Migraine Intervention With STARFlex Technology Trial
A Controversial Trial of Migraine and Patent Foramen Ovale Closure

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Recent epidemiological data suggest that up to 18% of women and 6% of men worldwide have suffered a migraine headache.¹,² Despite its common occurrence, our understanding of both migraine pathophysiology and the optimal means by which to control or abate symptoms remains severely limited.¹ For many years, the care of patients with migraines was left in the capable hands of general practitioners and neurologists. As information surfaced on the potential link between migraines and patent foramen ovale (PFO), however, some cardiologists became involved in the care of patients with migraines and were quickly humbled by the often debilitating nature of the disease process. Personally witnessing such intense suffering, the inconsistent effect of rescue medications, and the subsequent reliance on powerful intravenous narcotic agents to achieve some means of comfort until the storm subsides has been a sobering experience. With the development of implantable devices used to close potentially enabling PFOs, however, came a newfound hope in our ability to help these suffering people.

The potential causative link between migraines and PFO became apparent between 2000 and 2004, during which period many single-center reports demonstrated precipitous improvements in migraine frequency in patients undergoing percutaneous PFO closures for nonmigraine indications.³⁻⁵ When these preliminary reports surfaced, professional and media interest in this potential association escalated rapidly. This awareness established the groundwork for the Migraine Intervention With STARFlex Technology (MIST) trial, which, by incorporating important elements in trial design (eg, prospective, double-blinded, inclusion of a sham procedure), was viewed as an exciting and bold clinical investigation. The reports of thousands of patients with migraines calling to participate in MIST reaffirmed the notion that large numbers of patients were frustrated by being inadequately treated with both conventional (ie, medications) and unconventional (ie, acupuncture, Botox injections) means. The fact that these patients accepted the risks of undergoing an invasive cardiac procedure to potentially reduce their headache burden was a testament to their level of dissatisfaction with contemporary therapies.

Before the conclusion of the study, reports emerged confirming that a high percentage of patients screened for study inclusion had detectable right-to-left shunts and that their degree of shunting often was large, suggesting that the PFO anatomy in many patients with migraines was fundamentally dissimilar to the commonly seen probe-patent small PFOs seen in 23% to 28% of the general population.⁶ These early results further suggested that an association existed between PFO and migraines in many patients and that PFO was not merely an innocent remnant of the fetal circulation. Given these findings, the stage was set for a potentially clearcut therapeutic benefit in percutaneously closing an enabling PFO once the MIST follow-up was completed.

In the spring of 2006 at the American College of Cardiology annual scientific session, the MIST outcomes were finally presented to a large audience.⁶ Although the finding that the primary end point of complete cessation of migraines (ie, cure) was negative came as somewhat of a surprise to both the investigators and audience, in retrospect, it was felt by many that the expectation that PFO closure would result in migraine cure was fundamentally unrealistic. The preplanned secondary end point of a 50% reduction in migraine days, however, was achieved in 42% of patients in the device arm versus 23% in the sham arm (P=0.038).⁷ The statistically significant and clinically important reduction in the device arm was viewed as an unmistakable sign that PFO closure was beneficial even in patients refractory to medications. A reduction in migraine frequency rather than complete cessation was made the primary end point in subsequent PFO-migraine trials organized in the United States.

The final peer-reviewed results of MIST are reported in this issue of Circulation.⁸ Interestingly and somewhat disturbingly, MIST is now a completely negative study. These results are surprising and raise the question, What happened? To answer this question, several important issues need to be addressed.

MIST was a bold study in a very new area of clinical investigation. In light of this, the authors do a commendable job of reviewing the many aspects of trial design that may have ultimately contributed to the negative results of the study. In addition, they rightfully point out that current randomized trials in the United States and Europe have improved trial designs based on the results of MIST. Several additional issues at the foundation of the ongoing MIST controversy remain notable.

First and foremost, the de facto retraction of a positive clinical trial previously presented at a high-profile international meeting remains a major issue of concern from both the

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scientific and ethical perspectives. Even in late 2007, experts in the field continued to quote the positive secondary end points of MIST, and it is only now in wake of the published final results that we all appreciate the effervescence of such positivity. Although it is true that oral presentations of major late-breaking clinical trials at such meetings provide data that are preliminary and abbreviated with limited peer review, the inherent confidence in these presentations forms the groundwork for the credibility not only of the investigative process but also of the meeting, investigators, and sponsors. Perhaps most important, questions must be raised as to the potentially substandard quality of PFO evaluation and closure procedures performed in MIST patients. Relative to this concern, 3 quality issues stand out: the high frequency of patients found not to have a PFO during invasive evaluation (ie, quality of echocardiographic screening), the occurrence of several serious adverse events in a small device arm (ie, quality of procedure execution), and the unclear number of residual shunts (ie, device performance).

The lack of an established independent core laboratory for echocardiographic data analysis must haunt the trial investigators. The finding that 5 of 74 patients were found to have either no PFO at the time of their procedure or a PFO that could not be crossed by standard techniques raises serious concerns about the quality of echocardiographic screening used in the trial. Potentially, patients with pulmonary, not intracardiac, shunting were included in MIST. Furthermore, because balloon sizing of PFO was not performed during closure procedures, one can argue that the assessment of PFO anatomy was limited in scope and was excessively dependent on both a potentially flawed echocardiographic assessment and the vagaries of agitated saline assessment in the inherently dynamic process of intracardiac shunting. Although rigorous standardization of the performance of saline contrast echocardiography and subsequent data interpretation by independent observers would have greatly improved both the interpretation of and confidence in all future data, it is unfortunate that such a critical aspect of trial design was overlooked in the case of MIST.

Percutaneous PFO closure is regarded by some in the interventional cardiology community to be a remarkably simple and safe procedure with a brief learning curve. MIST required cardiologists performing PFO closure in the trial to have completed a minimum of 10 PFO closure procedures. Despite the relative technical simplicity of PFO closure, technical difficulties and complications may arise. Although the procedure itself carries a low major complication rate, ≈1.5% as assessed in the first few years after the introduction of the procedure, this rate will never reach 0. MIST, however, reported a higher-than-anticipated procedural complication rate (6.8%) with 1 case each of cardiac tamponade, pericardial effusion, and retroperitoneal bleed, in addition to 2 cases of atrial fibrillation, in only 74 patients enrolled in the device arm. Although the authors somewhat minimize the procedural complications by describing them as “transient” and conclude that the serious adverse events were equivalent between the 2 arms, it is important to note that the serious adverse events listed in Table 5 that were observed in the sham arm are not related to standard medical therapy for migraine but instead appear to be related to aspects of the study protocol (ie, required antiplatelet therapy). Furthermore, complications such as cardiac tamponade and retroperitoneal bleed are potentially life threatening, are unquestionably related to the procedure itself, and cannot be rationally offset by any of the serious adverse events observed in the sham arm.

The issue surrounding procedural complications brings us to this central question: What exactly is an acceptable risk-to-benefit ratio for procedure-related treatment of migraine headaches? After exclusion of 2 outliers in the device arm, a MIST exploratory analysis reports an average reduction in migraine burden of 2.2 versus 1.3 d/mo in the sham arm. Does a differential reduction of 0.9 d/mo in migraine frequency justify the nearly 7% or greater risk of a serious or potentially life-threatening procedural complication? Although the procedural risk should ideally approach 1% to 2%, the actual benefits of device-based therapy need to be demonstrated in a more unambiguous and clinically meaningful fashion before patients, providers, regulatory agencies, and healthcare insurers embrace this therapeutic approach.

Although 1 group reported that residual shunting was observed in 3 of 7 patients with persistent migraines and no improvement in migraine burden after PFO closure for secondary prevention of recurrent cerebrovascular events, the clinical importance of residual shunting on migraine burden after device implantation remains largely unknown. The issue of persistent shunting is of particular importance in MIST because migraine assessment was conducted at 3 to 6 months after implantation, a time period in which the process of device endothelialization is incomplete in many patients. Furthermore, the true rate of residual shunting in MIST remains controversial, unsettled, and a potential reason that MIST was a negative study. The actual number of patients with any persistent shunting after implantation is not reported in MIST. Instead, only those patients with moderate to large shunts (4 of 69 patients) are reported. The classification of shunting as “small” when <10 saline bubbles crossed into the left atrium within 5 cardiac cycles is an arbitrary definition at best and does little to assure clinicians that the observed degree of shunting was physiologically unimportant.

Worsening of preexisting and new-onset migraine with aura, aura alone, and nonspecific headaches has been reported in small numbers of adults and children immediately after atrial septal defect or PFO closure using a variety of devices. These symptoms are typically but not always transient and may respond to clopidogrel but nonetheless raise additional questions as to trial design, perceived risk-to-benefit analysis, and inherent pathophysiology of migraines.

Finally, clinical benefit in migraine-PFO closure trials must continue to use the self-reported frequency, severity, and duration of the subjective symptom of headache. This leads to the concern about the placebo effect, the necessity for binding, and the importance of a sham procedure done under general anesthesia. In addition, patients are screened by use of similar subjective data, potentially leading to enrolled patients who have similar symptoms but potentially a diversity of pathophysiological subtypes of the clinical syndrome...
of migraine. Treatment response would then be expected to be different. It is noteworthy that work is ongoing in finding biomarkers for migraine headaches. Furthermore, frequent headaches cause iron deposition in the periaqueductal gray area, and white matter hyperintensities are more common in migraine sufferers. Future trials may incorporate biomarkers and brain imaging to complement the reporting of subjective symptoms to distinguish subgroups in the migraine phenotype and to help direct treatment to those with a likely response.

Although the sky is certainly not falling in terms of the association between migraines and PFO or the potential benefits of PFO closure in patients with migraines, the controversies surrounding MIST must be appropriately addressed and resolved before any potential benefits of PFO closure in migraine patients can be implied with any level of certainty. In this light, the rush to bring off-label device closure to the migraine sufferer who cannot or will not participate in a clinical trial will hopefully be halted by the publication of MIST. With any luck, however, future data from ongoing clinical trials that are appropriately powered, better designed, and better executed will accomplish the ultimate goal of verifying that PFO closure is a viable therapeutic option for migraine sufferers.

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Disclosures
Dr Carroll is the part-time medical director of Medical Simulation Corp involved in training aspects of PFO closure. He is an investigator in PFO trials and a consultant for AGA Medical and St Jude Medical.

References

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