Transoesophageal echocardiography can help distinguish between patients with “symptomatic” and “asymptomatic” patent foramen ovale

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Abstract

Background: Incidence of patent foramen ovale (PFO) has been estimated at 25% in the general population and 6% for larger defects. Data on the relationship between PFO morphology and the risk of stroke are limited. PFO closure has become a common practice in many centres, although recent guidelines limit indications for such treatment to patients with cryptogenic (recurrent) stroke.

Aim: To investigate whether PFO morphology assessed by transoesophageal echocardiography (TOE) differed between patients with symptoms and those who had an asymptomatic PFO.

Methods: We analysed 88 consecutive patients (48 female, 40 male; mean age 36.1 ± 16.2 [range 18–59] years) who underwent TOE before transcatheter PFO closure due to a cryptogenic cerebrovascular event (Group I) and compared them to 88 consecutive patients (49 female, 39 male; mean age 35.7 ± 14.2 [range 18–57] years) with an asymptomatic PFO found incidentally on TOE (Group II). The diagnosis of stroke was based on the occurrence of a new acute focal neurological deficit, with neurological signs and symptoms persisting for > 24 h, subsequently confirmed by computed tomography and/or magnetic resonance imaging. Multiplane TOE was conducted as per guidelines using commercially available instruments. The interatrial septum was viewed in the transverse midoesophageal 4-chamber view and the longitudinal biatrial-bicaval view. PFO was diagnosed with intravenous injections of agitated saline while the patient was at rest and during the Valsalva manoeuvre. We analysed PFO size (resting and maximal separation of the septum primum and secundum during the Valsalva manoeuvre), tunnel length (maximal overlap of the septum primum and secundum), presence of an atrial septal aneurysm (excursion > 15 mm), shunt severity (mild: 3–5, moderate: 6–25, severe > 25 microbubbles) and prominence of the Eustachian valve.

Results: The two groups did not differ with respect to age and sex distribution. Group I showed larger PFO size (maximal separation 3.9 ± 1.4 vs. 1.3 ± 1.3 mm, p < 0.0001), longer tunnel length (14 ± 6 vs. 12 ± 5.5 mm, p < 0.05) and a greater frequency of atrial septal aneurysm (55% vs. 15%, p < 0.0001) compared to Group II (controls). Group I was also characterised by a higher proportion of large PFOs (≤ 4 mm; 50% vs. 18%, p < 0.001) and severe shunt (40% vs. 2%, p < 0.0001).

Conclusions: PFO in symptomatic patients is larger in size, has a longer tunnel and is more frequently associated with atrial septal aneurysm. Asymptomatic patients with PFO characteristics similar to that seen in stroke patients require more careful clinical evaluation. It may be debated whether such patients should be recruited to prospective trials to evaluate indications for PFO closure in stroke prevention.

Key words: patent foramen ovale, stroke, transoesophageal echocardiography

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Received: 28.06.2010 Accepted: 05.09.2012
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INTRODUCTION

Patent foramen ovale (PFO) is the most common type of interatrial communication, found in about 26% (range 17–35%) of the general population [1, 2].

When performing an autopsy in a young woman who died due to stroke, a German pathologist Cohnheim was the first to hypothesize in 1877 that stroke was due to paradoxical embolism [1, 2].

In Poland, about 60,000 strokes are diagnosed each year, and 30% of these strokes (i.e., about 18,000) are considered cryptogenic of strokes [3, 4]. Assuming that one third of all cryptogenic strokes may be associated with PFO, this gives about 6000 strokes annually due to this aetiology, a significant clinical, economic, and social problem. A strong relationship was shown between PFO size and the severity of neurological symptoms in patients with cerebral ischaemic events.

Currently, there are no standards on the management of patients with PFO and ischaemic stroke regarding both drug therapy and surgical or percutaneous PFO closure. Due to this lack of standards and guidelines, clear indications for PFO closure cannot be established but pending results of currently ongoing randomised studies, it seems reasonable to consider closure in patients with recurrent cryptogenic stroke, particularly if echocardiography indicates that PFO is associated with moderate to large shunting of contrast bubbles to the left atrium (LA) during Valvalva manoeuvre and or an atrial septal aneurysm has been identified. PFO size and the presence of the Eustachian valve also seem important factors. There have been few reports published in the literature regarding the association between PFO morphology and the risk of paradoxical embolism [5, 6].

Thus, it would be clinically important and useful if we were able to identify those among numerous subjects with PFO who are potentially at risk of paradoxical embolism.

The aim of this study was to evaluate whether PFO morphology assessed by transoesophageal echocardiography (TOE) might help in the identification of patients with potentially symptomatic PFO.

METHODS

We studied 88 consecutive patients (48 women, 40 men; mean age 36.1 ± 16.2 [range 18–59] years; Group I) with suspected PFO who underwent TOE in the Department of Cardiac and Vascular Diseases, Institute of Cardiology, Jagiellonian University Medical College, Cracow, Poland, from December 2001 to December 2008. Patients with an atrial septal defect and other congenital heart disease were excluded from the study. All patients suffered from a cerebral ischaemic event (transient ischaemic attack [TIA] or stroke). The diagnosis of a cerebral ischaemic event was made by a neurologist based on the presence of a new-onset acute neurological deficit lasting < 24 h (TIA) or > 24 h (stroke). In all patients, cerebral ischaemia was confirmed by magnetic resonance imaging (MRI) on T2 weighted images using 5 mm slices with no intersectional gap.

The control group (Group II) included 88 consecutive adult patients (49 women, 39 men, mean age 36.1 ± 16.2 [range 18–59] years) matched for gender and age who underwent TOE for other reasons than search for the aetiology of paradoxical embolism and in whom asymptomatic PFO was identified as the sole abnormality. All patients in the control group were consulted by a neurologist and underwent MRI on T2 weighted images using 5 mm slices with no intersectional gap. The control group included only patients with no neurological symptoms and no pathology identified by MRI.

Transoesophageal echocardiography was performed using a multiplane probe. PFO tunnel was measured in the longitudinal biatrial/bicaval view. We measured resting and maximal (during the Valsalva manoeuvre) separation of the septum primum and secundum at the communication with the LA, and tunnel length, i.e. maximal overlap of the septum primum and secundum (Fig. 1). “Large” PFO was defined as the tunnel length of ≥ 4 mm. PFO tunnel was imaged at rest and during the Valsalva manoeuvre after administration of 9 mL of normal saline mixed with 1 mL of patient blood through the basilic vein (Fig. 2).

Based on the amount of contrast bubbles appearing in the LA at rest and after Valvalva manoeuvre during 3 consecutive cardiac cycles, shunt severity was categorised as: (1) mild — with at least 3–5 microbubbles appearing in the LA; (2) moderate — with 6–25 microbubbles appearing in the LA; or (3) severe — with more than 25 microbubbles appearing in the LA.

We also looked for the presence of the Eustachian valve and atrial septal aneurysm, defined as maximal excursion of the interatrial septum of ≥ 15 mm.
Statistical analysis

Descriptive statistics for quantitative variables included arithmetic mean, standard deviation, and maximum and minimum values. Using the Shapiro-Wilk test, a hypothesis of normal variable distribution was rejected and thus nonparametric tests were used to compare arithmetic means and evaluate significance of differences between the variables. The nonparametric Mann-Whitney U test for independent samples was used to compare quantitative variables between the two groups, and the $\chi^2$ test was used to evaluate significance of intergroup differences between qualitative variables. Statistical hypotheses were verified at $\alpha < 0.05$. Statistical analysis was performed using the Statistica 6.0 package.

RESULTS

The two groups did not differ in regard to gender and age.

Neurological examination findings

Among symptomatic patients (Group I), neurological history included: single stroke event in 40 (45.5%) patients; two stroke events in 8 (9.1%) patients; stroke and TIA in 10 (11.4%) patients; TIA only in 30 (34%) patients.

On recruitment, 52 (59.1%) patients had no residual deficit, and 36 (40.9%) patients had a neurological deficit, including unilateral sensory deficit in 31.9%, unilateral plegia in 4.5%, homonymous hemianopsia in 3.4%, and hearing loss in 1.1%. No neurological abnormalities were found in the control group (Group II).

Magnetic resonance imaging findings

MRI showed hypodense areas corresponding to lacunar infarcts in all symptomatic patients (Group I). Overall, 234 hypodense areas were described, or mean 2.66 lesions per patient. These ischaemic changes were localised in the cerebellum in 25 (28.4%) patients, in the right hemisphere in 32 (36.4%) patients, and in the left hemisphere in 31 (35.2%) patients.

Transoesophageal echocardiography findings

Morphology of PFO tunnel and associated structures. As compared to Group II, Group I showed significantly larger maximal (during the Valsalva manoeuvre) separation of the septum primum and secundum (3.9 ± 1.4 vs. 1.3 ± 1.3 mm, $p < 0.0001$) and longer tunnel length (14 ± 6 vs. 12 ± 5.5 mm, $p < 0.05$). No difference was found between the two groups in regard to resting separation of the septum primum and secundum (1.5 ± 1.4 vs. 1.4 ± 1.9 mm, $p = 0.984$) (Table 1).

Table 1. Echocardiographic findings in Group I (symptomatic patent foramen ovale [PFO] patients) and Group II (asymptomatic PFO patients)

<table>
<thead>
<tr>
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<th>Group I (n = 88)</th>
<th>Group II (n = 88)</th>
<th>$p$</th>
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</thead>
<tbody>
<tr>
<td>Maximal PFO separation [mm]</td>
<td>3.9 ± 1.4</td>
<td>1.3 ± 1.3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Resting PFO separation [mm]</td>
<td>1.5 ± 1.4</td>
<td>1.4 ± 1.9</td>
<td>0.984</td>
</tr>
<tr>
<td>Length of PFO channel [mm]</td>
<td>14 ± 6</td>
<td>12 ± 5.5</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>
A “large” PFO (>4 mm) was more common among patients with a history of ischaemic cerebral event compared to asymptomatic patients (50% vs. 18%, p < 0.001).

Group I was also characterised by a significantly higher frequency of atrial septal aneurysm (55% vs. 15%, p < 0.0001) compared to Group II, while the proportion of patients with a prominent Eustachian valve did not differ between the two groups (27.3% vs. 22.7%, p = 0.756).

**Contrast echocardiography findings.** A severe shunt through PFO was found more frequently in Group I as compared to Group II (40% vs. 2%, p < 0.0001) (Table 2).

### DISCUSSION

It has been believed for many years that the presence of PFO is associated with an increased risk of paradoxical embolism which may cause a cryptogenic stroke. This association was shown mainly in young patients with strokes of unknown aetiology (cryptogenic) but attempts to identify a similar relationship were also undertaken in older subjects [7–10].

Management of these patients has been mainly based on the European Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008 [9] which also included PFO patients. Pharmacotherapy involves two major drug classes, namely antiplatelet drugs (acetylsalicylic acid [ASA] and clopidogrel) and oral anticoagulants. Studies on the efficacy of these two drug classes, including The Lausanne Stroke Registry, PFO In Cryptogenic Stroke Study Investigators, and Warfarin-Aspirin Recurrent Stroke Study, did not show significant differences between warfarin and ASA in terms of stroke and death rate (2.3–19.2%) [9–12]. In the recent European Association of Echocardiography guidelines, antithrombotic therapy in patients with PFO was recommended as an alternative to percutaneous closure in prevention of paradoxical embolism in patients with a haemodynamically significant PFO.

Appropriate management of PFO patients will be hopefully determined upon completion of randomised studies comparing drug therapy with interventional treatment. The CLOSURE I study in patients with PFO and a cryptogenic stroke, terminated prematurely due to slow recruitment, did not show any clear advantage of PFO closure using the Starflex occluder over anticoagulant treatment in the prevention of recurrent stroke. Results of this study were reported during the American Heart Association Scientific Sessions in 2010. Primary endpoints included stroke/TIA incidence, 30-day all-cause mortality, and 2-year mortality due to neurological causes in two drug therapy groups and an interventional therapy group. No significant differences in regard to the primary endpoint and recurrent neurological events were shown. Another study in patients with cryptogenic stroke and PFO treated with the Amplatzer PFO occluder, the RESPECT study, will be published in 2012.

Many experts in cardiology believe that completion of the remaining clinical trials will be very difficult if not impossible. This results from patient unwillingness to be assigned to a medical therapy group and await another stroke which would be required to change treatment strategy (i.e., perform interventional PFO closure). Khairy et al. [13] compared patients with PFO and a history of stroke who were treated either with percutaneous PFO closure or medically and found that the risk of recurrent stroke was significantly higher among medically treated patients (1.9% vs. 5.4% per year, p < 0.0001). However, approach to the management of PFO is still controversial in regard to both choice of the treatment approach and, importantly, patient selection. It is not clear whether all patients with PFO should be treated, or the treatment should be postponed until first or recurrent cerebral ischaemic event.

PFO is one of the most common cardiovascular anomalies in adults (1 in 4 subjects) and thus a strategy to treat every patient with PFO would be clearly wrong. Identification of large, significant PFOs may be difficult due to problems with the interpretation of the Valsalva manoeuvre. Performing the Valsalva manoeuvre during TOE may not be effective in all patients and required cooperation between the patient and the echocardiographer, and interpretation of the results depends on appropriate performance of the Valsalva manoeuvre. As a result, interpretation of the significance of PFO may be prone to errors.

An important clinical task would be thus to select those patients in whom PFO is associated with a potential risk of paradoxical embolism. Detailed morphological and functional evaluation of PFO is of practical importance as it allows identification of patients at an increased risk of paradoxical embolism.

Our results indicate more frequent coexistence of PFO and atrial septal aneurysm in patients with cryptogenic stroke which is consistent with findings reported by other authors [13, 14]. These observations seem to contradict a common belief the occurrence of stroke in subjects with atrial septal

### Table 2. Contrast echocardiography findings in Group I (symptomatic patients) and Group II (asymptomatic patients)

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 88)</th>
<th>Group II (n = 88)</th>
<th>P</th>
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<tbody>
<tr>
<td>Mild shunt</td>
<td>26 (29.5%)</td>
<td>43 (48.8%)</td>
<td>0.0542</td>
</tr>
<tr>
<td>Moderate shunt</td>
<td>27 (30.7%)</td>
<td>43 (48.8%)</td>
<td>0.0511</td>
</tr>
<tr>
<td>Severe shunt</td>
<td>35 (39.8%)</td>
<td>2 (2.3%)</td>
<td>&lt; 0.0001</td>
</tr>
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Conflict of interest: none declared

References


CONCLUSIONS

PFO in patients with a history of ischaemic cerebral events is more frequently associated with atrial septal aneurysm and is characterised by a longer tunnel, larger maximal separation of the septum primum and secundum, and a larger shunt compared to asymptomatic patients.

In a patient with unexplained neurological symptoms but no history of stroke, brain MRI should be considered to look for evidence of a cerebrovascular accident if a large PFO is identified by echocardiography.
Badanie echokardiograficzne przezprzełykowe może pomóc w różnicowaniu patologicznego i nieistotnego przetrwałego kanału owalnego

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Streszczenie

Wstęp: Przetrwały otwór owalny (PFO) stwierdza się u 6–25% populacji. Od wielu lat panuje przekonanie, że obecność PFO wiąże się z zwiększoną ryzykiem zatorowości skrzyżowanej, będącej przyczyną udarów kryptogennych mózgu. Związek ten udowodniono przede wszystkim u młodych chorych z udarami o niewyjaśnionej etiologii (kryptogennymi), ale poszukiwały się również podobnej zależności wśród osób starszych. Nadal kontrowersyjne pozostaje, czy istnieją takie cechy anatomiczne kanału owalnego, które mogą predysponować do zakrzepicy w kanał i w konsekwencji do zatorowości skrzyżowanej. Spowodować postępowania u chorych z PFO budzi kontrowersje ze względu na brak jednoznacznych wyników randomizowanych prób porównujących leczenie farmakologiczne i interwencyjne.

Cel: Celem pracy była ocena, czy morfologia kanału owalnego w echokardiografii przezprzełykowej (TEE) różni się u pacjentów bezobjawowych i u chorych z incydentami niedokrwiennymi mózgu o prawdopodobnej przyczynie zatorowości skrzyżowanej.

Metody: Badaniem objęto 88 kolejnych chorych (48 kobiet, 40 mężczyzn) w średnim wieku 36,1 ± 16,2 (18–59) roku, u których wykonano TEE przed przezskórną korekcją PFO z powodu incydentu niedokrwienia mózgu (Grupa I). Grupę kontrolną stanowiło 88 bezobjawowych osób [49 kobiet, 39 mężczyzn; średni wiek 35,7 ± 14,2 (18–57) roku], u których przypadkowo rozpoznano PFO w trakcie TEE (Grupa II). Diagnozę epizodu niedokrwiennego mózgu stawiał specjalista neurolog (u wszystkich chorych wykonano MRI/CT mózgu). Badanie TEE wykonano z zastosowaniem głowicy wielopłaszczyznowej. Mierzono spoczynkową i maksymalną (w czasie próby Valsalvy) separację między przegrodami tworzącymi kanał, określano rozmiar PFO i za tzw. „duże” PFO uznaANO kanał o długości ≥ 4 mm. PFO obrazowano w spoczynku i w czasie próby Valsalvy. Na podstawie liczby pęcherzyków kontrastu przechodzących do lewego przedsionka wyróżniano 3 stopnie przecieku przez PFO: mały (3–5 pęcherzyków), średni (6–25) i duży (> 25). Określano także obecność zastawki Eustachiusza i tętniaka przegrody międzyprzedsionkowej.

Wyniki: Grupy nie różniły się pod względem płci i wieku. W Grupie I stwierdzano istotnie statystycznie większą maksymalną separację blaszek PFO niż w Grupie II: 3,9 ± 1,4 vs. 1,3 ± 1,3 mm (p<0,001), jak również dłuższy kanał PFO w stosunku do Grupy II: 14 ± 6 vs. 12 ± 5,5 mm (p = 0,05). Nie zanotowano różnic między grupami pod względem spoczynkowej separacji blaszek PFO (1,5 ± 1,4 vs. 1,4 ± 1,9 mm (p = 0,984). W grupie chorych z epizodem niedokrwiennego mózgu w wywiadzie częściej niż u osób bez objawów stwierdzano obecność tzw. „dużego” PFO (kanal > 4 mm; 50% vs. 18%, p < 0,001). W Grupie I zaobserwowano istotnie statystycznie większą częstość występowania tętniaka międzyprzedsionkowej (55% vs. 15%, p < 0,0001) niż w Grupie II, nie stwierdzono natomiast różnic między grupami w zakresie częstości występowania przetrwałej zastawki Eustachiusza (27,3% vs. 22,7%, p = 0,756). W Grupie I częściej niż w Grupie II obserwowano istotnie dużą rozpiętość PFO (40% vs. 2%, p < 0,001).

Wnioski: Przetrwały kanał owalny u chorych z udowodnionym epizodem niedokrwiennego mózgu częściej współistnieje z tętniakiem przegrody międzyprzedsionkowej, cechuje się dłuższym kanałem i większą separacją maksymalną blaszek oraz większym przeciekami w porównaniu z PFO stwierdzanym u osób bez objawów. U chorego bez udaru mózgu z niejasnymi objawami neurologicznymi warto wziąć pod uwagę wdrożenie diagnostyki obrazowej (MRI mózgu) w celu poszukiwań zmian naczyniopochodnych w przypadku stwierdzenia w echokardiografii dużego PFO.

Słowa kluczowe: przetrwały kanał owalny, udar mózgu, badanie echokardiograficzne przezprzełykowe

Kardiol Pol 2012; 70, 12: 1258–1263

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