

The link between migraine and the heart

Introduction

Migraine is co-morbid with numerous other illnesses, including psychiatric disorders (depression, anxiety and bipolar disorder), epilepsy and stroke.¹ Strong pathophysiological links have been identified between migraine and these conditions. Historically, migraine has also been associated with heart disease,² but this has

proved difficult to confirm.¹ However, recent evidence has linked migraine to a common and usually benign defect of the heart, the patent foramen ovale (PFO). This MIPCA newsletter summarises these data, and briefly describes an ongoing placebo-controlled study which is investigating the effect of PFO closure on migraine.

What is a PFO?

During foetal development, the foramen ovale is the opening between the atrial septum primum and secundum that allows blood to flow from the right to the left atrium, facilitating circulation of oxygenated blood to the foetus. Following birth, the pulmonary circulation assumes the role of oxygenation. The resultant increased return of blood to

the left atrium leads to increased left atrial pressure, causing the eventual anatomical closure of the foramen ovale during early childhood. The anatomical fusion between these two septa is maintained in most adults, but in 15–25% it fails to take place, resulting in a PFO (Figure 1).³

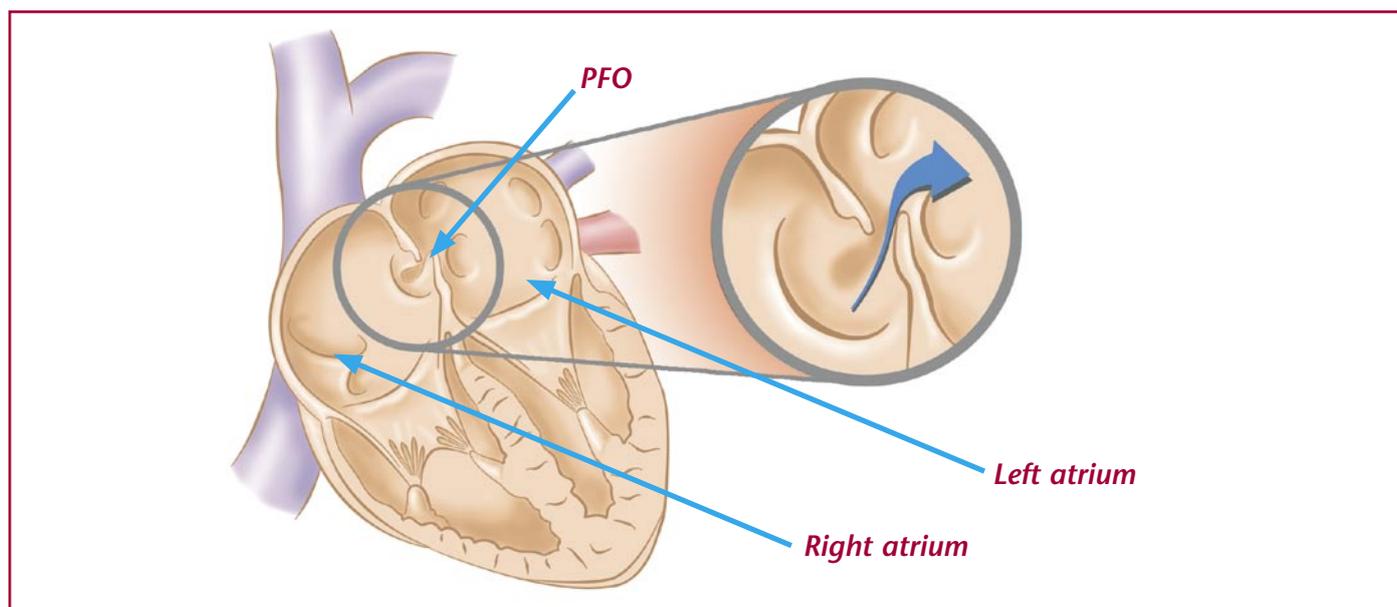


Figure 1. The patent foramen ovale (PFO).

What are the medical consequences of having a PFO?

Although the vast majority of people having a PFO experience no medical problems, the presence of PFOs is linked to stroke in younger patients, chronic obstructive pulmonary disease (COPD), obstructive sleep apnoea and pulmonary, gas and fat emboli. The prevalence of PFO in a group of stroke patients aged under 55 years was four-fold higher than in a group of control patients (40% versus 10%, $p < 0.001$).⁴ The association between PFO and stroke was stronger in patients with no identifiable cause (cryptogenic) for their stroke compared with those in whom a cause could be specified. The prevalence of stroke was also directly related to the size of the PFO.⁵

The aetiology of this interaction may be as follows. In the presence of a PFO, right-to-left shunting of blood may occur, allowing substances to bypass the lungs and travel

into the arterial circulation. A potential consequence may be platelet activation. Stroke or transient ischaemic attacks (TIA) may occur when clinically latent venous thrombi reach the brain via paradoxical embolism through the PFO.^{4,5} Other body areas (e.g. the heart, kidney, spleen, spinal cord and extremities) may also be affected by emboli, and PFOs can also permit the shunting of tumours or liver tissue. PFO is associated with decompression sickness ('the bends') in divers as a result of paradoxical gas emboli.⁶ PFO seems to be linked to COPD and sleep apnoea via systemic arterial oxygen desaturation.⁷ The current optimal way of treating these conditions is by percutaneous closure of the PFO, which is minimally invasive, effective and has a good risk profile.⁸ Several non-surgical devices are available for this procedure.

What is the link between PFOs and migraine?

The prevalence of migraine is very high in patients with PFO. A series of studies with patients being evaluated or treated for PFO / right-to-left shunts has demonstrated an overall prevalence of migraine of 22–57%, migraine with aura of 18–43% and migraine without aura of 14–21%

(Figure 2).^{9–13} Overall these values are about 2–6 fold higher for total migraine, 6–15 fold higher for migraine with aura and 2–3 fold higher for migraine without aura compared with values expected for the general population.¹

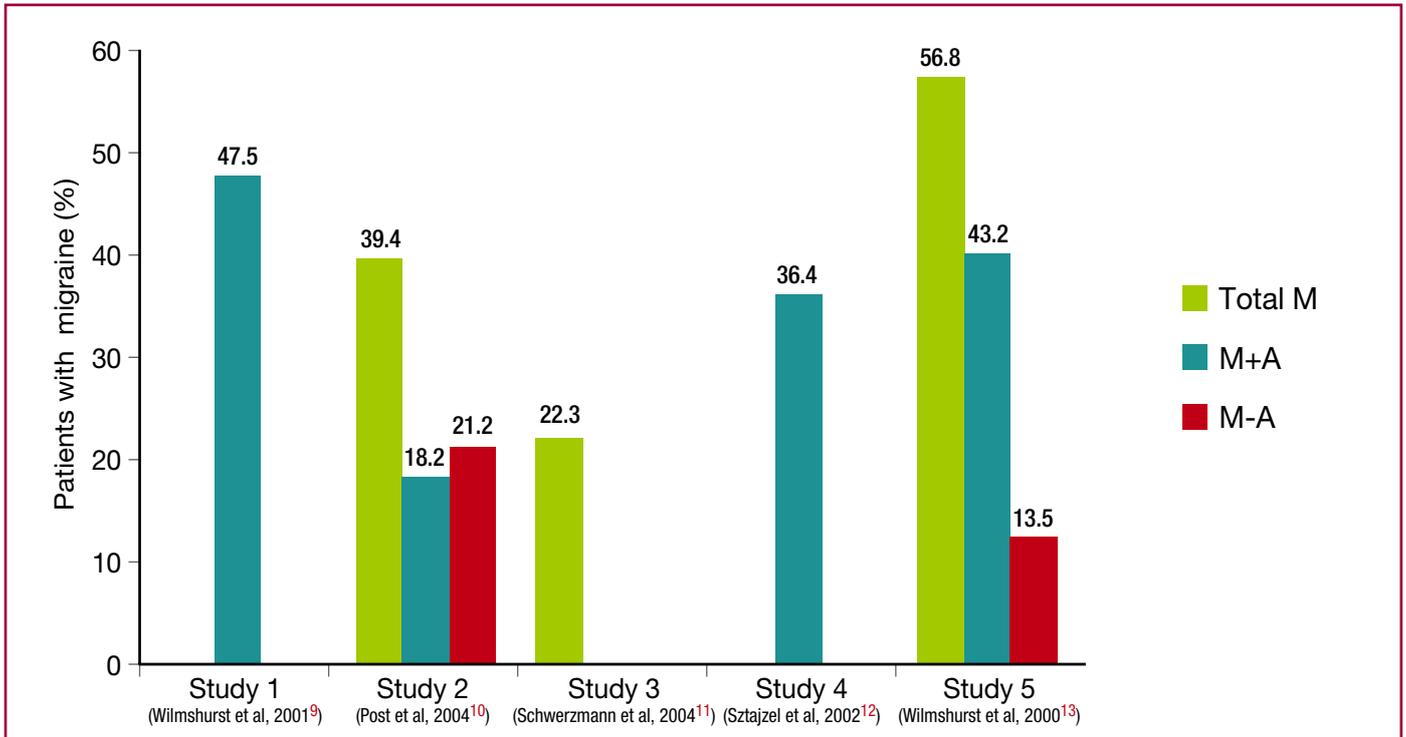


Figure 2. Proportion of patients with total migraine (Total M), migraine with aura (M+A) and migraine without aura (M-A) in a series of studies in patients being evaluated or treated for PFO / right-to-left shunts.^{9–13}

The prevalence of PFO in migraine sufferers is also much higher than expected. In two studies, 41–48% of patients had PFO associated with migraine with aura, compared with

16–20% in control subjects without migraine (Figure 3).^{14,15} However, the prevalence of PFO in patients with migraine without aura was similar to that of the control patients.¹⁵

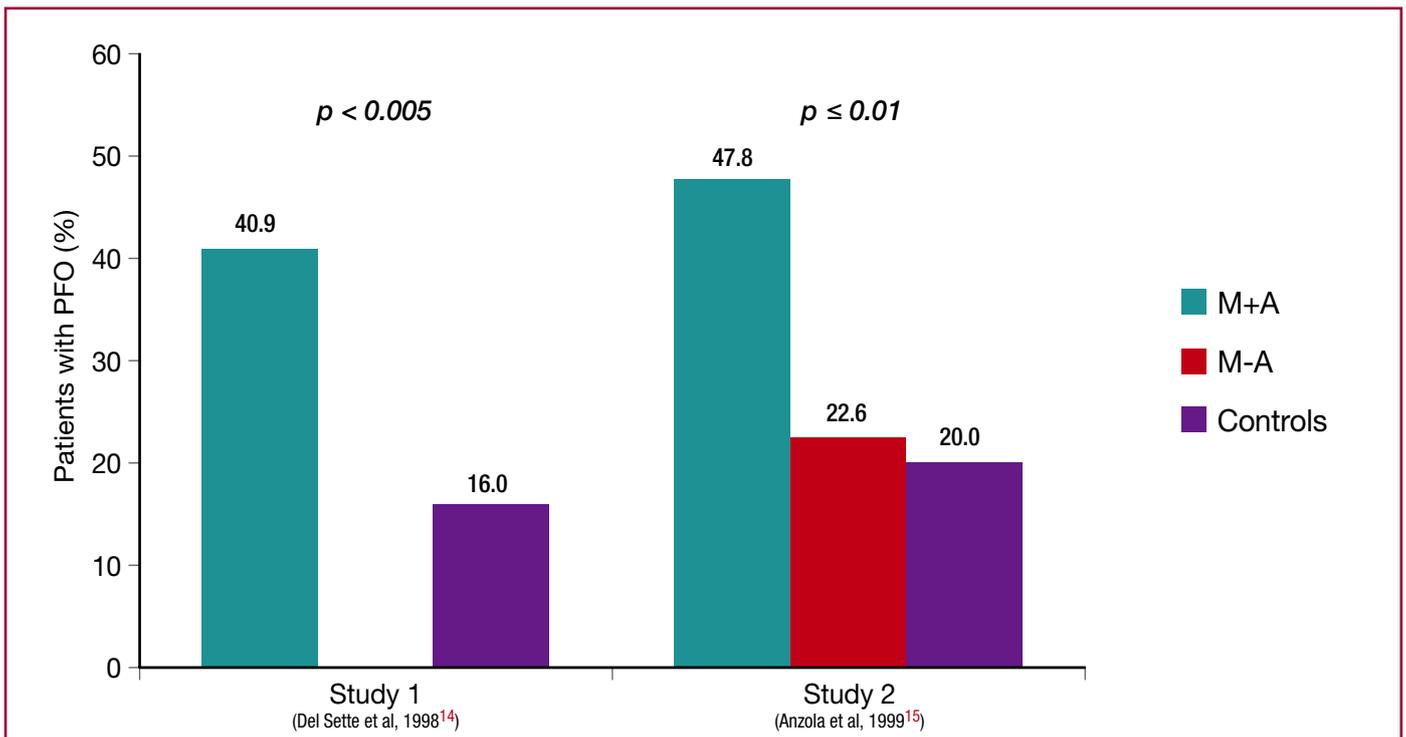


Figure 3. Proportion of patients with PFO / right-to-left shunts in patients suffering from migraine with aura (M+A), migraine without aura (M-A) and control patients without migraine.^{14,15}

These data show strong epidemiological associations between migraine with aura and PFO. Support for this link comes from a genetic study, which demonstrated autosomal dominant inheritance of PFOs and other atrial shunts, and a genetic linkage to inheritance of migraine with aura.¹⁶

There is a well-known epidemiological association of migraine with aura and stroke, which is particularly prevalent in young women aged under 45 years.¹ The association between PFO and stroke is also linked to younger people.⁴ Several of the studies above demonstrated an association between migraine with aura and PFO in patients with ischaemic stroke.^{10–13} A recent case-control study suggests that stroke risk factors differ in patients with migraine with aura and migraine without aura.¹⁷

- Risk factors for migraine with aura were a PFO or other

cardiac abnormality and oral contraceptive use.

- Risk factors for migraine without aura were hypertension, diabetes, hypercholesterolaemia, and coagulopathy.

It is feasible that stroke may arise in patients suffering from migraine with aura as a result of paradoxical cerebral emboli or chemical substances that are able to circulate to the brain due to the presence of PFOs. A recent report has shown a significantly greater number of subclinical brain infarcts in the posterior circulation territory of patients having migraine with aura compared with those having migraine without aura and control subjects.¹⁸ These data need to be interpreted with caution, however, as the relationship of migraine to cerebral white matter lesions remains controversial.¹⁹ Much more research is needed to confirm any link between migraine and brain lesions.

Does the treatment of PFOs affect migraine attacks?

PFO closure by transcatheter has become a commonly-used procedure to treat cryptogenic stroke, transient ischaemic attacks (TIAs) and sometimes decompression sickness in divers. The effect of these procedures on co-morbid

migraine has been examined in retrospective analyses from several studies,^{10–13, 20–22} and the results are summarised in Table 1.

Indication for PFO closure	Patients with migraine (n)	Endpoint	Follow-up period	Results
Cryptogenic stroke / paradoxical embolism ¹⁰	12 (M+A) 14 (M-A)	Migraine prevalence (%)	≥ 6 months	M+A prevalence decreased from 18.2% to 5.3% ($p < 0.05$). M-A prevalence decreased from 21.2% to 10.5% (NS).
Stroke / paradoxical embolism ¹¹	48	Reduction in migraine frequency (%)	1 year	M+A attacks reduced by 54% ($p = 0.001$). M-A attacks reduced by 62% ($p = 0.006$).
Cryptogenic stroke ¹²	39	Resolution of aura attacks	13 months	47% of M+A patients had aura attacks resolved following PFO closure or anticoagulant treatment.
Stroke / decompression illness ¹³	21	Resolution and improvement of migraine	Long-term	M+A patients: 44% resolution and 50% improved. M-A patients: 60% resolved and 0% improved.
Stroke / cerebral embolism ²⁰	17	Resolution and improvement of migraine	6 months	Migraine patients: 29% resolved, 59% substantially improved.
Stroke / TIAs ²¹	18	Resolution and improvement of migraine	6 months	Migraine patients: 38% resolved, 44% improved. Average frequency reduced from 3.06 / month to 0.05 / month.
Stroke ²²	215(stroke)	Reduction and improvement of migraine	1 year	Approx 25% of patients had migraine before closure. After PFO closure, headache resolved in 25% of the migraine patients.

M+A = migraine with aura; M-A = migraine without aura; NS = not significant

Table 1. Summary of data on migraine improvement in patients with stroke or decompression sickness being treated with PFO closure.

Overall, closure of PFOs led to the resolution or improvement of migraine in most patients. The results indicate that these procedures are beneficial in patients with migraine and PFOs, especially as the patients had no prior expectations

of migraine improvement. However, these results need to be viewed with a certain degree of caution. The studies were small and retrospective and were conducted in highly selected populations of patients.

Conclusions

Younger adults with PFOs or migraine have an increased risk of stroke or TIA. There is an abundance of epidemiological evidence that PFOs and migraine (particularly migraine with aura) frequently co-occur, and there may be a genetic link between the two conditions. Stroke may occur as a result of right-to-left shunting of blood through the atria, allowing emboli or toxic substances to reach the brain

without first being filtered through the lungs. Percutaneous closure of the PFO can result in a good outcome for appropriate stroke patients. Small retrospective studies indicate that these procedures improve the migraine also (particularly migraine with aura, which is most prevalent in these patients). These results require confirmation in a randomised, controlled clinical trial.

The MIST study is designed specifically to investigate whether PFO closure (using the STARFlex® Septal Repair

Implant, Figure 4) is an effective treatment for some patients with migraine headache.

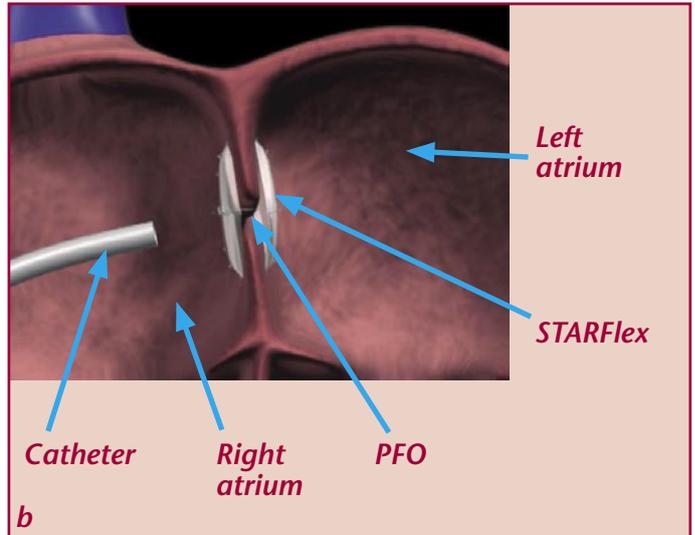
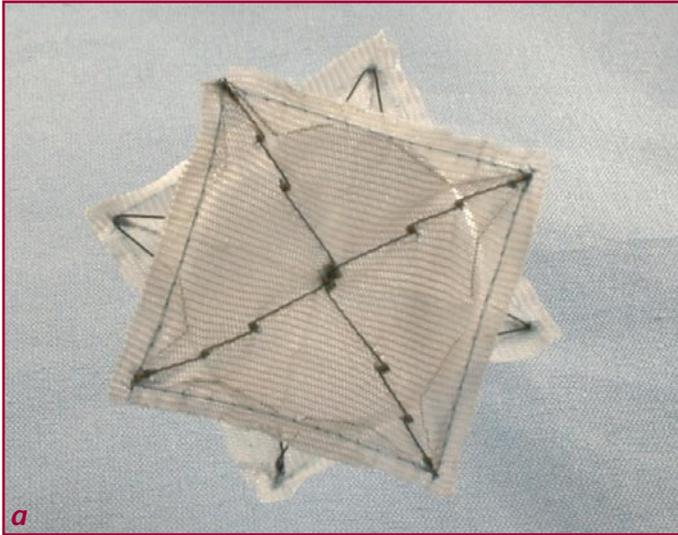


Figure 4. a. The STARFlex® Septal Repair Implant; b. The implant in position.

This is a prospective, multicentre, randomised, double-blind, placebo-controlled study in patients having migraine with aura who have frequent attacks (≥ 5 attacks per month) and are refractory to prophylactic medications (previous failure of two medication classes). Suitable patients are screened for the presence of a PFO, and if positive are randomised to receive the STARFlex® device or a sham (pseudo-simulated) procedure. The primary study endpoint is the incidence of

migraine headache during the analysis period. The study is currently ongoing. Further information on the MIST study can be obtained from www.migraine-mist.org, or by telephoning the Migraine Action Association (MAA) on 0870 050 5898. The MIST study is sponsored by a research grant from NMT Medical Inc., who manufacture the STARFlex® device, and is supported by MIPCA and MAA.

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If you are interested in joining MIPCA, please contact Ms Rebecca Salt, Merrow Park Surgery, Kingfisher Drive, Merrow, Guildford GU4 7EP: Tel 01483 450755: Fax 01483 456740.

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