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Management of Patients With Refractory Migraine and PFO: Is MIST I Relevant?

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The results of the randomized clinical trial entitled: Migraine Intervention with Starflex Technology (MIST), produced surprising and disappointing results on the effect of PFO closure to decrease migraine headaches. There have been allegations of misrepresentation of the effectiveness of this device. These issues have significant implications in how randomized clinical trials are performed that will impact current and future planned trials of PFO closure to treat migraine headaches. © 2008 Wiley-Liss, Inc.

Key words: patent foramen ovale/atrial septal defect; embolization; intracardiac echo

INTRODUCTION

In this era of evidence based medicine, clinicians, government agencies, and patients look to the results of randomized clinical trials as the best means to understand the mechanisms of disease as well as the effectiveness of the drug or device being tested. In this process, there are fundamental assumptions of integrity in acquiring and analyzing the clinical data. When there is a fracture of this public bond, the subsequent effects in terms of scientific validity, patient trust, and financial implications can be enormous. The present controversy over the conduct and conclusions of the Migraine Intervention with STARFlex Technology (MIST) trial provides an excellent case example where interests of researchers, business entities, and government supervising agencies are openly in conflict and reveal the forces that shape the current scientific environment of industry sponsored clinical research.

PATENT FORAMEN OVALE AS A CAUSE OF PATHOLOGY

The potential influence of a patent foramen ovale (PFO) on human health was barely recognized 20 years ago. Within that relatively short time frame, there have been progressively more reports suggesting that a PFO may be implicated as a pathway of right to left shunting of blood clots or humoral factors that produce a variety of pathologic conditions. These conditions include the following: cryptogenic stroke, decompression illness, paradoxical peripheral embolism, myocardial infarction in patients without coronary artery disease, high-altitude pulmonary edema, exacerbation of sleep apnea, intermittent oxygen desaturation usually in the upright position (orthodeoxia), and migraine headaches with or without aura.

The purpose of a patent foramen ovale is to permit oxygenated blood, returning from the placenta via the inferior vena cava, to bypass the nonaerated lungs, and deliver oxygen directly to the embryo's brain. Since the maternal transmission of oxygen is limited, the oxygen saturation of right atrial blood in utero is only 67%. If it were to continue the usual pathway through the nonaerated lungs before it was delivered to the brain, the saturation would presumably be insufficient to maintain adequate cerebral oxygenation. Humans are not the only animals with a PFO. All mammals are reported to have this evolutionary mechanism to preserve the brain. After birth, the lungs expand, the left

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atrial pressure rises above right atrial pressure and the flap of the septum primum closes against the septum secundum. In most cases, this tissue fuses to close the foramen ovale. However, in ~25% of humans, the septum primum and secundum do not fuse which produces a residual PFO.

PFO and Stroke

Although the possible mechanism of paradoxical embolism as a cause of stroke was recognized 150 years ago, the likelihood that PFO was mechanistically involved in cryptogenic stroke was thought to be very unusual. It has only been within the last 20 years with the increasing use of transesophageal echocardiography, that it has been recognized that there is a higher than expected prevalence of PFO in patients with cryptogenic stroke as well as other conditions. It is not the purpose of this article to review all of the data implicating PFO as a potential pathway for a paradoxical embolism to precipitate stroke or other peripheral embolic states. The reader can find several reviews on this topic [1–6]. Although there is much controversy and several conflicting observational reports on the relative prevalence of PFO in patients with stroke, the general consensus is that patients who do not have an obvious cause of stroke are three times as likely to have a PFO than do patients with a stroke who have predisposing conditions (such as atrial fibrillation or atherosclerosis). These observational studies obviously do not prove cause-and-effect, but they have laid the groundwork to justify spending the resources and effort for randomized clinical trials. The hypothesis of these trials is that closure of PFO will decrease the recurrence rate of stroke in those patients who have a stroke with cryptogenic etiology and PFO. There are currently two randomized trials in the United States that are testing this hypothesis: the CLOSURE trial using the CardioSeal device by NMT and the RESPECT trial using the Amplatzer PFO Occluder by AGA Medical.

PFO AND MIGRAINES: INCREASED PREVALENCE AND RANDOMIZED CLINICAL TRIALS

Just as the data of an increased prevalence of PFO in patients with cryptogenic stroke led to the development of randomized clinical trials to test this hypothesis, observational studies of the effect of PFO closure on migraine headaches have led to an intriguing hypothesis [7–14]. There are six reports in the literature from independent clinical centers in Europe and the United States that describe a dramatic decrease in the frequency of migraine headaches in patients who have a PFO closed because of cryptogenic stroke or other etiology. The first observation was that the prevalence of migraine headache in patients with cryptogenic stroke or decompression illness was three to four times as high as would be expected in the general population. The second observation is that closure of the PFO to prevent recurrent stroke produced the unexpected result of a dramatic reduction in the frequency of migraine headaches. In the combined experience of these observational studies, on average 60% of the people who had migraine before PFO closure claimed that their headaches were completely abolished following implantation of the device. An additional 20% of patients claimed that the frequency of their migraine headaches was reduced by at least 50%. These effects appear to be long lasting with many patients followed longer than 3 years. There is no medication that produces such a dramatic effect on migraine headaches. No one is claiming that this connection is proven, but it appears unlikely that six independent investigators would observe the same phenomenon if this were only a placebo effect. Nevertheless, these observations are only useful as a means to generate a hypothesis that needs to be tested in a prospective randomized clinical trial.

MIGRAINE INTERVENTION WITH STARFLEX TECHNOLOGY TRIAL

The migraine intervention with STARFlex technology (MIST) trial was the first randomized clinical trial of PFO closure in patients with severe migraine with aura. The investigators and the clinical trial sponsor, NMT, should be congratulated for recognizing the importance of the observational data and for launching this significant clinical investigation. The MIST trial obtained remarkable information even during its screening process. Patients with frequent migraine and symptoms of aura were asked to undergo a screening test using transthoracic echocardiography and an intravenous injection of agitated saline to look for right to left shunting. Remarkably, the incidence of right to left shunting was 60% in this population. The predominant etiology of the right to left shunt was thought to be a patent foramen ovale although pulmonary shunts were diagnosed in 5% of the cases. This in itself is an enormous contribution and should direct those involved in migraine research to understand why there should be such a connection between the brain and right to left shunting through the central circulation.

Although the MIST trial produced a great deal of enthusiasm that PFO closure might become an efficient method to help those people suffering from migraine headaches, the results of the trial as reported during the American College of Cardiology meeting in 2006 were disappointing. The primary endpoint of the trial, chosen because of the reports from the observational

studies, was that a significant number of patients in the device closure group would have complete abolition of their migraine headaches. This did not occur. In fact, of the 74 patients in the treatment group, only three reported complete cessation of their migraine headaches but this was no different than the control group which also had three people who no longer complained of migraine headaches despite the fact that their patent foramen ovale was not closed. This finding also underscores the importance of the placebo effect with migraine headaches and the difficulty of designing appropriate clinical trials when dealing with subjective endpoints such as cephalalgia. It is to the credit of the MIST investigators, that they designed a trial that had a sham procedure under general anesthesia to blind the patient as to whether or not they received a device to close their PFO.

The secondary endpoint of the MIST trial was the frequency of migraine headache days. In clinical studies using medications to treat migraine headaches, the standard criterion is that the drug should reduce the frequency of migraine days by 50% versus the control group [15]. In the initial reports of the MIST trial, the frequency of migraine days was reduced by 42% in the treatment arm and 23% in the control arm. This was statistically significant ($P < 0.04$) although not as dramatic as originally expected. In addition, the updated report presented at TCT in October 2007 found that the reduction in migraine days was no longer statistically significant [16]. They believed the reason for this was that there were two patients who had very frequent migraines which persisted following treatment. By excluding these two patients, the secondary endpoint of frequency of migraine headache days became statistically significant again. The justification for excluding these two patients may be arguable, but I believe it is more important to focus on the importance of identifying the appropriate patient population that should be studied in future trials. Specifically, patients with daily headaches should be excluded from future randomized trials because it is currently believed that these patients represent a form of a drug overdose and withdrawal phenomenon rather than the more usual patient with episodic migraine.

The main question that remains to be answered is why did the MIST trial not achieve the expected success and dramatic reduction in frequency of migraine headaches?

Two potential responses to this question have been proposed:

Hypothesis 1: the patient population with frequent migraines with aura is somehow fundamentally different from a mechanistic or physiologic basis than the patient populations that were treated in the observational studies, (i.e., patients with predominantly cryptogenic stroke who often had associated migraines).

Hypothesis 2: the right-to-left shunt in these patients was not effectively closed by the procedure. This could have occurred because patients had right to left pulmonary shunts (either in addition or instead of a PFO) or because the device that was used in the MIST trial was ineffective.

If the first hypothesis is correct, then we should expect to find similar results with other ongoing randomized trials using other devices in a similar patient population. As we learn more about the etiology of migraine headaches, it is to be expected that right-to-left humoral triggers account for only a certain portion of migraine headaches, even if a right to left is found. The patients with severe and frequent migraines may be different than patients with cryptogenic stroke and occasional migraines. However, if a device with a very low incidence of complications is available, it may still be reasonable to close PFO to treat migraine headache in those patient subsets that are found to be responsive to this therapy.

However, if the second hypothesis is correct, then the underlying pathophysiologic hypothesis may still be correct. In this light, the results of the MIST trial may not have demonstrated a reduction in migraine headaches because the right-to-left shunt was not adequately reduced. The results of current randomized trials may yet reveal that PFO closure is effective for reducing even severe, frequent migraine headaches provided that the right to left shunt is effectively closed.

With these concepts as background, let us examine the reported results of the MIST trial. The first distinction that needs to be made, is that there really are two versions of the reported results. Each version is supported by one of the primary cardiology clinical investigators in the trial. This information is publicly available and was disclosed at the TCT meeting in October 2007. It was also documented in a very thorough report in the electronic media, Heartwire, by science writer Shelley Wood. (Co-PI of MIST trial alleges data mismanagement, misinformation. theheart.org. [HeartWire > Interventional cardiology]; October 26, 2007. Accessed at http://www.theheart.org/article/821779.do).

The Official Version of the MIST Trial Results

Transthoracic echocardiograms were obtained at 6 months. During this examination, an agitated saline bubble study was performed through a peripheral vein following release of the Valsalva maneuver. The benefit of using this technique is that it is relatively easy to perform and less invasive than a transesophageal echocardiogram. Unfortunately, a transthoracic echo is more difficult to interpret than a transesophageal echo

in terms of the etiology of the right to left shunt. It may not be possible to distinguish whether the shunt is at the atrial level or through the pulmonary circulation. In addition, only a transesophageal echo will reveal enough information about the position of the device within the atrial septum to document the effectiveness of closure.

According to the presentation at TCT, effective closure was obtained in the device group in 94% of the cases (four cases with inadequate closure) [16]. The implication is that the failure to reach the primary endpoint and dramatically decrease the frequency of migraine headaches was not because of the presence of a large residual shunt.

The Unofficial Version of the MIST Trial Results

The allegation by Dr. Peter Wilmshurst, MD (one of the other principal investigators), is that 30–40% of patients assigned to device closure had large residual right-to-left shunts (22–30 patients with inadequate closure). The size of these shunts, according to Dr. Wilmshurst, were large enough to meet the original entry criteria into the study. The presence of the residual shunts was due to several possible causes. Dr. Wilmshurst believes that several of the patients had large pulmonary shunts to begin with. Since the screening study was a transthoracic echocardiogram with agitated saline bubble study and not a transesophageal echocardiogram, a distinction of where the shunt originated could not be made until the time of the procedure when the interatrial septum was probed with a guide wire. If a large pulmonary shunt was present, then it would be understandable that even effective closure of a patent foramen ovale would not inhibit all of the chemicals that could pass unmetabolized through the lungs and enter the cerebral circulation as potential triggers for migraine. Wilmshurst argues that this may be the case because there were seven patients who were randomized to the device arm, but there was no evidence for PFO at the time of the procedure. According to the protocol, these patients were still included in the device arm on an intention to treat basis.

Another possible explanation for a large residual shunt is inherent deficiencies in the device design. It has been described that with long PFO tunnels, the umbrella arms of the STARFlex device may not be able to fully open and produce the double clamshell configuration that is necessary for effective closure [4]. It was emphasized by the investigators of the MIST trial that the frequency of large shunts (43%) was higher than expected in this patient population. However, since there are no follow-up transesophageal echocardiograms and no independent interpretation of the 6-month transthoracic echocardiograms, we do not know what the evidence reveals in terms of the effectiveness of this particular device in forming a permanent seal of the atrial septum in this particular patient population. Even if Dr. Wilmshurst is correct in the number of large residual shunts, it still would not explain the finding that only 3 out of 74 patients assigned to the device arm had complete resolution of their migraine headaches. Presumably not all of these people had inadequate PFO closure or residual pulmonary shunts. Therefore the results of the MIST trial represent a combination of inadequate trial design and a device that had a higher than expected number of large residual shunts; but it also implies that this patient population with severe migraine headaches unresponsive to usual medical therapy is somehow more resistant to PFO closure alone. Perhaps future clinical trials should look at a slightly different patient population such as people with migraine and MRI abnormalities.

It is not the purpose of this manuscript to attempt to adjudicate the conflicting reports on the discrepancies in the 6-month echocardiographic data. It is hoped that governmental agencies within Britain or the United States will hold the company responsible for complete disclosure and independent review of the data so that the scientific community and the potential patient population can draw their own conclusions from complete disclosure and unbiased interpretation. But it is the purpose of this presentation to make it clear what is at stake and the need for clarifying this controversy. If there is evidence for a high incidence of residual right-to-left shunts in the device treated group within the MIST trial, then the fundamental hypothesis may still be correct: that right-to-left shunting may permit some chemical that ordinarily becomes metabolized in the lungs, to pass directly to the brain and trigger migraine headaches. In this context, the MIST trial did not meet its primary objective not because the hypothesis is incorrect, but because they did not effectively screen out patients with large pulmonary shunts or the device was not effective in completely preventing right-to-left shunts at the atrial level in patients with large PFOs. If either of these possibilities is documented by future independent analyses of the 6-month echocardiographic data, then it will have a significant impact on the design of future clinical trials. One lesson from this controversy is that future clinical trials should have a method for discriminating between intrapulmonary and cardiac shunts. Those patients with pulmonary shunts should be excluded from trials that attempt to determine whether PFO closure with a device can diminish migraine headaches. The second lesson is that follow-up studies must document that

adequate closure of the patent foramen ovale has been produced by the device being tested.

IMPLICATIONS OF THE MISSED RESULTS

Only an independent review of the 6-month follow-up echocardiographic data can provide a reliable and trustworthy interpretation of the incidence of residual shunts in the MIST treated group population. There is so much controversy with credible but opposing allegations from prime investigators in the study, that it is unclear whether we will ever know all the facts about this clinical trial. Hopefully the clinical trials that are currently underway in the United States will be better designed, more focused, with more accurate accumulation of the data, and regulation of the results.

REGULATORY ISSUES

There is concern that the results of the MIST trial are being obscured so that it does not appear as if the device is ineffective in closing patent foramen ovale.

Dr. Wilmshurst alleges that all of the echocardiograms were reviewed by an independent observer, Dr. Luc Missault at St. Jan Hospital, Brugges, Belgium. His findings should be included in all of the presentations on the MIST trial, including any article that describes the results. It would be hoped that the Multicentre Research Ethics Committee (MREC) and the Medicines and Healthcare Products Regulatory Agency (MHRA) in England would investigate the results of this clinical trial and ask for an independent review of the 6-month echocardiogram data. In addition, since the results of this trial are used as background information for the safety and efficacy of this device which is currently sold in the United States, it would appear appropriate if the FDA also required an independent review and eventual presentation of the data by an impartial echocardiographic core laboratory.

The fact that the company sponsor, NMT, is willing to spend millions of dollars more on another PFO closure trial to treat migraine headaches using their newest device, the BioStar, would also imply that they believe that the underlying hypothesis is correct, but that there is another explanation why the results of the MIST trial were not positive. What would be the justification for using the BioStar instead of the STARflex if it were not believed that it would be more effective and that a large residual shunt was the cause for the MIST trial to have unsatisfactory results? The natural deduction would be that NMT knows something about the MIST trial results that we do not.

Implications for Future Randomized Clinical Trials

There are important lessons to be learned from the controversy surrounding the MIST trial. Presumably the specifics of the inconsistencies in the reports of the MIST trial will be sorted out eventually and either replicated or refuted in subsequent randomized clinial trials of PFO closure in patients with severe migraine headaches. This series of articles in the CCI hopefully will force us to ask more questions of randomized trials and not to accept the results on face value. We need to evaluate the methodology and results which lead to the conclusions. Physicians must be good skeptics if we want to maintain our patients' trust.

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