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## Mini-Focus: Transcatheter Closure of ASD and PFO

# Association of Interatrial Shunts and Migraine Headaches

## Impact of Transcatheter Closure

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<b>OBJECTIVES</b>	To examine the relationship between patent foramen ovale (PFO) or atrial septal defect (ASD) with the incidence of migraine headache (MHA) and assess whether closure of the interatrial shunt in patients with MHA would result in improvement of MHA.
<b>BACKGROUND</b>	Migraine headache is present in 12% of adults and has been associated with interatrial communications. This study examined the relationship between PFO or ASD with the incidence of MHA and assessed whether closure of the interatrial shunt in patients with MHA would result in improvement of MHA.
<b>METHODS</b>	A sample of 89 (66 PFO/23 ASD) adult patients underwent transcatheter closure of an interatrial communication using the CardioSEAL (n = 22), Amplatzer PFO (n = 43), or the Amplatzer ASD (n = 24) device.
<b>RESULTS</b>	Before the procedure, MHA was present in 42% of patients (45% of patients with PFO and 30% of patients with ASD). At three months after the procedure, MHA disappeared completely in 75% of patients with MHA and aura and in 31% of patients with MHA without aura. Of the remaining patients, 40% had significant improvement ( $\geq 2$ grades by the Migraine Disability Assessment Questionnaire) of MHA.
<b>CONCLUSIONS</b>	Transcatheter closure of PFO or ASD results in complete resolution of MHA in 60% of patients (75% of patients with migraine and aura) and improvement in symptoms in 40% of the remaining patients. Interatrial communications may play a role in the etiology of MHA either through paradoxical embolism or humoral factors that escape degradation in bypassing the pulmonary circulation. A randomized trial is needed to determine whether transcatheter closure of interatrial shunts is an effective treatment for MHA. (J Am Coll Cardiol 2005; 45:489–92) © 2005 by the American College of Cardiology Foundation

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Because of increased associations, patent foramen ovale (PFO) has been implicated in the etiology of cryptogenic stroke secondary to paradoxical embolism (1,2), platypnea-orthodeoxia syndrome (3,4), neurologic decompression illness in scuba divers (3,5–7), and migraine headache (MHA) (5,8–13), especially in patients with migraine and aura.

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See page 496

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The purpose of this study was to examine the relationship between the presence of MHA in patients with either PFO discovered during evaluation of cryptogenic cerebrovascular accident or an atrial septal defect (ASD), and whether closure of these interatrial shunts had any effect on MHA.

### METHODS

**Patient population.** A total of 102 consecutive adult patients underwent transcatheter closure of an interatrial communication (26 ASD and 76 PFO) using the Amplatzer

PFO device (AGA Medical, Minneapolis, Minnesota) (n = 45), the CardioSEAL (NMT Medical, Inc., Boston, Massachusetts) (n = 30), or the Amplatzer atrial septal occluder device (n = 27). Of the 102 patients with successful closure of their interatrial communication, 97 were available for follow-up, and follow-up was obtained in 89 (92%).

**Procedure.** Patients were usually given aspirin (81 to 325 mg daily) and clopidogrel (75 mg daily) a few days before the procedure. When a patient had been taking warfarin, it was discontinued four days before the procedure. Procedures were performed without general anesthesia and on an outpatient basis after August 2001. For PFO closures, transesophageal echocardiography (TEE) (n = 65) (14) or intracardiac echo (n = 11) (14–16) were used to guide the procedure to ensure that the device was optimally placed. All ASD closures were done with TEE guidance. Heparin was routinely administered at the start of the procedure to achieve an activated clotting time  $>250$  s.

**Follow-up evaluation.** Patients were usually discharged taking aspirin (325 mg daily) and clopidogrel (75 mg daily). Standard endocarditis prophylaxis was prescribed. Warfarin use in addition to antiplatelet therapy was determined by the patient's concomitant disease. Patients were followed clini-

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**Abbreviations and Acronyms**

ASD = atrial septal defect  
MHA = migraine headache  
MIDAS = Migraine Disability Assessment Questionnaire  
PFO = patent foramen ovale  
TEE = transesophageal echocardiography

cally and TEE was performed at one month after implantation.

**Definitions of echocardiographic findings.** The presence of a residual shunt at follow-up TEE examination was determined by color-flow Doppler for left-to-right shunt (17) and by agitated saline contrast injection into an antecubital vein for the presence of right-to-left shunt (18). Residual shunts were categorized into none, small, and moderate to large by color Doppler flow and into none, small, moderate, and large by contrast injection. The presence or absence of an atrial septal aneurysm was determined as previously described (19). The presence of thrombus on the device in the follow-up period was defined as a new hypoechogenic non-planar, partially mobile structure.

**Assessment of migraine headaches.** Presence or absence of MHA was self-reported by patients on the basis of a diagnosis made by either their primary care physician or their neurologist. Migraine severity was assessed by using the previously validated Migraine Disability Assessment Questionnaire (MIDAS) (20-23). The MIDAS score is derived by adding up the number of functional days lost because of MHA and is graded from 1 to 4.

**Statistical analysis.** Continuous variables were analyzed using *t* tests and dichotomous variables were analyzed using chi-square tests. Continuous variables are expressed as mean values ± SD and dichotomous variables are expressed as a frequency percentage. A *p* value of <0.05 was considered to be statistically significant.

**RESULTS**

**PFO closure.** Of 76 patients, 50 (66%) were women and the mean age was 49 ± 13 years old (range 17 to 77 years). The majority of patients with PFO (52 of 76) had a PFO alone (68%); an atrial septal aneurysm was associated with the PFO in 24 patients (32%).

The CardioSEAL device was used in 30 patients, the Amplatzer PFO occluder device in 45 patients, and the Amplatzer septal occluder in 1 patient. A transseptal puncture technique was used in 15 patients (20%) (24).

Transesophageal echocardiography follow-up was available in 65 of 76 patients. The incidence of residual shunt did not differ between the CardioSEAL and the Amplatzer devices (4 of 26, 15% vs. 8 of 39, 21%, *p* = 0.27). All residual shunts were small (color Doppler jet <2 mm through the defect or the presence of 3 to 9 microbubbles in the left atrium by contrast injection). The incidence of

**Table 1.** Association of Migraine Headache With Interatrial Shunts and Impact of Transcatheter Closure

	All Patients (n = 89)	PFO (n = 66)	ASD (n = 23)
<b>Incidence of migraine</b>			
Any migraine	37 (42%)	30/66 (45%)	7/23 (30%)
MHA+	24 (27%)	20/66 (30%)	4/23 (17%)
MHA-	13 (15%)	10/66 (15%)	3/23 (13%)
<b>Any improvement</b>			
Any migraine	28/37 (76%)	24/30 (80%)	4/7 (57%)
MHA+	19/24 (79%)	16/20 (80%)	3/4 (75%)
MHA-	9/13 (69%)	8/10 (80%)	1/3 (33%)
<b>Resolution</b>			
Any migraine	22/37 (60%)	19/30 (63%)	3/7 (43%)
MHA+	18/24 (75%)	15/20 (75%)	3/4 (75%)
MHA-	4/13 (31%)	4/10 (40%)	0/3
<b>Improvement, but no resolution</b>			
Any migraine	6/37 (16%)	5/30 (17%)	1/7 (14%)
MHA+	1/24 (4%)	1/20 (5%)	0/4
MHA-	5/13 (38%)	4/10 (40%)	1/3 (33%)

ASD = atrial septal defect; MHA+ = migraine headache with aura; MHA- = migraine headache without aura; PFO = patent foramen ovale.

thrombus formation at one month was 22% in patients receiving the CardioSEAL device and 0% in patients receiving the Amplatzer PFO device (25).

**ASD closure.** Of 26 patients with successful ASD closure, the average age was 41 ± 15 years, and 76% of these patients were women. All ASD closures were accomplished using the Amplatzer septal occluder device under TEE guidance. Transesophageal echocardiography follow-up was available in 23 patients. There was no incidence of thrombus formation on any of the devices. A small residual shunt was present in 7 of 23 patients.

**Migraine headaches.** Preoperatively, MHA was present in 37 of 89 (42%) patients (24 with aura and 13 without aura). Of these 37 patients with MHA who had successful transcatheter interatrial closure, 28 (76%) either had complete resolution or significant improvement in their MHA. Tables 1 and 2 summarize the effect of closure of interatrial communications on patients with known MHA. Postoperatively, MHA disappeared completely in 22 of 37 patients

**Table 2.** Pattern of Headache Improvement in Patients After Closure of Interatrial Communication

	Before	After	p Value
<b>MHA episodes</b>			
Overall	12.4 ± 27.7	2.2 ± 5.4	0.004
Resolved completely	4.0 ± 6.4	0	0.008
Did not resolve completely	24.7 ± 31.5	5.5 ± 7.4	0.02
<b>MHA severity (scale of 1-10)</b>			
Overall	6.4 ± 10.7	3.7 ± 5.1	0.0003
Resolved completely	6.6 ± 10.1	0	<0.0001
Did not resolve completely	6.2 ± 3.2	5.8 ± 2.7	0.7
<b>MIDAS score</b>			
Overall	19.1 ± 47.1	5.2 ± 26.6	0.08
Resolved completely	16.8 ± 54.8	0	0.16
Did not resolve completely	22.7 ± 34.1	12.8 ± 41.4	0.24

MHA = migraine headache; MIDAS = Migraine Disability Assessment Questionnaire.

(60%), in 18 of 24 patients (75%) with MHA with aura, and in 4 of 13 patients (31%) with MHA without aura.

Of the remaining 15 patients, 6 (40%) had significant improvement of  $\geq 2$  grades in incidence and severity of MHA as assessed by the MIDAS questionnaire; there was no difference in the effect on MHA in the patients treated with the CardioSEAL device versus those treated with the Amplatzer device or in patients with or without a small residual shunt.

## DISCUSSION

The prevalence of MHA in the general population is 12% (26–28), but was 3.5 times higher (42%) in our patients with interatrial communications. The prominent finding of this observational study is that transcatheter closure of PFO or ASD results in complete resolution of MHA in the majority (60%) of patients and significant improvement ( $\geq 2$  MIDAS grades) in symptoms in a large portion (40%) of the remaining patients (overall, 76% of MHA resolve or improve). In addition, this symptomatic improvement of severe migraines persisted for the 12-month mean length of our follow-up. Our observations complement other reports (5,8–13) demonstrating an increased association of MHA in patients with interatrial communications.

The association between closure of interatrial communication and improvement of headache appears to be stronger with migraine and aura than with migraine without aura. In this population, 75% of patients with migraine with aura had complete resolution of their headache after successful closure of the interatrial communication versus 31% of patients with migraine headache without aura. However, a majority of patients (69%) with migraine without aura still experienced either a complete resolution of their migraine headache or significant improvement of  $\geq 2$  MIDAS grades.

Based on the association of PFO, cryptogenic stroke, and MHA, several new hypotheses have been proposed for the etiology of MHA. It has been postulated that a MHA is due to a small venous embolus that crosses the PFO paradoxically and passes to the cerebral circulation. Rather than inducing a stroke, the small embolus or platelet plug precipitates a spreading wave of depolarization that is recognized as the neurologic phenomenon of migraine. In support of this theory, one recent study demonstrated a 13.7-fold higher incidence of magnetic resonance imaging lesions in migraine patients with aura than in controls (29).

Alternatively, we hypothesize that migraine is precipitated in susceptible individuals by chemical substances that can pass directly through the atrial shunt before they can be detoxified in their first passage through the lungs. This substance, in elevated concentration, could cause migraine in susceptible individuals without a PFO, but if a PFO is present it could potentially shunt from the venous to the arterial system and reach the brain in a more concentrated packet than if a central shunt were not present. In this

hypothesis, the presence of a PFO also predisposes to paradoxical embolism and stroke and is the pathway for emboli that produce the magnetic resonance imaging lesions seen in patients with MHA (29). The “migraine stroke” is probably not caused by intense vasospasm, but may be a manifestation of a paradoxical embolism through a PFO.

Whatever theory of MHA is eventually validated, the profound improvement in this debilitating condition by closure of an interatrial shunt, as observed in these patients, raises the possibility of providing a substantive treatment for severe MHA. A prospective randomized trial is justified to determine whether closure of PFO in patients with MHA leads to significant reduction in the incidence of migraine compared to medical therapy.

**Study limitations.** This study was a retrospective evaluation and not a prospective randomized trial. The patient group being studied consisted primarily of patients with a history of cryptogenic stroke with a known interatrial communication and is not representative of the general population of patients with PFO. Although the MIDAS questionnaire is a well-established tool in the evaluation of the severity of MHA, it is a subjective method. All patients were taking clopidogrel for three months and taking aspirin indefinitely after closure of their interatrial communication; therefore, improvement in MHA could be attributed in part to use of these medications.

**Conclusions.** There is a 3.5-fold increased incidence of MHA in patients with a PFO or ASD who are undergoing transcatheter closure of their interatrial communication. Transcatheter closure of PFO or ASD in patients with MHA leads to resolution of or significant improvement in severity of MHA in the majority (76%) of patients. A prospective randomized trial is justified to determine whether closure of PFO in patients with MHA leads to significant reduction in the incidence of migraine compared with medical therapy.

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