Migraine and Patent Foramen Ovale (PFO)

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Topics

• Prevalence of PFO
• Is migraine related to PFO?
• Is PFO related to migraine?
• PFO should not be closed in migraine
Prevalence of PFO

- 17-23% of the population (autopsy)
- 25.6% transoesophageal echo (TEE)
- 2.2% atrial septal aneurysm (ASA)

Seib, 1934; Meissner et al, 1999;
First Study: Potential Source of Cerebral Embolism in Migraine with Aura

113 migraine + aura,
53 migraine - aura,
25 non-migraine controls

- Transcranial Doppler with agitated i.v. saline as contrast (air bubbles)
- PFO 48% Migraine + aura
- PFO 23% Migraine – aura
- PFO 20% Controls

Anzola et al, Neurology, 1999
Inheritance of PFO, ASD and Migraine with Aura

• Proband had large PFO (19) or ASD (1)
• 20 families underwent echocardiography (71)
• Artial shunts consistent with dominant inheritance
• Proband PFO and migraine with aura: 72% of relatives had shunt plus migraine with aura
• Proband had no PFO: 21% of relatives had migraine with aura

Wilmhorst et al, Heart 2004;90
Prevalence of migraine in patients with patent foramen ovale

14 studies with TCD or TEE

N = 2602

- Any migraine: 41%
- Migraine + aura: 38%
- Migraine – aura: 16%
- Controls: ??%

Tariq et al, Headache 2016;56:462-478

Migraine and PFO

• Meta-analysis of 18 publications
• Association between PFO and migraine OR 5.13
• Association between PFO and migraine with aura OR 3.21
• Association between migraine and PFO OR 2.54
• All studies biased

OR = Odds ratio; Schwedt and Dodick, Cephalalgia 2008
Table

<table>
<thead>
<tr>
<th>Reference (year)</th>
<th>Sample size</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilmshurst &amp; Nightingale et al (2001)</td>
<td>200</td>
<td>2.72 (2.09-3.36)</td>
</tr>
<tr>
<td>Sztajzel et al (2002)</td>
<td>74</td>
<td>1.82 (0.88-2.75)</td>
</tr>
<tr>
<td>Wilmshurst et al (2005)</td>
<td>200</td>
<td>5.88 (5.19-6.58)</td>
</tr>
<tr>
<td>Wilmshurst et al (2006)</td>
<td>60</td>
<td>3.60 (2.43-4.77)</td>
</tr>
<tr>
<td>Anzola et al (2006)</td>
<td>1,120</td>
<td>5.73 (5.46-6.00)</td>
</tr>
<tr>
<td>Kimmelstiel et al (2007)</td>
<td>169</td>
<td>5.00 (4.32-5.87)</td>
</tr>
<tr>
<td>Pooled</td>
<td>1,823</td>
<td>5.13 (4.67-5.59)</td>
</tr>
</tbody>
</table>

Figure 2 Strength of association between patent foramen ovale (PFO) and migraine. The odds ratios (ORs) for migraine and PFO ranged from 1.82 to 5.88, with a summary OR of 5.13 [95% confidence interval (CI) 4.67, 5.59].

Table

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<td>71</td>
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</tr>
<tr>
<td>Sztajzel et al (2002)</td>
<td>41</td>
<td>3.64 (2.25-5.03)</td>
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<tr>
<td>Wilmshurst et al (2005)</td>
<td>75</td>
<td>9.22 (7.71-10.73)</td>
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<td>Wilmshurst et al (2006)</td>
<td>33</td>
<td>1.75 (0.17-3.67)</td>
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<tr>
<td>Anzola et al (2006)</td>
<td>362</td>
<td>2.43 (1.09-2.87)</td>
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<tr>
<td>Kimmelstiel et al (2007)</td>
<td>60</td>
<td>1.74 (0.63-4.11)</td>
</tr>
<tr>
<td>Pooled</td>
<td>643</td>
<td>3.21 (2.38-4.17)</td>
</tr>
</tbody>
</table>

Figure 3 Strength of association between patent foramen ovale (PFO) and migraine with aura. The odds ratios (ORs) for PFO and migraine with aura ranged from 1.74 to 9.22, with a summary OR of 3.21 [95% confidence interval (CI) 2.38, 4.17].
North Manhattan Study (NOMAS)

Population based study

1101 probands without stroke

Migraine prevalence 16%

TTE with NaCl bubbles

PFO prevalence 15%
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

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. (Circulation. 2008;118:1419-1424.)
Migraine Headache and PFO: Case-Control Study

- Patients with migraine (N = 144)
- Age and sex matched controls (N = 144)
- Echocardiography, TCD
- PFO prevalence 26.4% versus 25.7%
- No difference for migraine with or without aura

Garg et al, Circulation 2010
Prevalence of patent foramen ovale in patients with migraine

20 studies with TCD or TEE

N = 2444

• Any migraine 47%
• Migraine + aura 67%
• Migraine – aura 25%
• Controls ??%

Tariq et al, Headache 2016;56:462-478
Conclusions

- Patients with migraine have a higher prevalence of PFO
- This is only true in case-control studies
- Population based studies do not show a higher prevalence of PFO in migraine
- Most probably both conditions have a common genetic background
Improvement of Migraine by PFO Closure

- First retrospective study
- 215 patients with percutaneous closure of PFO
- Prevalence of migraine (- 1 year): 48 (22%)
- Reduction in migraine frequency
  - Migraine with aura: - 54%
  - Migraine without aura: - 62%

Schwerzmann et al, Neurology 2004
Improvement of migraine by PFO closure

- All patients received aspirin 100 mg or clopidogrel for 6 months

- Aspirin has migraine prophylactic properties in men (Buring et al. 1990)

- Aspirin (300 mg) reduced migraine frequency by 29% (n=135) (Diener et al 2001)

Gianfranco Butera, MD, PhD, Giuseppe G. L. Biondi-Zoccai, MD, Mario Carminati, MD, Luigi Caputi, MD, Susanna Usai, MD, Gennaro Bussone, MD, Giovanni Meola, MD, Angelica Bibiana Delogu, MD, Imad Sheiban, MD, and Giuseppe Sangiorgi, MD

Migraine and PFO Closure: Systematic Review

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>% (SE)</th>
<th>% (random) 95% CI</th>
<th>Weight %</th>
<th>% (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jesurum</td>
<td>79.000 (4.6000)</td>
<td>79.00 [69.98, 88.02]</td>
<td>13.93</td>
<td>13.93</td>
</tr>
<tr>
<td>Stevin</td>
<td>85.000 (5.2000)</td>
<td>85.00 [74.81, 95.19]</td>
<td>12.28</td>
<td>12.28</td>
</tr>
<tr>
<td>dubiel</td>
<td>87.000 (4.9000)</td>
<td>87.00 [77.40, 96.60]</td>
<td>13.08</td>
<td>13.08</td>
</tr>
<tr>
<td>Morandi</td>
<td>88.200 (7.8000)</td>
<td>88.20 [72.91, 103.49]</td>
<td>7.31</td>
<td>7.31</td>
</tr>
<tr>
<td>Post</td>
<td>65.300 (9.3000)</td>
<td>65.30 [47.07, 83.53]</td>
<td>5.59</td>
<td>5.59</td>
</tr>
<tr>
<td>Schwerzmann</td>
<td>81.800 (8.8000)</td>
<td>81.80 [70.43, 93.17]</td>
<td>10.84</td>
<td>10.84</td>
</tr>
<tr>
<td>Rehman</td>
<td>70.000 (6.5000)</td>
<td>70.00 [57.26, 82.74]</td>
<td>9.40</td>
<td>9.40</td>
</tr>
<tr>
<td>Arzola</td>
<td>88.000 (4.5000)</td>
<td>88.00 [78.98, 97.02]</td>
<td>13.93</td>
<td>13.93</td>
</tr>
<tr>
<td>Gierdri</td>
<td>91.400 (4.7000)</td>
<td>91.40 [82.19, 100.61]</td>
<td>13.64</td>
<td>13.64</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>100.00 [70.25, 87.93]</td>
<td>100.00</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 13.91, df = 8 (P = 0.08), I^2 = 42.5\%$

Test for overall effect: $Z = 33.05 (P < 0.00001)$

Fig. 3. Forest plot of the rate of cure or improvement among patients with patent foramen ovale being treated with percutaneous closure.
Conclusion

Improvement of migraine with aura after PFO closure can be due to

• Spontaneous course of the disease (age, regression to the mean)
• Placebo effect
• Intake of aspirin or clopidogrel
• PFO closure might result in improvement of migraine as well as de novo migraine
• Prevention of paradoxical small emboli or passage of bioactive substances
Migraine prophylaxis by PFO closure

Interventional Cardiology

Migraine Intervention With STARFlex Technology (MIST) Trial
A Prospective, Multicenter, Double-Blind, Sham-Controlled Trial to Evaluate the Effectiveness of Patent Foramen Ovale Closure With STARFlex Septal Repair Implant to Resolve Refractory Migraine Headache

Andrew Dowson, MBBS, PhD; Michael J. Mullen, MBBS, MRCP, MD; Richard Peatfield, MD, FRCP; Keith Muir, MD, FRCP; Arif Anis Khan, MBBS, FCPS; Christopher Wells, MB, ChB, FRCA; Susan L. Lipscombe, MB, ChB, MRCP; Trevor Rees, MB, ChB; Joseph V. De Giovanni, MD, FRCP, FRCPCH, MOM; W. Lindsay Morrison, MD, FRCP; David Hildick-Smith, MD, FRCP; Giles Elrington, MD; W. Stewart Hillis, MB, ChB, FRCP, FRCS; Iqbal S. Malik, MA, MRCP, PhD; Anthony Rickards, MBBS, FRCP, FESC†
<table>
<thead>
<tr>
<th></th>
<th>Implant (n=74)</th>
<th></th>
<th>Sham procedure (n=73)</th>
<th></th>
<th>Statistical Analyses*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Analysis Phase</td>
<td>Baseline</td>
<td>Analysis Phase</td>
<td>Difference Between Implant</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>and Sham Arms (95% CI)</td>
</tr>
<tr>
<td>Patients with no migraine attacks, n</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>-0.06% (-6.45–6.34)</td>
</tr>
<tr>
<td>Frequency of migraine attacks/mo,</td>
<td>4.82±2.44</td>
<td>3.23±1.80</td>
<td>4.51±2.17</td>
<td>3.53±2.13</td>
<td>0.45 (-0.16–1.05)</td>
</tr>
<tr>
<td>mean±SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>66</td>
<td>66</td>
<td>73</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Total MIDAS score, median (range)</td>
<td>36 (3–108)</td>
<td>17 (0–270)</td>
<td>34 (2–189)</td>
<td>18 (0–240)</td>
<td>1 (-11–10)</td>
</tr>
<tr>
<td>n</td>
<td>66</td>
<td>67</td>
<td>69</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Headache d/3 mo (MIDAS), median (</td>
<td>27 (0–70)</td>
<td>18 (0–90)</td>
<td>30 (5–80)</td>
<td>21 (0–80)</td>
<td>1 (-5–6)</td>
</tr>
<tr>
<td>range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>66</td>
<td>67</td>
<td>69</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>HIT-6 total score, mean±SD</td>
<td>67.2±4.7</td>
<td>59.5±9.3</td>
<td>66.2±5.1</td>
<td>58.5±8.6</td>
<td>0 (-3–2)</td>
</tr>
<tr>
<td>n</td>
<td>67</td>
<td>67</td>
<td>69</td>
<td>73</td>
<td></td>
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</table>

Missing data were replaced by last observation carried forward. CI indicates confidence interval.
Complications of PFO Closure

• 256 consecutive patients
• 23 periprocedural complications (8.9%)
• Paradoxical air embolism
• Femoral hematoma
• Pericardial effusion
• 2 fatal thromboembolisms
• 2 TIA, 1 seizure

Onorato et al, J Interventional Cardiology 2003
PFO closure of patent foramen ovale in migraine with aura, a randomized controlled trial

Table 1  Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>PFO closure</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ± SD), (N), [min, max]</td>
<td>44.1 ± 10.7 (53) [21–61]</td>
<td>42.7 ± 11.0 (54) [20–62]</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8/53 (15%)</td>
<td>9/54 (17%)</td>
</tr>
<tr>
<td>Female</td>
<td>45/53 (85%)</td>
<td>45/54 (83%)</td>
</tr>
</tbody>
</table>

European Heart Journal (2016) 37, 2029–2036
doi:10.1093/eurheartj/ehw027

PFO Verschluß bei Migräne mit Aura nicht wirksam

Heinrich P. Mattle1*, Stefan Evers2†, David Hildick-Smith3, Werner J. Becker4, Helmut Baumgartner2, Jeremy Chataway5, Marek Gawel6, Hartmut Göbel7, Axel Heinze7, Eric Horlick8, Iqbal Malik5, Simon Ray9, Adam Zermansky10, Oliver Findling1, Stephan Windecker11, and Bernhard Meier11
PREMUIM Trial

A randomized sham-controlled trial in patients with „intractable migraine“

- N = 230 patients in the USA
- N = 123 PFO closure with the St. Jude Starflex occluder
- Primary endpoint percentage of responders
  - PFO closure: 38%
  - Sham procedure: 32%
- $P = 0.3$

Study failed primary endpoint

Study not published!!
Evidence FOR PFO closure

- The MIST Trial
  NEGATIVE
- The PREMIUM Trial
  NEGATIVE
- The PRIMA Trial
  NEGATIVE

Do we need more negative trials?
Doctors who are unable to help migraine patients will become aggressive

They will move to aggressive treatment methods
Tell your patients:

If a cardiologist proposes PFO closure get away as quickly as possible and look for a new headache physician.
I like debates

Thank you for your attention