

EDITORIAL COMMENT

The Effect of Persistent Foramen Ovale Closure on Migraine Remains an Enigma*

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The report in this issue of *JACC: Cardiovascular Interventions* from Vigna et al. (1) raises more questions about a confusing area of medicine—the role of persistent foramen ovale (PFO) closure in migraine.

Persistent foramen ovale is associated with a number of diseases including migraine with aura, cryptogenic stroke, and decompression illness (2–4). Other right-to-left shunts are also associated with these conditions, which suggests that a right-to-left shunt per se has an etiological role (5). It is postulated that in some people with migraine with aura a trigger substance passes across a shunt, but if this is so the trigger has not been identified. If this postulated mechanism is responsible for some cases, it cannot account for all because not all migraine sufferers have a shunt and many people with a shunt do not have migraine.

See page 107

Support for this hypothesis came from reports that, when patients who suffered presumed paradoxical embolism had their PFO closed to prevent recurrence, there was dramatic improvement in migraine in the majority of cases and often cessation of migraine (6–8). An improvement was also found in patients who had migraine without aura (6). These reports of improvement in migraine were from nonrandomized observational series. A placebo effect could not be excluded, although in the early series the patients had no prior expectation that PFO closure would have an effect on migraine and the magnitude of the effect was greater than previously reported for any placebo response. However, in

some patients migraine was not improved by PFO closure. In a few migraine became more frequent or severe, and occasionally PFO closure triggered migraine in people who had not had it before, particularly soon after the closure procedure. This could be modified by clopidogrel (9).

Publication of the results of the MIST (Migraine Intervention with STARFlex Technology) trial in March 2008 made unraveling the association between PFO and migraine more difficult (10). The MIST trial was a prospective multicenter randomized double-blind controlled trial to compare the effect of closure of moderate or large PFOs with the STARFlex implant and sham intervention in patients with severe and frequent migraine. The patients in the MIST trial differed from those in earlier observational studies, because patients with a history of stroke were excluded. They usually had more severe migraine. In the MIST trial, follow-up was for 6 months, with the patients receiving aspirin and clopidogrel for the first 3 months, and the headache analysis phase was during the second 3-month period.

The initial findings of MIST were encouraging, with 60.2% of patients found to have a right-to-left shunt, the majority of which were classified as a moderate or large PFO. One hundred forty-seven patients were randomized to either implantation of a STARFlex device or sham intervention. The final comparisons of the implant and sham groups showed no effect on the primary end point of cessation of migraine or secondary end points of improvement in migraine in either the intention-to-treat analysis or per-protocol population. The latter excluded the patients who were withdrawn because of adverse events or failure to cross or close a PFO. The implant arm had a high rate of procedural complications.

Vigna et al. have investigated the effects of PFO closure in a case control study of patients who seem to be clinically intermediate between the patients in the MIST trial and the observational studies of PFO closure in stroke patients. Their migraine was less severe than in the MIST trial but more severe than in observational studies. They had not had stroke but had subclinical magnetic resonance imaging brain lesions that might represent silent cerebral ischemic events. Magnetic resonance imaging brains scans were not performed in the MIST trial, but magnetic resonance imaging brain lesions are common in migraineurs, so it is certain that some of the patients in the MIST trial had brain lesions. Unlike MIST, patients with migraine without aura were included in the study by Vigna et al., and they had 6 months' assessment of migraine headaches before they were offered a closure procedure. Critically, there was no blinding of subjects to treatment. Eighty-two patients were offered a closure procedure "for prevention of white matter lesions progression or thromboembolism." The 29 who declined closure became the control group, and self-selection might have influenced outcomes in the 2 groups. The control

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From the Royal Shrewsbury Hospital, Shrewsbury, United Kingdom. Dr. Wilmshurst was co-principal investigator and principal cardiologist in the MIST trial. To avoid a financial conflict of interest he declined consultancy payments offered by the trial sponsor, NMT Medical. He was offered authorship of the MIST paper and declined to add his name to the list of authors. He is being sued for libel in the English High Court by NMT Medical for statements attributed to him on a U.S. website. He is defending the libel action.

group had their preventive medical therapy adjusted by a neurologist, who was in some way blind to the protocol, but those who had a closure procedure were not allowed preventive medication. Fifty-three patients had a closure procedure with a variety of devices. Antiplatelet medication was given for 6 months (rather than 3 months in MIST), and migraine symptoms were assessed for 6 months after the end of antiplatelet treatment (3 months in MIST). In the patients who had a closure procedure but not in control subjects, there were significant reductions in number of migraine attacks and disabling attacks. Compared with the medically treated control group, closure resulted in statistically significant and clinically important greater numbers of patients who had cessation of migraine attacks, cessation of disabling attacks, and over 50% reduction in migraine attacks.

Overall, the findings in the study by Vigna et al. (1) accord with results in open observational studies in patients with stroke and migraine. Therefore, we are left with a dilemma. Why are there such different results between the only randomized double-blind sham-control trial, the MIST trial, and all other trials? It is possible that in patients with migraine the placebo effect from an operative intervention might be much greater than the magnitude of placebo effects with drug treatments. There might be fundamental differences between migraineurs who have had stroke or cerebral ischemic injury and those without ischemic injury. Failure of migraine to respond to medical treatment, as required for entry in the MIST trial, might be an indication that there will be little response to PFO closure. The methods of patient selection might have resulted in unidentified differences between patients in the MIST trial and other studies. It is possible that in the MIST trial the analysis phase of the trial was too soon after implantation when there was inadequate device endothelialization, a residual effect from antiplatelet treatment or an early post-closure migraine-exacerbation effect. Does residual shunting, either atrial or pulmonary, play any part in failure of migraine to respond to PFO closure? If so, should studies of PFO closure require independent echocardiography core laboratory assessment of residual shunting, com-

parable to coronary stenosis assessment in coronary intervention studies, and full reporting of the findings?

The report by Vigna et al. (1) does not explain the relationship between PFO and migraine, but it does raise more questions, particularly with regard to the need for further double-blind sham-controlled trials of PFO closure for migraine.

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