of the Present and Previous Studies on ES Detection in ACS

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Present Study</th>
<th>Nadareisvili et al, 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, mean age</td>
<td>79%, 59 years</td>
<td>68%, 68 years</td>
</tr>
<tr>
<td>LV ejection fraction &lt;30%</td>
<td>1%</td>
<td>25%</td>
</tr>
<tr>
<td>LV thrombus</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>LV akinetic segment</td>
<td>33%</td>
<td>71%</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombolytic</td>
<td>9%</td>
<td>45%</td>
</tr>
<tr>
<td>Heparins</td>
<td>92%</td>
<td>94%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>100%</td>
<td>93%</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>92%</td>
<td>0</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitor</td>
<td>67%</td>
<td>0</td>
</tr>
<tr>
<td>ES prevalence</td>
<td>3%</td>
<td>17%</td>
</tr>
</tbody>
</table>

| Duration of the monitoring | 30 minutes | 30 minutes |
| Time of the monitoring | <72 hours after symptom onset | <72 hours after symptom onset |
| ES analysis | Manual using International criteria | Manual using International criteria |

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Disclosures
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