The PFO anatomy evaluation as possible tool to stratify the associated risks and the benefits arising from the closure

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Aims
According to the current guidelines, the patent foramen ovale (PFO) is still considered a qualitative factor and, as a consequence, its closure is recommended just on the basis of its ‘presence’.

Methods and results
In the year 2008, we evaluated 25 patients (mean age 62.7) with acute cerebrovascular event and 92 patients (mean age 27.3) suffering from migraine with aura. No PFO was reported in 79 patients. A venous-to-arterial circulation shunt had been shown in 38 patients (29 subjects with migraine and 9 subjects with prior stroke). According to the number of microbubbles arrived during the Valsava manoeuvre, we found: 25 small PFO, 6 moderate PFO, and 6 severe PFO. In the baseline population with migraine (n = 92), 32% (n = 29) had a PFO. A ‘large’ foramen was reported in ~9% of the migraine subjects. In the population with prior stroke (n = 25), 9 patients (36%) had a PFO. A ‘large’ foramen was reported in 45% of the patients with ischaemic stroke. We found embryonic recesses in 13% (n = 4) of the patients with migraine and PFO (n = 29) vs. 66% (n = 6) of the patients with ischaemic stroke and PFO (P = 0.01).

Conclusion
It is possible to suppose that not all PFO have the same prognostic value. The evaluation of two anatomical characteristics can allow to identify those foramina at higher risk and, as a consequence, the patients who could have a major benefit from the closure.

Keywords
PFO • Migraine with aura • Cerebrovascular event • Ictus • Closure • Prognostic value

Introduction
Since several years, particular attention was paid to the possible relationship between patent foramen ovale (PFO) and cryptogenic ischaemic stroke.1–8

The majority of the literature has considered the PFO as a ‘qualitative’ variable (present or absent). Poor attention was instead paid to the functional implications arising from the differences in the PFO anatomy.6 According to the current guidelines, the PFO is still considered a qualitative factor and, as a consequence, its closure (in patients with a prior cerebral ischaemic event) is recommended just on the basis of its ‘presence’.9–11 However, many anatomo-phatological studies have clearly showed ample differences in the PFO morphology.12–14 This wide variability regards both the size and the association to embryonic variants in the right atrium wall (i.e., Thebesian or Eustachian valves and atrial septal aneurysm).15–24 An interesting evidence came from a recent prospective study, which analysed in patients with PFO the rate of recurrent events after a prior stroke, with a mean follow-up of 7 years.25 A large PFO, as assessed by transoesophageal echocardiography (TEE), was associated to an increased relative risk of recurrence.26,27

In the management of patients with a prior stroke, the PFO (if it is present) should not be closed before the occurrence of a second cerebrovascular event.10,28–30 In this way, the current guidelines under light the absence of a strong causal relation
between the defect and the cerebral ischaemia. Nevertheless, the same guidelines, although do not take into consideration the size, report a higher risk in some anatomical variants (such as the association with atrial septum aneurysm), than in the classical PFO. These variants should be treated even after ‘the first’ ischaemic stroke.

Furthermore, in the past 10 years, the PFO has been shown as significantly related to migraine headaches with aura. The defect is detected in ~40% of patients with migraine. However, it is appropriate to raise a note of caution, because the presence of a casual relationship between PFO and migraine still needs to be confirmed. In patients with PFO (even in those with migraine), it is also possible to detect brain lesions (in particular, small nodularity near the cranial base) by the use of NMR. The clinical meaning of these lesions is still uncertain.

Several small case/control studies aimed at evaluating the benefits arising from the PFO closure on the rate of recurrence of migraine headache. Their results are not very clear. In spite of the reduction in the number of relapses reported in some case reports, any benefit seems to result in other cases.

A recently published multi-centre trial (the MIRST) showed no difference in the number of recurrent events of migraine headache in patients ‘with’ vs. ‘without’ PFO closure.

However, it should be noted that in the MIRST, as well as in the experiences we mentioned earlier, the PFO was still considered a qualitative variable and its closure was recommended just on the basis of its presence.

Is this approach really correct?

Is it correct to give the same prognostic value to the small and to the large PFO?

Is it possible to suppose an additional risk (and, as a consequence, a stronger indication to the closure) if embryonic recesses (able to guide the blood flow toward the defect) are present?

Last but not least, why so different diseases (cerebral ischaemia and migraine) are both associated with a higher incidence of PFO?

Furthermore, the PFO could be evaluated to identify possible differences associated to the stroke, rather than to the migraine.

Only long-term prospective studies can provide complete and detailed answers. However, our analysis, which aimed at answering to some of these questions, led us to reasonable conclusions. We reviewed all the symptomatic patients (with stroke and/or migraine) who referred to our centre and underwent routinely research for a PFO.

Methods

Characteristics of patients included

From January to December 2008, the Departments of Neurology and Internal Medicine sent 117 patients with prior stroke and/or migraine with aura to our Center for the Study of Preclinical Atherosclerosis and Cardiovascular Prevention for a PFO research.

In particular, the Department of Internal Medicine sent to our observation all the patients admitted in hospital during 2008 because of the occurrence of an ischaemic stroke (as assessed with CT) or clear signs of TIA. All these patients underwent the PFO research and, as a consequence, they were enrolled in our study. Any evaluated patient was excluded from the analysis.

The Department of Neurology sent all patients with migraine who referred to its centre for headaches. All these patients underwent the PFO research and so they were enrolled in our study. Any evaluated patient was excluded from the analysis in this case, too.

Ultrasound assessment of PFO

In the PFO evaluation, the gold standard is the TEE, which is considered a highly sensitive and specific method. Nevertheless, TEE is a semi-invasive, high cost procedure with an unfavourable tolerability and patient acceptance/adherence profile.

The literature has increasingly focused its attention on the possible diagnostic role of the trans-cranial Doppler (TCD), especially in the screening phase. The rigorous standardized TCD protocol is a useful diagnostic tool for detecting venous-to-arterial circulation shunts (v-aCS) with high specificity (94–100%) and sensitivity (92–100%). In our echocardiography centre, we used TCD as first-line approach in patients with cerebro-vascular events or migraine with aura. If no defect was detected, any other procedure was performed. When a PFO was assessed by TCD, a confirmation of the diagnosis was routinely researched by performing a basic trans-thoracic echocardiogram, a contrast echocardiogram, and, if necessary, a TEE, too.

As regards the TCD method we used, we usually placed the probe in the left trans-temporal window. We sampled the media cerebral artery in first step by the use of the colour Doppler and then by the use of the pulsed Doppler. In the meantime, 9 cc of saline solution + 1 cc of air were mixed in a 10 cc syringe. The resulting natural contrast was injected, in ~5 s, in the left brachial vein. Then, we evaluated the eventual sonography modifications due to the arrival of the injected microbubbles in the media cerebral artery. The contrast injection was performed twice: at rest and during cough and Valsava manoeuvres. The PFO was defined as the arrival, in baseline conditions, of one or more than one microbubbles during the following 10 s after the contrast injection. According to the number of microbubbles visualized by probe during the Valsava manoeuvre, we classified the ultrasound examinations into three groups, showing different foramen sizes: small PFO (<10 microbubbles), moderate PFO (more than 10 microbubbles), and severe PFO (‘shower effect’).

As established in the current guidelines, the trans-thoracic echocardiography evaluated the apical, the short parasternal axis, the long parasternal axis, and the under costal scans. If necessary, adjunctive scans were evaluated.

For the contrast in the trans-thoracic echocardiography, the same contrast we mentioned before was used. The PFO evaluation was performed in the apical and the under costal scans. Subsequently, the patients underwent contrast injections (at rest and after the Valsava manoeuvre). When necessary, the trans-oesophageal echocardiogram was performed according to the international guidelines. The PFO assessment was performed in baseline condition and after infusion of microbubbles. The contrast injection was performed twice: at rest and with the Valsava manoeuvres. In all cases in which the trans-cranial echo-colour Doppler reported a right-to-left circulation shunt, both the contrast trans-thoracic echocardiography and TEE confirmed the presence of the shunt due to the PFO. None shunt due to other causes was reported. In particular, any evaluated patient had an interatrial defect, whereas all the patients had a mobile membrane in the interatrial septum.

Reassessment of reports

The same operator evaluated all the patients. All reports have been stored as multimedia files. During the revaluation, we carefully re-examined these reports (paying particular attention to the functional PFO assessment and the anatomical features of the right atrium).
Statistics

Our study is an observational epidemiological study. In a first step, the differences between the various groups of patients were evaluated by a univariate analysis using the Student’s unpaired t-test. Then a multivariate analysis was performed by the use of the $\chi^2$ test. A $P < 0.05$ and a predictive value (odds ratio) with a confidence interval of 95% were considered as statistical significant. The reports were analysed in an anonymously way. As a consequence, no informed consent was requested to the patients, or to their guardians, to take part in the study.

Results

In the year 2008, we performed 127 transcranial echo-colour Doppler to research the presence of PFO. In particular, we evaluated 25 patients (mean age 62.7) with acute cerebrovascular event and 92 patients (mean age 27.3) with migraine with aura. The remaining 10 patients were evaluated for other causes and were excluded at all from the study. So, in the end, a total of 117 patients were enrolled. No PFO was reported in 79 control patients. A venous-to-arterial circulation shunt was proven in 38 patients (29 subjects with migraine and 9 subjects with prior stroke). According to the number of microbubbles arrived during the Valsava manoeuvre, we found: 26 small PFO, 6 moderate PFO, and 6 severe PFO. All cases were always confirmed by TTE and, if necessary, by TEE.

In the baseline population with migraine (n = 92), 32% of patients (n = 29) showed a PFO. In particular, 71% of this population had a small PFO, 18% a moderate PFO, and 9% a severe PFO. A ‘large’ foramen was subsequently reported in ~9% of migraine subjects.

In the population with prior stroke (n = 25), 9 patients (36%) had a PFO. In particular, 44% of this population had a small PFO, 11% a moderate PFO, and 45% a severe PFO. A big foramen was finally reported in 45% of the patients with ischaemic stroke (Table 1).

We also researched (by performing a trans-thoracic echocardiogram) the presence of embryonic recesses. We found recesses (which were often able to guide the blood flow toward the defect) in 31% of the subjects with an assessed PFO. Thirteen percent (n = 4) of the patients with migraine and PFO (n = 29) vs. 66% (n = 6) of the patients with ischaemic stroke and PFO (n = 9) had recesses in the right atrium (P = 0.01) (Table 1).

Discussion

In the last years, the international literature has analysed with increasing interest the association between PFO and cryptogenic stroke and/or migraine with aura.\(^1\)\(^–\)\(^6\),\(^31\)\(^–\)\(^37\) Until now, the majority of scientific evidence deals with the presence/absence of the interatrial communication. Poor attention was instead given to the possible functional implications of PFO morphology in the determination of the clinical outcome. Although every interatrial communication is potentially able to give a dangerous right-to-left circulation shunt, the abnormal shunts are not always able to allow the passage of thrombi. Furthermore, it is interesting to note that, although ~25%\(^43\)\(^–\)\(^45\) of the general population has a PFO, not all patients with a PFO will have a stroke or migraine. In the management of asymptomatic subjects with an interatrial communication, the evaluation of the anatomical features could provide further information to better stratify the risk of future events. In characterizing PFO morphology, some variables, such as the size of the shunt, should be evaluated. Unfortunately, so far just few studies\(^1\)\(^–\)\(^6\),\(^9\)\(^–\)\(^20\),\(^25\)\(^–\)\(^37\),\(^39\)\(^–\)\(^45\) have directly investigated this obvious relationship between size and risk, sometimes even coming to conflicting conclusions about the correlation between the PFO size and the number of identified pre-closure major clinical neurologic events assessed by MRI/CT.\(^46\) However, ample evidences supported the important role of embryonic recesses in the right atrium of patients with a PFO as strong predictor of cerebrovascular events.\(^15\)\(^–\)\(^20\) In spite of these assessments, the current guidelines for the stroke do not take into consideration the presence of this anatomical feature as a discriminatory variable. Our study has some limits: it analyses a small population and deals with the matter in an indirect way. A prospective long-term analysis could be more useful. By the way, our study seems to suggest, in our opinion, important conclusions. Indeed, it shows that ‘large’ foramina (45%) and embryonic recesses (66%) are frequently detected in those patients with PFO and history of acute cerebro-vascular events. Even if 44% of the stroke population in our study has a small PFO, the majority of subjects with cryptogenic cerebrovascular accidents shows larger PFOs and more frequently associated with recesses in the right atrium. We also analysed the incidence of PFO among the evaluated subjects for migraine: large foramen (9%) and embryonic recesses (13%) are not so common, but the most noticeable percentage of the migraine patients (71%) show a small PFO.

In lights of our result and of the above consideration, it is possible to suppose that not all PFO have the same prognostic value. The evaluation of two anatomical characteristics (the large size and the presence of recesses) can allow to identify those foramina at higher risk and, as a consequence, the patients who could have a major benefit from their closure.

Conflict of interest: none declared.

References

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