Patent Foramen Ovale and Migraine
A Cross-Sectional Study From the Northern Manhattan Study (NOMAS)

Tatjana Rundek, MD, PhD; Mitchell S.V. Elkind, MD, MS; Marco R. Di Tullio, MD; Emmanuel Carrera, MD; Zhezhen Jin, PhD; Ralph L. Sacco, MD, MS; Shunichi Homma, MD

Background—A causal relationship between patent foramen ovale (PFO) and migraine has been hypothesized, and improvement of migraine frequency and severity after percutaneous PFO closure has been reported. Population-based data on the relationship between PFO and migraine are sparse, however. The objective of this study was to examine the association between PFO and migraine among stroke-free individuals in an urban, population-based, multiethnic cohort.

Methods and Results—As a part of the ongoing Northern Manhattan Study (NOMAS), 1101 stroke-free subjects were assessed for self-reported history of migraine. The presence of PFO was assessed by transthoracic echocardiography. The mean age of the group was 69±10 years; 58% were women. Forty-eight percent were Caribbean Hispanic, 24% were white, 26% were black, and 2% were another race/ethnicity. The prevalence of self-reported migraine was 16% (13% migraine with aura). The prevalence of PFO was 15%. Migraine was significantly more frequent among younger subjects, women, and Hispanics. The prevalence of PFO was not significantly different between subjects who had migraine (26/178, or 14.6%) and those who did not (138/923, or 15.0%; P=0.9). In an adjusted multivariate logistic regression model, the presence of PFO was not associated with increased prevalence of migraine (odds ratio 1.01, 95% confidence interval 0.63 to 1.61). Increasing age was associated with lower prevalence of migraine in both subjects with a PFO (odds ratio 0.94, 95% confidence interval 0.90 to 0.99 per year) and those without PFO (odds ratio 0.97, 95% confidence interval 0.95 to 0.99 per year). The observed lack of association between PFO and migraine (with or without aura) was not modified by diabetes mellitus, hypertension, cigarette smoking, or dyslipidemia.

Conclusions—In this multiethnic, elderly, population-based cohort, PFO detected with transthoracic echocardiography and agitated saline was not associated with self-reported migraine. The causal relationship between PFO and migraine remains uncertain, and the role of PFO closure among unselected patients with migraine remains questionable.

Key Words: migraine disorders ■ epidemiology ■ echocardiography ■ foramen ovale, patent ■ risk factors

Migraine is a common, chronic, disabling neurovascular disorder characterized by attacks of severe headache, autonomic nervous system dysfunction, and, in some patients, an aura and neurological symptoms. The prevalence of migraine is as high as 18% in the general population. Migraine is one of the most disabling chronic disorders and ranks 19th worldwide among diseases that cause morbidity. The suffering associated with migraine headaches accounts for a significant loss in productivity and a substantial increase in healthcare-related costs. Patent foramen ovale (PFO) has a prevalence of 15% to 25% in the general population and up to 60% in patients with migraine with aura in case-control studies; however, the high prevalence of PFO in patients with migraine reported in case-control studies (which are relied upon because of a lack of population-based data) is most likely overestimated because of a biased selection of control groups.
Intervention with STARFLEX Technology [MIST] trial), however, did not reach its primary end point of a complete cessation of migraine attacks 6 months after PFO closure. Several clinical trials of PFO closure in refractory migraine are currently under way (MIST II, ESCAPE [Effect of Septal Closure of Atrial PFO on Events of Migraine with Premere], and PREMIUM [Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the AMPLATZER PFO Occluder Compared to Medical Management]), although the causal relationship between PFO and migraine remains uncertain and PFO closure among patients with migraine remains controversial. Interestingly, population-based data on the relationship between PFO and migraine are sparse, and the debate over whether the presence of PFO in individuals from the general population is related to migraine and stroke continues. The aim of the present study was to examine the association of PFO and migraine among stroke-free individuals from an urban, population-based, multiethnic cohort.

Methods

The Northern Manhattan Study (NOMAS) is an ongoing prospective cohort study of stroke-free individuals that was designed to determine stroke incidence, risk factors, and outcomes in a multiethnic urban population of the northern Manhattan (New York) area. The methods of subject recruitment and enrollment into NOMAS have been described previously. Briefly, community subjects from northern Manhattan were eligible if they (1) had never been diagnosed with a stroke, (2) were >39 years of age, and (3) resided in northern Manhattan for at least 3 months in a household with a telephone. Stroke-free subjects were identified by random-digit dialing with dual-frame sampling to identify both published and unpublished telephone numbers. Of the prospective study participants who were contacted telephonically, 90% agreed to attend an in-person visit. A total of 3298 subjects were recruited and enrolled in NOMAS between 1993 and 2001. The study was approved by the Institutional Review Board at the Columbia University Medical Center, and all participants gave written informed consent.

Information about risk factors was collected through interviews by trained research assistants, and physical and neurological examinations were performed by study physicians. Standardized questions were adapted from the Behavioral Risk Factor Surveillance System of the Centers for Disease Control and Prevention about the following conditions: hypertension, diabetes mellitus, hypercholesterolemia, cigarette smoking, peripheral vascular disease, and cardiac diseases. Assessments were conducted in English or Spanish depending on the primary language of the participant. Race/ethnicity was based on self-identification through a series of interview questions modeled after the US census and conforming to the standard definitions outlined by Directive 15. Standard techniques were used to measure blood pressure, height, weight, and fasting glucose as described in prior publications. Fasting lipid panels (including total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride) were measured with a Hitachi 705 automated spectrometer (Boehringer; Mannheim, Germany). Risk factors were defined as in prior publications. Hypertension was defined as a systolic blood pressure recording of 140 mm Hg or higher or a diastolic blood pressure reading of 90 mm Hg or higher or the patient’s self-report of a history of hypertension or antihypertensive drug use. Diabetes mellitus was defined by a fasting blood glucose level ≥126 mg/dL, the subject’s self-report of such a history, or insulin or oral hypoglycemic use. Dyslipidemia was defined as a history of elevated cholesterol, taking medications for elevated cholesterol, or a total cholesterol level >240 mg/dL. Current smoking was defined by smoking within the past year.

Definition of Migraine

A consecutive sample of 1101 subjects (34% of the parent NOMAS cohort) enrolled into NOMAS from 1997 to 2001 were asked to respond to a questionnaire on self-reported diagnosis of migraine. All NOMAS subjects were interviewed in person in a neurology research clinic. The subjects were questioned about self-reported migraine by trained research assistants. Individuals were asked the following questions: “Have you ever had migraine headaches?” for a past history of migraine; and “In the past year, have you had at least 1 headache, other than those caused by head injury, hangover, or a bad cold or flu?” for current migraine. Migraine was defined as a positive answer to either of these 2 questions. If self-reported migraine was described by a research assistant, a study neurologist (a stroke fellow or an attending physician) interviewed the subjects on migraine history at the time of neurological examination using a short, 15-minute questionnaire adapted from the International Headache Society Classification to record frequency and duration of headache, pain type, sensitivity to light and sound, visual disturbances, nausea, focal neurological symptoms, and medications. According to the recorded answers, the self-reported migraine was defined as closely as possible to the International Headache Society criteria as “migraine without aura” (recurrent headache with attacks that lasted 4 to 72 hours; unilateral, pulsating, aggravated by physical activity, and associated with nausea and/or photophobia and phonophobia) and “migraine with aura” (recurrent headache with attacks of completely reversible focal neurological symptoms that lasted <60 minutes after the aura symptoms). Typical aura was visual and/or sensory, with or without speech symptoms.

Echocardiographic Evaluation of PFO

Transesophageal 2-dimensional echocardiography (TEE) was performed in all study subjects according to the published protocol adopted from the recommendations of the American Society of Echocardiography. Saline contrast injection (aerated saline solution) with provocative maneuvers (Valsalva maneuver, sniff, cough) was used for detection of PFO. A PFO was considered present if any microbubble was seen in the left-sided cardiac chambers within 3 cardiac cycles from maximum right atrial opacification.

Statistical Analyses

The distribution of the variables of interest and of the other risk factor variables was examined. Means were calculated for continuous variables and proportions for categorical variables. Simple and multiple logistic regressions were used to analyze the association between presence of PFO and self-reported migraine before and after adjustment for potential confounding demographics (age, sex, and race/ethnicity) and vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, and current smoking) that are associated with endothelial dysfunction, a presumed mechanism in migraine. Statistical significance was determined at an α-level of 0.05 with 2-sided tests. Statistical analyses were conducted with SAS version 9.1 (SAS Institute, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

A sample of 1101 stroke-free individuals was analyzed in the present study. Demographics and clinical characteristics of this group did not differ significantly from the characteristics of the parent cohort. The mean age in the present sample was 69 ± 10 years (versus 69 ± 10 years in the parent cohort); 58% were women (versus 62%); and 48% were Caribbean Hispanics (versus 53%), 26% were black (versus 24%), and...
The prevalence of self-reported migraine in the cohort was 16% (178/1101) versus 53% in the parent cohort. The prevalence of PFO was 15% (164/1101) versus 5% (178/1101). The prevalence of current and former smoking was 54% (198/1101) versus 21% (236/1101). The prevalence of diabetes mellitus was 18% (198/1101) versus 21% (236/1101). The prevalence of hypertension was 67% (738/1101) versus 73% (736/1101). The prevalence of dyslipidemia was 48% (528/1101) versus 46% (462/1101). The prevalence of migraine was 16% (178/1101) versus 53% (236/1101). The prevalence of PFO was 15% (164/1101) versus 5% (178/1101).

In the present study, the prevalence of PFO was 15%, and the prevalence of self-reported migraine was 16% (13% with aura), but the number of subjects with migraine subtypes was not large enough to make a definitive statement about this difference. In addition, risk factors did not affect the relationship between PFO and self-reported migraine.

We could not confirm previous reports of the association of PFO with migraine or migraine with aura.\(^5\)\(^{-}\)\(^12\)\(^{31-33}\) Several possible reasons could account for this discrepancy. Unlike the present population-based study, most of the previous studies were case reports, case-control studies, or case series of highly selected patients with migraine, and therefore, the true associations in the populations could not be ascertained.

The study populations differed according to subject characteristics, diagnostic criteria for migraine, and methods for PFO detection (Table 3). Approximately half of the present cohort consisted of Caribbean Hispanics, among whom the prevalence of migraine was more than twice that of blacks and whites. Although the prevalence of PFO in migraine differed considerably between the studies, the most consistent finding was an increased prevalence of PFO among individuals with migraine and among those without self-reported migraine. PFO was slightly more prevalent in migraine with aura (19%) than in migraine without aura (11%), but the number of subjects with migraine subtypes was not large enough to make a definitive statement about this difference. In addition, risk factors did not affect the relationship between PFO and self-reported migraine.

## Discussion

In this cross-sectional analysis from an elderly, urban, multietnic, population-based cohort of 1101 stroke-free individuals, we did not find an association between presence of PFO detected with TTE and agitated saline and self-reported migraine. The prevalence of PFO of \(\approx 15\%\) was observed among individuals with self-reported migraine and among those without self-reported migraine. PFO was slightly more prevalent in migraine with aura (19%) than in migraine without aura (11%), but the number of subjects with migraine subtypes was not large enough to make a definitive statement about this difference. In addition, risk factors did not affect the relationship between PFO and self-reported migraine.

### Table 1. Demographics and Risk Factors in an Overall Cohort of 1101 Subjects, and Among Subjects With and Without Self-Reported Migraine

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Migraine*</th>
<th>No Migraine</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects (%)</td>
<td>1101 (100)</td>
<td>178 (16%)</td>
<td>923 (84%)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>69 (\pm) 10</td>
<td>61 (\pm) 9</td>
<td>71 (\pm) 10</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>639 (58)</td>
<td>128 (72)</td>
<td>508 (55)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic, n (%)</td>
<td>528 (48)</td>
<td>103 (58)</td>
<td>425 (46)</td>
<td></td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>286 (26)</td>
<td>36 (20)</td>
<td>249 (27)</td>
<td></td>
</tr>
<tr>
<td>White, n (%)</td>
<td>264 (24)</td>
<td>36 (20)</td>
<td>231 (25)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>738 (67)</td>
<td>123 (69)</td>
<td>618 (67)</td>
<td>0.58</td>
</tr>
<tr>
<td>Diabetes mellitus, n</td>
<td>198 (18)</td>
<td>27 (15)</td>
<td>171 (19)</td>
<td>0.23</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>528 (48)</td>
<td>79 (44)</td>
<td>462 (50)</td>
<td>0.17</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>198 (18)</td>
<td>36 (20)</td>
<td>148 (16)</td>
<td>0.17</td>
</tr>
<tr>
<td>PFO, n (%)</td>
<td>164 (15)</td>
<td>26 (14.6)</td>
<td>138 (15)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

* Migraine with aura, 22 (16%) of 140; without aura, 4 (11%) of 38 (P=0.42).

### Table 2. Predictors of Self-Reported Migraine, Including Presence of PFO (Multivariate Logistic Regression)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFO</td>
<td>1.01</td>
<td>0.63–1.61</td>
<td>0.90</td>
</tr>
<tr>
<td>Age</td>
<td>0.97</td>
<td>0.95–0.99</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hispanic vs white</td>
<td>1.18</td>
<td>0.75–1.87</td>
<td>0.47</td>
</tr>
<tr>
<td>Black vs white</td>
<td>0.76</td>
<td>0.45–1.27</td>
<td>0.29</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.13</td>
<td>0.78–1.64</td>
<td>0.52</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.66</td>
<td>0.43–1.02</td>
<td>0.07</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.12</td>
<td>0.78–1.59</td>
<td>0.55</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.36</td>
<td>0.99–2.10</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Significant interaction was observed for the relationship between PFO and migraine with diabetes mellitus, hypertension, dyslipidemia, or cigarette smoking (data not shown).
Vasoactive substances and platelet emboli, as well as their paradoxical bypass of the lung through a PFO, have been proposed to trigger the cortical spreading depression of the aura in subjects with PFO. A pattern of autosomal dominant inheritance in families with large PFOs or atrial septal defects has been identified. Coinheritance of PFO and endothelial and platelet abnormalities has been proposed to predispose an individual to migraine. These abnormalities and genetic determinants may be responsible for migraine, its type and severity, and its resistance to medical treatment. In addition, PFO has been proposed as a potential explanation of the severity, and its resistance to medical treatment. In addition, PFO closure should not be used as a treatment of migraine in the absence of sufficient evidence. Platelet activation, adhesion, and aggregation at the site of the occlusion device may release increased levels of serotonin, which triggers migrainous attacks, and these patients may benefit from antithrombotic therapy. Migraine is a complex neurological disorder with many possible exogenous and endogenous triggers, so any simple “cure” such as PFO closure is unlikely to exist. Therefore, until more evidence is obtained from ongoing large controlled trials, PFO closure should not be used as a treatment of migraine in clinical practice.

PFO Closure and Migraine
The results of several uncontrolled PFO closure studies have suggested a beneficial effect of the procedure on reduction of migraine frequency and duration; however, the first double-blind randomized trial, MIST I, did not achieve the primary efficacy end point of cessation of headache attacks during the 3 and 6 months after the procedure. The study also failed to achieve its secondary predefined end point. However, in the exploratory analysis, after exclusion of 2 patients in the implant group who accounted for more than one third of all migraine headache days throughout the entire study period, a significant reduction of 37% in median total migraine headache days for the implant group was observed compared with a 26% reduction in the sham group. Several randomized PFO closure trials of migraine are currently under way, but at present, no convincing scientific evidence exists to support PFO closure for treatment of migraine. Furthermore, the PFO closure procedure is associated with significant complications. Most of the patients in the MIST trial had at least 1 adverse event; 16 patients (11% of the intent-to-treat population) experienced serious adverse events, and 10 (7%) had serious adverse events that were definitely or possibly related to the device or procedure. In addition, PFO closure may trigger migraine. Recently, a substantial number of patients developed de novo migraine attacks after PFO closure. These individuals were younger than participants in the MIST trial, and bigger devices were used. Platelet activation, adhesion, and aggregation at the site of the occlusion device may release increased levels of serotonin, which triggers migrainous attacks, and these patients may benefit from antithrombotic therapy. Migraine is a complex neurological disorder with many possible exogenous and endogenous triggers, so any simple “cure” such as PFO closure is unlikely to exist. Therefore, until more evidence is obtained from ongoing large controlled trials, PFO closure should not be used as a treatment of migraine in clinical practice.

Study Limitations
The present study has several limitations. First, the presence of migraine was defined by self-reported history of signs and symptoms of migraine. Although we tried to maximize the accuracy of diagnosis by asking the questions used in the International Headache Society classification of migraine, and although our study neurologists reviewed the charts, a certain proportion of cases could have been misclassified. In addition, the recall bias in an older cohort such as that in the present study could have contributed to underreporting of the symptoms. However, the prevalence of self-reported migraine in the present study was similar to the prevalence expected in a general population. The higher prevalence of migraine with aura may be overestimated, however, because of recall bias. Second, the present study population is older than populations in most previous studies, and an association between migraine and PFO cannot be excluded in younger individuals on the basis of these data. Third, we used TTE to detect PFO instead of the more sensitive transesophageal echocardiography. This resulted in a lower prevalence of PFO (15%) than previously reported (17% to 26%). However, transesophageal echocardiography is a semi-invasive technique not suited for use in large epidemiological studies or in a low-risk population, and therefore, the present results are more relevant for general medical practice. Moreover, the PFOs that are missed by TTE have been shown to be small and characterized by small interatrial shunts and thus are possibly less relevant from a clinical standpoint. The other alternative would have been to perform transcranial Doppler contrast studies, which in conjunction with TTE would have increased the sensitivity of PFO detection. Transcranial

<table>
<thead>
<tr>
<th>Study</th>
<th>PFO Method</th>
<th>Migraine With Aura, n/N (%)</th>
<th>Migraine Without Aura, n/N (%)</th>
<th>No Migraine, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del Sette et al</td>
<td>TCD</td>
<td>18/44 (41)</td>
<td>NA</td>
<td>8/50 (16)</td>
</tr>
<tr>
<td>Anzola et al</td>
<td>TCD</td>
<td>54/113 (48)</td>
<td>12/53 (23)</td>
<td>5/25 (20)</td>
</tr>
<tr>
<td>Schwerzmann et al</td>
<td>TEE</td>
<td>44/93 (47)</td>
<td>NA</td>
<td>16/93 (17)</td>
</tr>
<tr>
<td>Dalla Volta et al</td>
<td>TCD</td>
<td>161/260 (62)</td>
<td>12/74 (16)</td>
<td>NA</td>
</tr>
<tr>
<td>Carod-Artal et al</td>
<td>TCD</td>
<td>25/48 (52)</td>
<td>32/93 (34)</td>
<td>NA</td>
</tr>
<tr>
<td>Domitrz et al</td>
<td>TCD</td>
<td>33/61 (54)</td>
<td>15/60 (25)</td>
<td>16/65 (25)</td>
</tr>
<tr>
<td>NOMAS</td>
<td>TTE</td>
<td>26/140 (19)</td>
<td>4/38 (11)</td>
<td>138/923 (15)</td>
</tr>
</tbody>
</table>

TCD indicates transcranial Doppler; TEE, transesophageal echocardiography.
Doppler data were not collected systematically in the present study. Finally, underascertainment of both PFO and migraine in the present study, although plausibly nondifferential, would also be expected to attenuate the observed association, again slightly weakening the negative finding of the study.

In conclusion, PFO and migraine are relatively frequent conditions in the general population, but their coexistence in an individual is uncommon. We did not find a significant association between migraine and PFO detected with TTE and agitated saline among elderly individuals from an urban, population-based, multicentric cohort. The causal relationship between PFO and migraine remains uncertain. Scientific evidence for PFO closure to reduce frequency of migraine is lacking. The present study did not evaluate the effect of PFO closure but indirectly supports the notion that the role of PFO closure among patients with refractory migraine remains questionable.

Sources of Funding

This investigation was supported by the Gilbert Baum Memorial Grant and the Goddess Fund for Stroke Research in Women (Dr Rundek), a research grant from the Swiss National Science Foundation PRFB-119620 and the SICPA Foundation, Lausanne, Switzerland (Dr Carrera), and by grants from the National Institute of Neurological Disorders and Stroke, R01 29993 (Drs Sacco, Elkind, and Rundek) and 33248 (Dr Di Tullio), K24 NS 02241 (Dr Di Tullio), K23 NS42912 (Dr Elkind), American Heart Association Kathleen Scott Research Fellowship (Dr Elkind) and the General Clinical Research Center (2 M01 RR00645).

Disclosures

Dr Homma is a Data Safety Monitoring Board member for the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial (AGA Medical). The remaining authors report no conflicts.

References

CLINICAL PERSPECTIVE

Although a causal relationship between patent foramen ovale (PFO) and migraine has been hypothesized, and improvement of migraine severity after percutaneous PFO closure has been reported, population-based data on this relationship are sparse. This study reports on the lack of a significant association between migraine and PFO detected with transthoracic echocardiography and agitated saline among 1101 stroke-free elderly individuals derived from an urban, population-based, multiethnic cohort. In this population, the prevalence of self-reported migraine was 16% (13% migraine with aura); the prevalence of PFO was 15%, and 2% of all individuals had migraine and PFO. Migraine was significantly more frequent among younger individuals, women, and Hispanics. The observed lack of association between PFO and migraine (with or without aura) was not modified by other traditional risk factors such as diabetes mellitus, hypertension, cigarette smoking, or dyslipidemia. This study demonstrates that PFO and migraine are relatively frequent conditions in the general population, but their coexistence in an individual is uncommon. Although this study did not evaluate the effect of PFO closure, it indirectly supports the notion that the role of PFO closure among patients with refractory migraine is questionable, because a “true” relationship between PFO and migraine remains uncertain.
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Correction

In the version of the article, “Patent Foramen Ovale and Migraine: A Cross-Sectional Study From the Northern Manhattan Study (NOMAS),” by Rundek et al that was posted online on September 15, 2008 (DOI: 10.1161/CIRCULATIONAHA.108.771303), an error occurred.

In the Clinical Perspective, the phrase, “and 2% of individuals with migraine had PFO,” should read, “and 2% of all individuals had migraine and PFO.”

The error has been corrected in the final print version of the article in the September 30, 2008, issue of the journal (Circulation. 2008;118:1419-1424) and in the current online version.

The authors regret the error.

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