Patent Foramen Ovale: Is Stroke Due to Paradoxical Embolism?

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Background and Purpose: A patent foramen ovale has been reported to be significantly more frequent in young stroke patients than in matched control subjects, and paradoxical embolism has been suggested as the main mechanism of stroke in this situation. The present study was designed to test this hypothesis.

Methods: Sixty-eight consecutive patients under 55 years of age presenting with an ischemic stroke had an extensive workup, including transthoracic echocardiography with contrast. We compared the prevalence of criteria for the diagnosis of paradoxical embolism in patients with and without a patent foramen ovale.

Results: A patent foramen ovale was found in 32 patients (47%). A Valsalva-provoking activity was present at stroke onset in six patients with a patent foramen ovale and in eight patients with no patent foramen ovale (\(\chi^2=0.1\), nonsignificant). Clinical/radiological features suggestive of an embolic mechanism were not more frequent in patients with a patent foramen ovale. Clinical evidence of deep vein thrombosis was present in one patient with a patent foramen ovale and in none of the others. No occult venous thrombosis was found in a subgroup of patients with a patent foramen ovale and no definite cause for stroke who underwent venography (n=13).

Conclusions: Our results do not support the hypothesis that paradoxical embolism is the primary mechanism of stroke in patients with a patent foramen ovale. (Stroke 1993;24:31–34)

Key Words • cerebral ischemia • embolism • foramen ovale, patent

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aradoxical embolism, defined as the systemic embolism of venous or right atrial origin through a right-to-left cardiac shunt, was formerly considered to be a rare cause of stroke. In almost all reported cases, the conduit for paradoxical embolism was a patent foramen ovale (PFO). Interest in paradoxical embolism has been rekindled by the advent of contrast echocardiography, a noninvasive and reliable technique for the detection of small right-to-left cardiac shunts. In 1988, two case-control studies demonstrated a significantly higher prevalence of PFO in young patients with ischemic stroke (40–50%) than in control subjects (10–15%).1,2 Whether, and to what extent, the excess prevalence of PFO in young stroke patients is related to paradoxical embolism remains unsettled.3 If one assumes that most strokes in patients with PFO are due to paradoxical embolism, then a higher prevalence of overt or occult deep venous thrombosis (DVT), or risk factors for DVT, would be expected in these patients than in stroke patients with no PFO. Likewise, an excess prevalence of Valsalva-provoking activities (which tran-

siently increase or provoke right-to-left shunting in patients with PFO) at stroke onset and of features suggesting cerebral embolism should theoretically be found in these patients. We specifically addressed these issues.

Subjects and Methods

Sixty-eight consecutive patients under 55 years of age with ischemic stroke were included in this study. None of these patients overlapped with those reported in a previous study4 by one of us. All patients had computed tomography and/or magnetic resonance imaging of the head. Cerebral angiography was performed in 62 patients, in 22 (35%) within 6 days after stroke onset. Routine laboratory studies included complete blood cell count; erythrocyte sedimentation rate; protein electrophoresis; antinuclear antibodies; glucose, serum cholesterol, and triglyceride levels; and prothrombin and activated partial thromboplastin times. Extensive platelet, coagulation, and fibrinolysis studies were performed in 44 patients.

Cardiac investigations. In addition to routine cardiac examination (including electrocardiography and chest roentgenography), all patients had transthoracic echocardiography with contrast. The contrast was obtained by injecting rapidly 5–10 ml isotonic saline or gelatin. We used two syringes, mounted on a three-way stopcock, to mix the saline or gelatin with air. This mixture was injected directly into an antecubital vein. Three to six contrast injections were systematically performed in each patient, in the resting state and...
during provocative maneuvers (Valsalva maneuver and cough test). The echocardiographic diagnosis of PFO was based on the appearance of more than five microcavitations into the left atrium within three cardiac cycles after total opacification of the right atrium.

**Search for deep venous thrombosis.** Clinical signs and risk factors for DVT (use of contraceptive agents, obesity, prolonged bed rest within the month before stroke onset) were systematically sought. Venography was performed in a subgroup of patients ($n=13$) according to the following criteria: 1) presence of PFO, 2) no definite cause for stroke, and 3) examination within 4 weeks after stroke onset. None of the patients examined by venography had severe motor (leg) deficit. For ethical reasons, venography was not performed in patients with no PFO or with PFO and a definite cause for stroke.

**Circumstances of onset.** All patients were asked about their activities within minutes preceding stroke onset. Sporting effort, straining at stool, intercourse, lifting a heavy weight, getting up, laughing, and coughing were considered as equivalents of Valsalva maneuvers. Information was obtained in 64 patients; in four patients with no evidence of right-to-left shunting the information was not available because of aphasia.

**Definite cause for stroke.** It was defined as any disease that has been clearly linked to the occurrence of stroke: arteriopathies such as dissections, atherosclerosis with stenosis of $>50\%$, or angiitis; coagulopathies and systemic disorders such as thromboembolism, disseminated intravascular coagulation, or lupus erythematosus; and cardiopathies such as mitral stenosis, atrial fibrillation, or acute myocardial infarction. The presence of a definite cause for stroke was assessed without knowledge of the results of contrast echocardiography. Atrial septal aneurysm and mitral valve prolapse were not considered to be definite causes for stroke, but only risk factors for stroke. Other risk factors included hypertension, diabetes mellitus, cigarette smoking, hypercholesterolemia, migraine according to the criteria of the International Headache Society, and previous or current use of contraceptive agents.

The patients were divided into two groups according to the presence of a right-to-left shunt detected by contrast transesophageal echocardiography. The two groups were compared according to criteria consistent with the diagnosis of paradoxical embolism: presence of DVT or risk factors for DVT, Valsalva-provoking activity at stroke onset, and features suggestive of an embolic mechanism. The presence of either arterial occlusion on early angiography or at least one of sudden onset, early loss of consciousness, and hemorrhagic or cortical infarct was considered to support the diagnosis of cerebral embolism. These criteria were assessed in each patient without knowledge of the results of contrast echocardiography. Percentages were compared by the $\chi^2$ test with the appropriate degrees of freedom. Quantitative data were compared by $t$ test.

**Results**

A positive contrast study was found in 32 patients (47%): 21 at rest, and 11 only after provocative maneuvers. This percentage rose to 57% when only patients with no definite cause for stroke were taken into account. In two patients, the right-to-left shunt was not due to PFO. One patient had a patent ductus arteriosus proven by aortography, and the other had an ostium primum defect with a left-to-right shunt at rest and a right-to-left shunt after Valsalva maneuver.

Characteristics of the patients with and without PFO are shown in Table 1. Mean age and sex ratio in the patients with PFO (36.8 years, male:female=1.5) did not differ significantly from those in patients with no PFO (40.2 years, male:female=2). A definite cause for stroke was found in one of the 32 patients with PFO and in 13 of the 36 patients with no PFO ($\chi^2=11.3, df=1, p<0.001$). Among the patients with no definite cause for stroke, 18 (56%) with PFO and 19 (53%) with no PFO had one or more risk factors for stroke (Table 1).

Table 2 shows the prevalence of criteria for paradoxical embolism in the patients with and without PFO. Risk factors for DVT were present in five patients with PFO and in 10 patients with no PFO ($\chi^2=1.4, df=1$, nonsignificant). Only one patient with PFO had overt clinical DVT. It occurred in a severely paralyzed leg 14 days after stroke onset and was confirmed by venous echo Doppler. No latent DVT was found on venography in the subgroup of 13 patients with PFO and no definite cause for stroke.

Valsalva-provoking activities at stroke onset were not more frequent in the patients with PFO than in the patients with no PFO ($\chi^2=0.1, df=1$). Such activities were present in six of the 32 patients with a right-to-left shunt (six of the 31 with no or questionable cause for their stroke) and in eight of the 32 patients with no PFO.

| Table 1. Characteristics of Patients With and Without Patent Foramen Ovale |
|-----------------|-----------------|-----------------|
| Characteristic   | With ($n=32$)   | Without ($n=36$) |
| Mean age (yr)    | 36.8            | 40.2            |
| Sex              |                 |                 |
| Female           | 13              | 12              |
| Male             | 19              | 24              |
| Definite cause for stroke | 1, 13  | 1, 13 |
| Dissection       | 1               | 5               |
| Acute myocardial infarction | 0, 1  | 0, 1   |
| Cerebral angiitis | 0, 1           | 0, 1            |
| Thromboembolisms | 0, 2            |                 |
| Lupus erythematosus + antiphospholipid antibodies | 0, 1 | 0, 1 |
| Disseminated intravascular coagulation | 0, 1 | 0, 1 |
| Atherosclerosis  | 0, 1            | 0, 1            |
| Mitral stenosis with atrial fibrillation | 0, 1 | 0, 1 |
| Risk factors for stroke |                 |                 |
| Mitral valve prolapse | 1 (1), 5 (2) |                  |
| Atrial septal aneurysm | 7 (7), 4 (3) |                  |
| Migraine         | 6 (6), 4 (2)    |                 |
| Oral contraceptive use | 3 (3), 5 (2) |                  |
| Diabetes mellitus | 2 (2), 2 (1)   |                 |
| Hypertension     | 0 (0), 8 (8)    |                 |
| Cigarette smoking | 8 (8), 15 (13) |                 |
| Hypercholesterolemia | 5 (5), 3 (3)   |                  |
| No risk factors  | 13 (13), 9 (4)  |                 |

Numbers in parentheses concern patients with no definite cause for stroke.
(five of the 21 patients with no or questionable cause) and no aphasia.

Clinical and radiological features suggestive of cerebral embolism did not differ significantly between the two groups (Table 2).

Discussion

The prevalence of PFO in this study was 47% (57% in those with strokes of undetermined etiology). A definite cause for stroke was found in only one of the 32 patients with a right-to-left shunt, compared with in 13 of the 36 patients with no PFO; the difference was significant. These findings are in agreement with previous case-control studies demonstrating a higher prevalence of PFO in young patients with stroke of unexplained etiology than in control subjects.12

The main criterion for paradoxical embolism is the presence of DVT. In our study, the only overt DVT was likely a consequence of the stroke since it occurred 2 weeks after the stroke in a severely paralyzed leg. The frequency of DVT secondary to stroke has been reported to be as high as 30% in studies using venous echo Doppler and fibrinogen leg scanning.10 The risk of DVT is related to the severity of the stroke and rises sharply as early as the second day after stroke onset.16 No excess of risk factors for DVT was found in our patients with PFO. Finally, we did not find any occult DVT on venography in 13 patients with PFO and no or mild to moderate leg motor deficit. Although the number of patients who underwent venography was relatively low, the low prevalence of DVT and risk factors for DVT in our study does not support a paradoxical embolic mechanism in stroke patients with PFO. Our results are similar to those reported by Gautier et al11 in their series of 29 patients with PFO and an unexplained stroke or transient ischemic attack. Only three occult DVT were found in 23 venographies performed within 2 days to 7 months after stroke onset. By contrast, in another study12 venography disclosed occlusion of a leg vein in 24 of 42 patients with PFO and cerebral (n = 36) or systemic (n = 6) ischemic events. However, no information is available concerning the severity of the motor deficit or the precise time interval between stroke onset and venography.

There are many pitfalls in the diagnosis of DVT that may lead to an underrecognition of DVT. Even in patients with documented pulmonary embolism, about 50% have no clinical signs of DVT. Furthermore, about 20% of patients with pulmonary embolism have no evidence of venous thrombosis using conventional diagnostic tests.13 As pulmonary emboli may be of an occult source, the lack of an identifiable source of many paradoxical emboli is not unexpected. In a review of 29 cases of clinically diagnosed paradoxical embolism, overt DVT was present in only three patients, and 14 were eventually found to have DVT.14 The source of emboli may remain undetected by conventional venography because of its location. In the two larger series of pathologically proven systemic paradoxical embolism,15,16 the sources of emboli (not stated in 20%) were the leg veins in only 33%; the other sites were the right atrium in 14%, pelvic veins in 25%, and miscellaneous sites in 8%. Other diagnostic tools, such as immunoscintigraphy, will probably improve our ability to detect DVT. Finally, DVT may disappear, either spontaneously or with anticoagulant therapy, before venography is performed.

A sustained elevation of the right heart pressure, usually due to pulmonary embolism,17 has long been considered a precondition for paradoxical embolism. However, contrast echocardiography has clearly demonstrated that the normal interatrial left-to-right pressure gradient can be transiently reversed either spontaneously during early systole1 or by Valsalva-provoking activities.18 In our study, Valsalva-provoking activities were not more frequent in patients with PFO than in patients with no PFO. Finally, we did not find any difference between the two groups regarding features
suggestive of cerebral embolism. However, the sensitivity and specificity of these clinical and radiological criteria are poor.7

In conclusion, our study confirms that the prevalence of PFO is high in young stroke patients and that stroke in patients with PFO is not associated with the conventional definite causes for stroke. In addition our study shows that conventional criteria for paradoxical embolism are not more frequent in patients with PFO than in patients with no PFO, which suggests that paradoxical embolism might not be the prevalent mechanism of stroke in patients with PFO. This conclusion must be tempered because of the relatively few patients who underwent venography. In addition, it is possible that the conventional criteria for paradoxical embolism on which the present study is based may be insufficient or inaccurate. The exact mechanism of stroke in patients with PFO and no definite cause for stroke remains unknown. The association between PFO and stroke might be partly explained by other PFO-associated cardiac or vascular abnormalities (confounding factors). For instance, PFO has been reported to be associated with mitral valve prolapse1 and atrial septal aneurysm.19 These potential confounding factors deserve further studies.

References

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