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Improvement of migraine headaches after percutaneous closure of patent foramen ovale for secondary prevention of paradoxical embolism

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ABSTRACT

Objectives Patent foramen ovale (PFO) has been linked to migraine, and an improvement in migraine prevalence or frequency has been reported after PFO closure for other reasons. We sought to identify whether there is a specific patient population of migraineurs which may be more susceptible to benefiting from PFO closure.

Design Retrospective cohort study.

Setting Tertiary care centre.

Participants 603 consecutive patients undergoing percutaneous PFO closure for secondary prevention of paradoxical embolism.

Interventions PFO closure using the Amplatzer PFO occluder.

Main outcome measures Improvement of migraine symptoms.

Results 150 patients (25%; aged 51±11 years) suffered from migraine, including 96 patients with migraine with aura. All implantation procedures were successful, without procedural complications. Contrast transoesophageal echocardiography at 6 months showed complete PFO closure in 136 patients (91%), whereas a minimal, moderate or large residual shunt persisted in 11 (7%), 2 (1%) or 1 (1%) patients, respectively. During 5.0±1.9 years of follow-up, one TIA and one ischaemic stroke occurred. Migraine headaches disappeared in 51 patients (34%) and improved in 72 additional patients (48%). Mean subjective improvement was 69±35%. Overall, mean headache frequency (from 2–3×/month to 1×/month; $p<0.001$), duration (from 4–72 to <4 h; $p<0.001$) and intensity (from 7±2 to 3±3; $p<0.001$) improved significantly. The prevalence of any migraine headaches (from 100% to 66%; $p<0.001$), migraine with aura (from 64% to 19%; $p<0.001$) and the number of patients taking any migraine medication (from 90% to 50%; $p<0.001$) decreased significantly. Both the presence of aura (OR 3.2; 95%CI 1.3 to 8.2; $p=0.014$) and high pain intensity at baseline (pain scale >5; OR 3.3; 95%CI 1.3 to 8.4; $p=0.013$) were independent predictors of response to PFO closure. A residual shunt had no influence on migraine improvement (OR 0.6; 95%CI 0.1 to 2.3; $p=0.42$).

Conclusions These results suggest that percutaneous PFO closure durably alters the spontaneous course of shunt-associated migraine, especially but not exclusively in case of migraine with aura.

Migraine is a common recurrent and disabling headache disorder affecting at least 10% of population, with a 3:1 female preponderance. A typical migraineur has one to two attacks per month, with a median duration of 24 h. Around one third of migraineurs have migraine with aura. Commonly used preventive medications such as propranolol, amitryptiline or anticonvulsants reduce headache frequency in the range of 30–50%, as compared to placebo. The diagnosis of migraine is purely clinical,[1] and its physiopathology is complex and not fully understood, with both genetic and environmental factors appearing to play an important role.[2] The association of migraine with right-to-left shunts, and patent foramen ovale (PFO) in particular, remains a matter of considerable debate. Indeed, in several studies of patients with migraine, especially of migraine with aura, the prevalence of either right-to-left shunt detected by transcranial Doppler,[3 4] presumably through a PFO, or of a directly visualised PFO[5] was around 50%, which is similar to the prevalence of PFO in patients with cryptogenic stroke. Furthermore, in patients with symptomatic PFO, such as paradoxical embolism[6] or decompression illness,[7] a higher prevalence of migraine has been reported. For migraine with aura, a common inheritable trait, consistent with autosomal dominant inheritance, linking migraine with aura with atrial septal abnormalities has been found in some families.[8] Overall, these findings suggest that PFO might be related to migraine, at least in a sizeable proportion of migraineurs. This led several experts to postulate that, in some migraineurs, headache attacks may be triggered by a certain amount of a yet-unidentified substance (vasoactive chemicals or microemboli) bypassing the lung filter through a shunt, mostly a PFO. However, in the recent elderly (mean age 69 years) population-based NOMAS study,[9] the presence of a PFO detected with transthoracic contrast echocardiography was not associated with self-reported migraine. This contradictory finding may be explained by the inadequate screen for the presence of a PFO. The effect of PFO closure on migraine is even more controversial. On one hand, several observational studies[10–21] reported a striking improvement in migraine prevalence or frequency after PFO closure performed for other reasons, mostly for secondary prevention of paradoxical embolism, but also for subclinical magnetic resonance imaging ischaemic brain lesions[21] or diving accidents. A study reporting migraine improvement after pulmonary fistulae closure in patients with hereditary haemorrhagic telangiectasia further corroborated the link between right-to-left shunt and migraine.[22] On the other

hand, in patients undergoing PFO closure solely for treatment of migraine headaches, the Migraine Intervention with STARFlex Technology trial (MIST),[23] the only prospective randomised controlled study featuring a sham procedure, failed to achieve the ambitious end point of cure in 40% of patients in the implant group. As migraine has a multi-factorial origin,[2] with at most 50% of migraineurs having a PFO, and most people with a documented shunt not suffering at all from migraine, we sought to identify whether there is a specific patient population of migraineurs that may be more susceptible to benefit from PFO closure.

METHODS

Patients

Among 603 consecutive patients undergoing percutaneous PFO closure using the Amplatzer PFO Occluder (APFO, AGA Medical Corporation, Golden Valley, Minnesota, USA) for secondary prevention of presumed paradoxical embolism between March 2000 and January 2007, 150 (25%) suffered from migraine: 96 (64%) had migraine with aura, and 54 (36%) migraine without aura. An embolic event was classified as paradoxical embolism when the following criteria were fulfilled: presence of PFO with or without atrial septal aneurysm with spontaneous or inducible interatrial right-to-left shunt during contrast transoesophageal echocardiography (TEE), clinically and/or radiologically confirmed ischaemic stroke, transient ischaemic attack or peripheral embolism, and exclusion of any other obvious cardiac, aortic or cerebrovascular cause. Migraine and migraine with aura were diagnosed according to the criteria of the International Headache Society.[1]

Echocardiography

The diagnosis of PFO and atrial septal aneurysm was based on contrast TEE, with aerated colloid solution injected into an antecubital vein at the end of a vigorous and sustained Valsalva manoeuvre. PFO was defined as flap-like opening in the atrial septum secundum, with the septum primum serving as one-way valve allowing for permanent or transient right-to-left shunt. Atrial septal aneurysm was diagnosed as abnormally redundant interatrial septum with an excursion of ≥10 mm into the right or left atrium and a diameter of the base of the aneurysm of at least 15 mm.[24] Spontaneous or provoked right-to-left shunt was semi-quantitatively graded according to the amount of bubbles detected in the left atrium after crossing the interatrial septum on a still frame: grade 0=none, grade 1=minimal (1–5 bubbles), grade 2=moderate (6–20 bubbles) and grade 3=severe (>20 bubbles).[25]

Amplatzer PFO occluder

The APFO is a self-expanding double-disc device manufactured from 0.127-mm nitinol wire with a polyester fabric patch sewn into both discs. At the time of this study, the device was commercially available in three sizes, with the dominant right atrial disc measuring 18, 25 or 35 mm, and the left atrial disc 18, 18 or 25 mm, respectively. The APFO can be constrained within an 8-F (18- or 25-mm device) or 9-F (35-mm device) delivery system and reassumes its double-disc shape upon release. It is fully retrievable and repositionable as long as it remains screwed onto its 0.9652-mm delivery cable, and it can be safely implanted without echocardiographic guidance in an outpatient procedure lasting less than 30 min.[26 27]

Percutaneous PFO closure

The procedure was performed under local anaesthesia as described previously.[26 27] Intra-procedural guidance by TEE or intracardiac echocardiography was not used. After venous access was gained via the right femoral vein, the PFO was crossed under fluoroscopic guidance in the anteroposterior view either by a standard length normal 0.889-mm guidewire alone, or with the help of a catheter, typically a 6-F multipurpose catheter. Balloon sizing was not used. A 25-mm device was selected for all cases save those with particularly low mobility (18 mm) or extremely long funnel with particularly large atrial septal aneurysm (35 mm). The so-called "Pacman Sign"[28] was used for verification of a correct position before unscrewing the device from the delivery cable. Haemostasis was achieved by manual compression, often done by the patients themselves. Patients were released to full physical activity a few hours after the procedure, and treated with acetylsalicylic acid 100 mg once daily for 6 months and clopidogrel 75 mg once daily for 1–6 months for antithrombotic protection. A transthoracic contrast echocardiography was performed before discharge to confirm correct and stable device position.

Follow-up evaluation

All patients were followed for up to 9 years. A contrast TEE was repeated 6 months after percutaneous PFO closure to assess for a residual shunt and to exclude a thrombus on the device. All patients were free to continue to use their preferred migraine medication throughout the study period. A structured questionnaire was used for evaluation of headache symptoms according to the criteria of the International Headache Society[1] before and after PFO closure. This questionnaire also addressed the frequency, duration and intensity of headache episodes, the occurrence of aura and inability to work during attacks and number and type of preventive and acute medications. Scales were used to evaluate the frequency (<1 per month; one per month; two to three times per month; once weekly; two to six times per week; once daily; ≥2 times daily), the duration (<4; 4–72; >72 h) and the intensity (from 0 to 10) of headache episodes. Patients also self-rated the overall improvement or worsening in per cent. Follow-up data collection was approved by the local Ethics Committee.

Statistical analysis

Continuous variables are expressed as mean±one SD, and were compared by a two-sided, paired *t* test. Estimates for the survival free from the composite of recurrent ischaemic stroke, transient ischaemic attack and peripheral embolism were obtained using the Kaplan–Meier method. Categorical variables are reported as counts and percentages. Dependent variables were compared by McNemar's χ^2 analysis and independent variables by χ^2 testing. Wilcoxon's signed rank test was used to compare migraine characteristics before and after percutaneous PFO closure. Binary logistic regression was performed to identify independent factors predicting response to PFO closure. The predictors were computed using a forwards stepwise method (likelihood ratio test). Statistical significance was assumed with a p value<0.05. All data were analysed with the use of SPSS software (V.15.0.1, SPSS Inc.).

RESULTS

In-hospital outcome

Demographic data are summarised in tables 1 and 2. All implantation procedures were successful. Among the 150 patients suffering from migraine, an 18-mm APFO was used in 13 patients (9%), a 25 mm in 116 (77%) and a 35 mm in 21 patients (14%). There were no procedural complications. Total procedure time, including incidental coronary angiography[29] in 105 patients (70%), was 37±18 min (median 34 min). Total fluoroscopy time was 6.9±7.3 min (median 5.0 min). In the 45 patients undergoing PFO

Table 1 Baseline characteristics

	All patients	Migraine group	*p* Values*	Migraine with aura	Migraine without aura	*p* Values†
Patients	603	150		96	54	
Age (years)	51±12 (16–84)	51±11 (26–77)	0.65	50±11 (26–74)	53±11 (29–77)	0.07
Female	237 (39%)	69 (46%)	0.05	47 (49%)	22 (41%)	0.39
Height (cm)	173±9	172±9	0.73	172±9	173±8	0.51
Weight (kg)	76±15	76±14	0.91	75±15	77±13	0.31
Body mass index (kg/m^2)	25.5±4.1	25.4±3.6	0.96	25.2±3.6	26±4	0.3
Atrial septal anatomy						
Left atrial size (mm)	37±6	37±7	0.63	36±6	38±10	0.16
PFO only	381 (63%)	90 (60%)	0.49	62 (65%)	28 (52%)	0.16
PFO and atrial septal aneurysm	222 (37%)	60 (40%)	0.32	34 (35%)	26 (48%)	0.22
Right-to-left shunt						
Grade 1	15 (2%)	5 (3%)	0.54	5 (5%)	0 (0%)	0.16
Grade 2	101 (17%)	23 (15%)	0.7	15 (16%)	8 (15%)	1
Grade 3	487 (81%)	122 (81%)	0.9	76 (79%)	46 (85%)	0.39
Cardiovascular risk factors						
Arterial hypertension	192 (32%)	43 (27%)	0.36	26 (27%)	17 (31%)	0.59
Diabetes mellitus	26 (4%)	4 (3%)	0.35	2 (2%)	2 (4%)	0.62
Smoking history	185 (31%)	45 (30%)	0.76	32 (33%)	13 (24%)	0.27
Total cholesterol (mmol/l)	5.1±1.1	5.2±1.0	0.18	5.3±1.1	5.2±0.8	0.49
Embolic index event						
Ischaemic stroke	347 (57%)	89 (59%)	0.51	52 (56%)	14 (26%)	0.12
Transient ischaemic attack	222 (37%)	54 (36%)	0.7	40 (42%)	37 (68%)	0.08
Peripheral embolism	34 (6%)	7 (5%)	0.68	4 (4%)	3 (6%)	0.7
Number of prior embolic events						
One	420 (70%)	106 (71%)	0.84	69 (72%)	37 (68%)	0.7
Two	98 (16%)	24 (16%)	0.9	12 (13%)	12 (22%)	0.16
Three	24 (4%)	6 (4%)	0.81	4 (4%)	2 (4%)	1
Four or more	59 (10%)	14 (9%)	1	11 (11%)	3 (6%)	0.38

*All patients versus migraine group.
†Migraine with aura versus migraine without aura.

closure only, total procedure time amounted to only 18±8 min (median 15 min) and fluoroscopy time was 4.0±2.7 min (median 3.3 min). Transthoracic contrast echocardiography after Valsalva manoeuvre within 24 h of percutaneous PFO closure detected a residual shunt in 22 patients (15%).

Echocardiographic outcome

Complete PFO closure as assessed by contrast TEE after Valsalva manoeuvre at 6 months was achieved in 136 patients (91%), whereas a minimal, moderate or large residual shunt persisted in 11 (7%), 2 (1%) or 1 (1%) patients, respectively. No thrombi

Table 2 Migraine baseline characteristics

	All migraineurs (*n* = 150)	Migraine with aura (*n* = 96)	Migraine without aura (*n* = 54)	*p* Values*
Migraine characteristics				
Duration of symptoms (years)	26±14	25±15	27±14	0.6
Frequency of migraine attacks				
<1 per month	53 (35%)	40 (42%)	13 (24%)	0.03
1 per month	48 (32%)	26 (27%)	22 (41%)	0.1
2–3 times per month	12 (8%)	6 (6%)	6 (11%)	0.35
Once weekly	30 (20%)	20 (21%)	10 (18%)	0.83
2–6 times per week	3 (2%)	1 (1%)	2 (4%)	0.29
Once daily	4 (3%)	3 (3%)	1 (2%)	0.54
Migraine duration				
<4 h	47 (31%)	26 (27%)	21 (39%)	0.15
4–72 h	95 (63%)	64 (67%)	31 (57%)	0.29
>72 h	8 (6%)	6 (6%)	2 (4%)	0.71
Migraine intensity (0–10)	7±2	8±2	7±2	0.09
Inability to work during migraine attacks	80 (53%)	58 (60%)	22 (41%)	0.02
Patients taking any migraine medication	135 (90%)	87 (91%)	48 (89%)	1

*Migraine with aura versus migraine without aura.

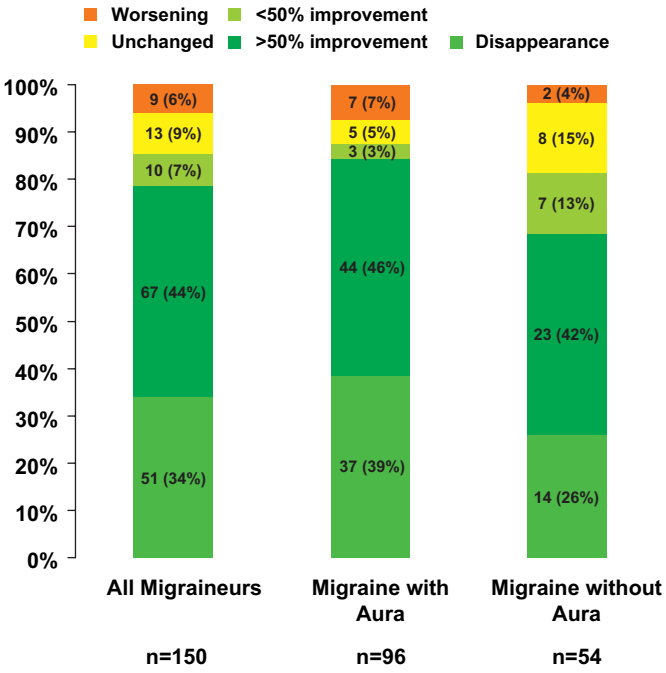

Figure 1 Evolution of migraine headaches after percutaneous PFO closure.

were detected on the devices. Two patients (1%) underwent implantation of a second device. No procedural complication occurred during the second intervention, and complete PFO closure could be achieved in both patients. Both patients reported an improvement of 50% following complete closure and were classified as treatment responders.

Late outcome

None of the 150 migraineurs was lost during 5.0±1.9 years of follow-up (median 4.9 years, total 750 patient years, maximum 9 years). One transient ischaemic attack and one minor ischaemic stroke occurred, but there were no deaths and no peripheral emboli. Survival free from recurrent ischaemic stroke, transient ischaemic attack and peripheral embolism was 100% at 1 year, 99% at 2 years and 98% at 5 years. After PFO closure, migraine headaches disappeared in 51 patients (34%; figure 1) and improved in 77 additional patients (51%): 20 patients (13%) reported a decrease of their headaches of 90%, 35 patients (23%) a decrease of 75%, 12 patients (8%) a decrease of 50% and 10 patients (7%) a decrease of 25%. Headaches remained unchanged in 13 patients (9%), and three patients (2%) experienced transient and six patients (4%) persistent worsening of their headaches. Mean subjective improvement was 69±35%, and 118 patients (79%) had a decrease of their headaches by at least 50%. Overall, mean headache frequency (from 2–3×/month to 1×/month; $p<0.001$), duration (from 4–72 to <4 h; $p<0.001$) and intensity (from 7±2 to 3±3; $p<0.001$) improved significantly. The prevalence of any migraine headaches (from 100% to 66%; $p<0.001$), migraine attacks preceded by an aura (from 64% to 19%; $p<0.001$) and the number of patients taking any migraine medication (from 90% to 50%; $p<0.001$) decreased significantly. Even among the 99 patients (66%) with persisting headaches, both migraine intensity (from 7±2 to 4±3; $p<0.001$) and duration (from 4–72 h to <4 h; $p<0.001$) decreased significantly.

Migraine with aura

Ninety-six patients (64%) had migraine with aura. Among them, headaches disappeared in 37 patients (39%; figure 1) and improved in 47 (49%): 14 patients (15%) reported a decrease of their headaches by 90%, 23 patients (24%) a decrease of 75%, seven patients (7%) a decrease of 50% and three patients (3%) a decrease of 25%, while headaches remained unchanged in five patients (5%) and worsened persistently in seven patients (7%). Thus, 81 out of 96 patients (84%) with migraine with aura had an improvement of at least 50% (vs 68% in patients without aura; $p=0.037$). Among patients with migraine with aura, the

Table 3 Predictors for migraine improvement after PFO closure

Responders versus non-responders			
	Responders	**Non-responders**	***p* Values***
Patients	113	37	
Age (years)	51±11 (26–77)	51±9 (29–68)	0.84
Female	50 (44%)	69 (46%)	0.57
Height (cm)	172±8	172±10	0.95
Weight (kg)	75±13	77±16	0.64
Body mass index (kg/m^2)	25.3±3.4	25.7±4.3	0.62
Atrial septal anatomy			
Left atrial size (mm)	37±8	38±7	0.38
PFO only	69 (61%)	21 (57%)	0.70
PFO and atrial septal aneurysm	44 (39%)	16 (43%)	0.7
Right-to-left shunt			
Grade 1	3 (3%)	2 (5%)	0.6
Grade 2	17 (15%)	6 (16%)	1
Grade 3	93 (82%)	29 (78%)	0.63
Cardiovascular risk factors			
Arterial hypertension	33 (29%)	10 (27%)	1
Diabetes mellitus	3 (3%)	1 (3%)	1
Smoking history	35 (31%)	10 (27%)	0.67
Total cholesterol (mmol/l)	5.3±1.1	5.0±0.8	0.12
Embolic index event			
Ischaemic stroke	69 (61%)	20 (54%)	0.56
Transient ischemic attack	39 (35%)	15 (41%)	0.56
Peripheral embolism	5 (4%)	2 (5%)	1
Number of prior embolic events			
One	76 (67%)	30 (81%)	0.14
Two	21 (19%)	3 (8%)	0.2
Three	5 (4%)	1 (3%)	0.1
Four or more	11 (10%)	3 (8%)	1
Migraine with aura	78 (69%)	18 (49%)	0.03
Migraine characteristics			
Duration of symptoms (years)	26±14	27±14	0.71
Frequency of migraine attacks			
<1 per month	41 (36%)	12 (32%)	0.7
1 per month	36 (32%)	12 (32%)	1
2–3 times per month	8 (7%)	4 (11%)	0.49
Once weekly	24 (21%)	6 (16%)	0.64
2–6 times per week	2 (2%)	1 (3%)	1
Once daily	2 (2%)	2 (6%)	0.25
Migraine duration			
<4 h	36 (32%)	11 (30%)	1
4–72 h	71 (63%)	24 (65%)	1
>72 h	6 (5%)	2 (5%)	1
Migraine intensity (0–10)	8±2	7±2	0.03
Inability to work during migraine attacks	62 (55%)	18 (49%)	0.7
Patients taking any migraine medication	104 (92%)	31 (84%)	0.33

*Responders versus non-responders.

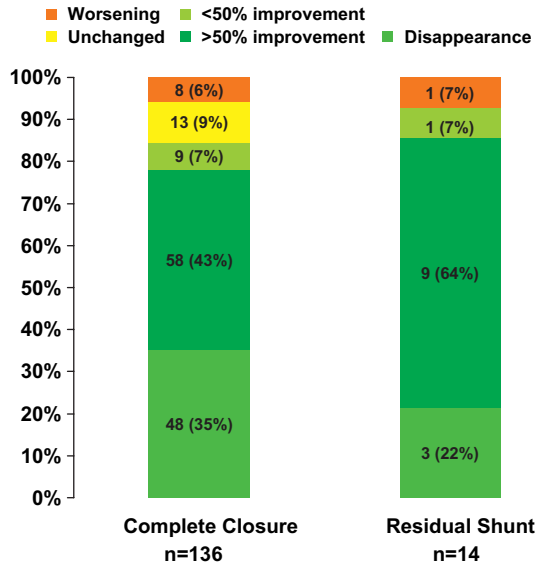

Figure 2 Evolution of migraine headaches in patients with complete PFO closure and in those with a residual shunt.

prevalence of migraine attacks preceded by an aura decreased from 100% to 27% ($p<0.001$), the prevalence of any migraine headaches from 100% to 61% ($p<0.001$) and the number of patients taking any migraine medication from 90% to 47% ($p<0.001$). In this subgroup, headache intensity (from 8±2 to 2±3; $p<0.001$), frequency (from 2–3×/month to 1×//month; $p<0.001$) and duration (from 4–72 to <4 h; $p<0.001$) decreased significantly. Even in patients with persisting headaches ($n=59$), headache intensity (from 8±2 to 4±2; $p<0.001$) and duration (from 4–72 to <4 h; $p<0.001$) improved significantly.

Migraine without aura

Fifty-four patients (36%) had migraine without aura. Following PFO closure, headaches disappeared in 14 patients (26%; figure 1), improved by at least 50% in 23 patients (42%) and by 25% in seven patients (13%), remained unchanged in eight patients (15%) and worsened persistently in two patients (4%). No patient previously suffering from migraine without aura developed an aura following PFO closure. In this subgroup headache intensity (from 8±2 to 2±3; $p<0.001$), frequency (from 2–3×/month to 1×/month; $p<0.001$) and duration (from 4–72 to <4 h; $p<0.001$) also decreased significantly. The prevalence of any migraine headaches (from 100% to 74%; $p<0.001$), and the number of patients taking any migraine medication (from 89% to 56%; $p<0.001$) decreased significantly.

Patterns of improvement

Following PFO closure, three patients (2%) experienced transient and six patients (4%) persistent worsening of their headaches. In 70% of the 128 patients reporting an improvement of their symptoms following PFO closure, this improvement took place immediately after PFO closure. In 26%, improvement took between a few weeks and up to 6 months, and in 4% 1–2 years was required. A lasting improvement was reported in 81% of the patients, while 5%, classified as non-responders, reported a transient improvement only.

Predictors for migraine improvement

Among the different patient and migraine characteristics studied (table 3), only the presence of an aura (OR 3.2; 95%CI 1.3 to 8.2; $p=0.014$) and high pain intensity at baseline (pain scale >5; OR 3.3; 95%CI 1.3 to 8.4; $p=0.013$) were independent predictors of migraine improvement by at least 50% in response to PFO closure. Of note, the 14 patients (9%) with a documented residual shunt at 6 months contrast TEE showed similar improvement in migraine duration, frequency and intensity in comparison to the group with complete PFO closure (91%). A residual shunt had no influence on migraine improvement by at least 50% (OR 0.6; 95%CI 0.1 to 2.3; $p=0.42$; figure 2).

DISCUSSION

Among 603 patients undergoing percutaneous PFO closure for secondary prevention of paradoxical embolism using a single contemporary PFO-dedicated device, 150 (25%) suffered from migraine, including 96 (16%) with migraine with aura. Although these figures are around twice as high as in the general population, they are in the lower range as compared to previous smaller observational studies with shorter follow-up[10–16 18] summarised in table 4. Survival free from recurrent embolic events was 98% at 5 years, which underscores the high clinical efficacy of percutaneous PFO closure, an important finding giving the low recurrence rates in natural history. After PFO closure, migraine headaches improved by at least 50% in 118 patients (79%), including 51 patients (34%) with complete migraine relief, an effect which

Table 4 Prevalence of migraine before and after percutaneous PFO closure for other reasons, in per cent

			Before closure		After closure	
	n	Follow-up (months)	Migraine	Migraine with aura	Migraine	Migraine with aura
Wilmshurst[10]	37	17	57	43	30*	24*
Schwerzmann† [11]	215	24	22	17	20	15
Post[12]	66	6	39	18	16*	5*
Azarbal[13]	66	3	45	30	17	8
Reisman[14]	162	9	35	24	≈15	Not reported
Giardini[15]	131	20	Not reported	27	Not reported	5*
Slavin[16]	120	30	42	33	≈14	≈10
Rigatelli[17]	10	11	100	100	0	0
Dubiel[18]	191	38	24	13	18	8
Morandi[19]	17	6	100	47	71*	12*
Anzola[20]	50	12	100	66	64*	44*
Vigna[21]	53	6	100	43	66*	19*
Present study	603	59	25	16	16*	10*

*$p<0.05$.
†29 migraine patients who received an Amplatzer PFO Occluder were also included in the present study.

lasted over long-term follow-up (mean 5 years) in the vast majority of cases. Both migraine attacks preceded by an aura[14] and high pain intensity at baseline were independent predictors of response to PFO closure. The completeness of PFO closure was not associated with migraine relief, which is disturbing from a physiopathology perspective.[14] However, only 14 out of 150 patients (9%) had a residual shunt on contrast TEE at 6 months, with only three patients (2%) having at least a moderate residual shunt. Based on the results of this and other observational trials, one can assume that, if a patient with migraine, and especially migraine with aura, undergoes PFO closure for another reason than his migraine, it is more likely that he will experience some improvement than that there will be no change or even worsening of his headaches. Furthermore, recurrence of migraine, once it has responded to PFO closure, will be unlikely.

In 17 patients with migraine headaches refractory to medical treatment undergoing percutaneous PFO closure solely for attempted treatment of their headaches, we recently reported[30] similar results, with complete cessation of headaches in 24% of patients, persisting but improved headaches in 47% and unchanged headaches in 29%. Overall, the prevalence of any migraine headaches decreased from 100% to 76% (p=ns), and the prevalence of migraine with aura from 82% to 24% (p=0.002). On the other hand, the only prospective randomised controlled study featuring a sham procedure, the MIST trial,[23] including 147 patients with drug-resistant migraine with aura, failed to reach both its primary and secondary end points, with only 4% of patients "cured" in each group at 6 months follow-up. But besides the ongoing controversy surrounding this study, notably about the quality of the echocardiographic screening and follow-up, unusually high procedural complication and residual shunt rates, presumably due to the type of device used, and the way the data were initially presented, there might be important differences between the patient populations considered. As opposed to the patients reported by the observational trials, who suffered from mostly moderate migraine which was incidental to the reason for PFO closure, patients with severe and refractory migraine, as those from the MIST trial, may prove less amenable to any kind of treatment.

Some limitations have to be considered in the interpretation of our results, the most important being the non-randomised nature of our study and the lack of a control group. Indeed, migraine is known for its spontaneous variability and also for a placebo response rate around 20–30% in well conducted contemporary clinical trials, while the response rates to preventive medications are about 50%. Besides, both acetylsalicylic acid[31 32] and clopidogrel[33] were shown to have a small effect on migraine. In our study, these drugs were recommended for up to 6 months, and the long follow-up (mean 5 years) beyond that period makes a pure placebo or drug effect highly unlikely. As in the other observational studies, virtually all our patients underwent PFO closure after having suffered a cerebral embolism, an event which may have altered the migraine course per se. Finally, it has to be emphasised that the true therapeutic efficacy of percutaneous PFO closure for migraine treatment as adjunct or alternative to medical treatment can only be ascertained by further randomised studies. With MIST II and ESCAPE abandoned, there are currently two remaining trials actively randomising patients: Percutaneous closure of PFO In Migraine with Aura (PRIMA), and Prospective Randomised investigation to Evaluate incidence of headache reduction in subjects with Migraine and PFO using the Amplatzer PFO Occluder compared to Medical management (PREMIUM). Unfortunately, due to slow enrolment, mostly caused by very restrictive inclusion criteria, results will take years to materialise.

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Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Ethics Committee of the Canton of Berne.

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Images in cardiology

Ectopia cordis with right and left ventricular diverticula

A newborn girl who was delivered vaginally at 37 weeks of gestation exhibited double-outlet right ventricle, pulmonary stenosis and persistent left superior vena cava accompanied with ectopia cordis (online video 1: shows her heart beating outside the body and the anterior interventricular sulcus). The case fulfilled the diagnostic criteria of Cantrell's pentalogy. Half of each of the right and left cardiac ventricles was exposed. An emergency operation was performed to place the exposed portion of the heart into the internal thoracic cavity. Expanded polytetrafluoroethylene (e-PTFE) was used as a substitute for the pericardium. Subsequently, skin flaps were designed on both the sides and sutured to each other such that they covered the e-PTFE patch-layered heart. After 2 months, modified Blalock-Taussig shunt was created on the right side to treat cyanosis. Computed tomography of the chest, which was performed after the palliative operation, showed the rightward-pointing heart apex and the presence of both right and left ventricular diverticula (panel A—B).

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►Additional video published online only. To view it, please visit the journal online (http://heart.bmj.com).

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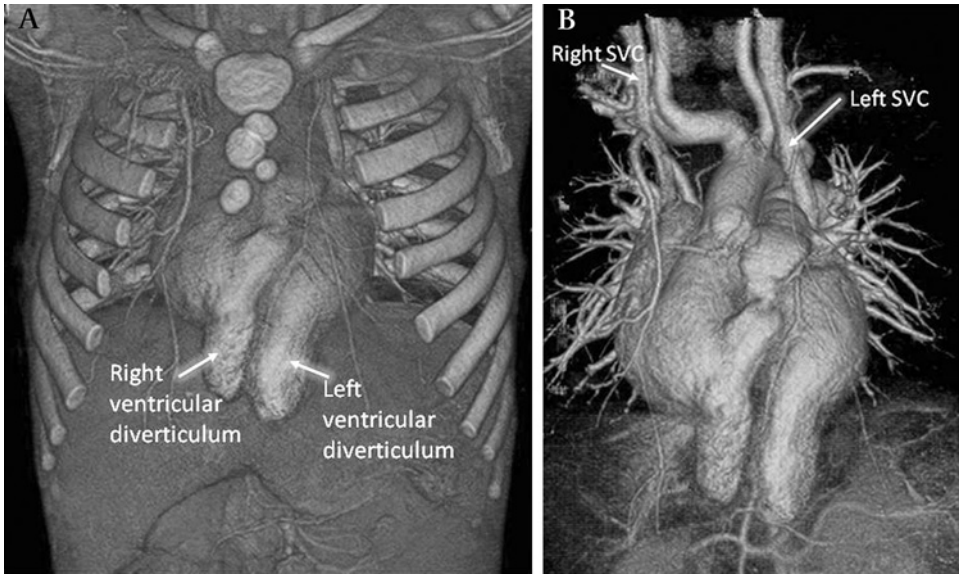

Panel A. The frontal view of the three-dimensional computed tomography shows sternum dysplasia and the rightward-pointing heart apex with the presence of both right (Rt.) and left ventricular diverticula. B. The three-dimensional computed tomography focussing on cardiac anatomy shows bilateral superior vena cava (SVC) and double outlet right ventricle with subpulmonary stenosis. A left anterior descending coronary artery passes in the middle of the two ventricular diverticula.