# High Frequency of Silent Pulmonary Embolism in Patients With Cryptogenic Stroke and Patent Foramen Ovale

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***Background and Purpose***—Deep vein thrombosis and pulmonary embolism (PE) prove venous embolic activity and enforce the suspicion of paradoxical embolism in patients with stroke with patent foramen ovale. Because it has implications in secondary prevention, we investigated the frequency of silent PE in such a cohort of patients.

***Methods***—Patients with cryptogenic stroke or transient ischemic attack and patent foramen ovale who underwent a ventilation perfusion scintigraphy were identified from a stroke registry. Blinded from clinical data, ventilation perfusion scintigraphy scans were re-evaluated independently by 2 experts. Patients showing at least a subsegmental defect were considered as having silent PE. Factors potentially associated with PE were analyzed.

***Results***—The evaluation included 151 patients. Median age was 55.2 years and 59.9% were male. In 56 (37%) patients, silent PE was found; a deep vein thrombosis was evident in 11 (7%) patients. Atrial septal aneurysm was identified in 39 patients and hypermobile atrial septum in 37 patients. Atrial septal aneurysm and hypermobile atrial septum were independently associated with PE. In females, intake of oral contraceptives showed certain association with PE (6 of 25 versus 3 of 40; $P=0.07$).

***Conclusions***—Silent PE frequently occurs in patients with cryptogenic stroke and patent foramen ovale, particularly when atrial septal aneurysm or hypermobile atrial septum are present. **(*Stroke*. 2011;42:822-824.)**

**Key Words:** deep vein thrombosis ■ paradoxical embolism ■ patent foramen ovale ■ pulmonary embolism ■ stroke



In patients with cryptogenic stroke (CS) and patent foramen ovale (PFO), the proposed pathomechanism is paradoxical embolism (PDE).[1] Silent pulmonary embolism (PE) is frequently observed in patients with high risk for venous thrombotic embolism.[2,3] Few cases describe acute PE succeeding PDE or vice versa.[4,5] To what extent silent PE occurs in patients with PFO and CS is unknown. So far, this has not been investigated systematically. Silent PE underlines the pathophysiological significance of PDE and may influence the strategy for secondary prevention.

The present study investigates the frequency of silent PE in a cohort of patients with CS and PFO.

## Methods

### Patients

From a stroke registry, 266 consecutive patients diagnosed with PFO by means of transesophageal echocardiography were identified. Patients with CS and ventilation perfusion scintigraphy were selected for the subsequent analysis (n=151). A CS was considered when the PDE represented the single probable mechanism for stroke.

Baseline data such as age, gender, and disability status were derived from a registry in which the patients had been prospectively included (the hospital-based stroke registry of the federal state Hesse [Germany]).[6] From patients' case files, the following data were added: intake of oral contraceptives, current and previous deep vein thrombosis (DVT), coagulopathy screening (factor V Leiden mutation, antiphospholipid antibodies, protein S and protein C deficiency, antithrombin III deficiency, and prothrombin G20210A mutation), and D-dimer levels assessed within 24 hours after admission.

### Transesophageal Echocardiography

To detect an interatrial shunt, the contrast agent Echovist was used. A massive shunt size was considered when >30 microbubbles were observed. An atrial septal aneurysm (ASA) was diagnosed in case the atrial septum extended ≥11 mm into the left or the right atrium. An excursion of ≥5 mm of the septum primum into either the left or right atrium with respect to a perpendicular line to the fossa ovalis plane was considered as hypermobile atrial septum (HAS).

### Ventilation Perfusion Scintigraphy

For ventilation scintigraphy, the radioaerosol delivery system VENTICIS II was used for nebulizing a solution of Tc99m-diethylenetriaminepenta-acetic acid. For perfusion scintigraphy, 90 MBq of Tc99m-labeled albumin macroaggregates were slowly injected intravenously during 3 to 4 breath cycles. Image acquisition was performed with a Siemens MultiSpect III gamma camera. Projection data were scatter corrected and reconstructed as for single photon emission tomography using an iterative reconstruction algorithm. A perfusion defect is visualized indirectly by perfusion

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**Table 1. Characteristics in Patients With Versus Without PE**

| | Total Cohort (n=151) | PE-Positive (n=56) | PE-Negative (n=95) | *P* |
|---|---|---|---|---|
| Age, (median) | 55.2 | 55.73 | 54.01 | 0.21 |
| National Institutes of Health Stroke Scale on admission in patients with stroke, median* (n=122) | 3 | 3 | 3 | 0.69 |
| Time delay symptom onset to V/Q in days, median | 6 | 7 | 6 | 0.63 |
| Sex | | | | 0.76 |
| Female | 65 (43%) | 25 (45%) | 40 (42%) | |
| Male | 86 (57%) | 31 (55%) | 55 (58%) | |
| Coagulopathy | 6 (4%) | 2 (4%) | 4 (4%) | 0.99 |
| Current smoking | 34 (23%) | 16 (29%) | 18 (19%) | 0.23 |
| Hypertension | 42 (28%) | 12 (21%) | 30 (32%) | 0.19 |
| Hypercholesterolemia | 28 (19%) | 7 (13%) | 21 (22%) | 0.19 |
| Diabetes | 9 (6%) | 2 (4%) | 7 (7%) | 0.48 |
| Shunt size >30 bubbles | 97 (64%) | 35 (63%) | 62 (65%) | 0.72 |
| Current DVT | 11 (7%) | 8 (14%) | 3 (3%) | 0.02 |
| ASA | 39 (26%) | 27 (48%) | 12 (13%) | <0.001 |
| HAS | 37 (25%) | 23 (41%) | 14 (15%) | <0.001 |
| Previous stroke or transient ischemic attack | 18 (12%) | 5 (9%) | 13 (13%) | 0.46 |
| Intake of oral contraceptives† (n=65) | 9 (14%) | 6 (24%) | 3 (8%) | 0.07 |
| D-dimer, μg/mL, assessed on admission, median (n=87)‡ | 0.13 | 0.13 | 0.17 | 0.59 |

*Analysis do not consider patients with transient ischemic attack (n=29).
†Analysis in females.
‡Reference range <0.19 μg/mL.
V/Q indicates ventilation perfusion scintigraphy.

scanning as a parenchymal defect related to the embolized artery and is confirmed by combined ventilation scanning, showing normal regional ventilation.

Blinded from clinical data, all scans were independently evaluated by 2 experts according to the Prospective Investigation Of Pulmonary Embolism Diagnosis (PIOPED) criteria modified for single photon emission tomography images as described by Reinartz et al.[7,8] In scans graded differently, a consensus read was undertaken. Scans showing at least subsegmental perfusion defects with corresponding regular ventilation were considered consistent with PE.

## Statistical Analysis

Nonparametric data were compared using a 2-tailed Mann-Whitney *U* test and dichotomized data were analyzed using Fisher exact test. Associated factors were entered into a logistic regression analysis.

## Results

In the final analysis, 151 patients were included. The median age was 55.2 years, 86 patients were male, and 29 patients presented with transient ischemic attack. Silent PE was detected in 56 patients (37%); in 11 patients, DVT was found (Table 1). The evaluation of the ventilation perfusion scintigraphy scans revealed an interrater agreement of 95.4% between the 2 experts. On the 7 scans graded differently, consensus for PE was achieved in 3 scans; 4 scans were judged normal.

Univariate analysis revealed statistically significant association between PE and ASA, HAS, and DVT. After performing the logistical regression, ASA, HAS, and current smoking were independently associated with PE (Table 2). In females, univariate analysis revealed some association of intake of oral contraceptives with PE (6 of 25 versus 3 of 40; $P=0.07$). As a consequence, the complete analysis was repeated excluding females with intake of oral contraceptives. ASA and HAS were still associated with PE.

## Discussion

In the present study, silent PE in patients with PFO and CS was depicted as a frequent finding (37%) and strongly associated with ASA and HAS. It is a crucial finding of high clinical relevance, which contributes to a better understanding of PDE in PFO, emerging new treatment strategies.

It remains a question of debate, however, whether there is a relation among silent PE, PFO, and the mechanism of PDE, respectively. One approach to the interpretation might be an appropriate control group, which so far is not available in our study. To put our results into a context, the frequency of silent PE in comparable populations with venous embolic risk needs to be considered for the interpretation. The higher the risk for venous embolic diseases, the higher the expected rate of silent PE.[2,9,10] Therefore, the high frequency of 37% silent

**Table 2. Logistical Regression for Assessing Parameters Independently Associated With Silent PE**

| N=151 | *P* (Univariate Analysis) | *P* (Logistical Regression) | OR | CI |
|---|---|---|---|---|
| ASA | <0.001 | <0.001 | 7.9 | 3.3–19.3 |
| Hypermobile atrial septum | <0.001 | 0.002 | 4.2 | 1.7–10.1 |
| Current DVT | 0.02 | 0.12 | 3.5 | 0.6–17.8 |
| Current smoking | 0.23 | 0.02 | 2.8 | 1.2–7.1 |

PE in our cohort corresponds to the expected frequency in populations with high risk for venous embolic diseases.

Because the perfusion defects did not result in clinical manifestation, it is difficult to assess whether they reflect recent events. The morphological analysis does not allow precise determination of the date of onset. Lack of elevated D-dimer levels in patients with PE might support the hypothesis of nonrecent events. Nevertheless, even this aspect remained unsolved; silent PE definitely reflects increased venous embolic activity.

Cuppini et al found silent PE in 59% of patients with acute DVT, mainly resolving after anticoagulant treatment.[2] Oral anticoagulation even prevents subsequent major pulmonary emboli once silent PE is detected.[9] This might suggest a substantial contribution of anticoagulant treatment in patients with CS, PFO, and silent PE.

In our study, silent PE was associated with DVT; however, it could not sufficiently be explained by DVT. ASA or HAS was identified as independent factors associated with silent PE, which supports their pathophysiological relevance. In this context, they may even be regarded as independent embolic sources.

In conclusion, silent PE is a frequent finding in patients with CS and PFO. It might reflect a venous embolic burden rather than a recent event. Our study adds further information on ASA and HAS as independent thrombotic factors. The role of anticoagulant treatment needs further clarification.

## Disclosures

None.

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