Morphological and Functional Characteristics of Patent Foramen Ovale and Their Embolic Implications

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Background and Purpose—Transesophageal echocardiography (TEE) has detected a high prevalence of patent foramen ovale (PFO) in stroke patients, but the clinical implications of the distinctive characteristics of this patency are still a matter of debate.

Methods—We studied 350 patients with acute ischemic stroke or transient ischemic attack (TIA) within 1 week of admission. Of these, 101 (29%) were identified by contrast TEE to have a PFO; 86 patients (25%) were cryptogenic stroke patients, and 163 were excluded because of the presence of a definite or possible arterial or clinical evidence of a source of emboli or small-vessel disease. Thirteen PFO subjects without a history of embolism were designated as the control group. All PFO and cryptogenic stroke patients were followed up by neurological visits.

Results—Compared with controls, PFO patients with acute stroke or TIA more frequently presented with a right-to-left shunt at rest and a higher membrane mobility (P<0.05). Patients with these characteristics were considered to be at high risk. During a median follow-up period of 31 months (range, 4 to 58 months), 8 PFO and 18 cryptogenic stroke patients experienced recurrent cerebrovascular events. The cumulative estimate of risk of cerebrovascular event recurrence at 3 years was 4.3% (95% confidence interval [CI], 0% to 10.2%) for “low-risk” PFO patients, 12.5% (95% CI, 0% to 26.1%) for “high-risk” PFO patients, and 16.3% (95% CI, 7.2% to 25.4%) for cryptogenic stroke patients (high-risk PFO versus low-risk PFO, P=0.05).

Conclusions—The association of right-to-left shunting at rest and high membrane mobility, as detected by contrast TEE, seems to identify PFO patients with cerebrovascular ischemic events who are at higher risk for recurrent brain embolism.

(Key Words: cerebral ischemia ■ echocardiography ■ embolism ■ foramen ovale, patent

Several studies with saline-contrast transesophageal echocardiography (TEE) have suggested an increased prevalence of patent foramen ovale (PFO) in patients with unexplained cerebral ischemia.1–5 However, the clinical significance of PFO is still, at present, a matter of debate.6–8 Recently, reports have been presented that characterize the distinctive echocardiographic characteristics of this abnormality and their relationship with paradoxical cerebral embolism.9,10 Our study was designed to (1) define the morphological characteristics of the PFO in patients with acute stroke or transient ischemic attack (TIA) and in normal subjects and (2) investigate and compare the recurrence of clinical stroke or TIA in PFO and cryptogenic stroke patients.

Subjects and Methods

Subjects
From November 1992 to October 1996, all patients with acute stroke or TIA admitted to the Department of Neurological Sciences at the University of Rome “La Sapienza” were screened for enrollment in the study. Stroke was defined as a focal neurological deficit of sudden onset that persisted beyond 24 hours in surviving patients11; TIA was defined as a focal neurological deficit resolving completely within 24 hours.11 Particular attention was taken to exclude episodes of transient global amnesia, loss of consciousness, fainting episodes, and focal symptoms associated with migraine headache12 that could have been misdiagnosed as TIA.

All patients underwent general medical and neurological examinations, chest radiography, general blood chemistry assay, and electrocardiography. Cerebrovascular risk factors such as hypertension, diabetes mellitus, obesity, hypercholesterolemia and/or hypertriglyceridemia, cigarette smoking, and contraceptive drug use were fully investigated. In addition, the presence and number of clinical cerebral ischemic episodes that had occurred before admission were screened. Moreover, all patients underwent carotid duplex (B-mode and Doppler) scanning, transcranial Doppler ultrasound, and cerebral CT and/or MRI.

This workup allowed us to classify the patients into different pathogenetic groups, in accordance with the modified criteria of Amarenco et al13: (1) patients with a definite or possible arterial or
cardiac source of emboli; (2) patients with small-vessel disease; and (3) patients who could not be classified into either of the above groups (stroke or TIA of undetermined origin).

Cardiac Imaging

By these criteria, all patients with stroke or TIA of undetermined origin were subjected to transthoracic and, immediately afterward, saline-contrast TEE examinations. Echocardiographic studies were performed by using commercially available ultrasound systems with 2.5- and 3.5-MHz transthoracic probes and 5-MHz biplane or 5/3.7-MHz multiplane transesophageal probes.

The saline-contrast study was performed both during normal respiration and during the Valsalva maneuver. In our experience, the most appropriate way to perform a diagnostic Valsalva maneuver is by asking the patient to start the maneuver at the moment of injection and to release the strain after complete opacification of the right atrium. The Valsalva maneuver was considered to have been correctly performed when the atrial septal membrane bulged into the left atrium. Informed consent for the saline-contrast TEE was obtained from all patients, and no complications occurred during the procedures.

Echocardiographic Criteria

A positive contrast examination was defined when 3 or more microbubbles appeared in the left atrium (Figure 1). The maximum number of shunted microbubbles visualized in a single frame, both during normal breathing and when induced by the Valsalva maneuver, within 3 cardiac cycles after entire right atrium opacification was counted. Contrast studies during a Valsalva maneuver were repeated when the first injection yielded a negative or a questionable result.

We considered the following parameters (Figure 2): (1) Fossa ovalis diameter; (2) septum primum membrane length; (3) fossa ovalis diameter-to-membrane length ratio; (4) PFO 1D and 2D diameter (in the vertical plane, the maximum opening between the septum primum and the septum secundum was measured at rest); and (5) membrane mobility. The sum of excursions at rest (the greatest leftward and rightward deflections of the septum primum with respect to a perpendicular line to the fossa ovalis plane) into either the left or right atrium of the membrane was calculated. All echocardiographic examinations were recorded on VHS videotape. All measurements were independently analyzed by offline frame-by-frame analysis by 2 cardiologists who were expert in echocardiography without their knowledge of the patient’s clinical history or diagnostic workup results.

Exclusion Criteria

To eliminate factors that might influence analysis of the specific morphological characteristics of PFO, we excluded from further analysis those patients with poor visualization of the fossa ovalis area, those with both PFO and a valve insufficiency graded more than mild (able to alter the cardiac chamber hemodynamic conditions), or those with left-to-right shunt as detected by color Doppler techniques (considered to represent small, atrial septal defects).

Follow-Up Information

Clinical data of PFO and cryptogenic stroke patients were regularly recorded by neurologists twice a year during a medical visit. Death due to brain infarct and new episodes of ischemic stroke and TIA were considered recurrent events. The diagnosis of stroke or TIA and death due to cerebral infarct was confirmed by CT scan or autopsy, respectively, in all cases.

Data Analysis

Thirteen consecutive PFO subjects, without a history of cerebral or systemic ischemia and with no detectable cardiac abnormalities other than right-to-left shunting, were selected as the control group. Statistical analysis was performed by the Mann-Whitney U test, ANOVA, χ² test, or Fisher’s exact test. The agreement between the 2 raters on TEE parameters was assessed by using Spearman’s correlation and the paired t test. Actuarial life-table analysis was used to estimate the risk of recurrent cerebrovascular events. A value of P<0.05 was considered significant. A Cox proportional-hazards model was used to account for potential confounding factors. All analyses were performed with BMDP statistical software. 15

Results

Patients

Using saline-contrast TEE, we studied 350 patients within 1 week of acute ischemic stroke or TIA. An intracardiac right-to-left shunt was detected in 101 patients (29%). In accordance with the above-mentioned criteria, we excluded 27 patients for the following reasons: contemporaneous presence of moderate-to-severe aortic and/or mitral valve insufficiency in 10; left-to-right–associated shunting due to small, atrial septal defects in 11; and poor visualization of the fossa ovalis area in 6.

<table>
<thead>
<tr>
<th></th>
<th>PFO (n=74)</th>
<th>Controls (n=13)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FO diameter, mm</td>
<td>17.9±3.3</td>
<td>16.2±2.7</td>
<td>0.09</td>
</tr>
<tr>
<td>M length, mm</td>
<td>27.8±6.3</td>
<td>26.5±6.3</td>
<td>0.50</td>
</tr>
<tr>
<td>FO/M length ratio</td>
<td>0.66±0.1</td>
<td>0.63±0.09</td>
<td>0.40</td>
</tr>
<tr>
<td>PFO opening, mm</td>
<td>2±1.3</td>
<td>1.5±1.2</td>
<td>0.20</td>
</tr>
<tr>
<td>M mobility, mm</td>
<td>7.5±4.3</td>
<td>4.9±3.6</td>
<td>0.04</td>
</tr>
<tr>
<td>PFO at rest, % (of patients)</td>
<td>45 (61%)</td>
<td>4 (31%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Mcb at Valsalva, max No.</td>
<td>27±28</td>
<td>26±26</td>
<td>0.90</td>
</tr>
</tbody>
</table>

M indicates fossa ovalis membrane; Mcb, shunted microbubbles; max, maximum. All values are mean±SD, unless indicated otherwise.

The remaining 74 PFO stroke patients (mean age, 53±14 years) were characterized as follows: 56 patients with “PFO alone” (ie, without any other detectable embolic source); and 18 patients with PFO and other potential cardiac or aortic sources of associated emboli, represented by complicated atheromatous lesions of the ascending aorta and/or arch in 9; mitral valve prolapse with a myxomatous valvular structure in 4; mitral and/or aortic valve fibrinous strands in 3; and massive mitral valve calcific degeneration in 2.

One-hundred sixty-three patients were excluded because of the presence of a definite or possible arterial or clinical evidence of the source of emboli or small-vessel disease. The remaining 86 cryptogenic stroke patients (mean age, 47±14 years) completed the follow-up period, and their data were available for comparison in assessing the recurrent risk of ischemic events.

Clinical Characteristics

No significant differences were detected with respect to classic cerebral ischemia risk factors among PFO and cryptogenic stroke patients versus controls. All patients were in sinus rhythm, and none presented clinical symptoms or echocardiographic findings of increased pulmonary pressure values.

Morphological and Functional Characteristics of PFO

The morphological and functional echocardiographic findings of the fossa ovalis structures in stroke/TIA patients and controls with PFO are listed in the Table. The prevalence of patency during normal breathing (ie, PFO at rest) was significantly higher (P=0.04) in patients with stroke or TIA as opposed to controls. Moreover, an increased fossa ovalis membrane mobility (P=0.04) was detected in PFO patients with stroke or TIA.

Recurrent Events During Follow-Up

No patient with PFO and acute stroke or TIA was lost to follow-up. During a median follow-up period of 31 months (range, 4 to 58 months), 8 (11%) patients suffered a new cerebrovascular event. Of these, 5 had a stroke (fatal event in 3 cases) and 3 had a TIA. Two patients died of neoplasm.

Eighty-six patients with cryptogenic acute stroke or TIA completed the follow-up period (median of 34 months; range, 5 to 60 months); 18 (21%) experienced a new cerebrovascular event. Of these, 11 had a stroke (no cases of related death) and 7 had a TIA. The recurrent cerebrovascular event occurred in patients who were taking 250 to 500 mg of aspirin and oral anticoagulants, with a targeted International Normalized Ratio between 2 and 3, as well as in patients not receiving such treatment.

To devise a risk scale for clinical event recurrence, data for patency at rest and membrane mobility were used to group PFO patients as follows: the high-risk group (n=27), including those with PFO at rest and membrane mobility >6.5 mm; and the low-risk group (n=47), including those with PFO (either at rest or during the Valsalva maneuver) and membrane mobility ≤6.5 mm, or those with membrane mobility >6.5 mm with PFO during the Valsalva maneuver only. The cutoff of 6.5 mm was chosen because it represented the median value of membrane mobility for the total PFO population.

The overall cumulative estimate of risk of stroke or TIA recurrence, at 3 years of follow-up, in the whole cohort of patients with PFO was 7.2% (95% CI, 1% to 13.5%), as opposed to 16.3% (95% CI, 7.2% to 25.4%) for patients with cryptogenic stroke (P=0.3) (Figure 3). Age-adjusted analysis did not reveal any statistical difference between cryptogenic and PFO patients in terms of risk of cerebrovascular ischemic recurrence. When PFO patients were analyzed separately, the risk of stroke or TIA recurrence, at 3 years of follow-up, was 4.3% (95% CI, 0% to 10.2%) for those with the low-risk pattern and 12.5% (95% CI, 0% to 26.1%) for those with the high-risk profile (P=0.05) (Figure 4).

Moreover, when only stroke events were considered in the analysis of follow-up data, the estimate of the risk of stroke recurrence, at 3 years of follow-up, was 2.1% (95% CI, 0% to 6.3%) for low-risk PFO patients, 5.3% (95% CI, 0% to 15.5%) for high-risk PFO patients, and 10.2% (95% CI, 2.8% to 17.6%) for cryptogenic stroke patients (Figures 5 and 6). These results were not modified by adjustment for age,
vascular risk factors, and treatment, as performed with the Cox proportional-hazards model.

Discussion

PFO is the anatomic means by which paradoxical embolic stroke is generally believed to develop,16–18 and saline-contrast TEE with provocative maneuvers is considered the method of choice in detecting it during life.4,19 However, whereas in a stroke population a higher PFO prevalence is found, demonstration of deep venous thrombosis or an elevation of right heart pressure values, thus permitting a shunt, is usually lacking.6 For this reason, several studies have focused on the anatomic and functional echocardiographic findings to define which PFOs are to be considered risk condition for stroke. A more severe right-to-left shunt and a larger opening of the PFO have been identified as the main characteristics in evaluating the likelihood of paradoxical embolism in stroke patients.20–23 On the other hand, the separation between the septum primum and septum secundum, and hence the degree of shunt, may vary from cardiac cycle to cardiac cycle as the hemodynamic and respiratory conditions change.24,25 Moreover, because of its anatomic characteristics (ie, short and angled conduit), it is usually neither simple nor correct to obtain measures of the maximum size of the opening, even by using high-frequency imaging systems. Regarding the semiquantitative grading of PFO shunting, several conditions seem to work against its use as a marker of increased risk for paradoxical embolism. In fact, the maximum degree of shunting is usually reached during provocative maneuvers (ie, Valsalva or cough), which are sometimes not obtainable by stroke patients, and these almost always differ from each other in the type and level of strain exerted. Moreover, the microbubble count is derived from a single 2D imaging plane, and this analysis does not reflect the exact amount of shunting.

The results of the present study suggest that a right-to-left shunt at rest, in the absence of a significant increase in right atrial mean pressure, is a marker of risk for cerebral ischemia in patients with PFO. Because of its valvelike nature, PFO may permit right-to-left shunting as the result of a transient, instantaneous pressure gradient between the right and left atria during the cardiac cycle, even without the need for pathological (ie, pulmonary hypertension states) or physiological (ie, Valsalva maneuvers or correlates) augmentation.26 To clarify this potential risk condition, one may suppose that patients who already have a shunt during quiet breathing have an increased exposure time for paradoxical embolism, as opposed to those with a shunt induced by provocative maneuvers only. As shown by clinical practice, the low pathophysiological importance of provocative-only shunts has been documented. In fact, no correlations were found between circumstances able to increase right cardiac chamber pressure (ie, sporting effort, lifting a heavy weight, coughing, and others considered as equivalents of the Valsalva maneuver) immediately preceding stroke onset and the presence of PFO.6

Our patients with PFO also had an associated increased fossa ovalis membrane mobility. With regard to this point, the boundary between “redundant mobile membrane” and “atrial septal aneurysm” is not a well-defined issue.27,28 Pearson and coworkers29 considered the sum of the excursions into the left and right atria >11 mm, with a fossa ovalis width >15 mm, as an echocardiographic diagnostic criterion. It should be noted that in the absence of anatomic and noninvasive “gold standard” criteria for the identification of true atrial septal aneurysm, every given definition may appear arbitrary.5,30 Nevertheless, atrial septal aneurysm has been correlated to ischemic stroke by several postulated mechanisms (ie, locus of thrombus generation, induction of supraventricular tachyarrhythmias, or association with mitral valve prolapse). The most plausible of these appears to be the underlying presence of interatrial communication.30 In fact, Mugge et al,31 in a large, multicenter, echocardiographic study of atrial septal aneurysm patients, found no morphological differences between those with and without previous cardiogenic embolism; only was an associated interatrial shunt significantly more frequent in patients with possible embolism. This conclusion has also been addressed by other investigators.32,33

Figure 4. Actuarial rate of survival without stroke and TIA in PFO patients with high and low embolic risk patterns. High-risk PFO indicates stroke patients with both PFO at rest and a membrane mobility >6.5 mm. Low-risk PFO are those stroke patients with (1) PFO, at rest or during the Valsalva maneuver, and a membrane mobility >6.5 mm or (2) membrane mobility >6.5 mm with patency during the Valsalva maneuver only.

Figure 5. Actuarial rate of survival without recurrent stroke events in cryptogenic stroke and PFO patients.

Figure 6. Actuarial rate of survival without recurrent stroke events in PFO patients with high and low embolic risk patterns. High-risk PFO indicates stroke patients with both PFO at rest and membrane mobility >6.5 mm. Low-risk PFO are those stroke patients with (1) PFO, at rest or during the Valsalva maneuver, and membrane mobility ≤6.5 mm or (2) membrane mobility >6.5 mm with patency during the Valsalva maneuver only.
The increased mobility of the fossa ovalis membrane in patients with PFO may play a significant role in permitting paradoxical shunt via a mechanical action in directing blood through the conduit. The preferential orientation of flow from the inferior vena cava is directed toward the foramen ovale through the eustachian valve, and it may be favored and enhanced by the flap motion of the membrane (Figure 7).

**PFO Patients at Higher Risk for Recurrent Cerebral Embolism**

Our study demonstrates that there are no differences between PFO and cryptogenetic stroke patients in terms of risk of recurrent cerebrovascular ischemic events. Moreover, even when stroke is analyzed separately from TIA, no significant results could be found between these 2 groups.

Few studies concerning cerebrovascular ischemic recurrence in PFO patients are available. This is partly due to its low incidence, as reported by Bogousslavsky et al., who demonstrated a rate of 3.8% per year of recurrent, nonfatal cerebrovascular ischemia during a 3-year follow-up period. Mas et al., investigating adult patients with PFO and a prior cerebrovascular ischemic event, detected a 6.7% risk rate for stroke or TIA at 2 years, with an increased rate to 9.0% in patients with both PFO and an atrial septal aneurysm. In addition, the potential synergistic effects of PFO and an atrial septal aneurysm with a >10-mm excursion have been postulated in a previous study of prevalence among young stroke patients <55 years of age. Our PFO stroke patients presented a similar recurrence rate of a stroke or TIA event (7.2% at 3 years). When high-risk and low-risk PFO patients are analyzed separately, a significant difference in risk of cerebrovascular ischemic recurrence is noted (12.5% versus 4.3% at 3 years of follow-up, \( P = 0.05 \)).

A major issue of the present study is that right-to-left shunting must already be present during normal breathing to identify the PFO as a potential risk factor for cerebral ischemia. Moreover, when this finding is associated with high mobility of the membrane, PFO patients are at a significantly greater risk for further cerebral ischemic events than are those with Valsalva-only shunting or small membrane mobility. This conclusion needs to be taken into account when stratification of cerebrovascular ischemic risk is required in patients with PFO.

When stroke episodes are examined separately from TIsAs, PFO patients at high risk present a higher prevalence of recurrence (15% versus 2%) as opposed to those with a low-risk profile. This result did not reach any statistical difference, probably due to the small sample size of the population studied and the relatively low number of recurrent episodes that occurred during the follow-up period. In PFO patients with stroke, several therapeutic options are available, ranging from no treatment through antiaggregants, anticoagulants, and transcatheter closure by device to surgical closure of the patency. However, it is still unclear which is the optimal strategy to adopt. In fact, cerebrovascular ischemic recurrence has been shown to affect patients treated with both antiaggregants and anticoagulants. Despite the fact that direct PFO closure by surgery or transcatheter device could be considered the optimal strategy in preventing paradoxical embolism, cerebrovascular ischemic recurrence has been documented even in this specific treatment subgroup. It is important to note that probably the more stringent the criteria chosen for paradoxical embolism and for high-risk PFO grading, the fewer mistakes the clinician will make in selecting the appropriate therapeutic option, particularly concerning patency closure.

**Limitations of the Study**

This study presents some limitations. To obtain a highly selected PFO population, we excluded 27 of 101 (27%) patients with right-to-left shunt. We decided not to consider as eligible those PFO patients with associated left-to-right shunting, because of anatomic implications. In fact, this type of communication should be classified as an interatrial defect, even where no lack of substance is detected at the fossa ovalis membrane level. Because of its valvelike nature, PFO does not shunt left to right, but in our series, 11% of patients were observed to have a bidirectional flow from the PFO conduit.
Further studies are required to fully clarify the anatomic implications and functional patterns of this finding.

Although our PFO population was presumed to have acute cerebral ischemia as a consequence of paradoxical embolism, no investigations were conducted to rule out the presence of a deep venous thrombosis. The source of emboli is frequently unexpected in a clinical scenario, as well as usually being undetectable by conventional diagnostic tests. In fact, the low sensitivity of the routine or even of more invasive tools has been underlined, even in patients with proven pulmonary embolism.\(^4\) Again, recent reports describe primary or secondary (transient or chronic) coagulation abnormalities in PFO patients that could be responsible for paradoxical embolism.\(^5\) In PFO patients at risk for paradoxical brain embolism recurrence, a right-to-left shunt is an independent predictor of major pulmonary embolism and severe pulmonary hypertension.\(^6\) Finally, the small sample size of the population studied does not allow us to reach definitive conclusion; however, the overall trend of our results strongly supports our findings on PFO patients at higher risk of recurrence cerebrovascular events. Further prospective, follow-up, multicenter studies are needed to confirm our hypothesis.

### Possible Clinical Implications

The significance of PFO detection varies according to the clinical and pathophysiological scenario. Its recognition in divers may lead them to refrain from scuba diving, in view of its documented correlation with paradoxical gas embolism and decompression sickness.\(^7\) In other conditions, such as major pulmonary embolism and severe pulmonary hypertension, a right-to-left shunt is an independent predictor of adverse outcome, with a high risk of death and arterial thromboembolic complications.\(^8\) In patients with unexplained stroke or TIA, saline-contrast TEE should be performed to rule out the presence of a cardiac or proximal aortic source of emboli. This study testifies to the usefulness of echocardiographic findings in predicting cerebrovascular ischemia in patients with PFO. In fact, shunting at rest with a high membrane mobility seems to identify those PFO patients at risk for paradoxical brain embolism recurrence. This issue needs to be taken into account for the stratification of risk in a single patient to indicate the correct management and to choose the optimal therapeutic option.

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