Shunt-Associated Migraine Responds Favorably to Atrial Septal Repair
A Case-Control Study

Gian P. Anzola, MD; Giovanni B. Frisoni, MD; Eva Morandi, MD; Francesco Casilli, MD; Eustaquio Onorato, MD, FSCAI

Background and Purpose—Transcatheter closure of patent foramen ovale (PFO) has been reported to improve migraine in patients with cerebrovascular disorders in noncontrolled studies. The aim of the study was to compare the course of migraine assessed prospectively over a 12-month period in symptomatic (for cerebrovascular disease) and asymptomatic patients undergoing PFO closure and in patients with PFO treated medically.

Methods—Twenty-three stroke symptomatic (SS; 39 ± 10 years of age; males/females [M/F] 5/18) and 27 stroke asymptomatic (SA; 40 ± 12 years of age; M/F 5/22) patients with migraine underwent PFO closure. Twenty-seven patients with migraine and PFO (controls [CTRLS]; 36 ± 11 years of age; M/F 4/23) were followed up medically. Migraine severity was assessed at baseline with a scale that takes into account the frequency, duration, and intensity of the attacks and the occurrence of aura (score range 0 to 10). Six months later, the patients were given a structured diary to annotate monthly with the same scale the characteristics of the attacks for the next 6 months. By the end of 1 year, the migraine score was averaged for the last 6 months.

Results—Baseline severity of migraine did not differ between groups (6.3 to 6.1 and 6.7 in SS, SA, and CTRLS groups, respectively). At the 1-year assessment, the overall migraine score had significantly improved by 3.7 and 2.8 points in SS and SA, respectively (P < 0.001 on repeated-measure ANOVA), whereas it had nonsignificantly worsened by 0.1 points in CTRLS. Multiple linear regression analysis showed that the improvement in SS and SA was independent of migraine type, age, and cerebrovascular risk factors. Twenty-one of 21 patients with migraine with aura in the CTRLS group still had aura at the end of follow-up, whereas only 3 of 14 among SA and 4 of 19 among SS continued to have migraine preceded by aura (P < 0.001 on Fisher exact test).

Conclusions—Compared with medical treatment, closure of PFO brings about a significant overall improvement in migraine. This seems to occur irrespective of migraine type and of previous cerebrovascular disease. In addition to the overall improvement, in migraine with aura, the occurrence of aura is dramatically reduced. (Stroke. 2006;37:000-000.)

Key Words: foramen ovale, patent ■ migraine

A right-to-left shunt (RLS), most often attributable to the persistence of patent foramen ovale (PFO), can be found in nearly half the sufferers of migraine with aura,1–3 and reciprocally, the prevalence of migraine in stroke patients with PFO is exceedingly high, ranging between 27% and 52% according to recent reports.4–7 This suggests that PFO may be causally related to migraine in a proportion of migraineurs.2 Indeed, PFO closure has been reported to improve migraine in patients with cerebrovascular disorders in noncontrolled observational studies.8–13

We addressed the issue of shunt-associated migraine in a case-control study in which we compared the course of migraine assessed prospectively over a 12-month period in symptomatic (for cerebrovascular disease) and asymptomatic patients undergoing PFO closure and in patients with PFO treated medically.

Materials and Methods
Starting in September 2000, all patients referred to the Division of Cardiology of the Humanitas Gavazzeni Clinic (F.C., E.O.) for transcatheter closure of PFO are being entered into a combined study protocol that includes a standardized history taking, a full neurological examination, computed tomography (CT) or MRI, the assessment of coagulation disorders, carotid ultrasound, transesophageal echocardiography (TEE), and a contrast-enhanced transcranial Doppler (ceTCD) test by a team of neurologists (G.P.A., E.M.). The transcranial Doppler test is performed according to the standardized procedure agreed on in the Consensus Conference of...
Venice. In brief, 10 mL of air-mixed saline is injected in the antecubital vein while simultaneously recording the Doppler signal from the right middle cerebral artery during normal breathing and before a Valsalva maneuver. In case of RLS, air microbubbles are detected on the spectral display of the insonated artery and may be counted, allowing a quantitative assessment of the amount of shunt. After this workup, patients with otherwise unexplained symptoms except for presumed paradoxical embolism who exhibit a significant RLS (>10 bubbles recorded in the middle cerebral artery) undergo transcatheter closure of PFO and are since followed up for up to 1 year postoperatively.

Among a cohort of 163 patients, seen from September 2000 to September 2003 and subjected to PFO closure, 50 (males/females [M/F] 10/40) were current migraineurs according to the criteria of the International Headache Society. In 23 patients (39±10 years of age; M/F 5/18), the presenting syndrome had been a stroke with territorial infarction confirmed by CT or MRI (stroke symptomatic [SS]), whereas 27 (40±12 years of age; M/F 5/22) presented with peripheral decompression sickness (n=3), angina with no proven coronary pathology (n=1), increasing frequency of scintillating scotoma in the last month (n=3), or suspected transient ischemic attack (TIA; n=20). In all these 27 patients, MRI was negative (stroke asymptomatic [SA]). The 20 patients with suspected TIA were included in the SA cohort because the clinical presentation did not match the World Health Organization criteria for TIA, and MRI was normal. Twenty-seven consecutive migraineurs with PFO, as confirmed by cTCD, TTE, and negative MRI (36±11 years of age; M/F 4/23), attending the outpatient migraine clinic of the S. Orsola Hospital and followed up medically served as controls (CTRLS).

On the occasion of the preoperative or baseline visit, patients were asked to rate the severity of their migraine in the last 6 months by means of multiple linear regression analysis. The statistical calculations were performed with SPSS (version 13.0) and GraphPad InStat (version 3.06). Frequencies were compared with Fisher’s exact test, scale variables with 1-way ANOVA, repeated-measure ANOVA, or t test when the distribution was normal or with nonparametric tests such as Mann–Whitney or Kruskal–Wallis (KW) when the distribution of data did not follow the normal distribution. The possibly confounding effect of migraine type, age, and cerebrovascular risk factors on outcome was assessed by means of multiple linear regression analysis.

Results

Basal variables are described in Table 2. CTRLS exhibited more risk factors for cerebrovascular disease than SS, probably because of the stringent criteria for PFO closure in stroke patients. Migraine with aura was over-represented in symptomatic than in asymptomatic interventional patients. However, basal migraine scores did not differ among groups (1-way ANOVA; F=1.030; P=0.362), as well as the amount of RLS (KW statistic 0.6315; P=0.7293 for shunt during normal breathing; KW statistic 2.945; P=0.2293 for shunt with Valsalva).

At the end of follow-up, overall migraine score dropped from 6.3 to 2.6 and from 6.1 to 3.3 in SS and SA patients, respectively, whereas in CTRLS, it remained stable from 6.7 to 6.8 (Table 3). The corresponding outcome measures were thus 3.7, 2.8, and 0.1 in SS, SA, and CTRLS patients, respectively. Repeated-measure ANOVA with outcome as within subject factor and condition (CTRLS, SS, and SA) as between subject factor showed that the outcome×condition interaction was statistically significant (F=22.841; P<0.0001). Post hoc comparisons with the Scheffé method showed that the main outcome effect was significantly

| TABLE 2. Basal Characteristics |
|------------------|---|---|---|---|
| Variable          | CTRLS | SS | SA | P  |
| Mean age±SD       | 36±11 | 39±11 | 40±12 | NS |
| M/F               | 4/23 | 5/18 | 5/22 | NS |
| MA+/MA−           | 21/6 | 19/4 | 14/13 | 0.036* |
| Average migraine duration in years | 18±3 | 20±3 | 19±4 | NS |
| No. of patients with ≥1 CVD RF | 21/27 | 11/23 | 15/27 | 0.039* |
| Degree of shunt (median) | 7/80 | 7/99 | 4/41 | NS |
| No. of bubbles | | | |
| Basal/Valsalva    | | | |
| Basal migraine score | 6.7±1.5 | 6.3±1.2 | 6.1±1.6 | NS |
different between CTRLS and SS ($P<0.0001$) and between CTRLS and SA ($P<0.0001$) but not between SA and SA ($P=0.820$; Figure 1). Multiple linear regression analysis confirmed that the outcome effect was independent of age, migraine type, and vascular risk factors (Table 4).

The subscores followed the same profile, with a drop in intensity, duration, and frequency of the attacks in interventional patients and a substantial stability in CTRLS (Table 3).

In terms of individual efficacy, SS, SA, and CTRLS patients were migraine-free (cured) at the end of follow-up in 10 of 23 (43%), 8 of 27 (30%), and 0 of 27 (0%) of cases (CTRLS versus SS $P=0.0001$; CTRLS versus SA $P=0.0043$), and they were improved by $\geq 1$ point in the severity scale in 12 of 23 (52%), 14 of 27 (52%), and 4 of 27 (15%), respectively (CTRLS versus SS $P=0.0067$; CTRLS versus SA $P=0.0084$).

One patient (4%) among SS, 3 (11%) among SA, and 18 (67%) among CTRLS patients were steady ($P=0.0001$ for both CTRLS versus SS and CTRLS versus SA), whereas 0 (0%) among SS, 2 (7%) among SA, and 5 (10%) among CTRLs (CTRLS versus SS $P=0.054$; CTRLS versus SA $P=0.4203$) had worsened by $\geq 1$ point at the 12-month follow-up (Figure 2). The proportion of cured or improved versus unchanged or worsened patients was significantly different between SS and CTRLS (odds ratio [OR], 0.008282; 95% CI, 0.0008553 to 0.08019; Fisher exact test; $P<0.0001$) and between SA and CTRLS (OR, 0.03953; 95% CI, 0.009372 to 0.1667; $P<0.0001$) but no different between SS and SA patients ($P=0.2044$). In summary, PFO closure resulted in an overall positive effect in 95% of SS and in 82% of SA patients but medical treatment in only 15% of CTRLS.

All 21 patients with migraine with aura (MA+) in the CTRLS group still had aura preceding the attacks on $\geq 1$ occasion at the end of follow-up, whereas only 3 of 14 SA and 4 of 19 SS patients had their attacks still forewarned by aura ($P<0.0001$ on Fisher exact test for SA versus CTRLS and SS versus CTRLS).

In SS and SA patients, the benefit of PFO closure affected approximately to the same extent both MA+ and migraine without aura (MA−): 34% of MA+ and 41% of MA− were migraine-free (MA+ versus MA− $P=0.7143$ and 53% of MA+ and 47% of MA− (MA+ versus MA− $P=1$) had improved at the end of follow-up.

Seven of the 50 interventional patients were left with some residual shunt ranging from 6 to 22 microbubbles, but in all cases, the residual shunt was $<10\%$ of the original shunt.

The majority of patients (20 of 27 CTRLS; 18 of 23 SS; and 21 of 27 SA) took nonsteroidal anti-inflammatory drugs to abort migraine attacks, and the remainder used triptans. All patients continued to use their preferred medication throughout the study period.

**Table 3. Migraine Severity Score**

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
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<tr>
<td></td>
<td>Total</td>
<td>Intensity</td>
<td>Duration</td>
<td>Frequency</td>
<td></td>
<td>Total</td>
<td>Intensity</td>
<td>Duration</td>
<td>Frequency</td>
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<tr>
<td>SS</td>
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<td>2.0</td>
<td>1.3</td>
<td>CTRLS</td>
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<td>2.0</td>
<td>2.0</td>
<td>1.8</td>
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<tr>
<td>SA</td>
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<td>3.3</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>CTRLS</td>
<td>6.7</td>
<td>2.0</td>
<td>2.0</td>
<td>1.9</td>
<td></td>
<td>6.8</td>
<td>2.1</td>
<td>2.0</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Figure 1. Mean outcome (basal–end score) in CTRLS, SA, and SS patients. Vertical lines represent 95% CI. CTRLS vs SA $P=0.0005$. CTRLS vs SS $P<0.0005$. 

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TABLE 4. Multiple Regression Analysis

<table>
<thead>
<tr>
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<th>95% CI</th>
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<tr>
<td>Migraine</td>
<td>0.16</td>
<td>-0.91</td>
<td>1.24</td>
<td>0.765</td>
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</tr>
</tbody>
</table>

Outcome as dependent variable. CTRLS group as reference. The variables age, RF (No. of cerebrovascular risk factors), and migraine type have no effect on the difference in outcome between CTRLS and SA and between CTRLS and SS. B indicates regression coefficient, the slope of the regression curve.

### Discussion

The serendipitous observation by Wilmshurst et al\(^8\) that PFO closure performed to prevent decompression sickness in a cohort of scuba divers had resulted in a dramatic decrease of migraine severity raised considerable interest on the possible curative effect of atrial septal repair on migraine. As a consequence, a number of publications reported a reduction in the frequency of attacks after PFO closure in 14% to 83% of patients,\(^{10,13}\) a decrease of ≥2 points in the MIDAS scale in 40% of patients,\(^{12}\) or a decrease of ≥1 point in a composite migraine severity scale in 59% of patients.\(^9\) Even more impressively, complete cessation of migraine attacks was reported in a proportion ranging from 29% to 84% of affected people after a follow-up of 6 to 24 months.\(^9,11-13\)

However, major methodological pitfalls make the validity of these results questionable. First, in all but 1 of the published studies, the assessment of migraine was done retrospectively on a subjective basis, which introduces the issue of recall bias. Second, all the reported patients had had a stroke or TIA, which could have altered the migraine course. Third, in no study was a control group included, the possible effect of aspirin given postprocedurally was not taken into account. Therefore, the placebo effect, the spontaneous variability of migraine, and the interference of medical treatment could have played a significant role.\(^{16}\)

To overcome these problems, we performed a prospective study comparing stroke patients with nonstroke patients and PFO closure with medical treatment. Moreover, the assessment of migraine was standardized and timed so as to avoid the interference of drugs prescribed in the early postprocedural follow-up.

This notwithstanding, 12 months after PFO closure, migraine was abolished in approximately 40% of interventional patients and improved in an additional 50%. The improvement occurred irrespective of previous stroke and involved roughly the same extent of both MA+ and MA−. In addition, approximately 80% of auras disappeared after treatment. In contrast, all medically treated patients continued to have migraine, although an overall improvement was noticed in 15% of them, and in none was aura eliminated. The 15% improvement observed in CTRLS, as well as the 4% worsening in treated patients, emphasizes the intrinsic variability of migraine course and the need to take it into account when evaluating therapeutic alternatives. Nevertheless, our findings clearly confirm the overall beneficial effect of atrial septal repair on migraine in the midterm, even if the absolute gain is somewhat less than that reported in the previous literature.

The association between RLS and migraine in normal people and in stroke patients,\(^1-7\) as well as the benefit showed by atrial septal repair, strongly suggests a pathophysiological link between migraine and PFO, possibly through the shunting of activated platelets, serotonin, or other chemicals.\(^8-17\) Although this interpretation remains speculative. The presence of a RLS, whatever the mechanism, may be the most potent trigger of migraine attacks in both MA+ and MA− and the main determinant of aura in MA+, hence its correction is expected to result in a significant overall improvement and in the disappearance of aura. Under this respect, the difference between MA+ and MA− could reflect different degrees of shunting and preliminary evidence suggests that the bubble load in brain vessels is greater in MA+ than in MA− (average number of bubbles 74 in MA− versus 104 in MA+; \(P<0.0001\)).\(^{18}\)

However, any interpretation of the causal link between PFO and migraine needs to take into account the fact that although PFO is found in nearly half the patients with MA+, its frequency in MA− is the same as in nonmigraineurs.\(^1-3\) For MA+, a common inheritable trait linking migraine with atrial septal abnormalities has been suggested by Wilmshurst et al,\(^9\) who studied 71 relatives of 20 probands with a significantly sized atrial shunt. The occurrence of atrial shunts was consistent with autosomal dominant inheritance. When the proband had migraine with aura and an atrial shunt, 15 of the 21 (71.4%) first-degree relatives with a significant RLS also had migraine with aura compared with 3 of 14 (21.4%) without a significant shunt (\(P<0.02\)), suggesting that the migraine trait may be inherited in association with atrial shunts, at least in some kinships.

These findings raise the issue of the possible existence of a specific subtype of MA+ associated to atrial shunts, the characteristics of which deserve further investigation.

Some inherent limitations of our study need to be considered. The case-control design inevitably exposes to the risks of selection and recall bias. CTRLS and cases were drawn...
from different settings; however, the recruitment was prospective and consecutive, demographic and clinical variables were equally balanced, and migraine severity at inclusion was not different among groups. Therefore, it seems most unlikely that the results are explained by different natural history.

The basal assessment of migraine severity, although retrospective, was performed with the same criteria of the diary given for prospective follow-up. Instead of using the MIDAS questionnaire, we preferred to record separately intensity, duration, and frequency of the attack, as well as the occurrence of aura, and weigh each component in a composite score so as to be able to explore possible selective effects of PFO closure. A differential recall bias for baseline severity assessment cannot be entirely ruled out, but we would deem it unlikely because interventional patients were given no hint on the possible procedural effects on migraine and CTRLs would have been expected to overestimate retrospective severity, which was not actually the case. The follow-up was relatively short, and no control patients were prescribed prophylactic medication. Therefore, the durability of the effect is unsettled, and it remains unknown whether medical prophylaxis would have been equally effective.

However, our results suggest that atrial septal repair modifies at least in the midterm the spontaneous course of shunt associated migraine and support the basis for prospective randomized controlled trials aimed at assessing the efficacy of interventional strategies compared with medical treatment.

Acknowledgments

G.P.A. conceived the study, collected data, and wrote the first draft. G.B.F. assisted in the statistical analysis and reviewed the manuscript. E.M. collected data and reviewed the manuscript. F.C. and E.O. performed intravascular interventions and reviewed the manuscript.

References

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