No indication for patent foramen ovale closure in migraine

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The relationship between patent foramen ovale (PFO) and migraine is much debated and controversial. Until recently, evidence on PFO closure to reduce migraine was based upon uncontrolled studies only; nevertheless an increasing number of medical specialists consider PFO closure to be a treatment option. We report on the current evidence of PFO closure in migraine, mainly based on the recently published first prospective double-blind, sham-controlled study.

A PFO is an incomplete fusion of the septum primum and secundum of the atrial septum, playing an important role in the foetus, but of no physiological significance after birth; it closes in most individuals. However, PFO will be found at autopsy in 20 to 30% of the general population.¹ Mainly based on association studies, it has been suggested that PFO plays a role in many entities, including the aetiology of migraine, stroke, hypoxia, sleep apnoea syndrome and decompression illness in scuba divers.

A more than twofold increase in the prevalence of PFO in patients with migraine with aura (MA) has been

found, compared with controls and patients with migraine without aura.² The association between PFO and MA, however, may be partly based on selection bias, as these migraine patients were recruited clinically. It is known that only 5% of migraine sufferers consult specialists; therefore, these selected patients are possibly not representative for the general migraine population. Other possible confounders are that investigators were often not blinded for the migraine diagnosis, and the successful assessment of PFO partly depends on the willingness of the patient to perform the Valsalva manoeuvre. Furthermore, an association between PFO and MA could be explained by a common genetic factor, without a direct causal relationship.³

There are several hypotheses as to how a PFO can cause migraine. It has been postulated that MA is caused by small venous microemboli that cross the PFO paradoxically, and then pass into the cerebral circulation. These microemboli may cause a spreading depression phenomenon analogous to the mechanism that causes migraine aura. Another hypothesis suggests that unknown vasoactive chemical substances bypass the pulmonary filter in much the same way, and this precipitates a migraine attack in susceptible individuals.

In the year 2000, closure of PFO in divers and stroke patients was reported to decrease the frequency and severity of migraine attacks.⁴ Since then, several uncontrolled retrospective studies also reported a decrease in migraine symptoms after PFO closure, although these studies had major methodological limitations. Retrospective collection of headache data, for example, is unreliable and recall bias has great influence on the findings. Migraine was not always diagnosed according to standardised criteria, and the placebo response in migraine can explain the observed findings. Moreover, all patients received aspirin or clopidogrel which could have diminished migraine attack frequency.⁵

The Migraine Intervention with Starflex Trial (MIST) was the first prospective, double-blind, sham-controlled study to evaluate the effects of PFO closure on MA.⁶ A total of 432 MA patients were screened for

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PFO by contrast transthoracic echocardiogram. Of these patients, 260 had a cardiac right-to-left shunt; 163 of them fulfilled the size criterion as they had a moderate-to-large diameter PFO (mean 9 mm). Sixteen of these 163 patients were excluded because they withdrew their consent, or in fact proved to have an ASD or pulmonary shunt. The remaining 147 patients were randomised for closure procedure (n=74) or sham closure (n=73). The two groups were balanced with respect to age, sex, race, baseline migraine frequency and medication use. After randomisation, nine more patients were excluded from the closure group; in five no PFO was present or no actual passage was possible, one patient suffered cardiac tamponade during the procedure, two were excluded due to side effects (chest pain and arrhythmia) and one was lost to follow-up. From the sham arm two patients were excluded after randomisation due to menorrhagia and stroke.

The primary endpoint of the study, complete cessation of migraine during three to six months after randomisation, failed to show any difference between the two groups, as this endpoint was reached by three patients in both groups. Also, none of the secondary endpoints showed significant differences between the two groups.

Complications and side effects

Severe side effects and complications, such as cardiac tamponade, pericardial effusion, chest pain and retroperitoneal bleeding, were reported in seven patients in the closure group. Minor complications, not further specified, were reported in nearly all the patients, mostly attributed to treatment with platelet inhibitors.

Comments on the MIST study

The study has several methodological weaknesses. Contrary to what the authors claim, no genuine intention to treat principle was followed, as several randomised patients were excluded before analysis. Migraine attack medication or prophylaxis use in the analysis phase was not mentioned; patients were only encouraged to continue their prophylaxis and not to start new treatments. Medication use can certainly have had a major influence on all outcome measures. Earlier (preliminary) results, presented during international cardiology and neurology meetings, reported on positive secondary endpoints: a 50% reduction in headache days (42% of the closure group vs. 23% in the sham group ($p=0.038$), a decrease in headache burden (frequency $\times$ duration of symptoms) 37 vs. 17% in the sham group ($p=0.033$).⁷ This difference with the final publication is remarkable, and gives rise to many speculations.⁸⁻¹⁰

Conclusion

There may be an epidemiological association between PFO and migraine with aura, but the causal relation remains uncertain. The initial positive reports about the MIST study were premature, as ultimately the MIST trial did not show any significant difference between PFO closure and sham closure on migraine. Given these results, earlier retrospective, uncontrolled studies on PFO closure for migraine prophylaxis should be interpreted with great caution. At present PFO closure is not an option for migraine prophylaxis. More randomised studies may be useful, although the side effects of PFO closure might not outweigh the benefits. Several trials initiated by different device manufactures are running at this moment and results are expected in the next few years.

Conflicts of interest

All authors, except for J.J. Bax, give scientific advice and participate in research for several pharmaceutical or medical device companies who develop and market migraine treatment. ■

References

- 1 Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc.* 1984;59:17-20.
- 2 Schwedt TJ, Demaerschalk BM, Dodick DW. Patent foramen ovale and migraine: a quantitative systematic review. *Cephalalgia.* 2008;28:531-40.
- 3 Wilmshurst PT, Pearson MJ, Nightingale S, Walsh KP, Morrison WL. Inheritance of persistent foramen ovale and atrial septal defects and the relation to familial migraine with aura. *Heart.* 2004;90:1315-20.
- 4 Wilmshurst PT, Nightingale S, Walsh KP, Morrison WL. Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. *Lancet.* 2000;356:1648-51.
- 5 Diener HC, Hartung E, Chrubasik J, Evers S, Schoenen J, Eikermann A, et al. A comparative study of oral acetylsalicylic acid and metoprolol for the prophylactic treatment of migraine. A randomized, controlled, double-blind, parallel group phase III study. *Cephalalgia.* 2001;21:120-8.
- 6 Dowson A, Mullen MJ, Peatfield R, Muir K, Khan AA, Wells C, et al. Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. *Circulation.* 2008;117:1397-404.
- 7 Dowson AJ, Wilmshurst P, Muir KW, Mullen M, Nightingale S. A Prospective, Multicenter, Randomized, Double Blind, Placebo-Controlled Trial to Evaluate the Efficacy of Patent Foramen Ovale Closure with the STARFlex Septal Repair Implant to Prevent Refractory Migraine Headaches: the MIST Trial: S61.002. *Neurology.* 2006;67:185.
- 8 Wood S. MIST published; editorial highlights discrepancies, implications for other migraine trials. *News Heartwire* 2008 March. Online <http://www.medscape.com> (21 April 2008).
- 9 Qui J. In search of a migraine cure: a matter of heart and mind. *Lancet Neurol.* 2008;7: 576-77.
- 10 Dyer C. News: Doctor is sued for comments on potential migraine device. *BMJ.* 2008;337:1076.