Silent Cerebral Infarcts in Patients With Pulmonary Embolism and a Patent Foramen Ovale
A Prospective Diffusion-Weighted MRI Study

Marie-Rose Clergeau, MD; Michèle Hamon, MD; Rémy Morello, MD; Eric Saloux, MD; Fausto Viader, MD; Martial Hamon, MD, FESC

Background and Purpose—Pulmonary embolism is thought to be associated with a small but definite risk of paradoxical embolism in patients with a patent foramen ovale (PFO). Although neurological complications are infrequent, the incidence of clinically silent brain infarction is unknown. We assessed the rate of clinically apparent and silent cerebral embolism in patients with pulmonary embolism in relation to the presence or not of a PFO.

Methods—We used diffusion-weighted MRI in patients hospitalized for a pulmonary embolism to assess cerebral embolic events. Sixty consecutive patients were evaluated at diffusion-weighted MRI. All patients underwent neurological assessment before diffusion-weighted MRI and a contrast echocardiography to detect PFO the next day.

Results—Diffusion-weighted MRI showed bright lesions in 6 patients among the 60 consecutive patients with pulmonary embolism in a pattern consistent with embolic events. There was only one patient with a neurological deficit. After contrast echocardiography, a PFO was diagnosed in 15 patients (25%). The frequency of silent brain infarcts in patients with a PFO was significantly higher than in patients without PFO (5 [33.3%] of 15 versus one [2.2%] of 45 patients, P=0.003). By logistic regression analysis, PFO was identified as an independent predictor of silent brain infarcts (OR, 34.9 [3.1 to 394.3]; P=0.004).

Conclusions—In pulmonary embolism, cerebral embolic events are more frequent than the apparent neurological complication rate. The prevalence of silent brain infarcts is closely related to the presence of a PFO suggesting a high incidence of unsuspected paradoxical emboli in those patients. (Stroke. 2009;40:00-00.)

Key Words: embolic stroke ■ embolism ■ MRI ■ patent foramen ovale ■ pulmonary embolism

In patients with a patent foramen ovale (PFO) and a hemodynamically significant pulmonary embolism, a small but definite risk of ischemic stroke exists.1,2 Anecdotal cases of paradoxical embolism with thrombus straddling in the PFO have been described in the literature. On the other hand, cryptogenic stroke associated with an increased prevalence of PFO, especially in young patients, further supports the hypothesis of paradoxical embolism in this setting.3–6 Experimental and clinical studies have shown that diffusion-weighted MRI allows sensitive and early detection of cerebral ischemia within minutes of onset, allowing unsuspected cerebral infarcts to be detected in different clinical settings.7–12 Clinically unapparent cerebral damage has never been assessed in a consecutive series of patients with pulmonary embolism. We aimed to prospectively assess the apparent neurological complication rate compared with the clinically silent embolism rate on cerebral diffusion-weighted MRI whether or not the patient had a PFO in patients hospitalized for a pulmonary embolism.

Methods

Patients
To be included in this prospective study, patients had to have a certified diagnosis of acute pulmonary embolism documented by the performance a pulmonary CT scan or a nuclear imaging study (ventilation–perfusion lung scans). Additionally, inclusion criteria were age >18 years and written consent. Exclusion criteria were contraindications to MRI (including claustrophobia) and cardiogenic shock at the time of pulmonary embolism diagnosis. This study was approved by our Institutional Review Board and the trial.gov identifier was NCT00831259.

Study End Points
The prevalence of recent silent brain infarcts (SBIs) as assessed by cerebral diffusion-weighted MRI was the primary end point of the study comparing patients with or without a PFO. The secondary end point was the occurrence of paradoxical embolism excluding SBI or clinically apparent stroke.

Neurological Assessment
All patients were examined by a neurologist either before or shortly after cerebral diffusion-weighted MRI. The neurologist was unaware
of the MRI results. Any previously unknown or unnoticed abnormality on the neurological examination was considered a neurological complication.

**Magnetic Resonance Imaging**

MRI was performed with 1.5-Tesla system (GE Health Care). The imaging protocol included a diffusion-weighted single-shot spin echo echoplanar sequence acquired in the AP-PC plane with 24 contiguous sections (diffusion gradient b values of 0 and 1000 s/mm², repetition time TR 7000 to 8000 ms, echo time TE 100 to 120 ms, slice thickness 6 mm with no gap, matrix of 128×128 pixels, and field of view of 240 mm) and fluid attenuated inversion recovery (TR/TE 10000/160 ms, TI 2200 ms). For diffusion-weighted MRI, the diffusion gradients were successively and separately applied in 3 orthogonal directions. Trace images were then generated and apparent diffusion coefficient maps calculated with a dedicated software tool (Functool; General Electric). The image analysis was performed independently by an experienced neuroradiologist blinded to the clinical data and unaware of the presence of a PFO. For analysis of diffusion-weighted MRI, the neuroradiologist was asked to determine the presence, size, number, and vascular distribution of any focal diffusion abnormalities (bright lesions).

**Contrast Echocardiography**

The presence of a PFO was defined as the passage of contrast in the left cavities within the first 4 cardiac cycles after the opacification of the right atrium during a Valsalva maneuver. All assessments were performed using second harmonic imaging as previously described. Atrial septal aneurysm was defined by the excursion of the atrial septum into the left or right atrium or both of >10 mm. Right ventricle dilation was defined by end diastolic diameter >30 mm measured from the parasternal short axis view or the right ventricle appearing larger than the left ventricle from the apical or subcostal 4-chamber view. The presence of pulmonary hypertension was defined by a tricuspid regurgitant jet velocity of >2.6 m/s on Doppler echocardiography.

**Sample Size Calculation**

We hypothesized that in patients with pulmonary embolus (PE) and a PFO, at least 30% of SBI would be detected by cerebral diffusion-weighted MRI. In patients without PFO, we hypothesized that <1% of similar lesions might be found. With 25% to 30% PFO in the general population, we needed 60 to 70 patients to demonstrate a significantly increased risk of SBI occurrence in patients with a PFO (α risk of 5% and β risk of 20%).

**Statistical Analysis**

Baseline characteristics of the study population are presented as counts and percents for categorical variables and as mean±SD for continuous variables. The risk of SBI in patients with PFO and other clinically important variables were analyzed univariately by Fisher exact test. To investigate whether having a PFO is independent of other clinical variables, a multiple logistic regression model was additionally applied to the primary major end point of the study (SBIs). The results are presented as estimated ORs with the corresponding 95% CIs. All significance tests were 2-sided with a value of P<0.05 considered to indicate clinical significance. The statistical analyses were performed using the SPSS 10.0.7 program (Chicago, Ill).

**Results**

A consecutive series of 71 patients hospitalized in our department with a confirmed diagnosis of acute PE between March 2006 and January 2009 were screened for inclusion. Sixty-five were recruited after informed consent signed. Of these, 60 had complete diffusion-weighted MRI and contrast echocardiography performed as summarized on the flow diagram of the study (29 men, 31 women; Figure 1).

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**Table 1. Clinical Characteristics of the Study Population**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients With PFO (n=15)</th>
<th>Patients Without PFO (n=45)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60 years</td>
<td>31 (51.7%)</td>
<td>24 (53.3%)</td>
<td>0.769</td>
</tr>
<tr>
<td>Peripheral arterial ischemia</td>
<td>3 (5.0%)</td>
<td>0 (0.0%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Stroke clinically apparent</td>
<td>1 (1.7%)</td>
<td>0 (0.0%)</td>
<td>0.250</td>
</tr>
<tr>
<td>Remote history of stroke or transient ischemic attack</td>
<td>3 (5.0%)</td>
<td>1 (2.2%)</td>
<td>0.151</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>2 (3.3%)</td>
<td>2 (4.4%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>1 (1.7%)</td>
<td>1 (2.2%)</td>
<td>1.000</td>
</tr>
<tr>
<td>History of PE</td>
<td>6 (10.0%)</td>
<td>4 (8.9%)</td>
<td>0.634</td>
</tr>
<tr>
<td>Active smoking</td>
<td>13 (21.7%)</td>
<td>8 (17.8%)</td>
<td>0.279</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (6.7%)</td>
<td>4 (8.9%)</td>
<td>0.564</td>
</tr>
<tr>
<td>Body mass index &gt;25 kg/m²</td>
<td>21 (35.0%)</td>
<td>16 (35.67%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (33.3%)</td>
<td>16 (35.6%)</td>
<td>0.753</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>16 (26.7%)</td>
<td>12 (26.7%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Right ventricle dilation</td>
<td>21 (35.0%)</td>
<td>16 (35.6%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Atrial septal aneurysym</td>
<td>8 (13.3%)</td>
<td>1 (2.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrilation</td>
<td>4 (6.7%)</td>
<td>2 (4.4%)</td>
<td>0.258</td>
</tr>
</tbody>
</table>
in 64%. Two patients presented cardiogenic shock during their hospital stay. The mean age of patients with or without PFO was similar (57.9 ± 21.9 versus 59.9 ± 18.3 years, respectively, \( P = 0.72 \)). Of 8 patients found to have an atrial septal aneurysm, 7 also had PFO, whereas one did not \( (P = 0.001) \).

All other baseline clinical characteristics of the study population were identical in the 2 groups.

Only one patient had focal neurological deficit, which was a left hemiparesis concomitant to the diagnosis of PE with diffusion-weighted MRI showing several lesions. The primary end point of the trial, that is, one or more silent brain infarcts as detected by cerebral diffusion-weighted MRI performed at a mean of 3 ± 1 days after the initial hospitalization, was reached by 6 patients (10%; Figure 2; Table 2). The prevalence of SBIs was significantly higher in patients with a PFO than in patients without PFO \( (5 \% [33.3\%] \text{ of } 15 \text{ versus one } [2.2\%] \text{ of } 45 \text{ patients, } P = 0.003) \) as well as peripheral arterial ischemia \( (P = 0.003) \).

Comparing patients with and without SBI, both PFO and atrial septal aneurysm were identified as determinants of cerebral embolism (Table 2). By logistic regression analysis, PFO was identified as an independent predictor of silent brain infarcts \( (OR, 34.9; 95\% CI, 3.1 \text{ to } 394.3; P = 0.004) \). All patients with positive MRI underwent ultrasound carotid assessment, and no significant stenosis was found in those patients. Diffusion-weighted MRI findings are listed in Table 3.

### Discussion

In PE, cerebral embolic events are more frequent than the apparent neurological complication rate. The prevalence of SBIs is closely related to the presence of a PFO suggesting a high incidence of unsuspected paradoxical emboli in those patients. The coexistence of pulmonary and paradoxical embolism was thought to be rare based on clinical assessment and mainly described in cohort of patients with major PE.\(^1\)\(^2\)

In the present study and for the first time to our knowledge, we demonstrate using diffusion-weighted MRI that paradoxical embolism with subsequent SBI is a frequent phenomenon in patients with a PFO.

### Table 2. Determinants of SBI on Diffusion-Weighted MRI in Patients With Acute Pulmonary Embolism

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients With SBI (n=6)</th>
<th>Patients Without SBI (n=45)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFO</td>
<td>15 (25.0%)</td>
<td>5 (83.3%)</td>
<td>10 (18.5%)</td>
</tr>
<tr>
<td>Age &gt;60 years</td>
<td>31 (51.7%)</td>
<td>5 (83.3%)</td>
<td>26 (48.1%)</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>2 (3.3%)</td>
<td>0 (0.0%)</td>
<td>2 (3.7%)</td>
</tr>
<tr>
<td>Peripheral arterial ischemia</td>
<td>3 (5.0%)</td>
<td>0 (0.0%)</td>
<td>3 (5.6%)</td>
</tr>
<tr>
<td>Stroke clinically apparent</td>
<td>1 (1.7%)</td>
<td>1 (16.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>History of stroke or transient ischemic stroke</td>
<td>3 (5.0%)</td>
<td>1 (16.7%)</td>
<td>2 (3.7%)</td>
</tr>
<tr>
<td>Prior history of PE</td>
<td>2 (3.3%)</td>
<td>0 (0.0%)</td>
<td>2 (3.7%)</td>
</tr>
<tr>
<td>Active smoking</td>
<td>13 (21.7%)</td>
<td>1 (16.7%)</td>
<td>12 (22.2%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (6.7%)</td>
<td>0 (0.0%)</td>
<td>4 (7.4%)</td>
</tr>
<tr>
<td>Body mass index &gt;25 kg/m(^2)</td>
<td>21 (35.0%)</td>
<td>0 (0.0%)</td>
<td>21 (38.9%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (33.3%)</td>
<td>1 (16.7%)</td>
<td>19 (35.2%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>16 (26.7%)</td>
<td>0 (0.0%)</td>
<td>16 (29.6%)</td>
</tr>
<tr>
<td>Right ventricle dilation</td>
<td>21 (35.0%)</td>
<td>2 (33.3%)</td>
<td>19 (35.2%)</td>
</tr>
<tr>
<td>Atrial septal aneurysm</td>
<td>8 (13.3%)</td>
<td>3 (50.0%)</td>
<td>5 (9.3%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4 (6.7%)</td>
<td>1 (16.7%)</td>
<td>3 (5.6%)</td>
</tr>
</tbody>
</table>

Paradoxical embolism and PFO have generated great interest during the last few years.\(^3\)\(^–\)\(^6\) Indeed, PFO is present with an increased frequency in patients with cryptogenic stroke suggesting that a venous thrombus crossing to the systemic circulation might cause the stroke. However, the reported prevalence of deep vein thrombosis in such patients is low and no systematic search for silent venous thromboembolism (silent pulmonary embolism) has been performed in patients with stroke. The absence of deep vein thrombosis,
also acknowledged in PE,15 may also reflect complete thrombus migration or thrombus originating from inaccessible veins as previously suggested.16 The difficulty of confirming the occurrence of paradoxical embolism has led to consider alternative explanations, including in situ thrombosis or atrial tachyarrhythmia.17,18 In this perspective of questioning the etiologic role of PFO in cryptogenic stroke and discussing the mechanism of thrombus formation, our study argues for the migration of venous source of thrombus. In keeping with this pathogenesis hypothesis, the clinical relevance of PFO is influenced by concurrent risk factors for venous thromboembolism.19

On the other hand, we know that patients having a cryptogenic ischemic stroke with PFO and atrial septal aneurysm have more frequently multiple acute diffusion-weighted MRI lesions, which may indicate an increased embolic risk.20 In keeping with this observation, 50% of our patients found with SBI had multiple lesions. To be noticed in our series, a higher trend of stroke or transient ischemic attack history was observed in patients with PFO. Our study performed in patients with nonmajor PE suggest also that in presence of a PFO, a right-to-left shunt favoring paradoxical embolism does not require severe pulmonary hypertension, which is indeed rarely documented in patients with cryptogenic stroke who have a PFO.14 As mentioned, concurrent but clinically unnoticed risk factors for venous thromboembolism may contribute to paradoxical embolism in patients with PFO. Systematic effective anticoagulation was used in all patients. Several factors, including the importance of pulmonary hypertension, PFO anatomy, anticoagulant regimen, and patients’ response to anticoagulation, might explain that only one third of patients with a PFO were found with SBI.

Depending on whether respiratory or neurological symptoms are predominant, one of these diagnoses might be missed. Given the interaction between these 2 pathologies in patient management, this is a critical issue that deserves further study. Indeed, treatment of the patient with concomitant PE and ischemic stroke exposes the patient to special risks such as aggravation of brain injuries by the use of thrombolysis or anticoagulant therapy. Whether SBIs expose to similar risks remains to be studied, but they might increase theoretically the risk of cerebral bleeding in case of thrombolysis, more frequently observed in PE than in acute myocardial infarction thrombolysis. To our knowledge, no systematic search for PFO has been carried out so far in patients having had brain hemorrhage after thrombolysis or anticoagulation for PE. Conversely, when stroke is the clinical presentation, PE might be undiagnosed and be associated with additional thromboembolism events and aggravation of cerebral hypoxia. Physicians both in intensive care units and in stroke centers must therefore be aware of the potentially deleterious effect of this association on patient outcomes. In case of PE, a thorough neurological examination should be performed and cerebral diffusion-weighted MRI considered to rule out cerebral infarction, especially when thrombolysis is discussed. Conversely, clinically unapparent PE might be looked for in patients with cryptogenic stroke found to have PFO.

This study has several limitations. First, longitudinal clinical follow-up and diffusion-weighted MRI were not performed and will need further examination in the future. Indeed, the impact of these SBIs on patient outcomes remains to be determined. Furthermore, the potential deleterious effect of these SBIs on the risk of bleeding complications during thrombolysis of patients with more severe PE is also an interesting issue deserving further studies. Our study in rather none severe PE was not powered to look at those end points. Second, the diagnosis of PFO was not ensured by transesophageal echocardiography. However, the transthoracic echocardiography using second harmonic imaging has been shown to have close diagnostic performance13,14 and the 25% prevalence of PFO found in our series is within the expected range.

**Conclusion**

The major finding of the present prospective study is that PFO is an independent predictor of SBIs in patients with PE. The high rate of SBIs observed in our study, if confirmed by other studies, might have important clinical implications. In the clinical setting of PE, the presence of a PFO might require cerebral diffusion-weighted MRI in potential candidates for thrombolysis. On the other hand, patients with cryptogenic stroke and a PFO may require a systematic search for silent thromboembolism to confirm the venous source of thrombus. Finally, the high prevalence of SBIs closely related to the presence of a PFO in patients with acute PE suggesting a high incidence of unsuspected paradoxical emboli in those patients deserves further longitudinal study to determine the impact on patient outcomes.
Disclosures

None.

References


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